Health Evidence Review Commission's Value-based Benefits Subcommittee

August 17, 2023

8:00 AM - 1:00 PM

Online Meeting

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Section 1.0

Call to Order

Agenda
Value-based Benefits Subcommittee (VbBS)
August 17, 2023

8:00 am–1:00pm

Online meeting

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** 1) Legislative update 2) Membership update 3) Update on in-person meetings 4) Feedback on advanced packet 5) June staff listening session report
III.	8:25 AM	**Straightforward/Consent Agenda** 1) Consent table 2) Straightforward guideline note changes 3) SOI4 revisions for EPSDT 4) MyChoice CDX test
IV	8:30	**Advisory Panel Reports** 1) BHAP report a. Unspecified reaction to severe stress *(Serious stress treatment)* b. Freespira for PTSD and panic disorder *(Electronic program that gives patients feedback)*
V	9:00	**New Codes** 1) July HCPCS 2) 2024 ICD-10-CM codes A. Straightforward codes a. Informational codes

	Time	Topic
		B. Codes requiring discussion a. Metabolic syndrome/insulin resistance b. Bronchiolitis obliterans c. SIBO d. Dense breasts e. Z62.813
VI	9:30	**New Discussion Items** A. Interstitial laser thermal therapy for epilepsy *(A brain surgery for patients that have epilepsy which is not helped by medications)*
	10:15	**BREAK**
VII	10:30	**Previous discussion items** A. Modifications for the solid organ transplant guideline *(Requirement to quit smoking for organ transplants (for example, heart, lung, liver) other than bone marrow)* B. Prostatic urethral lift for benign prostate enlargement with lower urinary tract symptoms *(Prostate surgeries and a 'lift' procedure to widen the urethra and place a hollow tube that lets urine leave the body)* C. Breast reduction for macromastia *(Surgery to reduce the size of breasts when they cause back and neck pain)*
VIII	11:00 AM	**New discussion items** A. 2023 Vaccine review a. Antitoxins and immunoglobulins *(Injections be given to a person when they are exposed to a virus or bacteria they do not have immunity to.)* b. 2023 vaccine review A. Coronary artery calcium scoring *(A scan that predicts heart attack risk)* B. CT colonography *(A scan to see whether a person has cancer of the gut (large bowel))* C. Breast cancer screening modalities a. Breast tomosynthesis *(Screening tests for breast cancer)* b. Additional studies for women with dense breasts D. Listening session topics: a. Fibromyalgia 2023 review *(Long-lasting disorder that causes pain, fatigue and trouble sleeping)* *E.* Fat incarceration in ventral hernias *(Body fat that gets trapped in some types of hernias)* F. PSMA PET scans for prostate cancer *(Screening for prostate cancer)*

	Time	Topic
		G. Cardiac resynchronization therapy *(Pacemaker and heart defibrillator placement for heart failure)* H. Changes to the Prioritized List required to conform with legislation regarding gender affirming care *(Services to support an individual's gender identity)*
IX	12:55 PM	**Public comment on topics not on the agenda**
X	1:00 PM	**Adjournment**

Value-based Benefits Subcommittee (VbBS) Summary

For Presentation to:
Health Evidence Review Commission on May 18, 2023

For specific coding recommendations and guideline wording, please see the text of the May 18, 2023 VbBS minutes.

Recommended Code Movement (Changes to the 10/1/2023 Prioritized List unless otherwise noted):

- Add various proprietary laboratory analysis (PLA) codes to the Diagnostic Procedures File; add one to a funded line. Add the PLA code for HIV viral resistance to an unfunded line.
- Delete the procedure code for a drug metabolic test for NUDT15 from an unfunded line and add to the Diagnostic Procedures File
- Move the procedure code for the second cervical artificial disc to a funded line
- Add the procedure code for YAG laser therapy to the funded line for hidradenitis suppurativa
- Add multiple procedure codes for various bariatric surgery procedures to a funded line

Item Considered but No Recommendations for Changes Made:

- No change was recommended to the non-coverage of single sided deafness in adults
- No change was recommended to the current placement of various circadian rhythm disorders on a non-funded line
- No coverage was added for magnetic esophageal sphincter augmentation devices to treat gastroesophageal reflux (GERD)
- Radiation therapy was not paired with Dupuytren's contracture of plantar fibromatosis

Recommended Guideline Changes (Changes to the 10/1/2023 Prioritized List unless otherwise noted):

- Edit the tonsillectomy guideline to broaden the definition of "attack" or infection
- Edit the cochlear implant guidelines to add coverage for use of cochlear implants for single sided deafness in children
- Delete the guideline regarding second bone marrow transplants
- Edit the spinal imaging guideline to specify that SPECT was not covered for pre-surgical evaluation
- Edit the guideline regarding artificial discs to allow coverage of a second artificial cervical disc
- Edit the bariatric surgery guideline to allow coverage for adolescents meeting certain criteria and to lower the required BMI for adults to $\geq$35 kg/m^2 ($\geq$30 with poorly controlled type 2 diabetes) – *Effective 1/1/2024*
- Make various straightforward guideline changes

Minutes
Value-based Benefits Subcommittee (VbBS)

Online meeting
May 18, 2023

Members Present: Holly Jo Hodges, MD, MBA, Chair; Brian Duty, MD, Vice-Chair; Kevin Olson, MD; Kathryn Schabel, MD; Adriane Irwin, PharmD; David Saenger, MD; Sara Love, ND

Members Absent: Cris Pinzon, MPH, RN; Mike Collins

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

Also Attending: Val King, MD, MPH, Shauna Durbin & Marcus Bachhuber, MD (OHSU Center for Evidence-based Policy); Dawn Mautner, MD, Jason Hurtado Daniels & Tim Menza, MD (Oregon Health Authority); Dr. Peggy Kelley; Heather Onoday RN, Susan Funatake (OHSU); John Goddard, MD (Kaiser Permanente); Sterling Hodgson, MD (Oregon Clinic); Queentela Benjamin & Deb Brugman (Foundation Medicine); Annemarie Benton; Derek Rogalsky, MD; Sara L Fletcher; Joan S; Laura Briggs; M; Maritza Herrera; Siobhan Hess; Val Halpin.

Call to Order, Minutes Approval, Staff Report

The meeting was called to order at 8:05 am and roll was called. A quorum of members was present at the meeting. Minutes from the March 9, 2023, VbBS meeting were reviewed and approved with no modifications.

Jason Gingerich gave the staff report. He discussed membership changes, gave a legislative update, and requested that members complete the retreat follow-up survey. He also discussed a pilot project to publish meeting materials earlier to allow greater public comment and input.

Straightforward/Consent Agenda

Discussion: There was no discussion about the consent agenda items, other than the solid organ transplant guideline suggested revisions.

Hodges requested that the proposed multi-organ transplant requirements have additional wording regarding coverage for a second organ simultaneous transplant when the second organ is required to improve the outcome of the first organ transplant. Staff will revise the draft recommendation to include this indication and bring back to the August VBBS meeting for further discussion.

Recommended Actions:

1) Modify Diagnostic Guideline D9 as shown in Appendix A
2) Modify GN118 as shown in Appendix A and add the guideline note to line 202 SLEEP APNEA, NARCOLEPSY AND REM BEHAVIORAL DISORDER
3) Modify GN 155 as shown in Appendix A
4) Modify GN21 as shown in Appendix A

MOTION: To approve the recommendations as presented in the consent agenda, and table the recommendation on modifications to the solid organ transplant guideline. CARRIES 7-0.

Tonsillectomy for recurrent infection

Discussion: Smits presented the meeting materials. There was minimal discussion.

Recommended Actions:

1) Modify GN36 as shown in Appendix A

MOTION: To approve the recommendations as presented. CARRIES 7-0.

Cochlear implants for unilateral deafness

Discussion: Smits presented the meeting materials. Dr. Peggy Kelley, the invited pediatric ENT expert, noted that single sided deafness (SSD) is a safety issue as well as a developmental issue in children. In adults, sound localization, balance and other developmental processes are complete and therefore adults receive less benefit from treatment for SSD. For children, cochlear implants support development, such as balance.

Public testimony

Sara Funatake, audiologist, OHSU: Funatake said that cochlear implants for SSD have been FDA-approved since 2019. Funatake said that cochlear implants need to be covered for pediatric patients as she has several patients paying out of pocket due to

lack of OHP coverage. She has pediatric patients with SSD who are on individualized education plans for reading and writing but return to grade level in these subjects after cochlear implantation. She said SSD can cause phobias in certain situations for patients. She also recommends coverage for adults with sudden sensorineural hearing loss. She notes that word understanding improves with adults with sudden SSD when treated with cochlear implantation. SSD increases patient anxiety and depression, and cochlear implantation improves their quality of life.

John Goddard, MD, otolaryngologist, Kaiser Permanente Portland: Goddard said that he has been a cochlear implant surgeon for more than 12 years. Patients with SSD (children or adults) are severely impacted by their hearing loss with loss of binaural summation and sound shadow. BAHA and CROS are not very helpful for adults, and strongly opposes using BAHA in children, as they create skin and other problems. Children struggle when they lose hearing in one ear. In his experience, adults and children benefit from unilateral cochlear implantation with improved quality of life. He strongly encouraged approving cochlear implants for SSD for children and adults.

Sterling Hodgson, MD, otolaryngologist, private practice: Hodgson has many adult patients with SSD. Patients with SSD lose volume and quality of hearing. Cross over technologies (e.g., BAHA, CROS) do not allow sound localization. SSD is very socially isolating and negatively affects brain development in children. SSD affects children's learning and education, which cochlear implantation could address. For adults, SSD reduces productivity and diminishes patients' ability to understand conversation. FDA-approved use of cochlear implants for SSD is evidence-based.

Subcommittee members were unanimously in favor of adding cochlear implants for SSD in children. The current literature does not clearly support use of cochlear implants for SSD in adults and members did not feel that any additional coverage of treatments should be added at this time. However, members expressed that this topic should be re-addressed once more evidence is published.

Recommended Actions:

1) Do not add coverage for any treatment modality for SSD in adults
2) Modify GN 31 and GN 143 as shown in Appendix A

MOTION: To approve the recommendations as presented. CARRIES 6-0 (Duty absent).

PLA code review

Discussion: Smits reviewed the summary document. There was no discussion. Smits noted that staff intends to identify PLA codes that need review on a quarterly to biannual basis.

Recommended Actions:

1) Advise HSD to place the following PLA codes on the Diagnostic Procedures File
    a. 0241U, 0202U, 0240U (COVID/flu/RSV tests)
    b. 0077U (mass spectrometry for diagnosis of multiple myeloma)
    c. 0027U (JAK2 test)
    d. 0279U (von Willebrand disease collagen binding)
    e. 0035U (Prion disease test)
    f. 0034U NUDT15 (drug metabolism gene testing)
    g. 0001U (DNA based blood typing)
2) Add 0058U to line 276 CANCER OF SKIN, EXCLUDING MALIGNANT MELANOMA
3) Place 0219U on Line 662 CONDITIONS FOR WHICH CERTAIN INTERVENTIONS ARE UNPROVEN, HAVE NO CLINICALLY IMPORTANT BENEFIT OR HAVE HARMS THAT OUTWEIGH BENEFITS
    a. Add an entry to GN173 as shown in Appendix A regarding 0219U
4) Remove CPT 81306 from line 662, advise HSD to place CPT 81306 on the Diagnostic Procedures File, and remove the GN173 entry for CPT 81306 as shown in Appendix A

MOTION: To approve the recommendations as presented. CARRIES 7-0.

Prostatic urethral lift

Discussion: Smits reviewed the summary document. Subcommittee members agreed to the staff recommended changes but requested that the term "refractory" be defined as it relates to medication trials. Smits noted the AUA defines refractory in their guideline as failure to resolve symptoms after 4 weeks with an alpha blocker or phosphodiesterase inhibitor or 6 months with a 5-alpha reductase inhibitor. Staff were directed to work with urologists to finalize a definition and bring this item back to the August VBBS meeting.

Recommended Actions:

1) Table this topic until a future meeting

Circadian rhythm disorders

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

Recommended Actions:

1) Make no change to the placement of ICD-10-CM G47.2 family (Circadian rhythm sleep disorder) on line 606 DISORDERS OF SLEEP WITHOUT SLEEP APNEA

MOTION: To approve the recommendations as presented. CARRIES 7-0.

Second bone marrow transplants

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

Recommended Actions:

1) Delete guideline note 14 as shown in Appendix A

MOTION: To approve the recommendations as presented. CARRIES 7-0.

Magnetic esophageal sphincter augmentation device

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

Recommended Actions:

1) Update the entry for CPT 43284 in GN173 as shown in Appendix A

MOTION: To approve the recommendations as presented. CARRIES 7-0.

Radiation therapy for Dupuytren's contracture and plantar fibromatosis

Discussion: Smits presented the summary document. The subcommittee did not recommend adding plantar fibromatosis to any biennial review.

Recommended Actions:

1) Make no change in the non-pairing of Dupuytren's contracture and plantar fibromatosis and radiation therapy

MOTION: To approve the recommendations as presented. CARRIES 7-0.

SPECT for spinal indications

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

Recommended Actions:

1) Modify Diagnostic Guideline D4 as shown in Appendix A

MOTION: To approve the recommendations as presented. CARRIES 7-0.

Two level cervical artificial disc

Discussion: Smits reviewed the summary document. There were several friendly amendments made to the guideline to clarify lack of coverage of the coding for second level lumbar artificial disc.

Recommended Actions:

1) Reverse the March 2023 decision and return two level artificial disc replacement to the funded and unfunded surgical back lines
    a. Return CPT 22858 (Total disc arthroplasty (artificial disc), anterior approach, including discectomy with end plate preparation (includes osteophytectomy for nerve root or spinal cord decompression and microdissection); second level, cervical (List separately in addition to code for primary procedure)) to lines 346 CONDITIONS OF THE BACK AND SPINE WITH URGENT SURGICAL INDICATIONS and 530 CONDITIONS OF THE BACK AND SPINE WITHOUT URGENT SURGICAL INDICATIONS
    b. Remove CPT 22858 from line 662 CONDITIONS FOR WHICH CERTAIN INTERVENTIONS ARE UNPROVEN, HAVE NO CLINICALLY IMPORTANT BENEFIT OR HAVE HARMS THAT OUTWEIGH BENEFITS
2) Reverse the March 2023 decision and remove the CPT code for two level artificial disc replacement from GN173 as shown in Appendix A
3) Modify GN101 as shown in Appendix A

MOTION: To approve the recommendations as modified. CARRIES 7-0.

YAG laser for treatment of hidradenitis suppurativa

Discussion: Smits reviewed the summary document.

Invited testimony was heard from Heather Onoday, NP at OHSU dermatology. She gave a presentation which summarized the pain and functional impacts of hidradenitis suppurativa (HS). This is an uncommon condition which is difficult to treat and results in high medical costs. There are higher suicide rates in the population with HS. Patients fail many treatments and therefore need more treatment options. Long-term complications of HS include infection, functional issues, and disability. YAG laser therapy destroys hair follicles, which effectively treats HS, and reduces sinus tracts and abscesses. Studies on YAG lasers in HS are small due to small numbers of patients with condition. Biopsies taken before and after YAG laser treatment show reduction in inflammation and fewer sinus tracts and abscesses. YAG laser therapy received the second highest level of recommendation in the expert guidelines, below only adalimumab. Adalimumab has higher side effects and risks and costs than YAG laser therapy. Other commonly used treatments, such as antibiotics and local surgery, have lower levels of evidence that YAG laser. Age, pregnancy and other conditions can affect what treatments are

available. Many of her patients with private insurance are treated for HS with YAG laser with significant improvement.

Discussion amongst the subcommittee centered around the need for long-term therapy and the costs associated with medication treatment, particularly with adalimumab. The group agreed that YAG later therapy should be added as a treatment for HS.

Recommended Actions:

1) Add CPT 17110-17111 (Destruction (eg, laser surgery, electrosurgery, cryosurgery, chemosurgery, surgical curettement), of benign lesions other than skin tags or cutaneous vascular proliferative lesions; up to 14 lesions/15 or more lesions) to line 418 MODERATE TO SEVERE HIDRADENITIS SUPPURATIVA

MOTION: To approve the recommendations as presented. CARRIES 7-0.

Coverage guidance: bariatric procedures

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 bariatric surgery.

Mautner asked if the requirement for requiring a psychosocial assessment came from the evidence review, and expressed concern that mental health assessments may be difficult to access due to workforce shortages. Cantor and King responded that nearly all of the studies were conducted within multidisciplinary care teams and is part of the standard of care. Walker said that the MBSAQIP accreditation ensures that the multidisciplinary care team is in place, so that may mitigate access issues. Mautner said that while she supports requirements that ensure high quality outcomes, these may introduce issues of access and equity.

Cantor completed her issue summary review, and recommended that adolescent be defined as 13 or older in alignment with the guideline from the American Academy of Pediatrics..

There was no public comment for this topic.

Saenger asked why the proposed wording for tobacco cessation section was shortened compared to the previous version. Smits said that this section was simplified given that the general smoking and elective surgery guideline was recently substantially revised and converted into a statement of intent; these changes came back in light of equity concerns. Saenger said this type of surgery is particularly affected by smoking and he preferred the more comprehensive language. Hodges agreed with Saenger. Olson said that when this guideline was first substantially revised in 2016, there were only 3 centers in the state and the MBSAQIP accreditation program was new; therefore, this body elected to be very comprehensive in its wording and guideline. Currently, there are 13 centers and the accreditation program is more

developed in its quality and safety requirements. Rogalsky said that the simplified language is preferred from the provider side. He said most of his patients are on OHP and the 2 nicotine test requirement turns into a barrier. He said that he would not operate on any patient who actively smokes.

Cantor asked the group to consider specifying a clinical glycemic target for the BMI 30.0-34.9 group. Gingerich said that the EbGS discussion concluded that if someone was able to effectively manage their diabetes with medication control, surgery would not be warranted. Inclusion of a glycemic target would prioritize access to surgery for those not able to effectively manage their diabetes despite trials of two medications. Olson said he supports specifying HbA1c of 8.0% to make it easier to operationalize. Saenger and Hodges agreed. Olson said he had hoped to see a stronger signal of benefit for the adolescent population. Hodges requested to conclude discussion on adults before moving the discussion to adolescents.

A motion was made to approve the amended changes to the Prioritized List based on the draft coverage guidance (adult populations) scheduled for review by HERC at its May 18, 2023 meeting. **Motion approved 7-0.**

Hodges opened discussion for the adolescent population, requesting for the age to be specified as aged 13 to 17 years old. Love expressed concern about access and follow up care. Hodges said that these issues are important but out of HERC's purview. Olson said that he was pleased to see that there is a center with adolescent accreditation, since adolescents have different needs than adults. Rogalsky said that he has already lined up a pediatrician and pediatric mental health specialist to pursue adolescent accreditation, and that expanding coverage will likely result in more accredited adolescent centers.

A motion was made to approve the amended changes to the Prioritized List based on the draft coverage guidance (adolescent population) scheduled for review by HERC at its May 18, 2023 meeting. **Motion approved 7-0.**

Recommended Actions:

1) Add the following CPT codes to Line 320 OBESITY IN ADULTS AND CHILDREN; OVERWEIGHT STATUS IN ADULTS WITH CARDIOVASCULAR RISK FACTORS and remove from line 662 CONDITIONS FOR WHICH CERTAIN INTERVENTIONS ARE UNPROVEN, HAVE NO CLINICALLY IMPORTANT BENEFIT OR HAVE HARMS THAT OUTWEIGH BENEFITS:

    a) 43842 Gastric restrictive procedure, without gastric bypass, for morbid obesity; vertical-banded gastroplasty
    b) 43843 Gastric restrictive procedure, without gastric bypass, for morbid obesity; Other than vertical-banded gastroplasty
    c) 43845 Gastric restrictive procedure with partial gastrectomy, pylorus-preserving duodenoileostomy and ileoileostomy (50 to 100 cm common channel) to limit absorption (biliopancreatic diversion with duodenal switch)
    d) 43886 Gastric restrictive procedure, open; revision of subcutaneous port

component only

e) 43887 Gastric restrictive procedure, open; removal of subcutaneous port component only

f) 43888 Gastric restrictive procedure, open; removal and replacement of subcutaneous port component only

g) 43999 Unlisted procedure, stomach

2) Modify GN173 as shown in Appendix B
3) Revise Guideline Note 8 BARIATRIC SURGERY as shown in Appendix A

MOTION: To approve the recommendations as modified. **CARRIES 6-0 (Schabel absent)**.

Public Comment

No additional public comment was received.

Issues for next meeting

- Solid organ transplant guideline updates
- Prostatic urethral lift for benign prostate enlargement with lower urinary tract symptoms

Next meeting

August 17, 2023, online.

Adjournment

The meeting adjourned at 1:00 PM.

DIAGNOSTIC GUIDELINE D4, ADVANCED IMAGING FOR LOW BACK PAIN

In patients with non-specific low back pain and no "red flag" conditions [see Table D4], imaging is not a covered service; otherwise work up is covered as shown in the table. Repeat imaging is only covered when there is a substantial clinical change (e.g. progressive neurological deficit) or new clinical indication for imaging (i.e. development of a new red flag condition). Repeat imaging for acute exacerbations of chronic radiculopathic pain is not covered.

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

Single photon emission computed tomography (SPECT) (CPT 78830-78832) is not covered for routine pre-operative evaluation of neck or back pain. SPECT of the spine may be covered in certain clinical situations (for example, evaluation for possible spinal infection when MRI is contraindicated or for evaluation of spinal stress fractures not visualized on x-ray in adolescents).

Table D4
Low Back Pain - Potentially Serious Conditions ("Red Flags") and Recommendations for Initial Diagnostic Work-up

Possible cause	Key features on history or physical examination	Imaging[1]	Additional studies[1]
Cancer	• History of cancer with new onset of LBP	MRI	ESR
	• Unexplained weight loss • Failure to improve after 1 month • Age >50 years • Symptoms such as painless neurologic deficit, night pain or pain increased in supine position	Lumbosacral plain radiography	
	• Multiple risk factors for cancer present	Plain radiography or MRI	
Spinal column infection	• Fever • Intravenous drug use • Recent infection	MRI	ESR and/or CRP
Cauda equina syndrome	• Urinary retention • Motor deficits at multiple levels • Fecal incontinence • Saddle anesthesia	MRI	None
Vertebral compression fracture	• History of osteoporosis • Use of corticosteroids • Older age	Lumbosacral plain radiography	None

Possible cause	Key features on history or physical examination	Imaging[1]	Additional studies[1]
Ankylosing spondylitis	• Morning stiffness • Improvement with exercise • Alternating buttock pain • Awakening due to back pain during the second part of the night • Younger age	Anterior-posterior pelvis plain radiography	ESR and/or CRP, HLA-B27
Nerve compression/ disorders (e.g. herniated disc with radiculopathy)	• Back pain with leg pain in an L4, L5, or S1 nerve root distribution present < 1 month • Positive straight-leg-raise test or crossed straight-leg-raise test	None	None
	• Radiculopathic signs[2] present >1 month • Severe/progressive neurologic deficits (such as foot drop), progressive motor weakness	MRI[3]	Consider EMG/NCV
Spinal stenosis	• Radiating leg pain • Older age • Pain usually relieved with sitting (Pseudoclaudication a weak predictor)	None	None
	• Spinal stenosis symptoms present >1 month	MRI[3]	Consider EMG/NCV

[1]Level of evidence for diagnostic evaluation is variable

[2]Radiculopathic signs are defined for the purposes of this guideline as the presence of any of the following:

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

[3]Only if patient is a potential candidate for surgery

Red Flag: Red flags are findings from the history and physical examination that may be associated with a higher risk of serious disorders.

CRP = C-reactive protein; EMG = electromyography; ESR = erythrocyte sedimentation rate; MRI = magnetic resonance imaging; NCV = nerve conduction velocity.

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

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

DIAGNOSTIC GUIDELINE D9, WIRELESS CAPSULE ENDOSCOPY

A) Wireless capsule endoscopy (CPT 91110 only) is covered ~~included on these lines~~ for diagnosis of:
   1) Obscure GI bleeding suspected to be of small bowel origin with iron deficiency anemia or documented GI blood loss
   2) Suspected Crohn's disease with prior negative work up

B) Wireless capsule endoscopy is not covered ~~included on these lines~~ for:
   1) Colorectal cancer screening
   2) Confirmation of lesions of pathology normally within the reach of upper or lower endoscopes (lesions proximal to the ligament of Treitz or distal to the ileum)

C) Wireless capsule endoscopy is only covered ~~included on these lines~~ when the following conditions have been met:
   1) Prior studies must have been performed and been non-diagnostic
      a) GI bleeding: upper and lower endoscopy
      b) Suspected Crohn's disease: upper and lower endoscopy, small bowel follow through
   2) Radiological evidence of lack of stricture
   3) Only covered once during any episode of illness
   4) FDA-approved devices must be used
   5) Patency capsule should not be used prior to procedure

Other types of wireless capsule endoscopy (i.e. CPT 91111-91113) are included in Guideline Note 173 INTERVENTIONS THAT ARE UNPROVEN, HAVE NO CLINICALLY IMPORTANT BENEFIT OR HAVE HARMS THAT OUTWEIGH BENEFITS FOR CERTAIN CONDITIONS.

[NOTE: HERC amended this guideline at the 5/19/2023 HERC meeting]

GUIDELINE NOTE 8, BARIATRIC SURGERY

Line 320

Bariatric/metabolic surgery (limited to Roux-en-Y gastric bypass, ~~and~~ sleeve gastrectomy, biliopancreatic duodenal switch, one anastomosis gastric bypass, single anastomosis duodenal-ileal bypass with gastrectomy) is included on Line 320 ~~when the following criteria are met~~ with specific criteria for adults and adolescents:

A) For adults aged ≥ 18 when ALL of the following criteria are met:
   1) The patient has obesity with a:
      a) BMI > 35 kg/m^2; OR
      b) BMI 30-34.9 kg/m^2 with Type 2 Diabetes Mellitus which has not met clinical glycemic 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; documented use of effective contraception, 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 > 35 kg/m^2 or 120% of the 95th percentile for age and sex AND a clinically significant comorbid condition; OR
    b) BMI > 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; documented use of effective contraception, 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 code 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, low acuity center, or a comprehensive center with Adolescent

accreditation) by the Metabolic and Bariatric Surgery Accreditation and Quality Improvement Program (MBSAQIP)

~~A) Age ≥ 18~~
~~B) The patient has obesity with a:~~
~~1) BMI ≥ 40 OR~~
~~2) BMI ≥ 35 with:~~
~~a) Type 2 diabetes, OR~~
~~b) at least two of the following other serious obesity-related comorbidities: hypertension, coronary heart disease, mechanical arthropathy in major weight bearing joint, sleep apnea~~
~~C) Repeat bariatric surgery is included when it is a conversion from a less intensive (such as gastric band or sleeve gastrectomy) to a more intensive surgery (e.g. Roux-en-Y). Repair of surgical complications (excluding failure to lose sufficient weight) are also included on this and other lines. Reversal of surgical procedures and devices is included on this line when benefits of reversal outweigh harms.~~
~~D) Participate in the following four evaluations and meet criteria as described.~~
~~1) Psychosocial evaluation: (Conducted by a licensed mental health professional)~~
~~a) Evaluation to assess potential compliance with post-operative requirements.~~
~~b) Must remain free of abuse of or dependence on alcohol during the six-month period immediately preceding surgery. No current use of any nicotine product or illicit drugs and must remain abstinent from their use during the six-month observation period. Testing will, at a minimum, be conducted within 1 month of the quit date and within 1 month of the surgery to confirm abstinence from illicit drugs. Tobacco and nicotine abstinence to be confirmed in active users by negative cotinine levels at least 6 months apart, with the second test within one month of the surgery date.~~
~~c) No mental or behavioral disorder that may interfere with postoperative outcomes[1].~~
~~d) Patient with psychiatric illness must be stable for at least 6 months.~~
~~2) Medical evaluation: (Conducted by OHP primary care provider)~~
~~a) Pre-operative physical condition and mortality risk assessed with patient found to be an appropriate candidate.~~
~~b) Optimize medical control of diabetes, hypertension, or other co-morbid conditions.~~
~~c) Female patient not currently pregnant with no plans for pregnancy for at least 2 years post-surgery. Contraception methods reviewed with patient agreement to use effective contraception through 2nd year post-surgery.~~
~~3) Surgical evaluation: (Conducted by a licensed bariatric surgeon associated with program[2])~~
~~a) Patient found to be an appropriate candidate for surgery at initial evaluation and throughout period leading to surgery.~~
~~b) Received counseling by a credentialed expert on the team regarding the risks and benefits of the procedure and understands the many potential~~

~~complications of the surgery (including death) and the realistic expectations of post-surgical outcomes.~~

~~4) Dietitian evaluation: (Conducted by licensed dietitian)~~

~~a) Counseling in dietary lifestyle changes~~

~~b) Counseling on post-operative dietary change requirements~~

~~E) Participate in additional evaluations:~~

~~1) Post-surgical attention to lifestyle, an exercise program and dietary changes and understands the need for post-surgical follow-up with all applicable professionals (e.g. nutritionist, psychologist/psychiatrist, exercise physiologist or physical therapist, support group participation, regularly scheduled physician follow-up visits).~~

~~[1] Many patients (>50%) have depression as a co-morbid diagnosis that, if treated, would not preclude their participation in the bariatric surgery program.~~

~~[2] All surgical services must be provided by a program with current accreditation (as a comprehensive center or low acuity center) by the Metabolic and Bariatric Surgery Accreditation and Quality Improvement Program (MBSAQIP)~~

~~**GUIDELINE NOTE 14, SECOND BONE MARROW TRANSPLANTS**~~

~~*Lines 94,113,115,130,163,179,217,260,288*~~

~~Second bone marrow transplants are not covered except for tandem autologous transplants for multiple myeloma.~~

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, ~~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.

GUIDELINE NOTE 31, COCHLEAR IMPLANTATION

Line 326

Patients will be considered candidates for bilateral cochlear implants if the following criteria are met:

A) Children who are either
   1) Any age with severe to profound sensorineural hearing loss in both ears (defined as 4-frequency PTA > 80 dB HL or 2-frequency PTA > 85); OR
   2) Aged 12 months an older with between 65 and 85 dB hearing loss in both ears whose early aided auditory skill development and speech and language progress indicate a persistent, or widening, gap in age appropriate auditory and language skills

B) Adults with bilateral severe to profound sensorineural hearing impairment (defined as >71 dB hearing loss in both ears) with limited benefit from appropriate hearing (or vibrotactile) aids. Limited benefit from amplification is defined by test scores of less than or equal to 60% correct in the best-aided listening condition on recorded tests of open-set sentence cognition

C) No medical contraindications

D) High motivation and appropriate expectations (both patient and family, when appropriate)

Patients will be considered candidates for unilateral cochlear implants if the following criteria are met:

A) The patient is a child under age 21; AND

B) Has severe to profound sensorineural hearing loss in one ear (defined as 4-frequency PTA > 90 dB HL) and normal hearing or mild hearing loss in the other ear; AND

C) Has obtained limited benefit from a one-month or longer trial of an appropriately fitted unilateral hearing aid, CROS hearing aid or other relevant assistive device in the ear to be implanted . Limited benefit as determined by aided speech perception test scores of 5% or less

on developmentally appropriate monosyllabic word lists when tested in the ear to be implanted alone.

D) No medical contraindications, including imaging showing no cochlear nerve deficiency in the deaf ear

E) High motivation and appropriate expectations (both patient and family, when appropriate)

~~Bilateral cochlear implants are included on this line. Simultaneous implantation appears to be more cost-effective than sequential implantation.~~

[NOTE: HERC amended this guideline at the 5/19/2023 HERC meeting to remove the wording in purple]

GUIDELINE NOTE 36, ADENOTONSILLECTOMY FOR INDICATIONS OTHER THAN OBSTRUCTIVE SLEEP APNEA

Lines 42,47,368,551

Tonsillectomy/adenotonsillectomy is an appropriate treatment for patients with:

~~A) Seven or more documented attacks of strep tonsillitis in a year or 5 or more documented attacks of strep tonsillitis in each of two consecutive years or 3 or more documented attacks of strep tonsillitis per year in each of the three consecutive years where an attack is considered a positive culture/screen and where an appropriate course of antibiotic therapy has been completed; or,~~

A) ~~B)~~Individuals ~~less than 18 years of age~~ with a history of recurrent throat infection

1) Throat infections must occur with a frequency of at least:

i) Seven episodes in the past year; **or**

ii) Five episodes per year for 2 years; **or**

iii) Three episodes per year for 3 years;

and

b) Documentation in the medical record for each episode of sore throat which includes at least one of the following:

i) Temperature greater than 38.3 °C (100.9 °F); **or**

ii) Cervical adenopathy; **or**

iii) Tonsillar exudates or erythema; **or**

iv) Positive test for Group A β-hemolytic streptococcus (GABHS); OR

B) A history of two or more peritonsillar abscesses OR when general anesthesia is required for the surgical drainage of a peritonsillar abscess and tonsillectomy is performed at the time of the surgical drainage; or,

C) Unilateral tonsillar hypertrophy in adults; unilateral tonsillar hypertrophy in children with other symptoms suggestive of malignancy.

ICD-10-CM J35.1 and J35.3 are included on Line 368 only for 1) unilateral tonsillar hypertrophy in adults and 2) unilateral tonsillar hypertrophy in children with other symptoms suggestive of malignancy. Bilateral tonsillar hypertrophy and unilateral tonsillar hypertrophy in children without other symptoms suggestive of malignancy are included only on Line 551.

See Guideline Notes D8 and 27 for diagnosis and treatment of obstructive sleep apnea in children.

GUIDELINE NOTE 101, ARTIFICIAL DISC REPLACEMENT

Lines 346,530

Artificial disc replacement (CPT ~~22856-22865~~ 22856-22859, 22861-22865) is included on Line 346 as an alternative to fusion for patients who meet criteria for spinal fusion procedures as defined in Guideline Note 37 only when all of the following criteria are met:

Lumbar artificial disc replacement

A) Patients must first complete a structured, intensive, multi-disciplinary program for management of pain, if covered by the agency;
B) Patients must be 60 years or under;
C) Patients must meet FDA approved indications for use and not have any contraindications. FDA approval is device specific but includes:
   - Failure of at least six months of conservative treatment
   - Skeletally mature patient
   - Replacement of a single disc for degenerative disc disease at one level confirmed by patient history and imaging
D) 2 level lumbar artificial disc replacement (CPT 22860) is not included on these lines

Cervical artificial disc replacement

A) Patients must meet FDA approved indications for use and not have any contraindications. FDA approval is device specific but includes:
B) Skeletally mature patient
C) Reconstruction of a single or 2 level disc following single or 2 level discectomy for intractable symptomatic cervical disc disease (radiculopathy or myelopathy) confirmed by patient findings and imaging.

Otherwise, artificial disc replacement is included on Line 530 or line 662.

Artificial disc replacement combined with fusion in a single procedure (hybrid procedure) is not covered.

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 118, SEPTOPLASTY

Lines 42,119,202,246,287,466,506,525,577

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 and not included on line 202 SLEEP APNEA, NARCOLEPSY AND REM BEHAVIORAL DISORDER.

GUIDELINE NOTE 143, TREATMENT OF UNILATERAL HEARING LOSS

Lines 311,446

Unilateral hearing loss treatment is Included on these lines only for children aged 20 and younger with the following conditions:

1. For mild to moderate sensorineural unilateral hearing loss (defined as 26-70 dB hearing loss at 500, 1000 and 2000 Hz), first line intervention should be a conventional hearing aid, with second line therapy being contralateral routing of signal (CROS) system
2. For severe to profound unilateral sensorineural hearing loss (defined as 71 dB hearing loss or greater at 500, 1000 and 2000 Hz), first line therapy should be a contralateral routing of signal (CROS) system with second line therapy being a bone anchored hearing aid (BAHA). BAHA SoftBand therapy may be first line therapy for children under age 5 or patients with severe ear deformities (e.g. microstia, severe canal atresia). Unilateral cochlear implants may be considered per Guideline Note 31 COCHLEAR IMPLANTATION.

~~Cochlear implants are not included on these lines for unilateral hearing loss per Guideline Note 31 COCHLEAR IMPLANTATION~~.

GUIDELINE NOTE 155, ELECTRIC TUMOR TREATMENT FIELDS FOR GLIOBLASTOMA

Line 294

Electric tumor treatment fields (~~codes~~ HCPCS ~~A4555 and~~ E0766) are included on this line only when

A) Used for the initial treatment of supratentorial glioblastoma
B) Used in combination with temozolomide
C) The patient is age 22 or older

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
0219U	Infectious agent (human immunodeficiency virus),	Insufficient evidence of effectiveness	May 2023

	targeted viral next-generation sequence analysis (ie, protease [PR], reverse transcriptase [RT], integrase [INT]), algorithm reported as prediction of antiviral drug susceptibility		
~~22858,~~ 22860	Total disc arthroplasty (artificial disc), anterior approach, including discectomy to prepare interspace (other than for decompression); second interspace, ~~cervical/~~lumbar	Insufficient evidence of effectiveness	November 2022
43284	Laproscopy, surgical, esophageal sphincter augmentation procedure, placement of sphincter augmentation device (ie, magnetic band)	Insufficient evidence of effectiveness	~~January, 2019~~ May 2023
43770~~,~~ ~~43842-43845,~~ ~~43886-43888~~	~~Gastric restrictive procedures (gastric band, other)~~ Laparoscopy, surgical, gastric restrictive procedure; placement of adjustable gastric restrictive device (e.g., gastric band and subcutaneous port components)	No evidence of effectiveness	~~October, 2016~~ May 2023
~~81306~~	~~NUDT15 (nudix hydrolase 15) (eg, drug metabolism) gene analysis~~	~~Insufficient evidence of effectiveness~~	~~November 2018~~

Section 2.0

Plain Language Materials

Value-based Benefits Subcommittee (VbBS)
Plain Language Summary of Topics
August 17, 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.

Straightforward Consent Table & Guideline Note Changes August 2023

Coverage question: Routine changes that may be approved without discussion.

Statement of Intent 4 Waiver-related Changes

Question: Should the List be updated to reflect Oregon Health Plan's newly approved 1115 demonstration waiver?

Should this change be made to the Prioritized List? Yes. The waiver requires changes related to the Early and Periodic Screening, Diagnosis and Treatment program (EPSDT) program, which focuses on services for members under the age of 21, and these changes should be reflected in the List.

Travel Vaccine Review 2023

Coverage question: Should certain uncovered vaccines be added to OHP to meet new federal government guidance?

Should OHP cover this treatment? Yes, it is mandatory.

Immunoglobulins and Antitoxins

Coverage question: Should certain injections be given to a person when they are exposed to a virus or bacteria that they are not immune to?

Should OHP cover this treatment? Yes, there are often no other treatments available.

Value-based Benefits Subcommittee (VbBS)
Plain Language Summary of Topics
August 17, 2023

MyChoice CDx

Coverage question: Should OHP cover a genetic test to check for ovarian cancer?

Should OHP cover this treatment? Yes, this test is recommended by respected national expert guidelines.

Unspecified Reaction to Severe Stress

Coverage question: Should OHP cover serious stress treatment when the code listed for finding out the cause of the condition (diagnosis) is not specific?

Should OHP cover this treatment? Yes, when the code is used for 30 days or fewer, until a more accurate diagnosis can be made.

Freespira for PTSD and Panic Disorder

Coverage question: Should OHP cover a device that measures breathing patterns for certain mental health conditions?

Should OHP cover this treatment? No, the published and reviewed evidence is not convincing that the technology works and the Behavioral Health Advisory Panel recommended against adding coverage.

July 2023 HCPCS Codes

Coverage question:
1) Should a procedure that helps stop weigh gain after weight loss surgery be covered?
2) Should a computer assisted test of heart function be covered?
3) Should new testing that analyzes the electrical activity in the stomach muscle be covered?

Should OHP cover this treatment?
1) No, there is not enough evidence that it works well.
2) No, this test appears to be experimental.
3) No, this test appears to be experimental.

Value-based Benefits Subcommittee (VbBS)
Plain Language Summary of Topics
August 17, 2023

Laser Interstitial Thermal Therapy for Epilepsy

Coverage question: Should laser brain surgery for patients that have epilepsy be covered when medication doesn't help?

Should OHP cover this treatment?
Option 1) Do not add coverage.
Option 2) Add coverage with a guideline for its use.
Option 3) Refer to the Evidence-based Guidelines Subcommittee for a potential coverage guidance.

Solid Organ Transplant Guideline August 2023 Revisions

Coverage question:
1) In February 2023, there was a new guideline about this topic. How should the section that says a patient should quit smoking before surgery be changed?
2) Should the requirements be more clear about when OHP covers transplants of two organs at the same time?

How should OHP coverage change?
1) The transplant program ensures a patient quits smoking before surgery
2) If a patient qualifies for transplants of both organs individually, they can have both organs transplanted at the same time

Prostate Procedure Guideline Modifications

Coverage question: Should OHP remove the requirement to try medications before having a procedure that helps urine leave the body when the prostate is too large? Should any changes be made to the requirements for a procedure that lifts prostate tissue out of the way so it does not block urine leaving the body?

Should OHP cover this treatment? The guideline on prostate procedures should be changed to no longer require medications. This is done to agree with expert guidelines. The age range for the lift procedure should be lowered to 45 years old because it has been approved for younger patients.

Value-based Benefits Subcommittee (VbBS)
Plain Language Summary of Topics
August 17, 2023

Breast Reduction for Macromastia

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? Staff recommends the Commission consider several options including no coverage or coverage in specific situations.

Coronary Artery Calcium Score

Coverage question: This scan produces multiple pictures to check if calcium is present in the blood vessels of the heart and, if so, how much. The test may predict the risk of heart attack.

Should OHP cover this treatment? No, there is not enough evidence that this test will prevent heart attacks or save lives. The test might reduce the need for medications in some patients, but it isn't clear which kinds of patients might benefit.

CT Colonography

Coverage question: Should OHP cover a relatively new diagnostic test that uses an X-ray scanner to examine the large bowel for cancer and polyps?

Should OHP cover this treatment? Yes, when a person with symptoms cannot have a colonoscopy.

Fibromyalgia 2023 Review

Coverage question: Should additional treatments for fibromyalgia, a long-lasting disorder that causes pain and tenderness throughout the body, as well as fatigue and trouble sleeping, be covered?

Should OHP cover this treatment? No, there are no effective treatments for this condition, although there are effective treatments for symptoms of fibromyalgia such as joint pain or mood issues that are already covered. (Some treatments for fibromyalgia, such as physical therapy and certain medications are not covered for fibromyalgia in the absence of other related conditions.)

Value-based Benefits Subcommittee (VbBS)
Plain Language Summary of Topics
August 17, 2023

Breast Cancer Screening August 2023

Coverage question:
1) Should breast cancer screening guidelines be updated to the 2023 United States Preventive Services Task Force's (USPSTF – an independent, volunteer panel of national experts in disease prevention and evidence-based medicine) recommendations?
2) Should breast tomosynthesis (3D mammography – a special breast picture that helps doctors check for potential problems or changes) be covered by OHP?

Should OHP cover this treatment?
1) There is no need to update OHP coverage; a yearly mammogram starting at age 40 is already covered.
2) Yes. Studies showed that 3D mammography improved how often cancer was discovered more than other tests.

Fat Incarceration in Ventral Hernias

Coverage question: Should OHP cover fixing certain types of hernia in the front of the abdomen when body fat gets stuck or trapped?

Should OHP cover this treatment? No, surgery might not always fix ventral hernias and these hernias usually aren't dangerous to your life.

PET Scan for Prostate Cancer

Coverage question: Should a specific type of imaging test be covered 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.

Value-based Benefits Subcommittee (VbBS)
Plain Language Summary of Topics
August 17, 2023

Cardiac Resynchronization Therapy

Coverage question: Should pacemaker and heart defibrillator placement for heart failure on the Prioritized List be changed?

Should OHP cover this treatment? Yes, for patients meeting certain conditions.

Gender Affirming Treatment List Changes Required to Comply with HB2002

Coverage question: Should HERC make the Prioritized List match House Bill 2002 which changes the laws about coverage of gender affirming treatment?

Should OHP cover this treatment? Yes. Even though the Prioritized List won't decide what kinds of gender affirming treatment are covered, aligning the list will make it easier for patients to access the care required by law.

Section 3.0

Staff Report

HERC Staff Listening Session

June 2023

Foot/nail care in facilities

A podiatrist spoke about lack of access to foot and nail care in skilled nursing facilities (SNF), rehabilitation facilities and similar settings. He spoke about the importance of treating nail conditions such as onychomycosis (toenail fungal infections) in these settings to both prevent spread and reduce the risk of secondary infections and subsequent adverse outcomes. He requested consideration of coverage for toenail care, toenail biopsies and lab testing, antifungal medications, and toenail debridement for patients in care facilities. In 2022, staff have previously heard similar concerns regarding access to nail/foot care for patients in facilities from aging services advocates.

A. HERC staff response: prepare a proposal to add coverage for foot and nail care to the preventive foot care line for patients in SNF, rehabilitation facilities and similar settings. This will involve moving codes for onychomycosis to the preventive foot care line and a new guideline for this line.

Vaginal birth after cesarean (also known as trial of labor after cesarean) at birth centers

Two advocates requested consideration of trial of labor after cesarean delivery (TOLAC) at birth centers. Currently, the Prioritized List guideline on out-of-hospital birth lists prior cesarean delivery as a contraindication to out-of-hospital birth. The advocates said that lack of payment for TOLAC at birth facilities reduces patients' ability to choose between TOLAC and elective repeat cesarean delivery, particularly in rural areas.

A. HERC staff response: HERC staff is working with CEBP and other parts of OHA to determine how best to address lack of access to TOLAC across Oregon.

Fibromyalgia

A primary care physician in Forest Grove spoke about the problems with non-coverage of fibromyalgia. She specifically requested consideration for coverage of SNRIs (such as duloxetine), physical therapy, exercise therapy, and muscle relaxers, as well as office visits for this condition.

a. HERC staff response: An updated review of the evidence related to treatments for fibromyalgia appears is included in these materials and the meeting agenda.

Section 4.0

Consent Agenda-

Straightforward Items

Consent Agenda Issues—August 2023

Code	Code Description	Line(s) Involved	Issue	Recommendation(s)
90678	Respiratory syncytial virus vaccine, preF, subunit, bivalent, for intramuscular use	3 PREVENTION SERVICES WITH EVIDENCE OF EFFECTIVENESS	90678 was placed on the Excluded file when reviewed as a new code in November 2022, as there was no vaccine with FDA approval that would utilize that code. The FDA approved new RSV vaccines from GSK and Pfizer for adults 60 years and older in May 2023. ACIP approved the vaccine for use in adults aged 60 and over with shared clinical decision-making at their July 2023 meeting.	Add 90678 to line 3 Advise HSD to move CPT 90678 from the Excluded File to the Ancillary file until the 10/1/2023 Prioritized List publication
31540 31541	Laryngoscopy, direct, operative, with excision of tumor and/or stripping of vocal cords or epiglottis; with operating microscope or telescope	314 CANCER OF ESOPHAGUS; BARRETT'S ESOPHAGUS WITH DYSPLASIA 372 BENIGN NEOPLASM OF RESPIRATORY AND INTRATHORACIC ORGANS	31540 and 31541 are very similar procedures. They both appear on lines 205, 287 and 637. 31540 does not appear on line 372 while 31541 does not appear on line 314	Add 31540 to line 372 Add 31541 to line 314
42831	Adenoidectomy, primary; age 12 or over	446 HEARING LOSS - OVER AGE OF FIVE	Guideline Note 51 includes adenoidectomy with PE tube insertion for children on lines 311, 446, and 476. Only the adenoidectomy CPT code for children under age 4 (CPT 42830) is currently on these lines. 42831 is not on line 311 (not appropriate as for children 5 and younger) or 446. CPT 42831 is on multiple other lines.	Add 42831 to line 446

Consent Agenda Issues—August 2023

Code(s)	Code Description	Line(s) Involved	Issue	Recommendation(s)
57500	Biopsy of cervix, single or multiple, or local excision of lesion, with or without fulguration	421 UTERINE POLYPS	57500 is only on line 25. There are multiple denied claims for pairing of 57500 with ICD-10 N84.1 (Polyp of cervix uteri) which is on line 421	Add 57500 to line 421
0001A, 0002A, 0003A, 0004A, 0011A, 0012A, 0013A, 0051A, 0052A, 0053A, 0054A, 0064A, 0071A, 0072A, 0073A, 0074A, 0081A, 0082A, 0083A, 0091A, 0092A, 0093A, 0094A, 0111A, 0112A, 0113A, 91300, 91301, 91305, 91306, 91307, 91308, 91309, 91311	Monovalent Moderna and Pfizer-BioNTech COVID-19 vaccines	3 PREVENTION SERVICES WITH EVIDENCE OF EFFECTIVENESS	As of April 18, 2023 the monovalent Moderna and Pfizer-BioNTech COVID-19 vaccines are no longer authorized for use in the United States	Remove these codes from line 3

Use of Respiratory Syncytial Virus Vaccines in Older Adults: Recommendations of the Advisory Committee on Immunization Practices — United States, 2023

Michael Melgar, MD[1]; Amadea Britton, MD[1]; Lauren E. Roper, MPH[1]; H. Keipp Talbot, MD[2]; Sarah S. Long, MD[3]; Camille N. Kotton, MD[4]; Fiona P. Havers, MD[1]

Abstract

Respiratory syncytial virus (RSV) is a cause of severe respiratory illness in older adults. In May 2023, the Food and Drug Administration approved the first vaccines for prevention of RSV-associated lower respiratory tract disease in adults aged ≥60 years. Since May 2022, the Advisory Committee on Immunization Practices (ACIP) Respiratory Syncytial Virus Vaccines Adult Work Group met at least monthly to review available evidence regarding the safety, immunogenicity, and efficacy of these vaccines among adults aged ≥60 years. On June 21, 2023, ACIP voted to recommend that adults aged ≥60 years may receive a single dose of an RSV vaccine, using shared clinical decision-making. This report summarizes the body of evidence considered for this recommendation and provides clinical guidance for the use of RSV vaccines in adults aged ≥60 years. RSV vaccines have demonstrated moderate to high efficacy in preventing RSV-associated lower respiratory tract disease and have the potential to prevent substantial morbidity and mortality among older adults; postmarketing surveillance will direct future guidance.

Introduction

In the United States, respiratory syncytial virus (RSV) causes seasonal epidemics of respiratory illness. Although the COVID-19 pandemic interrupted seasonal RSV circulation, the timing and number of incident cases of the 2022–23 fall and winter epidemic suggested a likely gradual return to pre-pandemic seasonality (*1*).

Each season, RSV causes substantial morbidity and mortality in older adults, including lower respiratory tract disease (LRTD), hospitalization, and death. Incidence estimates vary widely and are affected by undertesting and potentially low sensitivity of standard diagnostic testing among adults (*2*–*5*). Most adult RSV disease cases occur among older adults with an estimated 60,000–160,000 hospitalizations and 6,000–10,000 deaths annually among adults aged ≥65 years (*5*–*10*).

Adults with certain medical conditions, including chronic obstructive pulmonary disease, asthma, congestive heart failure, coronary artery disease, cerebrovascular disease, diabetes mellitus, and chronic kidney disease, are at increased risk for RSV-associated hospitalization (*11*–*13*), as are residents of long-term care facilities (*14*), and persons who are frail* or of advanced age (incidence of RSV-associated hospitalization among adults increases with age, with the highest rates among those aged ≥75 years) (*6*,*15*). RSV can also cause severe disease in persons with compromised immunity, including recipients of hematopoietic stem cell transplantation and patients taking immunosuppressive medications (e.g., for solid organ transplantation, cancer treatment, or other conditions) (*16*,*17*).

In May 2023, the Food and Drug Administration (FDA) approved the first vaccines for prevention of RSV-associated LRTD in adults aged ≥60 years. RSVPreF3 (Arexvy, GSK) is a 1-dose (0.5 mL) adjuvanted ($AS01_E$) recombinant stabilized prefusion F protein (preF) vaccine (*18*). RSVpreF (Abrysvo, Pfizer) is a 1-dose (0.5 mL) recombinant stabilized preF vaccine (*19*).

Methods

Since May 2022, CDC's Advisory Committee on Immunization Practices (ACIP) RSV Vaccines Adult Work Group (Work Group) met at least monthly to review available evidence regarding the safety, immunogenicity, and efficacy of the GSK and Pfizer RSV vaccines among adults aged ≥60 years. A systematic review of published and unpublished evidence of the efficacy and safety of these vaccines among persons aged ≥60 years was conducted. The body of evidence consisted of one phase 3 randomized controlled trial and one combined phase 1 and 2 (phase 1/2) randomized controlled trial for each vaccine. The Work Group used the Grading of Recommendations, Assessment, Development and Evaluation (GRADE) approach to independently determine the certainty of evidence for outcomes related to each vaccine, rated on a scale of high to very low certainty.† In evaluating safety, the

* Frailty is a multidimensional geriatric syndrome and reflects a state of increased vulnerability to adverse health outcomes. Although there is no consensus definition, one frequently used tool is the Fried frailty phenotype in which frailty is defined as a clinical syndrome with three or more of the following signs or symptoms: unintentional weight loss (10 lbs [4.5 kg] in the past year), self-reported exhaustion, weakness (grip strength), slow walking speed, and low physical activity.

† GRADE tables are available online for both the GSK RSV vaccine (https://www.cdc.gov/vaccines/acip/recs/grade/GSK-Adjuvanted-RSVPreF3-adults.html) and the Pfizer RSV vaccine (https://www.cdc.gov/vaccines/acip/recs/grade/Pfizer-Bivalent-RSVpreF-adults.html). For the GSK RSV vaccine, the efficacy estimates presented differ slightly from efficacy estimates included in the GRADE tables because the manufacturer used a different method from CDC to calculate vaccine efficacy. Estimates in this report are those of the manufacturer, and estimates in the GRADE tables are those calculated by CDC.

Straightforward Guideline Note Changes August 2023

Plain Language Summary:

Coverage question: Routine changes that may be approved without discussion.

Issue 1

Additional changes are needed for the severe inflammatory skin disease guideline, as additional JAK inhibitors are now on the market in addition to upadacitinib. Abrocitinib was just FDA approved and other medications are anticipated to be coming to the marked soon.

a. HERC staff recommendation:
    i. Modify Guideline Note 21 as shown below
        1. Changes approved in May 2021 are 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

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 (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.

Issue 2

The Diabetes Prevention Program guideline needs edits to better indicate that a person needs to be either prediabetic OR have been diagnosed with gestational diabetes.

a. HERC staff recommendation:

ii. Modify Guideline Note 21 as shown below

GUIDELINE NOTE 179, DIABETES PREVENTION PROGRAM

Line 3

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

To be eligible for referral to a CDC-recognized lifestyle change program, patients must meet ALL of the following requirements (A-E):

A) Be at least 18 years old; AND

B) Be overweight (body mass index ≥25; ≥23 if Asian; BMI percentile ≥85th percentile for 18-19 years old); AND

C) Have no current diagnosis of type 1 or type 2 diabetes; AND

D) Not have end-stage renal disease; AND

E) Meet one of the two criteria below:

1) Have a blood test result in the prediabetes range within the past year:
   a) Hemoglobin A1C: 5.7%–6.4% or
   b) Fasting plasma glucose: 100–125 mg/dL or
   c) Two-hour plasma glucose (after a 75 gm glucose load): 140–199 mg/dL or
2) Have a previous diagnosis of gestational diabetes

Statement of Intent 4 waiver-related changes

Plain Language Summary:

Question: Should the List be updated to reflect Oregon Health Plan's newly approved 1115 demonstration waiver?

Should this change be made to the Prioritized List? Yes. The waiver requires changes related to the Early and Periodic Screening, Diagnosis and Treatment program (EPSDT) program, which focuses on services for members under the age of 21, and these changes should be reflected in the List.

Question: Should Statement of Intent 4 be updated to reflect changes related to the 2022 waiver renewal?

Question source: Holly Jo Hodges, HERC member

Background: Statement of Intent 4 (SOI4) describes the role of the Prioritized List in OHP coverage and OHP's 1115 demonstration waiver approved from CMS. SOI4 needs to be updated for clarity and accuracy with changes that occurred in the 2022 waiver renewal process. Specifically, changes need to be made to reflect the implementation of services related to the Early and Periodic Screening, Diagnosis and Treatment program (EPSDT).

HERC staff recommendation:

1) Revise statement of intent 4 as follows
    a. There will be no substantive change to coverage from this change, but it will better reflect Oregon's newly approved demonstration waiver

STATEMENT OF INTENT 4: ROLE OF THE PRIORITIZED LIST IN COVERAGE

The Commission makes its prioritization decisions based on the best available published evidence about treatments for each condition. The Prioritized List prioritizes health services according to their importance for the population served and the legislature determines where to place the funding line on the Prioritized List.

The Commission recognizes that a condition and treatment pairing above the funding line does not necessarily mean that the service will be covered by the Oregon Health Plan (OHP). There may be other restrictions that apply, such as the service not being medically necessary or appropriate for an individual member. Likewise, the absence of a treatment and condition pairing above the funding line is not meant to be an absolute exclusion from coverage. Coverage may still be authorized under applicable federal and state laws, and Oregon's Medicaid State Plan and Waiver for an individual member. For example, OAR 410-141-3820

Statement of Intent 4 waiver-related changes

(Oregon Health Plan Benefit Package of Covered Services) includes services such as, but not limited to, the following:

- Diagnostic services, subject to the List's diagnostic guideline notes when applicable;
- Ancillary services (such as hospitalization, durable medical equipment, certain medications and anesthesia) provided for conditions appearing above the funding line, subject to the List's ancillary guideline notes when applicable; and
- Services paired with (or ancillary to) an unfunded condition which is causing or exacerbating a funded condition, the treatments for the funded condition are not working or contraindicated, and treatment of the unfunded condition would improve the outcome of treating the funded condition (the "Comorbidity Rule" OAR 410-141-3820(10))
- Services that are determined to be medically necessary and medically appropriate for an OHP member under the age of 21; coverage of these services is required by federal regulation under the Early and Periodic Screening, Diagnosis and Treatment program (EPSDT).
- Services paired with (or ancillary to) an unfunded condition (or otherwise not consistent with the funded region of the List) which, based on the child's individual circumstances, adversely affects the child's ability to grow, develop, or participate in school only when providing the unfunded service would improve the child's ability to grow, develop or participate in school.

~~In addition, Oregon's 1115(a) Waiver includes coverage for services such as, but not limited to:~~

- ~~Services on unfunded lines for children ages from birth through 1~~
- ~~Services provided for a condition appearing in the funded region of the List in conjunction with federal requirements for Early and Periodic Screening, Diagnosis and Treatment (EPSDT) and Oregon's waiver~~

~~As a result, the~~The Prioritized List must be used in conjunction with applicable OHP provisions found in federal and state laws, the State Plan and Waiver in coverage determination.

Travel Vaccine Review 2023

Plain Language Summary:

Coverage question: Should certain uncovered vaccines be added to OHP to meet new federal government guidance?

Should OHP cover this treatment? Yes, it is mandatory.

Coverage Question: Which vaccines that are currently on the Excluded file should be added for coverage based on new CMS directives?

Question source: HERC staff and OHA leadership

Background: On June 27, 2023, CMS issued a directive to Medicaid programs that requires vaccines be covered if FDA approved and ACIP recommended for adults, regardless of whether these vaccines are only recommended for travel or occupational use.

From CMS:

> CMS interprets the statutory amendments made by the Inflation Reduction Act to require state Medicaid and CHIP programs to cover, without cost sharing obligations, vaccines and their administration, provided that the vaccine is approved by the U.S. Food and Drug Administration (FDA) for use by adult populations and is administered in accordance with recommendations of ACIP. This coverage requirement will go into effect on October 1, 2023, and applies in both fee-for-service and managed care.
>
> As noted earlier, there are multiple categories of ACIP recommendations for adult vaccines, including recommendations described on the CDC/ACIP adult immunization schedule (as determined by age and risk and recommendations for shared clinical decision-making), and recommendations based on risk due to health condition, occupation, and travel. Beginning October 1, 2023, CMS interprets the reference to ACIP recommendations in section 1905(a)(13)(B) of the Act to include any category of ACIP recommendations. The IRA coverage requirement is therefore not limited to vaccines that ACIP includes on the immunization schedules or recommends for routine use.

Previous HSC/HERC reviews:

Many vaccines have been reviewed in the past and determined to only be used for travel or for persons in certain occupations. Therefore, these vaccine administration codes were added to the EXCLUDED file.

Travel Vaccine Review 2023

Current Prioritized List/Coverage status:

Multiple vaccines need to be added to line 3 PREVENTION SERVICES WITH EVIDENCE OF EFFECTIVENESS to comply with the CMS directive

Expert guidelines:

ACIP recommended vaccines and the supporting MMWR articles can be found at: https://www.cdc.gov/vaccines/hcp/acip-recs/index.html

HERC staff summary: Multiple vaccine CPT codes for vaccine administration for travel and occupational vaccines need to be added to line 3 PREVENTION SERVICES WITH EVIDENCE OF EFFECTIVENESS per CMS directives. As part of this review, HERC staff have found several vaccine administration codes that appear to be non-covered and need to be added to line 3.

HERC staff recommendation:

1) See recommended code changes on attached spreadsheet
2) Modify GN106 as shown below
    a. Changes recommended based on CT colonography review (see separate section of meeting materials) are shown here in purple

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
   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 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

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 that 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

CDC	Code Description	Current Placement	ACIP recommendation	Recommended Placement
90291	Cytomegalovirus immune globulin (CMV-IgIV), human, for intravenous use	NEVER REVIEWED	No vaccine is currently approved for	Advise HSD to add to Excluded file
90473	Immunization administration by intranasal or oral route; 1 vaccine (single or combination vaccine/toxoid)	NEVER REVIEWED		Add to line 3 PREVENTION SERVICES WITH EVIDENCE OF EFFECTIVENESS
90474	Immunization administration by intranasal or oral route; each additional vaccine (single or combination vaccine/toxoid)	NEVER REVIEWED		Add to line 3 PREVENTION SERVICES WITH EVIDENCE OF EFFECTIVENESS
90581	Anthrax vaccine, for subcutaneous or intramuscular use	ANCILLARY PROCEDURES	Recommended for military and certain occupational use	Add to line 3 PREVENTION SERVICES WITH EVIDENCE OF EFFECTIVENESS
90584	Dengue vaccine, quadrivalent, live, 2 dose schedule, for subcutaneous use	EXCLUDED FILE (TRAVEL VACCINES ETC.)	only recommended for children living in areas that are endemic for Dengue, which is not present in the US	Add to line 3 PREVENTION SERVICES WITH EVIDENCE OF EFFECTIVENESS
90585	Bacillus Calmette-Guerin vaccine (BCG) for tuberculosis, live, for percutaneous use	ANCILLARY PROCEDURES	Not included in ACIP recommendations	Advise HSD to remove from Ancillary and add to Excluded file

CDC	Code Description	Current Placement	ACIP recommendation	Recommended Placement
90586	Bacillus Calmette-Guerin vaccine (BCG) for bladder cancer, live, for intravesical use	ANCILLARY PROCEDURES		Add to line 271 CANCER OF BLADDER AND URETER
90587	Dengue vaccine, quadrivalent, live, 3 dose schedule, for subcutaneous use	EXCLUDED FILE (TRAVEL VACCINES ETC.)	only recommended for children living in areas that are endemic for Dengue, which is not present in the US	Add to line 3 PREVENTION SERVICES WITH EVIDENCE OF EFFECTIVENESS
90625	Cholera vaccine, live, adult dosage, 1 dose schedule, for oral use	EXCLUDED FILE (TRAVEL VACCINES ETC.)	Recommended for travel use	Add to line 3 PREVENTION SERVICES WITH EVIDENCE OF EFFECTIVENESS
90626	Tick-borne encephalitis virus vaccine, inactivated; 0.25 mL dosage, for intramuscular use	EXCLUDED FILE (TRAVEL VACCINES ETC.)	no U.S. recommendation	Continue Excluded
90627	Tick-borne encephalitis virus vaccine, inactivated; 0.5 mL dosage, for intramuscular use	EXCLUDED FILE (TRAVEL VACCINES ETC.)	no U.S. recommendation	Continue Excluded
90690	Typhoid vaccine, live, oral	EXCLUDED FILE (TRAVEL VACCINES ETC.)	Recommended for travel use	Add to line 3 PREVENTION SERVICES WITH EVIDENCE OF EFFECTIVENESS
90691	Typhoid vaccine, Vi capsular polysaccharide (ViCPs), for intramuscular use	EXCLUDED FILE (TRAVEL VACCINES ETC.)	Recommended for travel use	Add to line 3 PREVENTION SERVICES WITH EVIDENCE OF EFFECTIVENESS
90717	Yellow fever vaccine, live, for subcutaneous use	EXCLUDED FILE (TRAVEL VACCINES ETC.)	Recommended for travel use	Add to line 3 PREVENTION SERVICES WITH EVIDENCE OF EFFECTIVENESS

CDC	Code Description	Current Placement	ACIP recommendation	Recommended Placement
90738	Japanese encephalitis virus vaccine, inactivated, for intramuscular use	EXCLUDED FILE (TRAVEL VACCINES ETC.)	Recommended for travel use	Add to line 3 PREVENTION SERVICES WITH EVIDENCE OF EFFECTIVENESS
90758	Zaire ebolavirus vaccine, live, for intramuscular use	EXCLUDED FILE (TRAVEL VACCINES ETC.)	Recommended for use in certain occupations	Add to line 3 PREVENTION SERVICES WITH EVIDENCE OF EFFECTIVENESS

DEPARTMENT OF HEALTH & HUMAN SERVICES
Centers for Medicare & Medicaid Services
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CENTERS FOR MEDICARE & MEDICAID SERVICES
CENTER FOR MEDICAID & CHIP SERVICES

SHO# 23-003

RE: Mandatory Medicaid and Children's Health Insurance Program Coverage of Adult Vaccinations under the Inflation Reduction Act

June 27, 2023

Dear State Health Official:

The Centers for Medicare & Medicaid Services (CMS) is issuing this guidance on section 11405 of the Inflation Reduction Act (IRA) (Pub. L. 117-169). Beginning October 1, 2023, statutory amendments made by section 11405 of the IRA require Medicaid and Children's Health Insurance Program (CHIP) coverage and payment for approved adult vaccines recommended by the Advisory Committee on Immunization Practices (ACIP) and their administration, without cost sharing.

Overview

CMS interprets the statutory amendments made by the IRA to require state Medicaid and CHIP programs to cover, without cost sharing obligations, vaccines and their administration, provided that the vaccine is approved[1] by the U.S. Food and Drug Administration (FDA) for use by adult populations and is administered in accordance with recommendations of ACIP.[2] This coverage requirement will go into effect on October 1, 2023, and applies in both fee-for-service and managed care. Also, effective October 1, 2023, the statutory amendments made by the IRA modify the requirements that states must meet in order to claim a one percentage point increase in the federal medical assistance percentage (FMAP) for certain services described in sections 1905(a)(13)(A) and (B) and 1905(a)(4)(D) of the Social Security Act (the Act). The IRA adult vaccination[3] coverage requirements and the IRA's changes to the availability of this one percentage point FMAP increase are discussed in detail beginning on page 5 of this letter.

Background

Vaccines administered to recommended populations at recommended intervals can reduce morbidity, hospitalizations, and deaths, and save costs. Vaccines may reduce the overall burden

[1] "Licensed" is the statutory term under section 351 of the Public Health Service (PHS) Act for what is commonly referred to as approval of a biological product. When CMS uses the term "approval" to refer to FDA approval in this document, that term includes FDA licensure under section 351 of the PHS Act.
[2] To the extent possible, CMS has aligned its interpretation of section 11405 of the IRA with its interpretation of similar language added to the Medicare statute by section 11401 of the IRA. See CMS Center for Medicare's "Contract Year 2023 Program Guidance Related to Inflation Reduction Act Changes to Part D Coverage of Vaccines and Insulin," https://www.cms.gov/files/document/irainsulinvaccinesmemo09262022.pdf.
[3] In this document, CMS uses the term "vaccination" to refer both to a vaccine product and its administration. Similarly, "immunization," as used in the document, includes both a product and its administration.

of infections, which remain high in the United States. For example, the Centers for Disease Control and Prevention (CDC) estimates that influenza has resulted in between 140,000 to 710,000 hospitalizations and 12,000 to 52,000 deaths annually between 2010 and 2020.[4] An estimated 150,000 individuals per year are hospitalized because of pneumococcal pneumonia.[5] In 2020, there were 5 newly reported cases of hepatitis B per 100,000 persons.[6] The human papillomavirus (HPV) causes more than 37,000 cases of cancer each year.[7]

Vaccination rates are suboptimal for all adults, regardless of health coverage, but for adults enrolled in Medicaid, the vaccination rates for a range of vaccinations are lower than for adults with private health insurance coverage, including influenza, tetanus, herpes zoster, hepatitis A, hepatitis B, and HPV vaccinations.[8] Additionally, the COVID-19 public health emergency (PHE) had a negative impact on the rate of children receiving routine childhood vaccinations. Although child vaccination rates have rebounded since the beginning of the COVID-19 PHE, there is still a gap in child vaccinations compared to prior years.[9]

Current (Pre-IRA) Medicaid and CHIP Vaccination Coverage

As discussed below, prior to the effective date of the IRA's amendments, Medicaid coverage of vaccines and vaccine administration is mandatory in certain circumstances; otherwise, coverage is at a state's option.

States must cover, for beneficiaries under age 21 who are eligible for the Early and Periodic Screening, Diagnostic, and Treatment (EPSDT) benefit (including beneficiaries enrolled in Medicaid-expansion CHIPs who are eligible for EPSDT), appropriate immunizations (according to age and health history) on the CDC/ACIP pediatric immunization schedule. In addition, other vaccinations recommended by ACIP (including those that are recommended on the CDC/ACIP

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[4] Centers for Disease Control and Prevention, U.S. Department of Health and Human Services, 2022. Disease Burden of Flu. Atlanta, GA: CDC. Available at:https://www.cdc.gov/flu/about/burden/index.html#:~:text=CDC%20estimates%20that%20flu%20has,annually%20between%202010%20and%202020 .

[5] Centers for Disease Control and Prevention. U.S. Department of Health and Human Services, 2023: Fast Facts You Need to Know About Pneumococcal Disease. Atlanta, GA: CDC. Available at: https://www.cdc.gov/pneumococcal/about/facts.html#:~:text=Pneumococcal%20pneumonia%20causes%20an%20estimated,the%20United%20States%20in%202019 .

[6] Centers for Disease Control and Prevention, U.S. Department of Health and Human Services, 2022. Hepatitis B Surveillance 2020. Atlanta, GA: CDC. Available at: https://www.cdc.gov/hepatitis/statistics/2020surveillance/hepatitis-b.htm.

[7] Centers for Disease Control and Prevention. U.S. Department of Health and Human Services. 2022. How Many Cancers are Linked with HPV Each Year. Atlanta, GA. CDC. Available at: https://www.cdc.gov/cancer/hpv/statistics/cases.htm.

[8] Estimates were based on an analysis of 2015–2018 National Health Interview Survey data. Medicaid and CHIP Payment and Access Commission (MACPAC). March 2022 Report to Congress on Medicaid and CHIP: Chapter 2: Vaccine Access for Adults Enrolled in Medicaid. 2022. Available at: https://www.macpac.gov/wp-content/uploads/2022/03/Chapter-2-Vaccine-Access-for-Adults-Enrolled-in-Medicaid.pdf.

[9] https://www.cdc.gov/mmwr/volumes/70/wr/mm7023a2.htm; https://www.medicaid.gov/state-resource-center/downloads/covid-19-medicaid-data-snapshot-07312022.pdf.

adult immunization schedule[10] for beneficiaries aged 19 or 20) and non-ACIP-recommended vaccines and vaccine administration are covered for beneficiaries eligible for EPSDT, if the service is determined to be medically necessary for the beneficiary based on an individualized assessment and state medical necessity criteria.[11]

Coverage of certain vaccines and vaccine administration is also mandatory for certain adult Medicaid beneficiaries, including individuals enrolled in the Medicaid expansion group described at section 1902(a)(10)(A)(i)(VIII) of the Act, who receive their services through an alternative benefit plan (ABP) authorized under section 1937 of the Act.[12] In accordance with section 1937(b)(5) of the Act and 42 CFR 440.347(a), ABPs must include coverage of the ten essential health benefit (EHB) categories. One of the ten categories of EHB is "preventive and wellness services and chronic disease management." Under this category, current law and regulations require coverage, without cost sharing, of vaccinations that have in effect a recommendation for routine use from ACIP with respect to the individual involved.[13]

Additionally, under amendments made by the American Rescue Plan Act of 2021 (ARP) (Pub. L. 117-2), state Medicaid programs are required to cover COVID-19 vaccines and their administration described in section 1905(a)(4)(E) of the Act, without cost sharing, for nearly all Medicaid beneficiaries, including most eligibility groups receiving limited benefit packages under the state plan or a section 1115 demonstration.[14] This coverage requirement generally applies during the period beginning on March 11, 2021, and ending on the last day of the first calendar quarter that begins one year after the last day of the COVID-19 emergency period described in section 1135(g)(1)(B) of the Act[15] (referred to herein as the ARP coverage period). The COVID-19 emergency period described in section 1135(g)(1)(B) of the Act ended on May 11, 2023, and therefore the last day of the ARP coverage period is September 30, 2024.[16]

Aside from the COVID-19 vaccinations described in section 1905(a)(4)(E) of the Act, for all populations in Medicaid not eligible for EPSDT or receiving coverage through an ABP, coverage of vaccines and vaccine administration is currently optional. States can elect to cover vaccines

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[10] The pediatric immunization schedule identifies ACIP-recommended vaccines for those through age 18 and is available at: https://www.cdc.gov/vaccines/schedules/downloads/child/0-18yrs-child-combined-schedule.pdf. The adult immunization schedule identifies ACIP-recommended vaccines for those age 19 and older and is available at: https://www.cdc.gov/vaccines/schedules/downloads/adult/adult-combined-schedule.pdf.

[11] Section 1905(r)(1)(B)(iii) and (5) of the Act.

[12] Additionally, in accordance with 42 CFR § 440.345(a), states with ABPs must assure access to EPSDT services for eligible individuals under 21 years of age who are receiving coverage through an ABP. This would include vaccinations covered under EPSDT that would not otherwise be covered under the ABP.

[13] 42 CFR § 440.347(a)(9), 45 CFR §§ 156.110(a)(9), 156.115(a)(4), 147.130(a)(1)(ii).

[14] Additional information about the beneficiaries to whom this coverage requirement applies is provided in the COVID-19 vaccine toolkit, available at: https://www.medicaid.gov/state-resource-center/downloads/covid-19-vaccine-toolkit.pdf.

[15] The COVID-19 emergency period described in section 1135(g)(1)(B) of the Act is the period during which there exists the public health emergency (PHE) declared by the Secretary of Health and Human Services pursuant to section 319 of the PHS Act on January 31, 2020, entitled "Determination that a Public Health Emergency Exists Nationwide as the Result of the 2019 Novel Coronavirus," and any renewal of that declaration.

[16] See https://www.hhs.gov/about/news/2023/05/11/hhs-secretary-xavier-becerra-statement-on-end-of-the-covid-19-public-health-emergency.html and https://www.hhs.gov/about/news/2023/02/09/letter-us-governors-hhs-secretary-xavier-becerra-renewing-covid-19-public-health-emergency.html.

and vaccine administration for these populations under various mandatory benefits such as inpatient hospital services (42 CFR § 440.10), outpatient hospital services (42 CFR § 440.20(a)), physicians' services (42 CFR § 440.50(a)), and under certain optional benefits such as services of other licensed practitioners (42 CFR § 440.60), clinic services (42 CFR § 440.90), and preventive services (42 CFR § 440.130(c)) depending on how the state defines the amount, duration, and scope parameters for these benefits. States currently may also elect to cover approved adult vaccines recommended by ACIP and their administration as described in section 1905(a)(13)(B) of the Act (and must do so if they opt to claim a one percentage point FMAP increase for their Medicaid expenditures on certain services). As described in more detail below, the IRA makes coverage of the services described in section 1905(a)(13)(B) mandatory for all states, beginning October 1, 2023.

Any Medicaid cost sharing that a state elects to charge, including cost sharing for vaccines and vaccine administration, must be nominal and comply with requirements at sections 1916 and 1916A of the Act and regulations at 42 CFR § 447.50 through 440.57. Certain populations and services must be exempted from any Medicaid cost sharing, including pregnancy-related services, most beneficiaries under age 18 (under age 21 at state option), and American Indians/Alaska Natives who are currently receiving or have ever received items or services furnished by an Indian health care provider or through referral under contract health services.

For all separate CHIP enrollees, similar to the Medicaid ARP coverage requirement, states must cover COVID-19 vaccines and their administration, without cost sharing, in accordance with section 2103(c)(11)(A) and (e)(2) of the Act (as added/amended by the ARP) during the ARP coverage period. State CHIP programs must also cover ACIP-recommended vaccines and their administration for children enrolled in a separate CHIP, with no cost-sharing, per 42 CFR §§ 457.410(b)(2) and 457.520(b)(4). As of December 2022, all states that cover pregnant adults through a separate CHIP under section 2112 of the Act voluntarily cover ACIP-recommended vaccines and their administration for these beneficiaries, without cost-sharing. This coverage is optional until the IRA coverage mandate takes effect on October 1, 2023.

Current (Pre-IRA) Increase in FMAP for Certain Adult Vaccinations and Other Services

Pursuant to section 1905(b) of the Act, as amended by section 4106 of the Affordable Care Act, states that elect to cover the adult vaccinations described in section 1905(a)(13)(B) of the Act, as well as services described in section 1905(a)(13)(A) of the Act, without cost sharing, receive a one percentage point increase in the FMAP for their Medicaid expenditures for these services and for their Medicaid expenditures on the tobacco cessation services for pregnant individuals described in section 1905(a)(4)(D) of the Act.[17] This will change after October 1, 2023, under the IRA's amendments, as further discussed below.

Advisory Committee on Immunization Practices (ACIP)

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[17] Additional information is available at: https://www.medicaid.gov/federal-policy-guidance/downloads/SMD-13-002.pdf#:~:text=This%20letter%20provides%20guidance%20to%20states%20on%20section,package%20%28referred%20to%20as%20an%20alternative%20benefit%20plan%29 and https://www.medicaid.gov/affordable-care-act/provisions/downloads/4106-faqs-clean.pdf.

ACIP is a federal advisory committee composed of medical and public health experts, as well as a consumer representative, that provides advice and guidance to the Director of the CDC on the most effective means to prevent vaccine preventable diseases in the United States. Recommendations made by the ACIP are reviewed by the CDC Director and, if adopted, are published as official CDC recommendations in the Morbidity and Mortality Weekly Report.[18] [19]

ACIP also develops written recommendations—subject to adoption by the CDC Director—for the routine use[20] of vaccines for both pediatric and adult populations for inclusion on the CDC/ACIP immunization schedules. To inform its advice to the CDC Director, ACIP considers disease epidemiology, burden of disease, vaccine efficacy and effectiveness, vaccine safety, the quality of evidence reviewed, economic analyses, and implementation issues.

The ACIP makes vaccination recommendations for different groups of people. Recommendations are by age group (as shown in Table 1 of the annual adult immunization schedule) or by risk group (some of which are shown in Table 2 of the annual adult immunization schedule), including risk due to underlying condition, occupation, or travel.[21] Some of ACIP's recommendations are not considered routine (that is, are not included on the adult or pediatric immunization schedules) but reflect the same considerations as vaccines included on the immunization schedules.

Most of ACIP's recommendations, including those both on and off the adult immunization schedule as described above, are for vaccinations for everyone (without contraindication) in a designated age or risk group (standard recommendations). ACIP also makes recommendations for shared clinical decision-making, in which the health care provider and the patient or parent/guardian consider whether or not to vaccinate. These other recommendations are not always included on the annual immunization schedules. Vaccination recommendations for shared clinical decision-making that are listed on the CDC/ACIP immunization schedules are considered to be for routine use. However, when these recommendations are not included on the CDC/ACIP immunization schedules, they would not be considered to be for routine use. The key distinction between standard recommendations and shared clinical decision-making recommendations relates to whether there should be a default decision to vaccinate. For standard recommendations, the default decision should be to vaccinate the patient based on age group or other indication, unless contraindicated. For shared clinical decision-making recommendations, there is no default—the decision about whether or not to vaccinate may be informed by the best available evidence of who may benefit from vaccination; the individual's characteristics, values,

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[18] The ACIP holds three regular meetings each year, in addition to emergency sessions. For more information, see: https://www.cdc.gov/vaccines/acip/committee/role-vaccine-recommendations.html.

[19] ACIP also has a statutorily defined role with respect to the Vaccines for Children (VFC) program. For more information, please see: https://www.cdc.gov/vaccines/programs/vfc/index.html; https://www.cdc.gov/vaccines/programs/vfc/providers/resolutions.html.

[20] As defined for purposes of the vaccination coverage that must be included in Medicaid ABP coverage, ACIP recommendations for "routine use" are those that are listed on the CDC/ACIP immunization schedules. See 45 CFR 147.130(a)(1)(ii). References to "routine" vaccinations or "routine" ACIP recommendations in this SHO letter have that same meaning.

[21] https://www.cdc.gov/vaccines/schedules/hcp/imz/adult.html

and preferences; the health care provider's clinical discretion; and the characteristics of the vaccine being considered.[22]

Section 11405 of the IRA – New Mandatory Medicaid and CHIP Adult Vaccination Coverage

Section 11405(a)(1) of the IRA amended section 1902(a)(10)(A) of the Act to include, effective October 1, 2023, items and services described in section 1905(a)(13)(B) in the list of Medicaid benefits that must be available to categorically needy individuals (subject to the coverage limitations for certain eligibility groups in the language following section 1902(a)(10)(G)). This same provision of the IRA amended section 1902(a)(10)(C)(iv) of the Act to require, also effective October 1, 2023, Medicaid coverage of the items and services described in section 1905(a)(13)(B) of the Act for certain medically needy beneficiaries.[23] Section 11405(b)(1) of the IRA added mandatory coverage of the services described in section 1905(a)(13)(B) for CHIP enrollees at section 2103(c)(12) of the Act. Section 11405 also amended sections 1916(a)(2), 1916(b)(2), 1916A(b)(3)(B), and 2103(e)(2) of the Act to specify that states cannot impose cost sharing with respect to the vaccination coverage that is described in sections 1905(a)(13)(B) and 2103(c)(12) of the Act. Under these amendments, beginning October 1, 2023, state Medicaid and CHIP programs must cover approved adult vaccines recommended by ACIP, and their administration, without cost sharing; these requirements apply in both fee-for-service and managed care.

Section 1905(a)(13)(B) of the Act

CMS interprets section 1905(a)(13)(B) of the Act as follows, including for purposes of the IRA's amendments requiring state Medicaid and CHIP programs to cover the vaccinations described in that section, without cost sharing obligations. Section 1905(a)(13)(B) describes the following services: "with respect to an adult individual, approved vaccines recommended by the [ACIP] … and their administration[.]" CMS interprets this language to describe vaccines that are approved by the FDA for use by adult populations and administered in accordance with recommendations of ACIP. CMS does not interpret "approved" to include vaccines that FDA has authorized for use under emergency use authorization, but has not approved. The coverage described in section 1905(a)(13)(B) is both of the vaccines themselves (i.e., the vaccine doses), and their administration.

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[22] All ACIP recommendations by vaccine are available here: https://www.cdc.gov/vaccines/hcp/acip-recs/index.html.

[23] States that cover the medically needy must choose their medically needy benefit package. If a state that covers the medically needy elects to make services in institutions for mental diseases and/or intermediate care facilities for the developmentally disabled available to *any* medically needy group, the state's medically needy benefit package for *all* medically needy groups must include at least the services described in one of two options identified in section 1902(a)(10)(C)(iv) of the Act. Prior to the IRA's enactment, one of these options was "the care and services listed in paragraphs (1) through (5) and (17) of section 1905(a)," and section 11405(a)(1) of the IRA amended section 1902(a)(10)(C)(iv) to add section 1905(a)(13)(B) to this particular option. The other option in section 1902(a)(10)(C)(iv) is "the care and services listed in any 7 of the paragraphs numbered (1) through (24) of [section 1905(a)]." A state that elects the latter option for its medically needy benefit package could, but would not be required to, include the items and services described in section 1905(a)(13)(B) in its medically needy benefit package.

Additionally, CMS interprets an "adult individual," for purposes of section 1905(a)(13)(B) of the Act, to refer to beneficiaries 19 years of age or older, which is consistent with the adult immunization schedule that identifies ACIP-recommended vaccines for those age 19 and older. This also aligns with how CMS has historically interpreted section 1905(a)(13)(B) for purposes of the one percentage point FMAP increase established by section 4106 of the Affordable Care Act,[24] and is also aligned with the age at which a CHIP beneficiary is no longer a child for purposes of eligibility (as defined at section 2110(c)(1) of the Act).

As noted earlier, there are multiple categories of ACIP recommendations for adult vaccines, including recommendations described on the CDC/ACIP adult immunization schedule (as determined by age and risk and recommendations for shared clinical decision-making), and recommendations based on risk due to health condition, occupation, and travel. Beginning October 1, 2023,[25] CMS interprets the reference to ACIP recommendations in section 1905(a)(13)(B) of the Act to include any category of ACIP recommendations. The IRA coverage requirement is therefore not limited to vaccines that ACIP includes on the immunization schedules or recommends for routine use.[26] States should establish processes to monitor and implement any new or updated ACIP recommendations.

As previously explained, state Medicaid and CHIP programs are currently required to cover, without cost sharing, the COVID-19 vaccines and their administration described in section 1905(a)(4)(E) of the Act (for Medicaid) and 2103(c)(11)(A) of the Act (for CHIP) during the ARP coverage period, which will end on September 30, 2024. At the conclusion of the ARP coverage period, COVID-19 vaccinations that are approved by the FDA for use by adult populations and that are administered in accordance with any category of ACIP recommendations would be covered, without cost sharing, as part of the IRA-required adult vaccination coverage described in sections 1905(a)(13)(B) and 2103(c)(12) of the Act. However, states are currently required to cover COVID-19 vaccinations for a broader range of Medicaid eligibility groups than will receive the mandatory adult vaccination coverage under the IRA. For example, the ARP COVID-19 vaccination coverage requirements apply to certain limited-benefit eligibility groups, such as individuals eligible for family planning benefits, that will not receive the mandatory adult vaccination coverage under the IRA. This means that individuals in certain Medicaid eligibility groups that currently receive coverage of COVID-19 vaccinations described in section 1905(a)(4)(E) of the Act will not receive coverage for these services as part of the IRA-required adult vaccination coverage after the ARP coverage period ends.[27]

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[24] Questions & Answers on ACA Section 4106 Improving Access to Preventive Services for Eligible Adults in Medicaid: https://www.medicaid.gov/affordable-care-act/provisions/downloads/4106-faqs-clean.pdf.

[25] See footnote 28.

[26] As noted earlier, to the extent possible, CMS has aligned its interpretation of section 11405 of the IRA with its interpretation of similar language added to the Medicare statute by section 11401 of the IRA. See https://www.cms.gov/files/document/irainsulinvaccinesmemo09262022.pdf.

[27] Coverage of COVID-19 vaccinations described in section 1905(a)(4)(E) is required for nearly all Medicaid beneficiaries, including most eligibility groups receiving limited benefit packages under the state plan or a section 1115 demonstration, while the IRA-required adult vaccination coverage described in section 1905(a)(13)(B) is

Increased FMAP

As explained earlier, states that currently provide Medicaid coverage for services described in sections 1905(a)(13)(A) and (B) of the Act, without cost sharing, receive a one percentage point increase in their FMAP for their Medicaid expenditures for these services, as well as for their Medicaid expenditures for the tobacco cessation services for pregnant individuals described in section 1905(a)(4)(D) of the Act. Section 11405(a)(3) of the IRA amended section 1905(b) of the Act to specify that states that were covering, as of the date of enactment of the IRA (August 16, 2022), vaccinations described in section 1905(a)(13)(B) without cost sharing will receive a one percentage point increase in the FMAP for their Medicaid expenditures for these vaccination services for the first eight fiscal quarters that begin on or after October 1, 2023.[28] At the conclusion of the eight fiscal quarters (September 30, 2025), these states' Medicaid expenditures for vaccines and vaccine administration described in section 1905(a)(13)(B) of the Act will be matched at the applicable regular FMAP.

Effective October 1, 2023, states that opt to cover preventive services described in section 1905(a)(13)(A) of the Act without cost sharing will receive a one percentage point FMAP increase in their Medicaid expenditures for those services and for the tobacco cessation services for pregnant individuals described in section 1905(a)(4)(D) of the Act, and can continue to receive that FMAP increase even after September 30, 2025.

Provider Qualifications for Vaccinations

States generally have broad flexibility to establish Medicaid provider qualifications (subject to the Medicaid free choice of provider requirement), including qualifications for providers that administer vaccines. States may have licensure and scope of practice laws and regulations, and/or other policies governing who is authorized to administer vaccines. CMS encourages states to review current state laws and policies to ensure that a broad array of providers who work in diverse settings (e.g., physician offices, clinics, pharmacies, hospitals) are authorized to administer vaccines as this could help to maximize beneficiaries' access to vaccines.

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mandatory for all full-benefit categorically needy beneficiaries and (depending on the state's decisions about its Medicaid benefit packages) certain medically needy beneficiaries. Individuals in nearly all Medicaid eligibility groups are eligible for the ARP COVID-19 vaccination coverage described in section 1905(a)(4)(E) of the Act, including the following limited-benefit eligibility groups: individuals eligible only for family planning benefits; individuals eligible for tuberculosis-related benefits; and section 1115(a)(2) expenditure authority limited-benefit groups.

[28] In previous guidance about the one percentage point FMAP increase, CMS referenced the CDC/ACIP adult immunization schedule and did not explain whether states should cover approved adult vaccines administered according to the full range of ACIP recommendations (including vaccines not on the CDC/ACIP adult immunization schedule). See https://www.medicaid.gov/federal-policy-guidance/downloads/smd-13-002.pdf. Therefore, states can continue to receive the one percentage point FMAP increase after October 1, 2023, if, on August 16, 2022, they were providing the vaccination coverage that, under CMS's guidance as of August 16, 2022, permitted them to claim the one percentage point FMAP increase. Beginning on October 1, 2023, all states, including those who keep receiving the one percentage point FMAP increase after that date, will have to provide coverage in alignment with this guidance (i.e., the full range of ACIP recommendations).

Although states generally have broad flexibility to set Medicaid provider qualifications, states are reminded that HHS Public Readiness and Emergency Preparedness (PREP) Act declarations might identify certain practitioners as "covered persons" authorized to administer certain vaccines, such as those for COVID-19 and mpox.[29] These HHS PREP Act authorizations preempt conflicting state scope of practice or licensure laws and thus have Medicaid payment implications, as a result of the Medicaid free choice of provider requirement. Specifically, when a state covers a vaccination for a beneficiary, and a practitioner (such as a pharmacist or pharmacy technician) is authorized to administer that vaccine under an HHS PREP Act declaration, the state Medicaid program would be required to provide a pathway to paying that practitioner for the covered vaccine administration, when provided in accordance with the provisions of the HHS PREP Act declaration. States still must meet all other applicable federal requirements for covering the applicable benefit, such as reimbursing only those providers that are enrolled as Medicaid providers and covering vaccinations only for eligible individuals.

Payment for Vaccinations

Within the parameters of section 1902(a)(30)(A) of the Act, states have flexibility to set Medicaid payment rates for vaccines and vaccine administration. To help improve access to these services for Medicaid beneficiaries, CMS encourages states to consider setting payment rates for vaccines at actual acquisition cost and an adequate professional fee for administration to incentivize access to and availability of vaccines.

If states utilize a managed care delivery system to provide coverage for vaccines and vaccine administration, states should carefully analyze and assess their current managed care contracts and capitation rates for any necessary revisions or amendments in light of this guidance. As with all covered benefits in a Medicaid managed care plan contract, capitation rates must be developed to include all reasonable, appropriate, and attainable costs that are required under the terms of the contract, as specified in 42 CFR § 438.4(a). Payment to healthcare providers for vaccines and vaccine administration may be specified by the state in a Medicaid managed care plan's contract, subject to the CMS approval requirements for state directed payments in 42 CFR § 438.6(c),[30] or may be determined by each managed care plan.

For states that use a managed care delivery system for their separate CHIPs, payment rates from the state to the managed care entity must be based on public or private rates for comparable populations and comparable services, consistent with actuarially sound principles, and are subject to the rate development standards at 42 CFR § 457.1203(a). In addition, 42 CFR § 457.1203(b) allows for flexibility in setting higher rates if such rates are necessary to ensure

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[29] For more information on the Medicaid implications of the HHS COVID-19 PREP Act declaration, see: https://www.medicaid.gov/state-resource-center/downloads/covid-19-vaccine-toolkit.pdf; and for more information on the Medicaid implications of the HHS PREP Act declaration for smallpox, monkeypox, and orthopoxvirus medical countermeasures, see: https://www.medicaid.gov/resources-for-states/downloads/covid19allstatecall12062022.pdf and https://www.hhs.gov/sites/default/files/monkeypox-faq-pharmacy-partners.pdf.

[30] For more information on state directed payments, please visit: https://www.medicaid.gov/medicaid/managed-care/guidance/state-directed-payments/index.html.

sufficient provider participation or provider access or to enroll providers who demonstrate exceptional efficiency or quality in the provision of services.

State Plan Amendments (SPAs)

States that have not already included an attestation in the Medicaid state plan stating that they cover the vaccines and vaccine administration described in section 1905(a)(13)(B) of the Act must submit a coverage SPA with an effective date of no later than October 1, 2023. On the supplement to attachments 3.1-A and 3.1-B (if applicable) coverage pages for the preventive services benefit, states should attest to coverage under the Medicaid state plan of vaccines and vaccine administration described in section 1905(a)(13)(B) of the Act. States should provide an additional assurance stating that they have a method to ensure that, as changes are made to ACIP recommendations, they will update their coverage and billing codes to comply with those revisions. States that do not have an approved payment methodology for these services must also submit a payment SPA with an effective date of no later than October 1, 2023. As with any SPA submission, CMS expects states to comply with all applicable federal Medicaid SPA requirements.

States should generally not need to submit a Medicaid cost sharing SPA to attest to compliance with these requirements because standard language in the cost-sharing state plan templates already specifies that the state is compliant with requirements at sections 1916 and 1916A of the Act, which were amended by section 11405 of the IRA to prohibit cost sharing for the vaccines described in section 1905(a)(13)(B) and administration of such vaccines.

States will also need to submit a CHIP SPA pursuant to the CMS requirements at 42 CFR § 457.60(a). States should indicate that they are covering, without cost sharing, all approved adult vaccines that are administered in accordance with ACIP recommendations, per sections 2103(c)(12) and 2103(e)(2) of the Act. More information will be forthcoming about the CHIP SPAs.

Conclusion

Mandatory coverage of all approved ACIP-recommended adult vaccinations, without cost-sharing, will improve access to vaccinations for adult Medicaid and CHIP beneficiaries. This change also has the potential to prevent hospitalizations and deaths and reduce costs associated with preventable infections. Please submit any questions about this guidance to Kirsten Jensen, Director of the Division of Benefits and Coverage, at kirsten.jensen@cms.hhs.gov.

Sincerely,

Daniel Tsai
Deputy Administrator and Director

Immunoglobulins and Antitoxins

Plain Language Summary:

Coverage question: Should certain injections be given to a person when they are exposed to a virus or bacteria that they are not immune to?

Should OHP cover this treatment? Yes, there are often no other treatments available.

Coverage Question: Should certain immunoglobulin and antitoxin administration CPT codes be added to various lines on the Prioritized List?

Question source: HERC staff

Background: HERC staff have become aware of a variety of immunoglobulins and antitoxin administration codes that are currently non-covered according to the HERC database. Pharmacy and Therapeutics staff report that the HCPCS codes for the actual immunoglobulins and antitoxins appear to be open for payment.

Immunoglobulins and antitoxins are substances given to a person who has been exposed to a virus or bacteria and does not have immunity to it. These substances can help the body fight off the infection. In many cases, there are no other treatments available for the condition.

HERC staff worked with public health colleagues to create recommendations for placement of these administration codes.

Previous HSC/HERC reviews:
None of these codes have ever been previously reviewed.

Current Prioritized List/Coverage status:
None of these codes are currently on any list (Prioritized, Ancillary, etc.). The HERC database lists them as "NEVER REVIEWED"

Expert input: None

Immunoglobulins and Antitoxins

CPT code	Code Description	Comments/information from public health
90281	Immune globulin (Ig), human, for intramuscular use	Used for treatments such as post-exposure prophylaxis for hepatitis A in persons with liver disease
90283	Immune globulin (IgIV), human, for intravenous use	This is the code used for IV infusion of IVIG. The subcutaneous version (CPT 90284) is on line s 12, 73, 90, 94, 106, 113, 114, 115, 163, 251, 260, 303, 400, 419, 509
90287	Botulinum antitoxin, equine, any route	Used to treat botulism. The actual antitoxin is provided by the CDC.
90291	Cytomegalovirus immune globulin (CMV-IgIV), human, for intravenous use	Per public health, this is not generally used. There may be a limited utilization for prophylaxis in solid organ transplant patients. CMV is on lines 195, 198, 460 and 615.
90296	Diphtheria antitoxin, equine, any route	Diphtheria is very, very rare. However, if there is an exposure, the CDC would dispense this antitoxin.
90371	Hepatitis B immune globulin (HBIg), human, for intramuscular use	Public health recommends coverage.
90375	Rabies immune globulin (RIg), human, for intramuscular and/or subcutaneous use	RIg is used regularly for post-exposure prophylaxis following exposure to rabies-positive or high-risk mammal if person wasn't previously immunized. Rabies is on line 651 (ICD-10 A82).
90376	Rabies immune globulin, heat-treated (RIg-HT), human, for intramuscular and/or subcutaneous use	See above.
90389	Tetanus immune globulin (TIg), human, for intramuscular use	Used regularly for prophylaxis for dirty, tetanus-prone wounds. Consider adding to line 236 TETANUS
90393	Vaccinia immune globulin, human, for intramuscular use	Recommended for persons with severe reaction to smallpox vaccine, and for treatment of Mpox in high-risk persons (with certain skin conditions, immunocompromised, kids, pregnant, breastfeeding).
90396	Varicella-zoster immune globulin, human, for intramuscular use	Occasionally used for postexposure prophylaxis in high-risk persons (neonates, immunocompromised, pregnant women) without evidence of immunity.

HERC staff summary: There are various antitoxin and immunoglobulin administration codes that need to be added to various lines.

Immunoglobulins and Antitoxins

HERC staff recommendations:

1) Change this line title for line 302 PERTUSSIS AND ~~DIPTHERIA~~ DIPHTHERIA
2) Adopt the code placements shown below

CPT code	Code Description	Recommended Placement
90281	Immune globulin (Ig), human, for intramuscular use	Add to line 3 PREVENTION SERVICES WITH EVIDENCE OF EFFECTIVENESS
90283	Immune globulin (IgIV), human, for intravenous use	Add to all lines with CPT 90284: lines 12, 73, 90, 94, 106, 113, 114, 115, 163, 251, 260, 303, 400, 419, 509
90287	Botulinum antitoxin, equine, any route	Add to line 103 BOTULISM
90291	Cytomegalovirus immune globulin (CMV-IgIV), human, for intravenous use	No change recommended
90296	Diphtheria antitoxin, equine, any route	Add to line 302 PERTUSSIS AND ~~DIPTHERIA~~ DIPHTHERIA
90371	Hepatitis B immune globulin (HBIg), human, for intramuscular use	Add to line 3 PREVENTION SERVICES WITH EVIDENCE OF EFFECTIVENESS
90375	Rabies immune globulin (RIg), human, for intramuscular and/or subcutaneous use	Add to line 3 PREVENTION SERVICES WITH EVIDENCE OF EFFECTIVENESS
90376	Rabies immune globulin, heat-treated (RIg-HT), human, for intramuscular and/or subcutaneous use	Add to line 3 PREVENTION SERVICES WITH EVIDENCE OF EFFECTIVENESS
90389	Tetanus immune globulin (TIg), human, for intramuscular use	Add to line 3 PREVENTION SERVICES WITH EVIDENCE OF EFFECTIVENESS
90393	Vaccinia immune globulin, human, for intramuscular use	Add to line 3 PREVENTION SERVICES WITH EVIDENCE OF EFFECTIVENESS.
90396	Varicella-zoster immune globulin, human, for intramuscular use	Add to line 3 PREVENTION SERVICES WITH EVIDENCE OF EFFECTIVENESS.

MyChoice CDx

Plain Language Summary:

Coverage question: Should OHP cover a genetic test to check for ovarian cancer?

Should OHP cover this treatment? Yes, this test is recommended by respected national expert guidelines.

Coverage Question: Should the PLA code for MyChoice CDx sequencing test be added to the ovarian cancer line with a new guideline?

Question source: Myriad genetics

Background: MyChoice CDX is a next generation sequencing test that assesses the qualitative detection and classification of single nucleotide variants, insertions and deletions, and large rearrangement variants in protein coding regions and intron/exon boundaries of the BRCA1 and BRCA2 genes and the determination of Genomic Instability Score (GIS) which is an algorithmic measurement of Loss of Heterozygosity (LOH), Telomeric Allelic Imbalance (TAI), and Large-scale State Transitions (LST) using DNA isolated from formalin-fixed paraffin embedded (FFPE) tumor tissue specimens. The results of the test are used to identify individuals with ovarian cancer who may be eligible for treatment with certain chemotherapy agents.

Previous HSC/HERC reviews:

No previous review

Current Prioritized List/Coverage status:

238 CANCER OF OVARY contains the ICD-10-CM codes for ovarian cancer

0172U Oncology (solid tumor as indicated by the label), somatic mutation analysis of BRCA1 (BRCA1, DNA repair associated), BRCA2 (BRCA2, DNA repair associated) and analysis of homologous recombination deficiency pathways, DNA, formalin-fixed paraffin-embedded tissue, algorithm quantifying tumor genomic instability score

Expert guidelines:

1) **NCCN 2.2023** Ovarian Cancer
    a. In PAOLA-1 the population without BRCA1/2 mutations was further subdivided based on results of MyChoice CDx (Myriad Genetic Laboratories), a proprietary tumor tissue assay that uses multiple molecular tests and combines several metrics (loss of heterozygosity [LOH], telomeric allelic imbalance [TAI], and large-scale state transitions [LST] to determine the genomic instability score (GIS), a proxy measure for the presence of

homologous recombination deficiency. A GIS cutoff of 42 was used to define homologous recombination deficiency status based on a prior analyses of a population of breast and ovarian cancer cases showing that this cutoff identified 95% of patients who had BRCA1/2 deficiency, defined as either 1) one deleterious mutation in BRCA1 or BRCA2, with LOH in the wild-type copy; 2) two deleterious mutations in the same gene; or 3) promoter methylation of BRCA1 with LOH in the wild-type copy. Among those without BRCA1/2 mutations, the PFS benefit of maintenance olaparib was significant for those with homologous recombination deficiency (as defined by the proprietary assay) but was not significant for those who did not have homologous recombination deficiency. For this reason, the NCCN Panel included the following footnote relating to the use of maintenance bevacizumab + olaparib: In the absence of a BRCA1/2 mutation, homologous recombination deficiency status may provide information on the magnitude of benefit of PARP inhibitor therapy (category 2B).

2) **ASCO 2023**, Poly(ADP-Ribose) Polymerase Inhibitors in the Management of Ovarian Cancer: ASCO Guideline Rapid Recommendation Update
    a. Newly diagnosed ovarian cancer
        i. Patients with newly diagnosed stage III-IV EOC who are in complete or partial response to first-line platinum-based chemotherapy should be offered PARPi maintenance therapy in high-grade serous or endometrioid ovarian cancer…For those who are homologous recombination deficiency (HRD) positive, determined using FDA-approved companion diagnostic tests, rucaparib and niraparib are options. Niraparib or rucaparib may be offered for non-BRCAmut/HRDneg patients. (Type: Evidence-based, benefits outweigh harms; Evidence quality: High; Strength of recommendation: Strong.)

Other payer policies:

1) Aetna 2023
    a. 0172U listed as covered, unclear if there is specific coverage criteria
2) MODA 2023
    a. myChoice CDx will be covered to plan limitations for women who meet ALL the following criteria:
        i. 18 years old or older
        ii. Have advanced epithelial ovarian cancer, fallopian tube or primary peritoneal cancer and ONE of the following:
            1. Have been treated with three or more lines of chemotherapy and are being considered for treatment with niraparib (Zejula)
            2. Are in complete or partial response to two or more lines of platinum-based chemotherapy and are being considered for maintenance treatment with niraparib (Zejula)
            3. Are being considered for first line maintenance treatment with Olaparib (Lynparza) and bevacizuma

Regulatory guidelines:

1) FDA guideline for olaparib (Lynparza)

MyChoice CDx

a. Lynparza is a poly (ADP-ribose) polymerase (PARP) inhibitor indicated:
    i. Ovarian cancer
        1. Lynparza is indicated in combination with bevacizumab for the maintenance treatment of adult patients with advanced epithelial ovarian, fallopian tube or primary peritoneal cancer who are in complete or partial response to first-line platinum-based chemotherapy and whose cancer is associated with homologous recombination deficiency (HRD)-positive status defined by either:
            a. a deleterious or suspected deleterious BRCA mutation, and/or
            b. genomic instability
        2. MyChoice CDX is considered companion diagnostic testing

HERC staff summary:

MyChoice CDx testing is an FDA companion test for use with Lynparza. This testing is included in both ASCO and NCCN treatment guidelines, although use is a 2B recommendation in the NCCN guideline.

HERC staff recommendation:

1) Add PLA 0172U (Oncology (solid tumor as indicated by the label), somatic mutation analysis of BRCA1 (BRCA1, DNA repair associated), BRCA2 (BRCA2, DNA repair associated) and analysis of homologous recombination deficiency pathways, DNA, formalin-fixed paraffin-embedded tissue, algorithm quantifying tumor genomic instability score) to line 238 CANCER OF OVARY

Poly(ADP-Ribose) Polymerase Inhibitors in the Management of Ovarian Cancer: ASCO Guideline Rapid Recommendation Update

William P. Tew, MD[1]; Christina Lacchetti, MHSc[2]; and Elise C. Kohn, MD[3]; for the PARP Inhibitors in the Management of Ovarian Cancer Guideline Expert Panel

ASCO Rapid Recommendations Updates highlight revisions to select ASCO guideline recommendations as a response to the emergence of new and practice-changing data. The rapid updates are supported by an evidence review and follow the guideline development processes outlined in the ASCO Guideline Methodology Manual. The goal of these articles is to disseminate updated recommendations, in a timely manner, to better inform health practitioners and the public on the best available cancer care options.

BACKGROUND

In 2020, ASCO published a guideline on poly(ADP-ribose) polymerase inhibitor (PARPi) therapy in the management of ovarian cancer.[1] In June 2022, the ATHENA-MONO[2] phase III multinational, double-blind, randomized controlled trial (RCT) evaluating rucaparib monotherapy reported on the efficacy of rucaparib maintenance therapy compared with placebo in patients with stage III-IV epithelial ovarian cancer (EOC) who are in complete or partial response to first-line platinum-based chemotherapy. A significant improvement in progression-free survival (PFS) constituted a strong signal for an update of the 2020 ASCO guideline recommendation for first-line maintenance therapy. Furthermore, reports of detrimental overall survival (OS) from the ARIEL4 trial[3] (rucaparib), SOLO3 trial (olaparib),[4] and ENGOT-OV16/NOVA trial[5] (niraparib) constituted safety signals for recommendation updates for treatment in recurrent platinum-sensitive EOC (*BRCA* mutation or homologous recombination deficiency [HRD] positive status) and in unselected patient population second-line maintenance treatment, respectively.

METHODS

A targeted literature search was conducted to identify any additional phase III RCTs of PARPi in this patient population. No additional randomized trials were found, although three Dear Health Care Provider letters,[4-6] one abstract,[3] and changes in US Food and Drug Administration (FDA) labeling were identified. The original Expert Panel was reconvened to review the evidence from ATHENA-MONO[2] and reports of ARIEL4,[3] SOLO3,[4] ENGOT-OV16/NOVA[5] OS outcomes, and new GSK prescribing information[6] to approve the updated recommendation (see Appendix Figs A1 and A2, online only, for summary).

EVIDENCE REVIEW

Monk et al[2] reported that, compared with placebo, rucaparib maintenance in patients with newly diagnosed advanced ovarian cancer was associated with significantly longer PFS. The median PFS was 28.7 months (95% CI, 23.0 to not reached) with rucaparib versus 11.3 months (95% CI, 9.1 to 22.1) with placebo in the *BRCA*-mutant and homologous recombination deficiency (HRD) population, determined using FoundationOne CDx (log rank $P = .0004$; HR, 0.47; 95% CI, 0.31 to 0.72); 20.2 months (95% CI, 15.2 to 24.7) versus 9.2 months (95% CI, 8.3 to 12.2) in the intent-to-treat population (log-rank $P < .0001$; HR, 0.52; 95% CI, 0.40 to 0.68); and 12.1 months (95% CI, 11.1 to 17.7) versus 9.1 months (95% CI, 4.0 to 12.2) in the HRD-negative population (HR, 0.65; 95% CI, 0.45 to 0.95).

ARIEL4, a phase III RCT, evaluated rucaparib versus chemotherapy in patients with relapsed, *BRCA*-mutated, high-grade EOC who received two or more prior lines of chemotherapy. The final analysis of the secondary OS end point[3] (70% of death events reported) found an OS detriment for patients randomly assigned to rucaparib. In the intent-to-treat population, the median OS was 19.4 months in the rucaparib group compared with 25.4 months in the chemotherapy group, resulting in a HR of 1.31 (95% CI, 1.00 to 1.73), $P = .0507$. A withdrawal of FDA approval in the United States of rucaparib as a treatment for patients with *BRCA*-mutated EOC after two or more chemotherapies became effective on June 10, 2022.[7]

SOLO3 is a phase III trial comparing olaparib versus nonplatinum chemotherapy in patients with germline *BRCA*-mutated (g*BRCA*mut) platinum-sensitive relapsed ovarian cancer who had received at least two prior lines of platinum-based chemotherapy. At the final analysis (data cutoff: April 16, 2021),[4] there was no significant difference in OS, a secondary end point,

ASSOCIATED CONTENT

The companion to this article was published in the October 20, 2020 issue of *Journal of Clinical Oncology*. See accompanying article on page 3468

Appendix

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

Accepted on August 30, 2022 and published at ascopubs.org/journal/jco on September 23, 2022: DOI https://doi.org/10.1200/JCO.22.01934

HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use LYNPARZA safely and effectively. See full prescribing information for LYNPARZA.

LYNPARZA® (olaparib) tablets, for oral use
Initial U.S. Approval: 2014

---------- **RECENT MAJOR CHANGES** ----------

Indications and Usage (1)	5/2020
Dosage and Administration (2)	5/2020
Warnings and Precautions, Venous Thromboembolic Events (5.4)	5/2020

---------- **INDICATIONS AND USAGE** ----------

Lynparza is a poly (ADP-ribose) polymerase (PARP) inhibitor indicated:

Ovarian cancer

- for the maintenance treatment of adult patients with deleterious or suspected deleterious germline or somatic *BRCA*-mutated advanced epithelial ovarian, fallopian tube or primary peritoneal cancer who are in complete or partial response to first-line platinum-based chemotherapy. Select patients for therapy based on an FDA-approved companion diagnostic for Lynparza. (1.1, 2.1)
- in combination with bevacizumab for the maintenance treatment of adult patients with advanced epithelial ovarian, fallopian tube or primary peritoneal cancer who are in complete or partial response to first-line platinum-based chemotherapy and whose cancer is associated with homologous recombination deficiency (HRD)-positive status defined by either:
  - a deleterious or suspected deleterious *BRCA* mutation, and/or
  - genomic instability.

  Select patients for therapy based on an FDA-approved companion diagnostic for Lynparza (1.2, 2.1).
- for the maintenance treatment of adult patients with recurrent epithelial ovarian, fallopian tube or primary peritoneal cancer, who are in complete or partial response to platinum-based chemotherapy. (1.3)
- for the treatment of adult patients with deleterious or suspected deleterious germline *BRCA*-mutated (g*BRCA*m) advanced ovarian cancer who have been treated with three or more prior lines of chemotherapy. Select patients for therapy based on an FDA-approved companion diagnostic for Lynparza. (1.4, 2.1)

Breast cancer

- for the treatment of adult patients with deleterious or suspected deleterious g*BRCA*m, HER2-negative metastatic breast cancer who have been treated with chemotherapy in the neoadjuvant, adjuvant or metastatic setting. Patients with hormone receptor (HR)-positive breast cancer should have been treated with a prior endocrine therapy or be considered inappropriate for endocrine therapy. Select patients for therapy based on an FDA-approved companion diagnostic for Lynparza. (1.5, 2.1)

Pancreatic cancer

- for the maintenance treatment of adult patients with deleterious or suspected deleterious g*BRCA*m metastatic pancreatic adenocarcinoma whose disease has not progressed on at least 16 weeks of a first-line platinum-based chemotherapy regimen. Select patients for therapy based on an FDA-approved companion diagnostic for Lynparza. (1.6, 2.1)

Prostate cancer

- for the treatment of adult patients with deleterious or suspected deleterious germline or somatic homologous recombination repair (HRR) gene-mutated metastatic castration-resistant prostate cancer (mCRPC) who have progressed following prior treatment with enzalutamide or abiraterone. Select patients for therapy based on an FDA-approved companion diagnostic for Lynparza. (1.7, 2.1)

---------- **DOSAGE AND ADMINISTRATION** ----------

- Recommended dosage is 300 mg taken orally twice daily with or without food. See Full Prescribing Information for the recommended duration. (2.2)
- Patients receiving Lynparza for mCRPC should also receive a gonadotropin-releasing hormone (GnRH) analog concurrently or should have had bilateral orchiectomy. (2.2)
- For moderate renal impairment (CLcr 31-50 mL/min), reduce Lynparza dosage to 200 mg orally twice daily. (2.5)

---------- **DOSAGE FORMS AND STRENGTHS** ----------

Tablets: 150 mg, 100 mg (3)

---------- **CONTRAINDICATIONS** ----------

None. (4)

---------- **WARNINGS AND PRECAUTIONS** ----------

- Myelodysplastic Syndrome/Acute Myeloid Leukemia (MDS/AML): Occurred in <1.5% of patients exposed to Lynparza monotherapy and the majority of events had a fatal outcome. Monitor patients for hematological toxicity at baseline and monthly thereafter. Discontinue if MDS/AML is confirmed. (5.1)
- Pneumonitis: Occurred in <1% of patients exposed to Lynparza, and some cases were fatal. Interrupt treatment if pneumonitis is suspected. Discontinue if pneumonitis is confirmed. (5.2)
- Embryo-Fetal Toxicity: Can cause fetal harm. Advise of the potential risk to a fetus and to use effective contraception. (5.3, 8.1, 8.3)
- Venous thromboembolic events including pulmonary embolism occurred in 7% of patients with mCRPC. Monitor patients for signs and symptoms of venous thrombosis and pulmonary embolism and treat as medically appropriate. (5.4)

---------- **ADVERSE REACTIONS** ----------

Most common adverse reactions (≥10%) in clinical trials:

- as a single agent were nausea, fatigue (including asthenia), anemia, vomiting, diarrhea, decreased appetite, headache, neutropenia, dysgeusia, cough, dyspnea, dizziness, dyspepsia, leukopenia, thrombocytopenia, and abdominal pain upper. (6.1)
- in combination with bevacizumab were nausea, fatigue (including asthenia), anemia, lymphopenia, vomiting, diarrhea, neutropenia, leukopenia, urinary tract infection, and headache. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact AstraZeneca at 1-800-236-9933 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

---------- **DRUG INTERACTIONS** ----------

- Strong or moderate CYP3A inhibitors: Avoid concomitant use. If concomitant use cannot be avoided, reduce Lynparza dosage. (2.4, 7.2, 12.3)
- Strong or moderate CYP3A inducers: Avoid concomitant use. (7.2, 12.3)

---------- **USE IN SPECIFIC POPULATIONS** ----------

Lactation: Advise women not to breastfeed. (8.2)

See 17 for PATIENT COUNSELING INFORMATION and Medication Guide.

Revised: 5/2020

FULL PRESCRIBING INFORMATION: CONTENTS*

*Sections or subsections omitted from the full prescribing information are not listed.

FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

1.1 First-Line Maintenance Treatment of *BRCA*-mutated Advanced Ovarian Cancer

Lynparza is indicated for the maintenance treatment of adult patients with deleterious or suspected deleterious germline or somatic *BRCA*-mutated advanced epithelial ovarian, fallopian tube or primary peritoneal cancer who are in complete or partial response to first-line platinum-based chemotherapy. Select patients for therapy based on an FDA-approved companion diagnostic for Lynparza *[see Dosage and Administration (2.1)]*.

1.2 First-line Maintenance Treatment of HRD-positive Advanced Ovarian Cancer in Combination with Bevacizumab

Lynparza is indicated in combination with bevacizumab for the maintenance treatment of adult patients with advanced epithelial ovarian, fallopian tube or primary peritoneal cancer who are in complete or partial response to first-line platinum-based chemotherapy and whose cancer is associated with homologous recombination deficiency (HRD)-positive status defined by either:

- a deleterious or suspected deleterious *BRCA* mutation, and/or
- genomic instability.

Select patients for therapy based on an FDA-approved companion diagnostic for Lynparza *[see Dosage and Administration (2.1)]*.

1.3 Maintenance Treatment of Recurrent Ovarian Cancer

Lynparza is indicated for the maintenance treatment of adult patients with recurrent epithelial ovarian, fallopian tube or primary peritoneal cancer, who are in complete or partial response to platinum-based chemotherapy.

1.4 Advanced Germline *BRCA*-mutated Ovarian Cancer After 3 or More Lines of Chemotherapy

Lynparza is indicated for the treatment of adult patients with deleterious or suspected deleterious germline *BRCA*-mutated (g*BRCA*m) advanced ovarian cancer who have been treated with three or more prior lines of chemotherapy. Select patients for therapy based on an FDA-approved companion diagnostic for Lynparza *[see Dosage and Administration (2.1)]*.

1.5 Germline *BRCA*-mutated HER2-negative Metastatic Breast Cancer

Lynparza is indicated for the treatment of adult patients with deleterious or suspected deleterious g*BRCA*m, HER2-negative metastatic breast cancer, who have been treated with chemotherapy in the neoadjuvant, adjuvant, or metastatic setting. Patients with hormone receptor (HR)-positive breast cancer should have been treated with a prior endocrine therapy or be considered inappropriate for endocrine therapy. Select patients for therapy based on an FDA-approved companion diagnostic for Lynparza *[see Dosage and Administration (2.1)]*.

1.6 First-Line Maintenance Treatment of Germline *BRCA*-mutated Metastatic Pancreatic Adenocarcinoma

Lynparza is indicated for the maintenance treatment of adult patients with deleterious or suspected deleterious g*BRCA*m metastatic pancreatic adenocarcinoma whose disease has not progressed on at least 16 weeks of a first-line platinum-based chemotherapy regimen. Select patients for therapy based on an FDA-approved companion diagnostic for Lynparza *[see Dosage and Administration (2.1)]*.

1.7 HRR Gene-mutated Metastatic Castration-Resistant Prostate Cancer

Lynparza is indicated for the treatment of adult patients with deleterious or suspected deleterious germline or somatic homologous recombination repair (HRR) gene-mutated metastatic castration-resistant prostate cancer (mCRPC) who have progressed following prior treatment with enzalutamide or abiraterone. Select patients for therapy based on an FDA-approved companion diagnostic for Lynparza *[see Dosage and Administration (2.1)]*.

2 DOSAGE AND ADMINISTRATION

2.1 Patient Selection

Information on FDA-approved tests for the detection of genetic mutations is available at http://www.fda.gov/companiondiagnostics.

Select patients for treatment with Lynparza based on the presence of deleterious or suspected deleterious HRR gene mutations, including *BRCA* mutations, or genomic instability based on the indication, biomarker, and sample type (Table 1).

Table 1 Biomarker Testing for Patient Selection

Indication	Biomarker	Sample type	
		Tumor	Blood
First-line maintenance treatment of germline or somatic *BRCA*m advanced ovarian cancer*	*BRCA1*m, *BRCA2*m	X	X
First-line maintenance treatment of HRD-positive advanced ovarian cancer in combination with bevacizumab*	*BRCA1*m, *BRCA2*m and/or genomic instability	X	
Maintenance treatment of recurrent ovarian cancer	No requirement for biomarker testing		
Advanced g*BRCA*m ovarian cancer	*gBRCA1*m, *gBRCA2*m		X

g*BRCA*m HER2-negative metastatic breast cancer	*gBRCA1*m, *gBRCA2*m		X
First-line maintenance treatment of germline *BRCA*-mutated metastatic pancreatic adenocarcinoma	*gBRCA1*m, *gBRCA2*m		X
Germline or somatic HRR gene-mutated metastatic castration-resistant prostate cancer*	*ATM*m, *BRCA1*m, *BRCA2*m, *BARD1*m, *BRIP1*m, *CDK12*m, *CHEK1*m, *CHEK2*m, *FANCL*m, *PALB2*m, *RAD51B*m, *RAD51C*m, *RAD51D*m, *RAD54L*m	X	
	g*BRCA1*m, g*BRCA2*m		X

* Where testing fails or tissue sample is unavailable/insufficient, or when germline testing is negative, consider using an alternative test.

2.2 Recommended Dosage

The recommended dosage of Lynparza is 300 mg taken orally twice daily, with or without food.

If a patient misses a dose of Lynparza, instruct patient to take their next dose at its scheduled time. Instruct patients to swallow tablets whole. Do not chew, crush, dissolve, or divide tablet.

First-Line Maintenance Treatment of *BRCA*-mutated Advanced Ovarian Cancer

Continue treatment until disease progression, unacceptable toxicity, or completion of 2 years of treatment. Patients with a complete response (no radiological evidence of disease) at 2 years should stop treatment. Patients with evidence of disease at 2 years, who in the opinion of the treating healthcare provider can derive further benefit from continuous treatment, can be treated beyond 2 years.

First-Line Maintenance Treatment of HRD-positive Advanced Ovarian Cancer in Combination with Bevacizumab

Continue Lynparza treatment until disease progression, unacceptable toxicity, or completion of 2 years of treatment. Patients with a complete response (no radiological evidence of disease) at 2 years should stop treatment. Patients with evidence of disease at 2 years, who in the opinion of the treating healthcare provider can derive further benefit from continuous Lynparza treatment, can be treated beyond 2 years.

When used with Lynparza, the recommended dose of bevacizumab is 15 mg/kg every three weeks. Bevacizumab should be given for a total of 15 months including the period given with chemotherapy and given as maintenance. Refer to the Prescribing Information for bevacizumab when used in combination with Lynparza for more information.

Recurrent Ovarian Cancer, Germline *BRCA*m Advanced Ovarian Cancer, HER2-negative Metastatic Breast Cancer, Metastatic Pancreatic Adenocarcinoma, and HRR Gene-mutated Metastatic Castration-Resistant Prostate Cancer

Continue treatment until disease progression or unacceptable toxicity for:

- Maintenance treatment of recurrent ovarian cancer
- Advanced germline *BRCA*-mutated ovarian cancer
- Germline *BRCA*-mutated HER-2 negative metastatic breast cancer
- First-line maintenance treatment of germline *BRCA*-mutated metastatic pancreatic adenocarcinoma.
- HRR gene-mutated metastatic castration-resistant prostate cancer

Patients receiving Lynparza for mCRPC should also receive a gonadotropin-releasing hormone (GnRH) analog concurrently or should have had bilateral orchiectomy.

2.3 Dosage Modifications for Adverse Reactions

To manage adverse reactions, consider interruption of treatment or dose reduction. The recommended dose reduction is 250 mg taken twice daily.

If a further dose reduction is required, then reduce to 200 mg taken twice daily.

2.4 Dosage Modifications for Concomitant Use with Strong or Moderate CYP3A Inhibitors

Avoid concomitant use of strong or moderate CYP3A inhibitors with Lynparza.

If concomitant use cannot be avoided, reduce Lynparza dosage to:

- 100 mg twice daily when used concomitantly with a strong CYP3A inhibitor.
- 150 mg twice daily when used concomitantly with a moderate CYP3A inhibitor.

After the inhibitor has been discontinued for 3 to 5 elimination half-lives, resume the Lynparza dose taken prior to initiating the CYP3A inhibitor *[see Drug Interactions (7.2) and Clinical Pharmacology (12.3)]*.

2.5 Dosage Modifications for Renal Impairment

Moderate Renal Impairment

In patients with moderate renal impairment (CLcr 31-50 mL/min), reduce the Lynparza dosage to 200 mg orally twice daily *[see Use in Specific Populations (8.6) and Clinical Pharmacology (12.3)]*.

3 DOSAGE FORMS AND STRENGTHS

Tablets:

- 150 mg: green to green/grey, oval, bi-convex, film-coated, with debossment ‘OP150’ on one side and plain on the reverse side.
- 100 mg: yellow to dark yellow, oval, bi-convex, film-coated, with debossment ‘OP100’ on one side and plain on the reverse side.

4 CONTRAINDICATIONS

None.

5 WARNINGS AND PRECAUTIONS

5.1 Myelodysplastic Syndrome/Acute Myeloid Leukemia

In clinical studies enrolling 2351 patients with various cancers who received Lynparza as a single agent *[see Adverse Reactions (6.1)]*, the incidence of Myelodysplastic Syndrome/Acute Myeloid Leukemia (MDS/AML) was <1.5% (28/2351) and the majority of events had a fatal outcome. Of these, 25/28 patients had a documented *BRCA* mutation, 2 patients had g*BRCA* wildtype and in 1 patient the *BRCA* mutation status was unknown. Additional cases of MDS/AML have been documented in patients treated with Lynparza in combination studies and in postmarketing reports. The duration of therapy with Lynparza in patients who developed secondary MDS/cancer-therapy related AML varied from <6 months to >2 years. All of these patients had received previous chemotherapy with platinum agents and/or other DNA damaging agents including radiotherapy. Some of these patients also had a history of more than one primary malignancy or of bone marrow dysplasia.

Do not start Lynparza until patients have recovered from hematological toxicity caused by previous chemotherapy (≤Grade 1). Monitor complete blood count for cytopenia at baseline and monthly thereafter for clinically significant changes during treatment. For prolonged hematological toxicities, interrupt Lynparza and monitor blood counts weekly until recovery. If the levels have not recovered to Grade 1 or less after 4 weeks, refer the patient to a hematologist for further investigations, including bone marrow analysis and blood sample for cytogenetics. If MDS/AML is confirmed, discontinue Lynparza.

5.2 Pneumonitis

In clinical studies enrolling 2351 patients with various cancers who received Lynparza as a single agent *[see Adverse Reactions (6.1)]*, the incidence of pneumonitis, including fatal cases, was <1% (20/2351). If patients present with new or worsening respiratory symptoms such as dyspnea, cough and fever, or a radiological abnormality occurs, interrupt Lynparza treatment and promptly assess the source of the symptoms. If pneumonitis is confirmed, discontinue Lynparza treatment and treat the patient appropriately.

5.3 Embryo-Fetal Toxicity

Lynparza can cause fetal harm when administered to a pregnant woman based on its mechanism of action and findings in animals. In an animal reproduction study, administration of olaparib to pregnant rats during the period of organogenesis caused teratogenicity and embryo-fetal toxicity at exposures below those in patients receiving the recommended human dose of 300 mg twice daily. Apprise pregnant women of the potential hazard to a fetus and the potential risk for loss of the pregnancy. Advise females of reproductive potential to use effective contraception during treatment and for 6 months following the last dose of Lynparza. Based on findings from genetic toxicity and animal reproduction studies, advise male patients with female partners of reproductive potential or who are pregnant to use effective contraception during treatment and for 3 months following the last dose of Lynparza *[see Use in Specific Populations (8.1, 8.3)]*.

5.4 Venous Thromboembolic Events

Venous thromboembolic events, including pulmonary embolism, occurred in 7% of patients with metastatic castration resistant prostate cancer who received Lynparza plus androgen deprivation therapy (ADT) compared to 3.1% of patients receiving enzalutamide or abiraterone plus ADT in the PROfound study. Patients receiving Lynparza and ADT had a 6% incidence of pulmonary embolism compared to 0.8% of patients treated with ADT plus either enzalutamide or abiraterone. Monitor patients for signs and symptoms of venous thrombosis and pulmonary embolism and treat as medically appropriate, which may include long-term anticoagulation as clinically indicated.

6 ADVERSE REACTIONS

The following adverse reactions are discussed elsewhere in the labeling:

- Myelodysplastic Syndrome/Acute Myeloid Leukemia *[see Warnings and Precautions (5.1)]*
- Pneumonitis *[see Warnings and Precautions (5.2)]*
- Venous Thromboembolic Events *[see Warnings and Precautions (5.4)]*

6.1 Clinical Trial Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

The data described in the WARNINGS AND PRECAUTIONS reflect exposure to Lynparza as a single agent in 2351 patients; 1585 patients with exposure to 300 mg twice daily tablet dose including five controlled, randomized, trials (SOLO-1, SOLO-2, OlympiAD, POLO, and PROfound) and to 400 mg twice daily capsule dose in 766 patients in other trials that were pooled to conduct safety analyses. In these trials, 55% of patients were exposed for 6 months or longer and 31% were exposed for greater than one year in the Lynparza group.

In this pooled safety population, the most common adverse reactions in ≥10% of patients were nausea (60%), fatigue (55%), anemia (37%), vomiting (34%), diarrhea (25%), decreased appetite (23%), headache (16%), neutropenia (15%), dysgeusia (15%), cough (15%), dyspnea (14%), dizziness (12%), dyspepsia (12%), leukopenia (11%), thrombocytopenia (11%), and abdominal pain upper (10%).

First-Line Maintenance Treatment of *BRCA*-mutated Advanced Ovarian Cancer

SOLO-1

The safety of Lynparza for the maintenance treatment of patients with *BRCA*-mutated advanced ovarian cancer following first-line treatment with platinum-based chemotherapy was investigated in SOLO-1 *[see Clinical Studies (14.1)]*. Patients received Lynparza tablets 300 mg orally twice daily (n=260) or placebo (n=130) until disease progression or unacceptable toxicity. The median duration of study treatment was 25 months for patients who received Lynparza and 14 months for patients who received placebo.

Among patients who received Lynparza, dose interruptions due to an adverse reaction of any grade occurred in 52% and dose reductions due to an adverse reaction occurred in 28%. The most frequent adverse reactions leading to dose interruption or reduction of Lynparza were anemia (23%), nausea (14%), and vomiting (10%). Discontinuation due to adverse reactions occurred in 12% of patients receiving Lynparza. The most frequent adverse reactions that led to discontinuation of Lynparza were fatigue (3.1%), anemia (2.3%), and nausea (2.3%).

Tables 2 and 3 summarize adverse reactions and laboratory abnormalities in SOLO-1.

Table 2 Adverse Reactions[*] in SOLO-1 (≥10% of Patients Who Received Lynparza)

Adverse Reaction	Lynparza tablets n=260		Placebo n=130	
	All Grades (%)	Grades 3 – 4 (%)	All Grades (%)	Grades 3 – 4 (%)
Gastrointestinal Disorders				
Nausea	77	1	38	0
Abdominal pain[†]	45	2	35	1
Vomiting	40	0	15	1
Diarrhea[‡]	37	3	26	0
Constipation	28	0	19	0
Dyspepsia	17	0	12	0
Stomatitis[§]	11	0	2	0
General Disorders and Administration Site Conditions				
Fatigue[¶]	67	4	42	2
Blood and Lymphatic System Disorders				
Anemia	38	21	9	2
Neutropenia[#]	17	6	7	3
Leukopenia[Þ]	13	3	8	0
Thrombocytopenia[ß]	11	1	4	2
Infections and Infestations				
Upper respiratory tract infection/ influenza/nasopharyngitis/bronchitis	28	0	23	0
UTI[à]	13	1	7	0
Nervous System Disorders				
Dysgeusia	26	0	4	0
Dizziness	20	0	15	1
Metabolism and Nutrition Disorders				
Decreased appetite	20	0	10	0
Respiratory, Thoracic and Mediastinal Disorders				
Dyspnea[è]	15	0	6	0

* Graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE), version 4.0.
† Includes abdominal pain, abdominal pain lower, abdominal pain upper, abdominal distension, abdominal discomfort, and abdominal tenderness.
‡ Includes colitis, diarrhea, and gastroenteritis.
§ Includes stomatitis, aphthous ulcer; and mouth ulceration.
¶ Includes asthenia, fatigue, lethargy, and malaise.
# Includes neutropenia, and febrile neutropenia.
Þ Includes leukopenia, and white blood cell count decreased.
ϐ Includes platelet count decreased, and thrombocytopenia.
à Includes urosepsis, urinary tract infection, urinary tract pain, and pyuria.
è Includes dyspnea, and dyspnea exertional.

In addition, the adverse reactions observed in SOLO-1 that occurred in <10% of patients receiving Lynparza were increased blood creatinine (8%), lymphopenia (6%), hypersensitivity (2%), dermatitis (1%), and increased mean cell volume (0.4%).

Table 3 Laboratory Abnormalities Reported in ≥25% of Patients in SOLO-1

Laboratory Parameter*	Lynparza tablets n†=260		Placebo n†=130	
	Grades 1-4 (%)	Grades 3-4 (%)	Grades 1-4 (%)	Grades 3-4 (%)
Decrease in hemoglobin	87	19	63	2
Increase in mean corpuscular volume	87	-	43	-
Decrease in leukocytes	70	7	52	1
Decrease in lymphocytes	67	14	29	5
Decrease in absolute neutrophil count	51	9	38	6
Decrease in platelets	35	1	20	2
Increase in serum creatinine	34	0	18	0

* Patients were allowed to enter clinical studies with laboratory values of CTCAE Grade 1.
† This number represents the safety population. The derived values in the table are based on the total number of evaluable patients for each laboratory parameter.

First-line Maintenance Treatment of HRD-positive Advanced Ovarian Cancer in Combination with Bevacizumab

PAOLA-1

The safety of Lynparza in combination with bevacizumab for the maintenance treatment of patients with advanced ovarian cancer following first-line treatment containing platinum-based chemotherapy and bevacizumab was investigated in PAOLA-1 *[see Clinical Studies (14.2)]*. This study was a placebo-controlled, double-blind study in which 802 patients received either Lynparza 300 mg BID in combination with bevacizumab (n=535) or placebo in combination with bevacizumab (n=267) until disease progression or unacceptable toxicity. The median duration of treatment with Lynparza was 17.3 months and 11 months for bevacizumab post-randomization on the Lynparza/bevacizumab arm.

Fatal adverse reactions occurred in 1 patient due to concurrent pneumonia and aplastic anemia. Serious adverse reactions occurred in 31% of patients who received Lynparza/bevacizumab. Serious adverse reactions in >5% of patients included hypertension (19%) and anemia (17%).

Dose interruptions due to an adverse reaction of any grade occurred in 54% of patients receiving Lynparza/bevacizumab and dose reductions due to an adverse reaction occurred in 41% of patients who received Lynparza/bevacizumab.

The most frequent adverse reactions leading to dose interruption in the Lynparza/bevacizumab arm were anemia (21%), nausea (7%), vomiting (3%), and fatigue (3%), and the most frequent adverse reactions leading to reduction in the Lynparza/bevacizumab arm were anemia (19%), nausea (7%), and fatigue (4%).

Discontinuation due to adverse reactions occurred in 20% of patients receiving Lynparza/bevacizumab. Specific adverse reactions that most frequently led to discontinuation in patients treated with Lynparza/bevacizumab were anemia (4%) and nausea (3%).

Tables 4 and 5 summarize adverse reactions and laboratory abnormalities in PAOLA-1, respectively.

Table 4 Adverse Reactions[*] Occurring in ≥10% of Patients Treated with Lynparza/bevacizumab in PAOLA-1 and at ≥5% Frequency Compared to the Placebo/bevacizumab Arm

Adverse Reactions	Lynparza/bevacizumab n=535		Placebo/bevacizumab n=267	
	Grades 1-4 (%)	Grades 3-4 (%)	Grades 1-4 (%)	Grades 3-4 (%)
General Disorders and Administration Site Conditions				
Fatigue (including asthenia)[†]	53	5	32	1.5
Gastrointestinal Disorders				
Nausea	53	2.4	22	0.7
Vomiting	22	1.7	11	1.9
Blood and Lymphatic Disorders				
Anemia[‡]	41	17	10	0.4
Lymphopenia[§]	24	7	9	1.1
Leukopenia[‖]	18	1.9	10	1.5

* Graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE), version 4.0.

† Includes asthenia, and fatigue.

‡ Includes anemia, anemia macrocytic, erythropenia, haematocrit decreased, haemoglobin decreased, normochromic anemia, normochromic normocytic anemia, normocytic anemia, and red blood cell count decreased. Includes B-lymphocyte count decreased, lymphocyte count decreased, lymphopenia, and T-lymphocyte count decreased.

§ Includes B-lymphocyte count decreased, lymphocyte count decreased, lymphopenia, and T-lymphocyte count decreased.

‖ Includes leukopenia, and white blood cell count decreased.

The most common adverse reactions (≥ 10%) for patients receiving Lynparza/bevacizumab irrespective of the frequency compared with the placebo/bevacizumab arm were nausea (53%), fatigue (including asthenia) (53%), anemia (41%), lymphopenia, vomiting (22%), diarrhea (18%), neutropenia (18%), leukopenia (18%), urinary tract infection (15%), and headache (14%).

The adverse reactions that occurred in <10% of patients receiving Lynparza/bevacizumab were dysgeusia (8%), dyspnea (8%), stomatitis (5%), dyspepsia (4.3%), erythema (3%), dizziness (2.6%), and hypersensitivity (1.7%).

In addition, venous thromboembolic events occurred more commonly in patients receiving Lynparza/bevacizumab (5%) than in those receiving placebo/bevacizumab (1.9%).

Table 5 Laboratory Abnormalities Reported in ≥25% of Patients in PAOLA-1[*]

Laboratory Parameter[†]	Lynparza/bevacizumab n[†]=535		Placebo/bevacizumab n[‡]=267	
	Grades 1-4 (%)	Grades 3-4 (%)	Grades 1-4 (%)	Grades 3-4 (%)
Decrease in hemoglobin	79	13	55	0.4
Decrease in lymphocytes	63	10	42	3.0
Increase in serum creatinine	61	0.4	36	0.4
Decrease in leukocytes	59	3.4	45	2.2
Decrease in absolute neutrophil count	35	7	30	3.7
Decrease in platelets	35	2.4	28	0.4

* Reported within 30 days of the last dose.

† Patients were allowed to enter clinical studies with laboratory values of CTCAE Grade 1.

‡ This number represents the safety population. The derived values in the table are based on the total number of evaluable patients for each laboratory parameter.

Maintenance Treatment of Recurrent Ovarian Cancer

SOLO-2

The safety of Lynparza for the maintenance treatment of patients with platinum sensitive g*BRCA*m ovarian cancer was investigated in SOLO-2 *[see Clinical Studies (14.3)]*. Patients received Lynparza tablets 300 mg orally twice daily (n=195) or placebo (n=99) until disease progression or unacceptable toxicity. The median duration of study treatment was 19.4 months for patients who received Lynparza and 5.6 months for patients who received placebo.

Among patients who received Lynparza, dose interruptions due to an adverse reaction of any grade occurred in 45% and dose reductions due to an adverse reaction occurred in 27%. The most frequent adverse reactions leading to dose interruption or reduction of Lynparza were anemia (22%), neutropenia (9%), and fatigue/asthenia (8%). Discontinuation due to an adverse reaction occurred in 11% of patients receiving Lynparza.

Tables 6 and 7 summarize adverse reactions and laboratory abnormalities in SOLO-2.

Table 6 Adverse Reactions* in SOLO-2 (≥20% of Patients Who Received Lynparza)

Adverse Reaction	Lynparza tablets n=195		Placebo n=99	
	Grades 1-4 (%)	Grades 3-4 (%)	Grades 1-4 (%)	Grades 3-4 (%)
Gastrointestinal Disorders				
Nausea	76	3	33	0
Vomiting	37	3	19	1
Diarrhea	33	2	22	0
Stomatitis†	20	1	16	0
General Disorders and Administration Site Conditions				
Fatigue including asthenia	66	4	39	2
Blood and Lymphatic Disorders				
Anemia‡	44	20	9	2
Infections and Infestations				
Nasopharyngitis/URI/sinusitis/ rhinitis/influenza	36	0	29	0
Musculoskeletal and Connective Tissue Disorders				
Arthralgia/myalgia	30	0	28	0
Nervous System Disorders				
Dysgeusia	27	0	7	0
Headache	26	1	14	0
Metabolism and Nutrition Disorders				
Decreased appetite	22	0	11	0

* Graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE), version 4.0.

† Represents grouped term consisting of abscess oral, aphthous ulcer, gingival abscess, gingival disorder, gingival pain, gingivitis, mouth ulceration, mucosal infection, mucosal inflammation, oral candidiasis, oral discomfort, oral herpes, oral infection, oral mucosal erythema, oral pain, oropharyngeal discomfort, and oropharyngeal pain.

‡ Represents grouped term consisting of anemia, hematocrit decreased, hemoglobin decreased, iron deficiency, mean cell volume increased and red blood cell count decreased.

In addition, the adverse reactions observed in SOLO-2 that occurred in <20% of patients receiving Lynparza were neutropenia (19%), cough (18%), leukopenia (16%), hypomagnesemia (14%), thrombocytopenia (14%), dizziness (13%), dyspepsia (11%), increased creatinine (11%), edema (8%), rash (6%), and lymphopenia (1%).

Table 7 Laboratory Abnormalities Reported in ≥25% of Patients in SOLO-2

Laboratory Parameter*	Lynparza tablets n†=195		Placebo n†=99	
	Grades 1-4 (%)	Grades 3-4 (%)	Grades 1-4 (%)	Grades 3-4 (%)
Increase in mean corpuscular volume‡	89	-	52	-
Decrease in hemoglobin	83	17	69	0
Decrease in leukocytes	69	5	48	1
Decrease in lymphocytes	67	11	37	1
Decrease in absolute neutrophil count	51	7	34	3
Increase in serum creatinine	44	0	29	0
Decrease in platelets	42	2	22	1

* Patients were allowed to enter clinical studies with laboratory values of CTCAE Grade 1.
† This number represents the safety population. The derived values in the table are based on the total number of evaluable patients for each laboratory parameter.
‡ Represents the proportion of subjects whose mean corpuscular volume was > upper limit of normal (ULN).

Study 19

The safety of Lynparza as maintenance monotherapy was evaluated in patients with platinum sensitive ovarian cancer who had received 2 or more previous platinum containing regimens in Study 19 *[see Clinical Studies (14.3)]*. Patients received Lynparza capsules 400 mg orally twice daily (n=136) or placebo (n=128). At the time of final analysis, the median duration of exposure was 8.7 months in patients who received Lynparza and 4.6 months in patients who received placebo.

Adverse reactions led to dose interruptions in 35% of patients receiving Lynparza; dose reductions in 26% and discontinuation in 6% of patients receiving Lynparza.

Tables 8 and 9 summarize adverse reactions and laboratory abnormalities in Study 19.

Table 8 Adverse Reactions* in Study 19 (≥20% of Patients Who Received Lynparza)

Adverse Reaction	Lynparza capsules n=136		Placebo n=128	
	Grades 1-4 (%)	Grades 3-4 (%)	Grades 1-4 (%)	Grades 3-4 (%)
Gastrointestinal Disorders				
Nausea	71	2	36	0
Vomiting	35	2	14	1
Diarrhea	28	2	25	2
Constipation	22	1	12	0
Dyspepsia	20	0	9	0
General Disorders and Administration Site Conditions				
Fatigue (including asthenia)	63	9	46	3
Blood and Lymphatic Disorders				
Anemia†	23	7	7	1
Infections and Infestations				

Respiratory tract infection	22	2	11	0
Metabolism and Nutrition Disorders				
Decreased appetite	21	0	13	0
Nervous System Disorders				
Headache	21	0	13	1

* Graded according to NCI CTCAE v4.0.
† Represents grouped terms of related terms that reflect the medical concept of the adverse reaction.

In addition, the adverse reactions in Study 19 that occurred in <20% of patients receiving Lynparza were dysgeusia (16%), dizziness (15%), dyspnea (13%), pyrexia (10%), stomatitis (9%), edema (9%), increase in creatinine (7%), neutropenia (5%), thrombocytopenia (4%), leukopenia (2%), and lymphopenia (1%).

Table 9 Laboratory Abnormalities Reported in ≥25% of Patients in Study 19

Laboratory Parameter*	**Lynparza capsules n†=136**		**Placebo n†=129**	
	Grades 1-4 (%)	**Grades 3-4 (%)**	**Grades 1-4 (%)**	**Grades 3-4 (%)**
Decrease in hemoglobin	82	8	58	1
Increase in mean corpuscular volume‡	82	-	51	-
Decrease in leukocytes	58	4	37	2
Decrease in lymphocytes	52	10	32	3
Decrease in absolute neutrophil count	47	7	40	2
Increase in serum creatinine	45	0	14	0
Decrease in platelets	36	4	18	0

* Patients were allowed to enter clinical studies with laboratory values of CTCAE Grade 1.
† This number represents the safety population. The derived values in the table are based on the total number of evaluable patients for each laboratory parameter.
‡ Represents the proportion of subjects whose mean corpuscular volume was > ULN.

Advanced Germline *BRCA*-mutated Ovarian Cancer After 3 or More Lines of Chemotherapy

Pooled Data

The safety of Lynparza was investigated in 223 patients (pooled from 6 studies) with g*BRCA*m advanced ovarian cancer who had received 3 or more prior lines of chemotherapy *[see Clinical Studies (14.4)]*. Patients received Lynparza capsules 400 mg orally twice daily until disease progression or unacceptable tolerability. The median exposure to Lynparza in these patients was 5.2 months.

There were 8 (4%) patients with adverse reactions leading to death, two were attributed to acute leukemia, and one each was attributed to COPD, cerebrovascular accident, intestinal perforation, pulmonary embolism, sepsis, and suture rupture. Adverse reactions led to dose interruption in 40% of patients, dose reduction in 4%, and discontinuation in 7%.

Tables 10 and 11 summarize the adverse reactions and laboratory abnormalities from the pooled studies.

Table 10 Adverse Reactions Reported in Pooled Data (≥20% of Patients Who Received Lynparza)

Adverse Reaction	Lynparza capsules n=223	
	Grades 1-4 (%)	Grades 3-4 (%)
General Disorders		
Fatigue/asthenia	66	8
Gastrointestinal Disorders		
Nausea	64	3
Vomiting	43	4
Diarrhea	31	1
Dyspepsia	25	0
Decreased appetite	22	1
Blood and Lymphatic Disorders		
Anemia	34	18
Infections and Infestations		
Nasopharyngitis/URI	26	0
Musculoskeletal and Connective Tissue Disorders		
Arthralgia/musculoskeletal pain	21	0
Myalgia	22	0

Table 11 Laboratory Abnormalities Reported in ≥25% of Patients in Pooled Data

Laboratory Parameter*	Lynparza capsules n†=223	
	Grades 1-4 (%)	Grades 3-4 (%)
Decrease in hemoglobin	90	15
Mean corpuscular volume elevation	57	-
Decrease in lymphocytes	56	17
Decrease in platelets	30	3
Increase in creatinine	30	2
Decrease in absolute neutrophil count	25	7

* Patients were allowed to enter clinical studies with laboratory values of CTCAE Grade 1.

† This number represents the safety population. The derived values in the table are based on the total number of evaluable patients for each laboratory parameter.

The following adverse reactions and laboratory abnormalities have been identified in ≥10 to <20% of the 223 patients receiving Lynparza and not included in the table: cough (16%), constipation (16%), dysgeusia (16%), headache (15%), peripheral edema (14%), back pain (14%), urinary tract infection (14%), dyspnea (13%), and dizziness (11%).

The following adverse reactions and laboratory abnormalities have been identified in <10% of the 223 patients receiving Lynparza and not included in the table: leukopenia (9%), pyrexia (8%), peripheral neuropathy (5%), hypomagnesemia (5%), rash (5%), stomatitis (4%), and venous thrombosis (including pulmonary embolism) (1%).

Germline *BRCA*-mutated HER2-negative Metastatic Breast Cancer

OlympiAD

The safety of Lynparza was evaluated in g*BRCA*m patients with HER2-negative metastatic breast cancer who had previously received up to two lines of chemotherapy for the treatment of metastatic disease in OlympiAD *[see Clinical Studies (14.5)]*. Patients received either Lynparza tablets 300 mg orally twice daily (n=205) or a chemotherapy (capecitabine, eribulin, or vinorelbine) of the healthcare provider's choice (n=91) until disease progression or unacceptable toxicity. The median duration of study treatment was 8.2 months in patients who received Lynparza and 3.4 months in patients who received chemotherapy.

Among patients who received Lynparza, dose interruptions due to an adverse reaction of any grade occurred in 35% and dose reductions due to an adverse reaction occurred in 25%. Discontinuation due to an adverse reaction occurred in 5% of patients receiving Lynparza.

Tables 12 and 13 summarize the adverse reactions and laboratory abnormalities in OlympiAD.

Table 12 Adverse Reactions* in OlympiAD (≥20% of Patients Who Received Lynparza)

Adverse Reaction	Lynparza tablets n=205		Chemotherapy n=91	
	Grades 1-4 (%)	Grades 3-4 (%)	Grades 1-4 (%)	Grades 3-4 (%)
Gastrointestinal Disorders				
Nausea	58	0	35	1
Vomiting	30	0	15	1
Diarrhea	21	1	22	0
Blood and Lymphatic Disorders				
Anemia†	40	16	26	4
Neutropenia‡	27	9	50	26
Leukopenia§	25	5	31	13
General Disorders and Administration Site Conditions				
Fatigue (including asthenia)	37	4	36	1
Infections and Infestations				
Respiratory tract infection‖	27	1	22	0
Nervous System Disorders				
Headache	20	1	15	2

* Graded according to NCI CTCAE v4.0.
† Represents grouped terms consisting of anemia (anemia erythropenia, hematocrit decreased, hemoglobin decreased and red blood cell count decreased).
‡Represents grouped terms consisting of neutropenia (febrile neutropenia, granulocyte count decreased, granulocytopenia, neutropenia, neutropenic infection, neutropenic sepsis, and neutrophil count decreased).
§ Represents grouped terms consisting of leukopenia (leukopenia and white blood cell count decreased).
‖ Represents grouped terms consisting of bronchitis, influenza, lower respiratory tract infection, nasopharyngitis, pharyngitis, respiratory tract infection, rhinitis, sinusitis, upper respiratory tract infection, and upper respiratory tract infection bacterial.

In addition, adverse reactions in OlympiAD that occurred in <20% of patients receiving Lynparza were cough (18%), decreased appetite (16%), thrombocytopenia (11%), dysgeusia (9%), lymphopenia (8%),

dyspepsia (8%), dizziness (7%), stomatitis (7%), upper abdominal pain (7%), rash (5%), increase in serum creatinine (3%), and dermatitis (1%).

Table 13 Laboratory Abnormalities Reported in ≥25% of Patients in OlympiAD

Laboratory Parameter*	Lynparza tablets n†= 205		Chemotherapy n†= 91	
	Grades 1-4 (%)	Grades 3-4 (%)	Grades 1-4 (%)	Grades 3-4 (%)
Decrease in hemoglobin	82	17	66	3
Decrease in lymphocytes	73	21	63	3
Decrease in leukocytes	71	8	70	23
Increase in mean corpuscular volume‡	71	-	33	-
Decrease in absolute neutrophil count	46	11	65	38
Decrease in platelets	33	3	28	0

* Patients were allowed to enter clinical studies with laboratory values of CTCAE Grade 1.
† This number represents the safety population. The derived values in the table are based on the total number of evaluable patients for each laboratory parameter.
‡ Represents the proportion of subjects whose mean corpuscular volume was > ULN.

First-line Maintenance Treatment of Germline *BRCA*-mutated Metastatic Pancreatic Adenocarcinoma

POLO

The safety of Lynparza as maintenance treatment of germline *BRCA*-mutated metastatic pancreatic adenocarcinoma following first-line treatment with platinum-based chemotherapy was evaluated in POLO *[see Clinical Studies (14.6)]*. Patients received Lynparza tablets 300 mg orally twice daily (n=90) or placebo (n=61) until disease progression or unacceptable toxicity. Among patients receiving Lynparza, 34% were exposed for 6 months or longer and 25% were exposed for greater than one year.

Among patients who received Lynparza, dosage interruptions due to an adverse reaction of any grade occurred in 35% and dosage reductions due to an adverse reaction occurred in 17%. The most frequent adverse reactions leading to dosage interruption or reduction in patients who received Lynparza were anemia (11%), vomiting (5%), abdominal pain (4%), asthenia (3%), and fatigue (2%). Discontinuation due to adverse reactions occurred in 6% of patients receiving Lynparza. The most frequent adverse reaction that led to discontinuation of Lynparza was fatigue (2.2%).

Tables 14 and 15 summarize the adverse reactions and laboratory abnormalities in patients in POLO.

Table 14 Adverse Reactions[*] in POLO (Occurring in ≥10% of Patients who Received Lynparza)

Adverse Reaction	Lynparza tablets (n=91)[†]		Placebo (n=60)[†]	
	All Grades (%)	Grades 3 – 4 (%)	All Grades (%)	Grades 3 – 4 (%)
General Disorders and Administration Site Conditions				
Fatigue[‡]	60	5	35	2
Gastrointestinal Disorders				
Nausea	45	0	23	2
Abdominal pain[^]	34	2	37	5
Diarrhea	29	0	15	0
Constipation	23	0	10	0
Vomiting	20	1	15	2
Stomatitis[§]	10	0	5	0
Blood and Lymphatic System Disorders				
Anemia	27	11	17	3
Thrombocytopenia[‖]	14	3	7	0
Neutropenia[¶]	12	4	8	3
Metabolism and Nutrition Disorders				
Decreased appetite	25	3	7	0
Musculoskeletal and Connective Tissue Disorders				
Back pain	19	0	17	2
Arthralgia	15	1	10	0
Skin and Subcutaneous Tissue Disorder				
Rash[#]	15	0	5	0
Respiratory, Thoracic and Mediastinal Disorders				
Dyspnea[**]	13	0	5	2
Infections and Infestations				
Nasopharyngitis	12	0	3	0
Nervous System Disorders				
Dysgeusia	11	0	5	0

* Graded according to NCI CTCAE, version 4.0

† This number represents the safety population. The derived values in the table are based on the total number of evaluable patients for each laboratory parameter.

‡ Includes asthenia and fatigue

^ Includes abdominal pain, abdominal pain upper, abdominal pain lower

§ Includes stomatitis and mouth ulceration

‖ Includes platelets count decreased and thrombocytopenia

¶ Includes neutropenia, febrile neutropenia and neutrophil count decreased

Includes rash erythematous, rash macular and rash maculo-papular

**Includes dyspnea and dyspnea exertional

In addition, the adverse reactions observed in POLO that occurred in <10% of patients receiving Lynparza were cough (9%), abdominal pain upper (7%), blood creatinine increased (7%), dizziness (7%), headache (7%), dyspepsia (5%), leukopenia (5%), hypersensitivity (2%), and lymphopenia (2%).

Table 15 Laboratory Abnormalities Reported in ≥25% of Patients in POLO

Laboratory Parameter*	Lynparza tablets n†=91		Placebo n†=60	
	Grades 1-4 (%)	Grades 3-4 (%)	Grades 1-4 (%)	Grades 3-4 (%)
Increase in serum creatinine	99	2	85	0
Decrease in hemoglobin	86	11	65	0
Increase in mean corpuscular volume‡	71	-	30	-
Decrease in lymphocytes	61	9	27	0
Decrease in platelets	56	2	39	0
Decrease in leukocytes	50	3	23	0
Decrease in absolute neutrophil count	25	3	10	0

* Patients were allowed to enter POLO with hemoglobin ≥9 g/dL (CTCAE Grade 2) and other laboratory values of CTCAE Grade 1.

† This number represents the safety population. The derived values in the table are based on the total number of evaluable patients for each laboratory parameter.

‡ Represents the proportion of subjects whose mean corpuscular volume was > ULN.

HRR Gene-mutated Metastatic Castration-Resistant Prostate Cancer

PROfound

The safety of Lynparza as monotherapy was evaluated in patients with mCRPC and HRR gene mutations who have progressed following prior treatment with enzalutamide or abiraterone in PROfound *[see Clinical Studies (14.7)]*. This study was a randomized, open-label, multi-center study in which 386 patients received either Lynparza tablets 300 mg orally twice daily (n=256) or investigator's choice of enzalutamide or abiraterone acetate (n=130) until disease progression or unacceptable toxicity. Among patients receiving Lynparza, 62% were exposed for 6 months or longer and 20% were exposed for greater than one year.

Fatal adverse reactions occurred in 4% of patients treated with Lynparza. These included pneumonia (1.2%), cardiopulmonary failure (0.4%), aspiration pneumonia (0.4%), intestinal diverticulum (0.4%), septic shock (0.4%), Budd-Chiari Syndrome (0.4%), sudden death (0.4%), and acute cardiac failure (0.4%).

Serious adverse reactions occurred in 36% of patients receiving Lynparza. The most frequent serious adverse reactions (≥2%) were anemia (9%), pneumonia (4%), pulmonary embolism (2%), fatigue/asthenia (2%), and urinary tract infection (2%).

Dose interruptions due to an adverse reaction of any grade occurred in 45% of patients receiving Lynparza; dose reductions due to an adverse reaction occurred in 22% of Lynparza patients. The most frequent adverse reactions leading to dose interruption of Lynparza were anemia (25%) and thrombocytopenia (6%) and the most frequent adverse reaction leading to reduction of Lynparza was anemia (16%). Discontinuation due to adverse reactions occurred in 18% of Lynparza. The adverse reaction that most frequently led to discontinuation of Lynparza was anemia (7%).

Tables 16 and 17 summarize the adverse reactions and laboratory abnormalities, respectively, in patients in PROfound.

Table 16 Adverse Reactions[*] Reported in ≥10% of Patients in PROfound

Adverse Reactions	Lynparza tablets n=256		Enzalutamide or abiraterone n=130	
	Grades 1-4 (%)	Grades 3-4 (%)	Grades 1-4 (%)	Grades 3-4 (%)
Blood and lymphatic disorders				
Anemia[†]	46	21	15	5
Thrombocytopenia[‡]	12	4	3	0
Gastrointestinal disorders				
Nausea	41	1	19	0
Diarrhea	21	1	7	0
Vomiting	18	2	12	1
General disorders and administration site conditions				
Fatigue (including asthenia)	41	3	32	5
Metabolism and nutrition disorders				
Decreased appetite	30	1	18	1
Respiratory, thoracic, and mediastinal disorders				
Cough	11	0	2	0
Dyspnea	10	2	3	0

[*] Graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE), version 4.03

[†] Includes anemia and hemoglobin decreased

[‡] Includes platelet count decreased and thrombocytopenia

In addition, adverse reactions of clinical relevance in PROfound that occurred in <10% of patients receiving Lynparza were neutropenia (9%), venous thromboembolic events (7%), dizziness (7%), dysgeusia (7%), dyspepsia (7%), headache (6%), pneumonia (5%), stomatitis (5%), rash (4%), blood creatinine increase (4%), pneumonitis (2%), upper abdominal pain (2%), and hypersensitivity (1%).

Table 17 Laboratory Abnormalities Reported in ≥25% of Patients in PROfound

Laboratory Parameter*	Lynparza tablets n†= 256		Enzalutamide or abiraterone n†=130	
	Grades 1-4 n= 247 (%)	Grades 3-4 n=247 (%)	Grades 1-4 n=124 (%)	Grades 3-4 n=124 (%)
Decrease in hemoglobin	242 (98)	33 (13)	91 (73)	5 (4)
Decrease in lymphocytes	154 (62)	57 (23)	42 (34)	16 (13)
Decrease in leukocytes	130 (53)	9 (4)	26 (21)	0
Decrease in absolute neutrophil count	83 (34)	8 (3)	11 (9)	0

* Patients were allowed to enter clinical studies with laboratory values of CTCAE Grade 1.
† This number represents the safety population. The derived values in the table are based on the total number of evaluable patients for each laboratory parameter.

6.2 Postmarketing Experience

The following adverse reactions have been identified during post approval use of Lynparza. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

Immune System Disorders: Hypersensitivity (rash/dermatitis).

7 DRUG INTERACTIONS

7.1 Use with Anticancer Agents

Clinical studies of Lynparza with other myelosuppressive anticancer agents, including DNA damaging agents, indicate a potentiation and prolongation of myelosuppressive toxicity.

7.2 Effect of Other Drugs on Lynparza

Strong and Moderate CYP3A Inhibitors

Coadministration of CYP3A inhibitors can increase olaparib concentrations, which may increase the risk for adverse reactions *[see Clinical Pharmacology (12.3)]*. Avoid coadministration of strong or moderate CYP3A inhibitors. If the strong or moderate inhibitor must be coadministered, reduce the dose of Lynparza *[see Dosage and Administration (2.4)]*.

Strong and Moderate CYP3A Inducers

Concomitant use with a strong or moderate CYP3A inducer decreased olaparib exposure, which may reduce Lynparza efficacy *[see Clinical Pharmacology (12.3)]*. Avoid coadministration of strong or moderate CYP3A inducers.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

Based on findings in animals and its mechanism of action *[see Clinical Pharmacology (12.1)]*, Lynparza can cause fetal harm when administered to a pregnant woman. There are no available data on Lynparza use in pregnant women to inform the drug-associated risk. In an animal reproduction study, the administration of olaparib to pregnant rats during the period of organogenesis caused teratogenicity and embryo-fetal toxicity at exposures below those in patients receiving the recommended human dose of 300 mg twice daily *(see Data)*. Apprise pregnant women of the potential hazard to the fetus and the potential risk for loss of the pregnancy.

The estimated background risk of major birth defects and miscarriage for the indicated population is unknown. The estimated background risk in the U.S. general population of major birth defects is 2-4%; and the risk for spontaneous abortion is approximately 15-20% in clinically recognized pregnancies.

Data

Animal Data

In a fertility and early embryonic development study in female rats, olaparib was administered orally for 14 days before mating through to Day 6 of pregnancy, which resulted in increased post-implantation loss at a dose level of 15 mg/kg/day (with maternal systemic exposures approximately 7% of the human exposure (AUC_{0-24h}) at the recommended dose).

In an embryo-fetal development study, pregnant rats received oral doses of 0.05 and 0.5 mg/kg/day olaparib during the period of organogenesis. A dose of 0.5 mg/kg/day (with maternal systemic exposures approximately 0.18% of human exposure (AUC_{0-24h}) at the recommended dose) caused embryo-fetal toxicities including increased post-implantation loss and major malformations of the eyes (anophthalmia, microphthalmia), vertebrae/ribs (extra rib or ossification center; fused or absent neural arches, ribs, and sternebrae), skull (fused exoccipital), and diaphragm (hernia). Additional abnormalities or variants included incomplete or absent ossification (vertebrae/sternebrae, ribs, limbs) and other findings in the vertebrae/sternebrae, pelvic girdle, lung, thymus, liver, ureter, and umbilical artery. Some findings noted above in the eyes, ribs, and ureter were observed at a dose of 0.05 mg/kg/day olaparib at lower incidence.

8.2 Lactation

Risk Summary

No data are available regarding the presence of olaparib in human milk, or on its effects on the breastfed infant or on milk production. Because of the potential for serious adverse reactions in the breastfed infants from Lynparza, advise a lactating woman not to breastfeed during treatment with Lynparza and for one month after receiving the last dose.

8.3 Females and Males of Reproductive Potential

Pregnancy Testing

Recommend pregnancy testing for females of reproductive potential prior to initiating treatment with Lynparza.

Contraception

Females

Lynparza can cause fetal harm when administered to a pregnant woman *[see Use in Specific Populations (8.1)]*. Advise females of reproductive potential to use effective contraception during treatment with Lynparza and for at least 6 months following the last dose.

Males

Based on findings in genetic toxicity and animal reproduction studies, advise male patients with female partners of reproductive potential or who are pregnant to use effective contraception during treatment and for 3 months following the last dose of Lynparza. Advise male patients not to donate sperm during therapy and for 3 months following the last dose of Lynparza *[see Use in Specific Populations (8.1) and Nonclinical Toxicology (13.1)]*.

8.4 Pediatric Use

Safety and effectiveness of Lynparza have not been established in pediatric patients.

8.5 Geriatric Use

Of the 2351 patients with advanced solid tumors who received Lynparza tablets 300 mg orally twice daily as monotherapy, 596 (25%) patients were aged ≥65 years, and this included 137 (6%) patients who were aged ≥75 years. Seven (0.3%) patients were aged ≥85 years *[see Adverse Reactions (6.1)]*.

Of the 535 patients with advanced solid tumors who received Lynparza tablets 300 mg orally twice daily in combination with bevacizumab, 204 (38%) patients were aged ≥65 years, and this included 31 (6%) patients who were aged ≥75 years.

No overall differences in the safety or effectiveness of Lynparza were observed between these patients and younger patients.

8.6 Renal Impairment

No dosage modification is recommended in patients with mild renal impairment (CLcr 51 to 80 mL/min estimated by Cockcroft-Gault). Reduce Lynparza dosage to 200 mg twice daily in patients with moderate renal impairment (CLcr 31 to 50 mL/min) *[see Dosage and Administration (2.5)]*. There are no data in patients with severe renal impairment or end-stage disease (CLcr ≤30 mL/min) *[see Clinical Pharmacology (12.3)]*.

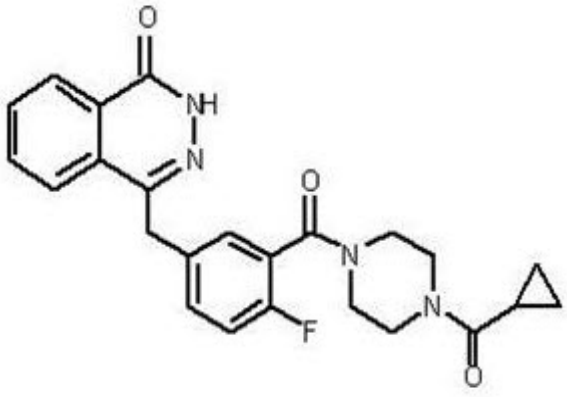
8.7 Hepatic Impairment

No adjustment to the starting dose is required in patients with mild or moderate hepatic impairment (Child-Pugh classification A and B). There are no data in patients with severe hepatic impairment (Child-Pugh classification C) *[see Clinical Pharmacology (12.3)]*.

11 DESCRIPTION

Olaparib is a poly (ADP-ribose) polymerase (PARP) inhibitor. The chemical name is 4-[(3-{[4-(cyclopropylcarbonyl)piperazin-1-yl]carbonyl}-4-fluorophenyl)methyl]phthalazin-1(2*H*)-one. The

empirical molecular formula for Lynparza is $C_{24}H_{23}FN_4O_3$ and the relative molecular mass is 434.46. It has the following chemical structure:



Olaparib is a crystalline solid, is non-chiral and shows pH-independent low solubility across the physiological pH range.

Lynparza (olaparib) tablets for oral use contain 100 mg or 150 mg of olaparib. Inactive ingredients in the tablet core are copovidone, mannitol, colloidal silicon dioxide, and sodium stearyl fumarate. The tablet coating consists of hypromellose, polyethylene glycol 400, titanium dioxide, ferric oxide yellow, and ferrosoferric oxide (150 mg tablet only).

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Olaparib is an inhibitor of poly (ADP-ribose) polymerase (PARP) enzymes, including PARP1, PARP2, and PARP3. PARP enzymes are involved in normal cellular functions, such as DNA transcription and DNA repair. Olaparib has been shown to inhibit growth of select tumor cell lines in vitro and decrease tumor growth in mouse xenograft models of human cancer, both as monotherapy or following platinum-based chemotherapy. Increased cytotoxicity and anti-tumor activity following treatment with olaparib were noted in cell lines and mouse tumor models with deficiencies in *BRCA1/2*, *ATM*, or other genes involved in the homologous recombination repair (HRR) of DNA damage and correlated with platinum response. In vitro studies have shown that olaparib-induced cytotoxicity may involve inhibition of PARP enzymatic activity and increased formation of PARP-DNA complexes, resulting in DNA damage and cancer cell death.

12.2 Pharmacodynamics

Cardiac Electrophysiology

The effect of olaparib on cardiac repolarization was assessed in 119 patients following a single dose of 300 mg and in 109 patients following multiple dosing of 300 mg twice daily. No clinically relevant effect of olaparib on QT interval was observed.

12.3 Pharmacokinetics

The area under the curve (AUC) of olaparib increases approximately proportionally following administration of single doses of 25 mg to 450 mg (0.08 to 1.5 times the recommended dose) and maximal concentrations (C_{max}) increased slightly less than proportionally for the same dose range. Olaparib showed time-dependent pharmacokinetics and an AUC mean accumulation ratio of 1.8 is observed at steady state following a dose of 300 mg twice daily.

The mean (CV%) olaparib C_{max} is 5.4 μg/mL (32%) and AUC is 39.2 μg*h/mL (44%) following a single 300 mg dose. The mean steady state olaparib C_{max} and AUC is 7.6 μg/mL (35%) and 49.2 μg*h/mL (44%), following a dose of 300 mg twice daily.

Absorption

Following oral administration of olaparib, the median time to peak plasma concentration is 1.5 hours.

Effect of Food

Co-administration of a high fat and high calorie meal (800-1000 kcal, 50% of the calorie content made up from fat) with olaparib slowed the rate (t_{max} delayed by 2.5 hours) of absorption, but did not significantly alter the extent of olaparib absorption (mean AUC increased by approximately 8%).

Distribution

The mean (± standard deviation) apparent volume of distribution of olaparib is 158 ± 136 L following a single 300 mg dose of Lynparza. The protein binding of olaparib is approximately 82% in vitro.

Elimination

The mean (± standard deviation) terminal plasma half-life of olaparib is 14.9 ± 8.2 hours and the apparent plasma clearance is 7.4 ± 3.9 L/h following a single 300 mg dose of Lynparza.

Metabolism

Olaparib is metabolized by cytochrome P450 (CYP) 3A in vitro.

Following an oral dose of radiolabeled olaparib to female patients, unchanged olaparib accounted for 70% of the circulating radioactivity in plasma. It was extensively metabolized with unchanged drug accounting for 15% and 6% of radioactivity in urine and feces, respectively. The majority of the metabolism is attributable to oxidation reactions with a number of the components produced undergoing subsequent glucuronide or sulfate conjugation.

Excretion

Following a single dose of radiolabeled olaparib, 86% of the dosed radioactivity was recovered within a 7-day collection period, 44% via the urine and 42% via the feces. The majority of the material was excreted as metabolites.

Specific Populations

Patients with Renal Impairment

In a renal impairment trial, the mean AUC increased by 24% and C_{max} by 15%, when olaparib was dosed in patients with mild renal impairment (CLcr=51-80 mL/min defined by the Cockcroft-Gault equation; n=13) and by 44% and 26%, respectively, when olaparib was dosed in patients with moderate renal impairment (CLcr=31-50 mL/min; n=13), compared to those with normal renal function (CLcr ≥81 mL/min; n=12). There was no evidence of a relationship between the extent of plasma protein binding of olaparib and creatinine clearance. There are no data in patients with severe renal impairment or end-stage renal disease (CLcr ≤30 mL/min).

Patients with Hepatic Impairment

In a hepatic impairment trial, the mean AUC increased by 15% and the mean C_{max} increased by 13% when olaparib was dosed in patients with mild hepatic impairment (Child-Pugh classification A; n=10) and the mean AUC increased by 8% and the mean C_{max} decreased by 13% when olaparib was dosed in patients with moderate hepatic impairment (Child-Pugh classification B; n=8), compared to patients with normal hepatic function (n=13). Hepatic impairment has no effect on the protein binding of olaparib and, therefore, total plasma exposure was representative of free drug. There are no data in patients with severe hepatic impairment (Child-Pugh classification C).

Drug Interaction Studies

Clinical Studies

CYP3A Inhibitors: Concomitant use of itraconazole (strong CYP3A inhibitor) increased olaparib C_{max} by 42% and AUC by 170%. Concomitant use of fluconazole (moderate CYP3A inhibitor) is predicted to increase olaparib C_{max} by 14% and AUC by 121%.

CYP3A Inducers: Concomitant use of rifampicin (strong CYP3A inducer) decreased olaparib C_{max} by 71% and AUC by 87%. Concomitant use of efavirenz (moderate CYP3A inducer) is predicted to decrease olaparib C_{max} by 31% and AUC by 60%.

In vitro Studies

CYP Enzymes: Olaparib is both an inhibitor and inducer of CYP3A and an inducer of CYP2B6. Olaparib is predicted to be a weak CYP3A inhibitor in humans.

UGT Enzymes: Olaparib is an inhibitor of UGT1A1.

Transporters: Olaparib is an inhibitor of BCRP, OATP1B1, OCT1, OCT2, OAT3, MATE1, and MATE2K. Olaparib is a substrate and inhibitor of the efflux transporter P-gp. The potential for olaparib to induce P-gp has not been evaluated.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenicity studies have not been conducted with olaparib.

Olaparib was clastogenic in an in vitro chromosomal aberration assay in mammalian Chinese hamster ovary (CHO) cells and in an in vivo rat bone marrow micronucleus assay. This clastogenicity is consistent with genomic instability resulting from the primary pharmacology of olaparib and indicates potential for genotoxicity in humans. Olaparib was not mutagenic in a bacterial reverse mutation (Ames) test.

In a fertility study, female rats received oral olaparib at doses of 0.05, 0.5, and 15 mg/kg/day for at least 14 days before mating through the first week of pregnancy. There were no adverse effects on mating and fertility rates at doses up to 15 mg/kg/day (maternal systemic exposures approximately 7% of the human exposure ($AUC_{0\text{-}24h}$) at the recommended dose).

In a male fertility study, olaparib had no effect on mating and fertility in rats at oral doses up to 40 mg/kg/day following at least 70 days of olaparib treatment (with systemic exposures of approximately 5% of the human exposure ($AUC_{0\text{-}24h}$) at the recommended dose).

14 CLINICAL STUDIES

14.1 First-Line Maintenance Treatment of *BRCA*-mutated Advanced Ovarian Cancer

The efficacy of Lynparza was evaluated in SOLO-1 (NCT01844986), a randomized (2:1), double-blind, placebo-controlled, multi-center trial in patients with *BRCA*-mutated advanced ovarian, fallopian tube, or primary peritoneal cancer following first-line platinum-based chemotherapy. Patients were randomized to receive Lynparza tablets 300 mg orally twice daily or placebo. Treatment was continued for up to 2 years or until disease progression or unacceptable toxicity; however, patients with evidence of disease at 2 years, who in the opinion of the treating healthcare provider could derive further benefit from continuous treatment, could be treated beyond 2 years. Randomization was stratified by response to first-line platinum-based chemotherapy (complete or partial response). The major efficacy outcome was investigator-assessed progression-free survival (PFS) evaluated according to Response Evaluation Criteria in Solid Tumors (RECIST), version 1.1.

A total of 391 patients were randomized, 260 to Lynparza and 131 to placebo. The median age of patients treated with Lynparza was 53 years (range: 29 to 82) and 53 years (range: 31 to 84) among patients on placebo. The ECOG performance status (PS) was 0 in 77% of patients receiving Lynparza and 80% of patients receiving placebo. Of all patients, 82% were White, 36% were enrolled in the U.S. or Canada, and 82% were in complete response to their most recent platinum-based regimen. The majority of patients (n=389) had germline *BRCA* mutation (g*BRCA*m), and 2 patients had somatic *BRCA*m (s*BRCA*m).

Of the 391 patients randomized in SOLO-1, 386 were retrospectively or prospectively tested with a Myriad BRACAnalysis test and 383 patients were confirmed to have deleterious or suspected deleterious

g*BRCA*m status; 253 were randomized to the Lynparza arm and 130 to the placebo arm. Two out of 391 patients randomized in SOLO-1 were confirmed to have s*BRCA*m based on an investigational Foundation Medicine tissue test.

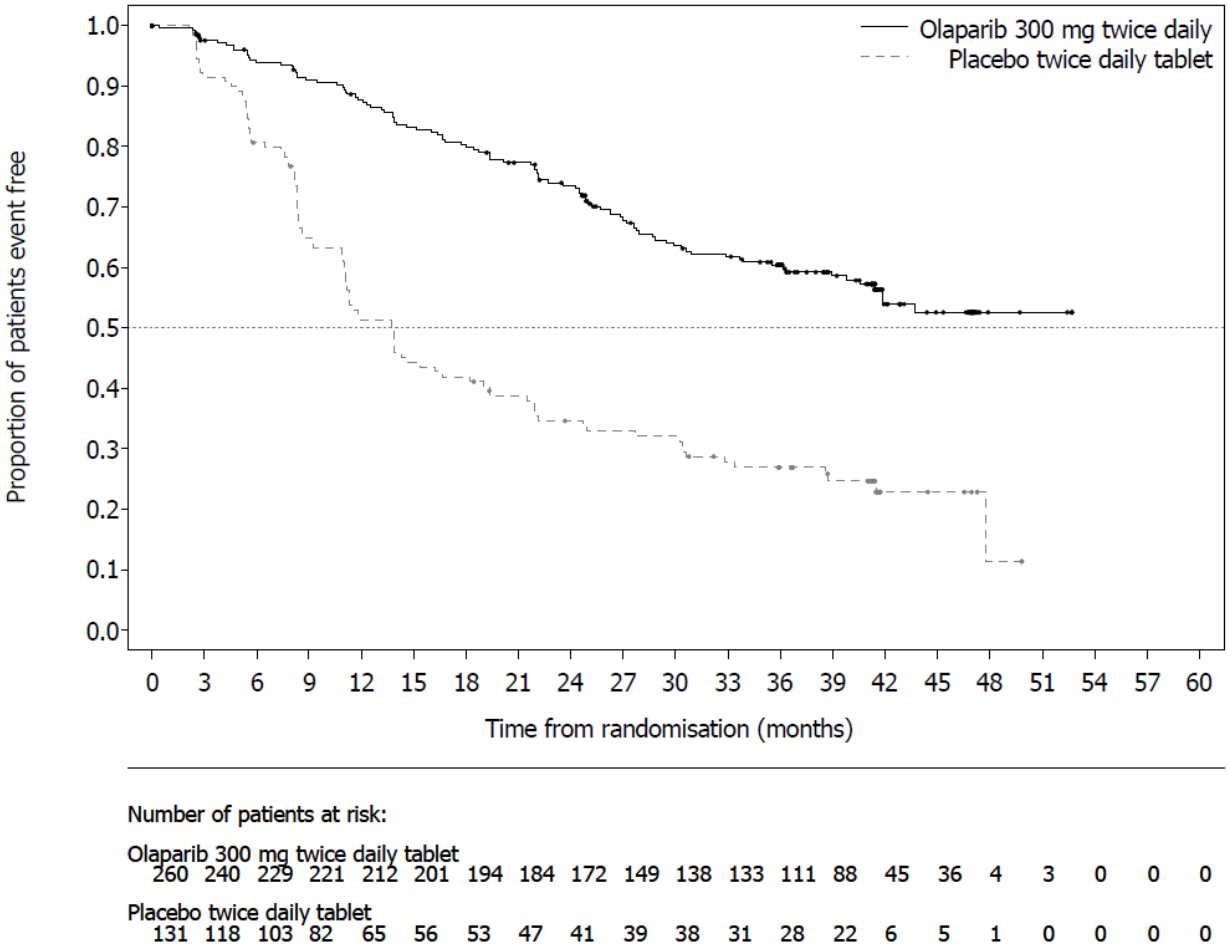
SOLO-1 demonstrated a statistically significant improvement in investigator-assessed PFS for Lynparza compared to placebo. Results from a blinded independent review were consistent. At the time of the analysis of PFS, overall survival (OS) data were not mature (21% of patients had died). Efficacy results are presented in Table 18 and Figure 1.

Table 18 Efficacy Results – SOLO-1 (Investigator Assessment)

	Lynparza tablets (n=260)	**Placebo (n=131)**
Progression-Free Survival*		
Number of events (%)	102 (39%)	96 (73%)
Median, months	NR	13.8
Hazard ratio† (95% CI)	0.30 (0.23, 0.41)	
p-value‡	<0.0001	

* Median follow up of 41 months in both treatment arms.
† A value <1 favors olaparib. Hazard ratio from a Cox proportional hazards model including response to previous platinum chemotherapy (complete response versus partial response) as a covariate.
‡ The p-value is derived from a stratified log-rank test.
NR not reached; CI Confidence Interval.

Figure 1 Kaplan-Meier Curves of Investigator-Assessed Progression-Free Survival - SOLO-1



14.2 First-line Maintenance Treatment of HRD-positive Advanced Ovarian Cancer in Combination with Bevacizumab

PAOLA-1

PAOLA-1 (NCT02477644) was a randomized, double-blind, placebo-controlled, multi-center trial that compared the efficacy of Lynparza in combination with bevacizumab versus placebo/bevacizumab for the maintenance treatment of advanced high-grade epithelial ovarian cancer, fallopian tube or primary peritoneal cancer following first-line platinum-based chemotherapy and bevacizumab. Randomization was stratified by first-line treatment outcome (timing and outcome of cytoreductive surgery and response to platinum-based chemotherapy) and t*BRCAm* status, determined by prospective local testing. All available clinical samples were retrospectively tested with Myriad myChoice® CDx. Patients were required to have no evidence of disease (NED) due to complete surgical resection, or who were in complete response (CR), or partial response (PR) following completion of first-line platinum-containing chemotherapy and bevacizumab. Patients were randomized (2:1) to receive Lynparza tablets 300 mg orally twice daily in combination with bevacizumab (n=537) 15 mg/kg every three weeks or

placebo/bevacizumab (n=269) Patients continued bevacizumab in the maintenance setting and started treatment with Lynparza after a minimum of 3 weeks and up to a maximum of 9 weeks following completion of their last dose of chemotherapy. Lynparza treatment was continued for up to 2 years or until progression of the underlying disease or unacceptable toxicity. Patients who in the opinion of the treating physician could derive further benefit from continuous treatment could be treated beyond 2 years. Treatment with bevacizumab was for a total of up to 15 months, including the period given with chemotherapy and given as maintenance.

The major efficacy outcome measure was investigator-assessed PFS evaluated according to RECIST, version 1.1. An additional efficacy endpoint was overall survival (OS).

The median age of patients in both arms was 61 years overall (range 26 to 87). Ovarian cancer was the primary tumor type in 86% of patients in both arms. Ninety six percent (96%) were serous histological type. The ECOG performance score was 0 in 70% of patients and 1 in 28% of patients, overall. All patients had received first-line platinum-based therapy and bevacizumab. First-line treatment outcomes at screening indicated that patients had no evidence of disease with complete macroscopic resection at initial debulking surgery (32%, both arms), no evidence of disease/ CR with complete macroscopic resection at interval debulking surgery (31%, both arms), no evidence of disease/ CR in patients who had either incomplete resection (at initial or interval debulking surgery) or no debulking surgery (15%, both arms) and patients with a partial response (22%, both arms). Thirty percent (30%) of patients in both arms had a deleterious mutation. Patients were not restricted by the surgical outcome with 65% having complete cytoreduction at initial or interval debulking surgery and 35% having residual macroscopic disease. Demographics and baseline disease characteristics were balanced and comparable between the study and placebo arms in the Intention to Treat (ITT) population and also in the HRD-positive subgroup.

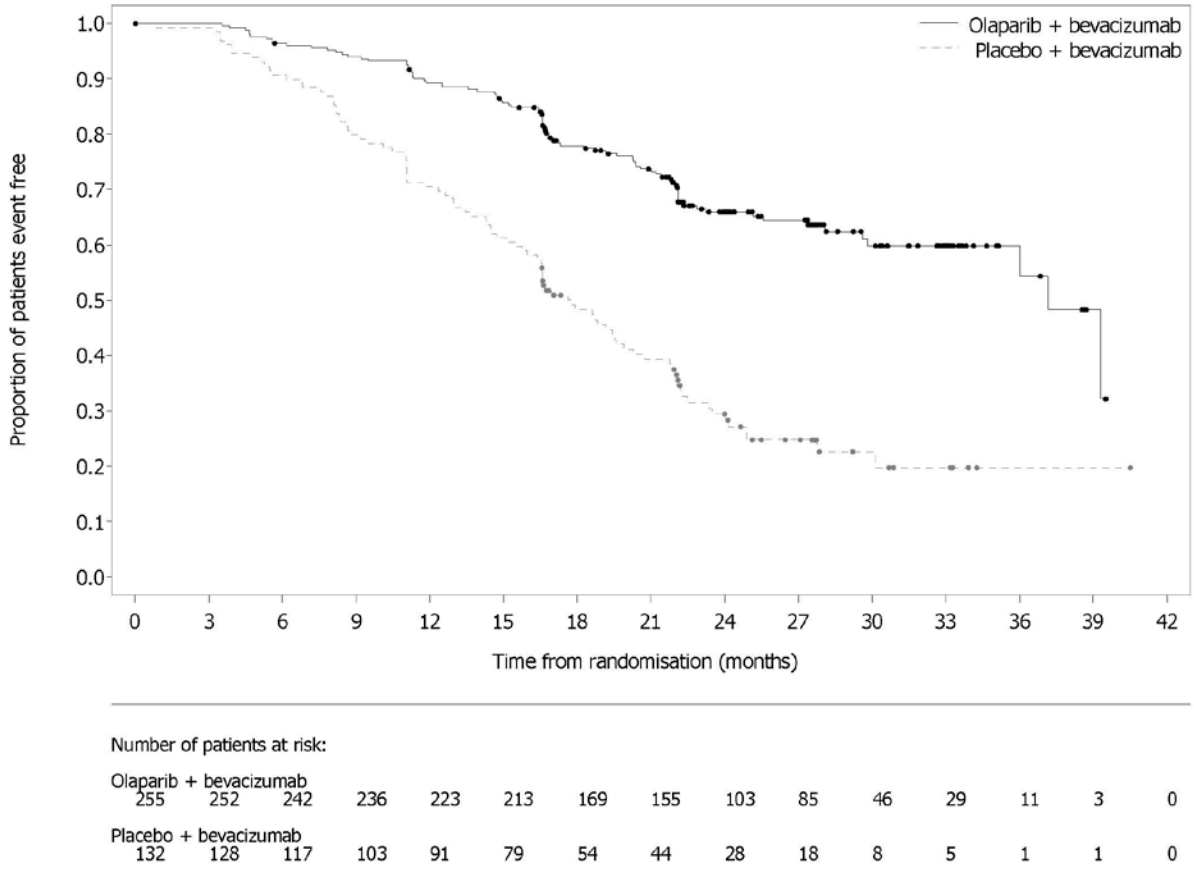
Efficacy results from a biomarker subgroup analysis of 387 patients with HRD-positive tumors, identified post-randomization using the Myriad myChoice® HRD Plus tumor test, who received Lynparza/bevacizumab (n=255) or placebo/bevacizumab (n=132), are summarized in Table 19 and Figure 2. Results from a blinded independent review of PFS were consistent. Overall survival data in this subpopulation were immature with 16% deaths.

Table 19 Efficacy Results – PAOLA-1 (HRD-positive status*, Investigator Assessment)

	Lynparza/bevacizumab (n=255)	**Placebo/bevacizumab (n=132)**
Progression-Free Survival		
Number of events (%)	87 (34%)	92 (70%)
Median, months	37.2	17.7
Hazard ratio[a] (95% CI)	0.33 (0.25, 0.45)	

* Median follow-up of 27.4 months in Lynparza/bevacizumab arm and 27.5 months in placebo/bevacizumab arm.
[a] The analysis was performed using an unstratified Cox proportional hazards model.
CI Confidence interval

Figure 2 Kaplan-Meier Curves of Investigator-Assessed Progression-Free Survival – PAOLA-1 (HRD-positive status)



14.3 Maintenance Treatment of Recurrent Ovarian Cancer

The efficacy of Lynparza was investigated in two randomized, placebo-controlled, double-blind, multi-center studies in patients with recurrent ovarian cancers who were in response to platinum-based therapy.

SOLO-2

The efficacy of Lynparza was evaluated in SOLO-2 (NCT01874353), a randomized (2:1) double-blind, placebo-controlled trial in patients with g*BRCA*m ovarian, fallopian tube, or primary peritoneal cancer. Patients were randomized to Lynparza tablets 300 mg orally twice daily or placebo until unacceptable toxicity or progressive disease. Randomization was stratified by response to last platinum chemotherapy (complete versus partial) and time to disease progression in the penultimate platinum-based chemotherapy prior to enrollment (6-12 months versus >12 months). All patients had received at least two prior platinum-containing regimens and were in response (complete or partial) to their most recent platinum-

based regimen. The major efficacy outcome measure was investigator-assessed PFS evaluated according to RECIST, version 1.1. An additional efficacy outcome measure was OS.

A total of 295 patients were randomized, 196 to Lynparza and 99 to placebo. The median age of patients treated with Lynparza was 56 years (range: 28 to 83) and 56 years (range: 39 to 78) among patients treated with placebo. The ECOG PS was 0 in 83% of patients receiving Lynparza and 78% of patients receiving placebo. Of all patients, 89% were White, 17% were enrolled in the U.S. or Canada, 47% were in complete response to their most recent platinum-based regimen, and 40% had a progression-free interval of 6-12 months since their penultimate platinum regimen. Prior bevacizumab therapy was reported for 17% of those treated with Lynparza and 20% of those receiving placebo. Approximately 44% of patients on the Lynparza arm and 37% on placebo had received three or more lines of platinum-based treatment.

All patients had a deleterious or suspected deleterious germline *BRCA* mutation as detected either by a local test (n=236) or central Myriad CLIA test (n=59), subsequently confirmed by BRACAnalysis CDx® (n=286).

SOLO-2 demonstrated a statistically significant improvement in investigator-assessed PFS in patients randomized to Lynparza as compared with placebo. Results from a blinded independent review were consistent. At the time of the analysis of PFS, OS data were not mature with 24% of events. Efficacy results are presented in Table 20 and Figure 3.

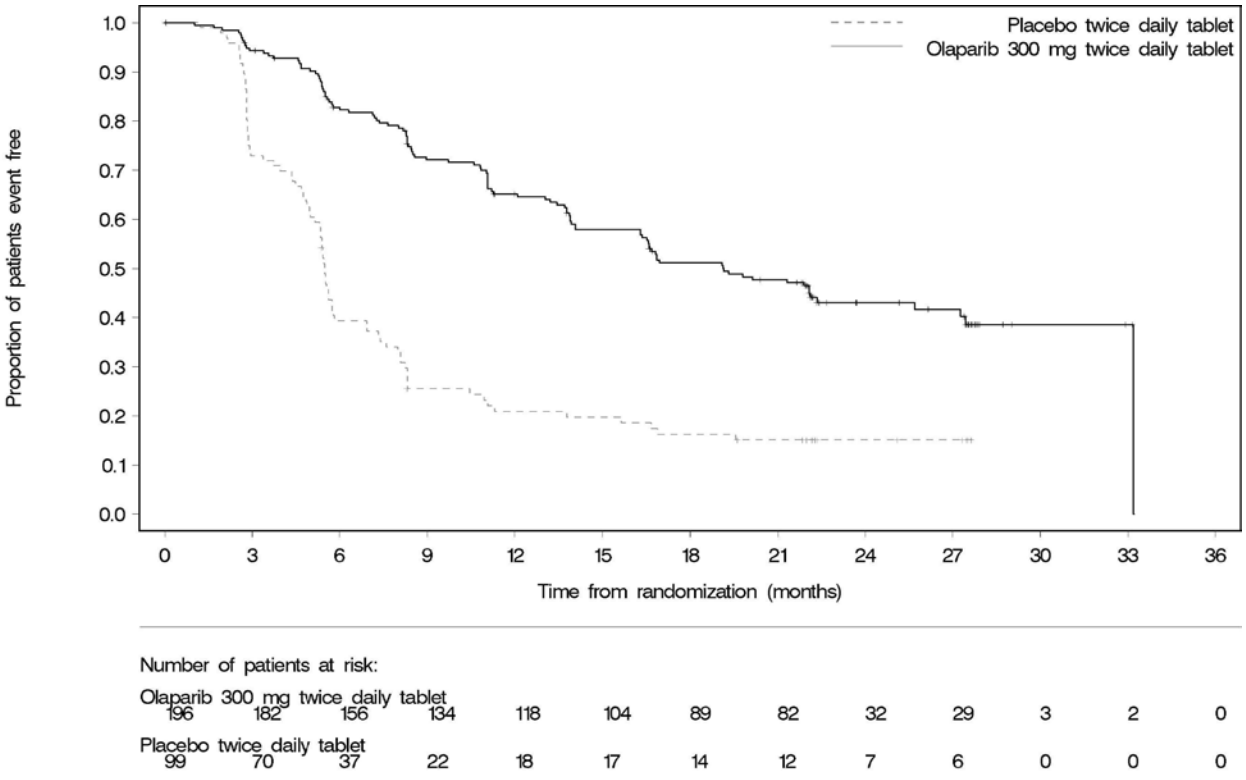
Table 20 Efficacy Results – SOLO-2 (Investigator Assessment)

	Lynparza tablets (n=196)	**Placebo (n=99)**
Progression-Free Survival		
Number of events (%)	107 (54.6%)	80 (80.8%)
Median, months	19.1	5.5
Hazard ratio* (95% CI)	0.30 (0.22, 0.41)	
p-value†	<0.0001	

* Hazard ratio from a Cox proportional hazards model including response to last platinum chemotherapy (complete response versus partial response) and time to disease progression in the penultimate platinum-based chemotherapy prior to enrollment (6-12 month versus >12 months) as covariates.

† The p-value is derived from a stratified log-rank test.

Figure 3 Kaplan-Meier Curves of Investigator-Assessed Progression-Free Survival – SOLO-2



Study 19

The efficacy of Lynparza was evaluated in Study 19 (NCT00753545), a randomized (1:1) double-blind, placebo-controlled trial in patients with platinum-sensitive ovarian cancer who had received 2 or more previous platinum-containing regimens. Patients were randomized to Lynparza capsules 400 mg orally twice daily or placebo until unacceptable toxicity or progressive disease. Randomization was stratified by response to last platinum chemotherapy (complete response versus partial response), time to disease progression in the penultimate platinum-based chemotherapy (6-12 months versus >12 months), and descent (Jewish versus non-Jewish). The major efficacy outcome measure was investigator-assessed PFS according to RECIST, version 1.0.

A total of 265 patients were randomized, 136 to Lynparza and 129 to placebo. The median age of patients treated with Lynparza was 58 years (range: 21 to 89) and 59 years (range 33 to 84) among patients treated with placebo. ECOG PS was 0 in 81% of patients receiving Lynparza and 74% of patients receiving placebo. Of all patients, 97% were White, 19% were enrolled in the US or Canada, 45% were in complete response following their most recent platinum chemotherapy regimen, and 40% had a progression-free interval of 6-12 months since their penultimate platinum. Prior bevacizumab therapy was reported for 13% of patients receiving Lynparza and 16% of patients receiving placebo.

A retrospective analysis for germline *BRCA* mutation status, some performed using the Myriad test, indicated that 36% (n=96) of patients from the ITT population had deleterious g*BRCA* mutation, including 39% (n=53) of patients on Lynparza and 33% (n=43) of patients on placebo.

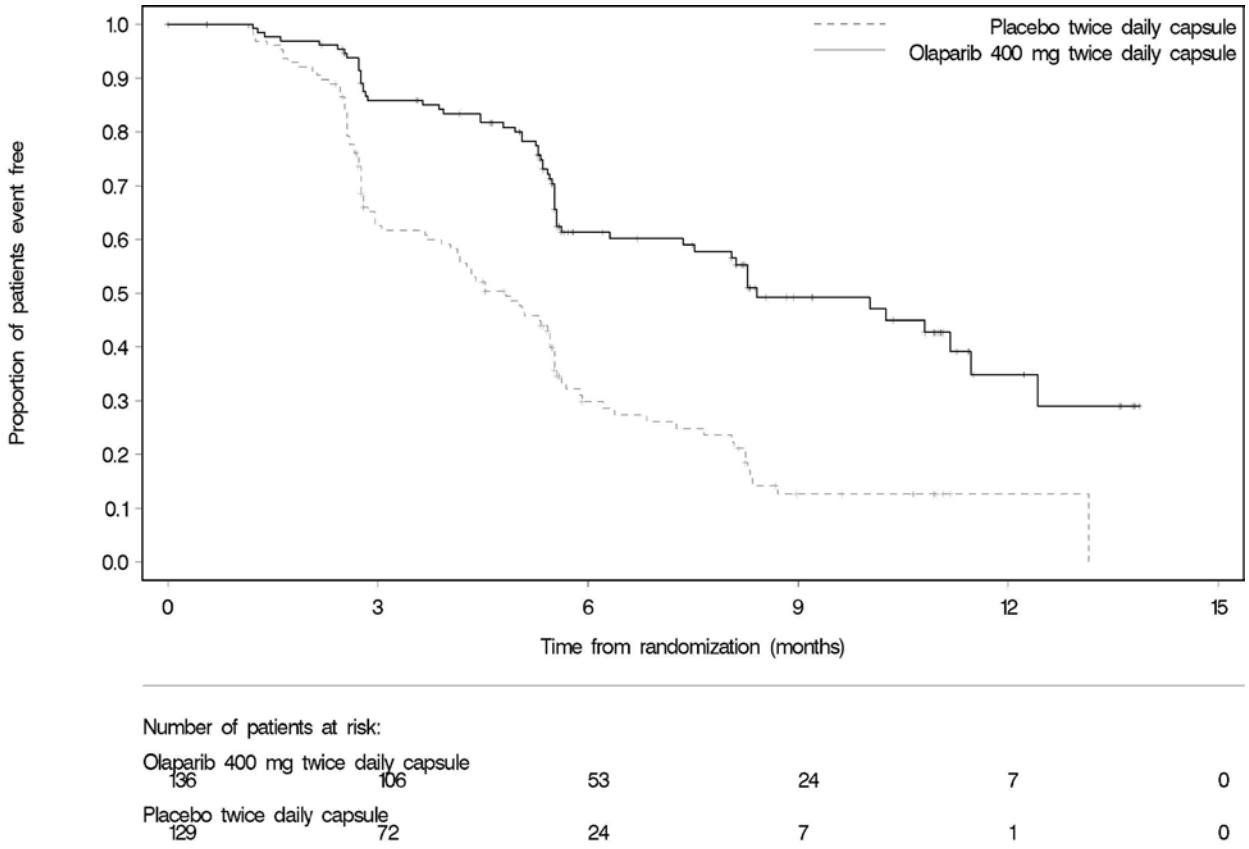
Efficacy results are presented in Table 21 and Figure 4. Study 19 demonstrated a statistically significant improvement in investigator-assessed PFS in patients treated with Lynparza versus placebo.

Table 21 Efficacy Results - Study 19 (Investigator Assessment)

	Lynparza capsules (n=136)	**Placebo (n=129)**
Progression-Free Survival		
Number of events (%)	60 (44%)	94 (73%)
Median, months	8.4	4.8
Hazard ratio* (95% CI)	0.35 (0.25, 0.49)	
p-value†	<0.0001	
Overall Survival‡		
Number of events (%)	98 (72%)	112 (87%)
Median, months	29.8	27.8
Hazard ratio (95% CI)	0.73 (0.55, 0.95)	

* Hazard ratio from a Cox proportional hazards model including response to last platinum chemotherapy (complete response versus partial response), time to disease progression in the penultimate platinum-based chemotherapy (6-12 months versus >12 months) and Jewish descent (yes versus no) as covariates.
† The p-value is derived from a Cox proportional hazards model.
‡ Without adjusting for multiple analyses.

Figure 4 Kaplan-Meier Curves of Investigator-Assessed Progression-Free Survival – Study 19



14.4 Advanced Germline *BRCA*-mutated Ovarian Cancer Treated with 3 or More Prior Lines of Chemotherapy

The efficacy of Lynparza was investigated in a single-arm study of patients with deleterious or suspected deleterious g*BRCA*m advanced cancers. A total of 137 patients with measurable, advanced g*BRCA*m ovarian cancer treated with three or more prior lines of chemotherapy were enrolled. All patients received Lynparza capsules 400 mg orally twice daily until disease progression or intolerable toxicity. The efficacy outcome measures were objective response rate (ORR) and duration of response (DOR) as assessed by the investigator according to RECIST, version 1.0.

The median age of the patients was 58 years, the majority were White (94%) and 93% had an ECOG PS of 0 or 1. Deleterious or suspected deleterious g*BRCA*m status was verified retrospectively in 97% (59/61) of the patients for whom blood samples were available by the BRACAnalysis CDx™.

Efficacy results are summarized in Table 22.

Table 22 Overall Response and Duration of Response in Patients with g*BRCA*-mutated Advanced Ovarian Cancer Who Received 3 or More Lines of Chemotherapy

	Lynparza Capsules n=137
Objective Response Rate (95% CI)	34% (26, 42)
Complete response	2%
Partial response	32%
Median DOR in months (95% CI)	7.9 (5.6, 9.6)

14.5 Treatment of Germline *BRCA*-mutated HER2-negative Metastatic Breast Cancer

The efficacy of Lynparza was evaluated in OlympiAD (NCT02000622), an open-label randomized (2:1) study in patients with g*BRCA*m HER2-negative metastatic breast cancer. Patients were required to have received treatment with an anthracycline (unless contraindicated) and a taxane, in the neoadjuvant, adjuvant or metastatic setting. Patients with hormone receptor-positive disease must have progressed on at least 1 endocrine therapy (adjuvant or metastatic), or have disease that the treating healthcare provider believed to be inappropriate for endocrine therapy. Patients with prior platinum therapy were required to have no evidence of disease progress during platinum treatment. No prior treatment with a PARP inhibitor was permitted. Patients were randomized to Lynparza tablets 300 mg orally twice daily or healthcare provider's choice of chemotherapy (capecitabine, eribulin, or vinorelbine, at standard doses) until progression or unacceptable toxicity. Randomization was stratified by prior use of chemotherapy for metastatic disease (yes vs no), hormone receptor status (hormone receptor positive vs triple negative), and previous use of platinum-based chemotherapy (yes vs no). The major efficacy outcome measure was PFS assessed by blinded independent central review (BICR) using RECIST version 1.1.

A total of 302 patients were randomized, 205 to Lynparza and 97 to chemotherapy. Among the 205 patients treated with Lynparza, the median age was 44 years (range: 22 to 76), 65% were White, 4% were males and all the patients had an ECOG PS of 0 or 1. Approximately 50% of patients had triple-negative tumors and 50% had estrogen receptor and/or progesterone receptor positive tumors and the proportions were balanced across treatment arms. Patients in each treatment arm had received a median of 1 prior chemotherapy regimen for metastatic disease; approximately 30% had not received a prior chemotherapy regimen for metastatic breast cancer. Twenty-one percent of patients in the Lynparza arm and 14% in the chemotherapy arm had received platinum therapy for metastatic disease. Seven percent of patients in each treatment arm had received platinum therapy for localized disease.

Of the 302 patients randomized onto OlympiAD, 299 were tested with the BRACAnalysis CDx® and 297 were confirmed to have deleterious or suspected deleterious g*BRCA*m status; 202 were randomized to the Lynparza arm and 95 to the healthcare provider's choice of chemotherapy arm.

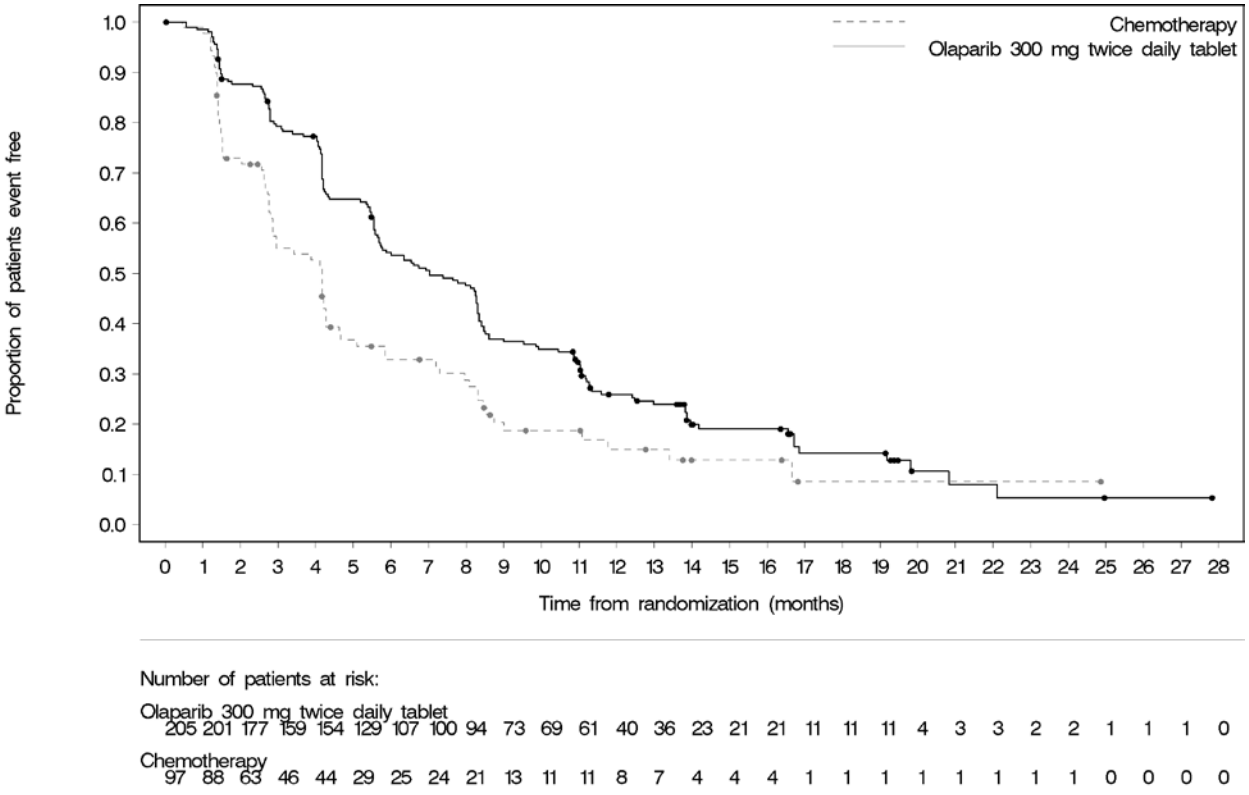
A statistically significant improvement in PFS was demonstrated for the Lynparza arm compared to the chemotherapy arm. Efficacy data for OlympiAD are displayed in Table 23 and Figure 5. Consistent results were observed across patient subgroups defined by study stratification factors. An exploratory analysis of investigator-assessed PFS was consistent with the BICR-assessed PFS results.

Table 23 Efficacy Results - OlympiAD (BICR-assessed)

	Lynparza tablets (n=205)	Chemotherapy (n=97)
Progression-Free Survival		
Number of events (%)	163 (80%)	71 (73%)
Median, months	7.0	4.2
Hazard ratio (95% CI)*	0.58 (0.43, 0.80)	
p-value†	0.0009	
Patients with Measurable Disease	n=167	n=66
Objective Response Rate (95% CI)‡	52% (44, 60)	23% (13, 35)
Overall Survival		
Number of events (%)	130 (63%)	62 (64%)
Median, months	19.3	17.1
Hazard ratio (95% CI)*	0.90 (0.66, 1.23)	

* Hazard ratio is derived from a stratified log-rank test, stratified by ER, PgR negative versus ER and or PgR positive and prior chemotherapy (yes versus no).
† For PFS, p-value (2-sided) was compared to 0.05.
‡ Response based on confirmed responses. The confirmed complete response rate was 7.8% for Lynparza compared to 1.5% for chemotherapy arm.

Figure 5 Kaplan-Meier Curves of Progression-Free Survival – OlympiAD



14.6 First-Line Maintenance Treatment of Germline *BRCA*-mutated Metastatic Pancreatic Adenocarcinoma

The efficacy of Lynparza was evaluated in POLO (NCT02184195), a randomized (3:2), double-blind placebo-controlled, multi-center trial. Patients were required to have metastatic pancreatic adenocarcinoma with a deleterious or suspected deleterious germline *BRCA* mutation (g*BRCA*m) and absence of disease progression after receipt of first-line platinum-based chemotherapy for at least 16 weeks. Patients were randomized to receive Lynparza tablets 300 mg orally twice daily or placebo until disease progression or unacceptable toxicity. The major efficacy outcome measure was PFS by BICR using RECIST, version 1.1 modified to assess patients with clinical complete response at entry who were assessed as having no evidence of disease unless they had progressed based on the appearance of new lesions. Additional efficacy outcome measures were OS and ORR.

A total of 154 patients were randomized, 92 to Lynparza and 62 to placebo. The median age was 57 years (range 36 to 84); 54% were male; 92% were White, 4% were Asian, and 3% were Black; baseline ECOG PS was 0 (67%) or 1 (31%). The median time from initiation of first-line platinum-based chemotherapy to randomization was 5.8 months (range 3.4 to 33.4 months). Seventy-five percent (75%) of patients received FOLFIRINOX with a median of 9 cycles (range 4-61), 8% received FOLFOX or XELOX, 4% received GEMOX, and 3% received gemcitabine plus cisplatin; 49% achieved a complete or partial response to platinum-based chemotherapy.

All patients had a deleterious or suspected deleterious germline *BRCA*-mutation as detected by the Myriad BRAC*Analysis*® or BRACAnalysis CDx® at a central laboratory only (n=106), local *BRCA* test only (n=4), or both local and central testing (n=44). Among the 150 patients with central test results, 30% had a mutation in *BRCA1;* 69% had a mutation in *BRCA2*; and 1 patient (1%) had mutations in both *BRCA1* and *BRCA2*.

Efficacy results of POLO are provided in Table 24 and Figure 6.

Table 24 Efficacy Results - POLO (BICR-assessed)

	Lynparza tablets (n=92)	**Placebo (n=62)**
Progression-Free Survival		
Number of events (%)*	60 (65%)	44 (71%)
Median, months (95% CI)	7.4 (4.1, 11.0)	3.8 (3.5, 4.9)
Hazard ratio** (95% CI)	0.53 (0.35, 0.81)	
p-value	0.0035	
Patients with Measurable Disease	n=78	n=52
Objective Response Rate (95% CI)	23% (14, 34)	12% (4, 23)
Complete response (%)	2 (2.6)	0
Partial response (%)	16 (21)	6 (12)
Duration of Response (DOR)		
Median time in months (95% CI)	25 (15, NC)	4 (2, NC)

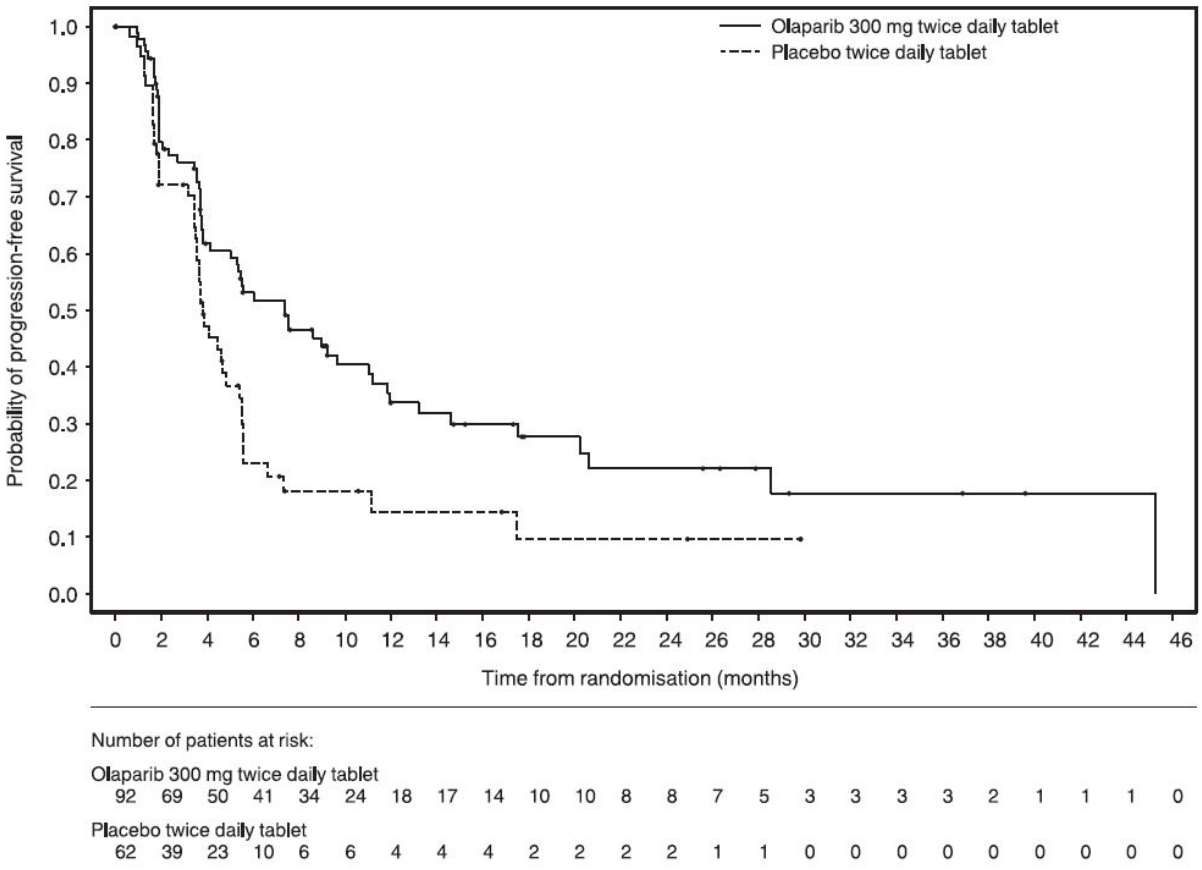
* Number of events: Progression – Lynparza 55, placebo 44; death before BICR-documented progression – Lynparza 5, placebo 0

** Hazard ratio, 95% CI, and p-value calculated from a log-rank test. A hazard ratio <1 favors Lynparza.

NC Not calculable

The result of an OS interim analysis conducted based on 67% information fraction did not show a statistically significant improvement in OS for Lynparza compared to placebo.

Figure 6 Kaplan-Meier Curves of BICR-Assessed Progression-Free Survival - POLO



14.7 HRR Gene-mutated Metastatic Castration-Resistant Prostate Cancer

The efficacy of Lynparza was evaluated in PROfound (NCT02987543), randomized, open-label, multi-center trial that evaluated the efficacy of Lynparza 300 mg twice daily versus a comparator arm of investigator's choice of enzalutamide or abiraterone acetate in men with metastatic castration-resistant prostate cancer (mCRPC). All patients received a GnRH analog or had prior bilateral orchiectomy. Patients needed to have progressed on prior enzalutamide or abiraterone for the treatment of metastatic prostate cancer and/or CRPC and have a tumor mutation in one of 15 genes involved in the homologous recombination repair (HRR) pathway.

Patients were divided into two cohorts based on HRR gene mutation status. Patients with mutations in either *BRCA1*, *BRCA2*, or *ATM* were randomized in Cohort A; patients with mutations among 12 other genes involved in the HRR pathway (*BARD1*, *BRIP1*, *CDK12*, *CHEK1*, *CHEK2*, *FANCL*, *PALB2*, *PPP2R2A*, *RAD51B*, *RAD51C*, *RAD51D*, or *RAD54L*) were randomized in Cohort B; patients with co-mutations (*BRCA1*, *BRCA2*, or *ATM* plus a Cohort B gene) were assigned to Cohort A. Although patients with *PPP2R2A* gene mutations were enrolled in the trial, Lynparza is not indicated for the treatment of patients with this gene mutation due to unfavorable risk-benefit. Patients were randomized (2:1), 256 to Lynparza arm and 131 to enzalutamide or abiraterone acetate arm; in Cohort A there were 245 (162 Lynparza arm and 83 in enzalutamide or abiraterone acetate arm) and in Cohort B there were 142 patients

(94 in Lynparza arm and 48 in enzalutamide or abiraterone acetate arm). Randomization was stratified by prior receipt of taxane chemotherapy and presence of measurable disease by RECIST 1.1. Treatment was continued until objective radiological disease progression determined by BICR. Upon radiological progression confirmed by BICR, patients randomized to enzalutamide or abiraterone acetate were given the option to switch to olaparib. Patients with HRR gene mutations were identified by tissue-based testing using the Foundation Medicine FoundationOne® clinical trial HRR assay performed at a central laboratory.

Determination of deleterious or suspected deleterious somatic or germline HRR mutation status in line with the FDA approved mutation classification and testing criteria for the Foundation Medicine F1CDx tissue-based assay and assessment of the germline-*BRCA* status using the Myriad BRACAnalysis CDx blood-based assay was performed retrospectively. Representation of individual gene mutations by cohort is provided in Table 25. No patients were enrolled who had mutations in two of the 15 pre-specified HRR genes: *FANCL* and *RAD51C*.

Table 25 Frequency of Patients with HRR Mutations Enrolled in PROfound

HRR Mutation	Cohort A N=245 n (%)	Cohort B* N=142 n (%)
Single mutation	224 (91)	135 (95)
BRCA2	127 (52)	1 (<1)
ATM	84 (34)	2 (1)
BRCA1	13 (5)	0
CDK12	0	89 (63)
CHEK2	0	12 (8)
PPP2R2A#	0	10 (7)
RAD51B	0	5 (4)
RAD54L	0	5 (4)
PALB2	0	4 (3)
BRIP1	0	3 (2)
CHEK1	0	2 (1)
BARD1	0	1 (<1)
RAD51D	0	1 (<1)
Co-occurring mutation**	21 (9)	7 (5)

* Three patients with single *BRCA2* or *ATM* gene mutations and 1 patient with co-occurring *BRCA2+CDK12* gene mutations were incorrectly assigned to Cohort B.

Lynparza is not indicated for patients with *PPP2R2A* mutations.

** Patients with co-occurring mutations (*BRCA1*, *BRCA2*, or *ATM* plus a Cohort B gene) were assigned to Cohort A.

In Cohort A+B, the median age was 69 years (range: 47 to 91 years) in both arms; 69% were White, 29% were Asian, and 1% were Black. The ECOG performance score was 0 or 1 in most patients (95%) in both arms. In patients treated with Lynparza, the proportion of patients with RECIST 1.1 measurable disease at baseline was 58%, including 17% with lung and 10% with liver metastases, respectively. At randomization, 66% of patients had received prior taxane chemotherapy, 40% had received enzalutamide, 38% had received abiraterone acetate, and 20% had received both enzalutamide and abiraterone acetate. Patient characteristics were well-balanced between arms.

The major efficacy outcome of the study was radiological progression free survival (rPFS) (Cohort A) as determined by BICR using RECIST version 1.1 and Prostate Cancer Clinical Trials Working Group 3 (PCWG3) (bone) criteria. Additional efficacy outcomes included confirmed objective response rate (ORR) (Cohort A), rPFS (combined Cohorts A+B) as assessed by BICR, and overall survival (OS) (Cohort A).

PROfound demonstrated a statistically significant improvement in BICR-assessed rPFS for Lynparza compared to investigator's choice of enzalutamide or abiraterone acetate in Cohort A and Cohort A+B. In an exploratory analysis for patients in Cohort B, the median rPFS was 4.8 months for Lynparza vs 3.3 months for comparator with a HR of 0.88 (95% CI 0.58, 1.36). The major efficacy outcome was supported by a statistically significant improvement in ORR by BICR for patients with measurable disease at baseline in Cohort A. In Cohort B, ORR by BICR was 3.7% (95% CI 0.5, 12.7) in Lynparza treated patients and 8.3% (95% CI 1.0, 27.0) in patients treated with enzalutamide or abiraterone acetate.

The final analysis of overall survival (OS) demonstrated a statistically significant improvement in OS in patients randomized to Lynparza compared to patients in the enzalutamide or abiraterone acetate arm in Cohort A.

Efficacy results of PROfound are provided in Tables 26 and 27 and Figures 7 and 8.

Table 26 Efficacy Results - PROfound (BICR-assessed)

	Cohort A		**Cohort A+B***	
	Lynparza tablets (n=162)	**Enzalutamide or Abiraterone acetate (n=83)**	**Lynparza tablets (n=256)**	**Enzalutamide or Abiraterone acetate (n=131)**
Radiological Progression-Free Survival (rPFS)				
Number of events (%)	106 (65)	68 (82)	180 (70)	99 (76)
Median (95% CI), in months	7.4 (6.2, 9.3)	3.6 (1.9, 3.7)	5.8 (5.5, 7.4)	3.5 (2.2, 3.7)
Hazard ratio (95% CI)[‖]	0.34 (0.25, 0.47)		0.49 (0.38, 0.63)	
p-value[¶]	<0.0001		<0.0001	
Confirmed ORR				
Patients with measurable disease at baseline	n=84	n=43	-	-

ORR, n (%)	28 (33)	1 (2)	-	-
(95% CI)	(23, 45)	(0, 12)	-	-
p-value	<0.0001		-	
Overall Survival	n=162	n=83	-	-
Number of events (%)	91 (56)	57 (69)	-	-
Median (95% CI), in months	19.1 (17.4, 23.4)	14.7 (11.9, 18.8)	-	-
Hazard ratio (95% CI)‖	0.69 (0.50, 0.97)		-	
p-value¶	0.0175		-	

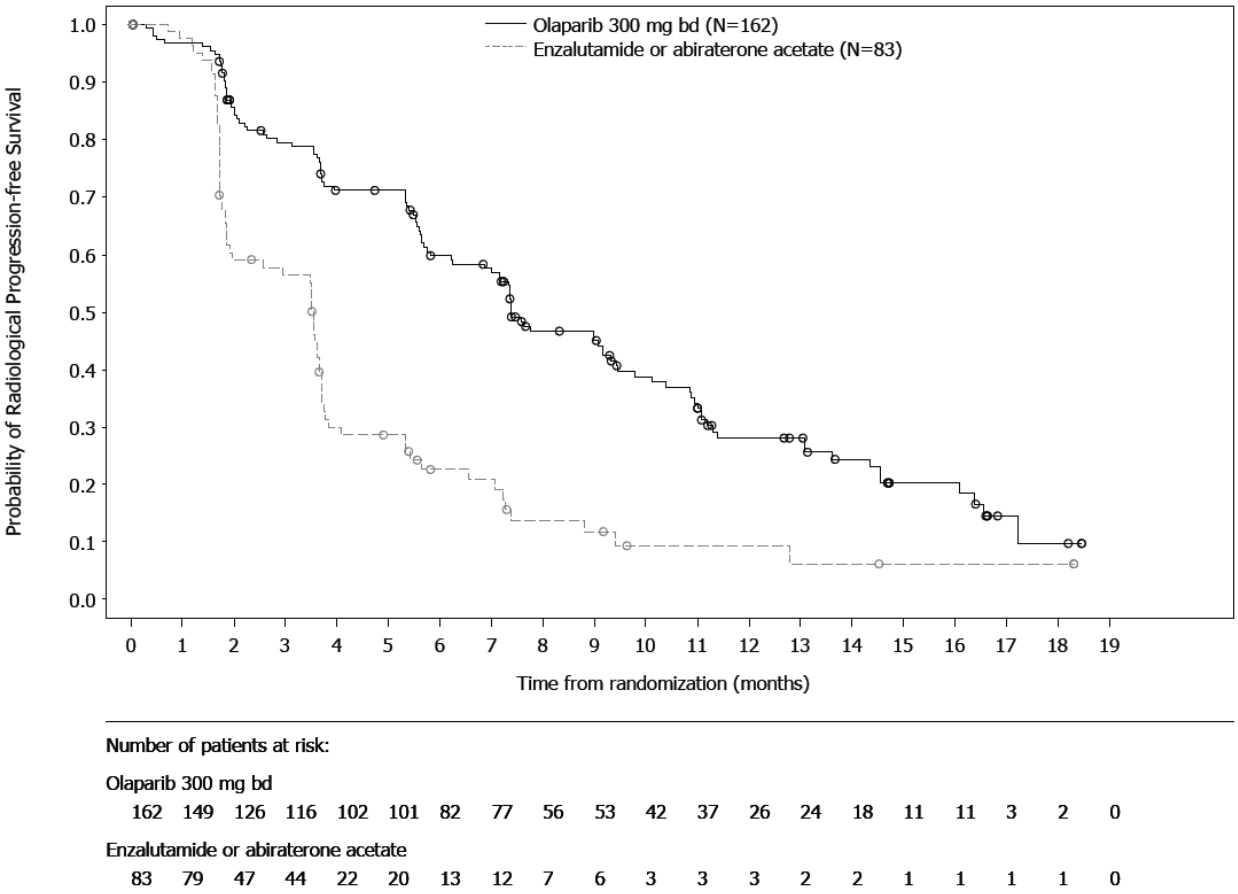
* Although 10 patients with *PPP2R2A* mutation were included in all analyses of Cohort A+B, Lynparza is not indicated for this population due to unfavorable risk-benefit.

‖ The HR and CI were calculated using a Cox proportional hazards model adjusted for prior taxane use and measurable disease. An HR <1 favors Lynparza 300 mg bd.

¶ The analysis was performed using the log-rank test stratified by prior taxane use and measurable disease.

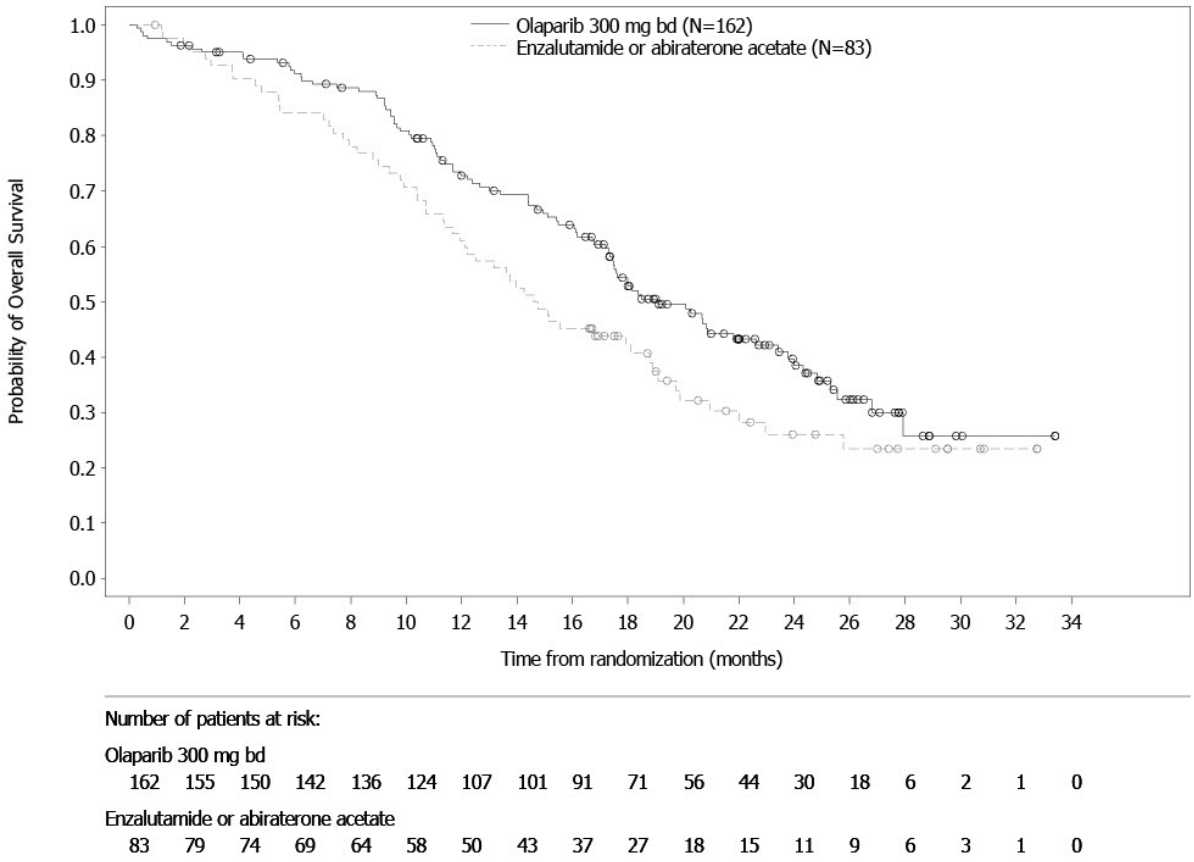
CI Confidence interval

Figure 7 Kaplan-Meier Curves of BICR-Assessed Radiological Progression-Free Survival – PROfound – Cohort A



Consistent results were observed in exploratory analyses of rPFS for patients who received or did not receive prior taxane therapy and for those with germline-*BRCA* mutations identified using the Myriad BRACAnalysis CDx assay compared with those with *BRCA* mutations identified using the Foundation Medicine F1CDx assay.

Figure 8 Kaplan-Meier Curves of Overall Survival – PROfound – Cohort A



Response data by HRR mutations for patients in the Lynparza arm are presented in Table 27. In the comparator arm of Cohorts A and B, a total of three patients achieved a partial response, including one patient with an *ATM* mutation alone and 2 patients with co-occurring mutations (one with *PALB2+PPP2R2A* and one with *CDK12+PALB2*).

Table 27 Response Rate and Duration of Response by HRR Mutation in Patients with Measurable Disease at Baseline on the Lynparza Arm – PROfound (BICR-assessed)

HRR mutation*	Patients (N=138)	Confirmed ORR†	
		n (%)	95% CI
Single mutation			
BRCA2	43	24 (56)	(40, 71)
ATM	30	3 (10)	(2, 27)
CDK12	34	2 (6)	(1, 20)
BRCA1	6	SD, PD (4), NE	NA
CHEK2	4	SD (2), PD (2)	NA
BRIP1	2	SD, PD	NA

PALB2	2	SD, PD	NA
CHEK1	1	PD	NA
RAD51B	1	SD	NA
RAD51D	1	PD	NA
RAD54L	1	SD	NA
Co-occurring mutations			
BRCA2/CDK12	2	PR, SD	NA
BRCA2/ATM	2	SD, SD	NA
BRCA2/BARD1	1	PD	NA
BRCA2/CHEK2	1	SD	NA
CDK12/CHEK1	1	SD	NA
CDK12/PALB2	1	PD	NA
BRCA2/CDK12/CHEK2	1	PD	NA
BRCA2/CHEK2/RAD51D	1	SD	NA

* No patients with *FANCL* or *RAD51C* enrolled. Three patients with *PPP2R2A* mutations had measurable disease, however, Lynparza is not indicated for patients with *PPP2R2A* mutation.
† In patients with a single *BRCA2* mutation the median duration of response in the Lynparza arm (n=24) was 5.6 months (95% C.I: 5.5, 9.2). In the 3 responders with a single *ATM* mutation in the Lynparza arm, the duration of response ranged from 5.8+ to 9.0 months. In the 2 responders with a single *CDK12* mutation in the Lynparza arm, the duration of response was 3.7 and 7.2 months. + denotes ongoing response.
PR Partial response; SD Stable disease; PD Progressive disease; NE Not evaluable; NA Not applicable due to small numbers or lack of response.

16 HOW SUPPLIED/STORAGE AND HANDLING

Lynparza is available as 150 mg and 100 mg tablets.

- 150 mg tablets: green to green/grey, oval, bi-convex, film-coated tablet, with debossment ‘OP150’ on one side and plain on the reverse, are available in:
    - Bottles of 60 tablets (NDC 0310-0679-60) and
    - Bottles of 120 tablets (NDC 0310-0679-12).
- 100 mg tablets: yellow to dark yellow, oval, bi-convex, film-coated tablet, with debossment ‘OP100’ on one side and plain on the reverse, are available in:
    - Bottles of 60 tablets (NDC 0310-0668-60) and
    - Bottles of 120 tablets (NDC 0310-0668-12).

Store at 20ºC to 25ºC (68ºF to 77ºF), excursions permitted to 15ºC to 30ºC (59ºF to 86ºF) [see USP Controlled Room Temperature]. Store in original bottle to protect from moisture.

17 PATIENT COUNSELING INFORMATION

Advise the patient to read the FDA-approved patient labeling (Medication Guide).

MDS/AML

Advise patients to contact their healthcare provider if they experience weakness, feeling tired, fever, weight loss, frequent infections, bruising, bleeding easily, breathlessness, blood in urine or stool, and/or laboratory findings of low blood cell counts, or a need for blood transfusions. This may be a sign of hematological toxicity or a more serious uncommon bone marrow problem called 'myelodysplastic syndrome' (MDS) or 'acute myeloid leukemia' (AML) which have been reported in patients treated with Lynparza *[see Warnings and Precautions (5.1)]*.

Pneumonitis

Advise patients to contact their healthcare provider if they experience any new or worsening respiratory symptoms including shortness of breath, fever, cough, or wheezing *[see Warnings and Precautions (5.2)]*.

Embryo-Fetal Toxicity

Inform pregnant women of the risk to a fetus and potential loss of the pregnancy. Advise females to inform their healthcare provider of known or suspected pregnancy *[see Use in Specific Populations (8.1)]*.

Advise females of reproductive potential to use effective contraception during treatment with Lynparza and for 6 months after the last dose *[see Use in Specific Populations (8.3)]*.

Advise male patients with female partners of reproductive potential or who are pregnant to use effective contraception during treatment and for 3 months after receiving the last dose of Lynparza. Advise male patients not to donate sperm during therapy and for 3 months following the last dose of Lynparza *[see Warnings and Precautions (5.3) and Use in Specific Populations (8.3)]*.

Venous Thromboembolic Events

Advise patients with metastatic castration-resistant prostate cancer to immediately report any signs or symptoms of thromboembolism such as pain or swelling in an extremity, shortness of breath, chest pain, tachypnea, and tachycardia *[see Warnings and Precautions (5.4)]*.

Lactation

Advise patients not to breastfeed while taking Lynparza and for one month after receiving the last dose *[see Use in Specific Populations (8.2)]*.

Drug Interactions

Advise patients and caregivers to inform their healthcare provider of all concomitant medications, including prescription medicines, over-the-counter drugs, vitamins, and herbal products. Inform patients to avoid grapefruit, grapefruit juice, Seville oranges, and Seville orange juice while taking Lynparza *[see Drug Interactions (7.2)]*.

Nausea/Vomiting

Advise patients that mild or moderate nausea and/or vomiting is very common in patients receiving Lynparza and that they should contact their healthcare provider who will advise on available antiemetic treatment options *[see Adverse Reactions (6.1)]*.

Distributed by:
AstraZeneca Pharmaceuticals LP
Wilmington, DE 19850

Medication Guide
Lynparza® (Lin-par-zah)
(olaparib)
tablets

What is the most important information I should know about Lynparza?

Lynparza may cause serious side effects, including:

Bone marrow problems called Myelodysplastic Syndrome (MDS) or Acute Myeloid Leukemia (AML). Some people who have ovarian cancer or breast cancer and who have received previous treatment with chemotherapy, radiotherapy or certain other medicines for their cancer have developed MDS or AML during treatment with Lynparza. MDS or AML may lead to death. If you develop MDS or AML, your healthcare provider will stop treatment with Lynparza.

Symptoms of low blood cell counts are common during treatment with Lynparza, but can be a sign of serious bone marrow problems, including MDS or AML. Symptoms may include:

- weakness
- weight loss
- fever
- frequent infections
- blood in urine or stool
- shortness of breath
- feeling very tired
- bruising or bleeding more easily

Your healthcare provider will do blood tests to check your blood cell counts:

- before treatment with Lynparza
- every month during treatment with Lynparza
- weekly if you have low blood cell counts that last a long time. Your healthcare provider may stop treatment with Lynparza until your blood cell counts improve.

Lung problems (pneumonitis). Tell your healthcare provider if you have any new or worsening symptoms of lung problems, including shortness of breath, fever, cough, or wheezing. Your healthcare provider may do a chest x-ray if you have any of these symptoms. Your healthcare provider may temporarily or completely stop treatment if you develop pneumonitis. Pneumonitis may lead to death.

Blood clots (Venous Thromboembolic Events). Some people with prostate cancer who take Lynparza along with gonadotropin-releasing hormone (GnRH) analog therapy may develop a blood clot in a deep vein, usually in the leg (venous thrombosis) or a clot in the lung (pulmonary embolism). Tell your healthcare provider if you have any symptoms such as pain or swelling in an extremity, shortness of breath, chest pain, breathing that is more rapid than normal (tachypnea), or heart beats faster than normal (tachycardia). Your healthcare provider will monitor you for these symptoms and may prescribe blood thinner medicine.

What is Lynparza?

Lynparza is a prescription medicine used to treat adults who have:

- advanced ovarian cancer, fallopian tube cancer, or primary peritoneal cancer with a certain type of inherited (germline) or acquired (somatic) abnormal *BRCA* gene. Lynparza is used alone as maintenance treatment after the cancer has responded to your first treatment with platinum-based chemotherapy. Your healthcare provider will perform a test to make sure that Lynparza is right for you.
- advanced ovarian cancer, fallopian tube cancer or primary peritoneal cancer with a certain type of abnormal *BRCA* gene or a positive laboratory tumor test for genomic instability called HRD. Lynparza is used in combination with another anti-cancer medicine, bevacizumab, as maintenance treatment after the cancer has responded to your first treatment with platinum-based chemotherapy. Your healthcare provider will perform a test to make sure that Lynparza is right for you.

- ovarian cancer, fallopian tube cancer, or primary peritoneal cancer, as maintenance treatment, when the cancer has come back. Lynparza is used after the cancer has responded to treatment with platinum-based chemotherapy.
- advanced ovarian cancer with a certain type of abnormal inherited *BRCA* gene, **and** have received treatment with 3 or more prior types of chemotherapy medicines. Your healthcare provider will perform a test to make sure that Lynparza is right for you.
- a certain type of abnormal inherited *BRCA* gene, human epidermal growth factor receptor 2 (HER2)-negative breast cancer that has spread to other parts of the body (metastatic). You should have received chemotherapy medicines, either before or after your cancer has spread. If you have hormone receptor (HR)-positive disease, you should have been treated with hormonal therapy. Your healthcare provider will perform a test to make sure that Lynparza is right for you.
- metastatic pancreatic cancer with a certain type of abnormal inherited *BRCA* gene. Lynparza is used as maintenance treatment after your cancer has not progressed on at least 16 weeks of treatment with platinum-based chemotherapy. Your healthcare provider will perform a test to make sure that Lynparza is right for you.
- prostate cancer with certain inherited or acquired abnormal genes called homologous recombination repair (HRR genes). Lynparza is used when the cancer has spread to other parts of the body (metastatic), and no longer responds to a medical or surgical treatment that lowers testosterone, and has progressed after treatment with enzalutamide or abiraterone. Your healthcare provider will perform a test to make sure Lynparza is right for you.

It is not known if Lynparza is safe and effective in children.

Before taking Lynparza, tell your healthcare provider about all of your medical conditions, including if you:

- have lung or breathing problems
- have kidney problems
- are pregnant, become pregnant, or plan to become pregnant. Lynparza can harm your unborn baby and may cause loss of pregnancy (miscarriage).
    - If you are able to become pregnant, your healthcare provider may do a pregnancy test before you start treatment with Lynparza.
    - **Females** who are able to become pregnant should use effective birth control (contraception) during treatment with Lynparza and for 6 months after the last dose of Lynparza. Talk to your healthcare provider about birth control methods that may be right for you. Tell your healthcare provider right away if you become pregnant or think you might be pregnant following treatment with Lynparza.
    - **Males** with female partners who are pregnant or able to become pregnant should use effective birth control (contraception) during treatment with Lynparza and for 3 months after the last dose of Lynparza.
    - Do not donate sperm during treatment with Lynparza and for 3 months after your final dose.
- are breastfeeding or plan to breastfeed. It is not known if Lynparza passes into your breast milk. Do not breastfeed during treatment with Lynparza and for 1 month after receiving the last dose of Lynparza. Talk to your healthcare provider about the best way to feed your baby during this time.

Tell your healthcare provider about all the medicines you take, including prescription and over-the-counter medicines, vitamins, and herbal supplements. Taking Lynparza and certain other medicines may affect how Lynparza works and may cause side effects.

How should I take Lynparza?

- Take Lynparza tablets exactly as your healthcare provider tells you.
- Do not change your dose or stop taking Lynparza unless your healthcare provider tells you to. Your healthcare provider may temporarily stop treatment with Lynparza or change your dose of Lynparza if you experience side effects.
- Your healthcare provider will decide how long you stay on treatment.
- **Do not** take more than 4 Lynparza tablets in 1 day. If you have any questions about Lynparza, please talk to your healthcare provider or pharmacist.
- Take Lynparza by mouth 2 times a day.
- Each dose should be taken about 12 hours apart.
- Swallow Lynparza tablets whole. Do not chew, crush, dissolve, or divide the tablets.
- Take Lynparza with or without food.
- If you are taking Lynparza for prostate cancer and you are receiving gonadotropin-releasing hormone (GnRH) analog therapy, you should continue with this treatment during your treatment with Lynparza unless you have had a surgery to lower the amount of testosterone in your body (surgical castration).
- If you miss a dose of Lynparza, take your next dose at your usual scheduled time. Do not take an extra dose to make up for a missed dose.
- If you take too much Lynparza, call your healthcare provider or go to the nearest hospital emergency room right away.

What should I avoid while taking Lynparza?

Avoid grapefruit, grapefruit juice, Seville oranges and Seville orange juice during treatment with Lynparza since they may increase the level of Lynparza in your blood.

What are the possible side effects of Lynparza?

Lynparza may cause serious side effects.

See "**What is the most important information I should know about Lynparza?**"

The most common side effects of Lynparza are:

- nausea or vomiting. Tell your healthcare provider if you get nausea or vomiting. Your healthcare provider may prescribe medicines to treat these symptoms.
- tiredness or weakness
- low red blood cell counts
- diarrhea
- loss of appetite
- headache
- low white blood cell counts
- changes in the way food tastes
- cough
- shortness of breath
- dizziness
- indigestion or heartburn
- low platelet counts
- upper stomach area (abdominal) pain

These are not all of the possible side effects of Lynparza.

Call your healthcare provider for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

How should I store Lynparza?

- Store Lynparza at room temperature, between 68°F to 77°F (20°C to 25°C).
- Store Lynparza in the original bottle to protect it from moisture.

Keep Lynparza and all medicines out of reach of children.

General information about the safe and effective use of Lynparza.

Medicines are sometimes prescribed for purposes other than those listed in a Medication Guide. Do not use Lynparza for a condition for which it was not prescribed. Do not give Lynparza to other people, even if they have the same symptoms you have. It may **harm** them.

You can ask your healthcare provider or pharmacist for information about Lynparza that is written for health professionals.

What are the ingredients in Lynparza?
Active ingredient: olaparib

Inactive ingredients:
Tablet contains: copovidone, mannitol, colloidal silicon dioxide and sodium stearyl fumarate
Tablet coating contains: hypromellose, polyethylene glycol 400, titanium dioxide, ferric oxide yellow and ferrosoferric oxide (150 mg tablet only)

Distributed by:
AstraZeneca Pharmaceuticals LP
Wilmington, DE 19850
For more information, call 1-800-236-9933 or go to www.Lynparza.com.
This Medication Guide has been approved by the U.S. Food and Drug Administration. Revised: 5/2020

Section 5.0

BHAP report

Unspecified Reaction to Severe Stress

Plain Language Summary:

Coverage question: Should OHP cover serious stress treatment when the code listed for finding out the cause of the condition (diagnosis) is not specific?

Should OHP cover this treatment? Yes, when the code is used for 30 days or fewer, until a more accurate diagnosis can be made.

Coverage Question: Should the diagnosis code for unspecified reaction to severe stress be added to a covered mental health line?

Question source: Tara Candela, BHAP member

Background: Historically, "unspecified" diagnosis codes were placed on the "Undefined Conditions" file and providers were asked to give a more specified code. Ms. Candela is requesting that ICD-10-CM F43.9 (Reaction to severe stress, unspecified) be added to a covered line. This code is used in counseling when the provider does not want to make another diagnosis, such as PTSD due to the early nature of the problem or the unclear final diagnosis.

Previous HSC/HERC reviews:

ICD-10-CM F43.9 has not been reviewed in more than 10 years

Current Prioritized List/Coverage status:

ICD-10-CM F43.9 (Reaction to severe stress, unspecified) is on the UNDEFINED CONDITIONS file

Similar codes such as ICD-10-CM F43.89 (Other reactions to severe stress) are on line 445 ADJUSTMENT DISORDERS. PTSD (ICD-10-CM F43.1 family) is on line 173 POSTTRAUMATIC STRESS DISORDER

Both lines 173 and 445 have psychotherapy procedure codes

BHAP input: ICD-10-CM F43.0 (Acute stress reaction) is on line 290 ACUTE STRESS DISORDER could be used rather than F43.9; however, F43.0 is time-limited **to use for only 30 days**. Roxanne Edwinson recommended adding coverage, she uses this code in her pediatric practice for children when it is not clear what stress is triggering the symptom. Many kids entering foster care get this diagnosis initially before a more in-depth evaluation can be completed. Meg Cary agreed that this diagnosis is used in pediatric psychiatric practice with individuals with complex trauma. She also noted that there can be cultural differences in how individuals express their symptoms. This code is similar to F43.20 (Adjustment disorder, unspecified) which is on line 445. The group recommended adding F43.9 to line 445.

Unspecified Reaction to Severe Stress

HERC staff recommendations:

1) Add ICD-10-CM F43.9 (Reaction to severe stress, unspecified) to line 445 ADJUSTMENT DISORDERS
    a. Advise HSD to removed F43.9 from the UNDEFINED CONDITIONS file

Freespira for PTSD and Panic Disorder

BHAP report for VBBS August 2023

Plain Language Summary:

Coverage question: Should OHP cover a device that measures breathing patterns for certain mental health conditions?

Should OHP cover this treatment? No, the published and reviewed evidence is not convincing that the technology works and the Behavioral Health Advisory Panel recommended against adding coverage.

Coverage Question: Should Freespira be covered as a treatment for panic disorder and PTSD?

Question source: Freespira

Background: Freespira is a device that measures carbon dioxide (CO_2) levels connected to an electronic app that gives patients feedback on their CO_2 levels. This feedback is intended to train patients on controlling and normalizing their breathing patterns. The system is used at home as a 4 week treatment program. It involves two 17 minutes sessions per day with the device and weekly coaching. Freespira is FDA approved for treatment of panic disorder and PTSD. Freespira must be prescribed by and used under the supervision of a licensed healthcare provider.

Freespira treatment is based on the theory that hyperventilation and other respiratory abnormalities play a significant role in the etiology or maintenance of panic disorder. The acute effects of hyperventilation and compensatory mechanisms include many physiological sensations that are consistent with those seen in anxiety and panic, including gastrointestinal distress, cold sensations, fatigue, rapid or irregular heartbeat, chest pain, impaired breathing, muscle tension, and paresthesia.

Freespira was discussed at the June 2023 BHAP meeting and BHAP did not recommend coverage.

Previous HSC/HERC reviews:

There are no previous reviews of any similar technology.

Current Prioritized List/Coverage status:

The following CPT codes are on lines 410 MIGRAINE HEADACHES and 541 TENSION HEADACHES

CPT 90875 Individual psychophysiological therapy incorporating biofeedback training by any modality (face-to-face with the patient), with psychotherapy (eg, insight oriented, behavior modifying or supportive psychotherapy); 30 minutes

CPT 90876 45 minutes

CPT 90901 Biofeedback training by any modality

Freespira for PTSD and Panic Disorder

BHAP report for VBBS August 2023

PTSD is on line 173 POSTTRAUMATIC STRESS DISORDER

Panic disorder is online 391 PANIC DISORDER; AGORAPHOBIA

Freespira submitted billing codes: CPT 90901 and HCPCS A9279 (Monitoring feature/device, stand-alone or integrated, any type, includes all accessories, components and electronics, not otherwise classified)

Evidence:

1) **MED 2023** Prescription Digital Therapeutics: Evidence, Reimbursement, and Coverage Policies
    a. Comments on a VA pilot study of Freespira
        i. The Palo Alto VA made this clinical trial open to non-Veterans, with study participants about two-thirds Veterans and one-third civilians (Palo Alto VA staff, personal communication). During the clinical trial, the researchers collected data at baseline, week 1, week 2, week 3, week 4, and at 2-month and 6-month follow-up (Palo Alto VA staff, personal communication). The predetermined time points analyzed and included in the publication for this clinical trial were week 4 of treatment, 2-month follow-up, and 6-month follow-up (Palo Alto VA staff, personal communication). However, the greatest benefit from Freespira occurred at week 1, which is not reported in the publication (Palo Alto VA staff, personal communication). This finding could be due to regression to the mean, unconscious bias from participants or study personnel, a placebo effect, or the product working through a different mechanism than proposed by the manufacturer (Palo Alto VA staff, personal communication). Freespira's model for how the product works is PTSD symptoms are reduced through the physiological processes of decreasing respiratory rate and increasing carbon dioxide output, and the first week is essentially meant to be a training week and not treatment per se (Palo Alto VA staff, personal communication). However, the results suggest that simply being told to be aware of one's breathing at 13 times per minute is enough to reduce PTSD symptoms (Palo Alto VA staff, personal communication).
        ii. The study also found some continued improvement in patients' PTSD symptoms, with 88% of participants having a clinically significant reduction in PTSD symptom severity 2 months after treatment. On average, PTSD symptom severity decreased by 48% from baseline to 2 months after treatment. About half of the participants in this study no longer met the diagnostic criteria for PTSD after the conclusion of the trial, and these changes continued through the 6- month follow-up period (Palo Alto VA staff, personal communication).
        iii. These outcomes are likely better than those for psychotherapies and medications used to treat PTSD, and there is likely a much lower potential for adverse side effects with Freespira compared with other types of treatment, but there have not been any direct comparator studies (Palo Alto VA staff, personal communication). Freespira was used as a standalone treatment in the clinical trial, but the FDA ultimately cleared Freespira as an adjunctive treatment, meaning people prescribed Freespira also need to be receiving another form of treatment (Palo Alto VA staff, personal communication).

iv. Due to the results from this clinical trial, Freespira has been approved for VA coverage at the national level, meaning individual Veterans Integrated Service Networks (VISNs) can choose whether to cover this product (Palo Alto VA staff, personal communication)

b. Highmark insurance pilot study
   i. The pilot project by Highmark and Freespira resulted in positive clinical and cost outcomes. Specifically, 86% of participants no longer had symptoms after the 28-day treatment protocol for Freespira, and 73% of participants still had an absence of symptoms 1 year after treatment. The pilot project was also able to reduce medical costs by 35% ($190 per member per month), emergency department costs by 65%, and pharmacy costs by 68%.

2) **Tolin 2017**, cohort study of Freespira
   a. Manufacturer funded study
   b. N=56 patients with panic disorder (intention to treat cohort)
      i. N=48 patients who completed treatment and had a post-treatment assessment
      ii. N=33 patients who completed 1 year follow up
      iii. Criteria
         1. Off medications or on stable medications for at least 3 months
         2. Excluded patients receiving psychological treatments or who had been unresponsive to CBT in the past 3 months, had substance dependence
      iv. Response was defined as a 40% or greater reduction in scores on the Panic Disorder Severity Scale (PDSS); remission was defined as a score of five or less on the PDSS
   c. The proportion of responders at post-treatment was 85.4% (SE=5.1%) in treatment completers, and 83.2% (SE=5.3%) in the intent to treat (ITT) sample. The rate of remission was 56.3% (SE=7.2%) in treatment completers, and 54.4% (SE=6.8%) in the ITT sample.
   d. At 12-month follow-up, the proportion of responders was 81.8% (SE=6.7%) in treatment completers
   e. There were no Serious Adverse Events (SAEs).
3) **Kaplan 2020**, cohort study of Freespira
   a. Funded as part of a health system innovation program
   b. N=52 patients with panic disorder
      i. N=45 patients who completed 15 or more sessions
   c. The cohort's PDSS score fell from baseline 14.4 (sd = 3.8) to 4.9 (sd = 3.4) immediately post-treatment and 4.4 (sd = 4.5) at 12 months.
   d. Immediately post-treatment, 48% of subjects were in remission, while 68% of subjects were in remission at 12 months (remission defined as a PDSS≤5)
4) **Cuyler 2022**, cohort study of Freespira
   a. N= 1,395 patients with panic disorder and N=174 patients with PTSD
   b. Manufacturer-funded study
   c. Manufacturer registry data
   d. Outcomes determined by in-app pre- and post-survey results
      i. Self-reported panic symptom severity was measured using the 7-item Panic Disorder Severity Scale. Self-reported PTSD symptom severity was measured using the 20-item PCL-5

ii. Baseline measures for both PD and PTSD scales were obtained by the referring clinician or recorded during an assessment/authorization interview by a licensed healthcare professional
iii. The post-treatment assessment of both the PDSS and the PCL-5 were administered on-screen via the tablet computer.

e. For the PD cohort, the mean PDSS score declined from 14.7 (sd = 5.8) at baseline to 7.2 (sd = 5.7) at post-treatment. This 7.5- point decline represents a 50% decrease, with a large effect size (Cohen's d = 1.3). PDSS reduction of at least 40% was attained by 911 patients [65.3% (95% CI-62.7%–67.8%)]

Submitted Literature

1) Madhusudhan 2020
    a. N=22 patient cohort study
2) Meuret 2008
    a. N=35 patients
        i. RCT of Freespira vs wait list controls
        ii. Significant reduction in PDSS scores in the treatment group, with no change in the wait list group
3) Meuret 2010
    a. N=41 patients
    b. RCT of individual weekly 1 hour in person sessions of respiratory skill training vs cognitive skill training
4) Ostacher 2021
    a. N=55 patient cohort study

Expert guidelines:

Freespira is not included in major treatment guidelines for PTSD or panic disorder

Other payer policies:

1) Anthem BCBS 2023 Mobile Device-Based Health Management Applications
    a. Does not cover Freespira
        i. Currently available evidence evaluation of Freespira lacks comparison to generally accepted standards of medical practice, is limited by small sample sizes despite the prevalence of panic disorder in the general population, and is subject to bias from loss to follow-up.
2) MED 2023 Prescription Digital Therapeutics: Evidence, Reimbursement, and Coverage Policies
    a. Summary of selected private payers' coverage determinations
        i. Assessed and denied coverage for Freespira
            1. Aetna
            2. Anthem BCBS
            3. Molina
            4. Paramount

ii. Assessed a approved coverage for Freespira
    1. HIghmark

BHAP input:

Testimony was heard from Monica Frederick and Bob Cuyler from Freespira. The BHAP discussion mainly centered on the lack of true comparison RCTs of the device, comparing the device to standard psychotherapy, medication therapy, etc. There was concern that this device is in the early stages of evaluation and the evidence does not yet support its use. Some members felt that this device looked promising and requested that HERC staff look at any additional research that Freespira could provide.

HERC staff reviewed additional studies provided by Freespira, which did not change previous HERC staff recommendations.

Since the BHAP meeting, HERC staff have become aware that Freespira was included in a May 2023 MED report. This report is now summarized in the Evidence section above.

Freespira for PTSD and Panic Disorder

BHAP report for VBBS August 2023

HERC staff summary:

The literature on the effect of Freespira on panic disorder and PTSD consists mostly of small cohort studies. One larger cohort study analyzes the results of self-reported data from patients who persisted in use of the device and completed a post-treatment survey, which creates a response bias in favor of the device being efficacious. The available studies are also subject to bias from loss of follow-up.

HERC staff/BHAP recommendation:

1) Do not add coverage for Freespira for panic disorder or PTSD

Appl Psychophysiol Biofeedback (2017) 42:51–58
DOI 10.1007/s10484-017-9354-4

A Multisite Benchmarking Trial of Capnometry Guided Respiratory Intervention for Panic Disorder in Naturalistic Treatment Settings

David F. Tolin[1,2] · Patrick B. McGrath[3] · Lisa R. Hale[4] · Daniel N. Weiner[5] · Ralitza Gueorguieva[6]

Published online: 13 February 2017

Abstract Panic disorder (PD) is associated with hyperventilation. The efficacy of a brief respiratory feedback program for PD has been established. The aim of the present study was to expand these results by testing a similar program with more clinically representative patients and settings. Sixty-nine adults with PD received 4 weeks of Capnometry Guided Respiratory Intervention (CGRI) using Freespira, which provides feedback of end-tidal CO_2 ($P_{ET}CO_2$) and respiration rate (RR), in four non-academic clinical settings. This intervention is delivered via home use following initial training by a clinician and provides remote monitoring of client adherence and progress by the clinician. Outcomes were assessed post-treatment and at 2- and 12-month follow-up. CGRI was associated with an intent-to-treat response rate of 83% and a remission rate of 54%, and large decreases in panic severity. Similar decreases were found in functional impairment and in global illness severity. Gains were largely sustained at follow-up. $P_{ET}CO_2$ moved from the slightly hypocapnic range to the normocapnic range. Benchmarking analyses against a previously-published controlled trial showed very similar outcomes, despite substantial differences in sample composition and treatment settings. The present study confirms prior clinical results and lends further support to the viability of CGRI in the treatment of PD.

Keywords Panic disorder · Breathing · Biofeedback · Respiration · Hyperventilation · Freespira

Introduction

Hyperventilation and other respiratory abnormalities play a significant role in the etiology or maintenance of panic disorder (PD) (Klein 1993; Ley 1985). Patients with PD show lower end-tidal (exhaled) CO_2 ($P_{ET}CO_2$), a marker of hyperventilation, compared to anxious or healthy controls (Meuret et al. 2008; Wilhelm et al. 2001). The acute effects of hyperventilation and compensatory mechanisms include many physiological sensations that are consistent with those seen in anxiety and panic, including gastrointestinal

Trial Registration: Clinicaltrials.gov NCT01955954.

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Applied Psychophysiology and Biofeedback (2020) 45:175–181
https://doi.org/10.1007/s10484-020-09465-0

Evaluating the Impact of Freespira on Panic Disorder Patients' Health Outcomes and Healthcare Costs within the Allegheny Health Network

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Published online: 27 April 2020

Abstract

Panic disorder (PD) is a debilitating condition that drives medical spending at least twice as high as medically matched controls. Excessive utilization of healthcare resources comes from emergency department (ED), medications, diagnostic testing, and physician visits. Freespira is an FDA-cleared digital therapeutic that treats PD and panic attacks (PA) by correcting underlying abnormal respiratory physiology. Efficacy of Freespira has been established in prior studies. This paper reports on a quality improvement program that investigated whether treating PD patients with Freespira would reduce medical costs and improve outcomes over 12-months. Panic symptoms were assessed using the Panic Disorder Severity Scale (PDSS). Pre-and post-treatment insurance claims determined costs. At baseline, mean Clinician Global Impression (CGI-S) was 4.4 (moderately/markedly ill), mean PDSS was 14.4 and mean PA frequency/week was 2 (range 0–5). Immediately post-treatment (week 5) mean CGI-S, PDSS and weekly PA frequency declined to 2.8 (borderline/mildly ill, 4.9 (remission) and 0.2 (range 0–2) respectively, $p < 0.001$. 82% reported PDSS decrease of ≥ 40% (clinically significant), 86% were PA-free. One-year post treatment mean CGI-S, PDSS and PA remained low at 2.1, 4.4, and 0.3 (range 0–1) respectively. 91% had PDSS decrease of ≥ 40%, 73% were PA-free. The majority of patients were panic attack free and/or reduced their symptoms and avoidance behaviors 1-year post Freespira treatment. Mean overall medical costs were reduced by 35% from $548 to $358 PMPM (per member per month) or an annual reduction of $2280. at 12 months post-treatment. There was a 65% reduction in ED costs from $87 to $30 PMPM. Median pharmacy costs were reduced by 68% from $73 to $23 PMPM.

Keywords Panic disorder · Panic attacks · Hyperventilation · Freespira · CGRI

Introduction

Epidemiologic data suggest that 3–4 percent of American adults suffer from panic disorder (PD), an anxiety disorder associated with marked impairment in social and occupational functioning, significant impact on quality of life, and high utilization of health care services (Deacon et al 2008). Fearful interpretation of bodily symptoms such as tachycardia, shortness of breath, chest tightness, and dizziness with catastrophic beliefs is the core of the diagnosis and differentiates it from the other anxiety disorders. The cardio-respiratory symptoms of panic mimic heart disease, and often lead to care-seeking in emergency departments (Fleet 1996, 2003) and cardiology settings (Dammen et al. 1999). Deacon et al (2008) reported that patients with PD visited family medicine and cardiology practices, and emergency departments with greater frequency than those with other anxiety disorders. Barsky et al. (1999) reported that patients with PD averaged 10.6 physician visits in 1 year versus 4.4 visits for patients without PD. Data from the National Comorbidity Survey Replication (Kessler et al. 2006) showed that 28.3% of respondents reported having had at least one panic attack in their lifetime, and 11.2% reported a panic attack in the prior year. The increased medical utilization rates noted in patients with PD bring about a high financial burden associated with the condition. Shirmeshan et al. (2013) estimated that the cost of ambulatory care of patients with anxiety disorders at $33 billion, with PD patients being included in this analysis. Retrospective claims

An interim analysis with fewer subjects was previously presented by Kaplan at the Annual Conference of Anxiety and Depression Association of America in April 2018.

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frontiers | Frontiers in Digital Health

TYPE Original Research
PUBLISHED 17 November 2022
DOI 10.3389/fdgth.2022.976001

OPEN ACCESS

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SPECIALTY SECTION
This article was submitted to Personalized Medicine, a section of the journal Frontiers in Digital Health

RECEIVED 22 June 2022
ACCEPTED 21 October 2022
PUBLISHED 17 November 2022

CITATION
Cuyler RN, Katdare R, Thomas S and Telch MJ (2022) Real-world outcomes of an innovative digital therapeutic for treatment of panic disorder and PTSD: A 1,500 patient effectiveness study.
Front. Digit. Health 4:976001.
doi: 10.3389/fdgth.2022.976001

Real-world outcomes of an innovative digital therapeutic for treatment of panic disorder and PTSD: A 1,500 patient effectiveness study

Robert N. Cuyler[1]*, Rahul Katdare[2], Simon Thomas[2] and Michael J. Telch[3]

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Objective: Prior clinical trials have shown consistent clinical benefit for Capnometry Guided Respiratory Intervention (CGRI), a prescription digital therapeutic for the treatment of panic disorder (PD) and post-traumatic stress disorder (PTSD). The purpose of this study is to report real-world outcomes in a series of patients treated with the intervention in clinical practice.
Design: This paper reports pre- and post-treatment self-reported symptom reduction, measures of respiratory rate and end-tidal carbon dioxide levels, drop-out and adherence rates drawn from an automatic data repository in a large real-world series of patients receiving CGRI for panic disorder and PTSD.
Setting: Patients used the intervention in their homes, supported by telehealth coaching.
Participants: Patients meeting symptom criteria for panic disorder ($n = 1{,}395$) or posttraumatic stress disorder ($n = 174$) were treated following assessment by a healthcare professional.
Intervention: Capnometry Guided Respiratory Intervention is a 28-day home-based treatment that provides breath-to-breath feedback of respiratory rate and exhaled carbon dioxide levels, aimed at normalizing respiratory style and increasing patients' mastery for coping with symptoms of stress, anxiety, and panic. Health coaches provide initial training with weekly follow up during the treatment episode. Remote data upload and monitoring facilitates individualized coaching and aggregate outcomes analysis.
Main outcome measures: Self-reported Panic Disorder Severity Scale (PDSS) and the Posttraumatic Stress Disorder Checklist for DSM-5 (PCL-5) scores were obtained at pre-treatment and post-treatment.
Results: Panic disorder (PD) patients showed a mean pre-to-post-treatment reduction in total PDSS scores of 50.2% ($P < 0.001$, $d = 1.31$). Treatment response rates for PD (defined as a 40% or greater reduction in PDSS total scores) were observed in 65.3% of the PD patients. PTSD patients showed a pre-to-post-treatment reduction in total PCL-5 scores of 41.1% ($P < 0.001$, $d = 1.16$). The treatment response rate for PTSD (defined as a ≥10-point reduction in PCL-5 scores) was 72.4%. In an additional analysis of response at the individual level, 55.7% of panic disorder patients and 53.5% of PTSD patients were classified as treatment responders using the Reliable Change Index. Patients with both normal and below-normal baseline exhaled CO_2

Section 6.0

New Codes

HCPCS code	Code description	Similar codes	Recommended Placement	Comments
C9784	Gastric restrictive procedure, endoscopic sleeve gastroplasty, with esophagogastroduodenoscopy and intraluminal tube insertion, if performed, including all system and tissue anchoring components	43775 Laparoscopy, surgical, gastric restrictive procedure; longitudinal gastrectomy (i.e., sleeve gastrectomy) is on line 320	320 OBESITY IN ADULTS AND CHILDREN; OVERWEIGHT STATUS IN ADULTS WITH CARDIOVASCULAR RISK FACTORS	
C9785	Endoscopic outlet reduction, gastric pouch application, with endoscopy and intraluminal tube insertion, if performed, including all system and tissue anchoring components		662 CONDITIONS FOR WHICH CERTAIN INTERVENTIONS ARE UNPROVEN, HAVE NO CLINICALLY IMPORTANT BENEFIT OR HAVE HARMS THAT OUTWEIGH BENEFITS	See issues
C9786	Echocardiography image post processing for computer aided detection of heart failure with preserved ejection fraction, including interpretation and report		662 CONDITIONS FOR WHICH CERTAIN INTERVENTIONS ARE UNPROVEN, HAVE NO CLINICALLY IMPORTANT BENEFIT OR HAVE HARMS THAT OUTWEIGH BENEFITS	See issues
C9787	Gastric electrophysiology mapping with simultaneous patient symptom profiling		662 CONDITIONS FOR WHICH CERTAIN INTERVENTIONS ARE UNPROVEN, HAVE NO CLINICALLY IMPORTANT BENEFIT OR HAVE HARMS THAT OUTWEIGH BENEFITS	See issues

HCPCS code	Code description	Similar codes	Recommended Placement	Comments
K1035	Molecular diagnostic test reader, nonprescription self-administered and self-collected use, fda approved, authorized or cleared	Replaces K1034 (Provision of covid-19 test, nonprescription self-administered and self-collected use, fda approved, authorized or cleared, one test count) that was only effective until May 11, 2023 [the end of the public health emergency]. K1034 was used for over the counter COVID testing. K1034 was an Ancillary code	ANCILLARY PROCEDURES	

July 2023 HCPCS Codes

Plain Language Summary:

Coverage question:

1) Should a procedure that helps stop weigh gain after weight loss surgery be covered?
2) Should a computer assisted test of heart function be covered?
3) Should new testing that analyzes the electrical activity in the stomach muscle be covered?

Should OHP cover this treatment?

1) No, there is not enough evidence that it works well.
2) No, this test appears to be experimental.
3) No, this test appears to be experimental.

Issues:

1) Endoscopic outlet reduction
    a. Code: **C9785** Endoscopic outlet reduction, gastric pouch application, with endoscopy and intraluminal tube insertion, if performed, including all system and tissue anchoring components
    b. Information: Transoral outlet reduction endoscopy (TORe) is a revisional therapy that can help manage weight regain after gastric bypass. During this procedure, an endoscopic suturing system is used to reduce the size of the gastrojejunal anastomosis. The goal is to delay gastric pouch emptying and enhance the sensation of satiety (fullness)
    c. Similar codes:
        i. Many bariatric surgery procedures are on line 320 OBESITY IN ADULTS AND CHILDREN; OVERWEIGHT STATUS IN ADULTS WITH CARDIOVASCULAR RISK FACTORS. Certain bariatric procedures such as gastric balloon are on line 662/GN173
    d. Evidence
        i. Vargas 2018, cohort study and meta-analysis of transoral outlet reduction for weight regain after gastric bypass
            1. N=130 patients for cohort portion of study
                a. Post Roux-n-Y gastric bypass; had regained weight
            2. N=3 studies (330 patients) for meta-analysis
                a. 2 additional studies with a total of 200 patients [Kumar and Thompson, Patel et al]
            3. The pooled weight lost at 12 months was 8.4 kg (95% CI 6.5–10.3)
            4. 14% of patients experienced nausea, 18% had pain and 8% required a repeat EGD. No serious adverse events reported.
            5. Conclusion When implemented as part of a multidisciplinary intervention, TORe using endoluminal suturing is safe, reproducible, and effective approach to manage weight recidivism after RYGB
    e. Other payer policies:

i. Premara BCBS 2023
    1. Transoral outlet reduction endoscopy (TORe procedure) is experimental and investigational
ii. United Healthcare 2023
    1. Transoral endoscopic surgery is experimental and investigational

f. HERC staff summary: transoral outlet reduction endoscopy is an experimental treatment for weight regain after gastric bypass surgery
g. HERC staff recommendation:
    i. Add HCPCS C9785 to line 662/GN173

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
C9785	Endoscopic outlet reduction, gastric pouch application, with endoscopy and intraluminal tube insertion	Insufficient evidence of benefit	August 2023

2) Computer aided echocardiogram
    a. Code: **C9786** Echocardiography image post processing for computer aided detection of heart failure with preserved ejection fraction, including interpretation and report
    b. Information: echocardiogram is a standard imaging test of the heart, which gives information on structures of the heart, such as valves, as well as function of the hear, such as ejection fraction. This ECHO version uses a computer to assist in detecting problems with the heart function
    c. Similar codes are on line 662:
        i. C7510-C7511 Bronchoscopy, rigid or flexible, with computer-assisted image-guided navigation
        ii. C8937 Computer-aided detection, including computer algorithm analysis of breast mri image data for lesion
    d. Evidence
        i. Liastuti 2022, systematic review on detecting left heart failure with echocardiography and machine learning
            1. N=14 studies
                a. All case series (N=100 to 12,925 patients)
            2. The literature included in this study has shown that AI has comparable performance in characterizing heart failure through echocardiography images, compared with the conventional method by medical practitioners, with an accuracy rate ranging from 57% to 99.3%
            3. Studies have shown that artificial intelligence has a high potential to serve as practical auxiliary assistance for medical practitioners to

differentiate normal and left heart failure patients through echocardiography.

e. Expert guidelines
    i. ACA/AHA/ASE 2019 transthoracic echocardiography data elements
        1. Do not mention computer aided detection
    ii. ACA/AHA/ASE 2019 transthoracic echocardiography training
        1. Do not mention computer aided detection
f. HERC staff summary: Computed aided detection is not included in expert recommendations on echocardiography, appears to be experimental
g. HERC staff recommendation:
    i. Add HCPCS C9786 to line 662/GN173

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
C9786	Echocardiography image post processing for computer aided detection of heart failure with preserved ejection fraction	Insufficient evidence of benefit	August 2023

3) Gastric electrical mapping
    a. Code: **C9787** Gastric electrophysiology mapping with simultaneous patient symptom profiling
    b. Information: gastric electrical mapping is a new technology that analyzes the electrical activity in the stomach muscle. This testing has been proposed as a possible new diagnostic evaluation for gastric functional disorders such as functional dyspepsia and idiopathic vomiting
    c. Evidence
        i. Carson 2021, review of gastric electrical activity
            1. Conventional electrogastrography has not achieved common clinical adoption due to limitations which are primarily technical.
            2. The last decade has seen the emergence of novel high-resolution methods for invasively mapping human gastric electrical activity in health and disease, providing important new insights into gastric physiology.
            3. the recent decade has seen extensive progress in the technical methods and physiological understanding of gastric electrical abnormalities. If an improved diagnostic strategy can now be achieved for subgroups of patients, it could allow enhanced understanding and communication, improved diagnostic efficiency, the introduction of novel biomarkers, and open the door to more personalized care

d. HERC staff summary: gastric electrophysiology appears to be experimental
e. HERC staff recommendation:
    i. Add HCPCS C9787 to line 662/GN173

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
C9787	Gastric electrophysiology mapping with simultaneous patient symptom profiling	Insufficient evidence of benefit	August 2023

Surg Endosc (2018) 32:252–259
https://doi.org/10.1007/s00464-017-5671-1

Transoral outlet reduction with full thickness endoscopic suturing for weight regain after gastric bypass: a large multicenter international experience and meta-analysis

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Received: 14 April 2017 / Accepted: 13 June 2017 / Published online: 29 June 2017

Abstract
Background and aims Many patients who undergo bariatric surgery will experience weight regain and effective strategies are needed to help these patients. A dilated gastrojejunal anastomosis (GJA) has been associated with weight recidivism after Roux-en-Y gastric bypass surgery (RYGB). Endoscopic transoral outlet reduction (TORe) with a full thickness endoscopic suturing device (Overstitch, Apollo Endosurgery, Austin, TX) is a minimally invasive therapeutic option. The primary aim of this project was to examine the safety and long-term efficacy data from three bariatric surgery centers and to conduct a systematic review and meta-analysis of the existing literature.
Methods Patients who underwent TORe with the Overstitch device from Jan 2013 to Nov 2016 at 3 participating bariatric surgery centers were included in the multicenter analysis. For the systematic review and meta-analysis, a comprehensive search of multiple English databases was conducted. Random effects model was used.
Results 130 consecutive patients across three centers underwent TORe with an endolumenal suturing device. These patients (mean age 47; mean BMI 36.8) had experienced 24.6% weight regain from nadir weight after RYGB. Average weight lost at 6, 12, and 18 months after TORe was 9.31 ± 6.7 kg ($N = 84$), 7.75 ± 8.4 kg ($N = 70$), 8 ± 8.8 kg ($N = 46$) ($p < 0.01$ for all three time points), respectively. The meta-analysis included 330 patients. The pooled weight lost at 12 months was 8.4 kg (95% CI 6.5–10.3) with no significant heterogeneity across included studies ($p = 0.07$). Overall, 14% of patients experienced nausea, 18% had pain and 8% required a repeat EGD. No serious adverse events reported.
Conclusion When implemented as part of a multidisciplinary intervention, TORe using endolumenal suturing is safe, reproducible, and effective approach to manage weight recidivism after RYGB and should be utilized early in the management algorithm of these patients.

Keywords Endoscopic · Bariatric surgery · Revision

Obesity is becoming a global health concern. In the U.S, over two thirds of the population is considered to be overweight or obese [1]. While nonsurgical methods have had modest success, metabolic surgery has been the most successful in the long-term [2–4]. With Laparoscopic Roux-en-Y (RYGB), patients can expect to lose around 60–80% of their excess weight at one year [5, 6]. High resolution rates of obesity related comorbidities and improved mortality have also been reported [7]. However, as longitudinal long-term prospective data are becoming

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Reviews in Cardiovascular Medicine

Rev. Cardiovasc. Med. **2022**; 23(12): 402
https://doi.org/10.31083/j.rcm2312402

Systematic Review

Detecting Left Heart Failure in Echocardiography through Machine Learning: A Systematic Review

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Academic Editor: Jerome L. Fleg
Submitted: 26 March 2022 Revised: 28 September 2022 Accepted: 30 September 2022 Published: 12 December 2022

Abstract

Background: Heart failure remains a considerable burden to healthcare in Asia. Early intervention, mainly using echocardiography, to assess cardiac function is crucial. However, due to limited resources and time, the procedure has become more challenging during the COVID-19 pandemic. On the other hand, studies have shown that artificial intelligence (AI) is highly potential in complementing the work of clinicians to diagnose heart failure accurately and rapidly. **Methods**: We systematically searched Europe PMC, ProQuest, Science Direct, PubMed, and IEEE following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines and our inclusion and exclusion criteria. The 14 selected works of literature were then assessed for their quality and risk of bias using the QUADAS-2 (Quality Assessment of Diagnostic Accuracy Studies). **Results**: A total of 2105 studies were retrieved, and 14 were included in the analysis. Five studies posed risks of bias. Nearly all studies included datasets in the form of 3D (three dimensional) or 2D (two dimensional) images, along with apical four-chamber (A4C) and apical two-chamber (A2C) being the most common echocardiography views used. The machine learning algorithm for each study differs, with the convolutional neural network as the most common method used. The accuracy varies from 57% to 99.3%. **Conclusions**: To conclude, current evidence suggests that the application of AI leads to a better and faster diagnosis of left heart failure through echocardiography. However, the presence of clinicians is still irreplaceable during diagnostic processes and overall clinical care; thus, AI only serves as complementary assistance for clinicians.

Keywords: heart failure; echocardiography; machine learning

1. Introduction

Heart failure (HF) remains a significant global health problem leading to high hospitalization and mortality rate despite advances in therapy [1]. The burden of the disease in Asia is particularly more pronounced, considering that it affects a younger population than in Europe and America [2,3]. Early detection and treatment of possible cases are mandatory to prevent disease progression and reduce health care costs.

Echocardiography is a widely recommended imaging modality for assessing cardiac function in HF patients [4,5]. Although echocardiography is non-invasive, harmless, and relatively inexpensive, some severe issues have arisen regarding its implementation. Echocardiography test is largely dependent on the user's skill, creating challenges for interpretation [6]. Furthermore, the terminology of left HF comprises a wide range of phenotypes, from those with systolic dysfunction or reduced ejection fraction (HFrEF) [EF <40%], diastolic dysfunction or preserved ejection fraction (HFpEF) [EF ≥50%], and the 'grey area' cases with mid-range ejection fraction (HFmrEF) [EF 40–49%] [5]. Diagnosing HFpEF from echocardiography alone is not a simple task as the European Society of Cardiology guidelines recommends combining with other diagnostic tests, including natriuretic peptides level and electrocardiogram (ECG) [5,7].

The most potential solution to the limitation of echocardiography interpretation lies in the application of automated methods, which have vastly evolved through computer technology. Artificial intelligence leverages computers and machines to mimic the human mind in problem-solving capacities. It enables training of large databases of various echocardiographic videos and images which have been previously confirmed by experts to achieve knowledge which is then used to identify endocardial pathologies in other cases [8].

Circulation: Cardiovascular Imaging

CLINICAL DATA STANDARDS

2019 ACC/AHA/ASE Key Data Elements and Definitions for Transthoracic Echocardiography

A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Data Standards (Writing Committee to Develop Clinical Data Standards for Transthoracic Echocardiography) and the American Society of Echocardiography

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Key Words: AHA Scientific Statements ■ health informatics ■ transthoracic echocardiography

https://www.ahajournals.org/journal/circimaging

The American Heart Association requests that this document be cited as follows: Douglas PS, Carabello BA, Lang RM, Lopez L, Pellikka PA, Picard MH, Thomas JD, Varghese P, Wang TY, Weissman NJ, Wilgus R. 2019 ACC/AHA/ASE key data elements and definitions for transthoracic echocardiography: a report of the American College of Cardiology/American Heart Association Task Force on Clinical Data Standards (Writing Committee to Develop Clinical Data Standards for Transthoracic Echocardiography) and the American Society of Echocardiography. *Circ Cardiovasc Imaging*. 2019;12:e000027. DOI: 10.1161/HCI.0000000000000027.

DOI: 10.1002/ccd.28313

ADVANCED TRAINING STATEMENT

WILEY

2019 ACC/AHA/ASE advanced training statement on echocardiography (revision of the 2003 ACC/AHA clinical competence statement on echocardiography)

A Report of the ACC Competency Management Committee

Developed in Collaboration with the American Thoracic Society, Society for Cardiovascular Angiography and Interventions, Society of Cardiovascular Anesthesiologists, and Society of Critical Care Medicine

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The document was approved by the American College of Cardiology Lifelong Learning Oversight Committee, the American Heart Association Science Advisory and Coordinating Committee, and the American Heart Association Executive Committee in December 2018, and by the American Society of Echocardiography Board of Directors in November 2018. For the purpose of transparency, disclosure information for the Lifelong Learning Oversight Committee, the approval body of the convening organization of this document, is available online.

The American College of Cardiology requests that this document be cited as follows: Wiegers SE, Ryan T, Arrighi JA, Brown SM, Canaday B, Damp JB, Diaz-Gomez JL, Figueredo VM, Garcia MJ, Gillam LD, Griffin BP, Kirkpatrick JN, Klarich KW, Lui GK, Maffett S, Naqvi TZ, Patel AR, Poulin M-F, Rose GA, Swaminathan M. 2019 ACC/AHA/ASE advanced training statement on echocardiography (revision of the 2003 ACC/AHA clinical competence statement on echocardiography): a report of the ACC Competency Management Committee. Developed in collaboration with the American Thoracic Society, Society for Cardiovascular Angiography and Interventions, Society of Cardiovascular Anesthesiologists, and Society of Critical Care Medicine. *Journal of the American College of Cardiology* 2019;02/07/j.jacc.2019.02.003.

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Received: 10 July 2020 | Revised: 11 October 2020 | Accepted: 3 November 2020

DOI: 10.1111/nmo.14048

REVIEW

Neurogastroenterology & Motility NGM WILEY

Body surface mapping of the stomach: New directions for clinically evaluating gastric electrical activity

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This work is supported by an NZ Health Research Council Programme Grant.

Abstract

Background: Gastric motility disorders, which include both functional and organic etiologies, are highly prevalent. However, there remains a critical lack of objective biomarkers to guide efficient diagnostics and personalized therapies. Bioelectrical activity plays a fundamental role in coordinating gastric function and has been investigated as a contributing mechanism to gastric dysmotility and sensory dysfunction for a century. However, conventional electrogastrography (EGG) has not achieved common clinical adoption due to its perceived limited diagnostic capability and inability to impact clinical care. The last decade has seen the emergence of novel high-resolution methods for invasively mapping human gastric electrical activity in health and disease, providing important new insights into gastric physiology. The limitations of EGG have also now become clearer, including the finding that slow-wave frequency alone is not a reliable discriminator of gastric dysrhythmia, shifting focus instead toward altered spatial patterns. Recently, advances in bioinstrumentation, signal processing, and computational modeling have aligned to allow non-invasive body surface mapping of the stomach to detect spatiotemporal gastric dysrhythmias. The clinical relevance of this emerging strategy to improve diagnostics now awaits determination.

Purpose: This review evaluates these recent advances in clinical gastric electrophysiology, together with promising emerging data suggesting that novel gastric electrical signatures recorded at the body surface (termed "body surface mapping") may correlate with symptoms. Further technological progress and validation data are now awaited to determine whether these advances will deliver on the promise of clinical gastric electrophysiology diagnostics.

KEYWORDS
biomarkers, dyspepsia, gastric electrical activity, gastroparesis, slow waves

1 | INTRODUCTION

Disorders of gastroduodenal function without an obvious organic cause are common, defined by the Rome IV criteria to include functional dyspepsia, chronic nausea, and vomiting disorders, in addition to belching and rumination disorders.[1] Patients must meet criteria based upon symptoms, along with the requirement that no evidence of organic, systemic, or metabolic disease that is likely to explain their symptoms is found on routine investigations (including at upper endoscopy).[1] However, other gastric disorders, particularly gastroparesis, may have a clinical picture which is indistinguishable from the functional nausea and vomiting disorders, despite being

Code	Code Description	Similar codes	Recommended Placement	Notes
A41.54	Sepsis due to Acinetobacter baumannii	Other A41.5 codes are on line 182	182 SEPTICEMIA	
B96.83	Acinetobacter baumannii as the cause of diseases classified elsewhere	Other "cause of diseases classified elsewhere" codes are INFORMATIONAL	INFORMATIONAL DIAGNOSES	
D13.91	Familial adenomatous polyposis		166 ANAL, RECTAL AND COLONIC POLYPS.	See Informational Issues
D13.99	Benign neoplasm of ill-defined sites within the digestive system	Parent code D13.9 (Benign neoplasm of ill-defined sites within the digestive system) is on line 638	638 BENIGN NEOPLASMS OF DIGESTIVE SYSTEM	
D48.110	Desmoid tumor of head and neck		199 CANCER OF SOFT TISSUE 401 BENIGN CONDITIONS OF BONE AND JOINTS AT HIGH RISK FOR COMPLICATIONS 559 BENIGN NEOPLASM OF BONE AND ARTICULAR CARTILAGE INCLUDING OSTEOID OSTEOMAS; BENIGN NEOPLASM OF CONNECTIVE AND OTHER SOFT TISSUE	See Informational Issues
D48.111	Desmoid tumor of chest wall		199, 401, 559	See Informational Issues
D48.112	Desmoid tumor, intrathoracic		199, 401, 559	See Informational Issues
D48.113	Desmoid tumor of abdominal wall		199, 401, 559	See Informational Issues
D48.114	Desmoid tumor, intraabdominal		199, 401, 559	See Informational Issues
D48.115	Desmoid tumor of upper extremity and shoulder girdle		199, 401, 559	See Informational Issues

Code	Code Description	Similar codes	Recommended Placement	Notes
D48.116	Desmoid tumor of lower extremity and pelvic girdle		199, 401, 559	See Informational Issues
D48.117	Desmoid tumor of back		199, 401, 559	See Informational Issues
D48.118	Desmoid tumor of other site		199, 401, 559	See Informational Issues
D48.119	Desmoid tumor of unspecified site		UNDEFINED CONDITIONS	See Informational Issues
D48.19	Other specified neoplasm of uncertain behavior of connective and other soft tissue		199, 401, 559	See Informational Issues
D57.04	Hb-SS disease with dactylitis	Other sickle cell diagnoses are on line 194	194 HEREDITARY ANEMIAS, HEMOGLOBINOPATHIES, AND DISORDERS OF THE SPLEEN	
D57.214	Sickle-cell/Hb-C disease with dactylitis	Other sickle cell diagnoses are on line 194	194 HEREDITARY ANEMIAS, HEMOGLOBINOPATHIES, AND DISORDERS OF THE SPLEEN	
D57.414	Sickle-cell thalassemia, unspecified, with dactylitis	Other sickle cell diagnoses are on line 194	194 HEREDITARY ANEMIAS, HEMOGLOBINOPATHIES, AND DISORDERS OF THE SPLEEN	
D57.434	Sickle-cell thalassemia beta zero with dactylitis	Other sickle cell diagnoses are on line 194	194 HEREDITARY ANEMIAS, HEMOGLOBINOPATHIES, AND DISORDERS OF THE SPLEEN	
D57.454	Sickle-cell thalassemia beta plus with dactylitis	Other sickle cell diagnoses are on line 194	194 HEREDITARY ANEMIAS, HEMOGLOBINOPATHIES, AND DISORDERS OF THE SPLEEN	
D57.814	Other sickle-cell disorders with dactylitis	Other sickle cell diagnoses are on line 194	194 HEREDITARY ANEMIAS, HEMOGLOBINOPATHIES, AND DISORDERS OF THE SPLEEN	

Code	Code Description	Similar codes	Recommended Placement	Notes
D61.02	Shwachman-Diamond syndrome		113 APLASTIC ANEMIAS; AGRANULOCYTOSIS; SICKLE CELL DISEASE Treatment: BONE MARROW TRANSPLANT 227 INTESTINAL MALABSORPTION 295 APLASTIC ANEMIAS	See Informational Issues
D89.84	IgG4-related disease		313 DISORDERS INVOLVING THE IMMUNE SYSTEM	See Informational Issues
E20.810	Autosomal dominant hypocalcemia	Parent code E20.8 (Other hypoparathyroidism) was on line 224	224 DISORDERS OF PARATHYROID GLAND; BENIGN NEOPLASM OF PARATHYROID GLAND; DISORDERS OF CALCIUM METABOLISM	
E20.811	Secondary hypoparathyroidism in diseases classified elsewhere	Other "diseases classified elsewhere" codes are INFORMATIONAL	INFORMATIONAL DIAGNOSES	
E20.812	Autoimmune hypoparathyroidism	Parent code E20.8 (Other hypoparathyroidism) was on line 224	224 DISORDERS OF PARATHYROID GLAND; BENIGN NEOPLASM OF PARATHYROID GLAND; DISORDERS OF CALCIUM METABOLISM	
E20.818	Other specified hypoparathyroidism due to impaired parathyroid hormone secretion	Parent code E20.8 (Other hypoparathyroidism) was on line 224	224 DISORDERS OF PARATHYROID GLAND; BENIGN NEOPLASM OF PARATHYROID GLAND; DISORDERS OF CALCIUM METABOLISM	
E20.819	Hypoparathyroidism due to impaired parathyroid hormone secretion, unspecified	Parent code E20.8 (Other hypoparathyroidism) was on line 224	224 DISORDERS OF PARATHYROID GLAND; BENIGN NEOPLASM OF PARATHYROID GLAND; DISORDERS OF CALCIUM METABOLISM	
E20.89	Other specified hypoparathyroidism	Parent code E20.8 (Other hypoparathyroidism) was on line 224	224 DISORDERS OF PARATHYROID GLAND; BENIGN NEOPLASM OF PARATHYROID GLAND; DISORDERS OF CALCIUM METABOLISM	

Code	Code Description	Similar codes	Recommended Placement	Notes
E74.05	Lysosome-associated membrane protein 2 [LAMP2] deficiency	Other glycogen storage diseases in the E74.0 family are on lines 71, 147, 241, 292, 345, 377 This condition is also known as glycogen storage disease IIb or Danon disease	71 NEUROLOGICAL DYSFUNCTION IN BREATHING, EATING, SWALLOWING, BOWEL, OR BLADDER CONTROL CAUSED BY CHRONIC CONDITIONS; ATTENTION TO OSTOMIES 147 GLYCOGENOSIS 241 ACUTE AND SUBACUTE NECROSIS OF LIVER; SPECIFIED INBORN ERRORS OF METABOLISM (E.G., MAPLE SYRUP URINE DISEASE, TYROSINEMIA) 292 NEUROLOGICAL DYSFUNCTION IN POSTURE AND MOVEMENT CAUSED BY CHRONIC CONDITIONS 345 NEUROLOGICAL DYSFUNCTION IN COMMUNICATION CAUSED BY CHRONIC CONDITIONS 377 DYSFUNCTION RESULTING IN LOSS OF ABILITY TO MAXIMIZE LEVEL OF INDEPENDENCE IN SELF-DIRECTED CARE CAUSED BY CHRONIC CONDITIONS THAT CAUSE NEUROLOGICAL DYSFUNCTION	This appears to cause eye and heart failure related issues, add to those lines? Or will primary dx be the other disease? Hypertrophic cardiomyopathy primary dx would be the actual disease this condition causes

Code	Code Description	Similar codes	Recommended Placement	Notes
E75.27	Pelizaeus-Merzbacher disease	Pelizaeus-Merzbacher disease (PMD) is a rare, progressive, and degenerative central nervous system disorder that deteriorates coordination, motor abilities, and cognitive function. Pelizaeus-Merzbacher disease was previously coded with E75.29 (Other sphingolipidosis) which is on lines 71,292,345,377	71 NEUROLOGICAL DYSFUNCTION IN BREATHING, EATING, SWALLOWING, BOWEL, OR BLADDER CONTROL CAUSED BY CHRONIC CONDITIONS; ATTENTION TO OSTOMIES 292 NEUROLOGICAL DYSFUNCTION IN POSTURE AND MOVEMENT CAUSED BY CHRONIC CONDITIONS 345 NEUROLOGICAL DYSFUNCTION IN COMMUNICATION CAUSED BY CHRONIC CONDITIONS 377 DYSFUNCTION RESULTING IN LOSS OF ABILITY TO MAXIMIZE LEVEL OF INDEPENDENCE IN SELF-DIRECTED CARE CAUSED BY CHRONIC CONDITIONS THAT CAUSE NEUROLOGICAL DYSFUNCTION	
E75.28	Canavan disease	Similar disease family to E75.27 above. Previously coded with E75.29 (Other sphingolipidosis) which is on lines 71, 292, 345, 377	71 NEUROLOGICAL DYSFUNCTION IN BREATHING, EATING, SWALLOWING, BOWEL, OR BLADDER CONTROL CAUSED BY CHRONIC CONDITIONS; ATTENTION TO OSTOMIES 292 NEUROLOGICAL DYSFUNCTION IN POSTURE AND MOVEMENT CAUSED BY CHRONIC CONDITIONS 345 NEUROLOGICAL DYSFUNCTION IN COMMUNICATION CAUSED BY CHRONIC CONDITIONS 377 DYSFUNCTION RESULTING IN LOSS OF ABILITY TO MAXIMIZE LEVEL OF INDEPENDENCE IN SELF-DIRECTED CARE CAUSED BY CHRONIC CONDITIONS THAT CAUSE NEUROLOGICAL DYSFUNCTION	

Code	Code Description	Similar codes	Recommended Placement	Notes
E79.81	Aicardi-Goutieres syndrome	Aicardi-Goutières syndrome is a rare inherited disease that mainly affects the brain, immune system, and the skin. This disease leads to mild to severe intellectual or physical impairments in most children. Other organs, including the eyes (glaucoma), thyroid (hypothyroidism), lungs (pulmonary hypertension), heart (cardiomyopathy), liver (autoimmune hepatitis), muscle (myopathy) and joints (arthropathy) may become involved. Similar codes: This syndrome was previously coded with G31.89 (Other specified degenerative diseases of nervous system) was on the dysfunction lines: 71,292,345,377	71 NEUROLOGICAL DYSFUNCTION IN BREATHING, EATING, SWALLOWING, BOWEL, OR BLADDER CONTROL CAUSED BY CHRONIC CONDITIONS; ATTENTION TO OSTOMIES 292 NEUROLOGICAL DYSFUNCTION IN POSTURE AND MOVEMENT CAUSED BY CHRONIC CONDITIONS 345 NEUROLOGICAL DYSFUNCTION IN COMMUNICATION CAUSED BY CHRONIC CONDITIONS 377 DYSFUNCTION RESULTING IN LOSS OF ABILITY TO MAXIMIZE LEVEL OF INDEPENDENCE IN SELF-DIRECTED CARE CAUSED BY CHRONIC CONDITIONS THAT CAUSE NEUROLOGICAL DYSFUNCTION	

Code	Code Description	Similar codes	Recommended Placement	Notes
E79.82	Hereditary xanthinuria		71 NEUROLOGICAL DYSFUNCTION IN BREATHING, EATING, SWALLOWING, BOWEL, OR BLADDER CONTROL CAUSED BY CHRONIC CONDITIONS; ATTENTION TO OSTOMIES 292 NEUROLOGICAL DYSFUNCTION IN POSTURE AND MOVEMENT CAUSED BY CHRONIC CONDITIONS 345 NEUROLOGICAL DYSFUNCTION IN COMMUNICATION CAUSED BY CHRONIC CONDITIONS 377 DYSFUNCTION RESULTING IN LOSS OF ABILITY TO MAXIMIZE LEVEL OF INDEPENDENCE IN SELF-DIRECTED CARE CAUSED BY CHRONIC CONDITIONS THAT CAUSE NEUROLOGICAL DYSFUNCTION	See Informational Issues
E79.89	Other specified disorders of purine and pyrimidine metabolism	Parent code E79.8 was on the dysfunction lines	71 NEUROLOGICAL DYSFUNCTION IN BREATHING, EATING, SWALLOWING, BOWEL, OR BLADDER CONTROL CAUSED BY CHRONIC CONDITIONS; ATTENTION TO OSTOMIES 292 NEUROLOGICAL DYSFUNCTION IN POSTURE AND MOVEMENT CAUSED BY CHRONIC CONDITIONS 345 NEUROLOGICAL DYSFUNCTION IN COMMUNICATION CAUSED BY CHRONIC CONDITIONS 377 DYSFUNCTION RESULTING IN LOSS OF ABILITY TO MAXIMIZE LEVEL OF INDEPENDENCE IN SELF-DIRECTED CARE CAUSED BY CHRONIC CONDITIONS THAT CAUSE NEUROLOGICAL DYSFUNCTION	

Code	Code Description	Similar codes	Recommended Placement	Notes
E88.43	Disorders of mitochondrial tRNA synthetases	Similar code E88.40 (Mitochondrial metabolism disorder, unspecified) is on lines 60,71,292,345,377	60 METABOLIC DISORDERS 71 NEUROLOGICAL DYSFUNCTION IN BREATHING, EATING, SWALLOWING, BOWEL, OR BLADDER CONTROL CAUSED BY CHRONIC CONDITIONS; ATTENTION TO OSTOMIES292 NEUROLOGICAL DYSFUNCTION IN POSTURE AND MOVEMENT CAUSED BY CHRONIC CONDITIONS 345 NEUROLOGICAL DYSFUNCTION IN COMMUNICATION CAUSED BY CHRONIC CONDITIONS 377 DYSFUNCTION RESULTING IN LOSS OF ABILITY TO MAXIMIZE LEVEL OF INDEPENDENCE IN SELF-DIRECTED CARE CAUSED BY CHRONIC CONDITIONS THAT CAUSE NEUROLOGICAL DYSFUNCTION	
E88.810	Metabolic syndrome		60 METABOLIC DISORDERS	See Discussion Issues
E88.811	Insulin resistance syndrome, Type A		60 METABOLIC DISORDERS	See Discussion Issues
E88.818	Other insulin resistance		60 METABOLIC DISORDERS	See Discussion Issues
E88.819	Insulin resistance, unspecified		60 METABOLIC DISORDERS	See Discussion Issues
E88.A	Wasting disease (syndrome) due to underlying condition	Most muscle wasting conditions are on lines 292,377. Cachexia (ICD10 R64) is on the DIAGNOSTIC WORKUP FILE (DWF)	292 NEUROLOGICAL DYSFUNCTION IN POSTURE AND MOVEMENT CAUSED BY CHRONIC CONDITIONS 377 DYSFUNCTION RESULTING IN LOSS OF ABILITY TO MAXIMIZE LEVEL OF INDEPENDENCE IN SELF-DIRECTED CARE CAUSED BY CHRONIC CONDITIONS THAT CAUSE NEUROLOGICAL DYSFUNCTION	

Code	Code Description	Similar codes	Recommended Placement	Notes
G11.5	Hypomyelination - hypogonadotropic hypogonadism - hypodontia		71 NEUROLOGICAL DYSFUNCTION IN BREATHING, EATING, SWALLOWING, BOWEL, OR BLADDER CONTROL CAUSED BY CHRONIC CONDITIONS; ATTENTION TO OSTOMIES 292 NEUROLOGICAL DYSFUNCTION IN POSTURE AND MOVEMENT CAUSED BY CHRONIC CONDITIONS 345 NEUROLOGICAL DYSFUNCTION IN COMMUNICATION CAUSED BY CHRONIC CONDITIONS 377 DYSFUNCTION RESULTING IN LOSS OF ABILITY TO MAXIMIZE LEVEL OF INDEPENDENCE IN SELF-DIRECTED CARE CAUSED BY CHRONIC CONDITIONS THAT CAUSE NEUROLOGICAL DYSFUNCTION 470 GONADAL DYSFUNCTION, MENOPAUSAL MANAGEMENT	See Informational Issues

Code	Code Description	Similar codes	Recommended Placement	Notes
G11.6	Leukodystrophy with vanishing white matter disease	All codes in the G11 family (Hereditary ataxia) are on the dysfunction lines	71 NEUROLOGICAL DYSFUNCTION IN BREATHING, EATING, SWALLOWING, BOWEL, OR BLADDER CONTROL CAUSED BY CHRONIC CONDITIONS; ATTENTION TO OSTOMIES 292 NEUROLOGICAL DYSFUNCTION IN POSTURE AND MOVEMENT CAUSED BY CHRONIC CONDITIONS 345 NEUROLOGICAL DYSFUNCTION IN COMMUNICATION CAUSED BY CHRONIC CONDITIONS 377 DYSFUNCTION RESULTING IN LOSS OF ABILITY TO MAXIMIZE LEVEL OF INDEPENDENCE IN SELF-DIRECTED CARE CAUSED BY CHRONIC CONDITIONS THAT CAUSE NEUROLOGICAL DYSFUNCTION	
G20.A1	Parkinson's disease without dyskinesia, without mention of fluctuations	Parent code G20 (Parkinson's disease) was on lines 71,249,292,345,377	71 NEUROLOGICAL DYSFUNCTION IN BREATHING, EATING, SWALLOWING, BOWEL, OR BLADDER CONTROL CAUSED BY CHRONIC CONDITIONS; ATTENTION TO OSTOMIES 249 PARKINSON'S DISEASE 292 NEUROLOGICAL DYSFUNCTION IN POSTURE AND MOVEMENT CAUSED BY CHRONIC CONDITIONS 345 NEUROLOGICAL DYSFUNCTION IN COMMUNICATION CAUSED BY CHRONIC CONDITIONS 377 DYSFUNCTION RESULTING IN LOSS OF ABILITY TO MAXIMIZE LEVEL OF INDEPENDENCE IN SELF-DIRECTED CARE CAUSED BY CHRONIC CONDITIONS THAT CAUSE NEUROLOGICAL DYSFUNCTION	

Code	Code Description	Similar codes	Recommended Placement	Notes
G20.A2	Parkinson's disease without dyskinesia, with fluctuations	See G20.A1	71, 249, 292, 345, 377	
G20.B1	Parkinson's disease with dyskinesia, without mention of fluctuations	See G20.A1	71, 249, 292, 345, 377	
G20.B2	Parkinson's disease with dyskinesia, with fluctuations	See G20.A1	71, 249, 292, 345, 377	
G20.C	Parkinsonism, unspecified	See G20.A1	71, 249, 292, 345, 377	
G23.3	Hypomyelination with atrophy of the basal ganglia and cerebellum	All codes in the G21 family (degenerative diseases of the ganglia) are on lines 71, 292, 345, 362, 377	71 NEUROLOGICAL DYSFUNCTION IN BREATHING, EATING, SWALLOWING, BOWEL, OR BLADDER CONTROL CAUSED BY CHRONIC CONDITIONS; ATTENTION TO OSTOMIES 292 NEUROLOGICAL DYSFUNCTION IN POSTURE AND MOVEMENT CAUSED BY CHRONIC CONDITIONS 345 NEUROLOGICAL DYSFUNCTION IN COMMUNICATION CAUSED BY CHRONIC CONDITIONS 362 DYSTONIA (UNCONTROLLABLE); LARYNGEAL SPASM 377 DYSFUNCTION RESULTING IN LOSS OF ABILITY TO MAXIMIZE LEVEL OF INDEPENDENCE IN SELF-DIRECTED CARE CAUSED BY CHRONIC CONDITIONS THAT CAUSE NEUROLOGICAL DYSFUNCTION	

Code	Code Description	Similar codes	Recommended Placement	Notes
G31.80	Leukodystrophy, unspecified	All codes in the G31 (Other degenerative diseases of nervous system) family are on the dysfunction lines	71 NEUROLOGICAL DYSFUNCTION IN BREATHING, EATING, SWALLOWING, BOWEL, OR BLADDER CONTROL CAUSED BY CHRONIC CONDITIONS; ATTENTION TO OSTOMIES 292 NEUROLOGICAL DYSFUNCTION IN POSTURE AND MOVEMENT CAUSED BY CHRONIC CONDITIONS 345 NEUROLOGICAL DYSFUNCTION IN COMMUNICATION CAUSED BY CHRONIC CONDITIONS 377 DYSFUNCTION RESULTING IN LOSS OF ABILITY TO MAXIMIZE LEVEL OF INDEPENDENCE IN SELF-DIRECTED CARE CAUSED BY CHRONIC CONDITIONS THAT CAUSE NEUROLOGICAL DYSFUNCTION	
G31.86	Alexander disease	Alexander disease is a demylinating degenerative brain disease. Treatment is focused on symptom management	71, 292, 345, 377	

Code	Code Description	Similar codes	Recommended Placement	Notes
G37.81	Myelin oligodendrocyte glycoprotein antibody disease		71 NEUROLOGICAL DYSFUNCTION IN BREATHING, EATING, SWALLOWING, BOWEL, OR BLADDER CONTROL CAUSED BY CHRONIC CONDITIONS; ATTENTION TO OSTOMIES 292 NEUROLOGICAL DYSFUNCTION IN POSTURE AND MOVEMENT CAUSED BY CHRONIC CONDITIONS 313 DISORDERS INVOLVING THE IMMUNE SYSTEM 345 NEUROLOGICAL DYSFUNCTION IN COMMUNICATION CAUSED BY CHRONIC CONDITIONS 377 DYSFUNCTION RESULTING IN LOSS OF ABILITY TO MAXIMIZE LEVEL OF INDEPENDENCE IN SELF-DIRECTED CARE CAUSED BY CHRONIC CONDITIONS THAT CAUSE NEUROLOGICAL DYSFUNCTION	See Informational Issues
G37.89	Other specified demyelinating diseases of central nervous system	Parent code G37.8 (Other specified demyelinating diseases of central nervous system) was on lines 71,251,292,345,377	71, 251, 292, 345, 377	
G40.C01	Lafora progressive myoclonus epilepsy, not intractable, with status epilepticus	Epilepsy diagnoses are on line 30 EPILEPSY AND FEBRILE CONVULSIONS	30 EPILEPSY AND FEBRILE CONVULSIONS	
G40.C09	Lafora progressive myoclonus epilepsy, not intractable, without status epilepticus	Epilepsy diagnoses are on line 30 EPILEPSY AND FEBRILE CONVULSIONS	30 EPILEPSY AND FEBRILE CONVULSIONS	

Code	Code Description	Similar codes	Recommended Placement	Notes
G40.C11	Lafora progressive myoclonus epilepsy, intractable, with status epilepticus	Epilepsy diagnoses are on line 30 EPILEPSY AND FEBRILE CONVULSIONS	30 EPILEPSY AND FEBRILE CONVULSIONS	
G40.C19	Lafora progressive myoclonus epilepsy, intractable, without status epilepticus	Epilepsy diagnoses are on line 30 EPILEPSY AND FEBRILE CONVULSIONS	30 EPILEPSY AND FEBRILE CONVULSIONS	
G43.E01	Chronic migraine with aura, not intractable, with status migrainosus	migraine diagnoses are on line 410	410 MIGRAINE HEADACHES	
G43.E09	Chronic migraine with aura, not intractable, without status migrainosus	migraine diagnoses are on line 410	410 MIGRAINE HEADACHES	
G43.E11	Chronic migraine with aura, intractable, with status migrainosus	migraine diagnoses are on line 410	410 MIGRAINE HEADACHES	
G43.E19	Chronic migraine with aura, intractable, without status migrainosus	migraine diagnoses are on line 410	410 MIGRAINE HEADACHES	

Code	Code Description	Similar codes	Recommended Placement	Notes
G90.B	LMNB1-related autosomal dominant leukodystrophy	LMNB1-related autosomal dominant leukodystrophy is a slowly progressive disorder of central nervous system white matter characterized by onset of autonomic dysfunction, spasticity, ataxia, tremor, bladder dysfunction, constipation, postural hypotension, erectile dysfunction, and (less often) impaired sweating, gait ataxia, dysdiadochokinesia, intention tremor, dysmetria, and nystagmus, sensory deficits, dysarthria, dysphagia. Treatment is symptomatic	71 NEUROLOGICAL DYSFUNCTION IN BREATHING, EATING, SWALLOWING, BOWEL, OR BLADDER CONTROL CAUSED BY CHRONIC CONDITIONS; ATTENTION TO OSTOMIES 292 NEUROLOGICAL DYSFUNCTION IN POSTURE AND MOVEMENT CAUSED BY CHRONIC CONDITIONS 345 NEUROLOGICAL DYSFUNCTION IN COMMUNICATION CAUSED BY CHRONIC CONDITIONS 362 DYSTONIA (UNCONTROLLABLE); LARYNGEAL SPASM 377 DYSFUNCTION RESULTING IN LOSS OF ABILITY TO MAXIMIZE LEVEL OF INDEPENDENCE IN SELF-DIRECTED CARE CAUSED BY CHRONIC CONDITIONS THAT CAUSE NEUROLOGICAL DYSFUNCTION	

Code	Code Description	Similar codes	Recommended Placement	Notes
G93.42	Megaloencephalic leukoencephalopathy with subcortical cysts	Other G93.4 family codes (encephalopathy) are on the dysfunction lines	71 NEUROLOGICAL DYSFUNCTION IN BREATHING, EATING, SWALLOWING, BOWEL, OR BLADDER CONTROL CAUSED BY CHRONIC CONDITIONS; ATTENTION TO OSTOMIES 292 NEUROLOGICAL DYSFUNCTION IN POSTURE AND MOVEMENT CAUSED BY CHRONIC CONDITIONS 345 NEUROLOGICAL DYSFUNCTION IN COMMUNICATION CAUSED BY CHRONIC CONDITIONS 362 DYSTONIA (UNCONTROLLABLE); LARYNGEAL SPASM 377 DYSFUNCTION RESULTING IN LOSS OF ABILITY TO MAXIMIZE LEVEL OF INDEPENDENCE IN SELF-DIRECTED CARE CAUSED BY CHRONIC CONDITIONS THAT CAUSE NEUROLOGICAL DYSFUNCTION	
G93.43	Leukoencephalopathy with calcifications and cysts	See G93.42	71, 292, 345, 377	
G93.44	Adult-onset leukodystrophy with axonal spheroids	See G93.42	71, 292, 345, 377	
H36.811	Nonproliferative sickle-cell retinopathy, right eye	Retinopathy codes are on line 95	95 DIABETIC AND OTHER RETINOPATHY	
H36.812	Nonproliferative sickle-cell retinopathy, left eye	Retinopathy codes are on line 95	95 DIABETIC AND OTHER RETINOPATHY	

Code	Code Description	Similar codes	Recommended Placement	Notes
H36.813	Nonproliferative sickle-cell retinopathy, bilateral	Retinopathy codes are on line 95	95 DIABETIC AND OTHER RETINOPATHY	
H36.819	Nonproliferative sickle-cell retinopathy, unspecified eye	Retinopathy codes are on line 95	95 DIABETIC AND OTHER RETINOPATHY	
H36.821	Proliferative sickle-cell retinopathy, right eye	Retinopathy codes are on line 95	95 DIABETIC AND OTHER RETINOPATHY	
H36.822	Proliferative sickle-cell retinopathy, left eye	Retinopathy codes are on line 95	95 DIABETIC AND OTHER RETINOPATHY	
H36.823	Proliferative sickle-cell retinopathy, bilateral	Retinopathy codes are on line 95	95 DIABETIC AND OTHER RETINOPATHY	
H36.829	Proliferative sickle-cell retinopathy, unspecified eye	Retinopathy codes are on line 95	95 DIABETIC AND OTHER RETINOPATHY	
H36.89	Other retinal disorders in diseases classified elsewhere		UNDEFINED CONDITIONS	
H50.621	Inferior oblique muscle entrapment, right eye	Similar code H50.60 (Mechanical strabismus, unspecified) is on line 393	393 STRABISMUS WITHOUT AMBLYOPIA AND OTHER DISORDERS OF BINOCULAR EYE MOVEMENTS; CONGENITAL ANOMALIES OF EYE; LACRIMAL DUCT OBSTRUCTION IN CHILDREN	
H50.622	Inferior oblique muscle entrapment, left eye	Similar code H50.60 (Mechanical strabismus, unspecified) is on line 393	393 STRABISMUS WITHOUT AMBLYOPIA AND OTHER DISORDERS OF BINOCULAR EYE MOVEMENTS; CONGENITAL ANOMALIES OF EYE; LACRIMAL DUCT OBSTRUCTION IN CHILDREN	

Code	Code Description	Similar codes	Recommended Placement	Notes
H50.629	Inferior oblique muscle entrapment, unspecified eye	Similar code H50.60 (Mechanical strabismus, unspecified) is on line 393	393 STRABISMUS WITHOUT AMBLYOPIA AND OTHER DISORDERS OF BINOCULAR EYE MOVEMENTS; CONGENITAL ANOMALIES OF EYE; LACRIMAL DUCT OBSTRUCTION IN CHILDREN	
H50.631	Inferior rectus muscle entrapment, right eye	Similar code H50.60 (Mechanical strabismus, unspecified) is on line 393	393 STRABISMUS WITHOUT AMBLYOPIA AND OTHER DISORDERS OF BINOCULAR EYE MOVEMENTS; CONGENITAL ANOMALIES OF EYE; LACRIMAL DUCT OBSTRUCTION IN CHILDREN	
H50.632	Inferior rectus muscle entrapment, left eye	Similar code H50.60 (Mechanical strabismus, unspecified) is on line 393	393 STRABISMUS WITHOUT AMBLYOPIA AND OTHER DISORDERS OF BINOCULAR EYE MOVEMENTS; CONGENITAL ANOMALIES OF EYE; LACRIMAL DUCT OBSTRUCTION IN CHILDREN	
H50.639	Inferior rectus muscle entrapment, unspecified eye	Similar code H50.60 (Mechanical strabismus, unspecified) is on line 393	393 STRABISMUS WITHOUT AMBLYOPIA AND OTHER DISORDERS OF BINOCULAR EYE MOVEMENTS; CONGENITAL ANOMALIES OF EYE; LACRIMAL DUCT OBSTRUCTION IN CHILDREN	
H50.641	Lateral rectus muscle entrapment, right eye	Similar code H50.60 (Mechanical strabismus, unspecified) is on line 393	393 STRABISMUS WITHOUT AMBLYOPIA AND OTHER DISORDERS OF BINOCULAR EYE MOVEMENTS; CONGENITAL ANOMALIES OF EYE; LACRIMAL DUCT OBSTRUCTION IN CHILDREN	
H50.642	Lateral rectus muscle entrapment, left eye	Similar code H50.60 (Mechanical strabismus, unspecified) is on line 393	393 STRABISMUS WITHOUT AMBLYOPIA AND OTHER DISORDERS OF BINOCULAR EYE MOVEMENTS; CONGENITAL ANOMALIES OF EYE; LACRIMAL DUCT OBSTRUCTION IN CHILDREN	

Code	Code Description	Similar codes	Recommended Placement	Notes
H50.649	Lateral rectus muscle entrapment, unspecified eye	Similar code H50.60 (Mechanical strabismus, unspecified) is on line 393	393 STRABISMUS WITHOUT AMBLYOPIA AND OTHER DISORDERS OF BINOCULAR EYE MOVEMENTS; CONGENITAL ANOMALIES OF EYE; LACRIMAL DUCT OBSTRUCTION IN CHILDREN	
H50.651	Medial rectus muscle entrapment, right eye	Similar code H50.60 (Mechanical strabismus, unspecified) is on line 393	393 STRABISMUS WITHOUT AMBLYOPIA AND OTHER DISORDERS OF BINOCULAR EYE MOVEMENTS; CONGENITAL ANOMALIES OF EYE; LACRIMAL DUCT OBSTRUCTION IN CHILDREN	
H50.652	Medial rectus muscle entrapment, left eye	Similar code H50.60 (Mechanical strabismus, unspecified) is on line 393	393 STRABISMUS WITHOUT AMBLYOPIA AND OTHER DISORDERS OF BINOCULAR EYE MOVEMENTS; CONGENITAL ANOMALIES OF EYE; LACRIMAL DUCT OBSTRUCTION IN CHILDREN	
H50.659	Medial rectus muscle entrapment, unspecified eye	Similar code H50.60 (Mechanical strabismus, unspecified) is on line 393	393 STRABISMUS WITHOUT AMBLYOPIA AND OTHER DISORDERS OF BINOCULAR EYE MOVEMENTS; CONGENITAL ANOMALIES OF EYE; LACRIMAL DUCT OBSTRUCTION IN CHILDREN	
H50.661	Superior oblique muscle entrapment, right eye	Similar code H50.60 (Mechanical strabismus, unspecified) is on line 393	393 STRABISMUS WITHOUT AMBLYOPIA AND OTHER DISORDERS OF BINOCULAR EYE MOVEMENTS; CONGENITAL ANOMALIES OF EYE; LACRIMAL DUCT OBSTRUCTION IN CHILDREN	
H50.662	Superior oblique muscle entrapment, left eye	Similar code H50.60 (Mechanical strabismus, unspecified) is on line 393	393 STRABISMUS WITHOUT AMBLYOPIA AND OTHER DISORDERS OF BINOCULAR EYE MOVEMENTS; CONGENITAL ANOMALIES OF EYE; LACRIMAL DUCT OBSTRUCTION IN CHILDREN	

Code	Code Description	Similar codes	Recommended Placement	Notes
H50.669	Superior oblique muscle entrapment, unspecified eye	Similar code H50.60 (Mechanical strabismus, unspecified) is on line 393	393 STRABISMUS WITHOUT AMBLYOPIA AND OTHER DISORDERS OF BINOCULAR EYE MOVEMENTS; CONGENITAL ANOMALIES OF EYE; LACRIMAL DUCT OBSTRUCTION IN CHILDREN	
H50.671	Superior rectus muscle entrapment, right eye	Similar code H50.60 (Mechanical strabismus, unspecified) is on line 393	393 STRABISMUS WITHOUT AMBLYOPIA AND OTHER DISORDERS OF BINOCULAR EYE MOVEMENTS; CONGENITAL ANOMALIES OF EYE; LACRIMAL DUCT OBSTRUCTION IN CHILDREN	
H50.672	Superior rectus muscle entrapment, left eye	Similar code H50.60 (Mechanical strabismus, unspecified) is on line 393	393 STRABISMUS WITHOUT AMBLYOPIA AND OTHER DISORDERS OF BINOCULAR EYE MOVEMENTS; CONGENITAL ANOMALIES OF EYE; LACRIMAL DUCT OBSTRUCTION IN CHILDREN	
H50.679	Superior rectus muscle entrapment, unspecified eye	Similar code H50.60 (Mechanical strabismus, unspecified) is on line 393	393 STRABISMUS WITHOUT AMBLYOPIA AND OTHER DISORDERS OF BINOCULAR EYE MOVEMENTS; CONGENITAL ANOMALIES OF EYE; LACRIMAL DUCT OBSTRUCTION IN CHILDREN	
H50.681	Extraocular muscle entrapment, unspecified, right eye	Similar code H50.60 (Mechanical strabismus, unspecified) is on line 393	393 STRABISMUS WITHOUT AMBLYOPIA AND OTHER DISORDERS OF BINOCULAR EYE MOVEMENTS; CONGENITAL ANOMALIES OF EYE; LACRIMAL DUCT OBSTRUCTION IN CHILDREN	
H50.682	Extraocular muscle entrapment, unspecified, left eye	Similar code H50.60 (Mechanical strabismus, unspecified) is on line 393	393 STRABISMUS WITHOUT AMBLYOPIA AND OTHER DISORDERS OF BINOCULAR EYE MOVEMENTS; CONGENITAL ANOMALIES OF EYE; LACRIMAL DUCT OBSTRUCTION IN CHILDREN	

Code	Code Description	Similar codes	Recommended Placement	Notes
H50.689	Extraocular muscle entrapment, unspecified, unspecified eye		UNDEFINED CONDITIONS	
H57.8A1	Foreign body sensation, right eye		DIAGNOSTIC WORKUP FILE (DWF)	
H57.8A2	Foreign body sensation, left eye		DIAGNOSTIC WORKUP FILE (DWF)	
H57.8A3	Foreign body sensation, bilateral eyes		DIAGNOSTIC WORKUP FILE (DWF)	
H57.8A9	Foreign body sensation, unspecified eye		DIAGNOSTIC WORKUP FILE (DWF)	
I1A.0	Resistant hypertension	Similar conditions are on line 75	75 HYPERTENSION AND HYPERTENSIVE DISEASE	
I20.81	Angina pectoris with coronary microvascular dysfunction	Parent code I20.8 (Other forms of angina pectoris) was on line 189	189 CHRONIC ISCHEMIC HEART DISEASE	
I20.89	Other forms of angina pectoris	Parent code I20.8 (Other forms of angina pectoris) was on line 189	189 CHRONIC ISCHEMIC HEART DISEASE	
I21.B	Myocardial infarction with coronary microvascular dysfunction	Similar codes are on line 69	69 ACUTE AND SUBACUTE ISCHEMIC HEART DISEASE, MYOCARDIAL INFARCTION	
I24.81	Acute coronary microvascular dysfunction	Parent code I24.8 (Other forms of acute ischemic heart disease) was on line 69	69 ACUTE AND SUBACUTE ISCHEMIC HEART DISEASE, MYOCARDIAL INFARCTION	
I24.89	Other forms of acute ischemic heart disease	Parent code I24.8 (Other forms of acute ischemic heart disease) was on line 69	69 ACUTE AND SUBACUTE ISCHEMIC HEART DISEASE, MYOCARDIAL INFARCTION	

Code	Code Description	Similar codes	Recommended Placement	Notes
I25.85	Chronic coronary microvascular dysfunction	Other codes is the I25.85 family are on line 189	189 CHRONIC ISCHEMIC HEART DISEASE	
I47.10	Supraventricular tachycardia, unspecified	Parent code I47.1 (Supraventricular tachycardia) was on line 347	347 CARDIAC ARRHYTHMIAS	
I47.11	Inappropriate sinus tachycardia, so stated	Parent code I47.1 (Supraventricular tachycardia) was on line 347	347 CARDIAC ARRHYTHMIAS	
I47.19	Other supraventricular tachycardia	Parent code I47.1 (Supraventricular tachycardia) was on line 347	347 CARDIAC ARRHYTHMIAS	
J15.61	Pneumonia due to Acinetobacter baumannii	Pneumonia codes are on line 204	204 PNEUMOCOCCAL PNEUMONIA, OTHER BACTERIAL	
J15.69	Pneumonia due to other Gram-negative bacteria	Pneumonia codes are on line 204	204 PNEUMOCOCCAL PNEUMONIA, OTHER BACTERIAL	
J44.81	Bronchiolitis obliterans and bronchiolitis obliterans syndrome		219 PULMONARY FIBROSIS 240 CONDITIONS REQUIRING HEART-LUNG AND LUNG TRANSPLANTATION	See Discussion Issues
J44.89	Other specified chronic obstructive pulmonary disease	Other COPD codes are on line 283	283 CHRONIC OBSTRUCTIVE PULMONARY DISEASE; CHRONIC RESPIRATORY FAILURE	
J4A.0	Restrictive allograft syndrome		219 PULMONARY FIBROSIS 240 CONDITIONS REQUIRING HEART-LUNG AND LUNG TRANSPLANTATION	See Discussionl Issues
J4A.8	Other chronic lung allograft dysfunction	See J44.89 and J4A.0 above	219 PULMONARY FIBROSIS 240 CONDITIONS REQUIRING HEART-LUNG AND LUNG TRANSPLANTATION	

Code	Code Description	Similar codes	Recommended Placement	Notes
J4A.9	Chronic lung allograft dysfunction, unspecified	See J44.89 and J4A.0 above	219 PULMONARY FIBROSIS 240 CONDITIONS REQUIRING HEART-LUNG AND LUNG TRANSPLANTATION	
K35.200	Acute appendicitis with generalized peritonitis, without perforation or abscess	Acute appendicitis codes are on line 47	47 DEEP ABSCESSES, INCLUDING APPENDICITIS AND PERIORBITAL ABSCESS	
K35.201	Acute appendicitis with generalized peritonitis, with perforation, without abscess		47 DEEP ABSCESSES, INCLUDING APPENDICITIS AND PERIORBITAL ABSCESS	
K35.209	Acute appendicitis with generalized peritonitis, without abscess, unspecified as to perforation		47 DEEP ABSCESSES, INCLUDING APPENDICITIS AND PERIORBITAL ABSCESS	
K35.210	Acute appendicitis with generalized peritonitis, without perforation, with abscess		47 DEEP ABSCESSES, INCLUDING APPENDICITIS AND PERIORBITAL ABSCESS	
K35.211	Acute appendicitis with generalized peritonitis, with perforation and abscess		47 DEEP ABSCESSES, INCLUDING APPENDICITIS AND PERIORBITAL ABSCESS	
K35.219	Acute appendicitis with generalized peritonitis, with abscess, unspecified as to perforation		47 DEEP ABSCESSES, INCLUDING APPENDICITIS AND PERIORBITAL ABSCESS	

Code	Code Description	Similar codes	Recommended Placement	Notes
K63.8211	Small intestinal bacterial overgrowth, hydrogen-subtype		553 OTHER NONINFECTIOUS GASTROENTERITIS AND COLITIS	See Discussion Issues
K63.8212	Small intestinal bacterial overgrowth, hydrogen sulfide-subtype		553 OTHER NONINFECTIOUS GASTROENTERITIS AND COLITIS	See Discussion Issues
K63.8219	Small intestinal bacterial overgrowth, unspecified		553 OTHER NONINFECTIOUS GASTROENTERITIS AND COLITIS	See Discussion Issues
K63.822	Small intestinal fungal overgrowth	Similar code B37.82 (Candidal enteritis) is on line 231	231 MYCOBACTERIA, FUNGAL INFECTIONS, TOXOPLASMOSIS, AND OTHER OPPORTUNISTIC INFECTIONS	
K63.829	Intestinal methanogen overgrowth, unspecified		553 OTHER NONINFECTIOUS GASTROENTERITIS AND COLITIS	See Discussion Issues
K68.2	Retroperitoneal fibrosis		180 URETERAL STRICTURE OR OBSTRUCTION; HYDRONEPHROSIS; HYDROURETER	See Informational Issues
K68.3	Retroperitoneal hematoma	Similar code S36.892 (Contusion of other intra-abdominal organs) is on line 79 INJURY TO INTERNAL ORGANS. Line 79 contains CPT codes for repair of retroperitoneal vaculature and placement of ureteral stents. CPT 49010 (Exploration, retroperitoneal area with or without biopsy(s)) is Diagnostic	79 INJURY TO INTERNAL ORGANS	

Code	Code Description	Similar codes	Recommended Placement	Notes
K90.821	Short bowel syndrome with colon in continuity	Previously coded with K91.2 (Postsurgical malabsorption, not elsewhere classified) which is on lines 227 and 239	227 INTESTINAL MALABSORPTION 239 SHORT BOWEL SYNDROME Treatment INTESTINE AND INTESTINE/LIVER TRANSPLANT	
K90.822	Short bowel syndrome without colon in continuity	See K90.821	227 INTESTINAL MALABSORPTION 239 SHORT BOWEL SYNDROME Treatment INTESTINE AND INTESTINE/LIVER TRANSPLANT	
K90.829	Short bowel syndrome, unspecified	See K90.821	227 INTESTINAL MALABSORPTION 239 SHORT BOWEL SYNDROME Treatment INTESTINE AND INTESTINE/LIVER TRANSPLANT	
K90.83	Intestinal failure	See K90.821	227 INTESTINAL MALABSORPTION 239 SHORT BOWEL SYNDROME Treatment INTESTINE AND INTESTINE/LIVER TRANSPLANT	
M80.0B1A	Age-related osteoporosis with current pathological fracture, right pelvis, initial encounter for fracture	Similar codes are on line for the specific fracture type	183 FRACTURE OF PELVIS, OPEN AND CLOSED	
M80.0B1D	Age-related osteoporosis with current pathological fracture, right pelvis, subsequent encounter for fracture with routine healing	Similar codes are on line for the specific fracture type	183 FRACTURE OF PELVIS, OPEN AND CLOSED	

Code	Code Description	Similar codes	Recommended Placement	Notes
M80.0B1G	Age-related osteoporosis with current pathological fracture, right pelvis, subsequent encounter for fracture with delayed healing	Similar codes are on line for the specific fracture type	183 FRACTURE OF PELVIS, OPEN AND CLOSED	
M80.0B1K	Age-related osteoporosis with current pathological fracture, right pelvis, subsequent encounter for fracture with nonunion	nonunion of pelvic fracture codes are on line 443	443 MALUNION AND NONUNION OF FRACTURE	
M80.0B1P	Age-related osteoporosis with current pathological fracture, right pelvis, subsequent encounter for fracture with malunion	nonunion of pelvic fracture codes are on line 443	443 MALUNION AND NONUNION OF FRACTURE	
M80.0B2A	Age-related osteoporosis with current pathological fracture, left pelvis, initial encounter for fracture	Similar codes are on line for the specific fracture type	183 FRACTURE OF PELVIS, OPEN AND CLOSED	

Code	Code Description	Similar codes	Recommended Placement	Notes
M80.0B2D	Age-related osteoporosis with current pathological fracture, left pelvis, subsequent encounter for fracture with routine healing	Similar codes are on line for the specific fracture type	183 FRACTURE OF PELVIS, OPEN AND CLOSED	
M80.0B2G	Age-related osteoporosis with current pathological fracture, left pelvis, subsequent encounter for fracture with delayed healing	Similar codes are on line for the specific fracture type	183 FRACTURE OF PELVIS, OPEN AND CLOSED	
M80.0B2K	Age-related osteoporosis with current pathological fracture, left pelvis, subsequent encounter for fracture with nonunion	nonunion of pelvic fracture codes are on line 443	443 MALUNION AND NONUNION OF FRACTURE	
M80.0B2P	Age-related osteoporosis with current pathological fracture, left pelvis, subsequent encounter for fracture with malunion	nonunion of pelvic fracture codes are on line 443	443 MALUNION AND NONUNION OF FRACTURE	

Code	Code Description	Similar codes	Recommended Placement	Notes
M80.0B9A	Age-related osteoporosis with current pathological fracture, unspecified pelvis, initial encounter for fracture	Similar codes are on line for the specific fracture type	183 FRACTURE OF PELVIS, OPEN AND CLOSED	
M80.0B9D	Age-related osteoporosis with current pathological fracture, unspecified pelvis, subsequent encounter for fracture with routine healing	Similar codes are on line for the specific fracture type	183 FRACTURE OF PELVIS, OPEN AND CLOSED	
M80.0B9G	Age-related osteoporosis with current pathological fracture, unspecified pelvis, subsequent encounter for fracture with delayed healing	Similar codes are on line for the specific fracture type	183 FRACTURE OF PELVIS, OPEN AND CLOSED	
M80.0B9K	Age-related osteoporosis with current pathological fracture, unspecified pelvis, subsequent encounter for fracture with nonunion	nonunion of pelvic fracture codes are on line 443	443 MALUNION AND NONUNION OF FRACTURE	

Code	Code Description	Similar codes	Recommended Placement	Notes
M80.0B9P	Age-related osteoporosis with current pathological fracture, unspecified pelvis, subsequent encounter for fracture with malunion	nonunion of pelvic fracture codes are on line 443	443 MALUNION AND NONUNION OF FRACTURE	
M80.8B1A	Other osteoporosis with current pathological fracture, right pelvis, initial encounter for fracture	Similar codes are on line for the specific fracture type	183 FRACTURE OF PELVIS, OPEN AND CLOSED	
M80.8B1D	Other osteoporosis with current pathological fracture, right pelvis, subsequent encounter for fracture with routine healing	Similar codes are on line for the specific fracture type	183 FRACTURE OF PELVIS, OPEN AND CLOSED	
M80.8B1G	Other osteoporosis with current pathological fracture, right pelvis, subsequent encounter for fracture with delayed healing	Similar codes are on line for the specific fracture type	183 FRACTURE OF PELVIS, OPEN AND CLOSED	

Code	Code Description	Similar codes	Recommended Placement	Notes
M80.8B1K	Other osteoporosis with current pathological fracture, right pelvis, subsequent encounter for fracture with nonunion	nonunion of pelvic fracture codes are on line 443	443 MALUNION AND NONUNION OF FRACTURE	
M80.8B1P	Other osteoporosis with current pathological fracture, right pelvis, subsequent encounter for fracture with malunion	nonunion of pelvic fracture codes are on line 443	443 MALUNION AND NONUNION OF FRACTURE	
M80.8B2A	Other osteoporosis with current pathological fracture, left pelvis, initial encounter for fracture	Similar codes are on line for the specific fracture type	183 FRACTURE OF PELVIS, OPEN AND CLOSED	
M80.8B2D	Other osteoporosis with current pathological fracture, left pelvis, subsequent encounter for fracture with routine healing	Similar codes are on line for the specific fracture type	183 FRACTURE OF PELVIS, OPEN AND CLOSED	

Code	Code Description	Similar codes	Recommended Placement	Notes
M80.8B2G	Other osteoporosis with current pathological fracture, left pelvis, subsequent encounter for fracture with delayed healing	Similar codes are on line for the specific fracture type	183 FRACTURE OF PELVIS, OPEN AND CLOSED	
M80.8B2K	Other osteoporosis with current pathological fracture, left pelvis, subsequent encounter for fracture with nonunion	nonunion of pelvic fracture codes are on line 443	443 MALUNION AND NONUNION OF FRACTURE	
M80.8B2P	Other osteoporosis with current pathological fracture, left pelvis, subsequent encounter for fracture with malunion	nonunion of pelvic fracture codes are on line 443	443 MALUNION AND NONUNION OF FRACTURE	
M80.8B9A	Other osteoporosis with current pathological fracture, unspecified pelvis, initial encounter for fracture	Similar codes are on line for the specific fracture type	183 FRACTURE OF PELVIS, OPEN AND CLOSED	

Code	Code Description	Similar codes	Recommended Placement	Notes
M80.8B9D	Other osteoporosis with current pathological fracture, unspecified pelvis, subsequent encounter for fracture with routine healing	Similar codes are on line for the specific fracture type	183 FRACTURE OF PELVIS, OPEN AND CLOSED	
M80.8B9G	Other osteoporosis with current pathological fracture, unspecified pelvis, subsequent encounter for fracture with delayed healing	Similar codes are on line for the specific fracture type	183 FRACTURE OF PELVIS, OPEN AND CLOSED	
M80.8B9K	Other osteoporosis with current pathological fracture, unspecified pelvis, subsequent encounter for fracture with nonunion	nonunion of pelvic fracture codes are on line 443	443 MALUNION AND NONUNION OF FRACTURE	
M80.8B9P	Other osteoporosis with current pathological fracture, unspecified pelvis, subsequent encounter for fracture with malunion	nonunion of pelvic fracture codes are on line 443	443 MALUNION AND NONUNION OF FRACTURE	

Code	Code Description	Similar codes	Recommended Placement	Notes
N02.B1	Recurrent and persistent immunoglobulin A nephropathy with glomerular lesion	All nephropathy codes are on lines 99 and 339	99 END STAGE RENAL DISEASE Treatment RENAL TRANSPLANT 339 CHRONIC KIDNEY DISEASE Treatment MEDICAL THERAPY INCLUDING DIALYSIS	
N02.B2	Recurrent and persistent immunoglobulin A nephropathy with focal and segmental glomerular lesion	All nephropathy codes are on lines 99 and 339	99, 339	
N02.B3	Recurrent and persistent immunoglobulin A nephropathy with diffuse membranoproliferative glomerulonephritis	All nephropathy codes are on lines 99 and 339	99, 339	
N02.B4	Recurrent and persistent immunoglobulin A nephropathy with diffuse membranous glomerulonephritis	All nephropathy codes are on lines 99 and 339	99, 339	
N02.B5	Recurrent and persistent immunoglobulin A nephropathy with diffuse mesangial proliferative glomerulonephritis	All nephropathy codes are on lines 99 and 339	99, 339	

Code	Code Description	Similar codes	Recommended Placement	Notes
N02.B6	Recurrent and persistent immunoglobulin A nephropathy with diffuse mesangiocapillary glomerulonephritis	All nephropathy codes are on lines 99 and 339	99, 339	
N02.B9	Other recurrent and persistent immunoglobulin A nephropathy	All nephropathy codes are on lines 99 and 339	99, 339	
N04.20	Nephrotic syndrome with diffuse membranous glomerulonephritis, unspecified	Nephrotic syndrome codes are on lines 99 and 339	99, 339	
N04.21	Primary membranous nephropathy with nephrotic syndrome	Nephrotic syndrome codes are on lines 99 and 339	99, 339	
N04.22	Seconday membranous nephropathy with nephrotic syndrome	Nephrotic syndrome codes are on lines 99 and 339	99, 339	
N04.29	Other nephrotic syndrome with diffuse membranous glomerulonephritis	Nephrotic syndrome codes are on lines 99 and 339	99, 339	
N06.20	Isolated proteinuria with diffuse membranous glomerulonephritis, unspecified	Similar N06 codes are on lines 99. 339	99, 339	

Code	Code Description	Similar codes	Recommended Placement	Notes
N06.21	Primary membranous nephropathy with isolated proteinuria	All nephropathy codes are on lines 99 and 339	99, 339	
N06.22	Seconday membranous nephropathy with isolated proteinuria	All nephropathy codes are on lines 99 and 339	99, 339	
N06.29	Other isolated proteinuria with diffuse membranous glomerulonephritis	Similar N06 codes are on lines 99. 339	99, 339	
O26.641	Intrahepatic cholestasis of pregnancy, first trimester		1 PREGNANCY	
O26.642	Intrahepatic cholestasis of pregnancy, second trimester		1 PREGNANCY	
O26.643	Intrahepatic cholestasis of pregnancy, third trimester		1 PREGNANCY	
O26.649	Intrahepatic cholestasis of pregnancy, unspecified trimester		1 PREGNANCY	
O90.41	Hepatorenal syndrome following labor and delivery	Parent code O90.4 (Postpartum acute kidney failure) was on line 1	1 PREGNANCY	
O90.49	Other postpartum acute kidney failure	See O90.41	1 PREGNANCY	

Code	Code Description	Similar codes	Recommended Placement	Notes
Q44.70	Other congenital malformation of liver, unspecified	Parent code Q44.7 (Other congenital malformations of liver) was on line 293	293 ANOMALIES OF GALLBLADDER, BILE DUCTS, AND LIVER	
Q44.71	Alagille syndrome	Parent code Q44.7 (Other congenital malformations of liver) was on line 293	293 ANOMALIES OF GALLBLADDER, BILE DUCTS, AND LIVER	
Q44.79	Other congenital malformations of liver	Parent code Q44.7 (Other congenital malformations of liver) was on line 293	293 ANOMALIES OF GALLBLADDER, BILE DUCTS, AND LIVER	
Q75.001	Craniosynostosis unspecified, unilateral	Parent code Q75.0 (Craniosynostosis) was on line 256	256 DEFORMITIES OF HEAD AND HANDICAPPING MALOCCLUSION	
Q75.002	Craniosynostosis unspecified, bilateral	See Q75.001	256 DEFORMITIES OF HEAD AND HANDICAPPING MALOCCLUSION	
Q75.009	Craniosynostosis unspecified	See Q75.001	256 DEFORMITIES OF HEAD AND HANDICAPPING MALOCCLUSION	
Q75.01	Sagittal craniosynostosis	See Q75.001	256 DEFORMITIES OF HEAD AND HANDICAPPING MALOCCLUSION	
Q75.021	Coronal craniosynostosis unilateral	See Q75.001	256 DEFORMITIES OF HEAD AND HANDICAPPING MALOCCLUSION	
Q75.022	Coronal craniosynostosis bilateral	See Q75.001	256 DEFORMITIES OF HEAD AND HANDICAPPING MALOCCLUSION	
Q75.029	Coronal craniosynostosis unspecified	See Q75.001	256 DEFORMITIES OF HEAD AND HANDICAPPING MALOCCLUSION	
Q75.03	Metopic craniosynostosis	See Q75.001	256 DEFORMITIES OF HEAD AND HANDICAPPING MALOCCLUSION	
Q75.041	Lambdoid craniosynostosis, unilateral	See Q75.001	256 DEFORMITIES OF HEAD AND HANDICAPPING MALOCCLUSION	

Code	Code Description	Similar codes	Recommended Placement	Notes
Q75.042	Lambdoid craniosynostosis, bilateral	See Q75.001	256 DEFORMITIES OF HEAD AND HANDICAPPING MALOCCLUSION	
Q75.049	Lambdoid craniosynostosis, unspecified	See Q75.001	256 DEFORMITIES OF HEAD AND HANDICAPPING MALOCCLUSION	
Q75.051	Cloverleaf skull	See Q75.001	256 DEFORMITIES OF HEAD AND HANDICAPPING MALOCCLUSION	
Q75.052	Pansynostosis	See Q75.001	256 DEFORMITIES OF HEAD AND HANDICAPPING MALOCCLUSION	
Q75.058	Other multi-suture craniosynostosis	See Q75.001	256 DEFORMITIES OF HEAD AND HANDICAPPING MALOCCLUSION	
Q75.08	Other single-suture craniosynostosis	See Q75.001	256 DEFORMITIES OF HEAD AND HANDICAPPING MALOCCLUSION	
Q87.83	Bardet-Biedl syndrome		71 NEUROLOGICAL DYSFUNCTION IN BREATHING, EATING, SWALLOWING, BOWEL, OR BLADDER CONTROL CAUSED BY CHRONIC CONDITIONS; ATTENTION TO OSTOMIES 292 NEUROLOGICAL DYSFUNCTION IN POSTURE AND MOVEMENT CAUSED BY CHRONIC CONDITIONS 345 NEUROLOGICAL DYSFUNCTION IN COMMUNICATION CAUSED BY CHRONIC CONDITIONS 377 DYSFUNCTION RESULTING IN LOSS OF ABILITY TO MAXIMIZE LEVEL OF INDEPENDENCE IN SELF-DIRECTED CARE CAUSED BY CHRONIC CONDITIONS THAT CAUSE NEUROLOGICAL DYSFUNCTION 470 GONADAL DYSFUNCTION, MENOPAUSAL MANAGEMENT	See Informational Issues

Code	Code Description	Similar codes	Recommended Placement	Notes
Q87.84	Laurence-Moon syndrome	Similar to Bardet-Biedl syndrome	71, 292, 345, 377	
Q87.85	MED13L syndrome	Rare genetic syndrome that causes intellectual disability, speech problems and behavioral problems. Craniofacial deformities are common, as is hypotonia, ataxia and epilepsy. Treatment is symptomatic	71, 292, 345, 377	
Q93.52	Phelan-McDermid syndrome	PMS is generally characterized by neonatal hypotonia (low muscle tone in the newborn), intellectual disability of varying degrees, absent to severely delayed speech, moderate to profound developmental delay, and minor dysmorphic features. Treatment is symptomatic	71, 292, 345, 377	
R09.A0	Foreign body sensation, unspecified		DIAGNOSTIC WORKUP FILE (DWF)	
R09.A1	Foreign body sensation, nose		DIAGNOSTIC WORKUP FILE (DWF)	
R09.A2	Foreign body sensation, throat		DIAGNOSTIC WORKUP FILE (DWF)	
R09.A9	Foreign body sensation, other site		DIAGNOSTIC WORKUP FILE (DWF)	
R40.2A	Nontraumatic coma due to underlying condition	Coma codes are DWF	DIAGNOSTIC WORKUP FILE (DWF)	
R92.30	Dense breasts, unspecified		INFORMATIONAL DIAGNOSES	See Discussion Issues

Code	Code Description	Similar codes	Recommended Placement	Notes
R92.311	Mammographic fatty tissue density, right breast		INFORMATIONAL DIAGNOSES	See Discussion Issues
R92.312	Mammographic fatty tissue density, left breast		INFORMATIONAL DIAGNOSES	See Discussion Issues
R92.313	Mammographic fatty tissue density, bilateral breasts		INFORMATIONAL DIAGNOSES	See Discussion Issues
R92.321	Mammographic fibroglandular density, right breast		INFORMATIONAL DIAGNOSES	See Discussion Issues
R92.322	Mammographic fibroglandular density, left breast		INFORMATIONAL DIAGNOSES	See Discussion Issues
R92.323	Mammographic fibroglandular density, bilateral breasts		INFORMATIONAL DIAGNOSES	See Discussion Issues
R92.331	Mammographic heterogeneous density, right breast		INFORMATIONAL DIAGNOSES	See Discussion Issues
R92.332	Mammographic heterogeneous density, left breast		INFORMATIONAL DIAGNOSES	See Discussion Issues
R92.333	Mammographic heterogeneous density, bilateral breasts		INFORMATIONAL DIAGNOSES	See Discussion Issues
R92.341	Mammographic extreme density, right breast		INFORMATIONAL DIAGNOSES	See Discussion Issues

Code	Code Description	Similar codes	Recommended Placement	Notes
R92.342	Mammographic extreme density, left breast		INFORMATIONAL DIAGNOSES	See Discussion Issues
R92.343	Mammographic extreme density, bilateral breasts		INFORMATIONAL DIAGNOSES	See Discussion Issues
T56.821A	Toxic effect of gadolinium, accidental (unintentional), initial encounter		102 POISONING BY INGESTION, INJECTION, MEDICINAL AND NON-MEDICINAL AGENTS	
T56.821D	Toxic effect of gadolinium, accidental (unintentional), subsequent encounter		102 POISONING BY INGESTION, INJECTION, MEDICINAL AND NON-MEDICINAL AGENTS	
T56.822A	Toxic effect of gadolinium, intentional self-harm, initial encounter		102 POISONING BY INGESTION, INJECTION, MEDICINAL AND NON-MEDICINAL AGENTS	
T56.822D	Toxic effect of gadolinium, intentional self-harm, subsequent encounter		102 POISONING BY INGESTION, INJECTION, MEDICINAL AND NON-MEDICINAL AGENTS	
T56.823A	Toxic effect of gadolinium, assault, initial encounter		102 POISONING BY INGESTION, INJECTION, MEDICINAL AND NON-MEDICINAL AGENTS	

Code	Code Description	Similar codes	Recommended Placement	Notes
T56.823D	Toxic effect of gadolinium, assault, subsequent encounter		102 POISONING BY INGESTION, INJECTION, MEDICINAL AND NON-MEDICINAL AGENTS	
T56.824A	Toxic effect of gadolinium, undetermined, initial encounter		102 POISONING BY INGESTION, INJECTION, MEDICINAL AND NON-MEDICINAL AGENTS	
T56.824D	Toxic effect of gadolinium, undetermined, subsequent encounter		102 POISONING BY INGESTION, INJECTION, MEDICINAL AND NON-MEDICINAL AGENTS	
T74.A1XA	Adult financial abuse, confirmed, initial encounter		INFORMATIONAL DIAGNOSES	BHAP reviewed
T74.A1XD	Adult financial abuse, confirmed, subsequent encounter		INFORMATIONAL DIAGNOSES	BHAP reviewed
T74.A2XA	Child financial abuse, confirmed, initial encounter		INFORMATIONAL DIAGNOSES	BHAP reviewed
T74.A2XD	Child financial abuse, confirmed, subsequent encounter		INFORMATIONAL DIAGNOSES	BHAP reviewed
T76.A1XA	Adult financial abuse, suspected, initial encounter		INFORMATIONAL DIAGNOSES	BHAP reviewed

Code	Code Description	Similar codes	Recommended Placement	Notes
T76.A1XD	Adult financial abuse, suspected, subsequent encounter		INFORMATIONAL DIAGNOSES	BHAP reviewed
T76.A2XA	Child financial abuse, suspected, initial encounter		INFORMATIONAL DIAGNOSES	BHAP reviewed
T76.A2XD	Child financial abuse, suspected, subsequent encounter		INFORMATIONAL DIAGNOSES	BHAP reviewed
W44.A0XA	Battery unspecified, entering into or through a natural orifice, initial encounter	If ingested, can be coded as foreign body in the GI tract. If in the ear or nose, can be codes as foreign body in these locations to allow treatment.	INFORMATIONAL DIAGNOSES	
W44.A0XD	Battery unspecified, entering into or through a natural orifice, subsequent encounter		INFORMATIONAL DIAGNOSES	
W44.A1XA	Button battery entering into or through a natural orifice, initial encounter		INFORMATIONAL DIAGNOSES	
W44.A1XD	Button battery entering into or through a natural orifice, subsequent encounter		INFORMATIONAL DIAGNOSES	

Code	Code Description	Similar codes	Recommended Placement	Notes
W44.A9XA	Other batteries entering into or through a natural orifice, initial encounter		INFORMATIONAL DIAGNOSES	
W44.A9XD	Other batteries entering into or through a natural orifice, subsequent encounter		INFORMATIONAL DIAGNOSES	
W44.B0XA	Plastic object unspecified, entering into or through a natural orifice, initial encounter		INFORMATIONAL DIAGNOSES	
W44.B0XD	Plastic object unspecified, entering into or through a natural orifice, subsequent encounter		INFORMATIONAL DIAGNOSES	
W44.B1XA	Plastic bead entering into or through a natural orifice, initial encounter		INFORMATIONAL DIAGNOSES	
W44.B1XD	Plastic bead entering into or through a natural orifice, subsequent encounter		INFORMATIONAL DIAGNOSES	

Code	Code Description	Similar codes	Recommended Placement	Notes
W44.B2XA	Plastic coin entering into or through a natural orifice, initial encounter		INFORMATIONAL DIAGNOSES	
W44.B2XD	Plastic coin entering into or through a natural orifice, subsequent encounter		INFORMATIONAL DIAGNOSES	
W44.B3XA	Plastic toy and toy part entering into or through a natural orifice, initial encounter		INFORMATIONAL DIAGNOSES	
W44.B3XD	Plastic toy and toy part entering into or through a natural orifice, subsequent encounter		INFORMATIONAL DIAGNOSES	
W44.B4XA	Plastic jewelry entering into or through a natural orifice, initial encounter		INFORMATIONAL DIAGNOSES	
W44.B4XD	Plastic jewelry entering into or through a natural orifice, subsequent encounter		INFORMATIONAL DIAGNOSES	

Code	Code Description	Similar codes	Recommended Placement	Notes
W44.B5XA	Plastic bottle entering into or through a natural orifice, initial encounter		INFORMATIONAL DIAGNOSES	
W44.B5XD	Plastic bottle entering into or through a natural orifice, subsequent encounter		INFORMATIONAL DIAGNOSES	
W44.B9XA	Other plastic object entering into or through a natural orifice, initial encounter		INFORMATIONAL DIAGNOSES	
W44.B9XD	Other plastic object entering into or through a natural orifice, subsequent encounter		INFORMATIONAL DIAGNOSES	
W44.C0XA	Glass unspecified, entering into or through a natural orifice, initial encounter		INFORMATIONAL DIAGNOSES	
W44.C0XD	Glass unspecified, entering into or through a natural orifice, subsequent encounter		INFORMATIONAL DIAGNOSES	

Code	Code Description	Similar codes	Recommended Placement	Notes
W44.C1XA	Sharp glass entering into or through a natural orifice, initial encounter		INFORMATIONAL DIAGNOSES	
W44.C1XD	Sharp glass entering into or through a natural orifice, subsequent encounter		INFORMATIONAL DIAGNOSES	
W44.C2XA	Intact glass entering into or through a natural orifice, initial encounter		INFORMATIONAL DIAGNOSES	
W44.C2XD	Intact glass entering into or through a natural orifice, subsequent encounter		INFORMATIONAL DIAGNOSES	
W44.D0XA	Magnetic metal object unspecified, entering into or through a natural orifice, initial encounter		INFORMATIONAL DIAGNOSES	
W44.D0XD	Magnetic metal object unspecified, entering into or through a natural orifice, subsequent encounter		INFORMATIONAL DIAGNOSES	

Code	Code Description	Similar codes	Recommended Placement	Notes
W44.D1XA	Magnetic metal bead entering into or through a natural orifice, initial encounter		INFORMATIONAL DIAGNOSES	
W44.D1XD	Magnetic metal bead entering into or through a natural orifice, subsequent encounter		INFORMATIONAL DIAGNOSES	
W44.D2XA	Magnetic metal coin entering into or through a natural orifice, initial encounter		INFORMATIONAL DIAGNOSES	
W44.D2XD	Magnetic metal coin entering into or through a natural orifice, subsequent encounter		INFORMATIONAL DIAGNOSES	
W44.D3XA	Magnetic metal toy entering into or through a natural orifice, initial encounter		INFORMATIONAL DIAGNOSES	
W44.D3XD	Magnetic metal toy entering into or through a natural orifice, subsequent encounter		INFORMATIONAL DIAGNOSES	

Code	Code Description	Similar codes	Recommended Placement	Notes
W44.D4XA	Magnetic metal jewelry entering into or through a natural orifice, initial encounter		INFORMATIONAL DIAGNOSES	
W44.D4XD	Magnetic metal jewelry entering into or through a natural orifice, subsequent encounter		INFORMATIONAL DIAGNOSES	
W44.D9XA	Other magnetic metal objects entering into or through a natural orifice, initial encounter		INFORMATIONAL DIAGNOSES	
W44.D9XD	Other magnetic metal objects entering into or through a natural orifice, subsequent encounter		INFORMATIONAL DIAGNOSES	
W44.E0XA	Non-magnetic metal object unspecified, entering into or through a natural orifice, initial encounter		INFORMATIONAL DIAGNOSES	

Code	Code Description	Similar codes	Recommended Placement	Notes
W44.E0XD	Non-magnetic metal object unspecified, entering into or through a natural orifice, subsequent encounter		INFORMATIONAL DIAGNOSES	
W44.E1XA	Non-magnetic metal bead entering into or through a natural orifice, initial encounter		INFORMATIONAL DIAGNOSES	
W44.E1XD	Non-magnetic metal bead entering into or through a natural orifice, subsequent encounter		INFORMATIONAL DIAGNOSES	
W44.E2XA	Non-magnetic metal coin entering into or through a natural orifice, initial encounter		INFORMATIONAL DIAGNOSES	
W44.E2XD	Non-magnetic metal coin entering into or through a natural orifice, subsequent encounter		INFORMATIONAL DIAGNOSES	
W44.E3XA	Non-magnetic metal toy entering into or through a natural orifice, initial encounter		INFORMATIONAL DIAGNOSES	

Code	Code Description	Similar codes	Recommended Placement	Notes
W44.E3XD	Non-magnetic metal toy entering into or through a natural orifice, subsequent encounter		INFORMATIONAL DIAGNOSES	
W44.E4XA	Non-magnetic metal jewelry entering into or through a natural orifice, initial encounter		INFORMATIONAL DIAGNOSES	
W44.E4XD	Non-magnetic metal jewelry entering into or through a natural orifice, subsequent encounter		INFORMATIONAL DIAGNOSES	
W44.E9XA	Other non-magnetic metal objects entering into or through a natural orifice, initial encounter		INFORMATIONAL DIAGNOSES	
W44.E9XD	Other non-magnetic metal objects entering into or through a natural orifice, subsequent encounter		INFORMATIONAL DIAGNOSES	
W44.F0XA	Objects of natural or organic material unspecified, entering into or through a natural orifice, initial encounter		INFORMATIONAL DIAGNOSES	

Code	Code Description	Similar codes	Recommended Placement	Notes
W44.F0XD	Objects of natural or organic material unspecified, entering into or through a natural orifice, subsequent encounter		INFORMATIONAL DIAGNOSES	
W44.F1XA	Bezoar entering into or through a natural orifice, initial encounter		INFORMATIONAL DIAGNOSES	
W44.F1XD	Bezoar entering into or through a natural orifice, subsequent encounter		INFORMATIONAL DIAGNOSES	
W44.F2XA	Rubber band entering into or through a natural orifice, initial encounter		INFORMATIONAL DIAGNOSES	
W44.F2XD	Rubber band entering into or through a natural orifice, subsequent encounter		INFORMATIONAL DIAGNOSES	
W44.F3XA	Food entering into or through a natural orifice, initial encounter		INFORMATIONAL DIAGNOSES	
W44.F3XD	Food entering into or through a natural orifice, subsequent encounter		INFORMATIONAL DIAGNOSES	

Code	Code Description	Similar codes	Recommended Placement	Notes
W44.F4XA	Insect entering into or through a natural orifice, initial encounter		INFORMATIONAL DIAGNOSES	
W44.F4XD	Insect entering into or through a natural orifice, subsequent encounter		INFORMATIONAL DIAGNOSES	
W44.F9XA	Other object of natural or organic material, entering into or through a natural orifice, initial encounter		INFORMATIONAL DIAGNOSES	
W44.F9XD	Other object of natural or organic material, entering into or through a natural orifice, subsequent encounter		INFORMATIONAL DIAGNOSES	
W44.G0XA	Other non-organic objects unspecified, entering into or through a natural orifice, initial encounter		INFORMATIONAL DIAGNOSES	
W44.G0XD	Other non-organic objects unspecified, entering into or through a natural orifice, subsequent encounter		INFORMATIONAL DIAGNOSES	

Code	Code Description	Similar codes	Recommended Placement	Notes
W44.G1XA	Audio device entering into or through a natural orifice, initial encounter		INFORMATIONAL DIAGNOSES	
W44.G1XD	Audio device entering into or through a natural orifice, subsequent encounter		INFORMATIONAL DIAGNOSES	
W44.G2XA	Combination metal and plastic toy and toy part entering into or through natural orifice, initial encounter		INFORMATIONAL DIAGNOSES	
W44.G2XD	Combination metal and plastic toy and toy part entering into or through natural orifice, subsequent encounter		INFORMATIONAL DIAGNOSES	
W44.G3XA	Combination metal and plastic jewelry entering into or through a natural orifice, initial encounter		INFORMATIONAL DIAGNOSES	

Code	Code Description	Similar codes	Recommended Placement	Notes
W44.G3XD	Combination metal and plastic jewelry entering into or through a natural orifice, subsequent encounter		INFORMATIONAL DIAGNOSES	
W44.G9XA	Other non-organic objects entering into or through a natural orifice, initial encounter		INFORMATIONAL DIAGNOSES	
W44.G9XD	Other non-organic objects entering into or through a natural orifice, subsequent encounter		INFORMATIONAL DIAGNOSES	
W44.H0XA	Other sharp object unspecified, entering into or through a natural orifice, initial encounter		INFORMATIONAL DIAGNOSES	
W44.H0XD	Other sharp object unspecified, entering into or through a natural orifice, subsequent encounter		INFORMATIONAL DIAGNOSES	
W44.H1XA	Needle entering into or through a natural orifice, initial encounter		INFORMATIONAL DIAGNOSES	

Code	Code Description	Similar codes	Recommended Placement	Notes
W44.H1XD	Needle entering into or through a natural orifice, subsequent encounter		INFORMATIONAL DIAGNOSES	
W44.H2XA	Knife, sword or dagger entering into or through a natural orifice, initial encounter		INFORMATIONAL DIAGNOSES	
W44.H2XD	Knife, sword or dagger entering into or through a natural orifice, subsequent encounter		INFORMATIONAL DIAGNOSES	
W44.8XXA	Other foreign body entering into or through a natural orifice, initial encounter		INFORMATIONAL DIAGNOSES	
W44.8XXD	Other foreign body entering into or through a natural orifice, subsequent encounter		INFORMATIONAL DIAGNOSES	
W44.9XXA	Unspecified foreign body entering into or through a natural orifice, initial encounter		INFORMATIONAL DIAGNOSES	

Code	Code Description	Similar codes	Recommended Placement	Notes
W44.9XXD	Unspecified foreign body entering into or through a natural orifice, subsequent encounter		INFORMATIONAL DIAGNOSES	
Y07.010	Husband, current, perpetrator of maltreatment and neglect		INFORMATIONAL DIAGNOSES	BHAP reviewed
Y07.011	Husband, former, perpetrator of maltreatment and neglect		INFORMATIONAL DIAGNOSES	BHAP reviewed
Y07.020	Wife, current, perpetrator of maltreatment and neglect		INFORMATIONAL DIAGNOSES	BHAP reviewed
Y07.021	Wife, former, perpetrator of maltreatment and neglect		INFORMATIONAL DIAGNOSES	BHAP reviewed
Y07.030	Male partner, current, perpetrator of maltreatment and neglect		INFORMATIONAL DIAGNOSES	BHAP reviewed
Y07.031	Male partner, former, perpetrator of maltreatment and neglect		INFORMATIONAL DIAGNOSES	BHAP reviewed
Y07.040	Female partner, current, perpetrator of maltreatment and neglect		INFORMATIONAL DIAGNOSES	BHAP reviewed

Code	Code Description	Similar codes	Recommended Placement	Notes
Y07.041	Female partner, former, perpetrator of maltreatment and neglect		INFORMATIONAL DIAGNOSES	BHAP reviewed
Y07.050	Non-binary partner, current, perpetrator of maltreatment and neglect		INFORMATIONAL DIAGNOSES	BHAP reviewed
Y07.051	Non-binary partner, former, perpetrator of maltreatment and neglect		INFORMATIONAL DIAGNOSES	BHAP reviewed
Y07.44	Child, perpetrator of maltreatment and neglect		INFORMATIONAL DIAGNOSES	BHAP reviewed
Y07.45	Grandchild, perpetrator of maltreatment and neglect		INFORMATIONAL DIAGNOSES	BHAP reviewed
Y07.46	Grandparent, perpetrator of maltreatment and neglect		INFORMATIONAL DIAGNOSES	BHAP reviewed
Y07.47	Parental sibling, perpetrator of maltreatment and neglect		INFORMATIONAL DIAGNOSES	BHAP reviewed
Y07.54	Acquaintance or friend, perpetrator of maltreatment and neglect		INFORMATIONAL DIAGNOSES	BHAP reviewed
Z02.84	Encounter for child welfare exam		INFORMATIONAL DIAGNOSES	BHAP reviewed

Code	Code Description	Similar codes	Recommended Placement	Notes
Z05.81	Observation and evaluation of newborn for suspected condition related to home physiologic monitoring device ruled out	Parent code Z05.8 (Observation and evaluation of newborn for other specified suspected condition ruled out) was on line 2	2 BIRTH OF INFANT	
Z05.89	Observation and evaluation of newborn for other specified suspected condition ruled out	See Z05.81	2 BIRTH OF INFANT	
Z16.13	Resistance to carbapenem	Similar codes are Informational	INFORMATIONAL DIAGNOSES	
Z22.340	Carrier of carbapenem-resistant Acinetobacter baumannii	Similar "carrier" codes are on line 622	622 PREVENTION SERVICES WITH LIMITED OR NO EVIDENCE OF EFFECTIVENESS	
Z22.341	Carrier of carbapenem-sensitive Acinetobacter baumannii	Similar "carrier" codes are on line 622	622 PREVENTION SERVICES WITH LIMITED OR NO EVIDENCE OF EFFECTIVENESS	
Z22.349	Carrier of Acinetobacter baumannii, unspecified	Similar "carrier" codes are on line 622	622 PREVENTION SERVICES WITH LIMITED OR NO EVIDENCE OF EFFECTIVENESS	
Z22.350	Carrier of carbapenem-resistant Enterobacterales	Similar "carrier" codes are on line 622	622 PREVENTION SERVICES WITH LIMITED OR NO EVIDENCE OF EFFECTIVENESS	

Code	Code Description	Similar codes	Recommended Placement	Notes
Z22.358	Carrier of other Enterobacterales	Similar "carrier" codes are on line 622	622 PREVENTION SERVICES WITH LIMITED OR NO EVIDENCE OF EFFECTIVENESS	
Z22.359	Carrier of Enterobacterales, unspecified	Similar "carrier" codes are on line 622	622 PREVENTION SERVICES WITH LIMITED OR NO EVIDENCE OF EFFECTIVENESS	
Z29.81	Encounter for HIV pre-exposure prophylaxis	Parent code Z29.8 (Encounter for other specified prophylactic measures) was on line 3	3 PREVENTION SERVICES WITH EVIDENCE OF EFFECTIVENESS	
Z29.89	Encounter for other specified prophylactic measures	See Z29.81	3 PREVENTION SERVICES WITH EVIDENCE OF EFFECTIVENESS	
Z55.6	Problems related to health literacy		INFORMATIONAL DIAGNOSES	BHAP reviewed
Z58.81	Basic services unavailable in physical environment		INFORMATIONAL DIAGNOSES	BHAP reviewed
Z58.89	Other problems related to physical environment		INFORMATIONAL DIAGNOSES	BHAP reviewed
Z59.10	Inadequate housing, unspecified		INFORMATIONAL DIAGNOSES	BHAP reviewed
Z59.11	Inadequate housing environmental temperature		INFORMATIONAL DIAGNOSES	BHAP reviewed
Z59.12	Inadequate housing utilities		INFORMATIONAL DIAGNOSES	BHAP reviewed
Z59.19	Other inadequate housing		INFORMATIONAL DIAGNOSES	BHAP reviewed
Z62.23	Child in custody of non-parental relative		INFORMATIONAL DIAGNOSES	BHAP reviewed

Code	Code Description	Similar codes	Recommended Placement	Notes
Z62.24	Child in custody of non-relative guardian		INFORMATIONAL DIAGNOSES	BHAP reviewed
Z62.814	Personal history of child financial abuse		INFORMATIONAL DIAGNOSES	BHAP reviewed
Z62.815	Personal history of intimate partner abuse in childhood	Personal history of child physical, psychological or sexual abuse are on line 445	445 ADJUSTMENT DISORDERS	BHAP reviewed
Z62.823	Parent-step child conflict	Other codes regarding caregiver-child conflict are on line 445	445 ADJUSTMENT DISORDERS	BHAP reviewed
Z62.831	Non-parental relative-child conflict	See Z62.823	445 ADJUSTMENT DISORDERS	BHAP reviewed
Z62.832	Non-relative guardian-child conflict	See Z62.823	445 ADJUSTMENT DISORDERS	BHAP reviewed
Z62.833	Group home staff-child conflict	See Z62.823	445 ADJUSTMENT DISORDERS	BHAP reviewed
Z62.892	Runaway [from current living environment]		INFORMATIONAL DIAGNOSES	BHAP reviewed
Z83.710	Family history of adenomatous and serrated polyps	Parent code Z83.71 (Family history of colonic polyps) was Informational	INFORMATIONAL DIAGNOSES	
Z83.711	Family history of hyperplastic colon polyps	See Z83.710	INFORMATIONAL DIAGNOSES	
Z83.718	Other family history of colon polyps	See Z83.710	INFORMATIONAL DIAGNOSES	
Z83.719	Family history of colon polyps, unspecified	See Z83.710	INFORMATIONAL DIAGNOSES	

Code	Code Description	Similar codes	Recommended Placement	Notes
Z91.141	Patient's other noncompliance with medication regimen due to financial hardship		INFORMATIONAL DIAGNOSES	
Z91.148	Patient's other noncompliance with medication regimen for other reason		INFORMATIONAL DIAGNOSES	
Z91.151	Patient's noncompliance with renal dialysis due to financial hardship		INFORMATIONAL DIAGNOSES	
Z91.158	Patient's noncompliance with renal dialysis for other reason		INFORMATIONAL DIAGNOSES	
Z91.A41	Caregiver's other noncompliance with patient's medication regimen due to financial hardship		INFORMATIONAL DIAGNOSES	
Z91.A48	Caregiver's other noncompliance with patient's medication regimen for other reason		INFORMATIONAL DIAGNOSES	
Z91.A51	Caregiver's noncompliance with patient's renal dialysis due to financial hardship		INFORMATIONAL DIAGNOSES	

Code	Code Description	Similar codes	Recommended Placement	Notes
Z91.A58	Caregiver's noncompliance with patient's renal dialysis for other reason		INFORMATIONAL DIAGNOSES	
Z91.A91	Caregiver's noncompliance with patient's other medical treatment and regimen due to financial hardship		INFORMATIONAL DIAGNOSES	
Z91.A98	Caregiver's noncompliance with patient's other medical treatment and regimen for other reason		INFORMATIONAL DIAGNOSES	
Z91.413	Personal history of adult financial abuse	All personal history of adult physical, psychological or sexual abuse codes are INFORMATIONAL	INFORMATIONAL DIAGNOSES	BHAP reviewed
Z91.414	Personal history of adult intimate partner abuse		INFORMATIONAL DIAGNOSES	BHAP reviewed
Z91.85	Personal history of military service		INFORMATIONAL DIAGNOSES	

2024 ICD-10-CM Code Placement Issues

Informational Issues

1) **D13.91** Familial adenomatous polyposis
    a. Information: Familial adenomatous polyposis (FAP) is a rare inherited cancer predisposition syndrome characterized by hundreds to thousands of precancerous colorectal polyps (adenomatous polyps). If left untreated, affected individuals inevitably develop cancer of the colon and/or rectum at a relatively young age. Partial or complete removal of the colon (colectomy) is usually recommended for individuals with classical FAP at an appropriate age, usually between the late teens and late 30s. Genetic counseling is recommended for individuals with familial adenomatous polyposis and their at-risk family members.
    b. Similar code: previously coded with D12.6 (Benign neoplasm of colon, unspecified) which is on line 166 ANAL, RECTAL AND COLONIC POLYPS. Line 166 contains colonoscopy and colectomy CPT codes
    c. HERC staff recommendation
        i. Place D13.91 on line 166 ANAL, RECTAL AND COLONIC POLYPS

2) **D48.11X** Desmoid tumors
    a. Information: Desmoid tumors are noncancerous growths that occur in the connective tissue. Desmoid tumors most often occur in the abdomen, arms and legs. Another term for desmoid tumors is aggressive fibromatosis. Some desmoid tumors are slow growing and don't require immediate treatment. Others grow quickly and are treated with surgery, radiation therapy, chemotherapy or other drugs
    b. Similar code: previously coded with D48.1 (Neoplasm of uncertain behavior of connective and other soft tissue) which was on lines 199 CANCER OF SOFT TISSUE, 401 BENIGN CONDITIONS OF BONE AND JOINTS AT HIGH RISK FOR COMPLICATIONS, 559 BENIGN NEOPLASM OF BONE AND ARTICULAR CARTILAGE INCLUDING OSTEOID OSTEOMAS; BENIGN NEOPLASM OF CONNECTIVE AND OTHER SOFT TISSUE
    c. HERC staff recommendation
        i. Place D48.111-D48.1118 and D48.19 on lines
            1. 199 CANCER OF SOFT TISSUE
            2. 401 BENIGN CONDITIONS OF BONE AND JOINTS AT HIGH RISK FOR COMPLICATIONS
            3. 559 BENIGN NEOPLASM OF BONE AND ARTICULAR CARTILAGE INCLUDING OSTEOID OSTEOMAS; BENIGN NEOPLASM OF CONNECTIVE AND OTHER SOFT TISSUE
        ii. Place D48.119 (Desmoid tumor of unspecified site) on the UNDEFINED CONDITIONS file

3) **D61.02** Shwachman-Diamond Syndrome
    a. Information: Schwachman-Diamond syndrome (SDS) is an autosomal recessive disorder that is the second most common cause of exocrine pancreatic insufficiency after cystic fibrosis. It presents with the common triad of exocrine pancreatic dysfunction, skeletal

abnormalities, and bone marrow dysfunction. However, cardiac abnormalities, immune dysfunction, and hematologic disorders are also reported.

b. Treatments: pancreatic enzymatic replacement, transfusions of packed red blood cells (PRBC) and platelets to treat anemia and thrombocytopenia, iron chelation if iron overload occurs, prompt treatment of infections resulting from leukopenia, hematopoietic stem cell transplant for bone marrow failure or myelodysplastic syndrome or resulting acute leukemia
c. Similar codes
    i. D61.01 (Constitutional (pure) red blood cell aplasia) are on line 113 APLASTIC ANEMIAS; AGRANULOCYTOSIS; SICKLE CELL DISEASE Treatment: BONE MARROW TRANSPLANT and line 295 APLASTIC ANEMIAS
    ii. D86.81 (Exocrine pancreatic insufficiency) is on line 227 INTESTINAL MALABSORPTION
d. HERC staff recommendation
    i. Place D61.02 and D48.19 on lines
        1. 113 APLASTIC ANEMIAS; AGRANULOCYTOSIS; SICKLE CELL DISEASE Treatment: BONE MARROW TRANSPLANT
        2. 227 INTESTINAL MALABSORPTION
        3. 295 APLASTIC ANEMIAS

4) **D89.84** IgG4- related disease
    a. information: Immunoglobulin G4-related disease (IgG4-RD) is an immune-mediated fibroinflammatory condition that is capable of affecting multiple organs. Commonly affected organs include the meninges, orbits causing proptosis, lungs, thyroid gland, and salivary glands. It can result in retroperitoneal fibrosis which can be associated with chronic periaortitis and often affecting the ureters leading to renal injury and hydronephrosis. It can result in sclerosing cholangitis and autoimmune pancreatitis.
    b. Treatments: glucocorticoids, Rituximab
    c. Similar codes: other codes in the D89.8 family are on lines 285 COMPLICATIONS OF A PROCEDURE ALWAYS REQUIRING TREATMENT and 313 DISORDERS INVOLVING THE IMMUNE SYSTEM. These codes are for graft vs host disease conditions. IgG4 related disease is not a graft vs host condition
    d. HERC staff recommendation
        i. Place D89.84 on line 313 DISORDERS INVOLVING THE IMMUNE SYSTEM

5) **E79.82** Hereditary zanthiuria
    a. Information: Hereditary xanthinuria is a condition that most often affects the kidneys. It is characterized by high levels of xanthine and very low levels of uric acid in the blood and urine. The excess xanthine can accumulate in the kidneys and other tissues. In the kidneys, xanthine can create kidney stones. These stones can impair kidney function and ultimately cause kidney failure. Related signs and symptoms can include abdominal pain, recurrent urinary tract infections, and hematuria. Less commonly, xanthine

crystals build up in the muscles, causing pain and cramping. In some people with hereditary xanthinuria, the condition does not cause any health problems

b. Treatment: There is no curative treatment. Low purine diet and high fluid intake is recommended. Since the solubility of xanthine is not affected by urinary pH, alkalization is of no value. When calculi are present, a pyelolithotomy might be necessary. The overall prognosis is favorable, even though, in some cases, the disease progresses to end-stage renal insufficiency.
c. Similar codes: previously coded with E79. 8 (Other disorders of purine and pyrimidine metabolism) which was on the dysfunction lines
d. Note: kidney stones and renal failure are on specific lines and these conditions can be coded if they are present to ensure pairing with appropriate treatments
e. HERC staff recommendation
    i. Place E79.82 on lines
        1. 71 NEUROLOGICAL DYSFUNCTION IN BREATHING, EATING, SWALLOWING, BOWEL, OR BLADDER CONTROL CAUSED BY CHRONIC CONDITIONS; ATTENTION TO OSTOMIES
        2. 292 NEUROLOGICAL DYSFUNCTION IN POSTURE AND MOVEMENT CAUSED BY CHRONIC CONDITIONS
        3. 345 NEUROLOGICAL DYSFUNCTION IN COMMUNICATION CAUSED BY CHRONIC CONDITIONS
        4. 377 DYSFUNCTION RESULTING IN LOSS OF ABILITY TO MAXIMIZE LEVEL OF INDEPENDENCE IN SELF-DIRECTED CARE CAUSED BY CHRONIC CONDITIONS THAT CAUSE NEUROLOGICAL DYSFUNCTION

6) **G11.5** Hypomyelination - hypogonadotropic hypogonadism - hypodontia
    a. Information: The condition is also known as 4H syndrome or Pol 3-related leukodystrophy. 4H leukodystrophy is a rare genetic disorder that affects the nervous system. People with 4H leukodystrophy often have motor problems, including stiffness of the muscles and joints and problems with balance and coordination. They may also have movement disorders, including tremor or difficulty controlling smooth movements of their arms and legs. 4H leukodystrophy is the combination of that myelin deficiency and two other conditions: hypogonadotropic hypogonadism (a condition that results in delayed puberty) and hypodontia (having fewer teeth than normal or an abnormal development of those teeth). This condition is very rare, with about 40 cases reported worldwide.
    b. Treatment: There is no known treatment for this condition other than managing symptoms
    c. Similar codes:
        i. All codes in the G11 family (Hereditary ataxia) are on the dysfunction lines
        ii. E29.1 is male hypogonadism is on line 470 GONADAL DYSFUNCTION, MENOPAUSAL MANAGEMENT
        iii. E28.39 is female hypogonadism is on line 470
        iv. Dental lines generally do not have ICD-10-CM codes

d. HERC staff recommendation:
    i. Place G11.6 on the dysfunction lines and line 470 GONADAL DYSFUNCTION, MENOPAUSAL MANAGEMENT

7) **G37.81** Myelin oligodendrocyte glycoprotein antibody disease
    a. Information: Myelin oligodendrocyte glycoprotein (MOG) antibody disease (MOGAD) is an autoimmune disorder that shares some symptoms with multiple sclerosis. MOGAD is associated with antibodies directed against MOG.
    b. Treatment: IVIG, IV steroids, plasma exchange, azathioprine, mycophenolate, prednisone, rituximab, toxilizumab
    c. Similar codes:
        i. Parent code G37.8 (Other specified demyelinating diseases of central nervous system) was on lines 71,251,292,345,377 (dysfunction lines and line 251 MULTIPLE SCLEROSIS AND OTHER DEMYELINATING DISEASES OF CENTRAL NERVOUS SYSTEM
        ii. CPT code 36514 (Therapeutic apheresis; for plasma pheresis) is on lines 90, 106,124, 126, 129, 131, 140, 141, 148, 159, 175, 194, 212, 234, 285, 313, 339, 458
    d. HERC staff recommendation
        i. Place G37.81 on the dysfunction lines and on Line 313 DISORDERS INVOLVING THE IMMUNE SYSTEM
            1. Line 313 contains the CPT codes for plasma exchange and IVIG

8) **K68.2** Retroperitoneal fibrosis
    a. Information: Retroperitoneal fibrosis, also known as Ormond's disease, is a disease of proliferating fibrous tissue in the retroperitoneum. It can affect the kidneys, aorta, ureters, and other structures. It can be caused by IgG4-related autoimmune disease, malignancy, medications such as hydralazine, radiotherapy, and certain infections.
    b. Treatment: glucocorticoids or other immunosuppressant medication. If the condition results in urinary obstruction, then surgery is required.
    c. Previously coded with N13.5 (Crossing vessel and stricture of ureter without hydronephrosis) which is on line 180 URETERAL STRICTURE OR OBSTRUCTION; HYDRONEPHROSIS; HYDROURETER.
    d. HERC staff recommendation:
        i. Place K68.2 on line 180 URETERAL STRICTURE OR OBSTRUCTION; HYDRONEPHROSIS; HYDROURETER

9) **Q87.83** Bardet-Biedl syndrome
    e. Information: Bardet-Biedl syndrome (BBS) is a genetic condition that impacts multiple body systems. It is classically defined by six features. Patients with BBS can experience problems with obesity, specifically with fat deposition along the abdomen. They often

also suffer from intellectual impairments. Commonly, the kidneys, eyes and function of the genitalia will be compromised. People with BBS may also be born with an extra digit on the hands. One characteristic is retinal dystrophy.

f. Treatment: The main treatment is aimed toward symptoms. As obesity is a common component to BBS, and is treated with lifestyle, exercise, and diet programs. Bariatric surgery is being investigated in this population. In 2022, the U.S. Food and Drug Administration (FDA) approved setmelanotide (Imcivree) as a treatment option for chronic weight management in adult and pediatric patients 6 years and older with obesity due to BBS.
g. Similar codes: Codes in the Q87 family are on the dysfunction lines
h. P&T input: weight loss drugs like setmelanotide are current excluded from coverage in our waiver; P&T staff will evaluate whether our waiver will allow coverage of this drug for Bardet-Biedl syndrome
i. HERC staff recommendation
    i. Place Q87.93 on the dysfunction lines
    ii. Allow P&T process to determine coverage, if any, of setmelanotide

2024 ICD-10-CM Code Placement Issues

Discussion Issues

1) **E88.810-E88.819** Metabolic syndrome/insulin resistance
    a. Information: Metabolic syndrome is a group of conditions that together raise the risk of coronary heart disease, diabetes, stroke, and other serious health problems. To make the diagnosis of metabolic syndrome, the patient must have 3 of the following: elevated blood pressure (above 130/85), elevated blood sugar (100mg/dL or higher fasting), high triglycerides (150mg/dL or higher), low HDL cholesterol, and abdominal obesity (more than 35 inches around the waist for women, more than 40 inches for men). About 1 in 3 adults in the US have metabolic syndrome. Metabolic syndrome is frequently caused by insulin resistance. Insulin resistance occurs when cells don't respond normally to insulin and the pancreas increases insulin production. Insulin resistance can lead to prediabetes and to diabetes. Currently, there is no standard test for insulin resistance.
    b. Treatment: weight loss, increased physical activity, healthy diet, management of high blood sugar, high cholesterol and blood pressure.
    c. Parent code (E88.81 METABOLIC DISORDERS) was on line 60 METABOLIC DISORDERS
        i. Line 60 contains CPT codes for health behavior and medical nutrition interventions
    d. Similar codes: overweight and obesity codes are on line 320 OBESITY IN ADULTS AND CHILDREN; OVERWEIGHT STATUS IN ADULTS WITH CARDIOVASCULAR RISK FACTORS and allow intensive counseling. Prediabetes (fasting blood sugar >100 mg/dL) is on line 3 PREVENTION SERVICES WITH EVIDENCE OF EFFECTIVENESS for the diabetes prevention program
    e. Previous review: none in at least the past 10 years.
    f. HERC staff recommendation:
        i. Place E88.810-E88.819 on line 60 METABOLIC DISORDERS
        ii. Add line 60 to the CGM guideline and modify the guideline as shown below
            1. Will not allow use of CGM for insulin resistance or metabolic syndrome
        iii. Alternate placement: line 320 OBESITY IN ADULTS AND CHILDREN; OVERWEIGHT STATUS IN ADULTS WITH CARDIOVASCULAR RISK FACTORS
            1. GUIDELINE NOTE 5, OBESITY AND OVERWEIGHT would then apply
            2. If patient has a BMI>25, they would qualify for line 320 regardless of E88.81X placement
        iv. If this condition develops into prediabetes, the patient would be eligible for the diabetes prevention program

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

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

Continuous glucose monitors are not ~~covered~~ included on these lines for people with type 2 diabetes or gestational diabetes, or for people with insulin resistance or metabolic syndrome.

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.

2) **J44.81** Bronchiolitis obliterans and bronchiolitis obliterans syndrome and **J4A.0** Restrictive allograft syndrome
   a. Information:
      i. Bronchiolitis obliterans is also known as obliterative bronchiolitis or constrictive bronchiolitis. When it occurs after lung transplantation or hematopoietic stem cell transplantation (HSCT), it is called bronchiolitis obliterans syndrome. Bronchiolitis obliterans is a type of obstructive lung disease of the small airways
      ii. Restrictive allograft syndrome is similar to bronchiolitis obliterans syndrome, but shows restrictive rather than obstructive physiology
   b. Treatment:
      i. Treatment of bronchiolitis obliterans syndrome after lung transplant involves augmenting immunosuppression since it is thought to be a form of chronic rejection. In addition to these therapies, controlling gastroesophageal reflux is also recommended to decrease bronchiolitis obliterans syndrome. In cases where bronchiolitis obliterans syndrome is progressive and severe, then re-transplantation of a lung may be indicated.
      ii. In non-transplant related bronchiolitis obliterans, removal from offending agents is essential. Immunosuppression with corticosteroids and cytotoxic agents like cyclophosphamide has been used for bronchiolitis obliterans related

to rheumatoid arthritis but has not been beneficial for bronchiolitis obliterans from toxic inhalation or post-infectious etiology

c. Similar codes: Previously coded with J84.115 (Respiratory bronchiolitis interstitial lung disease) which is on lines 219 PULMONARY FIBROSIS and 240 CONDITIONS REQUIRING HEART-LUNG AND LUNG TRANSPLANTATION
d. Chronic PPI therapy is on line 380 ESOPHAGITIS; GERD
e. HERC staff recommendation:
    i. Place **J44.81** and **J4A.0** on lines 219 PULMONARY FIBROSIS and 240 CONDITIONS REQUIRING HEART-LUNG AND LUNG TRANSPLANTATION
        1. Follows previous coding placement
    ii. Place J44.81 and J4A.0 on line 380 ESOPHAGITIS; GERD
    iii. Modify GN144 as shown below

GUIDELINE NOTE 144, PROTON PUMP INHIBITOR THERAPY FOR GASTROESOPHAGEAL REFLUX DISEASE (GERD)

Lines 314,380,513

Short term treatment (up to 8 weeks) of GERD without Barrett's (ICD-10-CM K20.8, K20.9, K21.0, K21.9) with proton pump inhibitor therapy is included on Line 380. Long term treatment of GERD without Barrett's with proton pump inhibitor therapy is included on Line 513.

Long term proton pump inhibitor therapy is included on Line 380 for Barrett's esophagus (ICD-10-CM K22.70), ~~and~~ eosinophilic esophagitis (ICD-10-CM K20.0), and bronchiolitis obliterans (ICD-10-CM J44.81 and J4A.0) and on Line 314 for Barrett's esophagus with dysplasia (ICD-10-CM K22.71).

1) **K63.8211-K63.8219 and K63.829** Small intestinal bacterial overgrowth
    a. Information: Small intestinal bacterial overgrowth (SIBO) is defined as the presence of excessive bacteria in the small intestine. SIBO is frequently implicated as the cause of chronic diarrhea and malabsorption. SIBO is defined as a bacterial population in the small intestine exceeding 10^5–10^6 organisms/mL. Normally, less than 10^3 organisms/mL are found in the upper small intestine. Structural abnormalities in the GI tract provide an ideal environment for bacterial colonization and overgrowth. GI tract surgeries that create a blind loop (eg, a Billroth II procedure or a Roux-en-Y anastomosis) predispose to bacterial stasis and overgrowth due to abnormal motility and ineffective clearance of retained food and secretions. Patients who have undergone jejunoileal bypass, an end-to-side enteroenteric anastomosis, or the creation of a Koch distal ileal pouch, are also at risk to develop SIBO. Other patients are also at risk, include patients with GI motility disorders, irritable bowel syndrome and the elderly. Symptoms of SIBO are nonspecific and include bloating, abdominal distension, abdominal pain or discomfort, diarrhea, fatigue, and weakness. The diagnosis of SIBO is controversial. There is substantial disagreement in the literature regarding which test is the most appropriate in either the clinical or research setting. Two tests are commonly employed: bacterial culture and breath tests. There is no consensus on the gold standard test for diagnosis SIBO. The

most commonly preformed test is breath testing. Per the North American Consensus statement on hydrogen and methane breath testing, an increase of greater than or equal to 20 parts per million (ppm) from baseline in hydrogen by 90 minutes is considered a positive test to diagnose SIBO. However, sensitivity and specificity for breath testing for the diagnosis of SIBO is poor. Given the limitations of breath tests for diagnosing SIBO—including the fact there is no gold standard for diagnosing the disease, rendering calculations of sensitivity and specificity moot—the utility of this testing modality has generated substantial controversy.

b. Treatment: Treatment aimed at correcting the underlying cause includes dietary, surgical, and medical therapies. A low FODMAP diet is recommended, but strict adherence is required. Surgical revision of altered small bowel anatomy may be beneficial in patients with SIBO secondary to small bowel diverticulosis, fistulas, or strictures. Patients with gastroparesis or small bowel dysmotility as the underlying cause of SIBO may benefit from the use of prokinetic agents. Although there are no Food and Drug Administration–approved medications to treat SIBO, the mainstay of treatment of SIBO has been oral antibiotics. Unfortunately, antibiotic regimens for SIBO have, in general, been poorly studied, given small numbers of patients and lack of placebo controls. There are known risks of antibiotic therapy, including medication side effects, promoting drug-resistant bacteria and Clostridium difficile colitis. Recurrence rates for SIBO following treatment with antibiotics are reported to be high but, given the myriad of uncertainties surrounding diagnosis and treatment efficacy, the accuracy of these rates of disease recurrence is unclear.
c. CPT code 91065 (Breath hydrogen or methane test (eg, for detection of lactase deficiency, fructose intolerance, bacterial overgrowth, or oro-cecal gastrointestinal transit)) is on the DIAGNOSTIC PROCEDURES file.
    i. No review was found in search of minutes for any prior review of this procedure code
    ii. Medicare has an NCD for CPT 91065, which limits use to evaluation of possible lactose malabsorption. Testing diagnosis of SIBO is specifically excluded from coverage. All private insurers surveyed had this policy as well for Medicare and Medicaid lines of business.
    iii. The test costs $66
    iv. The CCO medical directors did not want to put this code on PA as it is low cost
d. Similar diagnoses:
    i. SIBO was previously coded with either A04.9 (Bacterial intestinal infection, unspecified) which is on line 660 GASTROINTESTINAL CONDITIONS WITH NO OR MINIMALLY EFFECTIVE TREATMENTS OR NO TREATMENT NECESSARY or K90.89 (Other intestinal malabsorption) which is on lines 227 INTESTINAL MALABSORPTION and 553 OTHER NONINFECTIOUS GASTROENTERITIS AND COLITIS with placement governed by GN207.

GUIDELINE NOTE 207, OTHER INTESTINAL MALABSORPTION

Lines 227,553

ICD-10-CM K90.89 (Other intestinal malabsorption) is included on this line only for chronic steatorrhea, exudative enteropathy, and protein-losing enteropathy. Otherwise, it is included on Line 553.

e. Previous HSC/HERC discussion
    i. GN207 was added to the Prioritized List in 2009. In 2009, the discussion regarding ICD-9 579.8 (Other specified intestinal malabsorption) centered around the fact that this diagnosis includes both serious and minor conditions. Some members felt that this code should not be covered at all, others felt that the more serious sub-diagnoses should be covered, such as protein-losing enteropathy. The HSC felt that primary care visits should be covered for these diagnoses as well as additional diagnostic testing to determine a more specific diagnosis. The HSC concluded that the guideline which is now GN207 should be added to specify when this diagnosis is covered.
f. HERC staff summary
    i. SIBO is a controversial diagnosis with poorly studied diagnostic criteria and lack of evidence for its various treatments. SIBO secondary to small bowel diverticulosis, fistulas, or strictures could be treated with surgery when those other diagnoses are used. SIBO caused by gastroparesis or intestinal dysmotility can have prokinetic agents covered under those other diagnoses. The previous intent of the Health Services Commission was that the code used formerly to represent this diagnosis be placed on a non-covered line. Placing this code on a non-funded line will still allow office visits and diagnostic testing. Antibiotics that do not have prior authorization criteria will also be covered if prescribed for this condition. However, placement on a non-funded line will not allow automatic coverage of new treatments for this condition that become available. If these treatments are found to have evidence of efficacy, then the placement of this condition can be re-addressed.
g. HERC staff recommendation
    i. Add **K63.8211-K63.8219 and K63.829** (Small intestinal bacterial overgrowth) to line 553 OTHER NONINFECTIOUS GASTROENTERITIS AND COLITIS

2) **R92.3X** Dense breasts
    a. Information: dense breasts are diagnosed through mammography. Dense breasts appear more white than fatty breasts. Women with dense breasts have a higher risk of breast cancer than women with non-dense breasts. The cause of this association is unclear. Dense breasts make mammographic detection of tumors more difficult. There is controversy about what tests other than mammograms, if any, should be offered to women with dense breasts. Some experts recommend digital breast tomosynthesis, breast ultrasound or breast MRI for women with dense breasts.

b. Expert guidelines:
    i. **NCCN 1.2023** Breast cancer screening and diagnosis
        1. Dense breasts limit the sensitivity of mammography. Mammographically dense breast tissue is associated with an increased risk for breast cancer.
        2. For individuals with mammographically dense breast tissue (heterogeneously or extremely dense breast tissue), recommend counseling on the risks and benefits of supplemental screening.
        3. Handheld or automated ultrasound can increase cancer detection rates in individuals with dense breast tissue, but may increase recall and benign breast biopsies.
        4. Insufficient Evidence to Recommend for or Against Routine Population-Based MRI Screening: • Heterogeneously or extremely dense breast on mammography
        5. There is emerging evidence that breast scintigraphy and contrast-enhanced mammography may improve detection of early breast cancers among females with mammographically dense breasts; current evidence does not support their routine use as alternative screening procedures
c. HERC staff recommendation
    i. Advise HSD to place R92.3X on the Informational file

3) Existing code change:
    a. **Z62.813** (Personal history of forced labor or sexual exploitation in childhood) is INFORMATIONAL. All similar "personal history of abuse in childhood" codes are on line 445 ADJUSTMENT DISORDERS. BHAP recommended that all "personal history of" childhood trauma be placed on line 445 because children frequently cannot be given a more specific diagnosis early in their treatment after a trauma.
    b. HERC staff recommendation:
        i. Add ICD-10-CM Z62.813 to line 445 ADJUSTMENT DISORDERS

Highlights
June 28, 2023
Behavioral Health Advisory Panel
Online
3:00 pm--5:00 pm

Members Present: Lynnea Lindsey, PhD Chair; Kathy Savicki, LCSW; Gary Cobb; Eric Davis, MSW, CADC III, PSS; MSCP; Sheldon Levy, PhD; John Bischof, MD; Ryan Bair, DSW, LCSW; Ida Moadab, PhD; Adrienne Auxier, LPC; Evyan Daughterty, LCSW; Kati Jodinen, CADC II, QMHA; Roxanne Edwinson, PhD; Mikilah Johnson, LMFT; Tara Candela, JD, PMHNP-BC; Iris Sexton, LCSW.

Members Absent: Lori Krayer, APRN; Lisa Tovar, LCSW; Lauren Whipple, PSS, QMHA-R; Kessa Williams, LPC; Sandra Bumpus, MSW; Jason Achee; Asha Jetmalani, DO.

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

Also Attending: Robert Cuyler, PhD & Monica Frederick (Freespira); Doug Starr; Erin; Erin Porterl Holly Jo L Hodges, MD (Moda Health/EOCCO); Jessica; Jessica Compton (UHA); Jessica Cosato; Joanna Roquel Wilson; Laura Blanke; Linda WIlliams; Marissa Parr (UHA); sabhh; Bireland (Trillium Family).

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1. Call to order/purpose of meeting/staff updates

The meeting was called to order at 3:05 PM. Smits gave a short presentation on the purpose or BHAP and an overview of the HERC process. Introductions were done. Smits reported on internal OHA work on clubhouse services for patients with chronic mental illness. OHA outreach to the affected population found that this group expressed the most need for respite services, and OHA will be putting resources into those types of services rather than clubhouse services.

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2. PRIORITIZED LIST ISSUES

A. Undefined reaction to severe stress

Smits reviewed a summary document on ICD-10-CM F43.9 (Reaction to severe stress, unspecified). ICD-10-CM F43.0 (Acute stress reaction) is on line 290 ACUTE STRESS DISORDER could be used rather than F43.9; however, F43.0 is time-limited to use for only 30 days. Roxanne Edwinson recommended adding coverage, she uses this code in her pediatric practice for children when its not clear what stress is triggering the symptom. Many kids entering foster care get this diagnosis initially before a more in-depth evaluation can be completed. Meg Cary agreed that this diagnosis is used in pediatric psychiatric practice with

individuals with complex trauma. She also noted that there can be cultural differences in how individuals express their symptoms. This code is similar to F43.20 (Adjustment disorder, unspecified) which is on line 445. The group recommended adding F43.9 to line 445.

B. 2024 ICD-10-CM codes related to mental health

Smits reviewed the summary recommendations. There was minimal discussion regarding the new code placement other than ICD-10-CM Z02.84 (Encounter for child welfare exam). Members who work with children entering foster care noted that this code is only used for the required dental, mental health and physical exam that children are required to have when they enter the foster care system. This code is funded from ODHS, not Medicaid. The staff recommendation to place this code on the Diagnostic Workup File (DWF) was changed to INFORMATIONAL.

The additional ICD-10 code issues were discussed. The group agreed that ICD-10-CM Z62.813 (Personal history of forced labor or sexual exploitation in childhood) should be removed from INFORMATIONAL file and added to line 445. "Personal history of" childhood trauma codes are covered online 445 due to children frequently not having a diagnosis initially after a trauma. The "personal history of" adult trauma codes are appropriate for the Informational file as adults can be given a more specific diagnosis more easily.

C. Freespira for PTSD and Panic Disorder

Smits reviewed the summary document and staff recommendations.

Monica Frederick from Freespira testified. She described the research behind Freespira and noted that HERC staff had not included all studies. She noted that Freespira is covered by some Medicaid programs in Wisconsin as well as by Highmark BCBS and the Veterans Administration. She stated that Freespira can be used for treatment of panic disorder and PTSD in patients who don't have easy access to a therapist, particularly in rural areas. Patients use Freespira in their homes. She also noted that medications commonly used for panic disorder and PTSD, such as benzodiazepines, have significant side effects. Disordered breathing is a feature of panic and PTSD. Many symptoms of PD and PTSD (sweaty palms, SOB, etc) are also seen in hyperventilation. Freespira allows patients to learn a new skill that can continue to serve them. The process for getting access to the Freespira device is to have a mental health professional prescribe the device, then an RN from the company reaches out to make sure the patient is appropriate for this treatment, then the company sends out the device and the tablet needed to run it. Patients have weekly coaching sessions. The device is contraindicated in pregnancy, severe lung disease, and severe psychiatric disorders.

Bob Cuyler from Freespira testified. He noted that studies on the device were RCTs that used a wait list design. He stress the significant response rates to treatment. One early RCT of Freespira compared the device to in lab biofeedback. There were similar responses seen to both treatments. The company is seeking grant funding to study the effect on health care utilization of the device.

The BHAP discussion mainly centered on the lack of true comparison RCTs of the device, comparing the device to standard psychotherapy, medication therapy, etc. There was concern that this device is in the early stages of evaluation and the evidence does not yet support its use. Some members felt that this device looked promising, and requested that HERC staff look at any additional research that Freespira could provide. HERC staff will review any additional studies provided to see if they are more supportive of coverage. If not, then HERC staff will monitory the research on this device and bring it back to BHAP at a future meeting.

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3. Other issues

John Bischof noted that transcrania magmetic stimulation criteria are evolving and the indications in the Prioritized List guideline need to be updated. Staff will research this and bring this to a future BHAP meeting.

Gary Cobb asked the group about implementaition of traumatic bain injury screening for OHP patients. HERC staff will work with him to determine if there are any HERC coverage issues involved.

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4. ADJOURNMENT

The meeting was adjourned at 4:45 PM

Section 7.0

New Discussion Items

Laser Interstitial Thermal Therapy for Epilepsy

Plain Language Summary:

Coverage question: Should laser brain surgery for patients that have epilepsy be covered when medication doesn't help?

Should OHP cover this treatment?
Option 1) Do not add coverage.
Option 2) Add coverage with a guideline for its use.
Option 3) Refer to the Evidence-based Guidelines Subcommittee for a potential coverage guidance.

Coverage Question: Should laser interstitial thermal therapy (LITT), also known as laser ablation or stereotactic laser ablation, be paired with epilepsy on a covered line?

Question source: David Spencer, Professor of Neurology and Director of the OHSU Comprehensive Epilepsy Center

This topic was also nominated as a MED review topic in 2023, but not selected for review

Background: MR-guided laser interstitial thermal therapy (MRgLITT) is a treatment for refractory focal epilepsy which is considered to carry less risk than open neurosurgery. It involves the identification of the epileptogenic lesion on magnetic resonance imaging (MRI), and the insertion of a fine fiberoptic laser catheter into the target area through a burr hole in the skull. The procedure is carried out under continuous real-time MRI scanning to allow visualization of the exact target area and the surrounding tissue, and to monitor the temperature in the brain during the procedure. Laser energy is applied with the aim of ablating the target tissue while causing minimal damage to the surrounding area. LITT has also been studied for use in treating primary or metastatic brain tumors.

Standard treatment for epilepsy and brain tumors is anti-epileptic drugs. For patients who have epilepsy inadequately controlled by medical treatment, surgery is a treatment option. Standard surgery is an open craniotomy surgery to resect the portion of the brain that is the epileptic focus.

From Dr. Spencer:

> I'm getting…in touch…to raise the issue of coverage another procedure for the treatment of our patients with epilepsy: Laser interstitial thermal therapy (LITT), sometimes also called laser ablation or stereotactic laser ablation. One of our patients was recently denied coverage for this procedure despite strong medical indications for its use over open surgery. This prompted the question of whether a review of the guidelines for the coverage for this procedure is warranted. Similar to DBS for epilepsy, this would involve a relatively small number of patients and a very limited number of specialized centers.

Laser Interstitial Thermal Therapy for Epilepsy

From MED: State Medicaid administrators are interested in the evidence of effectiveness and potential harms of LITT for patients with drug-resistant epilepsy, brain tumors, radiation necrosis, and other populations who may be candidates for this treatment, as well as payer policies for LITT.

Previous HSC/HERC reviews:

LITT was reviewed as a new CPT code in November 2021. During that review, a 2019 CADTH report was reviewed which concluded: "Evidence of limited quality and quantity suggested that LITT proffers no advantage over stereotactic radiosurgery in inducing seizure freedom in patients with drug-resistant, medically intractable temporal lobe epilepsy. Relative to patients who were treated with stereotactic radiosurgery and craniotomy, patients treated with LITT appeared to experience fewer adverse events and complications. No comparative evidence on disease progression, overall survival, hospitalization, or quality of life was found. None of the studies reported on the incidence of epileptic episodes, post-operative pain, use of medication, or hospital readmissions. Considerable caution must be taken in interpreting the evidence presented in this report due to the paucity of comparative data and other limitations."

During the 2021 review, the NCCN 2.2021 guideline for CNS cancers was reviewed: "MRI-guided laser interstitial thermal therapy (LITT) (category 2B) may be considered for patients who are not surgical candidates (craniotomy or resection). Potential indications include relapsed brain metastases and radiation necrosis"

The decision in November 2021 was to place LITT on line 662/GN173

Current Prioritized List/Coverage status:

On line 174 GENERALIZED CONVULSIVE OR PARTIAL EPILEPSY WITHOUT MENTION OF IMPAIRMENT OF CONSCIOUSNESS:

> CPT 61735 Creation of lesion by stereotactic method, including burr hole(s) and localizing and recording techniques, single or multiple stages; subcortical structure(s) other than globus pallidus or thalamus

On line 662 CONDITIONS FOR WHICH CERTAIN INTERVENTIONS ARE UNPROVEN, HAVE NO CLINICALLY IMPORTANT BENEFIT OR HAVE HARMS THAT OUTWEIGH BENEFITS:

> CPT 61736-61737 Laser interstitial thermal therapy (LITT) of lesion, intracranial, including burr hole(s), with magnetic resonance imaging guidance, when performed; single trajectory for 1 simple lesion/ multiple trajectories for multiple or complex lesion(s)

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 660 CONDITIONS FOR WHICH CERTAIN INTERVENTIONS ARE UNPROVEN, HAVE NO CLINICALLY IMPORTANT BENEFIT OR HAVE HARMS THAT OUTWEIGH BENEFITS:

Laser Interstitial Thermal Therapy for Epilepsy

Procedure Code	Intervention Description	Rationale	Last Review
61736, 61737	Laser interstitial thermal therapy (LITT) of lesion, intracranial	Insufficient evidence of effectiveness	November 2021

Similar therapy guideline:

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 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

Laser Interstitial Thermal Therapy for Epilepsy

Evidence:

1) **Barot 2022**, systematic review and meta-analysis of MRI-guided laser interstitial thermal therapy for drug-resistant epilepsy
    a. N=28 studies (559 patients),
        i. all case series (5-58 patients), mostly retrospective
        ii. Landazuri et al 2020 included as in NHS 2021 below
        iii. Gross et al 2018 contained the same population as Drane et al 2015 in NHS 2021 below
    b. The overall prevalence of Engel class I outcome (free from disabling seizures) was 56% (95% CI 0.52% to 0.60%)
        i. 314 patients from 28 studies
    c. The prevalence of postoperative adverse events was 19% (95% CI 0.14% to 0.25%) and the most common adverse event was visual field deficits. The reoperation rate was 9% (95% CI 0.05% to 0.14%), which included repeat ablation and open resection
    d. MRgLITT is an effective and safe intervention for DRE with different disease etiologies.
2) **NHS 2021** MR-guided laser interstitial thermal therapy for children and adults with refractory focal epilepsy
    a. N=8 studies
        i. 3 systematic reviews (Sanjeet et al 2019, Wang et al 2020, Xue et al 2018) which included between 9 and 16 case series (N=189-414 patients)
        ii. 1 cohort study comparing stereotactic laser amygdalohippocampotomy (SLAH) or open resection (Drane et al 2015)
        iii. 2 retrospective case series (Bermudez et al 2020, N=26 patients; Gross et al 2018, N=58 patients)
        iv. 1 prospective case series (Landazuri et al 2020, N=42 patients)
        v. 1 cost utility study (Widjaja et al 2019)
    b. Seizure freedom
        i. Drug resistant focal epilepsy due to mix of etiologies:
            1. At more than six months follow-up, the SRMA by Wang et al 2020 (n=414) reported a mean seizure free (Engel class I) rate of 65% (95% CI 56 to 74) (I2=69.42 (p=0.00)). At 12 months follow-up Landazuri et al 2020 (n=42) reported a rate of Engel class I seizures of 64.3% (95% CI 48.0 to 78.5), Engel class II seizures of 9.5% (no CI reported), Engel class III seizures of 21.4% (no CI reported) and Engel class IV seizures of 4.8% (95% CI 0.6 to 16.2). At between seven days and 51 months follow-up (Xue et al 2018), meta-analysis of 12 case series (n=189) reported a pooled prevalence of Engel class I seizures of 61% (95% CI 54 to 68) (I2=14.5% (p=0.302)), meta-analysis of seven case series (n=135) reported a pooled prevalence of Engel class II seizures of 12% (95% CI 7 to 16) (I2=86.8% (p=0.000)), meta-analysis of six case series (n=135) reported a pooled prevalence of Engel class III seizures of 18% (95% CI 10 to 22) (I2=3.0% (p=0.397)), and meta-analysis of five case series (n=109) reported a pooled prevalence of Engel class IV seizures of 15% (95% CI 8 to 22), (I2=13.2% (p=0.330)).
    c. Drug resistant focal epilepsy of temporal lobe origin

i. At six months follow-up a comparator cohort study including adults with mesial temporal lobe epilepsy (Drane et al 2015) (n=58) reported that of 10 subjects having SLAH on their language dominant hemisphere, 7, 1, 2 and 0 had Engel class I, II, III and IV seizures respectively; of 22 subjects having open resection on their language dominant hemisphere 11, 5, 3 and 3 had Engel class I, II, III and IV seizures respectively; of 9 subjects having SLAH on their non-dominant hemisphere 4, 0, 2 and 3 had Engel class I, II, III and IV seizures respectively; and of 17 subjects having open resection on their non-dominant hemisphere 13, 2, 2 and 0 had Engel class I, II, III and IV seizures respectively (no significance measures reported). The small numbers and lack of statistical measures mean that no conclusions can be drawn about these seizure outcomes compared with the minimum clinically important difference (MCID) threshold defined in the PICO2

ii. At more than six months follow-up, the SRMA by Wang et al 2020 (n=266) reported a mean seizure free rate (Engel class I) of 59% (95% CI 53 to 65), (I 2 =0.00, (p=0.83)). Bermudez et al 2020 reported a rate of freedom from disabling seizures (not defined) of 85% (no CI reported) in patients with focal epilepsy of mesial temporal origin who had had MRgLITT on their dominant hemisphere (n=13) at mean 8.3 (+/-1.27) months follow-up. Bermudez et al 2020 also reported a rate of freedom from disabling seizures (not defined) of 75% (no CI reported) in patients with focal epilepsy of mesial temporal origin who had had MRgLITT on their non-dominant hemisphere (n=13) at mean 8.5 (+/-4.6) months follow-up

iii. At 12 months follow-up after the first procedure, one case series of patients with mesial temporal lobe epilepsy (Gross et al 2018) reported a rate of seizure freedom (Engel class I) of 48.3% (95% CI 35.9 to 50.8) (n=58). Gross et al 2018 also reported a rate of seizure freedom (Engel class I) of 58.1% (95% CI 43.3 to 71.6) in patients with mesial temporal lobe epilepsy who had mesial temporal sclerosis (n=43) and a rate of seizure freedom (Engel class I) of 20.0% (95% CI 6.3 to 46.0) in patients with mesial temporal lobe epilepsy who did not have mesial temporal sclerosis (n=15).

d. Neuropsychological outcomes
    i. Drane et al reported statistically significantly worse scores in naming and recognition in the open resection group (very low certainty of evidence)
e. Quality of life
    i. One case series provided evidence on quality of life using the QOLIE-314 score in patients with a range of etiologies (these included temporal lobe epilepsy and other etiologies, but the specific etiologies for those included in this outcome were not stated) (Landazuri et al 2020) (n=29) (higher score better). At baseline the median total QOLIE-31 score was 51.7 (range 8.7 to 77.3) and at latest follow-up (duration of follow-up not stated) it was 65.8 (range not stated) (p=0.2173).
f. No evidence was found on impact on cognitive development in children or need for medical therapy
g. Complications:
    i. At an unspecified follow-up period, two SRMAs (Wang et al 2020, Xue et al 2018) reported post-operative complications. Xue et al 2018 (n=101) reported a

pooled rate of postoperative complications of 24% (95% CI 16 to 32) (range across studies 15% to 43%) (I2=0%; p=0.629). At more than 6 months follow-up (actual follow-up not stated), Wang et al (n= not stated) reported a rate of complications of 7% (95% CI 4 to 11), a total of 27 complications. At 12 months follow-up, Gross et al 2018 (n=58) reported 5/58 (8.6%) patients had a visual field deficit, one of which (1.7%) was persistent and symptomatic. At a median 22.4 months (range 7-70 months) follow-up the SRMA by Sanjeet et al 2019 (n=207) reported an overall complication rate of 20% (95% CI 14 to 26) (I2 =0.00, p=0.63)

h. Conclusions
    i. Compared to baseline, all studies reported improvements in seizure outcomes at follow-up periods from seven days to a maximum of 51 months, for some patients with drug-resistant focal epilepsy due to a variety of etiologies in whom open neurosurgery carries a high risk of adverse effects. The proportion who were reported to be seizure free ranged from 20% to 71%, depending on the etiology and duration of follow-up.
    ii. One case series reported a significant improvement in two quality of life subscores after MRgLITT with no change in the overall quality of life score.
    iii. The studies identified for this review therefore provide very low certainty evidence that MRgLITT improves outcomes at follow-up for children and adults with refractory focal epilepsy in whom open neurosurgery carries a high risk of serious adverse effects. They also provide very low certainty evidence that neuropsychological outcomes are significantly worse in those undergoing open neurosurgery compared with MRgLITT, but no evidence on whether there is any significant difference in seizure outcomes after MRgLITT or open neurosurgery. It is not possible to draw conclusions about the outcomes of MRgLITT compared with continued medical therapy

i. Limitations
    i. The evidence from these studies must be regarded as very low certainty due to their design, conduct and reporting. There is a significant risk of bias associated with the case series design of three of the studies and with two of the SRMAs; the third SRMA excluded studies they judged to be at high risk of bias but still has some potential sources of bias. Limited details were provided about the study subjects included in all studies, and all three case series reported loss to follow-up

3) **Kohlhase 2021**, systematic review and meta-analysis of minimally invasive and traditional surgical approaches for refractory mesial temporal lobe epilepsy
    a. N=13 studies on MRgLITT (554 patients)
    b. N=24 surgical studies (1504 patients treated with anterior temporal lobe resection (ATL), 1326 patients treated with selective amygdalahippocampectomy (sAHE))
    c. Engel Class I (Engel-I) outcomes were achieved after MRgLITT in 57% (315/554, range = 33.3%–67.4%), ATL in 69% (1032/1504, range = 40%–92.9%), and sAHE in 66% (887/1326, range = 21.4%–93.3%). Meta-analysis revealed ATL and sAHE were both superior to MRgLITT (ATL: Q = 8.92, p = .002; sAHE: Q = 4.33, p = .037)
    d. The rate of major complications was 3.8% for MRgLITT, 10.9% for ATL, and 7.4% for sAHE; the differences did not show statistical significance. Neuropsychological deficits occurred after all procedures, with left-sided surgeries having a higher rate of verbal

memory impairment. Lateral functions such as naming or object recognition may be more preserved in MRgLITT.

Submitted literature:

None

Expert guidelines:

Drug resistant epilepsy

1) **Wu 2022**, The American Society for Stereotactic and Functional Neurosurgery Position Statement on Laser Interstitial Thermal Therapy for the Treatment of Drug-Resistant Epilepsy
    a. Indications for the Use of MRgLITT as a Treatment Option for Patients With DRE Include All of the Following Criteria
        i. Failure to respond to, or intolerance of, at least 2 appropriately chosen medications at appropriate doses for disabling and localization-related epilepsy AND
        ii. Well-defined epileptogenic foci or critical pathways of seizure propagation accessible by MRgLITT.
    b. Although this approach has thus far failed to match seizure freedom rates associated with open resection for indications such as MTLE and extensive focal cortical dysplasia, this shortcoming must be carefully considered and balanced with potential risks including neurocognitive side effects and procedural morbidity. In addition, it is important to remember that MRgLITT does not preclude the option of subsequent more extensive ablations or open surgery. Although long-term outcomes must be compared against proven surgical resection techniques, MRgLITT serves as a minimally invasive option that clearly provides greater benefit in patients with DRE than medical management alone

CNS cancer

1) NCCN 1.2023

a. MRI-guided laser interstitial thermal therapy (LITT)3-8 (category 2B)
    i. LITT may be considered for patients who are poor surgical candidates (craniotomy or resection). Potential indications include relapsed brain metastases, radiation necrosis, and recurrent glioblastoma.
b. LITT is a minimally invasive technique using photothermal technology and can be considered on a case-by-case basis for treatment of radiation necrosis in patients with a history of RT for primary brain tumor or metastatic disease. Consultation with adept neurosurgeons trained in LITT should be done when the procedure is considered.

Other payer policies:

1) Aetna 2023
    a. Aetna considers magnetic resonance-guided laser interstitial thermal therapy (MRgLITT) (e.g. the NeuroBlate and the Visualase Thermal Therapy System) medically necessary as an alternative to standard surgery when all the following criteria are met.
        i. Non-epileptic attacks such as cardiogenic syncope and psychogenic seizures have been ruled out; *and*

ii. The diagnosis of epilepsy has been documented, and the epileptic seizure type and syndrome has been clearly defined. In general, appropriate candidates for epilepsy surgery are members who are incapacitated by their frequent seizures as well as the toxicity of anti-epileptic drugs.
iii. Members' quality of life may significantly improve with surgery; *and*
iv. Seizures occur at a frequency that interferes with members' daily living and threatens their well being; *and*
v. There must have been an adequate period of therapy of two or more antiepileptic drugs, namely, the correct drugs used in the correct dosage, carefully monitored for treatment effects and members' compliance.

2) Anthem BCBS 2023
   a. The treatment of medically refractory epilepsy using stereotactic laser techniques (MRI-guided laser interstitial thermal ablation [MRIgLITT]), including stereotactic laser amygdalohippocampotomy (SLAH), is considered **medically necessary** when the following criteria are met:
      i. Documented disabling seizures despite the use of two or more tolerated antiepileptic drug regimens; **and**
      ii. Documented presence of two or fewer well delineated epileptogenic foci accessible by laser.
3) United Health Care 2023
   a. Laser interstitial thermal therapy is unproven and not medically necessary for treating any condition or diagnosis due to insufficient evidence of efficacy.

Expert input:

Dr. David Spencer, OHSU neurosurgery

As I think has been demonstrably the case with our prior discussions surrounding DBS therapy for epilepsy, this would be a restricted procedure that is done relatively infrequently, but there are instance when it is clearly the superior option for specific patients who might be unwilling to undergo resection or for whom resection poses unacceptable risks to memory or cognitive function.

In general, resection brings higher odds of seizure freedom but carries more risk for postoperative neurological/cognitive deficits and longer recovery times. Conversely, LITT offers slightly lower chance of seizure freedom, but lower risk of neurological complications and faster recovery time.

The OHSU neurosurgery team assisted HERC staff in drafting the guideline in option 2 below

Laser Interstitial Thermal Therapy for Epilepsy

HERC staff summary:

The literature on laser interstitial thermal therapy (LITT) for refractory epilepsy consist mainly of case series which are mostly retrospective. High quality systematic reviews find very low certainty evidence that LITT improves seizure control or quality of life and very low certainty evidence that LITT resulted in improved neuropsychological outcomes compared to open surgery. Systematic reviews and expert guidelines conclude that LITT results in lower seizure freedom rates compared to open resection. Other payers vary in coverage for LITT.

LITT is a 2B option for treatment of brain tumors in current NCCN guidelines.

HERC staff recommendation:

1) **Option 1**: do not add coverage for LITT
    a. Update the date of last review in GN173

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 660 CONDITIONS FOR WHICH CERTAIN INTERVENTIONS ARE UNPROVEN, HAVE NO CLINICALLY IMPORTANT BENEFIT OR HAVE HARMS THAT OUTWEIGH BENEFITS:

Procedure Code	Intervention Description	Rationale	Last Review
61736, 61737	Laser interstitial thermal therapy (LITT) of lesion, intracranial	Insufficient evidence of effectiveness	~~November 2021~~ August 2023

2) **Option 2**: Add coverage of LITT for refractory epilepsy with a new guideline as shown below
    a. Remove CPT 61736-61737 (Laser interstitial thermal therapy (LITT) of lesion, intracranial, including burr hole(s), with magnetic resonance imaging guidance, when performed; single trajectory for 1 simple lesion/ multiple trajectories for multiple or complex lesion(s)) from line 662
    b. Add CPT 61736-61737 to line 174 GENERALIZED CONVULSIVE OR PARTIAL EPILEPSY WITHOUT MENTION OF IMPAIRMENT OF CONSCIOUSNESS Treatment SINGLE FOCAL SURGERY
    c. Delete the GN173 entry for CPT 61736-61737
    d. Add a new guideline to line 174 regarding LITT as shown below

GUIDELINE NOTE XXX LASER INTERSTITIAL THERMAL THERAPY FOR REFRACTORY EPILEPSY

Line 174

Laser interstitial thermal therapy (LITT, CPT 61736-61737) 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 to respond to, or is intolerant of, at least 2 appropriately chosen medications at appropriate doses, AND

Laser Interstitial Thermal Therapy for Epilepsy

C) The patient has a well-defined epileptogenic foci or critical pathways of seizure propagation accessible by LITT; AND

D) Seizures occur at a frequency that affects the patient's daily living and the neurologist/neurosurgeon document that LITT procedure will likely significantly improve patient's quality of life

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 660 CONDITIONS FOR WHICH CERTAIN INTERVENTIONS ARE UNPROVEN, HAVE NO CLINICALLY IMPORTANT BENEFIT OR HAVE HARMS THAT OUTWEIGH BENEFITS:

Procedure Code	Intervention Description	Rationale	Last Review
~~61736, 61737~~	~~Laser interstitial thermal therapy (LITT) of lesion, intracranial~~	~~Insufficient evidence of effectiveness~~	~~November 2021~~

3) **Option 3:** refer to EBGS for coverage guidance review

Original research

Surgical outcomes between temporal, extratemporal epilepsies and hypothalamic hamartoma: systematic review and meta-analysis of MRI-guided laser interstitial thermal therapy for drug-resistant epilepsy

Niravkumar Barot ,[1] Kavita Batra ,[2] Jerry Zhang,[3] Mary Lou Klem,[4] James Castellano,[5] Jorge Gonzalez-Martinez,[6] Anto Bagic[7]

► Additional online supplemental material is published online only. To view, please visit the journal online (http://dx.doi.org/10.1136/jnnp-2021-326185).

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Received 26 January 2021
Accepted 20 June 2021
Published Online First 28 July 2021

To cite: Barot N, Batra K, Zhang J, *et al*. *J Neurol Neurosurg Psychiatry* 2022;**93**:133–143.

ABSTRACT

Background Approximately 1/3 of patients with epilepsy have drug-resistant epilepsy (DRE) and require surgical interventions. This meta-analysis aimed to review the effectiveness of MRI-guided laser interstitial thermal therapy (MRgLITT) in DRE.

Methods The Population, Intervention, Comparator and Outcome approach and Preferred Reporting Items for Systematic Reviews and Meta-Analyses were followed. PubMed, MEDLINE and EMBASE databases were systematically searched for English language publications from 2012 to Nov 2020. Data on the prevalence outcome using the Engel Epilepsy Surgery Outcome Scale (Class I–IV), and postoperative complications were analysed with 95% CIs.

Results Twenty-eight studies that included a total of 559 patients with DRE were identified. The overall prevalence of Engel class I outcome was 56% (95% CI 0.52% to 0.60%). Hypothalamic hamartomas (HH) patients had the highest seizure freedom rate of 67% (95% CI 0.57% to 0.76%) and outcome was overall comparable between mesial temporal lobe epilepsy (mTLE) (56%, 95% CI 0.50% to 0.61%) and extratemporal epilepsy (50% 95% CI 0.40% to 0.59%). The mTLE cases with mesial temporal sclerosis had better outcome vs non-lesional cases of mTLE. The prevalence of postoperative adverse events was 19% (95% CI 0.14% to 0.25%) and the most common adverse event was visual field deficits. The reoperation rate was 9% (95% CI 0.05% to 0.14%), which included repeat ablation and open resection.

Conclusion MRgLITT is an effective and safe intervention for DRE with different disease aetiologies. The seizure freedom outcome is overall comparable in between extratemporal and temporal lobe epilepsy; and highest with HH.

Trail registration number The study protocol was registered with the National Institute for Health Research (CRD42019126365), which serves as a prospective register of systematic reviews. It is an international database of prospectively registered systematic reviews with a focus on health-related outcomes. Details about the protocol can be found at https://wwwcrdyorkacuk/PROSPERO/.

INTRODUCTION

Epilepsy affects around 1.8% of total population of the USA, and approximately 1/3 of them suffer from ongoing seizures despite appropriate pharmacotherapy, which is classified as drug resistant epilepsy (DRE).[1] Among this cohort, surgical resection of the epileptogenic zone offers the greatest chance of seizure freedom with reduced morbidity and mortality.[2 3] Minimally invasive techniques such as MRI-guided laser interstitial thermal therapy (MRgLITT) seek to abate the epileptogenic zone while providing reduced morbidity and mortality, as compared with open resection. This technique is especially relevant in patients with midline or deep epileptogenic foci, traditionally requiring more complicated neurosurgical approaches.

MRgLITT is a minimally invasive procedure whereby the epileptogenic focus is ablated with laser energy. The targeted thermal energy leads to protein denaturation and coagulative necrosis.[4 5] The US Food and Drug Administration approved the Visualase Thermal Therapy System (Medtronic, Minnesota, USA) for ablation in neurosurgery in 2007.[6] Its first use in the treatment DRE patients was reported by Curry *et al*.[7] Several case series/retrospective reports and few prospective studies have shown promising results with the use of laser ablation to treat intractable epilepsy in patients with clear targets: mesial temporal sclerosis (MTS), tuberous sclerosis, MRI-evident focal cortical dysplasia, hypothalamic hamartoma (HH), periventricular nodular dysplasia and radiation necrosis.[4 8] In the absence of well-designed double-blind randomised control trials, a meta-analysis and systematic review of available pertinent literature can elucidate the current state of evidence and guide future investigations. The limited published reviews on effectiveness of MRgLITT have primarily focused on mTLE (mesial Temporal Lobe Epilepsy), or its comparison with radiofrequency ablation, some with focus on the technical aspects, and most without statistically rigorous metanalysis and some have biases of duplicate studies from the same centres.[9–13] Our work extends the prior literature by providing outcomes of seizure freedom, postoperative adverse events and importantly reoperations stratified based on the age, aetiologies and follow-up (FU) duration which includes studies across all ages and aetiologies in patients with DRE.

NHS England Evidence Review:

MR-guided laser interstitial thermal therapy for children and adults with refractory focal epilepsy when open neurosurgery carries a high risk of serious adverse effects

NHS England URN: 2006b

1. Introduction

This evidence review examines the clinical effectiveness, safety and cost effectiveness of MR-guided laser interstitial thermal therapy (MRgLITT) compared to open neurosurgical resection or continued medical therapy alone for children and adults with refractory focal epilepsy when open neurosurgery carries a high risk of serious adverse effects. Drug-resistant or refractory epilepsy can cause significant impairment of quality of life. Patients are at risk of recurrent physical and cerebral injury from seizures, status epilepticus (prolonged seizures), sudden death in epilepsy, other causes of fatality and psychological, psychiatric, financial and social comorbidities. Patients will have tried various anti-epileptic medications, often with adverse effects, and may have had frequent hospitalisations.

Causes of refractory focal epilepsy may include hippocampal sclerosis located in the medial temporal lobe, cortical dysplasia, heterotopic nodules, low grade glioneuronal tumours, scar tissue from brain trauma, meningitis or stroke, malformations and other lesions. In those who have refractory focal epilepsy and a well-defined epileptogenic zone, open neurosurgical removal or ablation of this part of the brain can be curative. However, for some patients, open neurosurgery can carry a high risk of causing severe neurological deficit.

MRgLITT is proposed as a treatment for refractory focal epilepsy which carries less risk than open neurosurgery. It involves the identification of the epileptogenic lesion on magnetic resonance imaging (MRI), and the insertion of a fine fibreoptic laser catheter into the target area through a burr hole in the skull. The procedure is carried out under continuous real-time MRI scanning to allow visualisation of the exact target area and the surrounding tissue, and to monitor the temperature in the brain during the procedure. Laser energy is applied with the aim of ablating the target tissue while causing minimal damage to the surrounding area.

In addition to considering the clinical effectiveness, safety and cost effectiveness of MRgLITT for drug-resistant focal epilepsy, the scope of this review also included the identification of possible subgroups of patients within the included studies who might benefit from treatment with MRgLITT more than others.

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2. Executive summary of the review

Eight studies were included in the evidence review (Bermudez et al 2020, Drane et al 2015, Gross et al 2018, Landazuri et al 2020, Sanjeet et al 2019, Wang et al 2020, Widjaja et al 2019, Xue et al 2018).

Three were systematic review and meta-analyses (SRMAs) (Sanjeet et al 2019, Wang et al 2020, Xue et al 2018) which included between nine and sixteen case series of between 189 and 414 patients who had MR-guided laser interstitial thermal therapy (MRgLITT).

One was a study comparing cohorts undergoing stereotactic laser amygdalohippocampotomy (SLAH) or open resection (Drane et al 2015).

Two included papers were retrospective case series; Bermudez et al 2020 included 26 patients and Gross et al 2018 included 58 patients. Landazuri et al 2020 was a case series which included prospectively collected data on 42 patients.

Widjaja et al 2019 was a cost-utility study comparing MRgLITT and surgery in patients with temporal lobe epilepsy. Three studies (Gross et al 2018, Wang et al 2020, Xue et al 2018) included both adults and children, Drane et al 2015 and Widjaja et al 2019 included adults only, and the remaining studies reported the mean age of subjects to be between 35 and 42 years but did not report the age range. Studies reported outcomes at timepoints ranging from six months to a maximum of 51 months after MRgLITT.

Research Question 1:

1. In adults and children with drug-resistant focal epilepsy who have identifiable epileptogenic zones, what is the clinical effectiveness of MRgLITT compared with open neurosurgical resection or continued medical therapy alone?

Critical outcomes

The critical outcomes for decision making are seizure freedom, neuropsychological outcomes and quality of life.

The certainty of the evidence for all critical outcomes was very low when assessed using modified GRADE.

Seizure freedom

In total seven studies (three SRMAs of between nine and sixteen case series, one comparator cohort study and three case series) provided evidence relating to seizure freedom for people with drug-resistant focal epilepsy treated with MRgLITT. Three studies reported outcomes for patients with epilepsy due to different aetiologies grouped together, six reported outcomes for patients with epilepsy of temporal lobe origin, and two also reported outcomes separately for patients with epilepsy due to other specific aetiologies. Seizure freedom was measured at different time points between seven days and 51 months after the procedure and was defined using the Engel classification[1] in six studies (Drane et

[1] Engel seizure classification: *Class I: Free of disabling seizures* (IA: Completely seizure-free since surgery; IB: Non disabling simple partial seizures only since surgery; IC: Some disabling seizures after surgery, but free of disabling

Received: 13 May 2020 | Revised: 29 January 2021 | Accepted: 29 January 2021

DOI: 10.1111/epi.16846

Epilepsia®

CRITICAL REVIEW – INVITED COMMENTARY

Comparison of minimally invasive and traditional surgical approaches for refractory mesial temporal lobe epilepsy: A systematic review and meta-analysis of outcomes

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[Correction added on 04 February, 2022, after first online publication: The author "Adam Strzelczyk" has been designated as co-corresponding author].

Abstract

Magnetic resonance-guided laser interstitial laser therapy (MRgLITT) and radiofrequency ablation (RFA) represent two minimally invasive methods for the treatment of drug-refractory mesial temporal lobe epilepsy (mTLE). We performed a systematic review and a meta-analysis to compare outcomes and complications between MRgLITT, RFA, and conventional surgical approaches to the temporal lobe (i.e., anterior temporal lobe resection [ATL] or selective amygdalohippocampectomy [sAHE]). Forty-three studies (13 MRgLITT, 6 RFA, and 24 surgery studies) involved 554, 123, 1504, and 1326 patients treated by MRgLITT, RFA, ATL, or sAHE, respectively. Engel Class I (Engel-I) outcomes were achieved after MRgLITT in 57% (315/554, range = 33.3%–67.4%), RFA in 44% (54/123, range = 0%–67.2%), ATL in 69% (1032/1504, range = 40%–92.9%), and sAHE in 66% (887/1326, range = 21.4%–93.3%). Meta-analysis revealed no significant difference in seizure outcome between MRgLITT and RFA ($Q = 2.74$, $p = .098$), whereas ATL and sAHE were both superior to MRgLITT (ATL: $Q = 8.92$, $p = .002$; sAHE: $Q = 4.33$, $p = .037$) and RFA (ATL: $Q = 6.42$, $p = .0113$; sAHE: $Q = 5.04$, $p = .0247$), with better outcome in patients at follow-up of 60 months or more. Mesial hippocampal sclerosis (mTLE + hippocampal sclerosis) was associated with significantly better outcome after MRgLITT (Engel-I outcome in 64%; $Q = 8.55$, $p = .0035$). The rate of major complications was 3.8% for MRgLITT, 3.7% for RFA, 10.9% for ATL, and 7.4% for sAHE; the differences did not show statistical significance. Neuropsychological deficits occurred after all procedures, with left-sided surgeries having a higher rate of verbal memory impairment. Lateral functions such as naming or object recognition may be more preserved in MRgLITT. Thermal therapies are effective techniques but show a significantly lower rate of Engel-I outcome in comparison to ATL and sAHE. Between MRgLITT and RFA there were no significant differences in Engel-I outcome, whereby the success of treatment seems to depend on the approach used (e.g., occipital approach). MRgLITT shows a similar rate of complications compared to

RFA, whereas patients undergoing MRgLITT may experience fewer major complications compared to ATL or sAHE and might have a more beneficial neuropsychological outcome.

KEYWORDS

mesial temporal lobe epilepsy, minimally invasive therapy, thermal ablation

1 | INTRODUCTION

Epilepsy is a common disorder, with mean prevalence rates of .55 % in high income countries; thus, it can be considered one of the most common neurological diseases worldwide with major impact on patients and the health care system.[1,2] Among focal epilepsies, temporal lobe epilepsy is the most common cause of medically refractory epilepsy, related, in about 70% of cases, to mesial temporal lobe epilepsy (mTLE) with hippocampal sclerosis (HS).[3] In such cases, anterior temporal lobe resection (ATL) and selective amygdalohippocampectomy (sAHE) are the principal, evidence-based treatment options.[4] The success rate of these surgical approaches is significantly superior to drug therapy alone in refractory temporal lobe epilepsy, ranging from 34% to 74% depending upon the presence of extratemporal lesions, history of febrile seizures, and the presence of HS.[5]

Although surgical therapy is the favored therapeutic option for temporal lobe epilepsies refractory to medical therapy, treatment-related adverse effects such as cognitive dysfunction, visual field defects (VFDs), intracranial bleeding, and inadvertent neurological damage are possible.[6] As such, newer minimally invasive therapies such as magnetic resonance-guided laser interstitial thermal therapy (MRgLITT) or radiofrequency ablation (RFA) represent promising alternatives to conventional surgery.[7] Both MRgLITT and RFA are thermoablative procedures that facilitate the destruction of the epileptogenic zone due to local heat development induced by a probe or electrode inserted through a burr hole.[8] Whereas MRgLITT uses the radiation of a neodymium-doped yttrium aluminum garnet laser, which is transported via optical fibers and generates heat by the absorption of photons in the tissue, RFA establishes a current flow between two electrodes for heat induction.[9,10] Both methods have already been successfully used in the treatment of refractory mTLE, making them attractive alternatives for patients with contraindications or in those who refuse to undergo open surgical treatment, and both may better spare cognitive functions as compared with conventional open surgery.[11,12] Among existing thermal ablative techniques, MRgLITT offers the advantage of magnetic resonance imaging (MRI) thermometry, which enables the direct measurement of the temperature in the area of the probe and the surrounding tissue, resulting in nearly real-time monitoring and optimization of the ablation zone.[11] As a result, MRgLITT has recently garnered increasing attention for the treatment of drug-refractory mTLEs.

Key Points

- There was no significant difference in seizure outcome (Engel Class I) or complication rate between MRgLITT and RFA
- MRgLITT and RFA were both inferior relative to conventional surgical approaches (ATL and sAHE) in terms of seizure outcome (Engel Class I)
- The most frequent complications following MRgLITT and RFA were visual field deficits and cranial nerve palsies, with patients showing a high probability of recovering within months
- MRgLITT and RFA seem to be more favorable in terms of complications compared to ATL or sAHE
- The presence of mTLE + HS as shown by magnetic resonance imaging predicted an Engel Class I outcome
- Cognitive outcome might be more favorable after MRgLITT compared to ATL and sAHE

Because the available data on the safety and efficacy of MRgLITT and RFA have been derived to date from single-arm retrospective studies, a direct comparison between the two thermoablative procedures and with conventional surgery is limited. Therefore, we sought to summarize the results of MRgLITT (outcomes and complications) via a systematic review and then compare them with those of similar thermoablative procedures such as RFA and conventional "gold-standard" surgical approaches (ATL and sAHE) in a meta-analysis.

2 | MATERIALS AND METHODS

This systematic review was designed according to the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidelines and recommendations.[13] The PICO model (i.e., population, intervention, comparison, outcome) was adopted to determine the parameters of a search

The American Society for Stereotactic and Functional Neurosurgery Position Statement on Laser Interstitial Thermal Therapy for the Treatment of Drug-Resistant Epilepsy

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This position statement will be published as an article titled "ASSFN Position Statement on MR Laser Interstitial Thermal Therapy for the Treatment of Drug-Resistant Epilepsy" online at ASSFN.org.

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Received, September 20, 2021.
Accepted, September 29, 2021.
Published Online, December 16, 2021.

Magnetic resonance image–guided laser interstitial thermal therapy (MRgLITT) is a novel tool in the neurosurgical armamentarium for the management of drug-resistant epilepsy. Given the recent introduction of this technology, the American Society for Stereotactic and Functional Neurosurgery (ASSFN), which acts as the joint section representing the field of stereotactic and functional neurosurgery on behalf of the Congress of Neurological Surgeons and the American Association of Neurological Surgeons, provides here the expert consensus opinion on evidence-based best practices for the use and implementation of this treatment modality. Indications for treatment are outlined, consisting of failure to respond to, or intolerance of, at least 2 appropriately chosen medications at appropriate doses for disabling, localization-related epilepsy in the setting of well-defined epileptogenic foci, or critical pathways of seizure propagation accessible by MRgLITT. Applications of MRgLITT in mesial temporal lobe epilepsy and hypothalamic hamartoma, along with its contraindications in the treatment of epilepsy, are discussed based on current evidence. To put this position statement in perspective, we detail the evidence and authority on which this ASSFN position statement is based.

KEY WORDS: Laser interstitial thermal therapy, Epilepsy, Mesial temporal lobe epilepsy, Hypothalamic hamartomas

Neurosurgery 90:155–160, 2022 DOI:10.1227/NEU.0000000000001799 www.neurosurgery-online.com

EXECUTIVE SUMMARY

Purpose of the Statement

1. To provide an evidence-based, best practices summary to guide healthcare providers in the use of magnetic resonance–guided laser interstitial thermal therapy (MRgLITT) in the management of epilepsy
2. To report a consensus opinion of the American Society for Stereotactic and Functional Neurosurgery (ASSFN) regarding the use of MRgLITT for intractable epilepsy

ABBREVIATIONS: ASSFN, American Society for Stereotactic and Functional Neurosurgery; **ATL,** anterior temporal lobectomy; **DRE,** drug-resistant epilepsy; **EZ,** epileptogenic zone; **HH,** hypothalamic hamartomas; **MRgLITT,** magnetic resonance–guided laser interstitial thermal therapy; **MTLE,** mesial temporal lobe epilepsy; **SAH,** amygdalohippocampectomy.; **vEEG,** video electroencephalography.

Importance of the ASSFN Statement

1. Stereotactic and functional neurosurgeons are domain-specific experts in the specialty literature and the practical use of stereotactic and open procedures for the surgical management of drug-resistant epilepsy (DRE).
2. Stereotactic and functional neurosurgeons are domain-specific experts in the comparative assessment of benefits, risks, and alternatives of surgical procedures for the management of patients with DRE.

Indications for the Use of MRgLITT as a Treatment Option for Patients With DRE Include All of the Following Criteria

1. Failure to respond to, or intolerance of, at least 2 appropriately chosen medications at appropriate doses for disabling and localization-related epilepsy AND
2. Well-defined epileptogenic foci or critical pathways of seizure propagation accessible by MRgLITT.

Section 8.0

Previously Discussed Items

Plain Language Summary:

Coverage question:

1) In February 2023, there was a new guideline about this topic. How should the section that says a patient should quit smoking before surgery be changed?
2) Should the requirements be more clear about when OHP covers transplants of two organs at the same time?

How should OHP coverage change?

1) The transplant program ensures a patient quits smoking before surgery
2) If a patient qualifies for transplants of both organs individually, they can have both organs transplanted at the same time

Coverage Questions:

1) How should the smoking cessation portion of the new solid organ transplant guideline be clarified?
2) How should coverage of a second simultaneous organ transplant be clarified?

Question sources:

1) HSD, OHSU transplantation program
2) VBBS

Background: A new guideline for solid organ transplantation was implemented February 1, 2023. HSD staff have asked for clarification regarding the tobacco cessation portion. Currently, the guideline requires "No tobacco smoking for at least 6 months unless the transplant is done on an emergent basis (other than for corneal transplants)." However, there is no specification about when the 6 month timeframe starts (initial evaluation vs listed for an organ vs other time). The timing of surgery is also difficult to be determined as it frequently is based on organ availability.

HSD staff is also asking for calcification about whether there needs to be objective evidence such as urine cotinine testing. The other guidelines that require 6 months of non-smoking have specific testing requirements. GN 100, GN 112 and GN 159 all requiring negative cotinine levels at least 6 months apart. Up to now, HSD staff have been following Ancillary Guideline A4 SMOKING CESSATION AND ELECTIVE SURGERY which only requires one month of cessation and requires objective testing [note: this guideline will be deleted and replaced with a Statement of Intent with the 10/1/2023 Prioritized List].

The OHSU Liver Transplant Team is also requesting clarification. Currently, OHSU requires 4-weeks of consecutive negative objective testing prior to considering a patient for approval and for listing for an organ. Patients are then randomly tested thereafter and must remain negative to continue to be on the transplant list.

At the May VBBS meeting, members asked for additional wording to be included in the revised combined organ transplant section to include scenarios in which the second organ is necessary to improve the outcome of the first organ.

Current Prioritized List/Coverage status:

[Note: modifications approved in January 2023 are shown which will be effective 10/1/23]

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 at least one negative cotinine level~~s 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 at least one negative cotinine level~~s 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).

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 at least one negative cotinine level~~s at least 6 months apart, with the second test within 1 month of the surgery date~~

Expert policy recommendations

1) **UNOS 2021** multi-organ allocation policy
    a) Clarified that patients requiring multiple organs be given priority for organs from the same ponor, with the “second required organ” defined as a kidney or liver

HERC staff summary:

Clarification is needed regarding the tobacco section of the new solid organ transplant guideline. The timing of transplant can be difficult to determine and the transplant programs have monitoring strategies already in place. HERC staff recommend allowing the transplant programs to continue their current standard of practice, as this will improve equity among OHP and privately insured patients and will reduce administrative burden on OHP reviewers and the transplant programs.

Additionally, staff recommends a revised simultaneous organ transplant entry that is broader and based on previous OAR wording. Additionally, staff notes that there are specific criteria for pancreas transplants with other organs that needs to be called out.

HERC staff recommendation:

1) Modify the new solid organ transplant guideline as shown below

GUIDELINE NOTE 42 SOLID ORGAN TRANSPLANTS
Lines 83,99,162,239,240,241,263,264,307,310,563

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

1) The patient must have irreversible end-stage organ disease or failure and must have medical therapy optimized; AND
2) The patient is a suitable surgical candidate for transplant surgery, indicated by ALL of the following:
    a. No significant uncontrolled co-morbidities such as (not an all-inclusive list):
        i. End-stage cardiac, renal, hepatic or other organ dysfunction unrelated to the primary indication for transplant
        ii. Uncontrolled HIV infection
        iii. Multiple organ compromise secondary to infection, malignancy, or condition with no known cure
        iv. Ongoing or recurrent active infections that are not effectively treated
        v. Psychiatric instability severe enough to jeopardize adherence to medical regimen
        vi. Active alcohol or illicit drug dependency; AND
    b. No tobacco smoking ~~for at least 6 months~~ as determined by the transplant program unless the transplant is done on an emergent basis (other than for corneal transplants); AND
    c. Demonstrated compliance with medical treatments and ability to understand and comply with the post-transplant immunosuppressive regimen

It is the intent of the Commission that transplant should be covered if the specific ICD-10-CM code is not included on the same lines as the transplant procedure codes, if it is determined to be the medically appropriate treatment for that particular patient's clinical situation.

HEART TRANSPLANT

Adults must have New York Heart Association (NYHA) Class III or IV cardiac disease or malignant ventricular arrhythmias unresponsive to medical and/or surgical therapy. Children must have intractable heart failure or a congenital abnormality not amenable to surgical correction.

LUNG TRANSPLANT

Patients must have symptoms at rest directed related to chronic pulmonary disease and resultant severe functional limitations.

~~COMBINED HEART/LUNG TRANSPLANTATIONS~~

~~The patent must meet criteria for both heart and lung transplantation and neither a heart transplant or lung transplant alone would be expected to improve the individual's condition and chances of survival.~~

KIDNEY TRANSPLANT

The patient must have one of the following:

1) End-stage renal disease requiring hemodialysis or continuous ambulatory peritoneal dialysis; OR
2) End-stage renal disease, evidence by a creatinine clearance below 20 ml/min or development of symptoms of uremia; OR
3) Chronic renal failure with anticipated deterioration to end-stage renal disease requiring dialysis

~~HEART-KIDNEY TRANSPLANTS~~

~~Patients under consideration for heart/kidney transplant must qualify for each individual type of transplant with the exception of any exclusions due to heart and/or kidney disease.~~

LIVER TRANSPLANT

The patient must have irreversible, end stage, liver damage with no other available treatment options.

PANCREAS TRANSPLANTS

Pancreas transplant alone are not included on any transplant line. Simultaneous pancreas kidney transplant (SPT) is only included on this line for type I diabetes mellitus with end stage renal disease (E10.2). Pancreas after kidney transplant (PAK) is only included on this line for other type I diabetes mellitus with secondary diagnosis of Z94.0 (Kidney transplant status).

ISLET CELL AUTOTRANSPLANT

Islet cell autotransplant (TP IAT) is only included on line 250 when done with total pancreatectomy AND when the patient meets ALL of the following criteria:

A) Has acquired intractable chronic pancreatitis
B) Has intractable abdominal pain despite optimal medical therapy
C) Has not responded to more conservative surgery including endoscopic pancreatic decompression or in whom such surgery is not clinically indicated
D) Has not responded to nerve block procedures or in whom these interventions are not clinically indicated
E) Has been assessed by the multidisciplinary team and determined to have pain of an organic nature and are thought likely to achieve significant pain reduction from TP IAT
F) Is an appropriate candidate for major surgery
G) Is able to adhere to the complex medical management required following TP IAT
H) Does not have type 1 diabetes, known pancreatic cancer or any other condition that would prevent isolation of islet cells for autotransplant

I) Does not have a condition (e.g. portal vein thrombosis or significant parenchymal liver disease such as cirrhosis of the liver) which increases the risks associated with islet cell transplant
J) Does not have any other contraindications such as active alcohol abuse

INTESTINE TRANSPLANT

Intestine transplant is included on this line only for patients with failure of total parenteral nutrition (TPN) as indicated by one of the following, and no contraindications to transplant:

A) Impending or overt liver failure due to TPN, indicated by elevated serum bilirubin and/or liver enzymes, splenomegaly, thrombocytopenia, gastro-esophageal varices, coagulopathy, peristomal bleeding, or hepatic fibrosis/cirrhosis;
B) Thrombosis of ≥ 2 central veins, including jugular, subclavian, and femoral veins;
C) Two or more episodes of systemic sepsis due to line infection, per year, or one episode of septic shock, acute respiratory distress syndrome, and/or line related fungemia;
D) Frequent episodes of dehydration despite IV fluid supplementation;
E) Other complications leading to loss of vascular access

COMBINED ORGAN TRANSPLANTATIONS

The patent must meet criteria for both organs being considered for transplant and there is no reasonable alternative medical or surgical therapy. See criteria above when combined organ transplants include pancreas transplant.

Prostate Procedure Guideline Modifications

Plain Language Summary:

Coverage question: Should OHP remove the requirement to try medications before having a procedure that helps urine leave the body when the prostate is too large? Should any changes be made to the requirements for a procedure that lifts prostate tissue out of the way so it does not block urine leaving the body?

Should OHP cover this treatment? The guideline on prostate procedures should be changed to no longer require medications. This is done to agree with expert guidelines. The age range for the lift procedure should be lowered to 45 years old because it has been approved for younger patients.

Coverage Question: How should the guideline regarding prostatic lift procedures be updated to reflect new FDA approval criteria for the devices?

Question source: Max Kaiser, CCO medical director

Background: Coverage for prostatic urethral lift procedures was added with a 2016 coverage guidance. This coverage guidance included the then-current FDA approval criteria for Urolift. The FDA has modified the criteria to lower the age of eligibility to 45 (from 50) and for a slightly more liberal prostatic volume (≤100 cc vs the prior ≤80 cc). The FDA has also removed the restriction that this procedure should not be done with median lobe hyperplasia.

Dr. Kaiser is requesting that guideline note 145 be updated to reflect the current FDA approval criteria. He is also requesting that the guideline be clarified to include that medication failure is required for urethral lift procedures.

From Dr. Kaiser:

> When reviewing an appeal I noticed there was a FDA Section 510(k) pre market approval for an updated version of the UroLift that lowers the approved age to 45 (the original product was 50 per the GN) and increases the prostate volume to <100 cc (the original product was <80 cc per the GN) - https://www.accessdata.fda.gov/cdrh_docs/pdf20/K201837.pdf. I don't know if in practice this replaced the old product. If it has it would be appropriate to update the GN.
>
> I would also request to update the GN to clarify medication failure is required for urethral lift procedures by re-stating the requirements per part D). Medication failure was part of the original guidance approved in 2018. As written, it's confusing if medication failure is required, as per part D), as part D) also requires a higher IPSS than is required in the urethral lift section.

Prostate Procedure Guideline Modifications

This topic was discussed at the March 2023 VBBS and HERC meetings. VBBS approved the staff recommended changes; however, HERC members were concerned that the suggested changes did not align with the current American Urology Association (AUA) guideline on management of BPH. Specifically, there were concerns that the AUA guideline still required a trial and failure of two medications together prior to proceeding to an invasive treatment. HERC staff were directed to review the current AUA guideline and seek expert input and opinion.

The 2021 AUA guideline recommends prostatic urethral lift only for men with prostates less than or equal to 80 ccs and only without median lobe hypertrophy based on lack of high quality studies of the procedure in men with larger prostates or with median lobe hypertrophy.

The 2021 AUA guidelines do not recommend trial and failure of two medications prior to invasive treatment. The AUA guideline only recommends medication as an option.

This topic was again discussed at the May 2023 VBBS meeting. The prostatic lift procedure guideline changes were considered appropriate. Discussion centered around proposed changes to the medication section of the guideline. VBBS members requested that the term "refractory to" medications be defined. Specifically, what length of time should be required for a trial of medications? In the 2021 AUA guidelines, alpha blockers and phosphodiesterase inhibitors are generally given a 4 week trial while 5-alpha reductase inhibitors require at least a 6 month trial.

After the VBBS meeting, Max Kaiser, a CCO medical director and HERC member, expressed concern to staff regarding the proposed wording change to allow medications to be not tried at patient discretion.

From Dr. Kaiser:

> Most specifically as paying for a procedure without medication failure is not the least costly option, and is for convenience, which are not covered per OAR.
>
> Skipping conservative care prior to invasive procedures is both not in line with our other guidelines e.g. hysterectomy, it's not in our member's best interest from a risk/benefit perspective as this is still an invasive procedure though admittedly the procedure and medications have favorable side effect rates and profiles, from the payor guidelines I reviewed it's not standard of practice, guidelines other than the AUA require meds first - the CMS guidelines in the packet and the NICE guidelines for BPH (https://www.nice.org.uk/guidance/cg97/chapter/Recommendations), and I'm not even sure it's standard practice as I haven't seen a request without med failure (admittedly I see a biased sample) – the guideline itself notes most patients choose medical therapy.
>
> The guideline notes surgery for those unwilling to use other therapies is a clinical principle and provides no evidence for this recommendation. I would thus consider it 'expert opinion' at best from a source with an interest in increasing surgical procedures. The medication recommendations on the other hand have A and B evidence levels. The statement is useful when considering exceptions, but is not appropriate to guide our overall treatment recommendations.

Prostate Procedure Guideline Modifications

The way our guideline is written captures the appropriate exceptions to medication per the AUA, and our exception process is appropriate for those edge cases where there are truly difficulties or reasons why medications can't or don't want to be used.

The medications are inexpensive with low side effect profiles – most of the side effects they discuss in the guideline are questionable with studies showing and not showing association. ED seems the most supported, though that may only earlier in treatment. SI is mentioned as having been studied in association with 5-ARIs with no comment on any outcomes in the AUA guideline. Per UpToDate this was from a global database report for adverse events which showed an association for younger patients and those treated for Alopecia, not those that are older or were treated for BPH.

The expert also mentioned concerns for Post-Finasteride Syndrome (PFS) and permanent sexual dysfunction. The guideline goes in depth about this syndrome noting it's controversial, poorly defined, and that "Overall, the existence of persistent sexual dysfunction following cessation of 5-ARI is currently not demonstrated by reliable scientific research."

Thus there is not adequate evidence to support removal of the medication requirement nor would it be in line with our own guidelines, rules, other payors, or other reputable guidelines.

Current Prioritized List/Coverage status:

GUIDELINE NOTE 145, TREATMENTS FOR BENIGN PROSTATE ENLARGEMENT WITH LOWER URINARY TRACT SYMPTOMS

Line 327

For men with lower urinary tract symptoms (LUTS) due to benign prostate hyperplasia (BPH), surgical procedures are included on this line for patients with one of the following:

A) Refractory urinary retention; OR
B) Recurrent urinary tract infections due to BPH; OR
C) Recurrent bladder stones or gross hematuria due to BPH; OR
D) Severe symptoms (International Prostate Symptom Score (IPSS) of 20-35) in patients who are not candidates for drug treatment due to intolerable side effects or have failed combination therapy with an alpha-blocker and 5-alpha reductase inhibitor for at least 3 months.

Prostatic urethral lift procedures (CPT 52441, 52442, HCPCS C9739, C9740) are included on Line 327 when the following criteria are met:

- Age 50 or older
- Estimated prostate volume < 80 cc
- IPSS ≥ 13
- No obstructive median lobe of the prostate identified on cystoscopy at the time of the procedure

The following interventions for benign prostate enlargement are not included on Line 327 due to lack of evidence of effectiveness:

Prostate Procedure Guideline Modifications

- Botulinum toxin
- HIFU (High Intensity Focused Ultrasound)
- TEAP (Transurethral Ethanol Ablation of the Prostate)
- Laser coagulation (for example, VLAP/ILC)
- Prostatic artery embolization

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

Expert guidelines:

1) **AUA 2021**, management of lower urinary tract symptoms attributed to benign prostatic hyperplasia: AUA guideline
    a. An initial trial of medical management over 4 weeks with an alpha blocker or PDE5, and over 6-12 months with a 5-ARI is reasonable in men with bothersome LUTS.
    b. Medications
        i. Clinicians should offer one of the following alpha blockers as a treatment option for patients with bothersome, moderate to severe LUTS/BPH: alfuzosin, doxazosin, silodosin, tamsulosin, or terazosin. (Moderate Recommendation; Evidence Level: Grade A)
        ii. For the purpose of symptom improvement, 5-ARI monotherapy should be used as a treatment option in patients with LUTS/BPH with prostatic enlargement as judged by a prostate volume of > 30cc on imaging, a prostate specific antigen (PSA) > 1.5ng/dL, or palpable prostate enlargement on digital rectal exam (DRE). (Moderate Recommendation; Evidence Level: Grade B)
        iii. 5-ARIs alone or in combination with alpha blockers are recommended as a treatment option to prevent progression of LUTS/BPH and/or reduce the risks of urinary retention and need for future prostate-related surgery. (Strong Recommendation; Evidence Level: Grade A)
        iv. For patients with LUTS/BPH irrespective of comorbid erectile dysfunction (ED), 5mg daily tadalafil should be discussed as a treatment option. (Moderate Recommendation; Evidence Level: Grade B)
        v. 5-ARI in combination with an alpha blocker should be offered as a treatment option only to patients with LUTS associated with demonstrable prostatic enlargement as judged by a prostate volume of > 30cc on imaging, a PSA >1.5ng/dL, or palpable prostate enlargement on DRE. (Strong Recommendation; Evidence Level: Grade A)
        vi. Anticholinergic agents, alone or in combination with an alpha blocker, may be offered as a treatment option to patients with moderate to severe predominant storage LUTS. (Conditional Recommendation; Evidence Level: Grade C)
        vii. Beta-3-agonists in combination with an alpha blocker may be offered as a treatment option to patients with moderate to severe predominate storage LUTS. (Conditional Recommendation; Evidence Level: Grade C)
        viii. Clinicians should not offer the combination of low-dose daily 5mg tadalafil with alpha blockers for the treatment of LUTS/BPH as it offers no advantages in

symptom improvement over either agent alone. (Moderate Recommendation; Evidence Level: Grade C)

c. Surgery is recommended for patients who have renal insufficiency secondary to BPH, refractory urinary retention secondary to BPH, recurrent urinary tract infections (UTIs), recurrent bladder stones or gross hematuria due to BPH, and/or with LUTS/BPH refractory to or unwilling to use other therapies. (Clinical Principle)

d. Prostatic Urethral Lift (PUL)

   i. PUL should be considered as a treatment option for patients with LUTS/BPH provided prostate volume 30-80cc and verified absence of an obstructive middle lobe. (Moderate Recommendation; Evidence Level: Grade C)

      1. The L.I.F.T study compared PUL to SHAM55 in 206 patients. It excluded patients with a prostate 80g or an obstructive middle lobe. The primary outcome was urinary symptom score. The mean change from baseline IPSS (MD: -5.2; 95%CI: -7.45, -2.95) and improvement in IPSS-QoL (MD: 1.2; 95%CI: 1.7, - 0.7) favored PUL.
      2. Since the last amendment, there have been retrospective chart reviews evaluating a small number of patients with prostate sizes between 81-100mL. The Panel recognizes that many devices do not necessarily lack efficacy in prostates below or above the size ranges stipulated in the Statements, but there is insufficient evidence to make formal recommendations beyond those sizes identified.
      3. The Panel limited this guideline statement to include patients with a prostate lacking an obstructive middle lobe, consistent with the L.I.F.T. study criteria. The Panel identified an observational cohort study (n=45 patients) observing improvements in urinary and sexual health outcomes from baseline in patients with an obstructive middle lobe following PUL. This study was excluded from formal efficacy analysis because it was a nonrandomized cohort study utilizing historic controls rather than an RCT.

   ii. PUL may be offered as a treatment option to eligible patients who desire preservation of erectile and ejaculatory function. (Conditional Recommendation; Evidence Level: Grade C)

e. Studies of comparative efficacy of behavioral and lifestyle intervention versus medical treatment; medical therapies versus MISTs; and surgical treatments compared to each other are lacking

Other payer policies:

1) Medicare LCD for the prostatic urethral lift requires that "The beneficiary has had an adequate trial of, but is refractory to or intolerant of, usual BPH medication" prior to coverage of prostatic urethral lifts and other urological procedures. Other Medicare LCDs for other minimally invasive prostate procedures (for example water vapor thermal therapy) state treatments are more specific: "Failure, contraindication or intolerance to at least 3 months of conventional medical therapy for LUTS/BPH (e.g., alpha blocker, PDE5 Inhibitor, finasteride/dutasteride)"
2) Aetna 2023
   a. Medications are covered as treatment for BHP resulting in LUTS, but no medication trial requirement is listed prior to covered surgical procedures for this condition

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3) Anthem BCBS 2023
    a. No medication requirement prior to covered surgical procedures for BPH
4) United Healthcare 2023
    a. No medication requirement prior to covered surgical procedures for BPH
5) Providence Medical Policy 2023
    a. Documented failure, contradiction, intolerance, or individual non-acceptance of pharmacological management
6) Wellmark BCBS 2023
    a. The individual has had an adequate trial of the usual prescribed BPH medications (alpha blockers, beta-3 agonists, PDE5s, anticholinergics, 5-ARIs) and is refractory or intolerant

Expert input:

Dr. Kamran Sajadi, OHSU urology:

1. The document is frankly incorrect in stating the AUA guidelines call for medical management before surgical therapy. From the AUA guidelines directly: "There also exist clinical scenarios in which conservative management—including lifestyle changes (e.g., fluid restriction, avoidance of substances with diuretic properties)—or pharmacological management are either inadequate or inappropriate. More recently, long-term use of medications for LUTS/BPH have been implicated in cognitive issues and depression. These situations merit consideration of one of the many invasive procedures available for the treatment of LUTS/BPH. Indications for these procedures include a desire by the patient to avoid taking a daily medication, failure of medical therapy to sufficiently ameliorate bothersome LUTS, intolerable pharmaceutical side effects, and/or the following conditions resulting from BPH and for which medical therapy is insufficient: acute and/or chronic renal insufficiency, refractory urinary retention, recurrent UTIs, recurrent bladder stones, and recalcitrant gross hematuria. Acute and chronic adverse events are associated with each class of medical therapy and can include cardiovascular and sexual effects."
2. The AUA Guidelines also state "Before starting a 5-ARI [e.g., finasteride], clinicians should inform patients of the risks of sexual side effects, certain uncommon physical side effects, and the low risks of prostate cancer." In addition, it should only be offered to those with objectively demonstrated prostatic enlargement >30cc (and other studies have shown >40cc) – statement 18.
3. My recommendation would be that patients should be OFFERED medical therapy but may decline.

Prostate Procedure Guideline Modifications

HERC staff summary:

The FDA approval criteria has changed for prostatic urethral lift (age 45, prostate volume <100 cc, approved for median lobe hypertrophy). However, the American Urology Association (AUA) continues to recommend use only in men with prostate volume between 30 and 80 cc, and without median lobe hypertrophy. The AUA states that use of prostatic urethral lifts in prostates larger than 80 cc or in median lobe hypertrophy is not supported by high quality studies. A recent NICE technology review came to the same conclusions that evidence is poor for larger prostate volumes and that other procedures are more efficacious for treatment in the setting of median lobe hypertrophy. Minor modifications should be made to the prostatic lift coverage criteria (reducing the age to 45) in the guideline regarding treatment for benign prostate enlargement. Additionally, renal insufficiency due to BHP should be added as a general indication for surgical options.

Expert input heard at the March 2023 meeting recommended removing the requirement for two medications to be tried and failed prior to invasive interventions. HERC staff have reviewed the 2021 AUA guideline, and there is no recommendation for a requirement to try and fail two medications prior to a prostate procedure. The AUA recommendations for combination therapy are "should be offered" or "may be offered" recommendations. Tadalafil "should not [be offered]" in combination with other medications. The AUA recommends surgery for patients "with LUTS/BPH refractory to or unwilling to use other therapies." Medicare requires a 3 month trial of medications prior to procedures. Most private payer policies surveyed either have no medication requirement, or required only "Documented failure, contradiction, intolerance, or individual non-acceptance of pharmacological management." Wellmark BCBS requires "an adequate trial" of medications. There is member concern regarding no longer requiring medication trials, as well as a need to define what is considered an adequate medication trial.

HERC staff recommendation:

1) Modify GN145 as shown below
    a. Discuss whether "individual non-acceptance" should be included in the medication trial section, which agrees with the AUA guideline but significantly changes the intent of this section
2) For the prostatic urethral lift, lower the age limit, but do not increase the prostate volume limit or remove the contraindication of an obstructing medial lobe, as the AUA guideline does not recommend these changes.

GUIDELINE NOTE 145, TREATMENTS FOR BENIGN PROSTATE ENLARGEMENT WITH LOWER URINARY TRACT SYMPTOMS

Line 327

For men with lower urinary tract symptoms (LUTS) due to benign prostate hyperplasia (BPH), surgical procedures are included on this line for patients with one of the following:

A) Renal insufficiency secondary to BPH; OR
B) Refractory urinary retention; OR
B) Recurrent urinary tract infections due to BPH; OR
C) Recurrent bladder stones or gross hematuria due to BPH; OR
D) Severe symptoms (International Prostate Symptom Score (IPSS) of 20-35) in patients with documented failure of, contraindication to, intolerance to **or individual non-acceptance of** at least 3 months of conventional pharmacologic management (for example, alpha blocker,

Prostate Procedure Guideline Modifications

phosphodiesterase Inhibitor, 5 alpha reductase inhibitor) ~~who are not candidates for drug treatment due to intolerable side effects or have failed combination therapy with an alpha-blocker and 5-alpha reductase inhibitor for at least 3 months~~.

Prostatic urethral lift procedures (CPT 52441, 52442, HCPCS C9739, C9740) are included on Line 327 (including for patients who do not meet the above criteria) when the following criteria are met:

- Age 45 ~~50~~ or older
- Estimated prostate volume ~~<~~ ≤ 80 cc
- IPSS ≥ 13
- No obstructive median lobe of the prostate identified on cystoscopy at the time of the procedure

The following interventions for benign prostate enlargement are not included on Line 327 due to lack of evidence of effectiveness:

- Botulinum toxin
- HIFU (High Intensity Focused Ultrasound)
- TEAP (Transurethral Ethanol Ablation of the Prostate)
- Laser coagulation (for example, VLAP/ILC)
- Prostatic artery embolization

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

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? Staff recommends the Commission consider several options including no coverage or coverage in specific situations.

Coverage Question: Should limited 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.

Previous HSC/HERC reviews:

Breast reduction for macromastia was reviewed in 2017. At that time, a 2014 CADTH report was reviewed, as well as a 2012 systematic review. Several cohort studies were also included in the review. The review concluded "There is a general lack of good quality studies on the effectiveness of breast reduction on treatment of neck and/or back pain related to macromastia. No RCTs were identified; only one study appeared to have a comparison group of any kind. Most studies are cohort studies or case series. The existing literature in this area does appear to indicate that patients have significant pain relief following surgery; however, the poor quality of the literature makes it difficult to make a definitive conclusion."

Breast Reduction for Macromastia

Based on the above review, GN166 was added to the Prioritized List specifying that breast reduction surgery for macromastia was not covered for neck or back pain due to lack of high quality evidence.

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

Evidence: [updated review since 2017]—

1) **Hansson 2021,** health technology assessment of breast reduction
    a. Swedish HTA comparing breast reduction to non-surgical treatment
        i. Non-surgical treatment included PT, weight loss and supportive bras
        ii. Indications for breast reduction in Sweden
            1. Breast volume > 800 ml per breast (Abdiu et al., 2008), as measured with breast cups (Hansson et al., 2014).
                a. twice the mean volume of an average breast
            2. Physical and psychosocial symptoms of breast hypertrophy.
            3. BMI ≤ 35
            4. Smoking cessation at least 4 weeks pre- and post-operatively
    b. N=15 articles
        i. 4 RCTs, reported in 8 articles
        ii. 3 cohort studies with a control group
        iii. 3 case series
        iv. 1 qualitative study
    c. Outcomes
        i. Mortality
            1. Three case series reported mortality. All three series are based on the National Surgery Quality Improvement Program (NSQIP) registry and therefore the cases are somewhat overlapping. No cases of 30-day mortality were reported by Fairchild et al. (2020) (0/283), Nelson et al. (2014) (0/2074), or by Simpson et al. (2019) (0/8108).
        ii. Complications
            1. For patients undergoing breast reduction the reported frequency of major complications varied from 2.4% to 14%, and frequency of minor complications from 2.4% to 69%
                a. Venous thromboembolism (0.2%, Nelson et al., 2014), pulmonary embolism (3.4%, Saarinemi et al., 2008; 0.2%, Nelson et al., 2014), surgical site infections, delayed wound healing
        iii. Health related quality of life
            1. Reported in 3 RCTs and 2 cohort studies
            2. Meta-analyses were performed for the studies using SF-6D and SF-36 (both physical and mental summary scores), including 142 and 155 patients, respectively
            3. The weighted mean difference (WMD) for SF-6D (score range 0.29–1.0) was 0.14 (95% CI 0.10–0.17) six months after surgery. Minimal important difference (MID) for SF-6D has been suggested to be in the range of 0.01 to 0.10 (Walters and Brazier, 2005), implying that 0.14 is a clinically relevant difference in HRQoL. The WMD for the physical summary score of SF-36 was 7.0 (95% CI 4.4–9.5) and 9.8 (95% CI 6.2–13) for the mental summary score (both scores ranging 0–100), 4-6 months after surgery.
            4. Conclusion: Breast reduction surgery compared with no surgery may result in a clinically relevant improvement in health-related quality of life in women with breast hypertrophy. Low certainty of evidence GRADE ⨁⨁◻◻)

iv. Depression symptoms
    1. Reported in 3 RCTs (N=215)
    2. Postoperative (4-6 months) depressive symptom rates were consistently lower in women undergoing breast reduction compared with no treatment or physiotherapy.
    3. Conclusion: Breast reduction surgery compared with no surgery may result in a clinically relevant reduction in depressive symptoms in women with breast hypertrophy. Low certainty of evidence (GRADE ⊕⊕)
v. Anxiety symptoms
    1. Reported in 2 RCTs (155 patients)
    2. Postoperative anxiety symptom rates after four and six months were significantly lower in both studies (Iwuagwu et al., 2006b; Saarinemi et al., 2009) in women who had undergone breast reduction surgery.
    3. Conclusion: Breast reduction surgery compared with no surgery may result in a clinically relevant reduction in anxiety symptoms in women with breast hypertrophy. Low certainty of evidence (GRADE ⊕⊕□ □)
vi. Sexuality related outcomes
    1. Reported in 1 RCT and 2 cohort studies (N=262)
    2. Sexual function was significantly improved by breast reduction surgery compared with no surgical intervention in the RCT, as were sexual function, sexual well-being, and sexual quality of life in the cohort studies.
    3. Conclusion: Breast reduction surgery compared with no surgery may result in a clinically relevant improvement in sexuality-related outcomes in women with breast hypertrophy. Low certainty of evidence (GRADE ⊕⊕)
vii. Work ability and sick leave was not reported in any of the included studies.
viii. Physical function
    1. Reported in 2 RCTs and 2 cohort studies (N=447)
    2. Both RCTs had a follow-up of six months and both reported a (statistically) significant improvement in physical function after surgery compared with controls.
    3. Conclusion: It is uncertain whether breast reduction surgery compared with no surgery affects physical function in women with breast hypertrophy. Very low certainty of evidence (GRADE ⊕)
ix. Pain
    1. Reported in 3 RCTS and 1 cohort study (N=420)
    2. The RCTs all reported significantly reduced pain after breast reduction surgery compared with no surgery and the cohort study reported a significant decrease in pain-related outcomes after breast reduction surgery compared with no surgery
    3. Conclusion: Breast reduction surgery compared with no surgery may result in a clinically relevant reduction of pain in women with breast hypertrophy. Low certainty of evidence (GRADE ⊕⊕)

d. Conclusions
    i. The results showed that complications are frequent after breast reduction surgery, and that the risk for complications increases with a BMI>30. Regarding

effects, breast reduction surgery may improve HRQoL and may reduce depressive symptoms, anxiety symptoms, and pain, compared with no surgery. It is uncertain whether breast reduction surgery improves physical function

ii. Several methodological limitations were identified in all included studies. Main issues included a lack of, or inconsistent, definition of breast hypertrophy and patients that are biased towards wanting a breast reduction, as well as short follow-up, lack of blinding, control groups being patients on a waiting list for a breast reduction, and that inter-group results sometimes were not reported

2) **Crittenden 2020**, prospective cohort study of quality of life after breast reduction surgery
   a. N=209 women in the mammaplasty group, 124 in the waiting list group, also included a normative population comparison
      i. Australia
      ii. No BMI limits, all patients had D cup or higher breast size
      iii. QOL measured using the SF-36
   b. Following surgery, participants on average spent less money on medications and treatments (AU$26.41 before surgery vs AU$5.73 after surgery per month, p<0.001) and took fewer days off work (4.5 days prior to surgery vs 0.1 days after surgery in the previous 6-month period, p=0.009) when compared with before surgery.
   c. Surgical group
      i. Mean SF-36 PCS and MCS scores significantly improved following surgery, increasing by 10.2 (95% CI; 8.2 to 12.1) and 9.2 (95% CI; 6.9 to 11.6) points, respectively (p<0.001). The mean change in SF-36 PCS and MCS scores was in excess of the developer-recommended 3-point minimal important difference (MID) threshold. SF-36 scores were stable at 6 and 12 months post-surgery
   d. Waitlist group
      i. No significant differences were observed when comparing spending on medications and number of days off work between baseline and 12 months following enrolment, with both remaining significantly higher than postoperative surgical participants (p<0.001). At 12 months post-baseline, SF-36 scores showed no significant improvement and remained significantly lower than population norms
      ii. Mean SF-36 PCS and MCS summary scores for women in the breast hypertrophy control group were significantly lower than those who underwent breast reduction surgery, with a mean difference of 10.6 (95% CI; 8.3 to 12.8) and 11.1 points (95%CI; 8.2 to 13.9), respectively (p<0.001)
   e. Conclusion Breast reduction significantly improved quality of life in women with breast hypertrophy. This increase was most pronounced within 3 months of surgery and sustained at 12-month follow-up

Submitted articles

1) **Wampler 2021**, cohort study of breast reduction outcomes
   a. Cohort study, N=238 patients
      i. comparison group: Mundy 2017 (1208 women with and without breast cancer)
   b. Mean preoperative BREAST-Q scores were below normative values (p < 0.001), and mean postoperative scores were above normative values (p < 0.001 for Satisfaction with

Breasts, Psychosocial Well-being, and Sexual Well-being; and p = 0.05 for Physical Well-being).

c. This study has shown that reduction mammaplasty profoundly improves patients' satisfaction with breast appearance, psychosocial well-being, sexual well-being, and physical well-being, to levels that approach or exceed established normative levels

2) **Torresetti 2022**, systematic review of the effects of breast reduction on lung function
   a. N=15 studies (382 patients)
   b. According to most included studies, reduction mammaplasty produces a change of objective respiratory parameters, such as spirometric tests or arterial blood gas (ABG) measurements; nevertheless, the clinical and functional relevance of the observed changes is debatable
3) **Cabral 2018**, cohort study on the effect of reduction mammoplasty
   a. N=107 patients
   b. There was a significant improvement in the scores of the scales: Psychosocial well-being, Sexual well-being, Physical wellbeing, and Satisfaction with the breasts compared to the preoperative assessment (p\0.0001).
   c. Conclusion Reduction mammaplasty improved the quality of life and provided high levels of patient satisfaction with outcomes 1 and 6 months postoperatively.
4) **Elfanagely 2021**, matched cohort study on breast reduction on health related quality of life
   a. N=100 patients (78 mammoplasty, 22 control)
      i. All 100 had a consult regarding breast reduction, patients retrospectively identified as having had or not had surgery
      ii. The most common reason for not undergoing surgery included insurance denial (55 percent), pending surgery until after weight loss (23 percent), and personal reasons (14 percent)
      iii. Quality of life significantly improved in each domain for those in the operative group ($p < 0.05$). Those who did not undergo breast reduction surgery realized no improvement in quality of life and had a downward trend in quality of life across two of the four domains
   b. Conclusions: Breast reduction surgery offers a significant improvement in quality of life for macromastia.
5) **Krucoff 2019**, cohort study on outcomes of breast reduction
   a. N=37 patients
   b. Overall, participants demonstrated high satisfaction and well-being. Mean Q-Scores for Satisfaction with Breasts and Sexual Well-being were significantly higher than normative values ($p = 0.0012$ and $p < 0.0001$, respectively), and were as follows: Satisfaction with Breasts, 66.6 ± 16.5 (normative, 57 ± 16); Psychosocial Well-being, 75.9 ± 21.3 (normative, 68 ± 1 9); Sexual Well-being, 72 ± 18.2 (normative, 55 ± 19); and Physical Well-being, 81.1 ± 13.6 (normative, 76 ± 11).
   c. Conclusions: Young reduction mammaplasty patients experience excellent breast-related quality of life decades after surgery. Compared with normative values, young reduction mammaplasty patients reported higher satisfaction with breasts and sexual well-being
6) **Waltho 2019**, Systematic review of the reported outcomes in breast reduction mammaplasty studies
   a. Excluded as no clinical outcomes reported (review of types of reported outcomes only)

7) **Manahan 2015**, Cohort study of breast reduction outcomes
    a. N=2152 breast surgeries on 1148 patients
    b. Excluded as reports of complications only

Expert guidelines:

1) **Perdikis 2022**, American Society of Plastic Surgeons Evidence-Based Clinical Practice Guideline Revision: Reduction Mammaplasty
    a. The work group recommends that postmenarche female patients presenting with breast hypertrophy should be offered reduction mammaplasty surgery as first-line therapy over non-operative therapy based solely on the presence of multiple symptoms rather than resection weight
    b. The work group recommends that clinicians counsel postmenarche patients with symptomatic breast hypertrophy considering reduction mammaplasty that they may have a higher risk of complications if they are older than 50 years, have a body mass index greater than 35 kg/m2, or require chronic corticosteroid use

Other payer policies:

Private payers

1) Premara BCBS 2022
    a. Reduction mammaplasty may be considered medically necessary for the treatment of macromastia when ALL of the following criteria are met:
        i. There are well-documented symptoms of physical functional impairment for at least 6-months duration (eg, shoulder, neck or back pain, or recurrent intertrigo [irritating moist rash] in the mammary folds) AND
        ii. The physical functional impairment has not resolved with appropriate conservative therapy (eg, weight loss, appropriate support bra, exercise/physical therapy, heat/cold treatment, appropriate non-steroidal anti-inflammatory drugs/muscle relaxants) AND
        iii. The amount of breast tissue to be removed meets the minimum weight
    b. Reduction mammaplasty is considered not medically necessary in the absence of a confirmed physical functional impairment or when the grams of breast tissue removed does not meet the sliding scale minimum amount.

2) Anthem BCBS 2022
    a. Reduction mammaplasty is considered **medically necessary** when either of the following criteria (I or II) are met:
        i. Individuals meeting BOTH of the following criteria (A and B):
            1. Presence of one or more of the following:
                a. A cervical or thoracic pain syndrome (upper back and shoulder pain), in which interference with daily activities or work has been documented. The pain is clearly related to the excess weight of the breast tissue and there has been at least 3 months of adequate conservative treatment with one or more of the following: special support garments (for example, special

support bras, bras with wide straps), NSAIDs, physical therapy, or similar modalities; **or**

b. Submammary intertrigo that is refractory to conventional medications and measures used to treat intertrigo, or shoulder grooving with ulceration unresponsive to conventional therapy; **or**

c. Thoracic outlet syndrome (to include ulnar paresthesias from breast size) that has not responded to at least 3 months of adequate conservative treatment.

and

2. The preoperative evaluation by the surgeon concludes that an appropriate amount of breast tissue, from at least one breast, will be removed, based upon body surface area or total mass to be removed and that there is a reasonable prognosis of symptomatic relief. The request for surgery must include: the individual's height and weight; the size and shape of the breast(s) causing symptoms; the anticipated amount of breast tissue to be removed. Pictures may be requested to document medical necessity.
3. **Note:** Medical records from the primary care physician and other providers (for example, physiatrist, orthopedic surgeon, etc.) who have diagnosed or treated the symptoms prompting this request may also be required.
4. The appropriate amounts (in grams) of breast tissue must be anticipated for removal from at least one breast, which is based on the individual's total body surface area (BSA) in meters squared.

or

b. Individuals, regardless of BSA, who are anticipated to have at least 1 kg. of breast tissue removed from each breast and who meet the following criteria:
    i. Presence of one or more of the following :
        1. A cervical or thoracic pain syndrome (upper back and shoulder pain), in which interference with daily activities or work has been documented. The pain is clearly related to the excess weight of the breast tissue and there has been at least 3 months of adequate conservative treatment with one or more of the following: special support garments (for example, special support bras, bras with wide straps), NSAIDs, physical therapy, or similar modalities; **or**
        2. Submammary intertrigo that is refractory to conventional medications and measures used to treat intertrigo, or shoulder grooving with ulceration unresponsive to conventional therapy; **or**
        3. Thoracic outlet syndrome (to include ulnar paresthesias from breast size) that has not responded to at least 3 months of adequate conservative treatment.

c. **Not Medically Necessary:**
    i. Breast reduction surgery is considered **not medically necessary** when the criteria above are not met including for breast cancer risk reduction.
    ii. The use of liposuction to perform breast reduction is considered **not medically necessary.**

iii. Breast reduction surgery is considered **cosmetic and not medically necessary** for the following conditions: poor posture, breast asymmetry, pendulousness, problems with clothes fitting properly and nipple-areola distortion.

3) Aetna 2023

a. Aetna considers breast reduction surgery medically necessary for non-cosmetic indications for women aged 18 or older or for whom growth is complete (i.e., breast size stable over one year) when *any* of the following criteria (A, B, or C) is met:

i. Macromastia: *all* of the following criteria must be met:

1. Member has persistent symptoms in at least two of the anatomical body areas below, directly attributed to macromastia and affecting daily activities for at least 1 year:
    a. Headaches;
    b. Pain in neck;
    c. Pain in shoulders;
    d. Pain in upper back;
    e. Painful kyphosis documented by X-rays;
    f. Pain/discomfort/ulceration from bra straps cutting into shoulders;
    g. Skin breakdown (severe soft tissue infection, tissue necrosis, ulceration hemorrhage) from overlying breast tissue;
    h. Upper extremity paresthesia *and*
2. *All* of the following criteria are met:
    a. Member has severe breast hypertrophy, documented by high-quality color frontal-view and side-view photographs; *and*
    b. There is a reasonable likelihood that the member's symptoms are primarily due to macromastia; *and*
    c. Reduction mammoplasty (also spelled as 'mammaplasty') is likely to result in improvement of the chronic pain; *and*
    d. Pain symptoms persist as documented by the physician despite at least a 3-month trial of therapeutic measures such as:
        i. Analgesic/non-steroidal anti-inflammatory drugs (NSAIDs) interventions and/or muscle relaxants
        ii. Dermatologic therapy of ulcers, necrosis and refractory infection
        iii. Physical therapy/exercises/posturing maneuvers
        iv. Supportive devices (e.g., proper bra support, wide bra straps)
        v. Chiropractic care or osteopathic manipulative treatment
        vi. Medically supervised weight loss program
        vii. Orthopedic or spine surgeon evaluation of spinal pain; *and*
    e. Women 50 years of age or older are required to have a mammogram that was negative for cancer performed within the two years prior to the date of the planned reduction mammoplasty; *and*

f. The surgeon estimates that at least the following amounts (in grams) of breast tissue, not fatty tissue, will be removed from each breast, based on the member's body surface area (BSA) calculated using the Mosteller formula

Note: Breast reduction surgery will be considered medically necessary for women meeting the symptomatic criteria specified above, regardless of BSA, with more than 1 kg of breast tissue to be removed per breast.

4) Cigna 2022

a. Breast reduction is considered medically necessary for the treatment of macromastia (i.e., large breasts) in women at least 18 years of age, or with completed breast growth, when ALL the following criteria are met:
   i. macromastia is causing at least ONE of the following conditions/symptoms that has been unresponsive to medical management:
      1. shoulder, upper back/ neck pain, and/or ulnar nerve palsy for which no other etiology has been found on appropriate evaluation
      2. intertrigo, dermatitis, eczema, or hidradenitis at the inframammary fold
   ii. preoperative photographs confirm the presence of:
      1. significant breast hypertrophy
      2. shoulder grooving from bra straps and/or intertrigo (if stated to be present)
   iii. average grams of tissue to be removed per breast are above the 22nd percentile on the Schnur Sliding Scale (see Appendix A) based on the individual's body surface area (BSA) or regardless of BSA, more than 1 kg of breast tissue will be removed per breast

Breast reduction for either of the following indications is considered cosmetic in nature and not medically necessary: • surgery is being performed to treat psychological symptomatology or psychosocial complaints, in the absence of significant physical, objective signs • surgery is being performed for the sole purpose of improving appearance

Suction lipectomy or ultrasonically-assisted suction lipectomy (liposuction) as a sole method of treatment for symptomatic macromastia is considered unproven

Other state Medicaid coverage

The following Medicaid states responded to a request regarding coverage. Massachusetts, Maryland, Rhode Island, Texas, Oklahoma, Idaho, South Dakota, and Indiana. All states that replied indicated that they have coverage for breast reduction for macromastia. Representative policies are shown below.

Massachusetts Medicaid 2019

MassHealth considers approval for coverage of breast reduction on an individual, case-by-case basis, MassHealth bases its determination of medical necessity for reduction mammoplasty on a combination of clinical data and the presence of indicators that would affect the relative risks and benefits of the procedure, including post-operative recovery. These clinical coverage criteria include, but are not limited to, the following:

1. The member has been diagnosed with one or more of the medical conditions below in 1.a through 1.f and meets the condition-specific criteria set forth below:

A) The member is female.

B) A comprehensive medical history and complete physical exam (including breast exam) has been conducted by the referring health care provider.
C) The member has a diagnosis of breast hypertrophy, or gigantomastia or macromastia (size D or higher).
D) At least one of the following criteria (i, ii, iii, or iv) is met:
    a. i. Back pain unresponsive to conservative treatments for three months within a year prior to this request. Conservative treatment must include at least three months of (a) a documented trial of analgesics, AND (b) physical therapy or chiropractic treatment, AND (c) use of support wear for the breasts.
    b. ii. Neck pain unresponsive to conservative treatments for three months within a year prior to this request. Conservative treatment must include at least three months of (a) a documented trial of analgesics, AND (b) physical therapy or chiropractic treatment, AND (c) use of support wear for the breasts.
    c. iii. Shoulder pain unresponsive to conservative treatments for three months within a year prior to this request. Conservative treatment must include at least three months of (a) a documented trial of analgesics, AND (b) physical therapy or chiropractic treatment, AND (c) use of support wear for the breasts.
    d. iv. Persistent severe intertrigo in the inframammary fold unresponsive to documented prescribed medication for at least three months within a year prior to this request.
E) The treating surgeon must specify the amount of tissue to be removed from each breast and the prognosis for improvement of symptoms pertinent to breast hypertrophy, or gigantomastia or macromastia.
F) Other etiologies of the symptoms listed above have been excluded.
G) In addition, women age 40 and older are required to have a negative screening mammogram within two years of the planned reduction mammoplasty.

2. Clinical Coverage for Adolescents (age 15 through 17): Reduction mammoplasty surgery may be medically necessary for individuals age 15 through 17 when all of the following criteria (a through c) are met:
A) The clinical coverage criteria in Sections II. A. 1 (a through f) are met.
B) The member has completed puberty (Tanner stage V).
C) The member has had at least 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

1) Reduction mammoplasty is not covered for normal sized breasts as described by the American Society of Plastic Surgeons (size C or smaller).
2) Reduction mammoplasty is not covered for surgically enlarged breasts with saline or silicone implants. Surgically enlarged breasts are not considered breast hypertrophy, or gigantomastia or macromastia
3) Reduction mammoplasty is not covered for bilateral reductions of less than 300 grams (1 cup size) per breast.

Maryland Medicaid
Reduction mammoplasty will be considered for coverage when ALL of the criteria below are met, confirmed with supporting medical documentation.
Criteria for Initial Approval
1) Documentation of a functional impairment (defined as adverse effect on activities of daily living) related to at least two of the following:

a. Chronic pain
    i. Chronic headaches.
    ii. Chronic upper back, neck, breast or shoulder pain.
b. Skin changes
    i. Signs and symptoms of intertriginous maceration and/or infection of the inframammary skin (e.g., hyperpigmentation, bleeding, chronic moisture, and evidence of skin breakdown refractory to dermatologic measures).
    ii. Shoulder grooving from bra straps.
c. Arthritic changes
    i. Signs and symptoms of nerve compression that are unresponsive to medical management (e.g., ulnar paresthesias) and evidenced by nerve conduction studies.
    ii. History of significant arthritic changes in the cervical or upper thoracic spine.
    iii. Thoracic outlet syndrome.
    iv. Acquired kyphosis that is attributed to macromastia.
d. Dysmorphic Syndrome
    i. Depression/significant anxiety related to macromastia. Medical opinion that these functional impairments are attributable to macromastia. ○ Documented exclusion of alternative etiologies (e.g., such as arthritis, multiple sclerosis, cervical spine disease, etc.) have been adequately ruled-out by means of diagnostics, as applicable.

2) Medical opinion that the proposed procedure is likely to result in significant improvement of the functional impairment.
3) Documentation that the functional impairments have persisted despite conservative management for at least six months:
    a. Unresponsive to medical therapies such as physical therapy, exercises, use of support garment or brace.
    b. Analgesic/non-steroidal anti-inflammatory drugs (NSAIDs) interventions and/or muscle relaxants.
    c. Dermatologic therapy of ulcers, necrosis and refractory skin infections.
    d. Chiropractic care or osteopathic manipulative treatment.
4) Documentation of the preoperative anticipated amount of breast tissue to be removed per breast. If anticipated that the patient will have at least 1 kg of breast tissue removed from each breast, please document that as well.
5) High-risk surgical patients with substantial medical comorbidities (such as cardiopulmonary disease and morbid obesity) may not be eligible for reduction mammoplasty, even if they meet the criteria listed above for breast reduction.

Oklahoma Medicaid

Reduction Mammoplasty is considered medically appropriate when ALL of the following are met:

A. Member has persistent symptoms affecting daily activities for at least one year as indicated by at least TWO of the following:

1. Back, neck or shoulder pain not related to other causes such as arthritis, poor posture, acute strains, excessive weight, etc.; OR
2. Upper extremity neuropathy; OR
3. Painful kyphosis documented by x-rays; OR
4. Pain/discomfort/ulceration from bra straps cutting into shoulders; OR
5. Inframammary intertrigo unresponsive to medical management; OR

6. Difficulty sleeping or breathing due to weight of the breasts; AND

B. Photographic documentation confirms severe breast hypertrophy; AND

C. Member has undergone an evaluation by a qualified provider (M.D., D.O., Physician Assistant or Nurse Practitioner) who has determined that ALL of the following criteria are met:

1) There is reasonable likelihood that the member's symptoms are primarily due to macromastia; AND

2) Reduction mammoplasty is likely to result in improvement of the chronic pain and/or other symptoms; AND

3) Pain symptoms persist as documented by the qualified provider despite at least a 3-month trial of the following therapeutic measures (a-c):

a) Analgesic/non-steroid anti-inflammatory drugs (NSAIDS) interventions (if not contraindicated); AND

b) Physical therapy/exercises/posturing maneuvers; AND

c) Supportive devices (e.g. proper bra support, wide straps) AND

D. Candidates for breast reduction should be at least 18 years of age. Requests for members under 18 years old will be considered on an individual basis, due to the sensitive nature of performing procedures on the developing breast; AND

E. Women 40 years of age or older are required to have a mammogram that was negative for cancer performed within the year prior to the date of the planned reduction mammoplasty; AND

F. Member should have a BMI of less than 30; AND

G. Member should be a non-smoker or should not have smoked within the past 6 weeks as documented by the surgeon. If questionable, should obtain a cotinine or carboxyhemoglobin level.

Note: Ptosis, nipple distortion, breast asymmetry and impaired self-esteem are not considered as medically necessary indications for breast reduction.

Expert Input

Juliana Hanson, OHSU breast surgeon

breast reduction is one of the most commonly performed procedures by plastic surgeons because of the dramatic improvements in quality of life that are apparent to every surgeon who performs this operation. Also, as you know, this operation has been extensively studied with regard to various techniques and safety factors since the 1950's. It is a testament to how widely studied this topic is that a pub med search of merely one facet of breast reduction, outcomes, reveals over 6,000 studies.

In support for the coverage of breast reduction by the OHP, I have tried to include some more recent literature focused on outcomes. As validated outcomes tools have been developed and become available, numerous studies have demonstrated significant improvements in multiple QOL measurements after breast reduction. The benefits for adolescents who suffer from the effects of macromastia are also well studied and documented.

Less convincing are the benefits of breast reduction on pulmonary function tests, or as a reliable means of achieving significant weight loss.

Breast Reduction for Macromastia

Public Comment Disposition

Commenter	Comment	Staff response
Douglas Carr, CCO medical director	I support the HERC recommendation for Reduction Mammoplasty Option #3	Thank you for your comment.

Breast Reduction for Macromastia

HERC staff summary:

The literature on the effects of mammaplasty on quality of life, pain, functional capacity (including sexual function) and psychological outcomes consists mainly of a few small RCTs with wait list control groups. The majority of the literature in this area are cohort studies, some of which compare outcomes to a normative group of women with macromastia who did not have surgery. These cohort studies show consistent improvement in physical and mental health outcomes after surgery.

A recent high quality health technology assessment concluded that complications are frequent after breast reduction surgery, and that the risk for complications increases with a BMI>30. Regarding effects, breast reduction surgery may improve HRQoL and may reduce depressive symptoms, anxiety symptoms, and pain, compared with no surgery (low certainty of evidence). It is uncertain whether breast reduction surgery improves physical function

Breast reduction is one of the most commonly performed surgeries in the US. The expert consulted by staff strongly recommends coverage of breast reduction for OHP patients.

Currently, breast reduction for macromastia is its own line, prioritized well below the current funding line on the Prioritized List. Coverage of breast reduction for macromastia requires a biennial review change. There is also a guideline (GN166) that explicitly does not allow use of the co-morbidity rule to make an exception for coverage for breast reduction. This guideline would need to be deleted or rewritten if coverage of any type is desired.

HERC staff recommendation options:

1) **Option 1**: make no change in the current low prioritization of breast reduction for macromastia and explicit non-coverage of macromastia as a comorbid condition
    a. No changes required to the Prioritized List

2) **Option** 2: Allow coverage of breast reduction when macromastia is a comorbid condition to neck or back pain, but do not reprioritize the line
    a. Delete Guideline Note 166

~~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.~~

3) **Option 3**: Allow coverage of breast reduction when macromastia is a comorbid condition to neck or back pain, but do not reprioritize the line. Modify the current guideline to allow CCOs to standardize the comorbidity exception review
    a. Revise GN166 as shown below

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

Breast reduction surgery is included on line 561 only when all of the following conditions are met:

1) The patient is aged 18 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 treatment, 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) Other etiologies of the pain or intertrigo in #3 above have been excluded; AND
6) Women age 40 and older are required to have a negative screening mammogram within two years of the planned reduction mammoplasty.

4) **Option 4:** Reprioritize the breast reduction for macromastia line effective January 1, 2026 with the next biennial Review Prioritized List
    a. Rescore line 561 MACROMASTIA as shown below
        i. Note: staff suggesting scoring results in the line still being in the non-funded region; scoring will need to be discussed in detail
    b. Modify GN166 as shown below
        i. Based on other state Medicaid policies

Line: 561
Condition:MACROMASTIA (See Guideline Notes 196 and 166)
Treatment:BREAST REDUCTION
Prioritization (current prioritization scores shown in parentheses)

Category 7 (7) Non-fatal condition where treatment is aimed at disease modification
Impact on Healthy Life 4 (1) 0-10
Impact on Pain and Suffering 2 (1) 0-5
Population effects 0 (0)
Vulnerable populations 0 (0)
Tertiary prevention 2 (1) 0-5
Effectiveness 4 (4) 0-5
Need for treatment 0.3 (0.2) 0-1
Net cost 1 (1) 0-5

SCORE 192 (48), PUTS ON near LINE 474 of the 10/2023 Prioritized List (unfunded, just below the funding line) (561)

Breast Reduction for Macromastia

GUIDELINE NOTE 166, BREAST REDUCTION SURGERY FOR MACROMASTIA

Lines ~~402,561~~ XXX

~~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 this line (XXX) only when all of the following conditions are met:

1) The patient is aged 18 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 treatment, 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) Other etiologies of the pain or intertrigo in #3 above have been excluded; AND
6) Women age 40 and older are required to have a negative screening mammogram within two years of the planned reduction mammoplasty.

Region Västra Götaland, HTA-centrum
Regional activity-based HTA [Verksamhetsbaserad HTA]
Health Technology Assessment
HTA report 2021:121

Effectiveness and safety of breast reduction surgery, compared with no surgery, in women with symptomatic breast hypertrophy

Hansson E, Eriksson M, Hallberg H, Jepsen C, Jivegård L, Liljegren A, Petzold M, Svensson M, Widmark-Jensen E, Wärnberg F, Bernhardsson S

VÄSTRA GÖTALANDSREGIONEN
SAHLGRENSKA UNIVERSITETSSJUKHUSET

Effectiveness and safety of breast reduction surgery, compared with no surgery, in women with symptomatic breast hypertrophy

[Effektivitet och säkerhet för bröstreduktionskirurgi, jämfört med ingen kirurgi, hos kvinnor med symtomgivande brösthypertrofi]

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Published January 2021
2021:121
Suggested citation: Effectiveness and safety of breast reduction surgery, compared with no surgery, in women with symptomatic breast hypertrophy [Effektivitet och säkerhet för bröstreduktionskirurgi hos kvinnor med symtomgivande brösthypertrofi]. Göteborg: Västra Götalandsregionen, Sahlgrenska Universitetssjukhuset, HTA-centrum: 2021. Regional activity-based HTA 2021:121

1. Abstract

Background: Breast hypertrophy is a condition that may give rise to physical and/or psychosocial problems, such as pain, headache, postural changes, bra strap grooves, intertrigo, inability to participate in exercise and sports, bullying, body image problems and problems with poorly fitting clothes. The condition affects many women and approximately 1,000 breast reduction surgeries per year are performed in Sweden.

Objective: The objective of this Health Technology Assessment (HTA) was to assess whether breast reduction surgery in women with symptomatic breast hypertrophy and a BMI ≤ 35, is better than no surgery regarding mortality, health-related quality of life, depressive symptoms, anxiety symptoms, sexuality-related outcomes, work ability, sick leave, physical function, pain, patient experience, and whether the surgery is safe to perform.

Methods: A systematic literature search was conducted in June 2020 in PubMed/Medline, Embase, the Cochrane Library, PsycInfo, and a number of HTA databases. The included articles were critically appraised and certainty of evidence was assessed using the GRADE approach. Meta-analyses were performed when possible.

Main results: Fifteen articles were included in this HTA; eight reporting findings from four RCTs, three cohort studies, three case series, and one qualitative study describing results of breast reduction surgery in women with symptomatic breast hypertrophy. Most studies had serious study limitations and problems with directness. Three RCTs and two cohort studies showed significantly improved *health-related quality of life* in patients who had undergone breast surgery compared with controls; weighted mean difference in the RCTs was 0.14 (95% CI 0.10–0.17) when measured with SF-6D (score range 0.29–1.0), 7.0 (95% CI 4.4–9.5) for SF-36 physical summary score, and 9.8 (95% CI 6.2–13) for SF-36 mental summary score (both ranging 0–100). Three RCTs showed significantly reduced *depressive symptoms* after surgery and two showed reduced levels of anxiety symptoms after surgery compared with controls. One RCT and two cohort studies showed significantly improved *sexuality-related outcomes* after surgery compared with controls. Three RCTs and one cohort study showed reduced pain after surgery compared with controls. Most effect sizes exceeded the reported minimal important difference for the scale. Certainty of evidence for the above outcomes is low (GRADE ⊕⊕◯◯). Two RCTs and two cohort studies reported significantly improved *physical function* after surgery compared with controls (very low certainty of evidence, GRADE ⊕◯◯◯). None of the included studies reported data regarding *work ability or sick leave*. The qualitative study showed that women experienced benefits, e.g. improved quality of life, but also some drawbacks in the form of scarring, from breast reduction surgery. Three case series reported a 30-day mortality of zero. Major complications reported after breast reduction surgery ranged from 2.4% to 14% and minor complications from 2.4% to 69%. The most severe complications were venous thromboembolism and pulmonary embolism, while the most frequent were surgical site infections and wound healing problems.

Concluding remarks: In women with symptomatic breast hypertrophy, breast reduction surgery compared with no surgery, may result in clinically relevant improvement of HRQoL and sexuality-related outcomes, and reduction of depressive symptoms, anxiety symptoms, and pain (GRADE ⊕⊕◯◯). It is uncertain whether physical function is affected (GRADE ⊕◯◯◯). Complications include a few serious complications, e.g. venous thromboembolism and infections, even though the most frequent complications are less severe. Reported thirty-day mortality was zero. There is a need for large well designed RCTs evaluating the long-term efficacy of breast reduction surgery in women with thoroughly defined symptomatic breast hypertrophy, as well as studies exploring women's experience of having had the procedure.

BMJ Open

Does breast reduction surgery improve health-related quality of life? A prospective cohort study in Australian women

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To cite: Crittenden T, Watson DI, Ratcliffe J, *et al*. Does breast reduction surgery improve health-related quality of life? A prospective cohort study in Australian women. *BMJ Open* 2020;**10**:e031804. doi:10.1136/bmjopen-2019-031804

► Prepublication history and additional material for this paper are available online. To view these files, please visit the journal online (http://dx.doi.org/10.1136/bmjopen-2019-031804).

Received 20 May 2019
Revised 11 December 2019
Accepted 18 December 2019

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ABSTRACT

Objectives To assess the health burden of breast hypertrophy and the comparative effectiveness of breast reduction surgery in improving health-related quality of life.

Design Prospective cohort study.

Setting A major public tertiary care hospital in Australia.

Participants Women with symptomatic breast hypertrophy who underwent breast reduction surgery were followed for 12 months. A comparison control cohort comprised women with breast hypertrophy who did not undergo surgery.

Interventions Bilateral breast reduction surgery for women in the surgical cohort.

Main outcome measures The primary outcome measure was health-related quality of life measured preoperatively and at 3, 6 and 12 months postoperatively using the Short Form-36 (SF-36) questionnaire. Secondary outcome measures included post-surgical complications.

Results 209 patients in the surgical cohort completed questionnaires before and after surgery. 124 patients in the control hypertrophy cohort completed baseline and 12-month follow-up questionnaires. At baseline, both groups had significantly lower scores compared with population norms across all scales ($p<0.001$). In the surgical cohort significant improvements were seen across all eight SF-36 scales ($p<0.001$) following surgery. Within 3 months of surgery scores were equivalent to those of the normal population and this improvement was sustained at 12 months. SF-36 physical and mental component scores both significantly improved following surgery, with a mean change of 10.2 and 9.2 points, respectively ($p<0.001$). In contrast, SF-36 scores for breast hypertrophy controls remained at baseline across 12 months. The improvement in quality of life was independent of breast resection weight and body mass index.

Conclusion Breast reduction significantly improved quality of life in women with breast hypertrophy. This increase was most pronounced within 3 months of surgery and sustained at 12-month follow-up. This improvement in quality of life is comparable to other widely accepted surgical procedures. Furthermore, women benefit from surgery regardless of factors including body mass index and resection weight.

Strengths and limitations of this study

- ► This large prospective longitudinal study reports 12-month follow-up using a validated patient-reported outcome measure for health-related quality of life assessment.
- ► The completion rate of the study was 83% for participants who underwent surgery.
- ► Comparisons were made with a control cohort of women with breast hypertrophy not undergoing surgery, and also to a normative female reference population.
- ► This was a non-randomised study design.

INTRODUCTION

Breast reduction surgery is a common plastic surgery procedure and it has previously been shown to be effective for relieving pain and functional problems associated with breast hypertrophy,[1–5] whereas conservative approaches to treatment such as physiotherapy, hormonal therapy and weight loss have much less impact.[6 7] However, despite clear published evidence to the contrary, breast reduction surgery is often regarded more as a cosmetic rather than a functional procedure by the general public and many medical professionals.[1 8 9] This is in spite of the finding that breast hypertrophy is a chronic health problem and relief of physical symptoms is the primary motivator for most women who are pursuing breast reduction surgery.[10]

The increasing demand for breast reduction surgery and increasing pressure to constrain healthcare spending have led to lengthy waiting times and restrictions placed on surgery in numerous countries and jurisdictions worldwide.[4 11–15] While 'rationing' of healthcare is an essential process in public healthcare systems globally, it has the potential to threaten equity of access to surgical

BREAST-Q Outcomes before and after Bilateral Reduction Mammaplasty

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Hanover and Lebanon, N.H.

Background: The BREAST-Q is the only questionnaire specific to bilateral breast reduction that was developed according to federal and international standards. Many payors mandate minimum resection weights for preapproval, despite lacking supportive evidence for this practice. This study aimed to assess changes in BREAST-Q scores after bilateral breast reduction, and determine whether compliance with Schnur requirements impacts improvement in patient-reported outcomes.

Methods: Patients presenting for bilateral breast reduction from 2011 to 2017 were asked to complete the BREAST-Q preoperatively and postoperatively. Multivariate regression analysis was performed to isolate factors associated with favorable outcomes.

Results: Complete data were available for 238 patients. Mean time to postoperative BREAST-Q was 213 days. Complications occurred in 31 patients (13.0 percent). Mean preoperative BREAST-Q scores were below normative values ($p < 0.001$), and mean postoperative scores were above normative values ($p < 0.001$ for Satisfaction with Breasts, Psychosocial Well-being, and Sexual Well-being; and $p = 0.05$ for Physical Well-being). Postoperative Physical Well-being scores were similar to normative values for resections less than Schnur ($p = 0.32$), but below norms for resections greater than Schnur ($p < 0.0001$). On multivariate regression ($n = 230$), complication and surgeon experience were the only independent predictors of lesser improvement on the Satisfaction with Breasts subscale.

Conclusions: This study is the largest to include both preoperative and postoperative bilateral breast reduction BREAST-Q scores, and to compare multiple subscales to normative data. Scores overwhelmingly increased, regardless of age or Schnur compliance. Complications negatively impacted degree of BREAST-Q improvement. Interestingly, postoperative Physical Well-being was slightly higher in women with non–Schnur-compliant resections. Bilateral breast reduction substantially improves patient welfare, and our data question the validity of insurer-mandated minimum resections. (*Plast. Reconstr. Surg.* 147: 382e, 2021.)

CLINICAL QUESTION/LEVEL OF EVIDENCE: Therapeutic, III.

According to American Society of Plastic Surgeons statistics, 43,591 nonreconstructive reduction mammaplasties were performed in 2018.[1] Today, reduction mammaplasty is widely accepted as a medically necessary, rather than cosmetic, procedure. Historically, though, insurers were suspicious of patients' motivations, and adopted a minimum resection weight of 350 to 500 g per breast for coverage.[2] This arbitrary mandate disadvantaged women with milder macromastia and with significant breast asymmetry, for whom the minimum resection weight could be deforming.

Attempting to address these issues, Schnur published a landmark article[2] normalizing resection weights to patient size. He collected data on body

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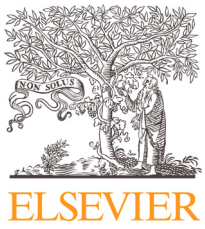
Received for publication November 12, 2019; accepted July 16, 2020.
Presented at Plastic Surgery The Meeting 2019, 88th Annual Meeting of the American Society of Plastic Surgeons, in San Diego, California, September 20 through 23, 2019.

DOI: 10.1097/PRS.0000000000007605

Disclosure: *The authors have no relevant disclosures to report.*

Journal of Plastic, Reconstructive & Aesthetic Surgery 75 (2022) 4335–4346



JPRAS
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Review

The effects of breast reduction on pulmonary functions: A systematic review

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Received 1 March 2021; accepted 18 August 2022

KEYWORDS
Breast reduction;
Reduction mammaplasty;
Pulmonary function;
Lung function;
Macromastia

Summary Breast reduction is one of the most commonly requested and performed plastic surgery procedures, and its psychological, esthetic, and analgesic benefits are well known. Several studies dealing with the effects of reduction mammoplasty on the physiology of respiration have been published in the past decades. This systematic review aims to assess whether bilateral breast reduction is associated with measurable improvement in lung function in women with macromastia. This review was performed in accordance with the PRISMA guidelines. PubMed, SCOPUS, and Web of Science databases were queried in search of clinical studies that investigated lung function in women undergoing breast reduction for macromastia and reported any type of parameter or outcome measure relevant to pulmonary function. The search yielded 394 articles of which 15 articles met our specific inclusion criteria. The primary outcome measures of the studies and their respective results were tabulated, contrasted, and compared. The 15 studies included in this review cover the period from 1974 to 2018. According to most included studies, reduction mammaplasty produces a change of objective respiratory parameters, such as spirometric tests or arterial blood gas (ABG) measurements; nevertheless, the clinical and functional relevance of the observed changes is debatable.

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https://doi.org/10.1016/j.bjps.2022.08.068

Aesth Plast Surg (2018) 42:388–395
https://doi.org/10.1007/s00266-017-1009-6

ORIGINAL ARTICLE BREAST SURGERY

Use of the BREAST-Q™ Survey in the Prospective Evaluation of Reduction Mammaplasty Outcomes

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Received: 14 August 2017 / Accepted: 18 October 2017 / Published online: 9 November 2017

Abstract

Introduction BREAST-Q™ is a patient-reported outcomes survey instrument with a specific module that evaluates breast reduction surgery. It allows assessment of patient's satisfaction with received treatment and evaluates the impact of surgery on different aspects of the patient's quality of life. This article aims to assess the satisfaction and quality of life of patients who underwent reduction mammaplasty.

Materials and Methods Women aged between 18 and 60 years, with a body mass index ranging from 19 to 30 kg/m^2, who were already scheduled for reduction mammaplasty, were included in the study. The Brazilian version of the BREAST-Q™ Reduction/Mastopexy Module (preoperative 1.0 and postoperative 1.0 versions) was self-applied preoperatively and 1 and 6 months after the operation.

Results One hundred and seven patients were included in the study and completed the 6-month follow-up. The median age was 33 years, and the median preoperative body mass index was 25 kg/m^2. The superomedial pedicle was used in 96.3% of the cases, and the total median weight of the resected breast was 1115 g. There was a significant improvement in the scores of the scales: *Psychosocial well-being, Sexual well-being, Physical well-being,* and *Satisfaction with the breasts* compared to the preoperative assessment ($p < 0.0001$). The scales *Satisfaction with the NAC* and *Satisfaction with the outcome*, available only in the postoperative version, demonstrated high satisfaction rates at the two postoperative periods evaluated.

Conclusion Reduction mammaplasty improved the quality of life and provided high levels of patient satisfaction with outcomes 1 and 6 months postoperatively.

Level of Evidence IV This journal requires that authors assign a level of evidence to each article. For a full description of these Evidence-Based Medicine ratings, please refer to the Table of Contents or the online Instructions to Authors www.springer.com/00266.

Keywords Breast · Surgery, plastic · Mammaplasty · Outcome assessment · Quality of life · Patient satisfaction

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Introduction

Symptoms associated with breast hypertrophy include neck, shoulder, and spine pain, headache, intertrigo within the inframammary fold, difficulty in performing activities of daily living, paresthesia in the hands (due to weight on the anterior chest wall and compression of the brachial plexus), difficulty in exercising, low self-esteem, and body

A Matched Comparison of the Benefits of Breast Reduction on Health-Related Quality of Life

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Background: Breast reduction surgery has consistently fallen within the top 10 surgical procedures performed by plastic surgeons. This is because of its capability to relieve the physical and psychological impact of macromastia. Although numerous women pursue consultation, many never undergo the procedure. The authors aim to quantify the impact of breast reduction surgery on quality of life by comparing patients who underwent breast reduction surgery with those who did not.
Methods: Patients seeking breast reduction surgery between 2016 and 2019 were identified. As standard-of-care, patients are surveyed during the consultation visit and postoperative visits using the BREAST-Q. The preoperative survey was readministered a second time for those who did not undergo breast reduction surgery. Propensity score matching, based on patient demographics, comorbidities, and breast examination, was used to balance baseline characteristics.
Results: A total of 100 propensity-matched patients were identified (operative, $n = 78$; nonoperative, $n = 22$). Mean participant age was 39.5 ± 25 years and mean body mass index was 31.1 ± 7.4 kg/m^2. Quality of life significantly improved in each domain for those in the operative group ($p < 0.05$). Those who did not undergo breast reduction surgery realized no improvement in quality of life and had a downward trend in quality of life across two of the four domains.
Conclusions: Breast reduction surgery offers a significant improvement in quality of life for macromastia. This matched study demonstrates that patients who are able to undergo breast reduction surgery have a statistically significant improvement in all aspects of quality of life, whereas nonsurgical patients experience no benefit with time, with a trend toward deterioration in specific domains. (*Plast. Reconstr. Surg.* 148: 729, 2021.)

The demand for reduction mammaplasty in the United States has remained persistent. For over two decades, since the earliest national data banks, it has fallen within the top 10 most common surgical procedures.[1] The prevalence of macromastia and the desire to seek symptomatic relief[2,3] have not wavered, but the willingness on the part of insurance companies to cover these procedures has. Macromastia not only results in functional disability caused by physical and psychological distress, but also represents a significant morbidity associated with decreased health-related quality of life.[3–5] Consequently, patients denied by insurance and unable to cover the procedure out of pocket are unable to pursue surgical treatment and the associated quality-of-life benefits.

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Received for publication April 2, 2020; accepted March 4, 2021.

DOI: 10.1097/PRS.0000000000008312

The proven efficacy of reduction mammaplasty on the physical and psychological burden of macromastia has been well documented in the literature.[4–14] Prior studies demonstrate lower than average health-related quality of life in women presenting for reduction mammaplasty for whom surgery results in a significant, quantifiable improvement.[15,16] However, these studies fail to capture quality-of-life data on patients who do not

Disclosure: *Dr. Fischer has received payments as a consultant for Gore, Integra LifeSciences, Allergan, and Becton-Dickinson during the time of this study. The remaining authors do not have any financial disclosures to report. This research did not receive financial support for the study.*

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Breast-Related Quality of Life in Young Reduction Mammaplasty Patients: A Long-Term Follow-Up Using the BREAST-Q

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Background: Reduction mammaplasty is the most effective means of improving symptoms of macromastia. Although studies have shown lasting benefits in adult patients, there is a paucity of data that explore this topic in young patients. In this study, the long-term satisfaction and well-being of young reduction mammaplasty patients was assessed.
Methods: A retrospective review was performed for all female patients younger than 25 years who underwent reduction mammaplasty performed by a single surgeon from 1980 to 2003. Demographic characteristics, comorbidities, surgical details, and length of follow-up were recorded. Participants completed the postoperative version of the BREAST-Q Reduction module. Responses were scored on a scale of 0 to 100. Scores were summarized with descriptive statistics and compared to normative values.
Results: Thirty-seven of 52 eligible participants completed the survey (response rate, 71.2 percent). Median age at surgery was 21 years (range, 12.4 to 24.6 years), and median follow-up was 21.4 years (range, 11.4 to 32.4 years). Overall, participants demonstrated high satisfaction and well-being. Mean Q-Scores for Satisfaction with Breasts and Sexual Well-being were significantly higher than normative values ($p = 0.0012$ and $p < 0.0001$, respectively), and were as follows: Satisfaction with Breasts, 66.6 ± 16.5 (normative, 57 ± 16); Psychosocial Well-being, 75.9 ± 21.3 (normative, 68 ± 1 9); Sexual Well-being, 72 ± 18.2 (normative, 55 ± 19); and Physical Well-being, 81.1 ± 13.6 (normative, 76 ± 11).
Conclusions: Young reduction mammaplasty patients experience excellent breast-related quality of life decades after surgery. Compared with normative values, young reduction mammaplasty patients reported higher satisfaction with breasts and sexual well-being. Surgeons and third-party payers should be aware of these data and advocate for young patients to gain access to care. (*Plast. Reconstr. Surg.* 144: 743e, 2019.)

Women with macromastia are known to experience a variety of physical and psychological challenges. These may include neck, back, and shoulder discomfort, in addition to poor body image, low self-esteem, and a lack of confidence in social interactions. Multiple studies have shown that regardless of surgical technique, reduction mammaplasty is associated with improved physical and psychological well-being in adult women with macromastia.[1–5]

In addition to affecting adult women, macromastia is also seen in adolescent patients and may be associated with endocrine changes, childhood obesity, and juvenile hypertrophy of the breast.[6] Although young patients experience many of the same symptoms as adults, controversy exists around performing reduction mammaplasty in a young patient population.[6–8] This is mainly because of concerns around postoperative complications that may include changes in nipple

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Received for publication June 3, 2018; accepted February 7, 2019.

DOI: 10.1097/PRS.0000000000006117

Disclosure: *The authors have no financial disclosures. No funding was received for this article.*

Related digital media are available in the full-text version of the article on www.PRSJournal.com.

American Society of Plastic Surgeons Evidence-Based Clinical Practice Guideline Revision: Reduction Mammaplasty

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Summary: A multidisciplinary work group involving stakeholders from various backgrounds and societies convened to revise the guideline for reduction mammaplasty. The goal was to develop evidence-based patient care recommendations using the new American Society of Plastic Surgeons guideline methodology. The work group prioritized reviewing the evidence around the need for surgery as first-line treatment, regardless of resection weight or volume. Other factors evaluated included the need for drains, the need for postoperative oral antibiotics, risk factors that increase complications, a comparison in outcomes between the two most popular techniques (inferior and superomedial), the impact of local anesthetic on narcotic use and other nonnarcotic pain management strategies, the use of epinephrine, and the need for specimen pathology. A systematic literature review was performed, and an established appraisal process was used to rate the quality of relevant scientific research (Grading of Recommendations Assessment, Development and Evaluation methodology). Evidence-based recommendations were made and strength was determined based on the level of evidence and the assessment of benefits and harms. (*Plast. Reconstr. Surg.* 149: 392e, 2022.)

PATIENT SAFETY

Quality of Care

Reduction mammaplasty is a procedure performed for symptomatic breast hypertrophy in more than 100,000 patients per year.[1] There is an extensive body of evidence demonstrating the efficacy of reduction mammaplasty in reducing both physical and psychological symptoms in patients with symptomatic breast hypertrophy.[2–9]

In 2012, the American Society of Plastic Surgeons published the first guideline on

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Received for publication August 16, 2020; accepted June 8, 2021.

DOI: 10.1097/PRS.0000000000008860

Disclosure: *Claire Dillingham is a key opinion leader and on the speakers bureau of Acell. John Fischer received payments as a consultant from Bard, Gore, and Integra. Christine Rohde is a consultant for Bard and Johnson and Johnson. The remaining authors have no financial interests to report.*

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Section 9.0

New Discussion Items

Coronary Artery Calcium Score

Plain Language Summary:

Coverage question: This scan produces multiple pictures to check if calcium is present in the blood vessels of the heart and, if so, how much. The test may predict the risk of heart attack.

Should OHP cover this treatment? No, there is not enough evidence that this test will prevent heart attacks or save lives. The test might reduce the need for medications in some patients, but it isn't clear which kinds of patients might benefit.

Coverage Question: Should coverage be added for coronary artery calcium score scoring; if so, for what indications and/or populations?

Question source: Staff, after introduction of Senate Bill 497 (bill introduced by Ben West, Clackamas County commissioner and nurse practitioner at a cardiology clinic)

Background: Coronary artery disease/cardiovascular disease (CAD/CVD) is a major cause of death and morbidity in the United States. Various methods have been proposed to estimate a patient's risk for CAD/CVD.

Current standard screening for coronary artery disease risk includes evaluation of blood pressure and blood lipid levels, and using these values in predictive equations that take into account sex, diabetes, smoking status and age. The Framingham Risk Score and the NIH risk factor calculator are widely used risk assessment tools. Persons with a 10-year CVD event risk less than 7.5% are considered at low risk, and those with a 10-year risk of 7.5% or greater are considered at high risk. High risk patients are recommended to be treated with statin therapy to lower cholesterol. High risk patients may also have invasive evaluations, such as coronary angiography.

The purpose of coronary artery calcium (CAC) scoring using computed tomography (CT) in asymptomatic patients is to assess who may benefit from preventative interventions (guide in lipid-lowering therapy, decisions on the use of aspirin and to assist in discussions regarding therapeutic lifestyle changes and modifications of cardiovascular risk factors) targeted to minimize the risk of atherosclerotic cardiovascular disease (CVD). This may be useful when the clinician and patient are uncertain whether to start a statin. A low CAC score may lead to the decision to not start or to discontinue statin therapy; conversely, a high CAC score may encourage a patient and provider to start statin therapy. Even with a low CAC score, however, certain patients should be treated with statins, such as patients with diabetes.

Previous HSC/HERC reviews:

CACS was last reviewed in 2013 as a coverage guidance. The conclusion of that review was "Coronary artery calcium scoring (CACS) should not be covered." The coverage guidance review included a 2010 NICE review, a 2009 USPSTF review, and a 2009 WA HTA report.

Coronary Artery Calcium Score

Current Prioritized List/Coverage status:

CPT 75571 (Computed tomography, heart, without contrast material, with quantitative evaluation of coronary calcium) is on line 662/GN173

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
75571	CT coronary calcium scoring	Insufficient evidence of benefit, unclear harms of radiation exposure	August, 2013 Coverage guidance

Evidence:

1) **Bell 2023**, Systematic review and meta-analysis on incremental value of a coronary artery calcium score beyond traditional cardiovascular risk assessment
    a. N=6 cohort studies which included 1043 CVS events in 17,961 patients
        i. Study size ranged from 470-5185 participants
        ii. Study populations had no history of CVD
        iii. Used 1 of the CVD risk calculators recommended by national guidelines (Framingham Risk Score, QRISK, pooled cohort equation, NZ PREDICT, NORRISK, or SCORE)
        iv. Included cohort studies: Wong 2009, Kavousi 2012, Hoffman 2016, Yeboah 2016, Geisel 2017, Moon 2019
    b. The C statistic for the CVD risk models without CACS ranged from 0.693 (95% CI, 0.661-0.726) to 0.80. The pooled gain in C statistic from adding CACS was 0.036 (95% CI, 0.020-0.052). [see explanation of C statistics below]. Among participants classified as being at low risk by the risk score and reclassified as at intermediate or high risk by CACS, 85.5% (65 of 76) to 96.4% (349 of 362) did not have a CVD event during follow-up (range, 5.1-10.0 years). Among participants classified as being at high risk by the risk score and reclassified as being at low risk by CACS, 91.4% (202 of 221) to 99.2% (502 of 506) did not have a CVD event during follow-up
        i. Staff interpretation: This article uses the c-statistic ("concordance") to estimate the diagnostic accuracy of the CAC score for CAD risk prediction. It is basically the same as AUROC (AUC) curve for understanding how well a test predicts a certain clinical outcome (0.5= like a coin toss, >0.7 good, >0.9 very good) in this study. Based on their results, the CACS helps with additional discrimination (pretty good c-stat ~0.69 to 0.80) for CVD risk assessment but the overall benefit is unclear compared with traditional risk evaluation methods (ASCVD, risk

scores, etc). This is consistent with the USPSTF 2018 conclusion that gave an "I" statement for CACS vs traditional risk assessment for prediction of CVD in asymptomatic adults.

c. Among participants classified as being at low risk by the risk equation, 0.4% (11 of 3139) to 2.2% (54 of 2471) were correctly reclassified as being at intermediate or high risk when a CACS was added to the model (ie, had a CVD event), and 2.1% (65 of 3139) to 14.4% (349 of 2416) were incorrectly reclassified as being at intermediate or high risk (did not have an event). The absolute rates in the study populations (total study sample used as the denominator) were 0.3% (13 of 4129) to 1.5% (54 of 3678) correctly reclassified, and 2.0% (65 of 3319) to 9.6% (496 of 5185) incorrectly reclassified. Among participants reclassified from low risk by the risk score to intermediate or high risk by CACS, 3.6% (13 of 362) to 14.5% (11 of 76) had a CVD event during follow-up, and 85.5% (65 of 76) to 96.4% (349 of 362) did not have a CVD event during follow-up
    i. HERC staff: For patients who score as low risk for heart attacks based on standard testing, CACS would correctly reclassify 4 to 22 people per 1000 people as being at high risk for a heart attack when they actually are but CACS would incorrectly reclassify 2 to 14 people per 1000 people as being high risk for a heart attack when they actually are not
d. Among participants classified as being at intermediate or high risk by the risk equation, 18.9% (34 of 180) to 29.3% (502 of 1713) were correctly reclassified as being at low risk when CACS was added to the model (did not have a CVD event), and 0.2% (4 of 1713) to 1.9% (19 of 1000) were incorrectly reclassified as being at low risk (had a CVD event). The absolute rates in the study populations were 1.0% (34 of 3319) to 12.2% (502 of 4129) correctly reclassified as being at low risk and 0.1% (2 of 3319) to 0.5% (19 of 3678) incorrectly reclassified as being at low risk. Among participants reclassified from intermediate or high risk by the risk score to low risk by CACS, 91.4% (202 of 221) to 99.2% (502 of 506) did not have a CVD event during follow-up, and 8.6% (19 of 221) to 0.8% (4 of 506) did have a CVD event during follow-up
    i. HERC staff: For patients who score as at high risk for heart attacks based on standard testing, CACS would correctly reclassify 189 to 293 people per 1000 people as being at low risk for a heart attack when they actually are low risk but CACS would incorrectly reclassify 2 to 19 people per 1000 people as being low risk for a heart attack when they actually are high risk
e. CONCLUSIONS AND RELEVANCE This systematic review and meta-analysis found that the CACS appears to add some further discrimination to the traditional CVD risk assessment equations used in these studies, which appears to be relatively consistent across studies. However, the modest gain may often be outweighed by costs, rates of incidental findings, and radiation risks. Although the CACS may have a role for refining risk assessment in selected patients, which patients would benefit remains unclear. At present, no evidence suggests that adding CACS to traditional risk scores provides clinical benefit

2) **AHRQ 2016**, Comparative effectiveness review for noninvasive testing for coronary artery disease
    a. N=46 studies
        i. Patients with no known CAD
        ii. Compared stress EKG, stress ECHO, SPECT, PET, CCTA, and calcium scoring with other noninvasive tests, usual care or no testing

Coronary Artery Calcium Score

b. No comparative studies of calcium scoring that met inclusion criteria were found
c. Two noncomparative studies of calcium scoring during CCTA in patients at intermediate pretest risk reported on predictive accuracy. One study was conducted in a single center outpatient setting (N=341) and the other included data from an international, multicenter registry (N=10,037). The follow-up period was 24 months in both studies. In terms of test-positive patients, the frequency of any cardiac event was substantially higher in both studies (5 and 8 per 100 people) compared with those who tested negative (0 and 1 per 100 people). The registry study also reported a higher risk of both mortality (1.8% vs. 0.4%) and MI (1.1% vs. 0.2%) in those who tested positive
d. Three noncomparative studies of calcium scoring in patients at low to intermediate pretest risk reported on predictive accuracy. One study was conducted in an outpatient setting (N=422), one in the ED (N=263), and the setting was unclear in the third study of patients who were referred for invasive coronary angiography (N=2088). Mean ages ranged from 47.3 to 58.6 years across studies and a slight majority of patients were male (49.3%–60%). In terms of test-positive patients, in all studies, the frequency of cardiac events was higher compared with test-negative patients. Across the two non-ED studies with mean follow-ups of 2.5 years, the frequency of any cardiac event was 5 and 11 per 100 people (vs. 1 per 100 people in both), mortality was 2 per 100 people in both (vs. 0 and 1 per 100 people), and MI was 1 and 2 per 100 people (vs. 0 events); in the ED study, over 5 years follow-up, the frequency of any cardiac event was 20 per 100 people compared with no events
e. One noncomparative study of calcium scoring in patients with an unclear pretest risk reported on predictive accuracy. A total of 255 patients were analyzed with a mean age of 58 ± 11 years; the proportion of males and females and relevant cardiac risk factors were not reported. Over a mean follow-up period of 42 months, the frequency of major adverse cardiac events was significantly higher in those who had a positive compared with a negative result: 20 versus 2 per 100 people
f. Conclusion: There was no clear difference in myocardial infarction (MI) or in all-cause mortality between different testing strategies across settings or pretest risk groups that included patients with intermediate pretest risk, based on low- to moderate-strength evidence from nine trials. Across studies, the frequency was low for all-cause mortality (0%–1.5% in outpatient settings, 0%–1.1% in emergency department [ED] settings past the initial visit) and for MI (0%– 0.8% in outpatients, 0%–3% in ED settings).
g. Coronary artery calcium scoring was found to have a 98-99% sensitivity, 35-40% specificity, 65-68% PPV, 93-95% NPV at finding CAD

Submitted literature:

1) **Lindholt 2022,** DANCAVAS trial
    a. RCT of men aged 65-74 in Denmark
        i. N=16,736 men in the group invited for screening for subclinical cardiovascular disease
            1. N=10,471 men actually underwent screening (62.6%)

2. Screening consisted of CAC scoring, atrial fibrillation screening, aortic and iliac aneurysm screening, and ankle-brachial blood pressure measurements (screening for peripheral vascular disease), blood pressure measurement, blood tests for diabetes and hypercholesterolemia

ii. N=29,790 men included in the control group (usual care)

iii. Outcome was death from any cause at 5 years (data from the Danish National Patient Registry)

iv. Measured medication use through the Danish National Prescription Registry

b. In intention-to-treat analyses, after a median follow-up of 5.6 years, 2106 men (12.6%) in the invited group and 3915 men (13.1%) in the control group had died (hazard ratio, 0.95; 95% confidence interval [CI], 0.90 to 1.00; P=0.06). The hazard ratio for stroke in the invited group, as compared with the control group, was 0.93 (95% CI, 0.86 to 0.99); for myocardial infarction, 0.91 (95% CI, 0.81 to 1.03); for aortic dissection, 0.95 (95% CI, 0.61 to 1.49); and for aortic rupture, 0.81 (95% CI, 0.49 to 1.35). There were no significant between-group differences in safety outcomes.

c. Conclusion: After more than 5 years, the invitation to undergo comprehensive cardiovascular screening did not significantly reduce the incidence of death from any cause among men 65 to 74 years of age

2) **Greenland 2018**, review of coronary calcium score and cardiovascular risk

a. 4 population-based cohorts (MESA, HNR, Rottendam, Framingham)

i. CAC was reported to predict cardiovascular events in these cohorts

b. A meta-analysis in low-risk women found that CAC >0 was present in approximately one-third and was associated with an increased risk for atherosclerotic cardiovascular disease (ASCVD) and modest improvement in prognostic accuracy compared with traditional risk factors.

c. A meta-analysis was conducted in elderly subjects (mean age 70 years) from among 4,778 participants from 3 U.S. cohorts, including MESA, Framingham, and the Cardiovascular Health Study. Over 11 years of follow-up, 405 coronary heart disease (CHD) and 228 stroke events occurred. CAC score (vs. age) had a greater association with incident CHD and modestly improved prediction of incident stroke

d. The Jackson Heart Study (conducted among African Americans) measured CAC during follow-up. In this population, CAC predicted risk beyond the traditional risk factors and has been shown to better identify persons most likely to benefit from preventive therapies

e. CAC scoring appears to be useful for making decisions about preventive statin and/or aspirin use.

Expert guidelines:

1) **USPSTF 2018,** risk assessment for cardiovascular disease

a. The USPSTF found adequate evidence that adding the ankle-brachial index (ABI), high-sensitive C-reactive protein (hsCRP) level, and coronary artery calcium (CAC) score to existing CVD risk assessment models results in small improvements in discrimination and risk reclassification; however, the clinical meaning of these changes is largely

unknown. Evidence on adding the ABI, hsCRP level, and CAC score to the Pooled Cohort Equations is limited. The USPSTF found inadequate evidence to assess whether treatment decisions guided by the ABI, hsCRP level, or CAC score, in addition to risk factors in existing CVD risk assessment models, leads to reduced incidence of CVD events or mortality. The USPSTF found adequate evidence to conceptually bound the harms of early detection and interventions as small. The USPSTF concludes that the current evidence is insufficient to assess the balance of benefits and harms of using the ABI, hsCRP level, or CAC score in risk assessment for CVD in asymptomatic adults to prevent CVD events.

b. A draft version of this recommendation statement was posted for public comment on the USPSTF website from January 16, 2018, to February 12, 2018. Many comments expressed belief that the evidence for risk assessment with CAC score was strong enough to warrant a separate positive recommendation. Although adding CAC score to traditional risk assessment models improved discrimination and reclassification, the USPSTF found inadequate evidence that this change would translate into improved health outcomes among asymptomatic patients. Several comments noted that the addition of nontraditional risk factors, especially CAC score, is useful for patients whose risk stratification is unclear or for those who fall into intermediate-risk groups. The USPSTF did not find convincing evidence that adding nontraditional risk factors to traditional risk factors improves reclassification in intermediate-risk groups. As clinical practice moves toward a single threshold for treatment, this concern may no longer be relevant in clinical decision making. Some comments also expressed belief that CAC score testing leads to better adherence to preventive therapies (ie, medications and lifestyle changes). The USPSTF carefully reviewed the available evidence and concluded that CAC score testing showed no benefit over traditional CVD risk assessment in preventive medication use or risk factor control.

2) **American College of Cardiology (ACC) 2018**, guideline on the management of cholesterol

a. In adults 40 to 75 years of age without diabetes mellitus and with LDL-C levels ≥70 mg/dL (≥1.8 mmol/L), at a 10-year ASCVD risk of ≥7.5%, start a moderate-intensity statin if a discussion of treatment options favors statin therapy. Risk-enhancing factors favor statin therapy. If risk status is uncertain, consider using coronary artery calcium (CAC) to improve specificity (see b below). If statins are indicated, reduce LDL-C levels by ≥30%, and if 10-year risk is ≥20%, reduce LDL-C levels by ≥50%

i. Risk-enhancing factors include family history of premature ASCVD; persistently elevated LDL-C levels ≥160 mg/dL (≥4.1 mmol/L); metabolic syndrome; chronic kidney disease; history of preeclampsia or premature menopause (age < 40 years); chronic inflammatory disorders (eg, rheumatoid arthritis, psoriasis, or chronic HIV); high-risk ethnic groups (eg, South Asian); persistent elevations of triglycerides ≥175 mg/dL (≥1.97 mmol/L); and, if measured in selected individuals, apolipoprotein B ≥130 mg/dL, high-sensitivity C-reactive protein ≥2.0 mg/L, ankle-brachial index < 0.9 and lipoprotein (a) ≥50 mg/dL or 125 nmol/L, especially at higher values of lipoprotein (a). Risk-enhancing factors may favor statin therapy in patients at 10-year risk of 5-7.5% (borderline risk).

ii. CAC score recommendation was class IIb, Level of Evidence B

b. In adults 40 to 75 years of age without diabetes mellitus and with LDL-C levels ≥70 mg/dL to 189 mg/dL (≥1.8-4.9 mmol/L), at a 10-year ASCVD risk of ≥7.5% to 19.9%, if a

decision about statin therapy is uncertain, consider measuring CAC. If CAC is zero, treatment with statin therapy may be withheld or delayed, except in cigarette smokers, those with diabetes mellitus, and those with a strong family history of premature ASCVD. A CAC score of 1 to 99 favors statin therapy, especially in those ≥55 years of age. For any patient, if the CAC score is ≥100 Agatston units or ≥75th percentile, statin therapy is indicated unless otherwise deferred by the outcome of clinician–patient risk discussion.

Other payer policies:

1) Evicore 2023
    a. Coronary calcium scoring as a standalone test is considered investigational in asymptomatic patients with any degree of CAD risk [CPT® 75571]
2) Aetna 2023
    a. Aetna considers a single calcium scoring by means of low-dose multi-slice CT angiography, ultrafast [electron-beam] CT, or spiral [helical] CT medically necessary for screening the following:
        i. Asymptomatic persons age 40 years and older with diabetes; *or*
        ii. Asymptomatic persons with an intermediate (10 % to 20 %) 10-year risk of cardiac events based on Framingham Risk Scoring or Pooled Cohort Equations
3) Wellmark BCBS 2022
    a. Coronary artery calcium (CAC) scoring detection by means of computed tomography (CT) (electron beam computed tomography [EBCT], helical computed tomography or multi-slice spiral CT [MSCT]) is considered not medically necessary for all indications, because the use of cardiac computed tomography (CT) coronary artery calcium (CAC) scoring has not been conclusively shown to impact net health outcomes.
4) Regence BCBS 2022
    a. The use of computed tomography to detect and quantify coronary artery calcification is considered investigational.
    b. For individuals who are asymptomatic with risk of CAD who receive CAC scoring, the evidence includes systematic reviews, RCTs, and nonrandomized studies. There is evidence on the predictive value of CAC score screening for cardiovascular disease among asymptomatic patients that demonstrates scanning can predict risk of CAD. However, evidence from high quality studies that demonstrate the use of CAC score measurement in clinical practice leads to changes in patient management or changes in individual risk behaviors that improve cardiac outcomes is lacking. The evidence is insufficient to determine the effects of the technology on health outcomes.

Equity concerns:

The 2018 ACC guideline (Grundy et al 2018) included a breakdown of CAC scoring based on racial and ethnic groups. South Asian men had similar scores to white men, but higher CACS than Black, Latino and Chinese Americans. South Asian women had similar CAC scores to other ethnicities. Hispanic people had similar CAC scoring to white people. Black people had significantly lower prevalence and severity of CACS. Given the lower scores in Black people, this test might underestimate the risk for CACS in this population. However, the Jackson Heart

Coronary Artery Calcium Score

Study measured CAC during follow-up. Among Black people, CAC predicted risk beyond the traditional risk factors.

Expert input:

David Sanger, cardiologist

> I use CAC frequently to better assess risk in intermediate risk patients. It is not useful in high risk or very low risk. And it is only designed for asymptomatic patients. Not for patients with chest pain

Abigail Khan, OHSU cardiology (comments from colleagues)

- We should consider the Lindholt trial which to my knowledge is the only RCT (attached). This is a negative trial overall but in the pre-specified subgroup of < 70, there was a benefit to screening (note that they didn't just do CAC though…)
- Wording in your document that states that there is "no clinical benefit" should be revised. There is a benefit, which is improved risk discrimination. The magnitude of this benefit is modest, but it is real, and has the potential to decrease costs. CAC scoring is cheap, and if it can avoid ~10 years of statins, it may be cost effective. Similarly, if CAC scoring allows providers to identify high risk individuals who benefit from statin, there is a potential clinical benefit from using a statin in someone who might not otherwise be prescribed it.
- I think what you mean is that no one has yet shown a decreased rate of death or other hard events from CAC. This is true, but this has mostly been unstudied. So—I think it's hard to say "There is no clinical benefit".
- I'm not sure how relevant the AHRQ review is to this discussion as it is largely about different types of non-invasive cardiac imaging done in totally different settings than CAC is used currently.

Coronary Artery Calcium Score

Public Comment Disposition

Commenter	Comment	Staff response
Kinsey Miller, MA	great idea to promote identifying and preventing cardiac issues by focusing on current and then potential areas to assist in lowering rates of cardia issue and focus on identifying patients who score within extra precautions range be given an opportunity to focus on wellness and prevention of cardiac issues, rather than full cardiac care. This may assist patients becoming more invested in their care, more productive and more wellness oriented and promotes the well being of cardiac testing, etc. as a positive intervention	Promotion of prevention of cardiac issues through diet, exercise, smoking cessation, and other lifestyle efforts should be part of routine patient care
Douglas Carr, CCO medical director	I support the HERC recommendation for no change to current policy for Coronary Artery Calcium scoring.	Thank you for your comment

Coronary Artery Calcium Score

HERC staff summary:

High quality systematic reviews and meta-analyses have found that coronary artery calcium scores provide some further discrimination in addition to traditional CVD risk assessment tools (i.e. Framingham or NIH risk calculators). However, there is no randomized clinical trial evidence that CACS as compared to traditional clinical care decreased the risk of death or major adverse cardiovascular events. USPSTF does not recommend this test for screening for CVD. Most major insurers are not covering this testing.

Cardiology experts recommend this test as a way to better improve risk discrimination among asymptomatic intermediate risk patients. CAC scores can better inform use of statin therapy in this population based on expert guidelines and expert input. However, the exact population for use of this test remains unclear.

HERC staff recommendation:

1) Continue non-coverage of coronary artery calcium screening based on unclear additional benefit to traditional CVD screening. Append this updated evidence review to the 2014 coverage guidance.
2) Update the entry to GN173 for CAC as shown below
    a. Update review date
    b. Remove statement on unknown harms of radiation based on expert input that the harms are no greater than with mammography or similar screening tests

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**
75571	CT coronary calcium scoring	Insufficient evidence of benefit~~, unclear harms of radiation exposure~~	~~August, 2013~~ August 2023 Coverage guidance

JAMA Internal Medicine | Original Investigation | LESS IS MORE

Evaluation of the Incremental Value of a Coronary Artery Calcium Score Beyond Traditional Cardiovascular Risk Assessment
A Systematic Review and Meta-analysis

Katy J. L. Bell, PhD; Sam White, MD; Omar Hassan, MD; Lin Zhu, PhD; Anna Mae Scott, PhD; Justin Clark, BA; Paul Glasziou, PhD

IMPORTANCE Coronary artery calcium scores (CACS) are used to help assess patients' cardiovascular status and risk. However, their best use in risk assessment beyond traditional cardiovascular factors in primary prevention is uncertain.

OBJECTIVE To find, assess, and synthesize all cohort studies that assessed the incremental gain from the addition of a CACS to a standard cardiovascular disease (CVD) risk calculator (or CVD risk factors for a standard calculator), that is, comparing CVD risk score plus CACS with CVD risk score alone.

EVIDENCE REVIEW Eligible studies needed to be cohort studies in primary prevention populations that used 1 of the CVD risk calculators recommended by national guidelines (Framingham Risk Score, QRISK, pooled cohort equation, NZ PREDICT, NORRISK, or SCORE) and assessed and reported incremental discrimination with CACS for estimating the risk of a future cardiovascular event.

FINDINGS From 2772 records screened, 6 eligible cohort studies were identified (with 1043 CVD events in 17 961 unique participants) from the US (n = 3), the Netherlands (n = 1), Germany (n = 1), and South Korea (n = 1). Studies varied in size from 470 to 5185 participants (range of mean [SD] ages, 50 [10] to 75.1 [7.3] years; 38.4%-59.4% were women). The *C* statistic for the CVD risk models without CACS ranged from 0.693 (95% CI, 0.661-0.726) to 0.80. The pooled gain in *C* statistic from adding CACS was 0.036 (95% CI, 0.020-0.052). Among participants classified as being at low risk by the risk score and reclassified as at intermediate or high risk by CACS, 85.5% (65 of 76) to 96.4% (349 of 362) did not have a CVD event during follow-up (range, 5.1-10.0 years). Among participants classified as being at high risk by the risk score and reclassified as being at low risk by CACS, 91.4% (202 of 221) to 99.2% (502 of 506) did not have a CVD event during follow-up

CONCLUSIONS AND RELEVANCE This systematic review and meta-analysis found that the CACS appears to add some further discrimination to the traditional CVD risk assessment equations used in these studies, which appears to be relatively consistent across studies. However, the modest gain may often be outweighed by costs, rates of incidental findings, and radiation risks. Although the CACS may have a role for refining risk assessment in selected patients, which patients would benefit remains unclear. At present, no evidence suggests that adding CACS to traditional risk scores provides clinical benefit.

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Multimedia
Supplemental content

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JAMA Intern Med. 2022;182(6):634-642. doi:10.1001/jamainternmed.2022.1262
Published online April 25, 2022. Last corrected on August 1, 2022.

Effective Health Care Program

Comparative Effectiveness Review
Number 171

Noninvasive Testing for Coronary Artery Disease

Archived: This report is greater than 3 years old. Findings may be used for research purposes, but should not be considered current.

Agency for Healthcare Research and Quality
Advancing Excellence in Health Care • www.ahrq.gov

Comparative Effectiveness Review

Number 171

Noninvasive Testing for Coronary Artery Disease

Prepared for:
Agency for Healthcare Research and Quality
U.S. Department of Health and Human Services
5600 Fishers Lane
Rockville, MD 20857
www.ahrq.gov

Contract No. 290-2012-00014-I

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AHRQ Publication No. 16-EHC011-EF
March 2016

Noninvasive Testing for Coronary Artery Disease

Structured Abstract

Objectives. This report evaluates the current state of evidence regarding effectiveness and harms of noninvasive technologies for the diagnosis of coronary artery disease (CAD) or dysfunction that results in symptoms attributable to myocardial ischemia in stable symptomatic patients who have no known history of CAD.

Data sources. Systematic searches of the following databases were conducted through July 2015: Ovid MEDLINE®, Cochrane CENTRAL, Cochrane Database of Systematic Reviews, and Evidence-Based Medicine Reviews–Health Technology Assessment. Bibliographies of relevant articles were also reviewed.

Review methods. Using predefined criteria, randomized controlled trials (RCTs) and observational studies comparing the effectiveness or safety of noninvasive cardiac testing—stress electrocardiography (ECG), stress echocardiography, single-photon emission computed tomography (SPECT), positron emission tomography, coronary computed tomography angiography (CCTA), and calcium scoring via computed tomography—with other noninvasive tests, usual care, or no testing were included. Analyses were stratified by pretest risk of CAD as reported by the authors. The quality of included studies was assessed, data extracted, and results summarized qualitatively and using meta-analysis where feasible. The strength of the evidence was assessed for primary outcomes to reflect the confidence in effect estimates: high strength of evidence (greatest confidence), moderate (moderate confidence), low (low confidence), and insufficient (no evidence or no confidence in the estimate).

Results. From 17,146 citations identified, 46 studies were included. Definition of pretest risk across studies varied. There was no clear difference in myocardial infarction (MI) or in all-cause mortality between different testing strategies across settings or pretest risk groups that included patients with intermediate pretest risk, based on low- to moderate-strength evidence from nine trials. Across studies, the frequency was low for all-cause mortality (0%–1.5% in outpatient settings, 0%–1.1% in emergency department [ED] settings past the initial visit) and for MI (0%–0.8% in outpatients, 0%–3% in ED settings). Invasive coronary angiography (ICA) was more common following CCTA than following various functional tests, with a large trial of CCTA versus functional testing providing high-strength evidence. Revascularization referral was more common following CCTA versus functional testing in general (high strength of evidence) and versus exercise ECG (low strength of evidence) but was similar compared with SPECT and usual care (low strength of evidence). In ED settings, additional testing was more common following CCTA than following SPECT (high strength of evidence) but less common versus usual care (moderate strength of evidence). Hospitalization was less common following CCTA than following usual care at the initial ED visit (moderate evidence for intermediate pretest risk; low evidence for low to intermediate pretest risk), but similar for CCTA and functional testing in outpatient settings (moderate strength of evidence). Few studies compared functional tests, and findings were inconsistent for ICA and revascularization referral; however, additional noninvasive testing was less common with SPECT than with exercise ECG (low strength of evidence for all outcomes). The impact of testing on post-test probability of CAD and

subsequent clinical decisions regarding treatment or further testing was not described in RCTs. Harms were rarely reported, and limited information regarding radiation exposure was provided.

Conclusions. A review of current studies found no clear differences between testing strategies across settings with regard to clinical or management outcomes on which to base recommendations for one strategy over another for any given pretest risk group that included patients with intermediate pretest risk. No conclusions regarding low-risk patients or high-risk patients without ACS are possible. Limited evidence from RCTs found no clear differences between CCTA and other strategies in clinical outcomes across risk groups, although anatomic testing may result in a higher frequency of referral for ICA and revascularization. The frequency of all-cause mortality and MI was low across studies in all settings. The absence of information on post-test risk stratification and subsequent decisionmaking precluded evaluation of the impact of testing on patient management or outcomes. Testing strategies vary in radiation exposure; there is inadequate comparative evidence to make judgments regarding exposure for the initial test or downstream testing. Assessment of harms was limited. Future research using more refined evidence-based definitions of pretest risk, coupled with information on post-test risk stratification, its impact on clinical management (treatment and referral for additional testing), and longer term followup to assess clinical outcomes, is needed to determine optimal testing strategies and roles of tests in different pretest risk groups.

JAMA | US Preventive Services Task Force | RECOMMENDATION STATEMENT

Risk Assessment for Cardiovascular Disease With Nontraditional Risk Factors

US Preventive Services Task Force Recommendation Statement

US Preventive Services Task Force

IMPORTANCE Cardiovascular disease (CVD) is the most common cause of death among adults in the United States. Treatment to prevent CVD events by modifying risk factors is currently informed by the Framingham Risk Score, the Pooled Cohort Equations, or similar CVD risk assessment models. If current CVD risk assessment models could be improved by adding more risk factors, treatment might be better targeted, thereby maximizing the benefits and minimizing the harms.

OBJECTIVE To update the 2009 US Preventive Services Task Force (USPSTF) recommendation on using nontraditional risk factors in coronary heart disease risk assessment.

EVIDENCE REVIEW The USPSTF reviewed the evidence on using nontraditional risk factors in CVD risk assessment, focusing on the ankle-brachial index (ABI), high-sensitivity C-reactive protein (hsCRP) level, and coronary artery calcium (CAC) score; the health benefits and harms of CVD risk assessment and treatment guided by nontraditional risk factors combined with the Framingham Risk Score or Pooled Cohort Equations compared with using either risk assessment model alone; and whether adding nontraditional risk factors to existing CVD risk assessment models improves measures of calibration, discrimination, and risk reclassification.

FINDINGS The USPSTF found adequate evidence that adding the ABI, hsCRP level, and CAC score to existing CVD risk assessment models results in small improvements in discrimination and risk reclassification; however, the clinical meaning of these changes is largely unknown. Evidence on adding the ABI, hsCRP level, and CAC score to the Pooled Cohort Equations is limited. The USPSTF found inadequate evidence to assess whether treatment decisions guided by the ABI, hsCRP level, or CAC score, in addition to risk factors in existing CVD risk assessment models, leads to reduced incidence of CVD events or mortality. The USPSTF found adequate evidence to conceptually bound the harms of early detection and interventions as small. The USPSTF concludes that the current evidence is insufficient to assess the balance of benefits and harms of using the ABI, hsCRP level, or CAC score in risk assessment for CVD in asymptomatic adults to prevent CVD events.

CONCLUSIONS AND RECOMMENDATION The USPSTF concludes that the current evidence is insufficient to assess the balance of benefits and harms of adding the ABI, hsCRP level, or CAC score to traditional risk assessment for CVD in asymptomatic adults to prevent CVD events. (I statement)

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Related article page 281 and **JAMA Patient Page** page 316

CME Quiz at jamanetwork.com/learning

Related article at jamacardiology.com

Author/Group Information: The US Preventive Services Task Force (USPSTF) members are listed at the end of this article.

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JAMA. 2018;320(3):272-280. doi:10.1001/jama.2018.8359
Published online July 10, 2018.

Circulation

CHOLESTEROL CLINICAL PRACTICE GUIDELINES

2018 AHA/ACC/AACVPR/AAPA/ABC/ACPM/ADA/AGS/APhA/ASPC/NLA/PCNA Guideline on the Management of Blood Cholesterol

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

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Key Words: AHA Scientific Statements ■ Guidelines ■ biomarkers, coronary artery calcium score ■ pharmacological ■ cardiovascular disease ■ cholesterol, LDL-cholesterol ■ diabetes mellitus ■ drug therapy ■ hydroxymethylglutaryl-CoA reductase inhibitors/statins ■ hypercholesterolemia ■ lipids ■ patient compliance ■ primary prevention ■ risk assessment ■ risk reduction discussion ■ risk treatment discussion, secondary prevention ■ ezetimibe ■ proprotein convertase subtilisin/kexin type 9 inhibitor (PCSK9) inhibitors

https://www.ahajournals.org/journal/circ

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The American Heart Association requests that this document be cited as follows: Grundy SM, Stone NJ, Bailey AL, Beam C, Birtcher KK, Blumenthal RS, Braun LT, de Ferranti S, Faiella-Tommasino J, Forman DE, Goldberg R, Heidenreich PA, Hlatky MA, Jones DW, Lloyd-Jones D, Lopez-Pajares N, Ndumele CE, Orringer CE, Peralta CA, Saseen JJ, Smith SC Jr, Sperling L, Virani SS, Yeboah J. 2018 AHA/ACC/AACVPR/AAPA/ABC/ACPM/ADA/AGS/APhA/ASPC/NLA/PCNA guideline on the management of blood cholesterol: a report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. *Circulation*. 2019;139:e1082–e1143. DOI: 10.1161/CIR.0000000000000625.

TABLE OF CONTENTS

TOP 10 TAKE-HOME MESSAGES TO REDUCE RISK OF ATHEROSCLEROTIC CARDIOVASCULAR DISEASE THROUGH CHOLESTEROL MANAGEMENT

1. **In all individuals, emphasize a heart-healthy lifestyle across the life course.** A healthy lifestyle reduces atherosclerotic cardiovascular disease (ASCVD) risk at all ages. In younger individuals, healthy lifestyle can reduce development of risk factors and is the foundation of ASCVD risk reduction. In young adults 20 to 39 years of age, an assessment of lifetime risk facilitates the clinician–patient risk discussion (see No. 6) and emphasizes intensive lifestyle efforts. In all age groups, lifestyle therapy is the primary intervention for metabolic syndrome.
2. **In patients with clinical ASCVD, reduce low-density lipoprotein cholesterol (LDL-C) with high-intensity statin therapy or maximally tolerated statin therapy.** The more LDL-C is reduced on statin therapy, the greater will be subsequent risk reduction. Use a maximally tolerated statin to lower LDL-C levels by ≥50%.
3. **In very high-risk ASCVD, use a LDL-C threshold of 70 mg/dL (1.8 mmol/L) to consider addition of nonstatins to statin therapy.** Very high-risk includes a history of multiple major ASCVD events or 1 major ASCVD event and multiple high-risk conditions. In very high-risk ASCVD patients, it is reasonable to add ezetimibe to maximally tolerated statin therapy when the LDL-C level remains ≥70 mg/dL (≥1.8 mmol/L). In patients at very high risk whose LDL-C level

remains ≥70 mg/dL (≥1.8 mmol/L) on maximally tolerated statin and ezetimibe therapy, adding a PCSK9 inhibitor is reasonable, although the long-term safety (>3 years) is uncertain and cost effectiveness is low at mid-2018 list prices.

4. **In patients with severe primary hypercholesterolemia (LDL-C level ≥190 mg/dL [≥4.9 mmol/L]), without calculating 10-year ASCVD risk, begin high-intensity statin therapy.** If the LDL-C level remains ≥100 mg/dL (≥2.6 mmol/L), adding ezetimibe is reasonable. If the LDL-C level on statin plus ezetimibe remains ≥100 mg/dL (≥2.6 mmol/L) and the patient has multiple factors that increase subsequent risk of ASCVD events, a PCSK9 inhibitor may be considered, although the long-term safety (>3 years) is uncertain and economic value is uncertain at mid-2018 list prices.
5. **In patients 40 to 75 years of age with diabetes mellitus and LDL-C ≥70 mg/dL (≥1.8 mmol/L), start moderate-intensity statin therapy without calculating 10-year ASCVD risk.** In patients with diabetes mellitus at higher risk, especially those with multiple risk factors or those 50 to 75 years of age, it is reasonable to use a high-intensity statin to reduce the LDL-C level by ≥50%.
6. **In adults 40 to 75 years of age evaluated for primary ASCVD prevention, have a clinician–patient risk discussion before starting statin therapy.** Risk discussion should include a review of major risk factors (eg, cigarette smoking, elevated blood pressure, LDL-C, hemoglobin A1C [if indicated], and calculated 10-year risk of ASCVD); the presence of risk-enhancing factors (see No. 8); the potential benefits of lifestyle and statin therapies; the potential for adverse effects and drug–drug interactions; consideration of costs of statin therapy; and patient preferences and values in shared decision-making.
7. **In adults 40 to 75 years of age without diabetes mellitus and with LDL-C levels ≥70 mg/dL (≥1.8 mmol/L), at a 10-year ASCVD risk of ≥7.5%, start a moderate-intensity statin if a discussion of treatment options favors statin therapy.** Risk-enhancing factors favor statin therapy (see No. 8). If risk status is uncertain, consider using coronary artery calcium (CAC) to improve specificity (see No. 9). If statins are indicated, reduce LDL-C levels by ≥30%, and if 10-year risk is ≥20%, reduce LDL-C levels by ≥50%.
8. **In adults 40 to 75 years of age without diabetes mellitus and 10-year risk of 7.5% to 19.9% (intermediate risk), risk-enhancing factors favor initiation of statin therapy (see No. 7).** Risk-enhancing factors include family history of premature ASCVD; persistently elevated LDL-C levels ≥160 mg/dL (≥4.1 mmol/L); metabolic syndrome; chronic kidney disease; history of preeclampsia or premature menopause (age <40 years); chronic inflammatory disorders (eg, rheumatoid arthritis, psoriasis, or chronic HIV); high-risk ethnic groups (eg, South Asian); persistent elevations of triglycerides ≥175 mg/dL (≥1.97 mmol/L); and, if measured in selected individuals, apolipoprotein B ≥130 mg/dL, high-sensitivity C-reactive protein ≥2.0 mg/L, ankle-brachial index <0.9 and lipoprotein (a) ≥50 mg/dL or 125 nmol/L, especially at higher values of lipoprotein (a). Risk-enhancing factors may favor statin therapy in patients at 10-year risk of 5-7.5% (borderline risk).
9. **In adults 40 to 75 years of age without diabetes mellitus and with LDL-C levels ≥70 mg/dL to 189 mg/dL (≥1.8-4.9 mmol/L), at a 10-year ASCVD risk of ≥7.5% to 19.9%, if a decision about statin therapy is uncertain, consider measuring CAC.** If CAC is zero, treatment with statin therapy may be withheld or delayed, except in cigarette smokers, those with diabetes mellitus, and those with a strong family history of premature ASCVD. A CAC score of 1 to 99 favors statin therapy, especially in those ≥55 years of age. For any patient, if the CAC score is ≥100 Agatston units or ≥75th percentile, statin therapy is indicated unless otherwise deferred by the outcome of clinician–patient risk discussion.
10. **Assess adherence and percentage response to LDL-C–lowering medications and lifestyle changes with repeat lipid measurement 4 to 12 weeks after statin initiation or dose adjustment, repeated every 3 to 12 months as needed.** Define responses to lifestyle and statin therapy by percentage reductions in LDL-C levels compared with baseline. In ASCVD patients at very high-risk, triggers for adding nonstatin drug therapy are defined by threshold LDL-C levels ≥70 mg/dL (≥1.8 mmol/L) on maximal statin therapy (see No. 3).

PREAMBLE

Since 1980, the American College of Cardiology (ACC) and American Heart Association (AHA) have translated scientific evidence into clinical practice guidelines with recommendations to improve cardiovascular health. These guidelines, which are based on systematic methods to evaluate and classify evidence, provide a foundation for the delivery of quality cardiovascular care. The ACC and AHA sponsor the development and publication of clinical practice guidelines without commercial

CT Colonography

Plain Language Summary:

Coverage question: Should OHP cover a relatively new diagnostic test that uses an X-ray scanner to examine the large bowel for cancer and polyps?

Should OHP cover this treatment? Yes, when a person with symptoms cannot have a colonoscopy.

HERC staff is seeking public comment on this topic.

Coverage Question: Should CT colonography be covered either population-wide or for a specific population(s) for screening, diagnosis or surveillance of colon cancer?

Question source: Holly Jo Hodges, CCO medical director

Background:

Computed tomographic colonography (CTC), also known as virtual colonoscopy, was developed as a minimally invasive method to examine the colon. This test has been suggested for use in screening and to detect abnormalities in the colon and rectum (for example, colorectal cancer [CRC] or colon polyps). CT colonography has the advantages of being noninvasive and not requiring sedation. If suspicious lesions are detected, the individual generally must undergo further testing via conventional colonoscopy.

CTC can be used for both screening for colon cancer in patients who have no symptoms and for diagnosis of colon pathology in patients who have symptoms such as rectal bleeding or a positive FIT stool test.

Standard screening tests for CRC include colonoscopy, FIT stool testing and flexible sigmoidoscopy. Standard diagnostic testing for individuals with symptoms concerning for possible CRC is colonoscopy.

Previous HSC/HERC reviews:

The last review of diagnostic CTC (CPT 74261-74262) was conducted in 2009 when new CPT codes were released for this procedure. At that time, the USPSTF found insufficient evidence to support the use of CTC for colon cancer screening. There was concern that CTC was inferior to colonoscopy for detecting colon masses and high level of concern about its inability to find smaller polyps. The recommendation at that time was for non-coverage. When line 662/GN173 were created, these codes were added without comment on the rationale.

CT Colonography

The last review of screening CTC (CPT 74263) was conducted in August 2021 in response to updated USPSTF recommendations for colon cancer screening. The updated USPSTF recommendation listed a variety of screening modalities, including CTC. Per the USPSTF review, colonoscopy, flexible sigmoidoscopy, hemoccult and FIT testing remained the only modalities for which use had shown both significant reduction in colorectal cancer incidence and morality. Based on this finding, HERC staff did not recommend adding coverage for CTC or for fecal DNA testing (Cologuard) or serum testing (Epi pro-Colon). CPT 74263 was left on line 502 and the guideline date of last review was updated.

Current Prioritized List/Coverage status:

74261-74262 (Computed tomographic (CT) colonography, diagnostic, including image postprocessing; with/without contrast material) are on line 662/GN173

74263 (Computed tomographic (CT) colonography, screening, including image postprocessing) is on line 502/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
74263, 81528, 81327, G0327	Screening CT colonography, FIT-DNA (Cologuard), mSEPT9, Chromoscopy	Insufficient evidence for use in population screening	August 2021

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
74261-74262	Computed tomographic (CT) colonography		December, 2009

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.

CT Colonography

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
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.

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.

CT Colonography

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 23, COLON CANCER SURVEILLANCE

Line 157

A) History and physical exam is indicated every 3 to 6 months for the first three years after primary therapy, then annually thereafter.
B) CEA testing should be performed every 2-3 months after colon resection for at least two years in patients with stage II or III disease for whom resection of liver metastases is clinically indicated
C) Colonoscopy is indicated every 3 to 5 years.
D) No other surveillance testing is indicated

Evidence:

1) **Lin 2021**, Screening for Colorectal Cancer Updated Evidence Report and Systematic Review for the US Preventive Services Task Force
    a) No studies found on the effect of CT colonography on colorectal cancer (CRC) incidence or mortality
        i) Only screening tests with evidence of effects on these outcomes are colonoscopy, flexible sigmoidoscopy, and FIT testing/hemoccult cards
    b) Nine fair- to good-quality studies (n = 6497) that evaluated screening CT colonography were included, 4 of which (n = 4821) also reported the test accuracy of colonoscopy
        i) Based on these studies, while both colonoscopy and CT colonography did not accurately identify all cancers, the number of CRCs in these studies was low and these studies were not powered to estimate the test accuracy for CRC
        ii) Based on 3 studies (n = 2290) that compared colonoscopy to a reference standard of CT colonography–enhanced colonoscopy or repeat colonoscopy, the per-person sensitivity for adenomas 10 mm or larger ranged from 0.89 (95% CI, 0.78-0.96) to 0.95 (95% CI, 0.74-0.99). The per-person sensitivity for adenomas 6 mm or larger ranged from 0.75 (95% CI, 0.63-0.84) to 0.93 (95% CI, 0.88-0.96). Specificity could be calculated only from 1 of the included studies and was 0.89 (95% CI, 0.86-0.91) for adenomas 10 mm or larger and 0.94 (95% CI, 0.92-0.96) for adenomas 6 mm or larger.
        iii) Based on 7 studies (n = 5328) evaluating CT colonography with bowel preparation, the sensitivity to detect adenomas 10 mm or larger ranged from 0.67 (95% CI, 0.45-0.84) to 0.94 (95% CI, 0.84-0.98) and specificity ranged from 0.86 (95% CI, 0.85-0.87) to 0.98 (95% CI, 0.96-0.99). Likewise, the sensitivity to detect adenomas 6 mm or larger ranged from 0.73 (95% CI, 0.58-0.84) to 0.98 (95% CI, 0.91-0.99) and specificity ranged from 0.80 (95% CI, 0.77-0.82) to 0.93 (95% CI, 0.90-0.96)
    c) Data from 17 studies (n = 89 073) showed little to no risk of serious adverse events (eg, symptomatic perforation) for screening CT colonography. While CT colonography may also require a follow-up colonoscopy, sufficient evidence was not found to estimate serious adverse events from colonoscopy follow-up. CT colonography also entails

exposure to low-dose ionizing radiation (range, 0.8 to 5.3 mSv), which may increase the risk of malignancy. Additionally, extracolonic findings on CT colonography were common (27 studies, n = 48 234). Approximately 1.3% to 11.4% of CT colonographies had potentially important extracolonic findings (CT Colonography Reporting and DataS ystem [C-RADS] category E4) that necessitated diagnostic follow-up. Additionally, 3.4% to 26.9% of CT colonographies had C-RADS category E3 findings, some of which may require additional workup because of incompletely characterized findings. Although some included studies did report the final diagnosis of extracolonic findings, it is still unclear if the detection of extracolonic findings represents an overall benefit (detection and treatment of clinically significant disease) or harm (unnecessary diagnostic workup or identification of condition not needing intervention).

Submitted literature:

None.

Expert guidelines:

1) **USPSTF 2021,** colorectal cancer screening
    a. Recommends CT colonography every 5 years as a screening modality
        i. Evidence available that CT colonography has reasonable accuracy to detect colorectal cancer and adenomas
        ii. No direct evidence evaluating effect of CT colonography on colorectal cancer mortality
        iii. Limited evidence about the potential benefits or harms of possible evaluation and treatment of incidental extracoloic findings, which are common. Extracolonic findings detected in 1.2%-11.4% of examinations, <3% required medical or surgical treatment
        iv. Additional harms include need for follow up abnormal results with colonoscopy
        v. Requires bowel preparation
        vi. Does not require sedation or anesthesia
        vii. More studies evaluating the direct effectiveness of screening with CT colonography on colorectal cancer mortality are needed, as well as more studies that report on long-term consequences of identifying extracolonic findings on colorectal cancer screening
2) **NCCN 2023,** colorectal cancer screening
    a. CT colonography is recommended for screening average risk patients every 5 years
    b. The methods recommended for average risk patient screening include colonoscopy, FIT, stool DNA testing (Cologuard), flexible sigmoidoscopy, and CT colonography
    c. CT colonography, also known as virtual colonoscopy or CTC, is evolving as a promising technique for CRC screening. CT colonography has the advantages of being noninvasive and not requiring sedation. The risk of test-related complications is also very low, and results of a systematic review suggest that CT colonography may be cost-effective when compared to colonoscopy. However, a positive finding requires a colonoscopy, and extracolonic findings—which are present in up to 16% of patients—pose a dilemma. These findings require further investigations and have a potential for both benefit and

harm. At the present time, data to determine the clinical impact of these incidental findings are insufficient.

d. Overall, available data indicate that CT colonography may be useful for the detection of larger polyps
e. CT colonography may be a more acceptable option to many individuals.

3) **American College of Gastroenterology 2021**, guideline for colorectal cancer screening
   a. We recommend colonoscopy and fecal immunochemical testing (FIT) as the primary screening modalities for CRC screening
      i. Strong recommendation, low quality of evidence
   b. We suggest consideration of the following screening tests for individuals unable or unwilling to undergo colonoscopy or FIT: flexible sigmoidoscopy, multitarget stool DNA test, CT colonography or colon capsule
      i. Conditional recommendation, very low quality of evidence
4) **American Cancer Society 2018**, guidelines for colorectal cancer screening for average risk adults
   a. Recommended screening tests
      i. Stool-based tests
         1. Fecal immunochemical test every year
         2. High-sensitivity, guaiac-based fecal occult blood test every year
         3. Multitarget stool DNA test every 3 years
      ii. Structural examinations
         1. Colonoscopy every 10 years
         2. CT colonography every 5 years
         3. Flexible sigmoidoscopy every 5 years
   b. CTC has sensitivity and specificity for cancer and advanced adenoma detection comparable to colonoscopy
   c. Incidental extracolonic findings may require workup, with unclear benefit-burden balance
   d. Exposure to low-dose radiation
   e. Colonoscopy required if test is positive
   f. Requires full bowel cleansing
5) **American College of Physicians 2023,** screening for colorectal cancer in average risk adults
   a. Clinicians should not use stool DNA, computed tomography colonography, capsule endoscopy, urine, or serum screening tests for colorectal cancer

Other payer policies:

2) Noridian 2023 [Oregon CMS LCD], Colon cancer screening
   a) CT colonography is not listed as a covered procedure for colon cancer screening
   b) Note: a retired Noridian LCD covering Oregon listed CTC as a diagnostic test only
3) CMS LCD 2019 (southeastern US)
   a) Virtual colonoscopy is only indicated in those patients in whom a diagnostic or surveillance instrument colonoscopy of the entire colon is incomplete due to an inability to fully pass the colonoscope proximally, and a repeat attempt is not indicated, or in

patients with a valid contraindication to the safe performance of an instrument colonoscopy. Incomplete colonoscopy must be due to 1 of the following:
   i) An obstructing neoplasm
   ii) Intrinsic scarring, stricture, aberrant anatomy, or obstruction from prior surgery, radiation, or diverticular disease
   iii) Extrinsic compression
b) There are few absolute contraindications to instrument colonoscopy. Relative contraindications do not create medical necessity for using CT colonography as a screening procedure, and the above indications must still be met. The following relative contraindications to instrument colonoscopy may be indications for CT colonography if well documented in the medical record:
   i) Severe coagulopathy
   ii) Long-term anticoagulation
   iii) Increased sedation risk (such as from severe chronic obstructive pulmonary disease (COPD) or previous anesthesia adverse reaction)
c) CT colonography is not covered when used for screening, or in the absence of signs or symptoms of disease, regardless of family history or other risk factors for the development of colonic disease. CT colonography is not covered when used as an alternative to instrument colonoscopy for screening or in the absence of signs or symptoms of disease. CT colonography is not covered following incomplete colonoscopy if the reason for the colonoscopy is other than one of those described above. CT colonography is intended for use in pre-operative planning when imaging of the non-visualized colon proximal to the obstruction is necessary in making decisions involving the approach to the patient.

4) CMS 2019 LCD (Northeastern US)
   a) CT colonography is indicated in those patients in whom a diagnostic (performed for signs/symptoms of disease) optical colonoscopy of the entire colon is incomplete. Failure to complete the optical colonoscopy may be secondary to conditions such as, but not limited to, an obstructing neoplasm, stricture, tortuosity, spasm, redundant colon diverticulitis, extrinsic compression or aberrant anatomy scarring from prior surgery.
   b) CT colonography is indicated when a board certified or board eligible gastroenterologist, a surgeon trained in endoscopy or a physician with equivalent endoscopic training determines from an evaluation of the patient that optical colonoscopy cannot be safely attempted.
   c) CT colonography is also indicated for the evaluation of a submucosal abnormality detected on colonoscopy or other imaging study.
   d) CT colonography should be performed soon after the failed standard colonoscopy, if appropriate, so that the patient will not have to endure repeat colonic preparation.
5) United Healthcare 2023
   a) Computed tomographic colonography is proven and medically necessary for any of the following:
      i) As a diagnostic tool for individuals on anticoagulation therapy
      ii) As a diagnostic tool for symptomatic individuals who are unable to undergo or tolerate a complete colonoscopy
      iii) As a screening test for colon cancer for average risk individuals
6) Aetna 2022, virtual gastrointestinal endoscopy

CT Colonography

a) Aetna considers virtual colonoscopy using computed tomography (CT colonography) performed every 5 years a medically necessary preventive service for colorectal cancer screening of average-risk asymptomatic persons 45 years of age or older.
b) Aetna considers diagnostic virtual colonoscopy medically necessary for colonic evaluation of:
    i) Symptomatic members with a known colonic obstruction when standard optical colonoscopy is contraindicated; *or*
    ii) Symptomatic members with an incomplete colonoscopy (e.g., due to diverticulosis, obstructive or stenosing colonic lesions, or redundant colon); *or*
    iii) Members who are receiving chronic anti-coagulation that cannot be interrupted; *or*
    iv) Members with complications from prior optical colonoscopy; *or*
    v) Members with active diverticulitis and an increased risk of perforation; *or*
    vi) Members with increased sedation risk (e.g., chronic obstructive pulmonary disease or previous adverse reaction to anesthesia); *or*
    vii) Members who are symptomatic and require colon examination less than 12 weeks after colon surgery

Expert input:

Dr. David Lieberman, Chief of Gastroenterology at OHSU:

…the data on CTC for screening is primarily limited to point sensitivity and specificity, not colorectal cancer (CRC) outcomes (such as mortality or incidence). However, we can infer that if CTC detects important pathology, and if patients then have colonoscopy, we would expect CRC mortality and incidence reductions.

The problems with widespread use of CTC for screening are

1. Cost – most cost-effectiveness studies show that this is not cost-effective relative to FIT or primary screening colonoscopy
2. Bowel prep. The bowel prep must be excellent to reduce likelihood of false positive studies. If patients have a (+) CTC, then they will need another prep for colonoscopy. From patient adherence standpoint, this is an important negative.

That said, in selected situations, CTC should be covered.

1. Patients with incomplete colonoscopy. Incomplete exams due to tortuous or redundant colon are an ideal example of where CTC can be helpful, and rule out important pathology in the portions of the colon not reached at colonoscopy.
2. Colonic strictures. This assumes the stricture has been fully interrogated and deemed benign.

You mention inability to tolerate sedation as possibly another reason to perform CTC. Here, the question is whether the patient would be a candidate for any subsequent evaluation if something is detected – i.e. colonoscopy or surgery. If the patient would not be a candidate for any follow-up after the CTC, one may argue that the CTC has not changed management. I think this is a tricky situation, that would require individualization based on patient circumstances.

To address your question, I think CTC should be available under specific circumstances, but I would not be in favor of approval for general screening due to the issues raised above.

CT Colonography

Public Comment Disposition

Commenter	Comment	Staff response
Douglas Carr, CCO medical director	I support the HERC recommendation for limited coverage of CT colonography as outlined	Thank you for your comment

CT Colonography

HERC staff summary:

Screening CT colonography is a recommended test for screening for colorectal cancer (CRC) by the USPSTF and NCCN. However, CT colonography has not been shown to impact CRC incidence or mortality, unlike colonoscopy or FIT stool testing. CT colonography has the advantage of being non-invasive, not requiring sedation or anesthesia, and having similar sensitivity and specificity for detection of CRC and polyps >6mm to colonoscopy, and may be more acceptable than colonoscopy to some patients. CT colonography has the disadvantages of requiring colonoscopy for follow up of abnormal results, low dose radiation exposure, and a high rate of extracolonic findings that may require additional testing and/or treatment. Payers vary in whether they cover CT colonography for any average risk adult for CRC screening. Many payers surveyed cover screening CT colonography when colonoscopy is not feasible due to known colonic obstruction, stricture, or compression, or due to patient coagulopathy or co-morbid conditions which make sedation or anesthesia unsafe. Many payers also cover CT colonography when a screening colonoscopy is unable to be completed with the CT colonography can be done on the same day. Oregon experts do not recommend CT colonography for routine screening.

Previous reviews of stool DNA based screening (Cologuard) found that this test has much lower sensitivity and specificity for finding polyps that either colonoscopy or CT colonography. However, this test is recommended as a screening test by the USPSTF and expert groups.

Diagnostic CT colonography is recommended by expert groups and generally covered by other payers as a method for evaluating symptomatic patients only when colonoscopy is unable to be completed due to known colonic obstruction, stricture, or compression, or due to patient coagulopathy or co-morbid conditions which make sedation or anesthesia unsafe. Oregon experts recommend use of CT colonography in a limited population for this indication.

HERC staff recommendations:

1) Diagnostic CT colonography: Add coverage only for symptomatic individuals when colonoscopy cannot be completed
    a. Advise HSD to add CPT 74261-74262 (Computed tomographic (CT) colonography, diagnostic, including image postprocessing; with/without contrast material) to the Diagnostic Procedures File
    b. 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
    c. Add a new Diagnostic guideline as shown below

CT Colonography

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
~~74261-74262~~	~~Computed tomographic (CT) colonography~~		~~December, 2009~~

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.

2) Screening CT colonography
    a. Add coverage only for patients unable to undergo colonoscopy due to colon structural problem
        i. 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
        ii. Modify GN106 as shown below
            1. Vaccine related recommended changes based on the 2023 vaccine review as shown in purple

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
~~74263,~~ 81528, 81327, G0327	~~Screening CT colonography,~~ FIT-DNA (Cologuard), mSEPT9, Chromoscopy	Insufficient evidence for use in population screening	~~August 2021~~ August 2923

CT Colonography

GUIDELINE NOTE 106, PREVENTIVE SERVICES

Lines 3,622

Included on Line 3 are the following preventive services:

E) 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.

F) 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.

G) 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.

H) 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 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

~~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 23, COLON CANCER SURVEILLANCE

Line 157

A) History and physical exam is indicated every 3 to 6 months for the first three years after primary therapy, then annually thereafter.
B) CEA testing should be performed every 2-3 months after colon resection for at least two years in patients with stage II or III disease for whom resection of liver metastases is clinically indicated
C) Colonoscopy is indicated every 3 to 5 years.
D) No other surveillance testing is indicated

JAMA | US Preventive Services Task Force | EVIDENCE REPORT

Screening for Colorectal Cancer
Updated Evidence Report and Systematic Review for the US Preventive Services Task Force

Jennifer S. Lin, MD; Leslie A. Perdue, MPH; Nora B. Henrikson, PhD; Sarah I. Bean, MPH; Paula R. Blasi, MPH

IMPORTANCE Colorectal cancer (CRC) remains a significant cause of morbidity and mortality in the US.

OBJECTIVE To systematically review the effectiveness, test accuracy, and harms of screening for CRC to inform the US Preventive Services Task Force.

DATA SOURCES MEDLINE, PubMed, and the Cochrane Central Register of Controlled Trials for relevant studies published from January 1, 2015, to December 4, 2019; surveillance through March 26, 2021.

STUDY SELECTION English-language studies conducted in asymptomatic populations at general risk of CRC.

DATA EXTRACTION AND SYNTHESIS Two reviewers independently appraised the articles and extracted relevant study data from fair- or good-quality studies. Random-effects meta-analyses were conducted.

MAIN OUTCOMES AND MEASURES Colorectal cancer incidence and mortality, test accuracy in detecting cancers or adenomas, and serious adverse events.

RESULTS The review included 33 studies (n = 10 776 276) on the effectiveness of screening, 59 (n = 3 491 045) on the test performance of screening tests, and 131 (n = 26 987 366) on the harms of screening. In randomized clinical trials (4 trials, n = 458 002), intention to screen with 1- or 2-time flexible sigmoidoscopy vs no screening was associated with a decrease in CRC-specific mortality (incidence rate ratio, 0.74 [95% CI, 0.68-0.80]). Annual or biennial guaiac fecal occult blood test (gFOBT) vs no screening (5 trials, n = 419 966) was associated with a reduction of CRC-specific mortality after 2 to 9 rounds of screening (relative risk at 19.5 years, 0.91 [95% CI, 0.84-0.98]; relative risk at 30 years, 0.78 [95% CI, 0.65-0.93]). In observational studies, receipt of screening colonoscopy (2 studies, n = 436 927) or fecal immunochemical test (FIT) (1 study, n = 5.4 million) vs no screening was associated with lower risk of CRC incidence or mortality. Nine studies (n = 6497) evaluated the test accuracy of screening computed tomography (CT) colonography, 4 of which also reported the test accuracy of colonoscopy; pooled sensitivity to detect adenomas 6 mm or larger was similar between CT colonography with bowel prep (0.86) and colonoscopy (0.89). In pooled values, commonly evaluated FITs (14 studies, n = 45 403) (sensitivity, 0.74; specificity, 0.94) and stool DNA with FIT (4 studies, n = 12 424) (sensitivity, 0.93; specificity, 0.85) performed better than high-sensitivity gFOBT (2 studies, n = 3503) (sensitivity, 0.50-0.75; specificity, 0.96-0.98) to detect cancers. Serious harms of screening colonoscopy included perforations (3.1/10 000 procedures) and major bleeding (14.6/10 000 procedures). CT colonography may have harms resulting from low-dose ionizing radiation. It is unclear if detection of extracolonic findings on CT colonography is a net benefit or harm.

CONCLUSIONS AND RELEVANCE There are several options to screen for colorectal cancer, each with a different level of evidence demonstrating its ability to reduce cancer mortality, its ability to detect cancer or precursor lesions, and its risk of harms.

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JAMA. 2021;325(19):1978-1997. doi:10.1001/jama.2021.4417
Corrected on July 20, 2021.

CME

ACG Clinical Guidelines: Colorectal Cancer Screening 2021

Aasma Shaukat, MD, MPH, FACG[1,2], Charles J. Kahi, MD, MSc, FACG[3-7], Carol A. Burke, MD, FACG[4], Linda Rabeneck, MD, MPH, MACG[5], Bryan G. Sauer, MD, MSc, FACG (GRADE Methodologist)[6] and Douglas K. Rex, MD, MACG[3]

Colorectal cancer (CRC) is the third most common cancer in men and women in the United States. CRC screening efforts are directed toward removal of adenomas and sessile serrated lesions and detection of early-stage CRC. The purpose of this article is to update the 2009 American College of Gastroenterology CRC screening guidelines. The guideline is framed around several key questions. We conducted a comprehensive literature search to include studies through October 2020. The inclusion criteria were studies of any design with men and women age 40 years and older. Detailed recommendations for CRC screening in average-risk individuals and those with a family history of CRC are discussed. We also provide recommendations on the role of aspirin for chemoprevention, quality indicators for colonoscopy, approaches to organized CRC screening and improving adherence to CRC screening. CRC screening must be optimized to allow effective and sustained reduction of CRC incidence and mortality. This can be accomplished by achieving high rates of adherence, quality monitoring and improvement, following evidence-based guidelines, and removing barriers through the spectrum of care from noninvasive screening tests to screening and diagnostic colonoscopy. The development of cost-effective, highly accurate, noninvasive modalities associated with improved overall adherence to the screening process is also a desirable goal.

SUPPLEMENTARY MATERIAL accompanies this paper at http://links.lww.com/AJG/B890 and http://links.lww.com/AJG/B891

Am J Gastroenterol 2021;116:458–479. https://doi.org/10.14309/ajg.0000000000001122

INTRODUCTION

In the United States, colorectal cancer (CRC) ranks second to lung cancer as a cause of cancer mortality and is the third most commonly occurring cancer in both men and women. A study estimated that in 2020 approximately 147,950 new CRC cases would have been diagnosed and 53,200 individuals would have died of the disease (1). Between 2011 and 2015, the average annual incidence rates per 100,000 population were 45.9 and 34.6 for men and women respectively (2). CRC incidence and mortality rates have shown a steady decline of approximately 1.7% and 3.2%, respectively per year. The decline began in the mid 1980s and has accelerated since the early 2000s. It is believed to be driven by changes in risk factors, early detection of cancer through CRC screening, and removal of precancerous polyps with colonoscopy, in addition to advances in surgical and treatment approaches.

Most CRCs develop through the adenoma-carcinoma sequence, presenting opportunities to prevent cancer by removing its precursor lesions, in addition to identifying CRC in its earliest, curable stages (3). Approximately 70% of sporadic CRCs develop from adenomatous polyps and 25%–30% arise from sessile serrated lesions (SSLs) through the SSL-to-carcinoma pathway (4). CRC screening efforts are directed toward removal of adenomas, SSLs and detection of early-stage CRC. Certain screening modalities such as colonoscopy, sigmoidoscopy, CT colonography and to a lesser extent stool-based testing, will detect advanced adenomatous polyps, whereas colonoscopy is optimal for the detection of SSLs. Endoscopic removal of polyps reduces CRC incidence and CRC mortality (5,6). Given new evidence regarding enhancing screening adherence, newer methods for CRC screening, and evidence to support the efficacy of screening, the purpose of this article is to update the 2009 American College of Gastroenterology (ACG) CRC screening guideline (7).

METHODS

The guideline is framed around several key questions which are outlined below. The key questions were developed by the authors and vetted through the ACG leadership. We placed emphasis on having practical recommendations that would be helpful for practicing providers in the United States. We conducted a focused literature search and used existing guidelines and technical reviews on CRC screening by key organizations. We used a modified Grading of Recommendations, Assessment, Development and Evaluation methodology (8) to evaluate the quality of the evidence and strength of recommendation. We used "we recommend" for strong recommendations and "we suggest" for conditional recommendations. Two Grading of Recommendations, Assessment, Development

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Received March 17, 2020; accepted December 2, 2020

and Evaluation–trained methodologists assisted in evidence synthesis and grading of the evidence.

Literature search

We conducted a comprehensive literature search with the help of a librarian from the University of Minnesota on the key questions using Ovid (MEDLINE), EMBASE, and the Cochrane databases from 1980 to October 2020. Emphasis was placed on studies from 2008 onward, since publication of the last guideline. The references for review articles were also searched. A detailed search strategy is provided in Supplementary Appendix 1 (see Supplementary Digital Content 1, http://links.lww.com/AJG/B890). The inclusion criteria were observational studies and randomized controlled trials (RCTs) with men and women age 40 years and older. Exclusion criteria were patients/populations with familial cancer syndromes (hereditary nonpolyposis colorectal cancer and polyposis syndromes) and special populations such as patients with human immunodeficiency virus or previous transplant. Outcomes included were CRC incidence, CRC mortality, incidence of colorectal advanced neoplasia defined as adenomas or SSL ≥10 mm, ≥3 adenomas/SSL, any villous histology, high-grade dysplasia or submucosal cancer in a colonic polyp or a traditional serrated adenoma, and harms of screening (complications, anesthesia-related complications, deaths, and overdiagnosis through additional testing).

Key questions

KQ1a. In average-risk individuals, what are the effectiveness and harms of CRC screening in reducing the incidence of advanced neoplasia and CRC, and CRC mortality?
KQ1b. How does the effectiveness vary by modality, age, and race?
KQ2. In average-risk individuals, how does the effectiveness of CRC screening vary by screening interval in reducing colorectal advanced neoplasia incidence, CRC incidence, and CRC mortality?
KQ3. In individuals with a family history of CRC or adenomatous polyps, what is the effectiveness of CRC screening in reducing CRC incidence and CRC mortality?
KQ4. In individuals with a family history of CRC or adenomatous polyps, how does the effectiveness of CRC screening vary by screening interval in reducing colorectal advanced neoplasia incidence, CRC incidence, and CRC mortality?
KQ5. In individuals with a family history of CRC or adenomatous polyps, how does the effectiveness of CRC screening vary by screening modality in reducing colorectal advanced neoplasia incidence, CRC incidence, and CRC mortality?
KQ6. What are the quality indicators for different modalities of CRC screening associated with diagnostic performance of the screening test and incidence of postcolonoscopy colorectal cancer?
KQ7. What are the effectiveness and harms of aspirin chemoprevention for the endpoints of reduction in the incidence of CRC or mortality of CRC?
KQ8. What interventions improve adherence to CRC screening and to each modality of screening?
KQ9. What interventions improve adherence to follow-up of a positive CRC screening test, such as fecal immunochemical testing (FIT)?

RESULTS

See Table 1 for summary and Supplementary Appendix 2 (see Supplementary Digital Content 2, http://links.lww.com/AJG/B891) for updates from the 2009 guideline. Results for individual questions are provided below.

KQ1a. In average-risk individuals, what are the effectiveness and harms of CRC screening in reducing incidence of advanced neoplasia and CRC, and CRC mortality?
KQ1b. How does the effectiveness vary by screening modality, age, and race?

Recommendations

1. We recommend CRC screening in average-risk individuals between ages 50 and 75 years to reduce incidence of advanced adenoma, CRC, and mortality from CRC.

Strong recommendation; moderate-quality evidence

2. We suggest CRC screening in average-risk individuals between ages 45 and 49 years to reduce incidence of advanced adenoma, CRC, and mortality from CRC.

Conditional recommendation; very low-quality evidence

3. We suggest that a decision to continue screening beyond age 75 years be individualized.

Conditional recommendation; very low-quality evidence

4. We recommend colonoscopy and FIT as the primary screening modalities for CRC screening.

Strong recommendation; low-quality evidence

5. We suggest consideration of the following screening tests for individuals unable or unwilling to undergo colonoscopy or FIT: flexible sigmoidoscopy, multitarget stool DNA test, CT colonography or colon capsule.

Conditional recommendation; very low-quality evidence

6. We suggest against Septin 9 for CRC screening.

Conditional recommendation, very low-quality of evidence

DISCUSSION

The "ideal" screening test should be noninvasive, have high sensitivity and specificity, be safe, readily available, convenient, and inexpensive. For CRC screening, there are multiple approved tests and strategies, each with its strengths and weaknesses. In some instances the "best" screening test can be considered the one that is acceptable to the patient and gets completed. One approach to CRC screening tests is to divide them as 1-step (direct) tests (i.e., colonoscopy, which is diagnostic and therapeutic) or 2-step tests that require colonoscopy if positive, to complete the screening process. All screening tests other than colonoscopy are 2-step tests. A major limitation of non–colonoscopy-based CRC screening tests (eg, stool-based, flexible sigmoidoscopy, CT colonography [CTC], or colon capsule [CC]) is that a positive test requires a follow-up colonoscopy. This 2-step testing approach represents a continuum of screening, requires strong systems-based support to complete the screening cascade, and is more effectively applied in organized screening (9). In the United States, there are few select health care systems with organized, programmatic screening, and most screening is accomplished with a 1-step opportunistic approach. Because the focus of the guideline is on providers practicing in the United States, the review highlights options for CRC screening currently in use, which mainly include colonoscopy, and in an

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CLINICAL GUIDELINE

Screening for Colorectal Cancer in Asymptomatic Average-Risk Adults: A Guidance Statement From the American College of Physicians (Version 2)

Amir Qaseem, MD, PhD, MHA; Curtis S. Harrod, PhD, MPH; Carolyn J. Crandall, MD, MS; and Timothy J. Wilt, MD, MPH, for the Clinical Guidelines Committee of the American College of Physicians*

Description: The purpose of this updated guidance statement is to guide clinicians on screening for colorectal cancer (CRC) in asymptomatic average-risk adults. The intended audience is all clinicians. The population is asymptomatic adults at average risk for CRC.

Methods: This updated guidance statement was developed using recently published and critically appraised clinical guidelines from national guideline developers since the publication of the American College of Physicians' 2019 guidance statement, "Screening for Colorectal Cancer in Asymptomatic Average-Risk Adults." The authors searched for national guidelines from the United States and other countries published in English using PubMed and the Guidelines International Network library from 1 January 2018 to 24 April 2023. The authors also searched for updates of guidelines included in the first version of our guidance statement. The Appraisal of Guidelines for Research and Evaluation II (AGREE II) instrument was used to assess the quality of eligible guidelines. Two guidelines were selected for adoption and adaptation by raters on the basis of the highest average overall AGREE II quality scores. The evidence reviews and modeling studies for these 2 guidelines were also used to synthesize the evidence of diagnostic test accuracy, effectiveness, and harms of CRC screening interventions and to develop our guidance statements.

Guidance Statement 1: *Clinicians should start screening for colorectal cancer in asymptomatic average-risk adults at age 50 years.*

Guidance Statement 2: *Clinicians should consider not screening asymptomatic average-risk adults between the ages of 45 to 49 years. Clinicians should discuss the uncertainty around benefits and harms of screening in this population.*

Guidance Statement 3: *Clinicians should stop screening for colorectal cancer in asymptomatic average-risk adults older than 75 years or in asymptomatic average-risk adults with a life expectancy of 10 years or less.*

Guidance Statement 4a: *Clinicians should select a screening test for colorectal cancer in consultation with their patient based on a discussion of benefits, harms, costs, availability, frequency, and patient values and preferences.*

Guidance Statement 4b: *Clinicians should select among a fecal immunochemical or high-sensitivity guaiac fecal occult blood test every 2 years, colonoscopy every 10 years, or flexible sigmoidoscopy every 10 years plus a fecal immunochemical test every 2 years as a screening test for colorectal cancer.*

Guidance Statement 4c: *Clinicians should not use stool DNA, computed tomography colonography, capsule endoscopy, urine, or serum screening tests for colorectal cancer.*

Ann Intern Med. doi:10.7326/M23-0779 **Annals.org**
For author, article, and disclosure information, see end of text.
This article was published at Annals.org on 1 August 2023.

Colorectal cancer (CRC) is the fourth highest in incidence (153 020) and second in mortality (52 550) among cancer types in the United States (1). Between 2000 and 2019, CRC incidence slightly increased in persons younger than 50 years (6.0 to 8.7 per 100 000), decreased in those aged 50 to 64 years (85 to 74 per 100 000), and more sharply decreased in persons aged 65 years or older (305 to 158 per 100 000); decreases may be attributable to screening (2). Incidence of CRC varies by biological sex and race and ethnicity, with males and non-Hispanic American Indian or Alaska Native persons and non-Hispanic Black persons having the highest rates; however, absolute differences between biological sex and racial and ethnic groups are small (2).

See also:

Editorial comment. 1127
Summary for Patients I-20

Web-Only
Supplement

* This paper, authored by Amir Qaseem, MD, PhD, MHA; Curtis S. Harrod, PhD, MPH; Carolyn J. Crandall, MD, MS; and Timothy J. Wilt, MD, MPH, was developed for the Clinical Guidelines Committee of the American College of Physicians. Individuals who served on the Clinical Guidelines Committee from initiation of the project until its approval were Timothy J. Wilt, MD, MPH† (Chair); Carolyn J. Crandall, MD, MS† (Vice Chair); Ethan M. Balk, MD, MPH†; Thomas G. Cooney, MD†; J. Thomas Cross, Jr., MD, MPH†; Nick Fitterman, MD†; Lauri A. Hicks, DO‡; Jennifer S. Lin, MD, MCR‡; Michael Maroto, JD, MBA†§; Adam J. Obley, MD†; Douglas K. Owens, MD, MS‡; Jeffrey Tice, MD†; and Janice E. Tufte†§. Members of the ACP Division of Clinical Policy: Kate Carroll, MPH‡; Itziar Etxeandia-Ikobaltzeta, PharmD, PhD‡; Curtis Harrod, PhD, MPH†; Amir Qaseem, MD, PhD, MHA†; Tatyana Shamliyan, MD, MS†; and Jennifer Yost, PhD, RN†. Approved by the ACP Board of Regents on 24 April 2023.
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Fibromyalgia 2023 Review

Plain Language Summary:

Coverage question: Should additional treatments for fibromyalgia, a long-lasting disorder that causes pain and tenderness throughout the body, as well as fatigue and trouble sleeping, be covered?

Should OHP cover this treatment? No, there are no effective treatments for this condition, although there are effective treatments for symptoms of fibromyalgia such as joint pain or mood issues that are already covered. (Some treatments for fibromyalgia, such as physical therapy and certain medications are not covered for fibromyalgia in the absence of other related conditions.)

Coverage Question: Should fibromyalgia be moved to a covered line; if so, what treatments should be paired on the covered line?

Question source: Dr. Hillary Lane, family physician from Forest Grove

Background: Fibromyalgia is a chronic disorder that causes pain and tenderness throughout the body, as well as fatigue and trouble sleeping. There is no cure for fibromyalgia, rather treatment is focused on managing symptoms. Treatment typically involves a combination of exercise or other movement therapies, psychological and behavioral therapy, and medications such as pregabalin.

Dr. Lane spoke at the June 2023 HERC staff listening session about the problems with non-coverage of fibromyalgia. She specifically requested consideration for coverage of SNRIs (such as duloxetine), physical therapy, exercise therapy, and muscle relaxers, as well as office visits for this condition.

Previous HSC/HERC reviews:

The prioritization of fibromyalgia was discussed at length in October 2013 as part of the 2014 biennial review, and no changes made. The 2013 review found that exercise and antidepressant therapy both had evidence of effectiveness for the treatment of fibromyalgia. It was determined that antidepressant therapy would be available if the patient had any comorbid depression or anxiety symptoms and that exercise was not available as a paid treatment for any condition.

Fibromyalgia was again discussed at length in August 2018, which multiple stakeholders testifying about the need for coverage and the effectiveness of various treatments. No changes were made based on that review. Fibromyalgia was again considered for reprioritization in May 2019, and the line prioritization scoring was reviewed and found to be appropriate based on the lack of evidence of effectiveness of treatments for this condition. That review also noted that exercise and antidepressant therapy could be effective but were either not covered for other conditions (exercise) or were readily available for patients with any psychiatric comorbidities (antidepressants). The treatment of

fibromyalgia with acupuncture was discussed in November 2022 and not added due to insufficient evidence of effectiveness of this treatment.

Current Prioritized List/Coverage status:

Fibromyalgia (ICD-10-CM F79.7) is located on line 531 FIBROMYALGIA, CHRONIC FATIGUE SYNDROME, AND RELATED DISORDERS

Evidence:

Literature published 2018 or later (since date of last review)

1) **Mascarenhas 2021**, Association of therapies with reduced pain and improved quality of life in patients with fibromyalgia: a systematic review and meta-analysis
    a. K=224 trials (N=29,962)
        i. Populations included: people with fibromyalgia according to any of the ACR criteria, regardless of age or sex, from any health care setting (95% of participants were women)
        ii. Interventions evaluated (compared with control or placebo intervention): antiemetics, cognitive behavioral therapy, TENS, hyperbaric oxygen therapy, magnetic field therapy, acupuncture, exercise, manual therapy, TMS, nutritional supplements, analgesics, EEG neurofeedback, CNS depressants, antidepressants, massage, anticonvulsants, balneotherapy, vibratory stimulation therapy, growth hormone
    b. High-quality evidence was found in favor of cognitive behavioral therapy (weighted mean difference [WMD], −0.9; 95% CI, −1.4 to −0.3) for pain in the short term{up to 3 months] and was found in favor of central nervous system depressants (WMD, −1.2 [95% CI, −1.6 to −0.8]) and antidepressants (WMD, −0.5 [95% CI, −0.7 to −0.4]) for pain in the medium term [3-12 months]. There was also high-quality evidence in favor of antidepressants (WMD, −6.8 [95% CI, −8.5 to −5.2]) for QOL in the short term and in favor of central nervous system depressants (WMD, −8.7 [95% CI, −11.3 to −6.0]) and antidepressants (WMD, −3.5 [95% CI, −4.5 to −2.5]) in the medium term. However, these associations were small and did not exceed the minimum clinically important change (2 points on an 11-point scale for pain and 14 points on a 101-point scale for QOL). Evidence for long-term [12 months or more] outcomes of interventions was lacking.
    c. CONCLUSIONS AND RELEVANCE This systematic review and meta-analysis suggests that most of the currently available therapies for the management of fibromyalgia are not supported by high-quality evidence. Some therapies may reduce pain and improve QOL in the short to medium term, although the effect size of the associations might not be clinically important to patients
2) **Farag, 2022**, comparative SR on amitriptyline and FDA approved treatments for fibromyalgia
    a. K=36 RCTs (N=11,930); median follow up, 12 weeks
        i. Comparative effectiveness and acceptability (defined as discontinuation of treatment owing to adverse drug reactions) associated with amitriptyline (off-label), pregabalin, duloxetine, and milnacipran (on-label) in reducing fibromyalgia symptoms.

   b. Compared with placebo, amitriptyline was associated with reduced sleep disturbances (SMD, −0.97; 95% CrI, −1.10 to −0.83), fatigue (SMD, −0.64; 95% CrI, −0.75 to −0.53), and improved quality of life (SMD, −0.80; 95% CrI, −0.94 to −0.65). Duloxetine 120 mg was associated with the highest improvement in pain (SMD, −0.33; 95% CrI, −0.36 to −0.30) and depression (SMD, −0.25; 95% CrI, −0.32 to −0.17) vs placebo.
   c. All treatments were associated with inferior acceptability (higher dropout rate) than placebo, except amitriptyline (OR, 0.78; 95% CrI, 0.31 to 1.66). According to the SUCRA-based relative ranking of treatments, duloxetine 120 mg was associated with higher efficacy for treating pain and depression, while amitriptyline was associated with higher efficacy for improving sleep, fatigue, and overall quality of life.
   d. Author's conclusions: These findings suggest that clinicians should consider how treatments could be tailored to individual symptoms, weighing the benefits and acceptability, when prescribing medications to patients with fibromyalgia

3) **Thorpe 2018**, Cochrane review of combination pharmacotherapy for the treatment of fibromyalgia
   a. N=16 studies (1474 patients)
      i. 3 studies on NSAIDs + benzodiazepines
      ii. 2 studies on amitriptyline + fluoxetine
      iii. 2 studies on amitriptyline with another agent
      iv. 2 studies on melatonin + antidepressant
      v. 1 study on carisoprodol, paracetamol, and caffeine
      vi. 1 study on tramadol and acetaminophen
      vii. 1 study on malic acid and magnesium
      viii. 1 study on MAOI + 5-hydroxytryptophan
      ix. 1 study on duloxetine and pregabalin
   b. Three studies found some evidence that combination pharmacotherapy reduced pain compared to monotherapy; these trials tested three different combinations: melatonin and amitriptyline, fluoxetine and amitriptyline, and pregabalin and duloxetine. Adverse events experienced by participants were not serious, and where they were reported (in 12 out of 16 studies), all participants experienced them, regardless of treatment. Common adverse events were nausea, dizziness, somnolence, and headache
   c. Authors' conclusions: There are few, large, high-quality trials comparing combination pharmacotherapy with monotherapy for fibromyalgia, consequently limiting evidence to support or refute the use of combination pharmacotherapy for fibromyalgia

4) **Welsch 2018**, Cochrane review of serotonin and noradrenaline reupake inhibitors (SNRIs) for fibromyalgia
   a. N=18 studies (7903 patients)
   b. The quality of evidence of all comparisons of desvenlafaxine, duloxetine and milnacipran versus placebo in studies with a parallel design was low due to concerns about publication bias and indirectness, and very low for serious adverse events due to concerns about publication bias, imprecision and indirectness. The quality of evidence of all comparisons of duloxetine and desvenlafaxine with other active drugs was very low due to concerns about publication bias, imprecision and indirectness.
   c. Duloxetine and milnacipran had no clinically relevant benefit over placebo for pain relief of 50% or greater. Duloxetine and milnacipran had a clinically relevant benefit over placebo in patient's global impression to be much or very much improved: 888 of 1710 (52%) on duloxetine and milnacipran (RD 0.19, 95% CI 0.12 to 0.26; NNTB 5, 95% CI 4 to 8) reported to be much or very much improved compared to 354 of 1208 (29%) of

participants on placebo. Duloxetine and milnacipran had a clinically relevant benefit compared to placebo for pain relief of 30% or greater. RD was 0.10; 95% CI 0.08 to 0.12; NNTB 10, 95% CI 8 to 12. Duloxetine and milnacipran had no clinically relevant benefit for fatigue (SMD -0.13, 95% CI -0.18 to -0.08; NNTB 18, 95% CI 12 to 29), compared to placebo. There were no differences between either duloxetine or milnacipran and placebo in reducing sleep problems (SMD -0.07; 95 % CI -0.15 to 0.01). Duloxetine and milnacipran had no clinically relevant benefit compared to placebo in improving health-related quality of life (SMD -0.20, 95% CI -0.25 to -0.15; NNTB 11, 95% CI 8 to 14). There were 794 of 4166 (19%) participants on SNRIs who dropped out due to adverse events compared to 292 of 2863 (10%) of participants on placebo (RD 0.07, 95% CI 0.04 to 0.10; NNTH 14, 95% CI 10 to 25).

   d. Authors' conclusions: Based on low-to very low-quality evidence, the SNRIs duloxetine and milnacipran provided no clinically relevant benefit over placebo in the frequency of pain relief of 50% or greater, but for patient's global impression to be much or very much improved and in the frequency of pain relief of 30% or greater there was a clinically relevant benefit. The SNRIs duloxetine and milnacipran provided no clinically relevant benefit over placebo in improving health-related quality of life and in reducing fatigue. Duloxetine and milnacipran did not significantly differ from placebo in reducing sleep problems. The dropout rates due to adverse events were higher for duloxetine and milnacipran than for placebo. On average, the potential benefits of duloxetine and milnacipran in fibromyalgia were outweighed by their potential harms. However, a minority of people with fibromyalgia might experience substantial symptom relief without clinically relevant adverse events with duloxetine or milnacipran. We did not find placebo-controlled studies with other SNRIs than desvenlafaxine, duloxetine and milnacipran

5) **Welsch 2018**, Cochrane review of mirtazapine for fibromyalgia
   a. N=3 studies (606 patients) comparing mirtazapine versus placebo
   b. We judged the evidence for all outcomes to be low- or very low-quality because of poor study quality, indirectness, imprecision, risk of publication bias, and sometimes low numbers of events.
   c. There was no difference between mirtazapine and placebo for any primary outcome: participant-reported pain relief of 50% or greater(22% versus 16%; RD 0.05, 95% confidence interval (CI) -0.01 to 0.12;three studies with 591 participants; low-quality evidence)
   d. Mirtazapine showed a clinically-relevant benefit compared to placebo for some secondary outcomes: participant-reported pain relief of 30% or greater (47% versus 34%; RD 0.13, 95% CI 0.05 to 0.21; number needed to treat for an additional beneficial outcome (NNTB) 8, 95% CI 5 to 20; three studies with 591 participants; low-quality evidence); participant-reported mean pain intensity (SMD -0.29, 95% CI -0.46 to -0.13;three studies with 591 participants; low-quality evidence); and participant-reported sleep problems (SMD -0.23, 95% CI -0.39 to -0.06; three studies with 573 participants; low-quality evidence). There was no benefit for improvement of participant-reported improvement of HRQoL of 20% or greater (58% versus 50%; RD 0.08, 95% CI -0.01 to 0.16; three studies with 586 participants; low-quality evidence); participant-reported fatigue (SMD-0.02, 95% CI-0.19 to 0.16;two studies with 533 participants; low-quality evidence); participant-reported negative mood (SMD -0.67, 95% CI -1.44 to 0.10; three studies with 588 participants; low-quality evidence); or

withdrawals due to lack of efficacy (1.5% versus 0.1%; RD 0.01, 95% CI -0.01 to 0.02; three studies with 605 participants; very low-quality evidence)

e. There was no difference between mirtazapine and placebo for participants reporting any adverse event
f. Author's: conclusions: Studies demonstrated no benefit of mirtazapine over placebo for pain relief of 50% or greater, PGIC, improvement of HRQoL of 20% or greater, or reduction of fatigue or negative mood. Clinically relevant benefits were shown for pain relief of 30% or greater, reduction of mean pain intensity, and sleep problems. Somnolence, weight gain, and elevated alanine aminotransferase were more frequent with mirtazapine than placebo. The quality of evidence was low or very low

Fibromyalgia 2023 Review

HERC staff summary:

Since the last major review of treatments for fibromyalgia in 2018, no new evidence for any therapy with clinically meaningful effectiveness has emerged for fibromyalgia itself. Fibromyalgia is a complex disease. Many of the symptoms that accompany fibromyalgia, such as joint pain, sleep problems or mood issues have effective treatments that are currently covered. Other treatments for fibromyalgia may be covered under the "co-morbidity rule" which allows coverage of a treatment for a non-covered condition when that will improve the outcome of a covered condition.

HERC staff recommendation:

1) Make no change in the current prioritization of fibromyalgia

JAMA Internal Medicine | Original Investigation

Association of Therapies With Reduced Pain and Improved Quality of Life in Patients With Fibromyalgia
A Systematic Review and Meta-analysis

Rodrigo Oliveira Mascarenhas, MSc; Mateus Bastos Souza, BAppSc; Murilo Xavier Oliveira, PhD; Ana Cristina Lacerda, PhD; Vanessa Amaral Mendonça, PhD; Nicholas Henschke, PhD; Vinícius Cunha Oliveira, PhD

IMPORTANCE Fibromyalgia is a chronic condition that results in a significant burden to individuals and society.

OBJECTIVE To investigate the effectiveness of therapies for reducing pain and improving quality of life (QOL) in people with fibromyalgia.

DATA SOURCES Searches were performed in the MEDLINE, Cochrane, Embase, AMED, PsycInfo, and PEDro databases without language or date restrictions on December 11, 2018, and updated on July 15, 2020.

STUDY SELECTION All published randomized or quasi-randomized clinical trials that investigated therapies for individuals with fibromyalgia were screened for inclusion.

DATA EXTRACTION AND SYNTHESIS Two reviewers independently extracted data and assessed risk of bias using the 0 to 10 PEDro scale. Effect sizes for specific therapies were pooled using random-effects models. The quality of evidence was assessed using the Grading of Recommendations Assessment (GRADE) approach.

MAIN OUTCOMES AND MEASURES Pain intensity measured by the visual analog scale, numerical rating scales, and other valid instruments and QOL measured by the Fibromyalgia Impact Questionnaire.

RESULTS A total of 224 trials including 29 962 participants were included. High-quality evidence was found in favor of cognitive behavioral therapy (weighted mean difference [WMD], −0.9; 95% CI, −1.4 to −0.3) for pain in the short term and was found in favor of central nervous system depressants (WMD, −1.2 [95% CI, −1.6 to −0.8]) and antidepressants (WMD, −0.5 [95% CI, −0.7 to −0.4]) for pain in the medium term. There was also high-quality evidence in favor of antidepressants (WMD, −6.8 [95% CI, −8.5 to −5.2]) for QOL in the short term and in favor of central nervous system depressants (WMD, −8.7 [95% CI, −11.3 to −6.0]) and antidepressants (WMD, −3.5 [95% CI, −4.5 to −2.5]) in the medium term. However, these associations were small and did not exceed the minimum clinically important change (2 points on an 11-point scale for pain and 14 points on a 101-point scale for QOL). Evidence for long-term outcomes of interventions was lacking.

CONCLUSIONS AND RELEVANCE This systematic review and meta-analysis suggests that most of the currently available therapies for the management of fibromyalgia are not supported by high-quality evidence. Some therapies may reduce pain and improve QOL in the short to medium term, although the effect size of the associations might not be clinically important to patients.

JAMA Intern Med. 2021;181(1):104-112. doi:10.1001/jamainternmed.2020.5651
Published online October 26, 2020.

Supplemental content

CME Quiz at jamacmelookup.com and CME Questions page 148

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Combination pharmacotherapy for the treatment of fibromyalgia in adults (Review)

Thorpe J, Shum B, Moore RA, Wiffen PJ, Gilron I

Thorpe J, Shum B, Moore RA, Wiffen PJ, Gilron I.
Combination pharmacotherapy for the treatment of fibromyalgia in adults.
Cochrane Database of Systematic Reviews 2018, Issue 2. Art. No.: CD010585.
DOI: 10.1002/14651858.CD010585.pub2.

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[Intervention Review]

Combination pharmacotherapy for the treatment of fibromyalgia in adults

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Editorial group: Cochrane Pain, Palliative and Supportive Care Group.
Publication status and date: Stable (no update expected for reasons given in 'What's new'), published in Issue 10, 2020.

Citation: Thorpe J, Shum B, Moore RA, Wiffen PJ, Gilron I. Combination pharmacotherapy for the treatment of fibromyalgia in adults. *Cochrane Database of Systematic Reviews* 2018, Issue 2. Art. No.: CD010585. DOI: 10.1002/14651858.CD010585.pub2.

ABSTRACT

Background

Fibromyalgia is a chronic widespread pain condition affecting millions of people worldwide. Current pharmacotherapies are often ineffective and poorly tolerated. Combining different agents could provide superior pain relief and possibly also fewer side effects.

Objectives

To assess the efficacy, safety, and tolerability of combination pharmacotherapy compared to monotherapy or placebo, or both, for the treatment of fibromyalgia pain in adults.

Search methods

We searched CENTRAL, MEDLINE, and Embase to September 2017. We also searched reference lists of other reviews and trials registries.

Selection criteria

Double-blind, randomised controlled trials comparing combinations of two or more drugs to placebo or other comparators, or both, for the treatment of fibromyalgia pain.

Data collection and analysis

From all studies, we extracted data on: participant-reported pain relief of 30% or 50% or greater; patient global impression of clinical change (PGIC) much or very much improved or very much improved; any other pain-related outcome of improvement; withdrawals (lack of efficacy, adverse events), participants experiencing any adverse event, serious adverse events, and specific adverse events (e.g. somnolence and dizziness). The primary comparison was between combination and one or all single-agent comparators. We also assessed the evidence using GRADE and created a 'Summary of findings' table.

Main results

We identified 16 studies with 1474 participants. Three studies combined a non-steroidal anti-inflammatory drug (NSAID) with a benzodiazepine (306 participants); two combined amitriptyline with fluoxetine (89 participants); two combined amitriptyline with a different agent (92 participants); two combined melatonin with an antidepressant (164 participants); one combined carisoprodol, paracetamol (acetaminophen), and caffeine (58 participants); one combined tramadol and paracetamol (acetaminophen) (315 participants); one combined malic acid and magnesium (24 participants); one combined a monoamine oxidase inhibitor with 5-hydroxytryptophan (200 participants); and one combined pregabalin with duloxetine (41 participants). Six studies compared the combination of multiple agents with each component alone and with inactive placebo; three studies compared combination pharmacotherapy with each individual component but did not include an inactive placebo group; two studies compared the combination

of two agents with only one of the agents alone; and three studies compared the combination of two or more agents only with inactive placebo.

Heterogeneity among studies in terms of class of agents evaluated, specific combinations used, outcomes reported, and doses given prevented any meta-analysis. None of the combinations of drugs found provided sufficient data for analysis compared with placebo or other comparators for our preferred outcomes. We therefore provide a narrative description of results. There was no or inadequate evidence in any comparison for primary and secondary outcomes. Two studies only reported any primary outcomes of interest (patient-reported pain relief of 30%, or 50%, or greater). For each 'Risk of bias' item, only half or fewer of studies had unequivocal low risk of bias. Small size and selective reporting were common as high risk of bias.

Our GRADE assessment was therefore very low for primary outcomes of pain relief of 30% or 50% or greater, PGIC much or very much improved or very much improved, any pain-related outcome, participants experiencing any adverse event, any serious adverse event, or withdrawing because of an adverse event.

Three studies found some evidence that combination pharmacotherapy reduced pain compared to monotherapy; these trials tested three different combinations: melatonin and amitriptyline, fluoxetine and amitriptyline, and pregabalin and duloxetine. Adverse events experienced by participants were not serious, and where they were reported (in 12 out of 16 studies), all participants experienced them, regardless of treatment. Common adverse events were nausea, dizziness, somnolence, and headache.

Authors' conclusions

There are few, large, high-quality trials comparing combination pharmacotherapy with monotherapy for fibromyalgia, consequently limiting evidence to support or refute the use of combination pharmacotherapy for fibromyalgia.

PLAIN LANGUAGE SUMMARY

Combinations of drugs versus single drugs to treat fibromyalgia pain in adults

Bottom line

There is no good evidence to prove or disprove that combining drugs is better than using single drugs for fibromyalgia.

Background

People with fibromyalgia experience constant, widespread pain, sleep problems, and fatigue. Common drugs such as paracetamol (acetaminophen) and ibuprofen are not usually effective. Medicines used to treat epilepsy or depression can sometimes be effective for fibromyalgia and other forms of long-lasting pain where there may be nerve damage. Many individuals with fibromyalgia take many different drugs to deal with pain. We did this review to find the evidence about using combinations of drugs compared to single drugs.

Study characteristics

In September 2017 we searched for clinical trials where combinations of medicines were used for fibromyalgia pain in adults. We found 16 studies evaluating combinations of drugs versus one drug for fibromyalgia pain.

Key results

These studies looked at combinations of all sorts of different drugs, but did not provide enough data to draw any conclusions. Many of the studies did not directly compare a combination of drugs with each single drug. They sometimes compared a combination of medicines with only one of the medicines in the combination, or with only placebo. This limited our ability to make any conclusions.

Most studies did not report any of the outcomes important to people with fibromyalgia. Some studies showed that a combination of drugs is better at reducing pain than one drug alone, but other studies showed that one drug alone is better than a combination of drugs. Other studies did not find any difference between combinations of drugs and single drugs.

Side effects were not severe, and generally were not different between combination therapy and monotherapy.

Quality of the evidence

We rated the quality of the evidence from studies using four levels: very low, low, moderate, or high. Very low-quality evidence means that we are very uncertain about the results. High-quality evidence means that we are very confident in the results. Overall, the quality of evidence for important outcomes was very low. None of the combinations of drugs provided enough information for our preferred outcomes. We think that new studies will be very likely to change any conclusions drawn from these studies.

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Serotonin and noradrenaline reuptake inhibitors (SNRIs) for fibromyalgia (Review)

Welsch P, Üçeyler N, Klose P, Walitt B, Häuser W

Welsch P, Üçeyler N, Klose P, Walitt B, Häuser W.
Serotonin and noradrenaline reuptake inhibitors (SNRIs) for fibromyalgia.
Cochrane Database of Systematic Reviews 2018, Issue 2. Art. No.: CD010292.
DOI: 10.1002/14651858.CD010292.pub2.

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[Intervention Review]

Serotonin and noradrenaline reuptake inhibitors (SNRIs) for fibromyalgia

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Editorial group: Cochrane Pain, Palliative and Supportive Care Group.
Publication status and date: Stable (no update expected for reasons given in 'What's new'), published in Issue 7, 2020.

Citation: Welsch P, Üçeyler N, Klose P, Walitt B, Häuser W. Serotonin and noradrenaline reuptake inhibitors (SNRIs) for fibromyalgia. *Cochrane Database of Systematic Reviews* 2018, Issue 2. Art. No.: CD010292. DOI: 10.1002/14651858.CD010292.pub2.

ABSTRACT

Background

Fibromyalgia is a clinically defined chronic condition of unknown etiology characterized by chronic widespread pain that often co-exists with sleep disturbances, cognitive dysfunction and fatigue. People with fibromyalgia often report high disability levels and poor quality of life. Drug therapy, for example, with serotonin and noradrenaline reuptake inhibitors (SNRIs), focuses on reducing key symptoms and improving quality of life. This review updates and extends the 2013 version of this systematic review.

Objectives

To assess the efficacy, tolerability and safety of serotonin and noradrenaline reuptake inhibitors (SNRIs) compared with placebo or other active drug(s) in the treatment of fibromyalgia in adults.

Search methods

For this update we searched CENTRAL, MEDLINE, Embase, the US National Institutes of Health and the World Health Organization (WHO) International Clinical Trials Registry Platform for published and ongoing trials and examined the reference lists of reviewed articles, to 8 August 2017.

Selection criteria

We selected randomized, controlled trials of any formulation of SNRIs against placebo or any other active treatment of fibromyalgia in adults.

Data collection and analysis

Three review authors independently extracted data, examined study quality, and assessed risk of bias. For efficacy, we calculated the number needed to treat for an additional beneficial outcome (NNTB) for pain relief of 50% or greater and of 30% or greater, patient's global impression to be much or very much improved, dropout rates due to lack of efficacy, and the standardized mean differences (SMD) for fatigue, sleep problems, health-related quality of life, mean pain intensity, depression, anxiety, disability, sexual function, cognitive disturbances and tenderness. For tolerability we calculated number needed to treat for an additional harmful outcome (NNTH) for withdrawals due to adverse events and for nausea, insomnia and somnolence as specific adverse events. For safety we calculated NNTH for serious adverse events. We undertook meta-analysis using a random-effects model. We assessed the evidence using GRADE and created a 'Summary of findings' table.

Main results

We added eight new studies with 1979 participants for a total of 18 included studies with 7903 participants. Seven studies investigated duloxetine and nine studies investigated milnacipran against placebo. One study compared desvenlafaxine with placebo and pregabalin. One study compared duloxetine with L-carnitine. The majority of studies were at unclear or high risk of bias in three to five domains.

The quality of evidence of all comparisons of desvenlafaxine, duloxetine and milnacipran versus placebo in studies with a parallel design was low due to concerns about publication bias and indirectness, and very low for serious adverse events due to concerns about publication bias, imprecision and indirectness. The quality of evidence of all comparisons of duloxetine and desvenlafaxine with other active drugs was very low due to concerns about publication bias, imprecision and indirectness.

Duloxetine and milnacipran had no clinically relevant benefit over placebo for pain relief of 50% or greater: 1274 of 4104 (31%) on duloxetine and milnacipran reported pain relief of 50% or greater compared to 591 of 2814 (21%) participants on placebo (risk difference (RD) 0.09, 95% confidence interval (CI) 0.07 to 0.11; NNTB 11, 95% CI 9 to 14). Duloxetine and milnacipran had a clinically relevant benefit over placebo in patient's global impression to be much or very much improved: 888 of 1710 (52%) on duloxetine and milnacipran (RD 0.19, 95% CI 0.12 to 0.26; NNTB 5, 95% CI 4 to 8) reported to be much or very much improved compared to 354 of 1208 (29%) of participants on placebo. Duloxetine and milnacipran had a clinically relevant benefit compared to placebo for pain relief of 30% or greater. RD was 0.10; 95% CI 0.08 to 0.12; NNTB 10, 95% CI 8 to 12. Duloxetine and milnacipran had no clinically relevant benefit for fatigue (SMD -0.13, 95% CI -0.18 to -0.08; NNTB 18, 95% CI 12 to 29), compared to placebo. There were no differences between either duloxetine or milnacipran and placebo in reducing sleep problems (SMD -0.07; 95 % CI -0.15 to 0.01). Duloxetine and milnacipran had no clinically relevant benefit compared to placebo in improving health-related quality of life (SMD -0.20, 95% CI -0.25 to -0.15; NNTB 11, 95% CI 8 to 14).

There were 794 of 4166 (19%) participants on SNRIs who dropped out due to adverse events compared to 292 of 2863 (10%) of participants on placebo (RD 0.07, 95% CI 0.04 to 0.10; NNTH 14, 95% CI 10 to 25). There was no difference in serious adverse events between either duloxetine, milnacipran or desvenlafaxine and placebo (RD -0.00, 95% CI -0.01 to 0.00).

There was no difference between desvenlafaxine and placebo in efficacy, tolerability and safety in one small trial.

There was no difference between duloxetine and desvenlafaxine in efficacy, tolerability and safety in two trials with active comparators (L-carnitine, pregabalin).

Authors' conclusions

The update did not change the major findings of the previous review. Based on low- to very low-quality evidence, the SNRIs duloxetine and milnacipran provided no clinically relevant benefit over placebo in the frequency of pain relief of 50% or greater, but for patient's global impression to be much or very much improved and in the frequency of pain relief of 30% or greater there was a clinically relevant benefit. The SNRIs duloxetine and milnacipran provided no clinically relevant benefit over placebo in improving health-related quality of life and in reducing fatigue. Duloxetine and milnacipran did not significantly differ from placebo in reducing sleep problems. The dropout rates due to adverse events were higher for duloxetine and milnacipran than for placebo. On average, the potential benefits of duloxetine and milnacipran in fibromyalgia were outweighed by their potential harms. However, a minority of people with fibromyalgia might experience substantial symptom relief without clinically relevant adverse events with duloxetine or milnacipran.

We did not find placebo-controlled studies with other SNRIs than desvenlafaxine, duloxetine and milnacipran.

PLAIN LANGUAGE SUMMARY

Serotonin and noradrenaline reuptake inhibitors for fibromyalgia

Bottom line

Duloxetine and milnacipran may reduce pain in people with fibromyalgia. However, some of these people may also experience side effects, such as nausea (feeling sick) and drowsiness. A minority of people with fibromyalgia experience symptom relief without side effects from duloxetine and milnacipran.

Background

People with fibromyalgia often have chronic (longer than three months) widespread pain, as well as problems with sleep, thinking and exhaustion. They often report poor health-related quality of life. There is no cure for fibromyalgia at present, so the treatments aim to relieve the symptoms and to improve health-related quality of life.

Serotonin and noradrenaline are chemicals which are produced by the human body, involved in the regulation of pain, sleep and mood. Low concentrations of serotonin have been reported in people with fibromyalgia. Serotonin and noradrenaline reuptake inhibitors (SNRIs) are a class of antidepressants that increase the concentration of serotonin and noradrenaline in the brain.

Study characteristics

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Mirtazapine for fibromyalgia in adults (Review)

Welsch P, Bernardy K, Derry S, Moore RA, Häuser W

Welsch P, Bernardy K, Derry S, Moore RA, Häuser W.
Mirtazapine for fibromyalgia in adults.
Cochrane Database of Systematic Reviews 2018, Issue 8. Art. No.: CD012708.
DOI: 10.1002/14651858.CD012708.pub2.

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[Intervention Review]

Mirtazapine for fibromyalgia in adults

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Editorial group: Cochrane Pain, Palliative and Supportive Care Group.
Publication status and date: Stable (no update expected for reasons given in 'What's new'), published in Issue 7, 2020.

Citation: Welsch P, Bernardy K, Derry S, Moore RA, Häuser W. Mirtazapine for fibromyalgia in adults. *Cochrane Database of Systematic Reviews* 2018, Issue 8. Art. No.: CD012708. DOI: 10.1002/14651858.CD012708.pub2.

ABSTRACT

Background

Fibromyalgia is a clinically defined chronic condition of unknown etiology characterised by chronic widespread pain, sleep disturbance, cognitive dysfunction, and fatigue. Many patients report high disability levels and poor quality of life. Drug therapy aims to reduce key symptoms, especially pain, and improve quality of life. The tetracyclic antidepressant, mirtazapine, may help by increasing serotonin and noradrenaline in the central nervous system (CNS).

Objectives

To assess the efficacy, tolerability and safety of the tetracyclic antidepressant, mirtazapine, compared with placebo or other active drug(s) in the treatment of fibromyalgia in adults.

Search methods

We searched the Cochrane Central Register of Controlled Trials (CENTRAL), MEDLINE, Embase, SCOPUS, the US National Institutes of Health, and the World Health Organization (WHO) International Clinical Trials Registry Platform for published and ongoing trials, and examined reference lists of reviewed articles, to 9 July 2018.

Selection criteria

Randomised controlled trials (RCTs) of any formulation of mirtazapine against placebo, or any other active treatment of fibromyalgia, in adults.

Data collection and analysis

Two review authors independently extracted study characteristics, outcomes of efficacy, tolerability and safety, examined issues of study quality, and assessed risk of bias, resolving discrepancies by discussion. Primary outcomes were participant-reported pain relief (at least 50% or 30% pain reduction), Patient Global Impression of Change (PGIC; much or very much improved), safety (serious adverse events), and tolerability (adverse event withdrawal). Other outcomes were health-related quality of life (HRQoL) improved by 20% or more, fatigue, sleep problems, mean pain intensity, negative mood and particular adverse events. We used a random-effects model to calculate risk difference (RD), standardised mean difference (SMD), and numbers needed to treat. We assessed the evidence using GRADE and created a 'Summary of findings' table.

Main results

Three studies with 606 participants compared mirtazapine with placebo (but not other drugs) over seven to 13 weeks. Two studies were at unclear or high risk of bias in six or seven of eight domains. We judged the evidence for all outcomes to be low- or very low-quality because of poor study quality, indirectness, imprecision, risk of publication bias, and sometimes low numbers of events.

There was no difference between mirtazapine and placebo for any primary outcome: participant-reported pain relief of 50% or greater (22% versus 16%; RD 0.05, 95% confidence interval (CI) -0.01 to 0.12; three studies with 591 participants; low-quality evidence); no data available for PGIC; only a single serious adverse event for evaluation of safety (RD -0.00, 95% CI -0.01 to 0.02; three studies with 606 participants; very low-quality evidence); and tolerability as frequency of dropouts due to adverse events (3% versus 2%; RD 0.00, 95% CI -0.02 to 0.03; three studies with 606 participants; low-quality evidence).

Mirtazapine showed a clinically-relevant benefit compared to placebo for some secondary outcomes: participant-reported pain relief of 30% or greater (47% versus 34%; RD 0.13, 95% CI 0.05 to 0.21; number needed to treat for an additional beneficial outcome (NNTB) 8, 95% CI 5 to 20; three studies with 591 participants; low-quality evidence); participant-reported mean pain intensity (SMD -0.29, 95% CI -0.46 to -0.13; three studies with 591 participants; low-quality evidence); and participant-reported sleep problems (SMD -0.23, 95% CI -0.39 to -0.06; three studies with 573 participants; low-quality evidence). There was no benefit for improvement of participant-reported improvement of HRQoL of 20% or greater (58% versus 50%; RD 0.08, 95% CI -0.01 to 0.16; three studies with 586 participants; low-quality evidence); participant-reported fatigue (SMD -0.02, 95% CI -0.19 to 0.16; two studies with 533 participants; low-quality evidence); participant-reported negative mood (SMD -0.67, 95% CI -1.44 to 0.10; three studies with 588 participants; low-quality evidence); or withdrawals due to lack of efficacy (1.5% versus 0.1%; RD 0.01, 95% CI -0.01 to 0.02; three studies with 605 participants; very low-quality evidence).

There was no difference between mirtazapine and placebo for participants reporting any adverse event (76% versus 59%; RD 0.12, 95 CI -0.01 to 0.26; three studies with 606 participants; low-quality evidence). There was a clinically-relevant harm with mirtazapine compared to placebo: in the number of participants with somnolence (42% versus 14%; RD 0.24, 95% CI 0.18 to 0.30; number needed to treat for an additional harmful outcome (NNTH) 5, 95% CI 3 to 6; three studies with 606 participants; low-quality evidence); weight gain (19% versus 1%; RD 0.17, 95% CI 0.11 to 0.23; NNTH 6, 95% CI 5 to 10; three studies with 606 participants; low-quality evidence); and elevated alanine aminotransferase (13% versus 2%; RD 0.13, 95% CI 0.04 to 0.22; NNTH 8, 95% CI 5 to 25; two studies with 566 participants; low-quality evidence).

Authors' conclusions

Studies demonstrated no benefit of mirtazapine over placebo for pain relief of 50% or greater, PGIC, improvement of HRQoL of 20% or greater, or reduction of fatigue or negative mood. Clinically-relevant benefits were shown for pain relief of 30% or greater, reduction of mean pain intensity, and sleep problems. Somnolence, weight gain, and elevated alanine aminotransferase were more frequent with mirtazapine than placebo. The quality of evidence was low or very low, with two of three studies of questionable quality and issues over indirectness and risk of publication bias. On balance, any potential benefits of mirtazapine in fibromyalgia were outweighed by its potential harms, though, a small minority of people with fibromyalgia might experience substantial symptom relief without clinically-relevant adverse events.

PLAIN LANGUAGE SUMMARY

Mirtazapine for treating fibromyalgia in adults

Bottom line

Mirtazapine at 15 mg to 45 mg daily is unlikely to substantially reduce pain in people with fibromyalgia. Mirtazapine can cause drowsiness, weight gain, and liver damage. A small number of people may experience some improvement (moderate pain relief, better sleep) without side effects from mirtazapine, but that cannot be predicted. The off-label use of mirtazapine can be considered, if established treatment options have failed.

Background

People with fibromyalgia often have chronic (longer than 3 months) widespread pain, and problems with sleeping, thinking, exhaustion, and poor quality of life. There is no cure for fibromyalgia. Treatments aim to improve symptoms (pain, sleep problems, fatigue) and quality of life.

Serotonin and noradrenaline are chemicals produced by the human body and are involved in pain, sleep, and mood. Low serotonin levels have been found in people with fibromyalgia. The antidepressant, mirtazapine, increases serotonin and noradrenaline levels in the brain.

Study characteristics

In July 2018 we searched for clinical trials where mirtazapine was used to treat fibromyalgia in adults. We found three studies with 606 participants. Studies were seven to 13 weeks long. They compared mirtazapine 15 mg to 45 mg daily against a fake medication (placebo).

Key results

There was no difference between mirtazapine and placebo for any primary outcome: mirtazapine and placebo reduced pain by 50% in two of 10 people (low-quality evidence). Only one single serious adverse event was available for evaluation of safety (very low-quality evidence). Three of 10 participants with mirtazapine and two of 10 participants with placebo dropped out of the trial due to side effects (low-quality evidence).

JAMA Network Open

Original Investigation | Neurology

Comparison of Amitriptyline and US Food and Drug Administration–Approved Treatments for Fibromyalgia

A Systematic Review and Network Meta-analysis

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Abstract

IMPORTANCE Amitriptyline is an established medication used off-label for the treatment of fibromyalgia, but pregabalin, duloxetine, and milnacipran are the only pharmacological agents approved by the US Food and Drug Administration (FDA) to treat fibromyalgia.

OBJECTIVE To investigate the comparative effectiveness and acceptability associated with pharmacological treatment options for fibromyalgia.

DATA SOURCES Searches of PubMed/MEDLINE, Cochrane Library, Embase, and Clinicaltrials.gov were conducted on November 20, 2018, and updated on July 29, 2020.

STUDY SELECTION Randomized clinical trials (RCTs) comparing amitriptyline or any FDA-approved doses of investigated drugs.

DATA EXTRACTION AND SYNTHESIS This study follows the Preferred Reporting Items for Systematic Reviews and Meta-analyses reporting guideline. Four independent reviewers extracted data using a standardized data extraction sheet and assessed quality of RCTs. A random-effects bayesian network meta-analysis (NMA) was conducted. Data were analyzed from August 2020 to January 2021.

MAIN OUTCOMES AND MEASURES Comparative effectiveness and acceptability (defined as discontinuation of treatment owing to adverse drug reactions) associated with amitriptyline (off-label), pregabalin, duloxetine, and milnacipran (on-label) in reducing fibromyalgia symptoms. The following doses were compared: 60-mg and 120-mg duloxetine; 150-mg, 300-mg, 450-mg, and 600-mg pregabalin; 100-mg and 200-mg milnacipran; and amitriptyline. Effect sizes are reported as standardized mean differences (SMDs) for continuous outcomes and odds ratios (ORs) for dichotomous outcomes with 95% credible intervals (95% CrIs). Findings were considered statistically significant when the 95% CrI did not include the null value (0 for SMD and 1 for OR). Relative treatment ranking using the surface under the cumulative ranking curve (SUCRA) was also evaluated.

RESULTS A total of 36 studies (11 930 patients) were included. The mean (SD) age of patients was 48.4 (10.4) years, and 11 261 patients (94.4%) were women. Compared with placebo, amitriptyline was associated with reduced sleep disturbances (SMD, −0.97; 95% CrI, −1.10 to −0.83), fatigue (SMD, −0.64; 95% CrI, −0.75 to −0.53), and improved quality of life (SMD, −0.80; 95% CrI, −0.94 to −0.65). Duloxetine 120 mg was associated with the highest improvement in pain (SMD, −0.33; 95% CrI, −0.36 to −0.30) and depression (SMD, −0.25; 95% CrI, −0.32 to −0.17) vs placebo. All treatments

(continued)

Key Points

Question What pharmacological treatments for adults with fibromyalgia are associated with the highest efficacy and acceptability?

Findings In this systematic review and network meta-analysis of 36 randomized clinical trials (11 930 patients with fibromyalgia), duloxetine (120 mg) was associated with higher efficacy in treating pain and depression, while amitriptyline was associated with higher efficacy and acceptability in improving sleep, fatigue, and health-related quality of life outcomes.

Meaning These findings suggest that with the heterogeneity of fibromyalgia symptoms, pharmacological treatments should be tailored to individual symptoms, including pain, sleep problems, depressed mood, fatigue, and health-related quality of life.

+ Supplemental content

Author affiliations and article information are listed at the end of this article.

Breast Cancer Screening August 2023

Plain Language Summary:

Coverage question:

1) Should breast cancer screening guidelines be updated to the 2023 United States Preventive Services Task Force's (USPSTF – an independent, volunteer panel of national experts in disease prevention and evidence-based medicine) recommendations?
2) Should breast tomosynthesis (3D mammography – a special breast picture that helps doctors check for potential problems or changes) be covered by OHP?

Should OHP cover this treatment?

1) There is no need to update OHP coverage; a yearly mammogram starting at age 40 is already covered.
2) Yes. Studies showed that 3D mammography improved how often cancer was discovered more than other tests.

Coverage Questions:

1) Should any changes be made to the Prioritized List based on the 2023 updated USPSTF recommendations and review of breast cancer screening?
2) Should coverage be added for breast tomosynthesis (3D mammography) based on USPSTF and/or NCCN recommendations?

Question source: HERC staff, multiple stakeholders

Background: The USPSTF recently updated their review and recommendations for breast cancer screening. Separately, there have been multiple issues related to breast cancer screening brought up by stakeholders in recent years. These include coverage of breast tomosynthesis (3D mammography) as well as coverage of ultrasound or breast MRI as supplemental screening for women with dense breasts. Dense breasts are more difficult to evaluate with mammography and associated with increased risk for developing breast cancer.

Breast cancer screening was last discussed in March 2017 as part of a coverage guidance for screening for women at above average risk. HTAS reviewed breast tomosynthesis as a screening modality for women with dense breasts, and concluded that it was not recommended, nor was any other additional screening modality: "For women with increased breast density, supplemental screening with breast ultrasound, MRI, or digital breast tomosynthesis is not recommended for coverage *(weak recommendation)*."

Breast cancer screening is covered in Guideline Note 106 PREVENTIVE SERVICES, which states that all "US Preventive Services Task Force (USPSTF) "A" and "B" Recommendations in effect and issued prior to January 1, 2022. https://www.uspreventiveservicestaskforce.org/uspstf/recommendation-topics/uspstf-a-and-b-recommendations/" are covered. GN106 also states that all "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." Are covered. Currently, "WPSI recommends that average-risk women initiate mammography screening no earlier than age 40 and no later than age 50. Screening mammography should occur at least biennially and as frequently as annually. Screening should continue through at least age 74 and age alone should not be the basis to discontinue screening."

Previous HSC/HERC reviews:

November 2014 [2015 CPT code review]
Digital breast tomosynthesis (CPT 77061-77063)

1) Definition: a new technology which acquires 3D images of the breast to assist in breast cancer screening and diagnosis. Generally, tomosynthesis is done together with traditional digital mammography.
2) Other guidelines/guidances
    a. **NCCN 2014**, breast cancer screening guideline
        i. Early studies show promise for tomosynthesis mammography. Two large trials showing a combined use of digital mammography and tomosynthesis resulted in improved cancer detection and decreased call back rates; of note, this is double the dose of radiation and is a factor in recommending this modality. Definitive studies are still pending.
        ii. Tomosynthesis is not included in their flow charts for routine breast cancer screening
3) Evidence
    a. **TEC 2014**, technology report
        i. N=6 studies
        ii. Insufficient evidence to permit conclusions on whether digital breast tomosynthesis improves detection of breast cancer or improves any health outcomes compared to conventional mammography
    b. **Houssami 2013**, systematic review
        i. N=13 studies
        ii. Authors conclusions: At present, there is insufficient evidence to justify a change from standard digital mammography to digital breast tomosynthesis however the available data strongly support investment in new large-scale population screening trials.
    c. **Rafferty 2013**, trial of tomosynthesis + digital mammography vs digital mammography alone
        i. N=1192 patients
            1. Included women scheduled for breast biopsy (i.e. not a screening population) as well as women who presented for screening
        ii. Diagnostic accuracy of tomosynthesis plus digital mammography was superior to digital mammography alone.
        iii. Recall rates for noncancerous cases for all readers decreased with the addition of tomosynthesis (range, 6%–67%; P = 0.001 for 25 readers, P = 0.03 for all readers).

iv. The increase in the rate of sensitivity was greatest for invasive cancers: 15% and 22% in studies 1 and 2 versus 3% for in situ cancers in both studies.
v. The authors concluded that the addition of tomosynthesis to digital mammography provides the dual benefit of significantly increased diagnostic accuracy and significantly reduced recall rates for noncancerous cases.
vi. Several authors had significant conflicts of interest; one was an employee of the company that manufactures the tomosynthesis machines and the study was funded by the manufacturer

d. **Skaane 2013**, trial of tomosynthesis tomosynthesis + digital mammography vs digital mammography alone
   i. N=12,631 patients
   ii. Detection rates, including those for invasive and in situ cancers, were 6.1 per 1000 examinations for mammography alone and 8.0 per 1000 examinations for mammography plus tomosynthesis (27% increase, adjusted for reader; *P* =.001). False-positive rates before arbitration were 61.1 per 1000 examinations with mammography alone and 53.1 per 1000 examinations with mammography plus tomosynthesis (15% decrease, adjusted for reader; *P* , .001). After arbitration, positive predictive values for recalled patients with cancers verified later were comparable (29.1% and 28.5%, respectively, with mammography alone and mammography plus tomosynthesis; *P* = .72). Twenty-five additional invasive cancers were detected with mammography plus tomosynthesis (40% increase, adjusted for reader; *P*, .001). The mean interpretation time was 45 seconds for mammography alone and 91 seconds for mammography plus tomosynthesis (*P* , .001).
   iii. Conclusion: The use of mammography plus tomosynthesis in a screening environment resulted in a significantly higher cancer detection rate and enabled the detection of more invasive cancers.
   iv. Study funded by the manufacturer and several authors had significant conflicts of interest; 2 were employees of the manufacturer

4) Other coverage policies:
   a. **BCBS 2014**: does not cover, investigational
   b. **Aetna 2014**: does not cover, investigational
5) HERC staff recommendation: **Non-covered List**
   a. Experimental, unclear what added value is for general population screening, has risk of increased radiation exposure
   b. Re-evaluate coverage when the results of a large NHS trial currently underway in the UK (TOMMY trial) and/or other large scale, definitive studies are released in a few years

Breast cancer screening was last discussed in March 2017 as part of a coverage guidance for screening for women at above average risk. HTAS reviewed breast tomosynthesis as a screening modality for women with dense breasts, and concluded that it was not recommended, nor was any other additional screening modalities: “For women with increased breast density, supplemental screening with breast

ultrasound, MRI, or digital breast tomosynthesis is not recommended for coverage *(weak recommendation)*."

Current Prioritized List/Coverage status:

CPT 76641-76642 (breast ultrasound) are DIAGNOSTIC PROCEDURES

CPT 77046-77047 (breast MRI) are DIAGNOSTIC PROCEDURES

CPT 77061-77062 (diagnostic digital breast tomosynthesis) and 77063 (screening digital breast tomosynthesis) are on line 662

CPT 77065-77067 (diagnostic mammography) are DIAGNOSTIC PROCEDURES

CPT 77067 (screening mammography) is on line 3 PREVENTION SERVICES WITH EVIDENCE OF EFFECTIVENESS

DIAGNOSTIC GUIDELINE D6, BREAST MRI

Breast MRI is covered in the following circumstances:

A) Annual breast MRI screening for high-risk patients
   1) For individuals with a genetic mutation known to confer a greater than 20% lifetime risk of breast cancer (e.g., BRCA1, BRCA2, Bannayan-Riley-Ruvalcaba syndrome, Cowden syndrome, or Li-Fraumeni syndrome), beginning 10 years prior to when the youngest family member was diagnosed with breast cancer (but not prior to age 25 years) or age 40 years, whichever comes first
   2) For individuals who received high dose chest radiation (≥ 20 Gray) between the ages of 10 and 30 years beginning 8 years after radiation exposure or at age 25, whichever is later
   3) For individuals with a lifetime risk of ≥ 20% as defined by models that are largely dependent on family history, beginning 10 years prior to when the youngest family member was diagnosed with breast cancer (but not prior to age 25 years) or age 40 years, whichever comes first

B) Evaluation of possible breast cancer
   1) To search for occult breast cancer in patients with Paget's disease of the nipple or in patients with axillary node metastasis when clinical examination and conventional breast imaging fail to detect a primary breast cancer
   2) For the further evaluation of suspicious clinical or imaging findings that remain indeterminate after complete mammographic and sonographic evaluations in lesions that do not meet criteria for breast biopsy

C) Preoperative breast MRI
   1) For patients with recently diagnosed breast cancer who qualify for MRI screening based on the high-risk criteria in section A above
   2) For determining the extent of cancer or presence of multi-focal or multi-centric tumor or the presence of contralateral cancer, in patients with a proven breast cancer and associated clinical or conventional indeterminate imaging findings suspicious for malignancy. This may include patients with invasive lobular carcinoma or extremely dense breast tissue (limiting

mammographic sensitivity), or when there are significant discrepancies in the estimated tumor size as measured on clinical exam, mammogram, and ultrasound

D) Evaluation of suspected breast implant rupture

1) Breast MRI is covered for evaluation of suspected breast implant rupture, if the MRI findings will aid the decision-

making for implant removal or aid the diagnostic evaluation of indeterminate clinical or conventional imaging findings in patients with implants

Breast MRI is NOT covered for breast cancer screening in women with increased breast density.

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

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
   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.

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

Breast Cancer Screening August 2023

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

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**
77061-77063	Digital breast tomosynthesis	No evidence of effectiveness	March 2017 Coverage Guidance

Breast Cancer Screening August 2023

Evidence:

1) **USPSTF 2023**, draft evidence review for breast cancer screening
    a. Mammography with Digital Breast Tomosynthesis. No eligible studies reported breast cancer mortality or other health outcomes to compare the effectiveness of screening with DBT versus DM only (KQ1). Intermediate outcomes that compared screening with DBT versus DM were reported in three RCTs (N = 130,196) and one nonrandomized study (N = 92,404) (KQ2). The trials screened all participants with the same screening modality at the second screening round, with DM in three trials and DBT in another. DBT was associated with increased detection of invasive cancer at the first screening round, (pooled RR 1.41, 95% CI 1.20 to 1.64, I2 8%, 3 trials; n = 129,492); but detection was not statistically different at the second screening round Screening for Breast Cancer v Kaiser Permanente EPC (pooled RR 0.87, 95% CI 0.73 to 1.05, I2 0%, 3 trials; n = 105,064) and there was no evidence of a reduced risk of progression to advanced cancer in the second round with DBT compared with DM. The NRSI found higher detection at round one for the group screened with DBT, but higher detection at round two for the group screened with DM at both rounds. The three trials and nonrandomized study reported tumor diameter, histologic grade, and node status. No statistically significant differences in these or other individual tumor prognostic characteristics were reported at the first or second round of screening for any of the included studies. Limited results stratified by age and density in two of the RCTs did not indicate differences in invasive cancer detection at a second round of screening for people who had been screened with DBT at the first screening round, but tests for interaction were not conducted and estimates were imprecise.
    b. Harms (KQ3). Three large RCTs reported no statistically significant difference in the rates of interval cancers following screening with DBT compared with DM (pooled RR 0.87, 95% CI, 0.64 to 1.17, k = 3, n = 130,196, I2 0%) but data from five nonrandomized studies were mixed, and interpretation was limited by differences in study design. The effects of DBT screening on recall, false-positive recalls, and biopsy rates varied between trials and by screening round, with no or small statistical differences between study groups, not consistently favoring DBT or DM. The cumulative rates of false-positive recall and false-positive biopsy were slightly lower with DBT compared with DM screening, regardless of screening interval (cumulative probability over 10 years: 50% vs 56% for annual screening, 36% vs 38% with biennial screening). An additional adverse effect of DBT reported, radiation exposure, was approximately two times higher in studies where DBT was performed in addition to DM, but exposure was similar in two studies that used DBT to generate synthetic DM images (DBT/sDM).
    c. Overall, the studies indicated no or minor differences between DBT and DM screening in effectiveness and potential harms.

Expert guidelines:

1) **NCCN 1.2023** breast cancer screening
    a. Annual screening mammogram with tomosynthesis is now the recommended screening modality for breast cancer (Category 1) for both average and high-risk women

i. "Tomosynthesis can decrease call back rates and improve cancer detection compared with 2D mammography alone."

b. NCCN suggests "consideration of supplemental screening for those with dense breasts

2) **USPSTF 2023** draft recommendations for breast cancer screening
   a. The USPSTF recommends biennial screening mammography for women ages 40 to 74 years
      i. Category B
   b. The USPSTF concludes that the current evidence is insufficient to assess the balance of benefits and harms of supplemental screening for breast cancer using breast ultrasonography or magnetic resonance imaging (MRI) in women identified to have dense breasts on an otherwise negative screening mammogram.
      i. Category I

Other payer policies:

1) Premara BCBS 2023
   a. Digital breast tomosynthesis (DBT) is covered for both diagnostic and screening uses
2) Aetna 2023
   a. Digital breast tomosynthesis (DBT) is covered for both diagnostic and screening uses

Expert input:

Dr. Melinda Muller, Chief Medical Officer of Legacy Health Systems

Legacy is pleased that the Health Evidence Review Commission draft recommendation proposes coverage of digital breast tomosynthesis (DBT), which is a tremendous benefit to our patients and for all women in Oregon and will make screening more equitable for all Oregonians.

For nearly eleven years, Legacy physicians and patients have experienced the advantages of increased cancer detection rates and decreased recall rates afforded by the early adoption of DBT technology in our breast centers. In our experience, the additional cancers detected by DBT are primarily invasive; introduction of DBT into our practiced has not significant increase in situ cancer detection.

The evidence and our institutional experience are clear and consistent: tomosynthesis has a high cancer detection rate than digital mammography alone, and a statistically significant reduction in recall rate (reducing the potential harm of false positive recalls).

Time and again, Legacy patients have benefitted from DBT. Many invasive breast cancers would not have been detected otherwise, and fewer patients have been unnecessarily recalled for additional imaging. By offering coverage of tomosynthesis,

HERC will directly improve patient care, population health, and the cost-effectiveness of health care in Oregon.

Breast Cancer Screening August 2023

HERC staff summary:

The updated USPSTF evidence review on breast cancer screening found no difference between conventional mammography and breast tomosynthesis (3D mammography) in terms of effectiveness and potential harms. NCCN updated breast cancer screening recommendations list breast tomosynthesis as the preferred screening modality (category 1), noting that "Tomosynthesis can decrease call back rates and improve cancer detection compared with 2D mammography alone." Based on these recommendations, HERC staff is recommending coverage of breast tomosynthesis.

Neither USPSTF nor NCCN recommend additional screening modalities for women with dense breasts beyond mammography.

No changes are needed to GN106 PREVENTIVE SERVICES regarding breast cancer screening, as yearly mammography beginning at age 40 is already included in the HRSA recommendations. The updated USPSTF recommendations will mirror that coverage.

HERC staff recommendations:

1) Remove CPT 77061-77062 (diagnostic digital breast tomosynthesis) and 77063 (screening digital breast tomosynthesis) from line 662 CONDITIONS FOR WHICH CERTAIN INTERVENTIONS ARE UNPROVEN, HAVE NO CLINICALLY IMPORTANT BENEFIT OR HAVE HARMS THAT OUTWEIGH BENEFITS
    a. Remove the entry for breast tomosynthesis from GN173
2) Advise HSD to add CPT 77061-77062 (diagnostic digital breast tomosynthesis) to the DIAGNOSTIC PROCEDURES file
3) Add CPT 77063 (screening digital breast tomosynthesis) to line 3 PREVENTION SERVICES WITH EVIDENCE OF EFFECTIVENESS

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
~~77061-77063~~	~~Digital breast tomosynthesis~~	~~No evidence of effectiveness~~	~~March 2017 Coverage Guidance~~

Evidence Synthesis

Number 231

Screening for Breast Cancer: A Comparative Effectiveness Review for the U.S. Preventive Services Task Force

Prepared for:
Agency for Healthcare Research and Quality
U.S. Department of Health and Human Services
5600 Fishers Lane
Rockville, MD 20857
www.ahrq.gov

Contract No. 75Q80120D00004, Task Order No. 75Q80121F32004

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AHRQ Publication No. 23-05303-EF-1
May 2023

This report is based on research conducted by the Kaiser Permanente Research Affiliates Evidence-based Practice Center (EPC) under contract to the Agency for Healthcare Research and Quality (AHRQ), Rockville, MD (Contract No. 75Q80120D00004, Task Order No. 75Q80121F32004). The findings and conclusions in this document are those of the authors, who are responsible for its contents; the findings and conclusions do not necessarily represent the views of AHRQ. Therefore, no statement in this report should be construed as an official position of AHRQ or of the U.S. Department of Health and Human Services.

The information in this report is intended to help healthcare decision makers—patients and clinicians, health system leaders, and policymakers, among others—make well-informed decisions and thereby improve the quality of healthcare services. This report is not intended to be a substitute for the application of clinical judgment. Anyone who makes decisions concerning the provision of clinical care should consider this report in the same way as any medical reference and in conjunction with all other pertinent information (i.e., in the context of available resources and circumstances presented by individual patients).

The final report may be used, in whole or in part, as the basis for development of clinical practice guidelines and other quality enhancement tools, or as a basis for reimbursement and coverage policies. AHRQ or U.S. Department of Health and Human Services endorsement of such derivative products may not be stated or implied.

Acknowledgments

The authors gratefully acknowledge the following individuals for their contributions to this project: Tracy Wolff and Howard Tracer at AHRQ; current and former members of the U.S. Preventive Services Task Force who contributed to topic deliberations; Patricia Ganz, MD, Gerald Gartlehner, MD, Nehmat Houssami, MBBS, MPH, MEd, PhD, Karla Kerlikowske, MD, and Lisa Newman, MD, MPH, FACS, FASCO, who provided expert review of the draft report; Erin Abramsohn, DrPH, on behalf of the Centers for Disease Control and Prevention, Sarah Temkim, MD, with the Office of Research on Women's Health, Anna Maria Nápoles, PhD, MPH, and Arielle Gillman, PhD, MPH, on behalf of the National Institute on Minority Health and Health Disparities for providing federal partner review of the draft report; and Heidi Nelson, MD, MPH, for mentoring and expert input. Thanks to Eric (Rocky) Feuer from the National Cancer Institute and Steve Scoppa for technical assistance obtaining detailed SEER breast cancer surveillance data. We also thank Leslie Perdue, MPH, Jill Pope, Melinda Davies, MA, and Tracy Beil, MS, for technical and editorial assistance.

Structured Abstract

Objective: We conducted this systematic review to support the U.S. Preventive Services Task Force (USPSTF) in updating its recommendations on breast cancer screening. Our review addresses the comparative effectiveness of breast cancer screening for improving health outcomes. The review compares different strategies regarding when to screen (e.g., age to start/stop screening, screening interval), screening modalities (e.g., digital breast tomosynthesis [DBT] vs digital mammography [DM]), supplemental screening, or screening strategies defined by breast cancer risk-markers.

Data Sources: We searched MEDLINE, Cochrane Central Register of Controlled Clinical Trials, and the Cochrane Database of Systematic Reviews and the reference lists of previous systematic reviews of breast cancer screening for relevant studies published through August 22, 2022.

Study Selection: We reviewed 10,378 abstracts and assessed 419 full-text articles for inclusion against prespecified inclusion criteria. Eligible studies were conducted in asymptomatic adults eligible for breast cancer screening without clinically significant genetic markers or syndromes associated with high breast cancer risk. Randomized trials and nonrandomized studies of interventions (NRSI) with concurrent comparison groups that reported data over multiple rounds of screening were included to compare health outcomes (e.g., breast cancer mortality) and intermediate outcomes (e.g., risk of advanced cancer); study criteria were broader for identifying potential screening harms. The review was limited to studies conducted in countries with "very high" Human Development Index scores.

Data Analysis: We conducted dual independent critical appraisal of all included studies and extracted study details and outcomes from fair- or good-quality studies. We narratively synthesized results by key question and for each screening comparison. We used random-effects meta-analyses to estimate pooled effects when appropriate. We graded the overall strength of evidence as high, moderate, low, or insufficient based on criteria adapted from the EPC Program.

Results: Health outcomes (KQ1) associated with different screening programs were reported in only two fair-quality NRSIs that addressed the age to stop screening or screening interval. For invasive cancer detection (KQ2), two studies addressed the effect of screening frequency on the characteristics of detected cancers, including one fair-quality RCT of multiple rounds of screening and one fair quality cases-only analysis from the Breast Cancer Surveillance Consortium (BCSC). Four studies of DBT compared with DM, three RCTs [2 good- and 1 fair-quality] and one NRSI reported screening outcomes from more than one round of screening and were included for KQ2. These studies reported characteristics of cancers detected at each round, necessary to assess whether screening resulted in stage shift toward less advanced cases with better prognosis. All 19 studies were included to examine potential harms of different screening approaches (KQ3).

Ages to start or stop screening. One fair-quality NRSI reported an emulated trial analysis of Medicare data (N=264,274) comparing the age to stop screening with reported breast cancer mortality and all-cause mortality (KQ1). Continued screening between the ages of 70 and 74 was

associated with decreased 8-year breast cancer mortality compared with a cessation of screening after age 70 (1 fewer death per 1000 women screened), but no difference was found with continued versus discontinued screening from ages 75 to 84.

Harms (KQ3). Limited evidence on potential risks of overdiagnosis and overtreatment was reported, with more diagnosis and treatment occurring with continued screening, without a mortality benefit.

Interval of Screening. A study conducted in Finland during the years 1985 to 1995 assigned participants (N=14,765) to annual or triennial screening invitations and reported similar breast cancer mortality and all-cause mortality between the two study groups (KQ1). Intermediate cancer detection and progression outcomes (KQ2) were reported in one fair-quality RCT (n = 76,022) in the United Kingdom comparing annual or triennial screening and in one fair-quality registry study using Breast Cancer Screening Consortium (BCSC) data (N = 15,440) to compare annual with biennial screening intervals. The characteristics of tumors diagnosed among those screened with annual versus triennial intervals did not differ in the RCT, though more cancers diagnosed were screen-detected with annual screening (RR: 1.64, 95% CI, 1.28 to 2.09).

In the nonrandomized study, all reported results were stratified by age or hormonal status. Detection of stage IIB+ cancers and cancers with less favorable prognostic characteristics did not differ by screening interval for any reported age groups. Comparisons by menopausal status suggested that premenopausal women with a biennial interval directly preceding their breast cancer diagnosis were at increased risk of stage IIB or higher tumors (RR: 1.28 [95% CI, 1.01 to 1.63], p=.04) and tumors with less favorable prognostic characteristics (RR: 1.11 [95% CI, 1.00 to 1.22], p=.047). For post-menopausal individuals, there was no statistical difference in tumor characteristics by the screening interval preceding diagnosis. The study did not conduct formal tests for interaction in the subgroup comparisons. Neither study reported mortality outcomes, so it is unclear whether these findings would have clinically significant effects on health outcomes.

Harms (KQ3). One RCT reported approximately one additional interval cancer per 1,000 with triennial screening compared with annual screening, and data from four nonrandomized studies were limited and inconsistent. Consistently higher cumulative false positive rates were seen with shorter intervals between screenings. The probability of having at least one false positive recall and biopsy over ten years of screening was higher with annual DBT screening compared with biennial screening, with annual screening resulting in approximately 50 additional false positive biopsies per 1,000 screened over 10 years. Cumulative false positive estimates were highest among young women with dense breasts who were screened annually.

Mammography with Digital Breast Tomosynthesis. No eligible studies reported breast cancer mortality or other health outcomes to compare the effectiveness of screening with DBT versus DM only (KQ1). Intermediate outcomes that compared screening with DBT versus DM were reported in three RCTs (N = 130,196) and one nonrandomized study (N = 92,404) (KQ2). The trials screened all participants with the same screening modality at the second screening round, with DM in three trials and DBT in another. DBT was associated with increased detection of invasive cancer at the first screening round, (pooled RR 1.41, 95% CI 1.20 to 1.64, I^2 8%, 3 trials; n = 129,492); but detection was not statistically different at the second screening round

(pooled RR 0.87, 95% CI 0.73 to 1.05, I^2 0%, 3 trials; n = 105,064) and there was no evidence of a reduced risk of progression to advanced cancer in the second round with DBT compared with DM. The NRSI found higher detection at round one for the group screened with DBT, but higher detection at round two for the group screened with DM at both rounds. The three trials and nonrandomized study reported tumor diameter, histologic grade, and node status. No statistically significant differences in these or other individual tumor prognostic characteristics were reported at the first or second round of screening for any of the included studies. Limited results stratified by age and density in two of the RCTs did not indicate differences in invasive cancer detection at a second round of screening for people who had been screened with DBT at the first screening round, but tests for interaction were not conducted and estimates were imprecise.

Harms (KQ3). Three large RCTs reported no statistically significant difference in the rates of interval cancers following screening with DBT compared with DM (pooled RR 0.87, 95% CI, 0.64 to 1.17, k = 3, n = 130,196, I^2 0%) but data from five nonrandomized studies were mixed, and interpretation was limited by differences in study design. The effects of DBT screening on recall, false-positive recalls, and biopsy rates varied between trials and by screening round, with no or small statistical differences between study groups, not consistently favoring DBT or DM. The cumulative rates of false-positive recall and false-positive biopsy were slightly lower with DBT compared with DM screening, regardless of screening interval (cumulative probability over 10 years: 50% vs 56% for annual screening, 36% vs 38% with biennial screening). An additional adverse effect of DBT reported, radiation exposure, was approximately two times higher in studies where DBT was performed in addition to DM, but exposure was similar in two studies that used DBT to generate synthetic DM images (DBT/sDM).

Supplemental screening. No eligible studies reported health outcomes when comparing supplemental screening with ultrasound or magnetic resonance imaging (MRI) to usual screening with mammography only (KQ1). No studies of supplemental screening with MRI or ultrasound were included for comparisons of benefit because the trials were incomplete and reported only one screening round (KQ2).

Harms (KQ3). In an RCT among women with dense breasts randomized to supplemental screening with MRI following a negative mammogram screening result, the risk of invasive interval cancer was reduced by approximately half (RR 0.47, 95% CI 0.29 to 0.77). Two studies of ultrasound screening in addition to mammogram did not find significant differences in the rates of interval cancers. Supplemental MRI screening for women with dense breasts with a negative mammography resulted in more recalls, false-positive recalls, and biopsies (95, 80, and 63 per 1,000 screened, respectively) than those receiving DM only. With supplemental ultrasound screening, 48 per 1,000 experienced recall in a trial among women ages 40 to 49 and in a BCSC registry analysis, referral to biopsy and false positive biopsy results were twice as high for the group screened with ultrasound compared with those receiving only mammography.

Limitations: Few published comparative effectiveness trials reported more than a single round of screening. Multiple screening rounds are necessary to identify potential intermediate effects of screening, such as stage shift, limiting conclusions about the potential health consequences of different approaches to screening. Data comparing screening outcomes for subgroups of women with different characteristics or breast cancer risk markers were limited, mainly providing

stratified results only without interaction tests. Findings from older studies included in the review may not be applicable to current programs using newer screening modalities and treatment advances.

Conclusions: We did not find evidence of lower breast cancer mortality or risk of progression to advanced cancer in eligible studies comparing different breast cancer screening strategies. There were downstream consequences (e.g., more false-positive results and biopsy) with supplemental screening. Regular mammography screening is associated with reduced breast cancer mortality for women ages 50 to 69, based on trials conducted over 20 years ago, and longer term followup from the trials has not altered these conclusions. Changes in population health, imaging technologies, and available treatments could limit the applicability of older trials. Additionally, nearly all of the trials were conducted outside of the United States and enrolled mainly White European populations. Inequities in breast cancer mortality and length of survival, especially for Black women, also warrants greater attention to health care interventions following screening, including prompt follow-up, diagnosis, and access to high quality treatment and support services, as well as more dedicated research to find effective treatments for triple negative cancers. The limited early evidence from newer comparative effectiveness trials does not yet provide answers to questions about the benefits or harms of different screening strategies, but ongoing and pending trials may further the science in coming years.

Fat Incarceration in Ventral Hernias

Plain Language Summary:

Coverage question: Should OHP cover fixing certain types of hernia in the front of the abdomen when body fat gets stuck or trapped?

Should OHP cover this treatment? No, surgery might not always fix ventral hernias and these hernias usually aren't dangerous to your life.

Coverage Question: Should the complicated hernia guideline be modified to clarify that fat incarceration or strangulation does not make a ventral hernia complicated?

Question source: Mark Buchholtz, CCO medical director

Background: Guideline Note 26 specifies when ventral/umbilical hernias are considered complicated and therefore covered on line 168 COMPLICATED HERNIAS; PERSISTENT HYDROCELE rather than on line 524 UNCOMPLICATED HERNIA AND VENTRAL HERNIA (OTHER THAN DIAPHRAGMATIC HERNIA) only when there is intestinal obstruction or gangrene. However, CCOs continue to get requests for ventral hernia repair with there is fat strangulation, using ICD-10-CM codes such as K42.0 (Umbilical hernia with obstruction, without gangrene) representing fat strangulation. GN26 has wording to try to clarify that this is not the correct use of such codes. CCO medical directors are requesting additional wording to further specify lack of coverage for fat strangulation.

Lack of coverage for fat strangulation in a ventral hernia is due to the fact that fat strangulation is not life-threatening, and repair of ventral hernias is complicated and has a high failure rate. Strangulated hernias that contain only fat can cause pain, but are not life-threatening. However, when a hernia that contains bowel becomes strangulated, life threatening complications such as bowel obstruction and bowel death (infarction) can occur.

Current Prioritized List/Coverage status:

ICD-10 codes for umbilical and ventral hernias without obstruction or gangrene are only on line 524 UNCOMPLICATED HERNIA AND VENTRAL HERNIA (OTHER THAN DIAPHRAGMATIC HERNIA).

ICD-10 codes for umbilical and ventral hernias with obstruction and/or gangrene are included on both lines 168 COMPLICATED HERNIAS; PERSISTENT HYDROCELE and 524

Fat Incarceration in Ventral Hernias

GUIDELINE NOTE 24, COMPLICATED HERNIAS

Lines 168,524

Complicated inguinal and femoral hernias in men are included on Line 168 if the hernia

A) Causes symptoms of intestinal obstruction and/or strangulation; OR
B) Is incarcerated (defined as non-reducible by physical manipulation); OR
C) Causes pain and functional limitations as assessed and documented by a medical professional; OR
D) Affects the patient's ability to obtain or maintain gainful employment.

Otherwise, inguinal and femoral hernias in men are included on Line 524.

Repair of inguinal and femoral hernias in women and in children age 18 or younger are included on Line 168 due to the different natural history of disease in these populations.

Ventral hernias are included on Line 524. Incarcerated ventral hernias (including incarcerated abdominal incisional and umbilical hernias) are included on Line 524, because the chronic incarceration of large ventral hernias does not place the patient at risk for impending strangulation. Ventral hernias are defined as anterior abdominal wall hernias and include primary ventral hernias (epigastric, umbilical, Spigelian), paratomal hernias and most incisional hernias (ventral incisional hernias). ICD-10-CM K42.0, K43.0, K43.3, K43.6 and K46.0 are included on Line 524 when used to designate incarcerated abdominal incisional and umbilical hernias without intestinal obstruction or gangrene.

HERC staff recommendation:

1) Modify GN26 as shown below

GUIDELINE NOTE 24, COMPLICATED HERNIAS

Lines 168,524

Complicated inguinal and femoral hernias in men are included on Line 168 if the hernia

A) Causes symptoms of intestinal obstruction and/or strangulation; OR
B) Is incarcerated (defined as non-reducible by physical manipulation); OR
C) Causes pain and functional limitations as assessed and documented by a medical professional; OR
D) Affects the patient's ability to obtain or maintain gainful employment.

Otherwise, inguinal and femoral hernias in men are included on Line 524.

Repair of inguinal and femoral hernias in women and in children age 18 or younger are included on Line 168 due to the different natural history of disease in these populations.

Ventral hernias are included on Line 524. Incarcerated ventral hernias (including incarcerated abdominal incisional and umbilical hernias) are included on Line 524, because the chronic incarceration of large ventral hernias does not place the patient at risk for impending strangulation. Ventral hernias are defined as anterior abdominal wall hernias and include primary ventral hernias (epigastric, umbilical,

Fat Incarceration in Ventral Hernias

Spigelian), paratomal hernias and most incisional hernias (ventral incisional hernias). ICD-10-CM K42.0, K43.0, K43.3, K43.6 and K46.0 are included on Line 524 when used to designate incarcerated abdominal incisional and umbilical hernias without intestinal obstruction or gangrene, including ventral hernias with only fat or other non-intestinal tissue causing obstruction or strangulation.

PET Scan for Prostate Cancer

Plain Language Summary:

Coverage question: Should a specific type of imaging test be covered 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.

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.

Current Prioritized List/Coverage status:

PET Scan for Prostate Cancer

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:
For monitoring tumor response during active therapy for purposes of treatment planning, PET is covered for

PET Scan for Prostate Cancer

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
      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 recommendation:

1) Modify Diagnostic Guideline D22 as shown below

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

Received Sep. 21, 2021; revision accepted Sep. 21, 2021.
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Published online Sep. 30, 2021.

American Urological Association (AUA)/
Society of Urologic Oncology (SUO)

APPROVED BY THE AUA BOARD OF DIRECTORS APRIL 2023

Authors' disclosure of potential conflicts of interest and author/staff contributions appear at the end of the article.

Reviewed and Updated 2023

ADVANCED PROSTATE CANCER: AUA/SUO GUIDELINE

(Published 2020; Amended 2023)

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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*)

12. Clinicians should obtain a baseline PSA and serial PSAs at three- to six-month intervals after initiation of ADT in mHSPC patients and consider periodic conventional imaging. (*Clinical Principle*)

13. In patients with mHSPC, clinicians should offer germline testing, and consider somatic testing and genetic counseling. (*Clinical Principle*)

Treatment

14. Clinicians should offer ADT with either LHRH agonists or antagonists or surgical castration in patients with mHSPC. (*Strong Recommendation; Evidence Level: Grade B*)

15. In patients with mHSPC, clinicians should offer ADT in combination with either androgen pathway directed therapy (abiraterone acetate plus prednisone, apalutamide, enzalutamide) or chemotherapy (docetaxel). (*Strong Recommendation; Evidence Level: Grade A*)

16. In selected patients with de novo mHSPC, clinicians should offer ADT in combination with docetaxel and either abiraterone acetate plus prednisone or darolutamide. (*Strong Recommendation; Evidence Level: [Abiraterone] Grade A/[Darolutamide] Grade B*)

17. In selected mHSPC patients with low-volume metastatic disease, clinicians may offer primary radiotherapy to the prostate in combination with ADT. (*Conditional Recommendation; Evidence Level: Grade C*)

18. Clinicians should not offer first generation antiandrogens (bicalutamide, flutamide, nilutamide) in combination with LHRH agonists in patients with mHSPC, except to block testosterone flare. (*Strong Recommendation; Evidence Level: Grade A*)

19. Clinicians should not offer oral androgen pathway directed therapy (e.g., abiraterone acetate plus prednisone, apalutamide, bicalutamide, darolutomide, enzalutamide, flutamide, nilutamide) without ADT for patients with mHSPC. (*Expert Opinion*)

NON-METASTATIC CASTRATION-RESISTANT PROSTATE CANCER

Prognosis

20. In nmCRPC patients, clinicians should obtain serial PSA measurements at three- to six-month intervals, and calculate a PSADT starting at the time of development of castration-resistance. (*Clinical Principle*)

21. Clinicians should assess nmCRPC patients for development of metastatic disease using conventional or PSMA PET imaging at intervals of 6 to 12 months. (*Expert Opinion*)

Treatment

22. Clinicians should offer apalutamide, darolutamide, or enzalutamide with continued ADT to nmCRPC patients at high risk for developing metastatic disease (PSADT ≤10 months). (*Strong Recommendation; Evidence Level Grade A*)

23. Clinicians may recommend observation with continued ADT to nmCRPC patients, particularly those at lower risk (PSADT >10 months) for developing metastatic disease. (*Clinical Principle*)

24. Clinicians should not offer systemic chemotherapy or immunotherapy to nmCRPC patients outside the context of a clinical trial. (*Clinical Principle*)

METASTATIC CASTRATION-RESISTANT PROSTATE CANCER

Prognosis

25. In mCRPC patients, clinicians should obtain baseline labs (e.g., PSA, testosterone, LDH, Hgb, alkaline phosphatase level) and review location of metastatic disease (lymph node, bone, visceral), disease-related symptoms, and performance status to inform discussions of prognosis and treatment decision-making. (*Clinical Principle*)

26. In mCRPC patients without PSA progression or new symptoms, clinicians should perform imaging at least annually. (*Expert Opinion*)

27. In mCRPC patients with disease progression (PSA or radiographic progression or new disease-related symptoms) having previously received docetaxel and androgen pathway inhibitor, who are considering ^{177}Lu-PSMA-617, clinicians should order PSMA PET imaging. (*Expert Opinion*)

28. In patients with mCRPC, clinicians should offer germline (if not already performed) and somatic genetic testing to identify DNA repair deficiency, microsatellite instability (MSI) status, tumor mutational burden, and other potential mutations that may inform prognosis and familial cancer risk, as well as direct potential targeted therapies. (*Clinical Principle*)

Treatment

29. In newly diagnosed mCRPC patients, who have not received prior androgen receptor pathway inhibitors, clinicians should offer continued ADT with abiraterone acetate plus prednisone, docetaxel, or enzalutamide. (*Strong Recommendation; Evidence Level: Grade A [abiraterone acetate plus prednisone and enzalutamide]/Grade B [docetaxel]*)

30. In mCRPC patients who are asymptomatic or minimally symptomatic, clinicians may offer sipuleucel-T. (*Conditional Recommendation; Evidence Level: Grade B*)

31. Clinicians should offer radium-223 to patients with symptoms from bony metastases from mCRPC and without known visceral disease or lymphadenopathy >3cm. (*Strong Recommendation; Evidence Level: Grade B*)

32. Clinicians should offer ^{177}Lu-PSMA-617 to patients with progressive mCRPC having previously received docetaxel and androgen pathway inhibitor with a positive PSMA PET imaging study. (*Strong Recommendation; Evidence Level Grade: B*)

33. In mCRPC patients who received prior docetaxel chemotherapy with or without prior abiraterone acetate plus prednisone or enzalutamide for the treatment of CRPC, clinicians may offer cabazitaxel. (*Conditional Recommendation; Evidence Level: Grade B*)

34. In mCRPC patients who received prior docetaxel chemotherapy and abiraterone acetate plus prednisone or enzalutamide, clinicians should recommend cabazitaxel rather than an alternative androgen pathway directed therapy. (*Strong Recommendation; Evidence Level: Grade B*)

35. Clinicians should offer a PARP inhibitor to patients with deleterious or suspected deleterious germline or somatic homologous recombination repair gene-mutated mCRPC following prior treatment with enzalutamide or abiraterone acetate, and/or a taxane-based chemotherapy. Platinum-based chemotherapy may be offered as an alternative for patients who cannot use or obtain a PARP inhibitor. (*Moderate Recommendation; Evidence Level: Grade C*)

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 pacemaker and heart defibrillator placement for heart failure on the Prioritized List be changed?

Should OHP cover this treatment? Yes, for patients meeting certain conditions.

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 ≥ 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

Writing Committee Members*

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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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Gender Affirming Treatment List Changes Required to Comply with HB2002

Plain Language Summary:

Coverage question: Should HERC make the Prioritized List match House Bill 2002 which changes the laws about coverage of gender affirming treatment?

Should OHP cover this treatment? Yes. Even though the Prioritized List won't decide what kinds of gender affirming treatment are covered, aligning the list will make it easier for patients to access the care required by law.

Background: House Bill 2002 passed the Oregon Legislature in June, and was signed by Governor Kotek on 7/13/2023. The bill has many provisions, but among them is Section 24, which takes effect January 1, 2024 and overrides the Prioritized List with respect to gender affirming care coverage for people on the Oregon Health Plan. The full text is provided below. A key provision (highlighted) references statute related to the Prioritized List, so the placement of services on the Prioritized List will have no effect on coverage of services. In addition, with narrow exceptions, paragraph (3) prohibits OHA or CCOs from applying medical necessity criteria, or for denying claims for gender affirming care if they are considered medically necessary by the provider and prescribed according to standards of care, which are not further defined. The law, which takes effect January 1, 2024, specifically prohibits denial of services because they are "cosmetic."

From HB 2002:

SECTION 24.

(1) As used in this section, "gender affirming treatment" means a procedure, service, drug, device or product that a physical or behavioral health care provider prescribes to treat an individual for incongruence between the individual's gender identity and the individual's sex assignment at birth.

(2) Notwithstanding ORS 414.065 and 414.690, medical assistance provided to a member of a coordinated care organization or a medical assistance recipient who is not enrolled in a coordinated care organization shall include gender affirming treatment.

(3) The Oregon Health Authority or a coordinated care organization may not:

(a) Deny or limit gender affirming treatment that is:

(A) Medically necessary as determined by the physical or behavioral health care provider who prescribes the treatment; and

(B) Prescribed in accordance with accepted standards of care.

(b) Deny as a cosmetic service a medically necessary procedure prescribed by a physical or behavioral health care provider as gender affirming treatment, including but not limited to:

(A) Tracheal shave;

(B) Hair electrolysis;

(C) Facial feminization surgery or other facial gender affirming treatment;

(D) Revisions to prior forms of gender affirming treatment; and

(E) Any combination of gender affirming treatment procedures.

(c) Deny or limit gender affirming treatment unless a physical or behavioral health care provider with experience prescribing or delivering gender affirming treatment has first reviewed and approved the denial of or the limitation on the treatment.

(4) A coordinated care organization must:

(a) Contract with a network of gender affirming treatment providers that is sufficient in numbers and geographic locations to meet the network adequacy standards prescribed by ORS 414.609 (1); and

(b)

(A) Ensure that gender affirming treatment services are accessible to all of the coordinated care organization's members without unreasonable delay; or

(B) Ensure that all members have geographical access to non-contracting providers of gender affirming treatment services without unreasonable delay.

(5) The authority shall monitor coordinated care organization compliance with the requirements of this section and may adopt rules necessary to carry out the provisions of this section.

Current Prioritized List/Coverage status:

Coverage of gender affirming medical interventions is currently included on line 312 GENDER DYSPHORIA/TRANSEXUALISM guided by Guideline Note 127 GENDER DYSPHORIA. The line includes a variety of medications, hormone treatments, surgical interventions and therapies, with certain limits.

Line:	312
Condition:	GENDER DYSPHORIA/TRANSEXUALISM (See Guideline Notes 127 and 196)
Treatment:	MEDICAL AND SURGICAL TREATMENT/PSYCHOTHERAPY
ICD-10:	F64.0-F64.9,Z87.890
CPT:	11980-11983,15273,15274,15771,15772,17110,17111,17380,19303,19316-19325, 19340-19350,19370,19371,51040,53405-53430,54120,54125,54520,54660,54690, 55150-55180,55866,55970,55980,56620,56625,56800-56810,57106,57107,57110, 57111,57291-57296,57335,57426,58150-58180,58260,58262,58275-58291,58353, 58356,58541-58544,58550-58554,58563,58570-58573,58660,58661,58720,58940, 64856,64859,90785,90832-90840,90846-90853,90882,90887,97110,97140,97161-97164,97530,98966-98972,99051,99060,99070,99078,99202-99215,99281-99285, 99341-99359,99366,99374,99375,99381-99404,99411-99416,99421-99449,99451, 99452,99487-99491,99495-99498,99605-99607
HCPCS:	C1789,G0068,G0071,G0176,G0177,G0248-G0250,G0318,G0323,G0425-G0427,G0459, G0463,G0466,G0467,G0469,G0470,G0490,G0511,G2012,G2211,G2251-G3003,H0004, H0023,H0032,H0034,H0035,H0038,H2010,H2014,H2027,H2032,H2033,H2038,S9484

Current guideline note:

GUIDELINE NOTE 127, GENDER DYSPHORIA

Line 312

Hormone treatment with GnRH analogues for delaying the onset of puberty and/or continued pubertal development is included on this line for gender questioning children and adolescents. This therapy

should be initiated at the first physical changes of puberty, confirmed by pubertal levels of estradiol or testosterone, but no earlier than Tanner stages 2-3. Prior to initiation of puberty suppression therapy, adolescents must fulfill eligibility and readiness criteria and must have a comprehensive mental health evaluation. Ongoing psychological care is strongly encouraged for continued puberty suppression therapy.

Cross-sex hormone therapy is included on this line for treatment of adolescents and adults with gender dysphoria who meet appropriate eligibility and readiness criteria. To qualify for cross-sex hormone therapy, the patient must:

A) have persistent, well-documented gender dysphoria
B) have the capacity to make a fully informed decision and to give consent for treatment
C) have any significant medical or mental health concerns reasonably well controlled
D) have a comprehensive mental health evaluation provided in accordance with Version 7 of the World Professional Association for Transgender Health (WPATH) Standards of Care (www.wpath.org).

Sex reassignment surgery is included for patients who are sufficiently physically fit and meet eligibility criteria. To qualify for surgery, the patient must:

A) have persistent, well documented gender dysphoria
B) for genital surgeries, have completed twelve months of continuous hormone therapy as appropriate to the member's gender goals unless hormones are not clinically indicated for the individual
C) have completed twelve months of living in a gender role that is congruent with their gender identity unless a medical and a mental health professional both determine that this requirement is not safe for the patient
D) have the capacity to make a fully informed decision and to give consent for treatment
E) have any significant medical or mental health concerns reasonably well controlled
F) for breast/chest surgeries, have one referral from a mental health professional provided in accordance with version 7 of the WPATH Standards of Care.
G) For genital surgeries, have two referrals from mental health professionals provided in accordance with version 7 of the WPATH Standards of Care.

Electrolysis (CPT 17380) and laser hair removal (CPT 17110,17111) are only included on this line as part of pre-surgical preparation for chest or genital surgical procedures also included on this line. These procedures are not included on this line for facial or other cosmetic procedures or as pre-surgical preparation for a procedure not included on this line.

Mammoplasty (CPT 15771, 15772, 19316, 19325, 19340, 19342, 19350) is only included on this line when 12 continuous months of hormonal (estrogen) therapy has failed to result in breast tissue growth of Tanner Stage 5 on the puberty scale OR there is any contraindication to, intolerance of or patient refusal of hormonal therapy.

Revisions to surgeries for the treatment of gender dysphoria are only covered in cases where the revision is required to address complications of the surgery (wound dehiscence, fistula, chronic pain directly related to the surgery, etc.). Revisions are not covered solely for cosmetic issues.

Pelvic physical therapy (CPT 97110,97140,97161-97164, and 97530) is included on this line only for pre- and post-operative therapy related to genital surgeries also included on this line and as limited in Guideline Note 6 REHABILITATIVE AND HABILITATIVE THERAPIES.

Gender Affirming Treatment List Changes Required to Comply with HB2002

HERC staff summary:

Even though these changes will not be legally binding coverage criteria, aligning the list with the coverage described in HB 2002 may reduce administrative barriers to coverage.

In order to reduce barriers to accessing the services which must be covered by law, we recommend adding various CPT codes to line 312 GENDER DYSPHORIA/TRANSEXUALISM, and modifying Guideline Note 127 to reference the law. In addition, several other guideline notes changes are recommended in order to remove barriers to coverage for certain services.

HERC staff recommendations:

1) Add procedure codes in the attached spreadsheet to line 312 to reflect procedures commonly considered to be included in standards of care.
   a. Advise HSD to remove codes from the Excluded and Exempt files when appropriate
2) Modify Guideline Note 127 as shown below
3) Rename line 312 GENDER ~~DYSPHORIA/TRANSEXUALISM~~ AFFIRMING TREATMENT
4) Modify other guidelines relating to gender affirming treatment as shown below

GUIDELINE NOTE 127 GENDER ~~DYSPHORIA~~ AFFIRMING TREATMENT
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.

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

~~Cross-sex hormone therapy is included on this line for treatment of adolescents and adults with gender dysphoria who meet appropriate eligibility and readiness criteria. To qualify for cross-sex hormone therapy, the patient must:~~

~~A) have persistent, well-documented gender dysphoria~~
~~B) have the capacity to make a fully informed decision and to give consent for treatment~~
~~C) have any significant medical or mental health concerns reasonably well controlled~~
~~D) have a comprehensive mental health evaluation provided in accordance with Version 7 of the World Professional Association for Transgender Health (WPATH) Standards of Care (www.wpath.org).~~

Gender Affirming Treatment List Changes Required to Comply with HB2002

~~Sex reassignment surgery is included for patients who are sufficiently physically fit and meet eligibility criteria. To qualify for surgery, the patient must:~~

- ~~A) have persistent, well documented gender dysphoria~~
- ~~B) for genital surgeries, have completed twelve months of continuous hormone therapy as appropriate to the member's gender goals unless hormones are not clinically indicated for the individual~~
- ~~C) have completed twelve months of living in a gender role that is congruent with their gender identity unless a medical and a mental health professional both determine that this requirement is not safe for the patient~~
- ~~D) have the capacity to make a fully informed decision and to give consent for treatment~~
- ~~E) have any significant medical or mental health concerns reasonably well controlled~~
- ~~F) for breast/chest surgeries, have one referral from a mental health professional provided in accordance with version 7 of the WPATH Standards of Care.~~
- ~~G) For genital surgeries, have two referrals from mental health professionals provided in accordance with version 7 of the WPATH Standards of Care.~~

~~Electrolysis (CPT 17380) and laser hair removal (CPT 17110,17111) are only included on this line as part of pre-surgical preparation for chest or genital surgical procedures also included on this line. These procedures are not included on this line for facial or other cosmetic procedures or as pre-surgical preparation for a procedure not included on this line.~~

~~Mammoplasty (CPT 15771, 15772, 19316, 19325, 19340, 19342, 19350) is only included on this line when 12 continuous months of hormonal (estrogen) therapy has failed to result in breast tissue growth of Tanner Stage 5 on the puberty scale OR there is any contraindication to, intolerance of or patient refusal of hormonal therapy.~~

~~Revisions to surgeries for the treatment of gender dysphoria are only covered in cases where the revision is required to address complications of the surgery (wound dehiscence, fistula, chronic pain directly related to the surgery, etc.). Revisions are not covered solely for cosmetic issues.~~

~~Pelvic physical therapy (CPT 97110,97140,97161-97164, and 97530) is included on this line only for pre- and post-operative therapy related to genital surgeries also included on this line and as limited in Guideline Note 6 REHABILITATIVE AND HABILITATIVE THERAPIES.~~

GUIDELINE NOTE 6, REHABILITATIVE AND HABILITATIVE THERAPIES

Lines 31,46,57,68,71,73,80,90,91,127,131,132,136,150,153,160,178,183,184,196,200,201,207,254, 256,272,285,287,292,300,301,309,317,341,345,348,355,356,359,376,377,398,401,402,408,416,417, 422,424,432,443,457,464,467,468,478,486,497,509,556,559,572,590,608

The quantitative limits in this guideline note do not apply to mental health or substance abuse conditions or for gender affirming treatment.

A total of 30 visits per year of rehabilitative therapy and a total of 30 visits per year of habilitative therapy (physical, occupational and speech therapy) are included on these lines when medically

appropriate. Additional visits, not to exceed 30 visits per year of rehabilitative therapy and 30 visits per year of habilitative therapy, may be authorized in cases of a new acute injury, surgery, or other significant change in functional status. Children under age 21 may have additional visits authorized beyond these limits if medically appropriate. Massage therapy (CPT 97124) is included in these service limits. When billing CPT 97124, there must be a minimum of 8 minutes of massage provided. Massage is limited to no more than one session per week.

Physical, occupational and speech therapy are only included on these lines when the following criteria are met:

A) therapy is provided by a licensed physical therapist, occupational therapist, speech language pathologist, physician, or other practitioner licensed to provide the therapy,
B) there is objective, measurable documentation of clinically significant progress toward the therapy plan of care goals and objectives,
C) the therapy plan of care requires the skills of a medical provider, and
D) the client and/or caregiver cannot be taught to carry out the therapy regimen independently.

No limits apply while in a skilled nursing facility for the primary purpose of rehabilitation, an inpatient hospital or an inpatient rehabilitation unit.

Spinal cord injuries, traumatic brain injuries, or cerebral vascular accidents are not subject to the visit limitations during the first year after an acute injury.

GUIDELINE NOTE 67, BROW PTOSIS

Lines 312,393,472,654

Brow ptosis repair is included on line 312 for gender affirming treatment.

Brow ptosis repair is included on Line 393 for congenital brow ptosis in children only when ALL the following criteria are met:

A) The condition developed within the first year of life, and
B) Ptosis interferes with field of vision, and
C) The child has abnormal head posture (e.g., head tilt or turn, chin up or chin down), amblyopia or strabismus or is at high risk for development of amblyopia.

Brow ptosis repair is included on Line 472 for acquired brow ptosis only when ALL the following criteria are present:

A) Brow ptosis is causing a functional impairment of upper/outer visual fields with documented complaints of interference with vision or visual field related activities such as difficulty reading or driving due to upper brow drooping, looking through eyelashes, or seeing the upper eyelid skin, and
B) Photographs show the eyebrow below the supraorbital rim, and
C) Overhanging skin due to brow ptosis is sufficiently low to produce a visually significant field restriction of approximately 30 degrees or less from fixation or a central "pseudo-margin to reflex distance" of 2.0 mm or less, and

D) The visual field impairment cannot be corrected by an upper lid blepharoplasty alone. Otherwise, brow ptosis repair is included on Line 654.

GUIDELINE NOTE 118, SEPTOPLASTY

Lines 42,119,246,287,312,466,506,525,577
Septoplasty is included on line 312 for gender affirming treatment.

Septoplasty is included on ~~these~~ lines 42, 119, 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 130, BLEPHAROPLASTY

Lines 312, 472

Blepharoplasty is ~~covered~~ included on line 312 for gender affirming treatment.

Blepharoplasty is ~~covered~~ included on line 472 when 1) a minimum of 30 degrees of visual field loss exists with upper lid skin/margin in repose, 2) upper eyelid position contributes to difficulty tolerating a prosthesis in an anophthalmic socket, OR 3) essential blepharospasm or hemifacial spasm is present.

Gender Affirming Treatment List Changes Required to Comply with HB2002

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 660 CONDITIONS FOR WHICH CERTAIN INTERVENTIONS ARE UNPROVEN, HAVE NO CLINICALLY IMPORTANT BENEFIT OR HAVE HARMS THAT OUTWEIGH BENEFITS:

Procedure Code	Intervention Description	Rationale	Last Review
~~15773, 15774~~	~~Grafting of autologous fat harvested by liposuction technique to face, eyelids, mouth, neck, ears, orbits, genitalia, hands, and/or feet~~	~~Insufficient evidence of effectiveness; utilization mainly for cosmetic purposes~~	~~November 2019~~
~~15820-15821~~	~~Blepharoplasty, lower eyelid~~	~~No clinically important benefit~~	~~May, 2018~~

GUIDELINE NOTE 216, RHINOPLASTY

Lines 42,119,202,246,287,312,466,506,525

Rhinoplasty is included on line 312 for gender affirming treatment.

Rhinoplasty is included on lines 42, 119, 202, 246, 287, 466, 506 and 525 ~~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

SECTION 23. Section 24 of this 2023 Act is added to and made a part of ORS chapter 414.

SECTION 24. (1) As used in this section, "gender-affirming treatment" means a procedure, service, drug, device or product that a physical or behavioral health care provider prescribes to treat an individual for incongruence between the individual's gender identity and the individual's sex assignment at birth.

(2) Notwithstanding ORS 414.065 and 414.690, medical assistance provided to a member of a coordinated care organization or a medical assistance recipient who is not enrolled in a coordinated care organization shall include gender-affirming treatment.

(3) The Oregon Health Authority or a coordinated care organization may not:

(a) Deny or limit gender-affirming treatment that is:

(A) Medically necessary as determined by the physical or behavioral health care provider who prescribes the treatment; and

(B) Prescribed in accordance with accepted standards of care.

(b) Deny as a cosmetic service a medically necessary procedure prescribed by a physical or behavioral health care provider as gender-affirming treatment, including but not limited to:

(A) Tracheal shave;

(B) Hair electrolysis;

(C) Facial feminization surgery or other facial gender-affirming treatment;

(D) Revisions to prior forms of gender-affirming treatment; and

(E) Any combination of gender-affirming treatment procedures.

(c) Deny or limit gender-affirming treatment unless a physical or behavioral health care provider with experience prescribing or delivering gender-affirming treatment has first reviewed and approved the denial of or the limitation on the treatment.

(4) A coordinated care organization must:

(a) Contract with a network of gender-affirming treatment providers that is sufficient in numbers and geographic locations to meet the network adequacy standards prescribed by ORS 414.609 (1); and

(b)(A) Ensure that gender-affirming treatment services are accessible to all of the coordinated care organization's members without unreasonable delay; or

(B) Ensure that all members have geographical access to non-contracting providers of gender-affirming treatment services without unreasonable delay.

(5) The authority shall monitor coordinated care organization compliance with the requirements of this section and may adopt rules necessary to carry out the provisions of this section.

Code	Prioritized List Placement	Code Description	Recommendation	Additional notes/Comments from experts
11920	EXCLUDED FILE (TRAVEL VACCINES ETC.)	Tattooing, intradermal introduction of insoluble opaque pigments to correct color defects of skin, including micropigmentation; 6.0 sq cm or less	Add to 312 ; remove from Excluded file	These codes are used to bill for nipple-areola complex tattoos.
11921	EXCLUDED FILE (TRAVEL VACCINES ETC.)	Tattooing, intradermal introduction of insoluble opaque pigments to correct color defects of skin, including micropigmentation; 6.1 to 20.0 sq cm	Add to 312 ; remove from Excluded file	These codes are used to bill for nipple-areola complex tattoos.
11922	EXCLUDED FILE (TRAVEL VACCINES ETC.)	Tattooing, intradermal introduction of insoluble opaque pigments to correct color defects of skin, including micropigmentation; each additional 20.0 sq cm, or part thereof (List separately in addition to code for primary procedure)	Add to 312 ; remove from Excluded file	These codes are used to bill for nipple-areola complex tattoos.
11950	555	Subcutaneous injection of filling material (eg, collagen); 1 cc or less	Add to 312	
11951	555	Subcutaneous injection of filling material (eg, collagen); 1.1 to 5.0 cc	Add to 312	
11952	555	Subcutaneous injection of filling material (eg, collagen); 5.1 to 10.0 cc	Add to 312	
11954	555	Subcutaneous injection of filling material (eg, collagen); over 10.0 cc	Add to 312	
13131	1,47,82,120,207,229,242,276 and 6 other lines	Repair, complex, forehead, cheeks, chin, mouth, neck, axillae, genitalia, hands and/or feet; 1.1 cm to 2.5 cm	Add to 312	
13132	1,47,82,112,207,229,242,276 and 6 other lines	Repair, complex, forehead, cheeks, chin, mouth, neck, axillae, genitalia, hands and/or feet; 2.6 cm to 7.5 cm	Add to 312	
13133	1,47,82,207,229,242,276,321 and 3 other lines	Repair, complex, forehead, cheeks, chin, mouth, neck, axillae, genitalia, hands and/or feet; each additional 5 cm or less (List separately in addition to code for primary procedure)	Add to 312	

Code	Prioritized List Placement	Code Description	Recommendation	Additional notes/Comments from experts
15773	662	Grafting of autologous fat harvested by liposuction technique to face, eyelids, mouth, neck, ears, orbits, genitalia, hands, and/or feet; 25 cc or less injectate	Add to 312; remove from GN173/Line 662	
15774	662	Grafting of autologous fat harvested by liposuction technique to face, eyelids, mouth, neck, ears, orbits, genitalia, hands, and/or feet; each additional 25 cc injectate, or part thereof (List separately in addition to code for primary procedure)	Add to 312; remove from GN173/Line 662	
15775	EXCLUDED FILE (TRAVEL VACCINES ETC.)	Punch graft for hair transplant; 1 to 15 punch grafts	Add to 312 ; remove from Excluded file	
15776	EXCLUDED FILE (TRAVEL VACCINES ETC.)	Punch graft for hair transplant; more than 15 punch grafts	Add to 312 ; remove from Excluded file	
15777	502	Implantation of biologic implant (eg, acellular dermal matrix) for soft tissue reinforcement (ie, breast, trunk) (List separately in addition to code for primary procedure)	No change	This code was recommended for addition by experts. HERC placed acellular dermal matrix on this line because of ineffectiveness and concerning potential for harms, though coverage may be required by HB 2002 for gender-affirming treatment.
15820	662	Blepharoplasty, lower eyelid;	Add to 312; remove from GN173/Line 662	
15821	662	Blepharoplasty, lower eyelid; with extensive herniated fat pad	Add to 312; remove from GN173/Line 662	
15822	351,472	Blepharoplasty, upper eyelid;	Add to 312	Modify GN130 to clarify that the limits in the guideline do not apply to line 312.
15823	351,472	Blepharoplasty, upper eyelid; with excessive skin weighting down lid	Add to 312	Modify GN130 to clarify that the limits in the guideline do not apply to line 312.

Code	Prioritized List Placement	Code Description	Recommendation	Additional notes/Comments from experts
15824	EXCLUDED FILE (TRAVEL VACCINES ETC.)	Rhytidectomy; forehead	Add to 312 ; remove from Excluded file	
15825	EXCLUDED FILE (TRAVEL VACCINES ETC.)	Rhytidectomy; neck with platysmal tightening (platysmal flap, P-flap)	Add to 312 ; remove from Excluded file	
15826	EXCLUDED FILE (TRAVEL VACCINES ETC.)	Rhytidectomy; glabellar frown lines	Add to 312 ; remove from Excluded file	
15828	EXCLUDED FILE (TRAVEL VACCINES ETC.)	Rhytidectomy; cheek, chin, and neck	Add to 312 ; remove from Excluded file	
15829	EXCLUDED FILE (TRAVEL VACCINES ETC.)	Rhytidectomy; superficial musculoaponeurotic system (SMAS) flap	Add to 312 ; remove from Excluded file	
15830	625	Excision, excessive skin and subcutaneous tissue (includes lipectomy); abdomen, infraumbilical panniculectomy	Add to 312	This code is used to bill for panniculectomies, which are not in the funded region after weight loss surgery due to unfavorable balance of benefits and harms.
15832	625	Excision, excessive skin and subcutaneous tissue (includes lipectomy); thigh	Add to 312	
15833	625	Excision, excessive skin and subcutaneous tissue (includes lipectomy); leg	Add to 312	
15834	625	Excision, excessive skin and subcutaneous tissue (includes lipectomy); hip	Add to 312	
15835	625	Excision, excessive skin and subcutaneous tissue (includes lipectomy); buttock	Add to 312	
15839	625	Excision, excessive skin and subcutaneous tissue (includes lipectomy); other area	Add to 312	
15876	625	Suction assisted lipectomy; head and neck	Add to 312	

Code	Prioritized List Placement	Code Description	Recommendation	Additional notes/Comments from experts
15877	625	Suction assisted lipectomy; trunk	Add to 312	
15878	625	Suction assisted lipectomy; upper extremity	Add to 312	
15879	625	Suction assisted lipectomy; lower extremity	Add to 312	
17110	137,312,387,401,559,589,613	Destruction (eg, laser surgery, electrosurgery, cryosurgery, chemosurgery, surgical curettement), of benign lesions other than skin tags or cutaneous vascular proliferative lesions; up to 14 lesions	No change-already covered	Current limitation to surgical site preparation will be removed from the guideline note.
17111	137,312,401,559,613	Destruction (eg, laser surgery, electrosurgery, cryosurgery, chemosurgery, surgical curettement), of benign lesions other than skin tags or cutaneous vascular proliferative lesions; 15 or more lesions	No change-already covered	Current limitation to surgical site preparation will be removed from the guideline note.
17380	312,587	Electrolysis epilation, each 30 minutes	No change-already covered	Current limitation to surgical site preparation will be removed from the guideline note.
19357	191, 636	Tissue expander placement in breast reconstructi	Add to 312	
20912	577	Cartilage graft; nasal septum	Add to 312	Revise GL 118, 216 to clarify that the limitations in these guidelines do not apply to line 312.
21025	184,200,401,559	Excision of bone (eg, for osteomyelitis or bone abscess); mandible	Add to 312	
21026	184,200,401,559	Excision of bone (eg, for osteomyelitis or bone abscess); facial bone(s)	Add to 312	
21120	256,285,424,617	Genioplasty; augmentation (autograft, allograft, prosthetic material)	Add to 312	
21121	199,256,617	Genioplasty; sliding osteotomy, single piece	Add to 312	

Code	Prioritized List Placement	Code Description	Recommendation	Additional notes/Comments from experts
21122	256,617	Genioplasty; sliding osteotomies, 2 or more osteotomies (eg, wedge excision or bone wedge reversal for asymmetrical chin)	Add to 312	
21123	256,617	Genioplasty; sliding, augmentation with interpositional bone grafts (includes obtaining autografts)	Add to 312	
21125	617	Augmentation, mandibular body or angle; prosthetic material	Add to 312	
21127	617	Augmentation, mandibular body or angle; with bone graft, onlay or interpositional (includes obtaining autograft)	Add to 312	
21137	256	Reduction forehead; contouring only	Add to 312	
21138	256	Reduction forehead; contouring and application of prosthetic material or bone graft (includes obtaining autograft)	Add to 312	
21139	256	Reduction forehead; contouring and setback of anterior frontal sinus wall	Add to 312	
21141	256	Reconstruction midface, LeFort I; single piece, segment movement in any direction (eg, for Long Face Syndrome), without bone graft	Add to 312	
21142	256	Reconstruction midface, LeFort I; 2 pieces, segment movement in any direction, without bone graft	Add to 312	
21143	256	Reconstruction midface, LeFort I; 3 or more pieces, segment movement in any direction, without bone graft	Add to 312	
21145	256,617	Reconstruction midface, LeFort I; single piece, segment movement in any direction, requiring bone grafts (includes obtaining autografts)	Add to 312	

Code	Prioritized List Placement	Code Description	Recommendation	Additional notes/Comments from experts
21146	256,617	Reconstruction midface, LeFort I; 2 pieces, segment movement in any direction, requiring bone grafts (includes obtaining autografts) (eg, ungrafted unilateral alveolar cleft)	Add to 312	
21147	256,617	Reconstruction midface, LeFort I; 3 or more pieces, segment movement in any direction, requiring bone grafts (includes obtaining autografts) (eg, ungrafted bilateral alveolar cleft or multiple osteotomies)	Add to 312	
21172	256	Reconstruction superior-lateral orbital rim and lower forehead, advancement or alteration, with or without grafts (includes obtaining autografts)	Add to 312	
21175	256	Reconstruction, bifrontal, superior-lateral orbital rims and lower forehead, advancement or alteration (eg, plagiocephaly, trigonocephaly, brachycephaly), with or without grafts (includes obtaining autografts)	Add to 312	
21188	256	Reconstruction midface, osteotomies (other than LeFort type) and bone grafts (includes obtaining autografts)	Add to 312	
21193	202,256,617	Reconstruction of mandibular rami, horizontal, vertical, C, or L osteotomy; without bone graft	Add to 312	
21208	202,617	Osteoplasty, facial bones; augmentation (autograft, allograft, or prosthetic implant)	Add to 312	
21209	202,617	Osteoplasty, facial bones; reduction	Add to 312	
21270	256	Malar augmentation, prosthetic material	Add to 312	
30400	466,506,577	Rhinoplasty, primary; lateral and alar cartilages and/or elevation of nasal tip		

Code	Prioritized List Placement	Code Description	Recommendation	Additional notes/Comments from experts
30410	466,506,577	Rhinoplasty, primary; complete, external parts including bony pyramid, lateral and alar cartilages, and/or elevation of nasal tip		
30420	228,466,506,577	Rhinoplasty, primary; including major septal repair		
30430	EXCLUDED FILE (TRAVEL VACCINES ETC.)	Rhinoplasty, secondary; minor revision (small amount of nasal tip work)	Add to 312 ; remove from Excluded file	
30435	466,506	Rhinoplasty, secondary; intermediate revision (bony work with osteotomies)	Add to 312	
30450	228,466,506	Rhinoplasty, secondary; major revision (nasal tip work and osteotomies)	Add to 312	
30465	466,506,577	Repair of nasal vestibular stenosis (eg, spreader grafting, lateral nasal wall reconstruction)	Add to 312	
30520	42,119,246,287,466,506,525 ,577 and 2 other lines	Septoplasty or submucous resection, with or without cartilage scoring, contouring or replacement with graft	Add to 312	Revise septoplasty guideline to clarify it's covered without the conditions that apply to other indications.
31750	64,71,81,100,285,424	Tracheoplasty; cervical	Add to 312	
40654	207,276,300	Repair lip, full thickness; over one-half vertical height, or complex	Add to 312	
51102	71,79,86,327,352	Aspiration of bladder; with insertion of suprapubic catheter	Add to 312	
52281	21,214,271,327,329	Cystourethroscopy, with calibration and/or dilation of urethral stricture or stenosis, with or without meatotomy, with or without injection procedure for cystography, male or female	Add to 312	
53010	468,591	Urethrotomy or urethrostomy, external (separate procedure); perineal urethra, external	Add to 312	

Code	Prioritized List Placement	Code Description	Recommendation	Additional notes/Comments from experts
53020	86,327	Meatotomy, cutting of meatus (separate procedure); except infant	Add to 312	
53400	86,327	Urethroplasty; first stage, for fistula, diverticulum, or stricture (eg, Johannsen type)	Add to 312	
53450	86,275,327	Urethromeatoplasty, with mucosal advancement	Add to 312	
53520	431	Closure of urethrostomy or urethrocutaneous fistula, male (separate procedure)	Add to 312	
54348	285,434	Repair of hypospadias complication(s) (ie, fistula, stricture, diverticula); requiring extensive dissection, and urethroplasty with flap, patch or tubed graft (including urinary diversion, when performed)	Add to 312	Experts: This code may be used to bill for a post-phalloplasty procedure.
54352	285,434	Revision of prior hypospadias repair requiring extensive dissection and excision of previously constructed structures including re-release of chordee and reconstruction of urethra and penis by use of local skin as grafts and island flaps and skin brought	Add to 312	Experts: This code may be used to bill for a post-phalloplasty procedure.
54360	434	Plastic operation on penis to correct angulation	Add to 312	
54400	523	Insertion of penile prosthesis; non-inflatable (semi-rigid)	Add to 312	
54401	523	Insertion, Penile Prosthesis; Inflatable (Self-Contained)	Add to 312	
54405	523	Insertion of multi-component, inflatable penile prosthesis, including placement of pump, cylinders, and reservoir	Add to 312	

CPT codes to add to Line 312

Code	Prioritized List Placement	Code Description	Recommendation	Additional notes/Comments from experts
54406	285,523	Removal of all components of a multi-component, inflatable penile prosthesis without replacement of prosthesis	Add to 312	
54408	523	Repair of component(s) of a multi-component, inflatable penile prosthesis	Add to 312	
54410	523	Removal and replacement of all component(s) of a multi-component, inflatable penile prosthesis at the same operative session	Add to 312	
54411	523	Removal and replacement of all components of a multi-component inflatable penile prosthesis through an infected field at the same operative session, including irrigation and debridement of infected tissue	Add to 312	
54415	285,523	Removal of non-inflatable (semi-rigid) or inflatable (self-contained) penile prosthesis, without replacement of prosthesis	Add to 312	
54416	523	Removal and replacement of non-inflatable (semi-rigid) or inflatable (self-contained) penile prosthesis at the same operative session	Add to 312	
54417	523	Removal & Replace, Non-Inflatable/Inflatable Penile Prosthesis Infect, W/Irrig & Debride	Add to 312	
54440	207,434	Plastic operation of penis for injury	Add to 312	Experts: This code is used to bill for erectile device placement or removal.
54530	111,258,329	Orchiectomy, radical, for tumor; inguinal approach	Add to 312	Experts: This code is used to bill for erectile device placement or removal.
55120	440	Removal of foreign body in scrotum	Add to 312	This code may be used to bill for a revision that includes the removal of a fragment of a prosthesis.

CPT codes to add to Line 312

Code	Prioritized List Placement	Code Description	Recommendation	Additional notes/Comments from experts
57120	468	Colpocleisis (Le Fort type)	Add to 312	
57425	457,468	Laparoscopy, surgical, colpopexy (suspension of vaginal apex)	Add to 312	
58120	25,37,208,353,404,421,423, 439	Dilation and curettage, diagnostic and/or therapeutic (nonobstetrical)	Add to 312	
58263	25,51,191,208,395,404,468	Vaginal hysterectomy, for uterus 250 g or less; with removal of tube(s), and/or ovary(s), with repair of enterocele	Add to 312	
58267	51,208,468	Vaginal hysterectomy, for uterus 250 g or less; with colpo-urethrocystopexy (Marshall-Marchetti-Krantz type, Pereyra type) with or without endoscopic control	Add to 312	
58270	51,208,468	Vaginal hysterectomy, for uterus 250 g or less; with repair of enterocele	Add to 312	
58292	51,191,208,395,404,468	Vaginal hysterectomy, for uterus greater than 250 g; with removal of tube(s) and/or ovary(s), with repair of enterocele	Add to 312	
58294	51,208,468	Vaginal hysterectomy, for uterus greater than 250 g; with repair of enterocele	Add to 312	
58300	6,191,208,423,470	Insertion of intrauterine device (IUD)	Add to 312	
58301	6,191,285,423,424,470	Removal of intrauterine device (IUD)	Add to 312	
58740	37,51,61,238,395,430,470,5 32 and 2 other lines	Lysis of adhesions (salpingolysis, ovariolysis)	Add to 312	
64905	66,207,416,505,528,500	Nerve pedicle transfer; first stage	Add to 312	This code is used to bill for a procedure related to phalloplasties.
64910	207	Nerve repair; with synthetic conduit or vein allograft (eg, nerve tube), each nerve	Add to 312	
67900	351,472	Repair of brow ptosis (supraciliary, mid-forehead or coronal approach)	Add to 312	Edit guideline to clarify coverage

Code	Prioritized List Placement	Code Description	Recommendation	Additional notes/Comments from experts
76376	662	3D rendering with interpretation and reporting of computed tomography, magnetic resonance imaging, ultrasound, or other tomographic modality with image postprocessing under concurrent supervision; not requiring image postprocessing on an independent workstation	No change	Experts say this code is used to bill for pre-surgical imaging. HERC typically does not cover 3d rendering because it has not been shown to add clinical value, though coverage may be required by HB 2002 for gender affirming treatment. Adding this code to line 312 may cause administrative challenges for plans for other claims.
76377	662	3D rendering with interpretation and reporting of computed tomography, magnetic resonance imaging, ultrasound, or other tomographic modality with image postprocessing under concurrent supervision; requiring image postprocessing on an independent workstation	No change	Experts say this code is used to bill for pre-surgical imaging. HERC typically does not cover 3d rendering because it has not been shown to add clinical value, though coverage may be required by HB 2002 for gender affirming treatment.
92507	57,66,68,90,91,127,178,196 and 8 other lines	Treatment of speech, language, voice, communication, and/or auditory processing disorder; individual	Add to 312	Modify GN6
92508	57,66,68,90,91,127,178,196 and 8 other lines	Treatment of speech, language, voice, communication, and/or auditory processing disorder; group, 2 or more individuals	Add to 312	Modify GN6
97606	8,27,47,79,205,207,235,285 and 2 other lines	Negative pressure wound therapy (eg, vacuum assisted drainage collection), utilizing durable medical equipment (DME), including topical application(s), wound assessment, and instruction(s) for ongoing care, per session; total wound(s) surface area greate	Add to 312	

Code	Prioritized List Placement	Code Description	Recommendation	Additional notes/Comments from experts
S2900	502	Surgical techniques requiring use of robotic surgical system (list separately in addition to code for primary procedure)	No change	This code was recommended for addition by experts. HERC typically does not cover robotic surgery because more cost effective treatments are available.