Health Evidence Review Commission's Value-based Benefits Subcommittee

August 12, 2021

8:00 AM - 1:00 PM

Online Meeting

Join online meeting here

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Section 1.0

Call to Order

AGENDA
VALUE-BASED BENEFITS SUBCOMMITTEE
8/12/2021
8:00am - 1:00pm
Virtual Meeting
All times are approximate

Note: public testimony on specific agenda topics will be taken at the time that agenda item is discussed

I. Call to Order, Roll Call, Approval of Minutes – Kevin Olson **8:00 AM**

II. Staff report – Ariel Smits and Jason Gingerich **8:05 AM**
- **A.** Update on membership
- **B.** Update on RAC process underway
- **C.** Legislative update
- **D.** Errata

III. Straightforward/Consent agenda – Ariel Smits **8:15 AM**
- **A.** Consent table
- **B.** Wig guideline consolidation
- **C.** Hernia guideline and line title clarification
- **D.** Obstructive sleep apnea guidelines merge
- **E.** Gender dysphoria coding update
- **F.** Items not reviewed in past 5 years
    - A. Femoroacetabular impingement syndrome

IV. COVID coding issues **8:25 AM**
- **A.** New COVID-19 HCPCS codes
- **B.** COVID antibody testing

V. 2022 ICD-10 code placement **8:30 AM**
- **A.** Straightforward code placements
- **B.** Code placements requiring discussion
    - **A.** Thrombocytosis
    - **B.** Hereditary alpha tryptasemia
    - **C.** Cervicogenic headache
    - **D.** Immune effector cell-associated neurotoxicity syndrome
    - **E.** Gastric intestinal metaplasia
    - **F.** Contact dermatitis due to bodily fluids
    - **G.** Hematopoietic stem cell transplantation-associated thrombotic microangiopathy [HSCT-TMA]
    - **H.** Sjogren syndrome with dental involvement
    - **I.** Nonsuicidal self-harm

J. Pediatric feeding disorder
K. Post COVID-19 condition, unspecified

VI. Previous discussion topics **9:30 AM**

A. Breast Cancer Index
B. PET scans
A. PET for breast cancer
B. PET/MRI for aducanumab (Aduhelm)
C. PET scan guideline clarification

VII. Break **10:00 AM**

VIII. New Discussion topics **10:15 AM**

A. Preventive services guideline
A. USPSTF colon cancer screening 2021
B. Clarifying Bright Futures as EPSDT periodicity
B. Occipital neuralgia
C. Smoking cessation and elective surgery
D. Rhinoplasty and septoplasty
E. Radiofrequency ablation for uterine fibroids
F. Radiofrequency water vapor ablation of prostate for LUTS
G. Thrush

IX. Coverage guidances

A. Deep brain stimulation for refractory epilepsy **12:00 PM**

X. Public comment **12:55 PM**

XI. Adjournment – Kevin Olson **1:00 PM**

Value-based Benefits Subcommittee Recommendations Summary
For Presentation to:
Health Evidence Review Commission on May 20, 2021

For specific coding recommendations and guideline wording, please see the text of the 5/20/2021 VbBS minutes.

RECOMMENDED CODE MOVEMENT (changes to the 10/1/2021 Prioritized List unless otherwise noted)

- Delete the procedure code for use of bamlanivimab from a funded line as this medication no longer has FDA emergency use authorization
- Add procedure codes for a new COVID-19 vaccine to a funded line
- Add the procedure code for nebulizer therapy to a funded line for pairing with COVID-19 diagnoses
- Add the procedure code for breast cancer index to a funded line (in conjunction with cancer biomarkers guideline changes below)
- Add the diagnosis code for port wine stains to a funded line (in conjunction with hemangiomas guideline changes below)
- Delete multiple diagnosis codes for partial and full tendon tears to more appropriate funded and unfunded lines
- Approve various straightforward coding changes

ITEMS CONSIDERED BUT NO RECOMMENDATIONS FOR CHANGES MADE

- Additional procedures for treatment of tarsal tunnel syndrome were reviewed but not added for pairing
- Non coverage of the Maquet procedure was affirmed
- Addition of platelet rich plasma for treatment of nonhealing lower extremity diabetic wounds was considered but not added as a pairing. (The code was added to a guideline to clarify the intent to continue noncoverage.)

RECOMMENDED GUIDELINE CHANGES (changes to the 10/1/2021 Prioritized List unless otherwise noted)

- Edit the PET scan guideline to allow rescans during active therapy for classic Hodgkin's lymphoma
- Delete two diagnostic guidelines as duplicative of the preventive services guideline
- Add a new guideline regarding when surgery is covered for tethered cord syndrome
- Rename and edit the hemangiomas guideline regarding when treatment is covered for port wine stains
- Edit the cancer biomarker guideline to clarify when the breast cancer index test is covered

VALUE-BASED BENEFITS SUBCOMMITTEE
Virtual Meeting
May 20, 2021
9:00 AM – 1:00 PM

Members Present: Kevin Olson, MD, Chair; Holly Jo Hodges, MD, MBA, Vice-chair; Cris Pinzon, MPH, BSN, BS, RN; Kathryn Schabel, MD; Brian Duty, MD; Mike Collins; Adriane Irwin, PharmD; Regina Dehen, ND, LAc.

Members Absent: None

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

Also Attending: Libbie Rascon (OHA); Patti Maloney; Mary; Holli Thomas; Siobhan Hess; Julie Dhossche, MD & Tracy Funk, MD (OHSU).

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

  The meeting was called to order at 9:00 am and roll was called. A quorum of members was present at the meeting. Minutes from the March 11, 2021 VbBS meeting were reviewed and approved without change.

  Gingerich gave a brief legislative update. He also updated the subcommittee on the Oregon Health Plan waiver update process. He noted that there are coverage guidances moving forward that will likely come to the August meeting.

  Gingerich then gave a presentation regarding proposed ethics and bylaw revisions for HERC and its subcommittees.

  Smits reviewed the errata document.

- **Topic: Straightforward/Consent Agenda**

  Discussion: There was no discussion about the consent agenda items.

  Recommended Actions:
  1) Add 95115-95180 (Allergen immunotherapy) to line 102 POISONING BY INGESTION, INJECTION, AND NON-MEDICINAL AGENTS
  2) Rename line 102 POISONING BY INGESTION, INJECTION, MEDICINAL AND NON-MEDICINAL AGENTS
  3) Remove 21230 and 21235 (Graft; ear cartilage, autogenous) from all lines on the Prioritized List
     a. Advise HSD to place 21230 and 21235 to the Ancillary Procedures File

  MOTION: To approve the recommendations stated in the consent agenda. CARRIES 8-0.

- **Topic: COVID coding updates**

  Discussion: Smits presented the topic summary. There was no discussion.

  Cris Pinzon disclosed a personal interest: this vaccine comes out of a research group she worked with more than 10 years ago.

  Recommended Actions:
  1) Remove HCPCS M0239 (Intravenous infusion, bamlanivimab-xxxx, includes infusion and post administration monitoring) from line 399 INFLUENZA, COVID-19 AND OTHER NOVEL RESPIRATORY VIRAL ILLNESS and advise HSD to place on the Never Covered File
  2) Advise HSD to remove HCPCS Q0239 (Injection, bamlanivimab-xxxx, 700 mg) from the Ancillary File and place on the Never Covered File
  3) Add CPT 91304 (Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) (coronavirus disease [COVID-19]) vaccine, recombinant spike protein nanoparticle, saponin-based adjuvant), 0041A (first dose) and 0042A (second dose) to line 3 PREVENTION SERVICES WITH EVIDENCE OF EFFECTIVENESS
     a. Advise HSD to place these codes on the Ancillary List until the next published Prioritized List
     b. Codes will become effective upon the FDA issuing an Emergency Use Authorization (EUA) and ACIP issuing a recommendation for use per GN106
  4) Add CPT 94640 (Pressurized or nonpressurized inhalation treatment for acute airway obstruction for therapeutic purposes and/or for diagnostic purposes such as sputum induction with an aerosol generator, nebulizer, metered dose inhaler or intermittent positive pressure breathing (IPPB) device) to line 399 INFLUENZA, COVID-19 AND OTHER NOVEL RESPIRATORY VIRAL ILLNESS

  MOTION: To recommend the code changes as presented. CARRIES 8-0.

- **Topic: Breast cancer index re-review**

Discussion: Smits presented the topic summary.

Dehen disclosed that she has a personal interest as a breast cancer survivor and as an advocate for breast cancer patients'; she said she has a bias towards access to information for patients.

Public testimony

Holli Thomas, a breast cancer patient: She said she has no conflicts of interests, other than that she currently has breast cancer. She said that the Commission's guideline D22 on PET scans is outdated. She said she has the most deadly form of breast cancer but has outrun it multiple times. She said that a PET scan would show the molecular movement of her cells. She had a recurrence of her cancer last year, and her PET scan showed cancer in her lymph nodes. She has had multiple CT scans, but is being denied PET scans. She requested that VbBS recommend to HERC a coverage of PET scans for breast cancer. She said that NCCN has changed their guidelines regarding PET scans for breast cancer. She requested that PET be covered for breast cancer, not for initial staging, but they should be allowed to be used for initial staging. Since it's not covered for initial staging, the plan won't cover it for treatment monitoring. She said she has been told that the CCOs have the ability to approve as an exception, but her CCO is denying that.

The subcommittee briefly discussed PET for breast cancer and directed staff to review this topic and bring back to a future meeting for discussion.

HERC staff submitted a friendly amendment to the staff proposal for the BCI topic to add the CPT code for breast cancer index to the breast cancer line and remove from line 662. There was no other discussion on the breast cancer index topic.

Recommended Actions:

1) Add CPT 81518 (Oncology (breast), mRNA, gene expression profiling by real-time RT-PCR of 11 genes (7 content and 4 housekeeping), utilizing formalin-fixed paraffin-embedded tissue, algorithms reported as percentage risk for metastatic recurrence and likelihood of benefit from extended endocrine therapy) to line 191 CANCER OF BREAST; AT HIGH RISK OF BREAST CANCER, remove from line 662 CONDITIONS FOR WHICH CERTAIN INTERVENTIONS ARE UNPROVEN, HAVE NO CLINICALLY IMPORTANT BENEFIT OR HAVE HARMS THAT OUTWEIGH BENEFITS:
2) Modify GN 148 as shown in Appendix A
3) Remove the entry for Breast Cancer Index from GN173 as shown in Appendix A

MOTION: To recommend the code and guideline note changes as modified. CARRIES 8-0.

- **Topic: PET rescans during Hodgkin's therapy**

Discussion: Smits presented the topic summary. Hodges suggested creating a separate section to clarify when PET scan is covered during therapy. The subcommittee changed staff-suggested wording to improve clarity.

There was discussion about clarifying the PET guideline as some parts are confusing. Staff agreed to work on revisions that clarify the guideline sections with HERC leadership and CCO medical directors and bring this guideline back to the August meeting along with the PET for breast cancer re-review.

Recommended Actions:

1) Modify Diagnostic Guideline D22 as shown in Appendix A

MOTION: To recommend the guideline note changes as modified. CARRIES 7-0. *(Absent: Collins)*

- **Topic: Partial and full tendon tears**

Discussion: Smits reviewed the summary document. Hodges expressed concern about adding the shoulder injury line to the sprains/strains guideline because pain is sometimes a sufficient reason for coverage of shoulder sprains and strains. She felt the current line titles specifying the degree of sprain or strain in the shoulder was sufficient. Schabel felt that the staff proposed changes were preferable, as there are a lot of alternative treatments for patients with these condition in the shoulder when the symptom is pain alone. The decision was to accept the staff recommendations.

Recommended Actions:

1) Modify Guideline Note 98 SIGNIFICANT INJURIES TO LIGAMENTS, TENDONS AND MENISCI as shown in Appendix A
    a. Add line 418 DISORDERS OF SHOULDER, INCLUDING SPRAINS/STRAINS GRADE 4 THROUGH 6 to GN98
2) Remove the following ICD-10-CM codes from line 634 SUPERFICIAL WOUNDS WITHOUT INFECTION AND CONTUSIONS or line 608 SPRAINS AND STRAINS OF ADJACENT MUSCLES AND JOINTS, MINOR
    a. S46 (Unspecified injury of other muscles, fascia and tendons of upper arm), S56 (Unspecified injury of other muscles, fascia and tendons of lower arm), S76 (Unspecified injury of other muscles, fascia and tendons of hip and thigh), S86.1-S86.9 (Unspecified injury of other muscles, fascia and tendons of lower leg), S96.90 (Unspecified injury of unspecified muscle and tendon at ankle and foot level)
3) Remove S86.01 (Strain of right Achilles tendon) from line 376 DISRUPTIONS OF THE LIGAMENTS AND TENDONS OF THE ARMS AND LEGS, EXCLUDING THE KNEE, RESULTING IN SIGNIFICANT INJURY/IMPAIRMENT
4) Add ICD-10-CM S46.11 (Unspecified injury of muscle, fascia and tendon of other parts of biceps) to lines 418 DISORDERS OF SHOULDER, INCLUDING SPRAINS/STRAINS GRADE 4 THROUGH 6 and 608 SPRAINS AND STRAINS OF ADJACENT MUSCLES AND JOINTS, MINOR
5) Add the following ICD-10-CM codes to lines 376 DISRUPTIONS OF THE LIGAMENTS AND TENDONS OF THE ARMS AND LEGS, EXCLUDING THE KNEE, RESULTING IN SIGNIFICANT INJURY/IMPAIRMENT and 608 SPRAINS AND STRAINS OF ADJACENT MUSCLES AND JOINTS, MINOR
    a. S46.21 (Unspecified injury of muscle, fascia and tendon of other parts of biceps), S56 (Unspecified injury of other muscles, fascia and tendons of lower arm), S76.00 (Unspecified injury of muscle, fascia and tendon of hip), S86.01 (Strain of right Achilles tendon), S86.30 (Unspecified injury of muscle(s) and tendon(s) of peroneal muscle group at lower leg level), S86.31 (Strain of muscle(s) and tendon(s) of peroneal muscle

group at lower leg level), S96.90 (Unspecified injury of unspecified muscle and tendon at ankle and foot level)

6) Add the following ICD-10-CM codes to lines 376 DISRUPTIONS OF THE LIGAMENTS AND TENDONS OF THE ARMS AND LEGS, EXCLUDING THE KNEE, RESULTING IN SIGNIFICANT INJURY/IMPAIRMENT, 418 DISORDERS OF SHOULDER, INCLUDING SPRAINS/STRAINS GRADE 4 THROUGH 6, and 608 SPRAINS AND STRAINS OF ADJACENT MUSCLES AND JOINTS, MINOR
    a. S46.30 (Unspecified injury of muscle, fascia and tendon of triceps), S46.80 (Unspecified injury of other muscles, fascia and tendons at shoulder and upper arm level), S46.9 (Unspecified injury of unspecified muscle, fascia and tendon at shoulder and upper arm level)
7) Add the following ICD-10-CM codes to lines 376 DISRUPTIONS OF THE LIGAMENTS AND TENDONS OF THE ARMS AND LEGS, EXCLUDING THE KNEE, RESULTING IN SIGNIFICANT INJURY/IMPAIRMENT, 431 INTERNAL DERANGEMENT OF KNEE AND LIGAMENTOUS DISRUPTIONS OF THE KNEE, RESULTING IN SIGNIFICANT INJURY/IMPAIRMENT, and 608 SPRAINS AND STRAINS OF ADJACENT MUSCLES AND JOINTS, MINOR
    a. S76.19 (Other specified injury of unspecified quadriceps muscle, fascia and tendon), S76.30 (Unspecified injury of muscle, fascia and tendon of the posterior muscle group at thigh level), S76.80 (Unspecified injury of other specified muscles, fascia and tendons at thigh level), S76.90 (Unspecified injury of unspecified muscles, fascia and tendons at thigh level), S86.10 (Unspecified injury of other muscle(s) and tendon(s) of posterior muscle group at lower leg level), S86.20 (Unspecified injury of muscle(s) and tendon(s) of anterior muscle group at lower leg level), S86.21 (Strain of muscle(s) and tendon(s) of anterior muscle group at lower leg level), S86.80 (Unspecified injury of other muscle(s) and tendon(s) at lower leg level), S86.81 (Strain of other muscle(s) and tendon(s) at lower leg level, right leg), S86.90 (Unspecified injury of unspecified muscle(s) and tendon(s) at lower leg level), and S86.91 (Strain of unspecified muscle(s) and tendon(s) at lower leg level)

MOTION: To recommend the code and guideline note changes as presented. CARRIES 7-0. *(Absent: Collins)*

- **Topic: Re-review of treatments for patellar subluxation**

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

Recommended Actions:

1) Modify GN173 as shown in appendix A

MOTION: To recommend the guideline note changes as presented. CARRIES 8-0.

- **Topic: USPSTF screening recommendation updates**

Discussion: Smits reviewed the summary documents on proposed changes based on USPSTF screening recommendation updates for lung cancer and for carotid artery disease. There was no discussion.

Recommended Actions:

1) Delete Diagnostic Guideline D14, LUNG CANCER SCREENING as shown in Appendix A
2) Delete Diagnostic Guideline D13, SCREENING FOR CAROTID ARTERY STENOSIS as shown in Appendix A

MOTION: To recommend the guideline note changes as presented. CARRIES 8-0.

- **Topic: Tethered cord**

Discussion: Smits reviewed the summary document. Hodges asked for clarification of what was meant by "constipation unresponsive to medications." She wondered whether the number of medications tried should be specified, or the length of each medication trial. The group felt that the proposed wording regarding constipation was not needed, unless providers request something similar as an indication in the future. The subcommittee members felt that the rest of the proposed guideline was acceptable as written.

Recommended Actions:

1) Adopt a new guideline regarding tethered cords as shown in Appendix B

MOTION: To recommend the addition of the new guideline note as modified. CARRIES 8-0.

- **Topic: Rhinoplasty and septoplasty coverage clarification**

Discussion: Smits reviewed the summary document. There was discussion about when rhinoplasty and/or septoplasty would ever be indicated as part of sinus surgery. HERC staff was directed to review the medically necessary indications for rhinoplasty and septoplasty with ENT, sleep medicine, and plastic surgery specialists and bring back revised coverage recommendations to a future meeting.

- **Topic: Platelet rich plasma for non-healing lower extremity diabetic wounds**

Discussion: Smits reviewed the summary document. Hodges raised concerns that the evidence presented did not include any long-term outcomes. Pinzon was concerned about the NICE recommendation against coverage. Hodges noted that this therapy is very expensive and Olson noted that addition of coverage would result in a large amount of utilization. Schabel and Duty voiced opinions that coverage should not be adopted due to high cost and lack of evidence of impact on important outcomes such as hospitalization or limb amputation. The decision was to add the HCPCS code for platelet rich plasma for wound care to line 662/GN173 due to insufficient evidence of effectiveness.

Recommended Actions:

1) Add HCPCS G0460 (Autologous platelet rich plasma for chronic wounds/ulcers, including phlebotomy, centrifugation, and all other preparatory procedures, administration and dressings, per treatment) to line 662 CONDITIONS FOR WHICH CERTAIN INTERVENTIONS ARE UNPROVEN, HAVE NO CLINICALLY IMPORTANT BENEFIT OR HAVE HARMS THAT OUTWEIGH BENEFITS

2) Modify GN173 as shown in Appendix A

MOTION: To recommend the code and guideline note changes as modified. CARRIES 8-0.

- **Topic: Port wine stain treatment**

Discussion: Smits reviewed the summary document. Drs. Julie Dhossche and Tracy Funk, pediatric dermatologists from OHSU, gave a presentation. There was some discussion among the subcommittee members about whether there should be a lower limit on the size of the lesion treated. Dhossche felt that there should not be, as even a small lesion of the face can have psychosocial impacts, and because lesions that are small on a baby can grow with the baby. Pinzon pointed out that treatment of even a small lesion can prevent downstream negative psychosocial consequences.

Recommended Actions:

1) Add ICD-10-CM Q82.5 (Congenital non-neoplastic nevus) to line 321 DERMATOLOGIC HEMANGIOMAS, COMPLICATED
2) Change the line title of line 321 to DERMATOLOGIC HEMANGIOMAS, COMPLICATED; PORT WINE STAINS
3) Modify GN 13 as shown in Appendix A
    a. Add GN 13 to line 656 DERMATOLOGICAL CONDITIONS WITH NO OR MINIMALLY EFFECTIVE TREATMENTS OR NO TREATMENT NECESSARY

MOTION: To recommend the code and guideline note changes as presented. CARRIES 8-0.

- **Public Comment:**

No additional public comment was received.

- **Issues for next meeting:**

- Wig guideline merge
- PET scans for breast cancer
- Indications for medically necessary rhinoplasty and septoplasty

- **Next meeting:**

August 12, 2021 as a virtual meeting.

- **Adjournment:**

The meeting adjourned at 12:10 PM.

Appendix A
Deleted and Revised Guideline Notes

Deleted Guidelines Notes

~~**DIAGNOSTIC GUIDELINE D13, SCREENING FOR CAROTID ARTERY STENOSIS**~~
~~Screening for carotid artery stenosis (CPT 93880) in the general primary care population is not a covered service.~~

~~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 D14, LUNG CANCER SCREENING**~~
~~Low dose computed tomography is included for annual screening for lung cancer in persons aged 55 to 80 years who have a 30 pack-year smoking history and currently smoke or have quit within the past 15 years. Screening should be discontinued once a person has not smoked for 15 years or develops a health problem that substantially limits life expectancy or the ability or willingness to have curative lung surgery. Current smokers should be offered evidence based smoking cessation interventions.~~

Revised Guideline Notes

DIAGNOSTIC GUIDELINE D22, PET SCAN GUIDELINES

PET Scans are covered for diagnosis of the following cancers only:

- Solitary pulmonary nodules and non-small cell lung cancer
- Evaluation of cervical lymph node metastases when CT or MRI do not demonstrate an obvious primary tumor.

For diagnosis, PET is covered only when it will avoid an invasive diagnostic procedure, or will assist in determining the optimal anatomic location to perform an invasive diagnostic procedure.

PET scans are covered for the initial staging of the following cancers:

- Cervical cancer only when initial MRI or CT is negative for extra-pelvic metastasis
- Head and neck cancer when initial MRI or CT is equivocal
- Colon cancer
- Esophageal cancer
- Solitary pulmonary nodule
- Non-small cell lung cancer
- Lymphoma
- Melanoma

For initial staging, PET is covered when clinical management of the patient will differ depending on the stage of the cancer identified and either:

A) the stage of the cancer remains in doubt after standard diagnostic work up, OR
B) PET replaces one or more conventional imaging studies when they are insufficient for clinical management of the patient.

Appendix A
Deleted and Revised Guideline Notes

For monitoring tumor response during active therapy for purposes of treatment planning, PET is covered for classic Hodgkin's lymphoma treatment only. PET is not covered to monitor tumor response during the planned course of therapy for any other cancer.

Restaging is covered only for cancers for which staging is covered and for thyroid cancer if recurrence is suspected and l131 scintography is negative. For restaging, PET is covered after completion of treatment for the purpose of detecting residual disease, for detecting suspected recurrence or to determine the extent of a known recurrence. ~~PET is not covered to monitor tumor response during the planned course of therapy.~~ PET scans are NOT indicated for routine follow up of cancer treatment or routine surveillance in asymptomatic patients.

PET scans are also indicated for preoperative evaluation of the brain in patients who have intractable seizures and are candidates for focal surgery. PET scans are NOT indicated for cardiac evaluation.

GUIDELINE NOTE 13, HEMANGIOMAS, COMPLICATED; PORT WINE STAINS
Lines 321,627,656
Dermatologic hemangiomas (ICD-10-CM D18.01 Hemangioma and Lymphangioma of skin and subcutaneous tissue) are included on Line 321 when they are ulcerated, infected, recurrently hemorrhaging, or function-threatening (e.g. eyelid hemangioma). Otherwise, they are included on Line 627.

ICD-10-CM Q82.5 (Congenital non-neoplastic nevus) is included on line 321 only when representing port wine stains. For all other diagnoses, it is included on line 656. Treatment of port wine stains is only included on line 321 when treatment is with pulsed dye lasers and:

1) When lesions are located on the face and neck; OR
2) When lesions are located on the trunk or extremities AND are associated with recurrent bleeding or painful nodules.

Otherwise, treatment of port wine stains is included on line 656.

GUIDELINE NOTE 98, SIGNIFICANT INJURIES TO LIGAMENTS, TENDONS AND MENISCI

Lines 376,418,431,608

Significant injuries to ligaments, tendons and/or menisci are those that result in clinically demonstrable joint instability or mechanical interference with motion. Significant injuries are covered on Line 376, 418, or 431 ~~or Line 431~~ for both medical and surgical interventions non-significant injuries are included on Line 608.

Iliotibial (IT) band syndrome (ICD10 M76.3) is included on Line 376 only for pairing with 2 physical therapy visits with a provider licensed to provide physical therapy services, anti-inflammatory medications, and primary care office visits. Otherwise, it is included on Line 608.

Appendix A
Deleted and Revised Guideline Notes

GUIDELINE NOTE 148, BIOMARKER TESTS OF CANCER TISSUE

Lines 157,184,191,229,262,271,329

The use of tissue of origin testing (e.g. CPT 81504) is included on Line 662 CONDITIONS FOR WHICH CERTAIN INTERVENTIONS ARE UNPROVEN, HAVE NO CLINICALLY IMPORTANT BENEFIT OR HAVE HARMS THAT OUTWEIGH BENEFITS.

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

- Oncotype DX Breast Recurrence Score (CPT 81519) for breast tumors that are estrogen receptor positive, HER2 negative, and either lymph node negative, or lymph node positive with 1-3 involved nodes.
- EndoPredict (CPT 81522) and Prosigna (CPT 81520 or PLA 0008M) for breast tumors that are estrogen receptor positive, HER2 negative, and lymph node negative.
- MammaPrint (using CPT 81521 or HCPCS S3854) for breast tumors that are estrogen receptor or progesterone receptor positive, HER2 negative, lymph node negative, and only in those cases categorized as high clinical risk.

For early stage breast cancer that is estrogen receptor positive, HER2 negative, and lymph node negative, Breast Cancer Index (CPT 81518) is included on line 191 when the patient is willing to use the test results in a shared decision-making process regarding prolonged adjuvant endocrine therapy.

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

Oncotype DX Breast DCIS Score (CPT 81479) is ~~and Breast Cancer Index (CPT 81518) are~~ included on Line 662 CONDITIONS FOR WHICH CERTAIN INTERVENTIONS ARE UNPROVEN, HAVE NO CLINICALLY IMPORTANT BENEFIT OR HAVE HARMS THAT OUTWEIGH BENEFITS.

For melanoma, BRAF gene mutation testing (CPT 81210) is included on Line 229. DecisionDx-Melanoma (CPT 81529) is included on Line 662.

For lung cancer, epidermal growth factor receptor (EGFR) gene mutation testing (CPT 81235) is included on Line 262 only for non-small cell lung cancer. KRAS gene mutation testing (CPT 81275) is not included on this line.

For colorectal cancer, KRAS gene mutation testing (CPT 81275) is included on Line 157. BRAF (CPT 81210) and Oncotype DX are not included on this line. Microsatellite instability (MSI) is included on the Line 662.

For bladder cancer, Urovysion testing is included on Line 662.

Appendix A
Deleted and Revised Guideline Notes

For prostate cancer, Oncotype DX Genomic Prostate Score, Prolaris Score Assay (CPT 81541), and Decipher Prostate RP (CPT 81542) are included on Line 662.

For thyroid cancer, Afirma gene expression classifier (CPT 81546) is included on Line 662.

The development of this guideline note was informed by a HERC coverage guidance on Biomarkers Tests of Cancer Tissue for Prognosis and Potential Response to Treatment; the prostate-related portion of that coverage guidance was superseded by a Coverage Guidance on Gene Expression Profiling for Prostate Cancer. 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
G0460	Autologous platelet rich plasma for chronic wounds/ulcers, including phlebotomy, centrifugation, and all other preparatory procedures, administration and dressings, per treatment	Insufficient evidence of effectiveness	May, 2021
27418	Anterior tibial tubercleplasty (eg, Maquet type procedure)	Harms outweigh benefits, more efficacious procedures exist	May, 2021 ~~May, 2011~~
~~81518~~	~~Oncology (breast), mRNA, gene expression profiling by real-time RT-PCR of 11 genes (7 content and 4 housekeeping), utilizing formalin-fixed paraffin-embedded tissue, algorithms reported as percentage risk for metastatic recurrence and likelihood of benefit from extended endocrine therapy~~	~~Insufficient evidence of effectiveness~~	~~November 2018~~ ~~Coverage Guidance May, 2018~~

Appendix B
New Guideline Notes

GUIDELINE NOTE XXX TETHERED CORD
Lines 346,529

Surgical repair of tethered cord is included on line 346 for patient when the following conditions are met:

1) Symptoms:
    a. Infants and pre-walking/toilet trained children with cutaneous markers or orthopedic deformities; OR
    b. Children and adults with bladder and bowel incontinence of neurologic origin AND/OR sensorimotor lower extremity deficits; AND
2) Imaging:
    a. Ultrasound findings consistent with tethered cord for infants up to 3 months; OR
    b. MRI findings consistent with tethered cord (i.e. conus termination below the L2 vertebral body, intradural or extradural lipoma, lipomeningocele, lipomyelomeningocele, split cord malformation, low conus termination at the L2 vertebral body with thickened non-fatty filum in a symptomatic patient, or previous myelomeningocele repair or other spinal surgery resulting in fibrous adhesions).

Surgery for tethered cord in patients not meeting the above criteria are included on line 529.

Section 2.0

Staff Report

Section 3.0

Consent Agenda-

Straightforward Items

Consent Agenda Issues—August 2021

Code	Code Description	Line(s) Involved	Issue	Recommendation(s)
Q52.9	Congenital malformation of female genitalia, unspecified	332 CONDITIONS REQUIRING HYPERBARIC OXYGEN THERAPY 353 STRUCTURAL CAUSES OF AMENORRHEA	ICD10 Q52.9 erroneously appears on line 332. It should appear on line 353, along with all other Q52 codes	Remove Q52.9 from line 332 Add Q52.9 to line 353
C9778	Colpopexy, vaginal; minimally invasive extra-peritoneal approach (sacrospinous)	455 URINARY INCONTINENCE 466 UTERINE PROLAPSE; CYSTOCELE	HCPCS C9778 is a new HCPCS code effective June, 2021. It is similar to CPT 57425 Laparoscopy, surgical, colpopexy (suspension of vaginal apex) which is on lines 455 and 466	Add C9778 to lines 455 and 466
S46.10 S46.20	Unspecified injury of muscle, fascia and tendon of long head of biceps Unspecified injury of muscle, fascia and tendon of other parts of biceps	376 DISRUPTIONS OF THE LIGAMENTS AND TENDONS OF THE ARMS AND LEGS, EXCLUDING THE KNEE, RESULTING IN SIGNIFICANT INJURY/IMPAIRMENT 418 DISORDERS OF SHOULDER, INCLUDING SPRAINS/STRAINS GRADE 4 THROUGH 6 608 SPRAINS AND STRAINS OF ADJACENT MUSCLES AND JOINTS, MINOR 634 SUPERFICIAL WOUNDS WITHOUT INFECTION AND CONTUSIONS	At the May, 2021 meeting, ICD10 S46.10 and S46.20 had the correct code description but incorrect codes in the approved coding changes for partial and full tendon tears. The incorrect codes S46.11 and S46.21 should stay on their current lines (418 and 608). S46.10 and S46.20 should be removed from line 634 and placed on lines 418 and 608 (S46.10) and lines 376 and 608 (S46.20)	Add S46.10 to lines 418 and 608 Remove S46.10 from line 634 Add S46.20 to lines 376 and 608 Remove S46.20 from line 634

Consent Agenda Issues—August 2021

Code	Code Description	Line(s) Involved	Issue	Recommendation(s)
20912	Cartilage graft; nasal septum	160 TRAUMATIC AMPUTATION OF ARM(S), HAND(S), THUMB(S), AND FINGER(S) (COMPLETE)(PARTIAL) WITH AND WITHOUT COMPLICATION	CPT 20912 is mistakenly on line 160. It should remain only on line 576 DEVIATED NASAL SEPTUM, ACQUIRED DEFORMITY OF NOSE, OTHER DISEASES OF UPPER RESPIRATORY TRACT	Remove 20912 from line 160
G0452	Molecular pathology procedure; physician interpretation and report		G0452 is currently "suspend for review" which is a file for codes that require manual determination of what service is being provided. This code is used for the pathologist time for interpreting a molecular test. It is more appropriate to be Diagnostic.	Advise HSD to remove G0452 from the SUSPEND FOR REVIEW file Advise HSD to add G0452 to the DIAGNOSTIC PROCEDURES file

Wig Guidelines Merge

Issue: at the March, 2021 VBBS/HERC meeting, coding specifications were deleted and some items previously in coding specifications were make into new guidelines. One new guideline involved wigs. HERC staff have identified that there was a pre-existing wig guideline and propose combining the new, not yet implemented guideline and the old guideline.

GUIDELINE NOTE XXX WIGS
Line 424,586
ICD-10-CM codes L58.0 (Acute radiodermatitis), L64.0 (Drug-induced androgenic alopecia) and L65.8 (Other specified nonscarring hair loss) are only included on this line for pairing with HCPC A9282 (Wig). Otherwise these ICD10 codes are included on line 586.

GUIDELINE NOTE 157, WIGS
Line 424
Wigs (HCPCS A9282) are covered only for hair loss due to chemotherapy or radiation therapy.

HERC staff recommendations:

1) Do not include the new wig guideline from the March 2021 meeting in the October 1, 2021 Prioritized List
2) Modify Guideline Note 157 as shown below
    a. Add to line 586 DISEASE OF NAILS, HAIR AND HAIR FOLLICLES

GUIDELINE NOTE 157, WIGS
Line 424,586
Wigs (HCPCS A9282) are covered only for hair loss due to chemotherapy or radiation therapy.

ICD-10-CM codes L58.0 (Acute radiodermatitis), L64.0 (Drug-induced androgenic alopecia) and L65.8 (Other specified nonscarring hair loss) are only included on line 424 for pairing with HCPC A9282 (Wig). Otherwise, these ICD10 codes are included on line 586.

Hernia Guideline and Line Title Clarification

Issue: in March 2021, the HERC adopted a revised guideline regarding hernias which will take effect January 1, 2022. There continues to be some questions regarding intent of coverage for children due to the language in the line titles. This language now appears redundant to the wording in the guideline and is no longer necessary. HERC staff suggest some clarifying language below.

HERC staff recommendations:

1) Rename Line 168 COMPLICATED HERNIAS; ~~UNCOMPLICATED INGUINAL HERNIA IN CHILDREN AGE 18 AND UNDER;~~ PERSISTENT HYDROCELE.
2) Rename 524 UNCOMPLICATED HERNIA AND VENTRAL HERNIA (OTHER THAN ~~INGUINAL HERNIA IN CHILDREN AGE 18 AND UNDER OR~~ DIAPHRAGMATIC HERNIA)
3) Revise the version of Guideline Note 24 scheduled for inclusion on the Prioritized List on January 1, 2022

GUIDELINE NOTE 24, COMPLICATED HERNIAS

Lines 168,524

Complicated inguinal and femoral hernias in men are included on Line 168 if the hernia

1) causes symptoms of intestinal obstruction and/or strangulation; OR
2) is incarcerated (defined as non-reducible by physical manipulation); OR
3) causes pain and functional limitations as assessed and documented by a medical professional OR
4) Affects the patient's ability to obtain or maintain gainful employment.

Repair of inguinal and femoral hernias in women and in children age 18 and younger are included on Line 168 due to the different natural history of disease in ~~this~~ 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), parastomal hernias and most incisional hernias (ventral incisional hernias). 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.

Obstructive Sleep Apnea Guidelines Clarification

Question: Should the three obstructive sleep apnea (OSA) guidelines be merged into two for clarity and east of use?

Question source: CCO medical directors

Issue: Currently, there are three guidelines for OSA. Diagnostic Guideline D8 outlines the diagnostic testing coverage for adults with symptoms of sleep apnea. Guideline note 27 outlines the treatment options for adults once they receive an OSA diagnosis. Guideline note 118 contains both the diagnostic testing coverage as well as the treatment coverage for OSA for children. The existence of three guidelines can be confusing for reviewers. Additionally, CCO medical directors are unclear if GN118 applies to symptom codes such as snoring as it is not a diagnostic guideline and the ICD10 codes for snoring and similar conditions are not on line 202 SLEEP APNEA, NARCOLEPSY AND REM BEHAVIORAL DISORDER.

Current Prioritized List guidelines:

DIAGNOSTIC GUIDELINE D8, DIAGNOSTIC TESTING FOR OBSTRUCTIVE SLEEP APNEA (OSA) IN ADULTS
In adults with clinical signs and symptoms consistent with obstructive sleep apnea (OSA), a home sleep study is the first-line diagnostic test for most patients, when available.

Polysomnography in a sleep lab is indicated as a first-line test for patients with significant cardiorespiratory disease, potential respiratory muscle weakness due to a neuromuscular condition, awake hypoventilation or suspicion of sleep related hypoventilation, chronic opioid medication use, history of stroke or severe insomnia. If a patient has had an inconclusive (or negative) home sleep apnea test and a clinical suspicion for OSA remains, then attended polysomnography is included on this line. Split night diagnostic protocols are required when a diagnosis of OSA is confirmed in the first portion of the night.

For portable devices, Type II-III are included on this line. Type IV sleep testing devices must measure three or more channels, one of which is airflow, to be included on this line. Sleep testing devices that are not Type1-IV and measure three or more channels that include actigraphy, oximetry, and peripheral arterial tone, are included on this line.

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 27, SLEEP APNEA

Line 202

CPAP is covered initially when all of the following conditions are met:

- 12 week 'trial' period to determine benefit. This period is covered if apnea-hypopnea index (AHI) or respiratory disturbance index (RDI) is greater than or equal to 15 events per hour; or if between 5 and 14 events with additional symptoms including one or more of the following:
    - excessive daytime sleepiness defined as either an Epworth Sleepiness Scale score>10 or daytime sleepiness interfering with ADLs that is not attributable to another modifiable sedating condition (e.g. narcotic dependence), or
    - documented hypertension, or

  - ischemic heart disease, or
  - history of stroke;
- Providers must provide education to patients and caregivers prior to use of CPAP machine to ensure proper use; and
- Positive diagnosis through polysomnogram (PSG) or Home Sleep Test (HST).

CPAP coverage subsequent to the initial 12 weeks is based on documented patient tolerance, compliance, and clinical benefit. Compliance (adherence to therapy) is defined as use of CPAP for at least four hours per night on 70% of the nights during a consecutive 30-day period.

Mandibular advancement devices (oral appliances) are covered for those for whom CPAP fails or is contraindicated.

Surgery for sleep apnea in adults is not included on this line (due to lack of evidence of efficacy). Surgical codes are included on this line only for children who meet criteria according to Guideline Note 118 OBSTRUCTIVE SLEEP APNEA DIAGNOSIS AND TREATMENT FOR CHILDREN.

Hypoglossal nerve stimulation for treatment of obstructive sleep apnea is not included on this line due to insufficient evidence of effectiveness and evidence of harm.

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, OBSTRUCTIVE SLEEP APNEA DIAGNOSIS AND TREATMENT FOR CHILDREN

Line 202

Obstructive sleep apnea (OSA) in children (18 or younger) must be diagnosed by

A) nocturnal polysomnography with an AHI >5 episodes/h or AHI>1 episodes/h with history and exam consistent with OSA, OR
B) nocturnal pulse oximetry with 3 or more SpO2 drops <90% and 3 or more clusters of desaturation events, or alternatives desaturation (>3%) index >3.5 episodes/h, OR
C) use of a validated questionnaire (such as the Pediatric Sleep Questionnaire or OSA 18), OR
D) consultation with a sleep medicine specialist.

Polysomnography and/or consultation with a sleep medicine specialist to support the diagnosis of OSA and/or to identify perioperative risk is recommended for

A) high-risk children (i.e. children with cranio-facial abnormalities, neuromuscular disorders, Down syndrome, etc.)
B) children with equivocal indications for adenotonsillectomy (such as discordance between tonsillar size on physical examination and the reported severity of sleep-disordered breathing),
C) children younger than three years of age

Adenotonsillectomy is an appropriate first line treatment for children with OSA. Weight loss is recommended in addition to other therapy in patients who are overweight or obese. Adenoidectomy without tonsillectomy is only covered when a child with OSA has previously had a tonsillectomy, when

tonsillectomy is contraindicated, or when tonsillar hypertrophy is not present. More complex surgical treatments are only included on this line for children with craniofacial anomalies.

Intranasal corticosteroids are an option for children with mild OSA in whom adenotonsillectomy is contraindicated or for mild postoperative OSA.

CPAP is covered for a 3 month trial for children through age 18 who have

A) undergone surgery or are not candidates for surgery, AND
B) have documented residual sleep apnea symptoms (sleep disruption and/or significant desaturations) with residual daytime symptoms (daytime sleepiness or behavior problems)

CPAP will be covered for children through age 18 on an ongoing basis if:

- There is documentation of improvement in sleep disruption and daytime sleepiness and behavior problems with CPAP use
- Annual re-evaluation for CPAP demonstrates ongoing clinical benefit and compliance with use, defined as use of CPAP for at least four hours per night on 70% of the nights in a consecutive 30 day period

HERC staff recommendation:

1) Merge Diagnostic Guideline D8, Guideline 27 and Guideline 118 into two guidelines as shown below
    a. Delete statement about weight loss being recommended as part of the treatment plan for children. This is a best practice statement, not a coverage statement.

DIAGNOSTIC GUIDELINE D8, DIAGNOSTIC TESTING FOR OBSTRUCTIVE SLEEP APNEA (OSA) ~~IN ADULTS~~

For adults over the age of 18 years:

A) For patients ~~In adults~~ with clinical signs and symptoms consistent with obstructive sleep apnea (OSA), a home sleep study is the first-line diagnostic test for most patients, when available.
    1) For portable devices, Type II-III are included on this line. Type IV sleep testing devices must measure three or more channels, one of which is airflow, to be included on this line. Sleep testing devices that are not Type I-IV and measure three or more channels that include actigraphy, oximetry, and peripheral arterial tone, are included on this line.

B) Polysomnography in a sleep lab is indicated as a first-line test for patients with significant cardiorespiratory disease, potential respiratory muscle weakness due to a neuromuscular condition, awake hypoventilation or suspicion of sleep related hypoventilation, chronic opioid medication use, history of stroke or severe insomnia.

C) If a patient has had an inconclusive (or negative) home sleep apnea test and a clinical suspicion for OSA remains, then attended polysomnography is included on this line. Split night diagnostic protocols are required when a diagnosis of OSA is confirmed in the first portion of the night.

~~For portable devices, Type II-III are included on this line. Type IV sleep testing devices must measure three or more channels, one of which is airflow, to be included on this line. Sleep testing devices that are not Type1-IV and measure three or more channels that include actigraphy, oximetry, and peripheral arterial tone, are included on this line~~.

For children age of 18 years or younger:

A) Obstructive sleep apnea (OSA) ~~in children (18 or younger)~~ must be diagnosed by
    1) nocturnal polysomnography with an AHI >5 episodes/h or AHI>1 episodes/h with history and exam consistent with OSA, OR
    2) nocturnal pulse oximetry with 3 or more SpO2 drops <90% and 3 or more clusters of desaturation events, or alternatives desaturation (>3%) index >3.5 episodes/h, OR
    3) use of a validated questionnaire (such as the Pediatric Sleep Questionnaire or OSA 18), OR
    4) consultation with a sleep medicine specialist.

B) Polysomnography and/or consultation with a sleep medicine specialist to support the diagnosis of OSA and/or to identify perioperative risk is recommended for
    1) high-risk children (i.e. children with cranio-facial abnormalities, neuromuscular disorders, Down syndrome, etc.)
    2) children with equivocal indications for adenotonsillectomy (such as discordance between tonsillar size on physical examination and the reported severity of sleep-disordered breathing), children younger than three years of age

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 27, TREATMENT OF SLEEP APNEA

Line 202

For adults over the age of 18 years:

A) CPAP is covered initially when all of the following conditions are met:
   1) 12 week 'trial' period to determine benefit. This period is covered if apnea-hypopnea index (AHI) or respiratory disturbance index (RDI) is greater than or equal to 15 events per hour; or if between 5 and 14 events with additional symptoms including one or more of the following:
   2) excessive daytime sleepiness defined as either an Epworth Sleepiness Scale score>10 or daytime sleepiness interfering with ADLs that is not attributable to another modifiable sedating condition (e.g. narcotic dependence), or
   3) documented hypertension, or
   4) ischemic heart disease, or
   5) history of stroke
   6) Additionally
      a) Providers must provide education to patients and caregivers prior to use of CPAP machine to ensure proper use; and
      b) Positive diagnosis through polysomnogram (PSG) or Home Sleep Test (HST).

B) CPAP coverage subsequent to the initial 12 weeks is based on documented patient tolerance, compliance, and clinical benefit. Compliance (adherence to therapy) is defined as use of CPAP for at least four hours per night on 70% of the nights during a consecutive 30-day period.

C) Mandibular advancement devices (oral appliances) are covered for those for whom CPAP fails or is contraindicated.

D) Surgery for sleep apnea in adults is not included on this line (due to lack of evidence of efficacy). Surgical codes are included on this line only for children who meet criteria below ~~according to Guideline Note 118 OBSTRUCTIVE SLEEP APNEA DIAGNOSIS AND TREATMENT FOR CHILDREN~~.

E) Hypoglossal nerve stimulation for treatment of obstructive sleep apnea is not included on this line due to insufficient evidence of effectiveness and evidence of harm.

For children age of 18 years or younger:

A) Adenotonsillectomy is an appropriate first line treatment for children with OSA. ~~Weight loss is recommended in addition to other therapy in patients who are overweight or obese.~~ Adenoidectomy without tonsillectomy is only covered when a child with OSA has previously had a tonsillectomy, when tonsillectomy is contraindicated, or when tonsillar hypertrophy is not present. More complex surgical treatments are only included on this line for children with craniofacial anomalies.

B) Intranasal corticosteroids are an option for children with mild OSA in whom adenotonsillectomy is contraindicated or for mild postoperative OSA.

C) CPAP is covered for a 3 month trial for children through age 18 who have
   1) undergone surgery or are not candidates for surgery, AND
   2) have documented residual sleep apnea symptoms (sleep disruption and/or significant desaturations) with residual daytime symptoms (daytime sleepiness or behavior problems)

D) CPAP will be covered for children through age 18 on an ongoing basis if:
   1) There is documentation of improvement in sleep disruption and daytime sleepiness and behavior problems with CPAP use, AND

2) Annual re-evaluation for CPAP demonstrates ongoing clinical benefit and compliance with use, defined as use of CPAP for at least four hours per night on 70% of the nights in a consecutive 30 day period

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, OBSTRUCTIVE SLEEP APNEA DIAGNOSIS AND TREATMENT FOR CHILDREN**~~

~~*Line 202*~~

~~Obstructive sleep apnea (OSA) in children (18 or younger) must be diagnosed by~~

E) ~~nocturnal polysomnography with an AHI >5 episodes/h or AHI>1 episodes/h with history and exam consistent with OSA, OR~~
F) ~~nocturnal pulse oximetry with 3 or more SpO2 drops <90% and 3 or more clusters of desaturation events, or alternatives desaturation (>3%) index >3.5 episodes/h, OR~~
G) ~~use of a validated questionnaire (such as the Pediatric Sleep Questionnaire or OSA 18), OR~~
H) ~~consultation with a sleep medicine specialist.~~

~~Polysomnography and/or consultation with a sleep medicine specialist to support the diagnosis of OSA and/or to identify perioperative risk is recommended for~~

D) ~~high-risk children (i.e. children with cranio-facial abnormalities, neuromuscular disorders, Down syndrome, etc.)~~
E) ~~children with equivocal indications for adenotonsillectomy (such as discordance between tonsillar size on physical examination and the reported severity of sleep-disordered breathing),~~
F) ~~children younger than three years of age~~

~~Adenotonsillectomy is an appropriate first line treatment for children with OSA. Weight loss is recommended in addition to other therapy in patients who are overweight or obese. Adenoidectomy without tonsillectomy is only covered when a child with OSA has previously had a tonsillectomy, when tonsillectomy is contraindicated, or when tonsillar hypertrophy is not present. More complex surgical treatments are only included on this line for children with craniofacial anomalies.~~

~~Intranasal corticosteroids are an option for children with mild OSA in whom adenotonsillectomy is contraindicated or for mild postoperative OSA.~~

~~CPAP is covered for a 3 month trial for children through age 18 who have~~

C) ~~undergone surgery or are not candidates for surgery, AND~~
D) ~~have documented residual sleep apnea symptoms (sleep disruption and/or significant desaturations) with residual daytime symptoms (daytime sleepiness or behavior problems)~~

~~CPAP will be covered for children through age 18 on an ongoing basis if:~~

- ~~There is documentation of improvement in sleep disruption and daytime sleepiness and behavior problems with CPAP use~~

- ~~Annual re-evaluation for CPAP demonstrates ongoing clinical benefit and compliance with use, defined as use of CPAP for at least four hours per night on 70% of the nights in a consecutive 30 day period~~

Surgical Coding for Gender Dysphoria
August 2021 Update

Question: should various CPT codes used for gender dysphoria "top" and "bottom" surgery be added to the gender dysphoria line?

Question source: Jens Berli MD, Christine Milano MD, and Daniel Dugi MD, OHSU Gender Surgery program

Issue: The OHSU Gender Surgery program identified several codes that are missing from the gender dysphoria line. Previously, the HERC has indicated intent to cover breast and genital surgery for patients who desire to transition to their lived gender. The requested codes are all currently on other covered lines.

Additionally, the gender dysphoria line is attached to the guideline specifying with breast implant revision is covered, but the CPT codes for these revisions are not included on the line.

HERC staff recommendations:

1) Add to line 312 GENDER DYSPHORIA/TRANSEXUALISM for chest surgery
    a. 19370 Revision of peri-implant capsule, breast, including capsulotomy, capsulorrhaphy, and/or partial capsulectomy
    b. 19371 Peri-implant capsulectomy, breast, complete, including removal of all intracapsular contents
    c. Will be governed by GUIDELINE NOTE 196, BREAST SURGERY REVISION
2) Add to line 312 GENDER DYSPHORIA/TRANSEXUALISM for "bottom" surgery
    a. 15273-15274 Application of skin substitute graft to trunk
    b. 51040 Cystostomy, cystotomy with drainage
    c. 64856 Suture of major peripheral nerve, arm or leg, except sciatic; including transposition
    d. 64859 Suture of each additional major peripheral nerve

Appendix

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 19316, 19324-19325, 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 196, BREAST SURGERY REVISION

*Lines 191,285,**312**,424,560,636,642*

Revision of previous breast reconstruction, augmentation, or other breast surgery is 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.). For capsular contracture, only stage 4 contractures with chronic pain are covered for revision surgery/capsulotomy. Revisions of breast reconstruction, augmentation or other breast surgery are not covered solely for cosmetic issues.

Femoroacetabular Impingement Syndrome
August 2021 Review

Issue: Femoroacetabular impingement syndrome (FAI) was last reviewed in 2013. At that time, coverage was added with a guideline based on a strong recommendation from the coverage guidance. The major decision factor for the coverage guidance was strong patient preferences for a surgical option other than total hip replacement. The evidence was noted to be of very low quality. The older 2011 Washington HTA report as well as two NICE technologies reviews were included in the 2013 coverage guidance review.

From the 2013 coverage guidance:

> In its review of public comment, the HTAS elected to make a strong recommendation for coverage for FAI surgery for selected patients despite insufficient evidence of effectiveness. This decision resulted from a discussion of the guidance development framework in which the subcommittee found no alternative effective treatments for patients who have met the criteria described in the recommended draft coverage guidance language. Based on this pathway the subcommittee found that there was similar or less risk with than no treatment. The subcommittee also found that treatment is prevalent and that further research is not reasonable at this time as it would be difficult to recruit patients. Based on expert input and information from other payers, the subcommittee adopted coverage criteria to restrict the procedure to patients who have failed conservative therapy.

HERC staff was made aware of an updated Washington HTA report on this topic which came to the conclusion that the evidence was insufficient for coverage. HERC staff felt that FAI coverage should be re-reviewed based on the HTA report.

Current Prioritized List status
On line 356 RHEUMATOID ARTHRITIS, OSTEOARTHRITIS, OSTEOCHONDRITIS DISSECANS, AND ASEPTIC NECROSIS OF BONE
29914 Arthroscopy, hip, surgical; with femoroplasty (ie, treatment of cam lesion)
29915 Arthroscopy, hip, surgical; with acetabuloplasty (ie, treatment of pincer lesion
29916 Arthroscopy, hip, surgical; with labral repair

GUIDELINE NOTE 114, FEMOROACETABULAR IMPINGEMENT SYNDROME

Line 356

ICD-10-CM M25.85 (Other specified joint disorders, hip), M24.15 (Other articular cartilage disorders, hip) and M76.2 (Iliac crest spur) pair with CPT codes 29914-29916 (Arthroscopy, hip, surgical) and are included on Line 356 only for the diagnosis and treatment of femoroacetabular impingement syndrome.

Surgery for femoroacetabular impingement syndrome is included on this line only for patients who meet all of the following criteria:

A) Adult patients, or adolescent patients who are skeletally mature with documented closure of growth plates; and
B) Other sources of pain have been ruled out (e.g., lumbar spine pathology, SI joint dysfunction, sports hernia); and

C) Pain unresponsive to physical therapy and other non-surgical management and conservative treatments (e.g., restricted activity, cortisone injections, nonsteroidal anti-inflammatory drugs) of at least three months duration, or conservative therapy is contraindicated; and
D) Moderate-to-severe persistent hip or groin pain that significantly limits activity and is worsened by flexion activities (e.g., squatting or prolonged sitting); and
E) Positive impingement sign (i.e., sudden pain on 90 degree hip flexion with adduction and internal rotation or extension and external rotation); and
F) Radiographic confirmation of FAI (e.g., pistol-grip deformity, alpha angle greater than 50 degrees, coxa profunda, and/or acetabular retroversion); and
G) Do not have advanced osteoarthritis (i.e., Tönnis grade 2 or 3) and/or severe cartilage damage (i.e., Outerbridge grade III or IV).

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

Evidence

1) **WA HTA 2019**, Hip Surgery Procedures for Treatment of Femoroacetabular Impingement Syndrome – Re-review https://www.hca.wa.gov/assets/program/femoroacetabular-impingement-syndrome-final-rpt-20191022.pdf
    a. N=5 studies (3 RCTs [n=569 patients], 2 observational comparative cohort studies [N=221 patients])
        i. Longest follow up 24 months
    b. Outcomes-function (operative vs non-operative treatment)
        i. One RCT reported that more arthroscopy patients compared with physical therapy (PT) patients achieved clinically important improvements in function according to the Hip Outcome Score Activities of Daily Living (HOS-ADL) subscale: minimal clinically important difference (MCID) ≥9 points (51% vs. 32%; RR 1.6, 95% CI 1.1 to 2.3) and final score >87 points (48% vs. 19%; RR 2.5, 95% CI 1.5 to 4.0) (SOE: low) short term (8 months).
        ii. Improvement favoring arthroscopy versus PT was seen for function based on the International Hip Outcome Tool (iHOT-33) (3 RCTs; pooled MD 1.94 on a 0-100 scale, 95% CI 0.13 to 3.03, I2=0%) and the HOS-Sport subscale (2 RCTs; pooled MD 10.98 on a 0-100 scale, 95% CI 5.67 to 16.30, I2=0%) at 6 to 8 months; however, only the difference on the HOS-Sport subscale is likely clinically significant. (SOE: low)
        iii. No clear difference between groups was seen for functional outcomes at any other timepoint measured: i-HOT-33 at 12 months (2 trials) and 24 months (1 trial), and no difference the HOS-ADL and HOS-Sport subscales at 12 and 24 months in one RCT. (SOE: low for the i-HOT-33 at 12 months; insufficient for the i-HOT-33 at 24 months and the HOS-ADL and -Sport subscales at both timepoints).
        iv. Two observational studies at moderately high risk of bias, one in adults and one in adolescents, reported similar functional results between patients who went on to have arthroscopy versus those who received conservative care only based on the modified Harris Hip Score (2 studies), Non-Arthritic Hip Score (NAHS, 2 studies) and the Western Ontario and McMasters Osteoarthritis Index (1 study) at a mean of 27 months. In the study evaluating adolescent athletes, there was no difference between treatment groups (arthroscopy versus PT with or without steroid injection) in the proportion of patents who returned to sport
        v. No comparative long-term evidence (≥ 5 years) regarding comparative benefit of operative versus non-operative care was identified
    c. Outcomes-Pain
        i. Greater improvement in pain based on the Copenhagen hip and groin outcome score (HAGOS) was reported by patients who received arthroscopy versus PT at 8 months (adjusted MD 12.7, 95% CI 8.1 to 17.2) in one RCT; the difference may be clinically important, but the confidence interval is wide.
    d. Safety
        i. Across 2 RCTs comparing arthroscopy vs. PT there were no deaths; serious and non-serious treatment-related AEs were more common following arthroscopy as might be expected given its invasive nature. (SOE: low)
        ii. Across RCTs, systematic reviews of case series, comparative surgery cohorts, and additional case series in adults it appears that the frequency of most serious

surgical complications may be low (<3%). Surgical complications with higher risks included nerve injury (0% to 25%; 0% to 9% excluding outliers) and revision surgery (0% to 8%). In adolescent patients, limited information from case series also suggests that the complication rate is low (<3%); no cases of physeal arrest/growth disturbance, femoral fracture, nonunion of the greater trochanter, avascular necrosis, acute iatrogenic slipped capital femoral epiphysis, or iatrogenic instability were seen in any study of adolescent patients. (SOE: low)

e. Differential efficacy based on patient characteristics
    i. Two RCTs, both comparing arthroscopy with PT, formally evaluated effect modification. Age was found to modify the treatment effect in one of the two trials with results suggesting that difference in function may be greater and in favor of arthroscopy compared with physiotherapy for younger patients with the effect decreasing with increasing age; however the strength of evidence was insufficient.

Femoroacetabular Impingement Syndrome
August 2021 Review

HERC staff summary

The recent update to the Washington HTA report on femorolacetabular impingement syndrome surgical treatments found limited evidence of effectiveness, but also limited evidence of harms. There has been no update to the NICE reviews of this therapy. HTAS recommended coverage of FAI surgery with a strong recommendation based on values and preferences and expert input. The coverage guidance noted the lack of evidence of effectiveness. Given that the evidence base has not substantially changed since the most recent HTAS review, HERC staff does not feel that this topic needs to be re-reviewed by HTAS at this time.

HERC staff recommendation

1) Make no change in the current placement of the ICD-10 or CPT codes for femoroacetabular impingement syndrome and no change to the current guideline regarding surgical procedures for treatment of FAI

Section 4.0

COVID Coding Issues

COVID-19 Related Codes
August 2021

Issues: Several new HCPCS codes were issued in May and June, 2021 related to treatment of COVID-19. Also, additional monoclonal antibody therapies have received FDA EUA or have had

Sotrovimab is a new monoclonal antibody which received FDA EUA on May 26, 2021. From the FDA: The data supporting this EUA for sotrovimab are based on an interim analysis from a phase 1/2/3 randomized, double-blind, placebo-controlled clinical trial in 583 non-hospitalized adults with mild-to-moderate COVID-19 symptoms and a positive SARS-CoV-2 test result. Of these patients, 291 received sotrovimab and 292 received a placebo within five days of onset of COVID-19 symptoms. The primary endpoint was progression of COVID-19 (defined as hospitalization for greater than 24 hours for acute management of any illness or death from any cause) through day 29. Hospitalization or death occurred in 21 (7%) patients who received placebo compared to 3 (1%) patients treated with sotrovimab, an 85% reduction.

Tocilizumab is a monoclonal antibody against interleukin-6 receptor-alpha that is used to treat certain inflammatory diseases. Better outcomes in patients with severe Covid-19 pneumonia who received tocilizumab have been observed in case reports and supported by retrospective observational cohort studies that showed a rapid reduction in fever, a reduced use of oxygen support and mechanical ventilation, and a reduction in lung manifestations. Tocilizumab for the treatment of COVID-19 received an FDA EUA on June 24, 2021. It was already FDA approved for treatment of other conditions such as rheumatoid arthritis.

The combination of casirivimab and imdevimab recently had an expanded FDA EUA to allow use in both high risk outpatients with mild to moderate COVID-19 symptoms AND for post-exposure prophylaxis for unvaccinated high risk persons (including persons in the same nursing home or other close living setting without known exposure). This combination is available in both an IV and a subcutaneous formulation. NOTE: ICD-10-CM Z20.822 (Contact with and (suspected) exposure to COVID-19) is on line 3 PREVENTION SERVICES WITH EVIDENCE OF EFFECTIVENESS only.

NOTE: As of June 25, 2021, the distribution of bamlanivimab and etesevimab together and etesevimab alone (to pair with existing facility supply of bamlanivimab) has been paused until further notice due to concerns about treatment failure with certain SARS-CoV-2 variants.

On 7/31/21, a new CPT code for a 3rd dose of Pfizer vaccine was released.

Drug	**Setting**		**Route**		**Indications**	
	Outpt	Inpt	IV	Sub-Q	Mild to moderate COVID-19 in high risk pts	Post-exposure prophylaxis
Sotrovimab	X		X		X	
Casirivimab and imdevimab	X		X	X	X	X
Bamlanivimab and etesevimab	X		X		X	
Tocilizumab		X	X		X	

COVID-19 Related Codes
August 2021

HERC staff recommendations:

1) Add HCPCS M0243 (Intravenous infusion, casirivimab and imdevimab includes infusion and post administration monitoring) to line 3 PREVENTION SERVICES WITH EVIDENCE OF EFFECTIVENESS
    a. Keep on line 399
    b. Line 3 placement to allow pairing with ICD-10-CM Z20.822 (Contact with and (suspected) exposure to COVID-19) for prophylactic therapy
2) Make the coding placements shown below

Code	Code Description	Recommended Placement
0003A	Third dose, Pfizer vaccine	3 PREVENTION SERVICES WITH EVIDENCE OF EFFECTIVENESS
M0201	Covid-19 vaccine administration inside a patient's home; reported only once per individual home per date of service when only covid-19 vaccine administration is performed at the patient's home	3
M0244	Intravenous infusion, casirivimab and imdevimab includes infusion and post administration monitoring the home or residence; this includes a beneficiary's home that has been made provider based to the hospital during the covid 19 public health emergency	3 PREVENTION SERVICES WITH EVIDENCE OF EFFECTIVENESS 399 INFLUENZA, COVID-19 AND OTHER NOVEL RESPIRATORY VIRAL ILLNESS
M0246	Intravenous infusion, bamlanivimab and etesevimab, includes infusion and post administration monitoring in the home or residence; this includes a beneficiary's home that has been made provider based to the hospital during the covid 19 public health emergency	399 **NOTE: Recommend to HSD to not open code until FDA re-allows distribution**
M0247	Intravenous infusion, sotrovimab, includes infusion and post administration monitoring	399
M0248	Intravenous infusion, sotrovimab, includes infusion and post administration monitoring in the home or residence; this includes a beneficiary's home that has been made provider-based to the hospital during the covid-19 public health emergency	399
M0249	Intravenous infusion, tocilizumab, for hospitalized adults and pediatric patients (2 years of age and older) with covid-19 who are receiving systemic corticosteroids and require supplemental oxygen, non-invasive or invasive mechanical ventilation, or extracorporeal membrane oxygenation (ECMO) only, includes infusion and post administration monitoring, first dose	399
M0250	second dose	399
Q0244	Injection, casirivimab and imdevimab, 1200 mg	ANCILLARY PROCEDURES FILE

Q0247	Injection, sotrovimab, 500 mg	ANCILLARY PROCEDURES FILE
Q0249	Injection, tocilizumab, for hospitalized adults and pediatric patients (2 years of age and older) with covid-19 who are receiving systemic corticosteroids and require supplemental oxygen, non-invasive or invasive mechanical ventilation, or extracorporeal membrane oxygenation (ECMO) only, 1 mg	ANCILLARY PROCEDURES FILE

June 3, 2021

Regeneron Pharmaceuticals, Inc.
Attention: Yunji Kim, PharmD
Director, Regulatory Affairs
777 Old Saw Mill River Road
Tarrytown, NY 10591

RE: Emergency Use Authorization 091

Dear Dr. Kim:

On February 4, 2020, pursuant to Section 564(b)(1)(C) of the Act, the Secretary of the Department of Health and Human Services (HHS) determined that there is a public health emergency that has a significant potential to affect national security or the health and security of United States citizens living abroad, and that involves the virus that causes coronavirus disease 2019 (COVID-19).[1] On the basis of such determination, the Secretary of HHS on March 27, 2020, declared that circumstances exist justifying the authorization of emergency use of drugs and biological products during the COVID-19 pandemic, pursuant to Section 564 of the Federal Food, Drug, and Cosmetic Act (the Act) (21 U.S.C. 360bbb-3), subject to terms of any authorization issued under that section.[2]

On November 21, 2020, the Food and Drug Administration (FDA) issued an Emergency Use Authorization (EUA) for emergency use of REGEN-COV (casirivimab and imdevimab, administered together)[3] for the treatment of mild to moderate COVID-19 in adults and pediatric patients (12 years of age and older weighing at least 40 kg) with positive results of direct SARS-CoV-2 viral testing, and who are at high risk for progressing to severe COVID-19 and/or hospitalization. Casirivimab and imdevimab are recombinant human IgG1 monoclonal antibodies that target the receptor binding domain of the spike protein of SARS-CoV-2. They are investigational drugs and are not approved for any indication.

[1] U.S. Department of Health and Human Services, *Determination of a Public Health Emergency and Declaration that Circumstances Exist Justifying Authorizations Pursuant to Section 564(b) of the Federal Food, Drug, and Cosmetic Act, 21 U.S.C. § 360bbb-3*. February 4, 2020.
[2] U.S. Department of Health and Human Services, *Declaration that Circumstances Exist Justifying Authorizations Pursuant to Section 564(b) of the Federal Food, Drug, and Cosmetic Act, 21 U.S.C. § 360bbb-3*, 85 FR 18250 (April 1, 2020).
[3] The November 21, 2020 EUA referred to the authorized product as "casirivimab and imdevimab, administered together". Regeneron subsequently requested, and FDA concurred, that the authorized labeling be revised to add references to authorized products' trade name, "REGEN-COV".

On February 3, 2021, FDA reissued the November 21, 2020 letter.[4] Thereafter, on February 25, 2021, FDA reissued the February 3, 2021 letter.[5]

On June 3, 2021, again having concluded that revising this EUA is appropriate to protect the public health or safety under section 564(g)(2) of the Act, FDA is reissuing the February 25, 2021 letter in its entirety, authorizing revisions to the authorized use[6] for REGEN-COV, a change in dosing of REGEN-COV from 2400 mg (1200 mg casirivimab and 1200 mg imdevimab) to 1200 mg (600 mg casirivimab and 600 mg imdevimab), and the addition of a new presentation consisting of a single vial containing casirivimab and imdevimab co-formulated in a 1:1 ratio for either intravenous infusion or subcutaneous injection. New conditions have been incorporated on the provision of samples of the authorized REGEN-COV to the U.S. Department of Health and Human Services, upon request, and the submission of certain genomic sequencing and virology information to the FDA by a specified date. Revisions to existing conditions on advertising and promotion and manufacturing practices and other editorial changes have also been incorporated.

Based on review of the analysis of phase 3 data from COV-2067[7] (NCT04425629), a phase 1/2/3 randomized, double-blind, placebo-controlled trial evaluating the safety and efficacy of a single intravenous infusion of 600 mg casirivimab and 600 mg imdevimab in outpatients (non-hospitalized) with SARS-CoV-2 infection, it is reasonable to believe that REGEN-COV may be effective for the treatment of mild to moderate COVID-19 in adults and pediatric patients (12 years of age and older weighing at least 40 kg) with positive results of direct SARS-CoV-2 viral testing, and who are at high risk for progression to severe COVID-19, including hospitalization or death, and that, when used under the conditions described in this authorization, the known and potential benefits of REGEN-COV outweigh the known and potential risks of such product.

Having concluded that the criteria for issuance of this authorization under Section 564(c) of the Act are met, I am authorizing the emergency use of REGEN-COV for treatment of COVID-19, as described in the Scope of Authorization section of this letter (Section II) and subject to the terms of this authorization.

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[4] FDA revised the condition on requesting changes to this authorization, including changes to the authorized Fact Sheets. New conditions were also incorporated relating to the development of instructional or educational materials, as well as certain mandatory reporting requirements for healthcare facilities and providers. In addition to certain editorial and/or clarifying revisions, the Fact Sheet for Healthcare Providers was revised to include information on the new mandatory reporting requirements on therapeutics information and utilization data for healthcare facilities and providers. Updated safety information and details on possible side effects were also incorporated into the authorized Fact Sheets.

[5] FDA revised the condition on instructional and educational materials. New conditions were also incorporated on the establishment of a process for monitoring genomic databases for the emergence of global viral variants of SARS-CoV-2 and the assessment, if requested by FDA, of the activity of the authorized REGEN-COV against any global SARS-CoV-2 variant(s) of interest.

[6] Upon re-issuance of this letter, the authorized use for REGEN-COV will read as follows: REGEN-COV (casirivimab and imdevimab) co-formulated product and REGEN-COV (casirivimab and imdevimab) supplied as individual vials to be administered together is authorized for emergency use for the treatment of mild to moderate coronavirus disease 2019 (COVID-19) in adults and pediatric patients (12 years of age and older weighing at least 40 kg) with positive results of direct SARS-CoV-2 viral testing, and who are at high risk for progression to severe COVID-19, including hospitalization or death.

[7] Referred to as trial R10933-10987-COV-2067 in previous iterations of this Letter of Authorization.

I. Criteria for Issuance of Authorization

I have concluded that the emergency use of REGEN-COV for the treatment of COVID-19 when administered as described in the Scope of Authorization (Section II) meets the criteria for issuance of an authorization under Section 564(c) of the Act, because:

1. SARS-CoV-2 can cause a serious or life-threatening disease or condition, including severe respiratory illness, to humans infected by this virus;

2. Based on the totality of scientific evidence available to FDA, it is reasonable to believe that REGEN-COV may be effective in treating mild to moderate COVID-19 in adults and pediatric patients (12 years of age and older weighing at least 40 kg) with positive results of direct SARS-CoV-2 viral testing, and who are at high risk for progression to severe COVID-19, including hospitalization or death, and that, when used under the conditions described in this authorization, the known and potential benefits of REGEN-COV outweigh the known and potential risks of such products; and

3. There is no adequate, approved, and available alternative to the emergency use of REGEN-COV for the treatment of mild to moderate COVID-19 in adults and pediatric patients (12 years of age and older weighing at least 40 kg) with positive results of direct SARS-CoV-2 viral testing, and who are at high risk for progression to severe COVID-19, including hospitalization or death.[8]

II. Scope of Authorization

I have concluded, pursuant to Section 564(d)(1) of the Act, that the scope of this authorization is limited as follows:

- Distribution of the authorized REGEN-COV will be controlled by the United States (U.S.) Government for use consistent with the terms and conditions of this EUA. Regeneron will supply REGEN-COV to authorized distributor(s)[9], who will distribute to healthcare facilities or healthcare providers as directed by the U.S. Government, in collaboration with state and local government authorities as needed;

- REGEN-COV will be used only by healthcare providers to treat mild to moderate COVID-19 in adults and pediatric patients (12 years of age and older weighing at least 40 kg) with positive results of direct SARS-CoV-2 viral testing, and who are at high risk for progressing to severe COVID-19, including hospitalization or death;

- The monoclonal antibodies that comprise REGEN-COV, casirivimab and imdevimab, may only be administered together;

[8] No other criteria of issuance have been prescribed by regulation under Section 564(c)(4) of the Act.
[9] "Authorized Distributor(s)" are identified by Regeneron as an entity or entities allowed to distribute authorized REGEN-COV.

- REGEN-COV is not authorized for use in the following patient populations[10]:
    - Adults or pediatric patients who are hospitalized due to COVID-19, or
    - Adults or pediatric patients who require oxygen therapy due to COVID-19, or
    - Adults or pediatric patients who require an increase in baseline oxygen flow rate due to COVID-19 in those patients on chronic oxygen therapy due to underlying non-COVID-19-related comorbidity.

- REGEN-COV may only be administered in settings in which health care providers have immediate access to medications to treat a severe infusion reaction, such as anaphylaxis, and the ability to activate the emergency medical system (EMS), as necessary.

- REGEN-COV is authorized for intravenous infusion. Subcutaneous injection is authorized as an alternative route of administration when intravenous infusion is not feasible and would lead to delay in treatment.

- The use of REGEN-COV covered by this authorization must be in accordance with the dosing regimens as detailed in the authorized Fact Sheets.

Product Description

REGEN-COV is available in two distinct presentations:

Dose pack bags: Dose pack bags will include a sufficient number of vials of casirivimab and imdevimab to prepare up to two treatment doses.[11] Casirivimab and imdevimab are each supplied in individual single use vials. Individual vials and carton container labeling for casirivimab and imdevimab included in dose pack bags are clearly marked "For Use under Emergency Use Authorization." Casirivimab and imdevimab are recombinant neutralizing human IgG1 monoclonal antibodies that target the receptor binding domain of the spike protein of SARS-CoV-2.

Casirivimab is available as 300 mg/2.5 mL (120 mg/mL) or 1332 mg/11.1 mL (120 mg/mL) sterile, preservative-free aqueous solution to be diluted prior to infusion. Imdevimab is available as 300 mg/2.5

[10] Benefit of treatment with REGEN-COV has not been observed in patients hospitalized due to COVID-19. Monoclonal antibodies, such as casirivimab and imdevimab, may be associated with worse clinical outcomes when administered to hospitalized patients with COVID-19 requiring high flow oxygen or mechanical ventilation.

[11] Individual vials of casirivimab and imdevimab distributed in interstate commerce prior to the reissuance of this letter remain authorized for emergency use. FDA is not requiring that such product be repackaged given the public health need for the product. The use of the individual vials of casirivimab and imdevimab must be consistent with the terms and conditions of this authorization. Individual vial labels for casirivimab and imdevimab and carton labeling may be clearly marked with either "Caution: New Drug - Limited by Federal (or United States) law to investigational use" or with "For use under Emergency Use Authorization (EUA)". Some vial labels and carton labeling of casirivimab and imdevimab may be instead labeled with the Investigational New Drug (IND) clinical trial code name as "REGN10933" and "REGN10987", respectively.

mL (120 mg/mL) or 1332 mg/11.1 mL (120 mg/mL) sterile, preservative-free aqueous solution to be diluted prior to infusion.

The dose pack bags containing unopened vials of casirivimab injection and imdevimab injection should be stored under refrigerated temperature at 2°C to 8°C (36°F to 46°F). The vials should be kept in the individual original cartons to protect from light.

Co-formulated solution of REGEN-COV: The co-formulated solution of REGEN-COV contains two antibodies in a 1:1 ratio in a single dose vial consisting of 600 mg casirivimab and 600 mg of imdevimab per 10 mL (60 mg/60 mg per mL). Individual vials of co-formulated REGEN-COV are clearly marked "For Use under Emergency Use Authorization." Casirivimab and imdevimab are recombinant neutralizing human IgG1 monoclonal antibodies that target the receptor binding domain of the spike protein of SARS-CoV-2.

Co-formulated casirivimab and imdevimab is a sterile, preservative-free, clear to slightly opalescent, colorless to pale yellow solution. Co-formulated REGEN-COV may be administered via intravenous infusion or subcutaneous injection.

Either presentation of REGEN-COV as described above may be prepared for intravenous infusion or subcutaneous injection.

> IV administration: Solution in vial requires dilution prior to administration. The prepared infusion solution is intended to be used immediately. If immediate administration is not possible, store diluted casirivimab and imdevimab solution in the refrigerator at 2°C to 8°C (36°F to 46°F) for no more than 36 hours or at room temperature up to 25°C (77°F) for no more than 4 hours. If refrigerated, allow the infusion solution to equilibrate to room temperature for approximately 30 minutes prior to administration.
>
> Subcutaneous injection: The prepared syringes should be administered immediately. If immediate administration is not possible, store the prepared casirivimab and imdevimab syringes in the refrigerator between 2ºC to 8ºC (36ºF to 46ºF) for no more than 4 hours or at room temperature up to 25ºC (77ºF) for no more than 4 total hours. If refrigerated, allow the syringes to equilibrate to room temperature for approximately 20 minutes prior to administration.

REGEN-COV is authorized for emergency use with the following product-specific information required to be made available to healthcare providers and patients/caregivers, respectively, through Regeneron's website at www.REGENCOV.com:

- Fact Sheet for Health Care Providers: Emergency Use Authorization (EUA) of REGEN-COV (casirivimab and imdevimab)

- Fact Sheet for Patients, Parents and Caregivers: Emergency Use Authorization (EUA) of REGEN-COV (casirivimab and imdevimab) for Coronavirus Disease 2019 (COVID-19)

I have concluded, pursuant to Section 564(d)(2) of the Act, that it is reasonable to believe that the known and potential benefits of REGEN-COV, when used for the treatment of COVID-19

and used in accordance with this Scope of Authorization (Section II), outweigh the known and potential risks.

I have concluded, pursuant to Section 564(d)(3) of the Act, based on the totality of scientific evidence available to FDA, that it is reasonable to believe that REGEN-COV may be effective for the treatment of COVID-19 when used in accordance with this Scope of Authorization (Section II), pursuant to Section 564(c)(2)(A) of the Act.

Having reviewed the scientific information available to FDA, including the information supporting the conclusions described in Section I above, I have concluded that REGEN-COV (as described in this Scope of Authorization (Section II)) meets the criteria set forth in Section 564(c) of the Act concerning safety and potential effectiveness.

The emergency use of your product under an EUA must be consistent with, and may not exceed, the terms of the Authorization, including the Scope of Authorization (Section II) and the Conditions of Authorization (Section III). Subject to the terms of this EUA and under the circumstances set forth in the Secretary of HHS's determination under Section 564(b)(1)(C) described above and the Secretary of HHS's corresponding declaration under Section 564(b)(1), REGEN-COV is authorized to treat mild to moderate COVID-19 illness in adults and pediatric patients (12 years of age and older weighing at least 40 kg) with positive results of direct SARS-CoV-2 viral testing, who are at high risk for progression to severe COVID-19 illness, including hospitalization or death, as described in the Scope of Authorization (Section II) under this EUA, despite the fact that it does not meet certain requirements otherwise required by applicable federal law.

III. Conditions of Authorization

Pursuant to Section 564 of the Act, I am establishing the following conditions on this authorization:

Regeneron and Company (Regeneron) and Authorized Distributors

A. Regeneron and authorized distributor(s) will ensure that the authorized REGEN-COV is distributed as directed by the U.S. government, and the authorized labeling (i.e., Fact Sheets) will be made available to healthcare facilities and/or healthcare providers consistent with the terms of this letter.

B. Regeneron and authorized distributor(s) will ensure that appropriate storage and cold chain is maintained until the product is delivered to healthcare facilities and/or healthcare providers.

C. Regeneron and authorized distributor(s) will ensure that the terms of this EUA are made available to all relevant stakeholders (e.g., U.S. government agencies, state and local government authorities, authorized distributors, healthcare facilities, healthcare providers) involved in distributing or receiving authorized REGEN-COV. Regeneron will provide to all relevant stakeholders a copy of this letter of authorization and communicate any subsequent amendments that might be made to this letter of authorization and its authorized accompanying materials (i.e., Fact Sheets).

D. Regeneron may request changes to this authorization, including to the authorized Fact Sheets for REGEN-COV. Any request for changes to this EUA must be submitted to the Office of Infectious Diseases/Office of New Drugs/Center for Drug Evaluation and Research. Such changes require appropriate authorization prior to implementation.[12]

E. Regeneron may develop and disseminate instructional and educational materials (e.g., materials providing information on product administration and/or patient monitoring) that are consistent with the authorized emergency use of REGEN-COV as described in this letter of authorization and authorized labeling, without FDA's review and concurrence, when necessary to meet public health needs. Any instructional and educational materials that are inconsistent with the authorized labeling for REGEN-COV are prohibited. Should the Agency become aware of any instructional or educational materials that are inconsistent with the authorized labeling for REGEN-COV, the Agency will require Regeneron to cease distribution of such instructional and educational materials.

F. Regeneron will report to FDA serious adverse events and all medication errors associated with the use of the authorized REGEN-COV that are reported to Regeneron using either of the following options.

   Option 1: Submit reports through the Safety Reporting Portal (SRP) as described on the FDA SRP web page.

   Option 2: Submit reports directly through the Electronic Submissions Gateway (ESG) as described on the FAERS electronic submissions web page.

   Submitted reports under both options should state: "REGEN-COV use for COVID-19 under Emergency Use Authorization (EUA)." For reports submitted under Option 1, include this language at the beginning of the question "Describe Event" for further analysis. For reports submitted under Option 2, include this language at the beginning of the "Case Narrative" field.

G. All manufacturing facilities will comply with Current Good Manufacturing Practice requirements.

[12] The following types of revisions may be authorized without reissuing this letter: (1) changes to the authorized labeling; (2) non-substantive editorial corrections to this letter; (3) new types of authorized labeling, including new fact sheets; (4) new carton/container labels; (5) expiration dating extensions; (6) changes to manufacturing processes, including tests or other authorized components of manufacturing; (7) new conditions of authorization to require data collection or study; (8) new strengths of the authorized product, new product sources (e.g., of active pharmaceutical ingredient) or of product components. For changes to the authorization, including the authorized labeling, of the type listed in (3), (6), (7), or (8), review and concurrence is required from the Counter-Terrorism and Emergency Coordination Staff/Office of the Center Director/CDER and the Office of Counterterrorism and Emerging Threats/Office of the Chief Scientist.

H. Regeneron will submit information to the Agency within three working days of receipt of any information concerning significant quality problems with distributed drug product of REGEN-COV that includes the following:

- Information concerning any incident that causes the drug product or its labeling to be mistaken for, or applied to, another article; or
- Information concerning any microbiological contamination, or any significant chemical, physical, or other change or deterioration in the distributed drug product, or any failure of one or more distributed batches of the product to meet the established specifications.

If a significant quality problem affects unreleased product and may also impact product(s) previously released and distributed, then information should be submitted for all potentially impacted lots.

Regeneron will include in its notification to the Agency whether the batch, or batches, in question will be recalled. If FDA requests that these, or any other batches, at any time, be recalled, Regeneron must recall them.

If not included in its initial notification, Regeneron must submit information confirming that Regeneron has identified the root cause of the significant quality problems and taken corrective action, and provide a justification confirming that the corrective action is appropriate. Regeneron must submit this information as soon as possible but no later than 45 calendar days from the initial notification.

I. Regeneron will manufacture REGEN-COV to meet all quality standards and per the manufacturing process and control strategy as detailed in Regeneron's EUA request. Regeneron will not implement any changes to the description of the product, manufacturing process, facilities and equipment, and elements of the associated control strategy that assure process performance and quality of the authorized product, without notification to and concurrence by the Agency as described under condition D.

J. Regeneron will list the single dose pack bag and the co-formulated product containing casirivimab and imdevimab with unique NDC product codes from each other and the NDC product codes of the single ingredient listings under the marketing category of Unapproved Drug-Other. As applicable, different vial sizes should be identified by a different package NDC within the product NDC. Further, the listing will include each establishment where manufacturing is performed for the drug and the type of operation performed at such establishment.

K. Through a process of inventory control, Regeneron and authorized distributor(s) will maintain records regarding distribution of the authorized casirivimab and imdevimab (i.e., lot numbers, quantity, receiving site, receipt date).

L. Regeneron and authorized distributor(s) will make available to FDA upon request any records maintained in connection with this EUA.

M. Regeneron will establish a process for monitoring genomic database(s) for the emergence of global viral variants of SARS-CoV-2. A summary of Regeneron's process should be submitted to the Agency as soon as practicable, but no later than 30 calendar days of the issuance of this letter, and within 30 calendar days of any material changes to such process. Regeneron will provide reports to the Agency on a monthly basis summarizing any findings as a result of its monitoring activities and, as needed, any follow-up assessments planned or conducted.

N. FDA may require Regeneron to assess the activity of the authorized REGEN-COV against any global SARS-CoV-2 variant(s) of interest (e.g., variants that are prevalent or becoming prevalent that harbor substitutions in the target protein or in protein(s) that interact with the target protein). Regeneron will perform the required assessment in a manner and timeframe agreed upon by Regeneron and the Agency. Regeneron will submit to FDA a preliminary summary report immediately upon completion of its assessment followed by a detailed study report within 30 calendar days of study completion. Regeneron will submit any relevant proposal(s) to revise the authorized labeling based on the results of its assessment, as may be necessary or appropriate based on the foregoing assessment.

O. Regeneron shall provide samples as requested of the authorized REGEN-COV to the U.S. Department of Health and Human Services (HHS) for evaluation of activity against emerging global viral variants of SARS-CoV-2, including specific amino acid substitution(s) of interest (e.g., variants that are highly prevalent or that harbor substitutions in the target protein) within 5 business days of any request made by HHS. Analyses performed with the supplied quantity of authorized REGEN-COV may include, but are not limited to, cell culture potency assays, protein binding assays, cell culture variant assays (pseudotyped virus-like particles and/or authentic virus), and *in vivo* efficacy assays.

P. Regeneron will submit to FDA all sequencing data assessing REGEN-COV, including sequencing of any participant samples from the full analysis population from COV-2067 that have not yet been completed no later than July 30, 2021. Regeneron will provide the Agency with a frequency table reporting all substitutions detected for all participants at all available time points at a frequency ≥5%.

Q. Regeneron will submit to FDA all SARS-CoV-2 nasopharyngeal viral shedding and blood viral load data, including quantitation of viral load for any participant samples from the full analysis population for which REGEN-COV is currently authorized from COV-2067 that have not yet been completed, no later than July 30, 2021.

<u>Healthcare Facilities to Whom the Authorized REGEN-COV Is Distributed and Healthcare Providers Administering the Authorized Casirivimab and Imdevimab</u>

R. Healthcare facilities and healthcare providers will ensure that they are aware of the letter of authorization, and the terms herein, and that the authorized Fact Sheets are made available to healthcare providers and to patients and caregivers, respectively, through appropriate means, prior to administration of REGEN-COV.

S. Healthcare facilities and healthcare providers receiving REGEN-COV will track serious adverse events that are considered to be potentially attributable to REGEN-COV use and must report these to FDA in accordance with the Fact Sheet for Healthcare Providers. Complete and submit a MedWatch form (www.fda.gov/medwatch/report.htm), or Complete and submit FDA Form 3500 (health professional) by fax (1-800-FDA-0178) (these forms can be found via link above). Call 1-800-FDA-1088 for questions. Submitted reports should state, "REGEN-COV use for COVID-19 under Emergency Use Authorization" at the beginning of the question "Describe Event" for further analysis.

T. Healthcare facilities and healthcare providers will ensure that appropriate storage and cold chain is maintained until the product is administered consistent with the terms of this letter.

U. Through a process of inventory control, healthcare facilities will maintain records regarding the dispensed authorized REGEN-COV (i.e., lot numbers, quantity, receiving site, receipt date), product storage, and maintain patient information (e.g., patient name, age, disease manifestation, number of doses administered per patient, other drugs administered).

V. Healthcare facilities will ensure that any records associated with this EUA are maintained until notified by Regeneron and/or FDA. Such records will be made available to Regeneron, HHS, and FDA for inspection upon request.

W. Healthcare facilities and providers will report therapeutics information and utilization data as directed by the U.S. Department of Health and Human Services.

Conditions Related to Printed Matter, Advertising and Promotion

X. All descriptive printed matter, advertising, and promotional materials relating to the use of the REGEN-COV under this authorization shall be consistent with the authorized labeling, as well as the terms set forth in this EUA, and meet the requirements set forth in section 502(a) and (n) of the Act and FDA implementing regulations. In addition, such materials shall:

- Be tailored to the intended audience.
- Not take the form of reminder advertisements, as that term is described in 21 CFR 202.1(e)(2)(i), 21 CFR 200.200 and 21 CFR 201.100(f).
- Present risk information concurrently in the audio and visual parts of the presentation for advertisements disseminated through media such as radio, television, or telephone communications.
- Be accompanied by the authorized labeling.
- Be submitted to FDA accompanied by Form FDA-2253 at the time of initial dissemination or first use.

If the Agency notifies Regeneron that any descriptive printed matter, advertising or promotional materials do not meet the terms set forth in conditions X-Z of this EUA, Regeneron must cease distribution of such descriptive printed matter, advertising, or promotional materials in accordance with the Agency's notification. Furthermore, as part

of its notification, the Agency may also require Regeneron to issue corrective communication(s).

Y. No descriptive printed matter, advertising, or promotional materials relating to the use of REGEN-COV under this authorization may represent or suggest that REGEN-COV is safe or effective when used for the treatment of mild-to-moderate COVID-19 in adults and pediatric patients (12 years of age and older weighing at least 40 kg) with positive results of direct SARS-CoV-2 viral testing, and who are at high risk for progression to severe COVID-19, including hospitalization or death.

Z. All descriptive printed matter, advertising, and promotional material, relating to the use of the REGEN-COV clearly and conspicuously shall state that:

- REGEN-COV has not been approved, but has been authorized for emergency use by FDA under an EUA, to treat mild-to-moderate COVID-19 in adults and pediatric patients (12 years of age and older weighing at least 40 kg) with positive results of direct SARS-CoV-2 viral testing, and who are at high risk for progression to severe COVID-19, including hospitalization or death; and

- The emergency use of REGEN-COV is only authorized for the duration of the declaration that circumstances exist justifying the authorization of the emergency use of drugs and biological products during the COVID-19 pandemic under Section 564(b)(1) of the Act, 21 U.S.C. § 360bbb-3(b)(1), unless the declaration is terminated or authorization revoked sooner.

IV. Duration of Authorization

This EUA will be effective until the declaration that circumstances exist justifying the authorization of the emergency use of drugs and biological products during the COVID-19 pandemic is terminated under Section 564(b)(2) of the Act or the EUA is revoked under Section 564(g) of the Act.

Sincerely,

--/S/--

RADM Denise M. Hinton
Chief Scientist
Food and Drug Administration

FACT SHEET FOR HEALTHCARE PROVIDERS
EMERGENCY USE AUTHORIZATION (EUA) OF SOTROVIMAB

AUTHORIZED USE

The U.S. Food and Drug Administration (FDA) has issued an Emergency Use Authorization (EUA) to permit the emergency use of the unapproved product sotrovimab for the treatment of mild-to-moderate coronavirus disease 2019 (COVID-19) in adults and pediatric patients (12 years of age and older weighing at least 40 kg) with positive results of direct SARS-CoV-2 viral testing, and who are at high risk for progression to severe COVID-19, including hospitalization or death.

LIMITATIONS OF AUTHORIZED USE

- Sotrovimab is not authorized for use in patients:
  - who are hospitalized due to COVID-19, OR
  - who require oxygen therapy due to COVID-19, OR
  - who require an increase in baseline oxygen flow rate due to COVID-19 (in those on chronic oxygen therapy due to underlying non-COVID-19 related comorbidity).
- Benefit of treatment with sotrovimab has not been observed in patients hospitalized due to COVID-19. SARS-CoV-2 monoclonal antibodies may be associated with worse clinical outcomes when administered to hospitalized patients with COVID-19 requiring high flow oxygen or mechanical ventilation.

Sotrovimab has been authorized by FDA for the emergency use described above.

Sotrovimab is not FDA-approved for this use.

Sotrovimab is authorized only for the duration of the declaration that circumstances exist justifying the authorization of the emergency use of sotrovimab under section 564(b)(1) of the Act, 21 U.S.C. § 360bbb-3(b)(1), unless the authorization is terminated or revoked sooner.

This EUA is for the use of the unapproved product sotrovimab for the treatment of mild-to-moderate COVID-19 in adults and pediatric patients (12 years of age and older weighing at least 40 kg) with positive results of direct SARS-COV-2 viral testing, and who are at high risk for progression to severe COVID-19, including hospitalization or death *[see Limitations of Authorized Use]*.

The following medical conditions or other factors may place adults and pediatric patients (12 to 17 years of age weighing at least 40 kg) at higher risk for progression to severe COVID-19:

- Older age (for example ≥65 years of age)
- Obesity or being overweight (for example, adults with BMI >25 kg/m^2, or if 12 to 17 years

of age, have BMI ≥85th percentile for their age and gender based on CDC growth charts, https://www.cdc.gov/growthcharts/clinical_charts.htm)

- Pregnancy
- Chronic kidney disease
- Diabetes
- Immunosuppressive disease or immunosuppressive treatment
- Cardiovascular disease (including congenital heart disease) or hypertension
- Chronic lung diseases (for example, chronic obstructive pulmonary disease, asthma [moderate-to-severe], interstitial lung disease, cystic fibrosis and pulmonary hypertension)
- Sickle cell disease
- Neurodevelopmental disorders (for example, cerebral palsy) or other conditions that confer medical complexity (for example, genetic or metabolic syndromes and severe congenital anomalies)
- Having a medical-related technological dependence (for example, tracheostomy, gastrostomy, or positive pressure ventilation [not related to COVID 19])

Other medical conditions or factors (for example, race or ethnicity) may also place individual patients at high risk for progression to severe COVID-19, and authorization of sotrovimab under the EUA is not limited to the medical conditions or factors listed above. For additional information on medical conditions and factors associated with increased risk for progression to severe COVID-19, see the CDC website: https://www.cdc.gov/coronavirus/2019-ncov/need-extra-precautions/people-with-medical-conditions.html. Healthcare providers should consider the benefit-risk for an individual patient.

Circulating SARS-CoV-2 viral variants may be associated with resistance to monoclonal antibodies. Healthcare providers should review the Antiviral Resistance information in Section 15 of this Fact Sheet for details regarding specific variants and resistance, and refer to the CDC website (https://www.cdc.gov/coronavirus/2019-ncov/cases-updates/variant-proportions.html) as well as information from state and local health authorities regarding reports of viral variants of importance in their region to guide treatment decisions.

Sotrovimab may only be administered in settings in which healthcare providers have immediate access to medications to treat a severe infusion reaction, such as anaphylaxis, and the ability to activate the emergency medical system (EMS), as necessary.

Sotrovimab must be administered after dilution by intravenous (IV) infusion.

Healthcare providers must submit a report on all medication errors and **ALL SERIOUS ADVERSE EVENTS** potentially related to sotrovimab. See Sections 8 and 9 of the Full EUA

Prescribing Information for reporting instructions below.

- See the Full EUA Prescribing Information for complete dosage, administration, and preparation instructions.
- The authorized dosage for sotrovimab is one single IV infusion of 500 mg administered as soon as possible after a positive viral test for SARS-CoV-2 and within 10 days of symptom onset *[see Dosage and Administration (2.2) and Clinical Trial Results and Supporting Data for EUA (18)]*.
- Sotrovimab is available as a concentrated solution and must be diluted prior to administration.
- Administer 500 mg of sotrovimab by IV infusion over 30 minutes.
- Clinically monitor patients during infusion and observe patients for at least 1 hour after infusion is complete.
- Patients treated with sotrovimab should continue to self-isolate and use infection control measures (e.g., wear mask, isolate, social distance, avoid sharing personal items, clean and disinfect "high touch" surfaces, and frequent handwashing) according to CDC guidelines.

The authorized dosage may be updated as additional data from clinical trials becomes available.

For information on clinical trials that are testing the use of sotrovimab in COVID-19, please see www.clinicaltrials.gov.

Contraindications

None.

Dosing

Patient Selection and Treatment Initiation

This section provides essential information on the unapproved product sotrovimab, for the treatment of mild-to-moderate COVID-19 in adults and pediatric patients (12 years of age and older weighing at least 40 kg) with positive results of direct SARS-CoV-2 viral testing, and who are at high risk for progression to severe COVID-19, including hospitalization or death *[see Limitations of Authorized Use]*.

The following medical conditions or other factors may place adults and pediatric patients (12 to 17 years of age weighing at least 40 kg) at higher risk for progression to severe COVID-19:

- Older age (for example ≥65 years of age)
- Obesity or being overweight (for example, adults with BMI >25 kg/m^2, or if 12 to 17 years of age, have BMI ≥85th percentile for their age and gender based on CDC growth charts, https://www.cdc.gov/growthcharts/clinical_charts.htm)

- Pregnancy
- Chronic kidney disease
- Diabetes
- Immunosuppressive disease or immunosuppressive treatment
- Cardiovascular disease (including congenital heart disease) or hypertension
- Chronic lung diseases (for example, chronic obstructive pulmonary disease, asthma [moderate-to-severe], interstitial lung disease, cystic fibrosis, and pulmonary hypertension)
- Sickle cell disease
- Neurodevelopmental disorders (for example, cerebral palsy) or other conditions that confer medical complexity (for example, genetic or metabolic syndromes and severe congenital anomalies)
- Having a medical-related technological dependence (for example, tracheostomy, gastrostomy, or positive pressure ventilation [not related to COVID 19])

Other medical conditions or factors (for example, race or ethnicity) may also place individual patients at high risk for progression to severe COVID-19, and authorization of sotrovimab under the EUA is not limited to the medical conditions or factors listed above. For additional information on medical conditions and factors associated with increased risk for progression to severe COVID-19, see the CDC website: https://www.cdc.gov/coronavirus/2019-ncov/need-extra-precautions/people-with-medical-conditions.html. Healthcare providers should consider the benefit-risk for an individual patient.

Dosage

The dosage of sotrovimab for the treatment of mild-to-moderate COVID-19 in adults and pediatric patients (12 years of age and older weighing at least 40 kg) is 500 mg of sotrovimab. Sotrovimab should be given as soon as possible after positive results of direct SARS-CoV-2 viral testing and within 10 days of symptom onset. Sotrovimab must be diluted and administered as a single intravenous infusion over 30 minutes.

Dosage Adjustment in Specific Populations

No dosage adjustment is recommended based on renal impairment, during pregnancy or while lactating *[see Full EUA Prescribing Information, Use in Specific Populations (11)]*.

Preparation and Administration

Preparation

Sotrovimab is supplied in a single-dose vial and must be diluted prior to administration.

Sotrovimab injection should be prepared by a qualified healthcare professional using aseptic technique.

- Gather the materials for preparation:
    - Polyvinyl chloride (PVC) or polyolefin (PO), sterile, prefilled infusion bag. Choose one of the following sizes: prefilled 50-mL or 100-mL infusion bag containing 0.9% Sodium Chloride Injection, and
    - One vial of sotrovimab (500 mg/8 mL).
- Remove one vial of sotrovimab from refrigerated storage and allow to equilibrate to room temperature, protected from light, for approximately 15 minutes.
- Inspect the vial of sotrovimab visually for particulate matter and discoloration prior to administration. Should either be observed, the solution must be discarded and a fresh solution prepared. Sotrovimab is a clear, colorless or yellow to brown solution.
- Gently swirl the vial several times before use without creating air bubbles. **Do not shake the vial.**
- Withdraw 8 mL of sotrovimab from one vial and inject into the prefilled infusion bag containing 0.9% Sodium Chloride Injection.
- Discard any product remaining in the vial.
- Prior to the infusion, gently rock the infusion bag back and forth by hand 3 to 5 times. **Do not invert the infusion bag.** Avoid forming air bubbles.
- This product is preservative-free; therefore, the diluted infusion solution should be administered immediately. If immediate administration is not possible, store the diluted solution of sotrovimab up to 4 hours at room temperature (20°C to 25°C [68°F to 77°F]) or refrigerated up to 24 hours (2°C to 8°C [36°F to 46°F]).

Administration

Sotrovimab infusion solution should be administered by a qualified healthcare professional.

- Gather the materials for infusion:
    - Polyvinyl chloride (PVC) or polyolefin (PO) infusion set, and
    - Use of a 0.2 micron polyethersulfone (PES) filter is strongly recommended.
- Attach the infusion set to the IV bag using standard bore tubing.
- Prime the infusion set.
- Administer the entire infusion solution in the bag over 30 minutes. Due to potential overfill of prefilled saline bags, the entire infusion solution in the bag should be administered to avoid underdosage.
- Do not administer as an IV push or bolus.
- The prepared infusion solution should not be administered simultaneously with any other

medication. The compatibility of sotrovimab with IV solutions and medications other than 0.9% Sodium Chloride Injection is not known.

- Once infusion is complete, **flush the tubing** with 0.9% Sodium Chloride to ensure delivery of the required dose.
- If the infusion must be discontinued due to an infusion reaction, discard unused product.
- Clinically monitor patients during infusion and observe patients for at least 1 hour after infusion is complete.

Storage

Refrigerate unopened vials at 2°C to 8°C (36°F to 46°F) in original carton. Do not freeze or shake. Protect from light.

Warnings

There are limited clinical data available for sotrovimab. Serious and unexpected adverse events may occur that have not been previously reported with use of sotrovimab.

Hypersensitivity Including Anaphylaxis and Infusion-Related Reactions

Serious hypersensitivity reactions, including anaphylaxis, have been observed with administration of sotrovimab *[see Full EUA Prescribing Information, Overall Safety Summary (6.1)]*. If signs and symptoms of a clinically significant hypersensitivity reaction or anaphylaxis occur, immediately discontinue administration and initiate appropriate medications and/or supportive care.

Infusion-related reactions, occurring during the infusion and up to 24 hours after the infusion, have been observed with administration of sotrovimab. These reactions may be severe or life threatening.

Signs and symptoms of infusion-related reactions may include:

- fever, difficulty breathing, reduced oxygen saturation, chills, fatigue, arrhythmia (e.g., atrial fibrillation, sinus tachycardia, bradycardia), chest pain or discomfort, weakness, altered mental status, nausea, headache, bronchospasm, hypotension, hypertension, angioedema, throat irritation, rash including urticaria, pruritus, myalgia, vaso-vagal reactions (e.g., pre-syncope, syncope), dizziness, and diaphoresis.

Consider slowing or stopping the infusion and administer appropriate medications and/or supportive care if an infusion-related reaction occurs.

Hypersensitivity reactions occurring more than 24 hours after the infusion have also been reported with the use of SARS-CoV-2 monoclonal antibodies under Emergency Use Authorization.

Clinical Worsening After SARS-CoV-2 Monoclonal Antibody Administration

Clinical worsening of COVID-19 after administration of SARS-CoV-2 monoclonal antibody treatment has been reported and may include signs or symptoms of fever, hypoxia or increased respiratory difficulty, arrythmia (e.g., atrial fibrillation, tachycardia, bradycardia), fatigue, and altered mental status. Some of these events required hospitalization. It is not known if these events were related to SARS-CoV-2 monoclonal antibody use or were due to progression of COVID-19.

Limitations of Benefit and Potential for Risk in Patients with Severe COVID-19

Benefit of treatment with sotrovimab has not been observed in patients hospitalized due to COVID-19. SARS-CoV-2 monoclonal antibodies may be associated with worse clinical outcomes when administered to hospitalized patients with COVID-19 requiring high flow oxygen or mechanical ventilation. Therefore, sotrovimab is not authorized for use in patients *[see Limitations of Authorized Use]*:

- who are hospitalized due to COVID-19, OR
- who require oxygen therapy due to COVID-19, OR
- who require an increase in baseline oxygen flow rate due to COVID-19 (in those on chronic oxygen therapy due to underlying non-COVID-19 related comorbidity).

Side Effects

Adverse events have been reported with sotrovimab *[see Full EUA Prescribing Information, Overall Safety Summary (6.1)]*.

Additional adverse events associated with sotrovimab may become apparent with more widespread use.

INSTRUCTIONS FOR HEALTHCARE PROVIDERS

As the healthcare provider, you must communicate to your patient or parent/caregiver, as age appropriate, information consistent with the "Fact Sheet for Patients, Parents, and Caregivers" (and provide a copy of the Fact Sheet**)** prior to the patient receiving sotrovimab, including:

- FDA has authorized the emergency use of sotrovimab for treatment of mild-to-moderate COVID-19 in adults and pediatric patients (12 years of age and older weighing at least 40 kg) with positive results of direct SARS-CoV-2 viral testing, and who are at high risk for progression to severe COVID-19, including hospitalization or death *[see Limitations of Authorized Use]*.
- The patient or parent/caregiver has the option to accept or refuse sotrovimab.
- The significant known and potential risks and benefits of sotrovimab and the extent to which such risks and benefits are unknown.

- Information on available alternative treatments and the risks and benefits of those alternatives, including clinical trials.
- Patients treated with sotrovimab should continue to self-isolate and use infection control measures (e.g., wear mask, isolate, social distance, avoid sharing personal items, clean and disinfect "high touch" surfaces, and frequent handwashing) according to CDC guidelines.

For information on clinical trials that are testing the use of sotrovimab for COVID-19, please see www.clinicaltrials.gov.

MANDATORY REQUIREMENTS FOR ADMINISTRATION OF SOTROVIMAB UNDER EMERGENCY USE AUTHORIZATION

In order to mitigate the risks of using this unapproved product under the EUA and to optimize the potential benefit of sotrovimab, the following steps are required. Use of sotrovimab under this EUA is limited to the following (all requirements **must** be met):

1. Treatment of mild-to-moderate COVID-19 in adults and pediatric patients (12 years of age and older weighing at least 40 kg) with positive results of direct SARS-CoV-2 viral testing, and who are at high risk for progression to severe COVID-19, including hospitalization or death *[see Limitations of Authorized Use]*.
2. As the healthcare provider, communicate to your patient or parent/caregiver information consistent with the "Fact Sheet for Patients, Parents, and Caregivers" prior to the patient receiving sotrovimab. Healthcare providers (to the extent practicable given the circumstances of the emergency) must document in the patient's medical record that the patient/caregiver has been:
    a. Given the "Fact Sheet for Patients, Parents, and Caregivers",
    b. Informed of alternatives to receiving authorized sotrovimab, and
    c. Informed that sotrovimab is an unapproved drug that is authorized for use under this Emergency Use Authorization.
3. Patients with known hypersensitivity to any ingredient of sotrovimab must not receive sotrovimab.
4. The prescribing healthcare provider and/or the provider's designee is/are responsible for mandatory reporting of all medication errors and serious adverse events* potentially related to sotrovimab within 7 calendar days from the onset of the event. The reports should include unique identifiers and the words "Sotrovimab use for COVID-19 under Emergency Use Authorization (EUA)" in the description section of the report.
    - Submit adverse event reports to FDA MedWatch using one of the following methods:
        - Complete and submit the report online at www.fda.gov/medwatch/report.htm, or

- Complete and submit a postage-paid FDA Form 3500 (https://www.fda.gov/media/76299/download) and return by:
  - Mail to MedWatch, 5600 Fishers Lane, Rockville, MD 20852-9787, or
  - Fax (1-800-FDA-0178), or
- Call 1-800-FDA-1088 to request a reporting form.
- Submitted reports should include in the field name, "Describe Event, Problem, or Product Use/Medication Error" the statement "Sotrovimab use for COVID-19 under Emergency Use Authorization (EUA)."

*Serious Adverse Events are defined as:

- death;
- a life-threatening adverse event;
- inpatient hospitalization or prolongation of existing hospitalization;
- a persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions;
- a congenital anomaly/birth defect;
- a medical or surgical intervention to prevent death, a life-threatening event, hospitalization, disability, or congenital anomaly.

5. The prescribing healthcare provider and/or the provider's designee is/are responsible for mandatory responses to requests from FDA for information about adverse events and medication errors following receipt of sotrovimab.
6. OTHER REPORTING REQUIREMENTS
   - In addition, please provide a copy of all FDA MedWatch forms to:

     GlaxoSmithKline, Global Safety
     Fax: 919-287-2902
     Email: WW.GSKAEReportingUS@gsk.com

     Or call the GSK COVID Contact Center at 1-866-GSK-COVID (866-475-2684) to report adverse events.

APPROVED AVAILABLE ALTERNATIVES

There is no adequate, approved and available alternative to sotrovimab for the treatment of mild-to-moderate COVID-19 in adults and pediatric patients (12 years of age and older weighing at least 40 kg) with positive results of direct SARS-CoV-2 viral testing, and who are at high risk for progression to severe COVID-19, including hospitalization or death. Additional information on COVID-19 treatments can be found at http://www.covid19treatmentguidelines.nih.gov/. The

healthcare provider should visit https://clinicaltrials.gov/ to determine whether the patient may be eligible for enrollment in a clinical trial.

AUTHORITY FOR ISSUANCE OF THE EUA

The Secretary of the Department of Health and Human Services (HHS) has declared a public health emergency that justifies the emergency use of drugs and biological products during the COVID-19 pandemic. In response, the FDA has issued this EUA, as requested by GlaxoSmithKline, for the unapproved product, sotrovimab, for the treatment of mild-to-moderate COVID-19 in adults and pediatric patients (12 years of age and older weighing at least 40 kg) with positive results of direct SARS-COV-2 viral testing, and who are at high risk for progression to severe COVID-19, including hospitalization or death.[1] As a healthcare provider, you must comply with the mandatory requirements of this EUA (see above).

Although limited scientific information is available, based on the totality of the scientific evidence available to date, it is reasonable to believe that sotrovimab may be effective for the treatment of mild-to-moderate COVID-19 in certain at-risk patients as specified in this Fact Sheet. You may be contacted and asked to provide information to help with the assessment of the use of the product during this emergency.

This EUA for sotrovimab will end when the Secretary determines that the circumstances justify the EUA no longer exist or when there is a change in the approval status of the product such that an EUA may no longer be needed.

CONTACT INFORMATION

For additional information visit www.sotrovimabinfo.com

If you have questions, please call the GSK COVID Contact Center at 1-866-GSK-COVID (866-475-2684).

END SHORT VERSION FACT SHEET

Long Version Begins on Next Page

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[1] The healthcare provider should visit https://clinicaltrials.gov/ to determine whether there is an active clinical trial for the product in this disease/condition and whether enrollment of the patient(s) in a clinical trial is more appropriate than product use under this EUA.

FULL EUA PRESCRIBING INFORMATION

FULL EUA PRESCRIBING INFORMATION: CONTENTS*

1 AUTHORIZED USE
2 DOSAGE AND ADMINISTRATION
- 2.1 Patient Selection
- 2.2 Dosage
- 2.3 Dosage Adjustment in Specific Populations
- 2.4 Dose Preparation and Administration

3 DOSAGE FORMS AND STRENGTHS
4 CONTRAINDICATIONS
5 WARNINGS AND PRECAUTIONS
- 5.1 Hypersensitivity Including Anaphylaxis and Infusion-Related Reactions
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6 OVERALL SAFETY SUMMARY
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7 PATIENT MONITORING RECOMMENDATIONS
8 ADVERSE REACTIONS AND MEDICATION ERRORS REPORTING REQUIREMENTS AND INSTRUCTIONS
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*Sections or subsections omitted from the full prescribing information are not listed.

1 AUTHORIZED USE

Sotrovimab is authorized for use under an Emergency Use Authorization (EUA) for the treatment of mild-to-moderate coronavirus disease 2019 (COVID-19) in adults and pediatric patients (12 years of age and older weighing at least 40 kg) with positive results of direct SARS-CoV-2 viral testing, and who are at high risk for progression to severe COVID-19, including hospitalization or death *[see Clinical Trial Results and Supporting Data for EUA (18)]*.

LIMITATIONS OF AUTHORIZED USE

- Sotrovimab is not authorized for use in patients:
  - who are hospitalized due to COVID-19, OR
  - who require oxygen therapy due to COVID-19, OR
  - who require an increase in baseline oxygen flow rate due to COVID-19 (in those on chronic oxygen therapy due to underlying non-COVID-19 related comorbidity).
- Benefit of treatment with sotrovimab has not been observed in patients hospitalized due to COVID-19. SARS-CoV-2 monoclonal antibodies may be associated with worse clinical outcomes when administered to hospitalized patients with COVID-19 requiring high flow oxygen or mechanical ventilation *[see Warnings and Precautions (5.2)]*.

2 DOSAGE AND ADMINISTRATION

2.1 Patient Selection

Sotrovimab should be administered as soon as possible after a positive viral test for SARS-CoV-2 and within 10 days of symptom onset in adults and pediatric patients (12 years of age and older weighing at least 40 kg) who are at high risk for progression to severe COVID-19, including hospitalization or death *[see Authorized Use (1) and Clinical Trial Results and Supporting Data for EUA (18)]*.

The following medical conditions or other factors may place adults and pediatric patients (12 to 17 years of age weighing at least 40 kg) at higher risk for progression to severe COVID-19:

- Older age (for example, ≥65 years of age)
- Obesity or being overweight (for example, adults with BMI >25 kg/m^2, or if 12 to 17, have BMI ≥85th percentile for their age and gender based on CDC growth charts, https://www.cdc.gov/growthcharts/clinical_charts.htm)
- Pregnancy
- Chronic kidney disease
- Diabetes
- Immunosuppressive disease or immunosuppressive treatment
- Cardiovascular disease (including congenital heart disease) or hypertension
- Chronic lung diseases (for example, chronic obstructive pulmonary disease, asthma [moderate-to-severe], interstitial lung disease, cystic fibrosis, and pulmonary hypertension)
- Sickle cell disease
- Neurodevelopmental disorders (for example, cerebral palsy) or other conditions that confer medical complexity (for example, genetic or metabolic syndromes and severe congenital anomalies)
- Having a medical-related technological dependence (for example, tracheostomy, gastrostomy, or positive pressure ventilation [not related to COVID 19])

Other medical conditions or factors (for example, race or ethnicity) may also place individual patients at high risk for progression to severe COVID-19, and authorization of sotrovimab under the EUA is not limited to the medical conditions or factors listed above. For additional information on medical conditions and factors associated with increased risk for progression to severe COVID-19, see the CDC website: https://www.cdc.gov/coronavirus/2019-ncov/need-extra-precautions/people-with-medical-conditions.html. Healthcare providers should consider the benefit-risk for an individual patient.

2.2 Dosage

The dosage of sotrovimab in adults and pediatric patients (12 years of age and older weighing at least 40 kg) is a single IV infusion of 500 mg. Sotrovimab should be given as soon as possible after positive results of direct SARS-CoV-2 viral testing and within 10 days of symptom onset. Sotrovimab must be diluted and administered as a single intravenous infusion over 30 minutes.

2.3 Dosage Adjustment in Specific Populations

Pregnancy or Lactation

No dosage adjustment is recommended in pregnant or lactating women *[see Use in Specific Populations (11.1, 11.2)]*.

Pediatric Use

No dosage adjustment is recommended in pediatric patients who weigh at least 40 kg and are 12 years of age and older. Sotrovimab is not authorized for patients under 12 years of age or pediatric patients weighing less than 40 kg *[see Use in Specific Populations (11.3)]*.

Geriatric Use

No dosage adjustment is recommended in geriatric patients *[see Use in Specific Populations (11.4)]*.

Renal Impairment

No dosage adjustment is recommended in patients with renal impairment *[see Use in Specific Populations (11.5)]*.

2.4 Dose Preparation and Administration

Preparation

Sotrovimab is supplied in a single-dose vial and must be diluted prior to administration.

Sotrovimab injection should be prepared by a qualified healthcare professional using aseptic technique:

- Gather the materials for preparation:
    - Polyvinyl chloride (PVC) or polyolefin (PO), sterile prefilled infusion bag. Choose one of the following sizes: prefilled 50-mL or 100-mL infusion bag containing 0.9% Sodium Chloride Injection, and
    - One vial of sotrovimab (500 mg/8 mL).
- Remove one vial of sotrovimab from refrigerated storage and allow to equilibrate to room temperature, protected from light, for approximately 15 minutes.
- Inspect the vial of sotrovimab visually for particulate matter and discoloration prior to administration. Should either be observed, the solution must be discarded and fresh solution

prepared. Sotrovimab is a clear, colorless or yellow to brown solution.

- Gently swirl the vial several times before use without creating air bubbles. **Do not shake the vial.**
- Withdraw 8 mL of sotrovimab from one vial and inject into the prefilled infusion bag containing 0.9% Sodium Chloride Injection.
- Discard any product remaining in the vial.
- Prior to the infusion, gently rock the infusion bag back and forth by hand 3 to 5 times. **Do not invert the infusion bag.** Avoid forming air bubbles.
- This product is preservative-free; therefore, the diluted infusion solution should be administered immediately. If immediate administration is not possible, store the diluted solution of sotrovimab up to 4 hours at room temperature (20°C to 25°C [68°F to 77°F]) or refrigerated up to 24 hours (2°C to 8°C [36°F to 46°F]).

Administration

Sotrovimab infusion solution should be administered by a qualified healthcare professional.

- Gather the materials for infusion:
  - Polyvinyl chloride (PVC) or polyolefin (PO) infusion set, and
  - Use of a 0.2 micron polyethersulfone (PES) filter is strongly recommended.
- Attach the infusion set to the IV bag using standard bore tubing.
- Prime the infusion set.
- Administer the entire infusion solution in the bag over 30 minutes. Due to potential overfill of prefilled saline bags, the entire infusion solution in the bag should be administered to avoid underdosage.
- Do not administer as an IV push or bolus.
- The prepared infusion solution should not be administered simultaneously with any other medication. The compatibility of sotrovimab with IV solutions and medications other than 0.9% Sodium Chloride Injection is not known.
- Once infusion is complete, **flush the tubing** with 0.9% Sodium Chloride to ensure delivery of the required dose.
- If the infusion must be discontinued due to an infusion reaction, discard unused product.
- Clinically monitor patients during infusion and observe patients for at least 1 hour after infusion is complete.

Storage

This product is preservative-free; therefore, the diluted infusion solution should be administered

immediately. If immediate administration is not possible, store the diluted infusion solution for up to 24 hours at refrigerated temperature (2°C to 8°C [36°F to 46°F]) or up to 4 hours at room temperature (20°C to 25°C [68°F to 77°F]) including transportation and infusion time. If refrigerated, allow the infusion solution to equilibrate to room temperature for approximately 15 minutes prior to administration.

3 DOSAGE FORMS AND STRENGTHS

Sotrovimab is a sterile, preservative-free, clear, colorless or yellow to brown solution available as:

- Injection: 500-mg/8-mL (62.5-mg/mL) solution in a single-dose vial for intravenous infusion after dilution.

4 CONTRAINDICATIONS

None.

5 WARNINGS AND PRECAUTIONS

There are limited clinical data available for sotrovimab. Serious and unexpected adverse events may occur that have not been previously reported with sotrovimab use.

5.1 Hypersensitivity Including Anaphylaxis and Infusion-Related Reactions

Serious hypersensitivity reactions, including anaphylaxis, have been observed with administration of sotrovimab *[see Overall Safety Summary (6.1)]*. If signs and symptoms of a clinically significant hypersensitivity reaction or anaphylaxis occur, immediately discontinue administration and initiate appropriate medications and/or supportive care.

Infusion-related reactions, occurring during the infusion and up to 24 hours after the infusion, have been observed with administration of sotrovimab. These reactions may be severe or life threatening.

Signs and symptoms of infusion-related reactions may include *[see Overall Safety Summary (6.1)]*:

- fever, difficulty breathing, reduced oxygen saturation, chills, fatigue, arrhythmia (e.g., atrial fibrillation, sinus tachycardia, bradycardia), chest pain or discomfort, weakness, altered mental status, nausea, headache, bronchospasm, hypotension, hypertension, angioedema, throat irritation, rash including urticaria, pruritus, myalgia, vaso-vagal reactions (e.g., pre-syncope, syncope), dizziness, and diaphoresis.

Consider slowing or stopping the infusion and administer appropriate medications and/or supportive care if an infusion related reaction occurs.

Hypersensitivity reactions occurring more than 24 hours after the infusion have also been reported with the use of SARS-CoV-2 monoclonal antibodies under Emergency Use

Authorization.

5.2 Clinical Worsening After SARS-CoV-2 Monoclonal Antibody Administration

Clinical worsening of COVID-19 after administration of SARS-CoV-2 monoclonal antibody treatment has been reported and may include signs or symptoms of fever, hypoxia or increased respiratory difficulty, arrythmia (e.g., atrial fibrillation, tachycardia, bradycardia), fatigue, and altered mental status. Some of these events required hospitalization. It is not known if these events were related to SARS-CoV-2 monoclonal antibody use or were due to progression of COVID-19.

5.3 Limitations of Benefit and Potential for Risk in Patients with Severe COVID-19

Benefit of treatment with sotrovimab has not been observed in patients hospitalized due to COVID-19. SARS-CoV-2 monoclonal antibodies may be associated with worse clinical outcomes when administered to hospitalized patients with COVID-19 requiring high flow oxygen or mechanical ventilation. Therefore, sotrovimab is not authorized for use in patients *[see Limitations of Authorized Use]*:

- who are hospitalized due to COVID-19, OR
- who require oxygen therapy due to COVID-19, OR
- who require an increase in baseline oxygen flow rate due to COVID-19 in those on chronic oxygen therapy due to underlying non-COVID-19 related comorbidity.

6 OVERALL SAFETY SUMMARY

6.1 Clinical Trials Experience

The ongoing Phase 1/2/3 double-blind, placebo-controlled, randomized study enrolled 1,057 non-hospitalized patients with COVID-19 (COMET-ICE). The safety of sotrovimab is primarily based on an interim analysis from 868 patients through Day 15 *[see Clinical Trial Results and Supporting Data for EUA (18)]*.

All patients received a single 500-mg infusion of sotrovimab (n = 430) or placebo (n = 438). Two patients experienced treatment interruptions due to infusion site extravasation; infusion was completed for each.

Infusion-related reactions, including immediate hypersensitivity reactions, have been observed in 1% of patients treated with sotrovimab and 1% of patients treated with placebo in COMET-ICE. Reported events that started within 24 hours of study treatment were pyrexia, chills, dizziness, dyspnea, pruritus, rash, and infusion-related reactions; all events were Grade 1 (mild) or Grade 2 (moderate).

One case of anaphylaxis was reported following sotrovimab infusion in a study in hospitalized patients; the infusion was immediately discontinued, and the patient received epinephrine. The event resolved but recurred within 2 hours; the patient received another dose of epinephrine and

improved with no additional reactions. Other serious infusion-related reactions (including immediate hypersensitivity reactions) reported following sotrovimab infusion in the hospitalized study included Grade 3 (serious) or Grade 4 (life-threatening) bronchospasm and shortness of breath. These events were also reported following infusion of placebo. Sotrovimab is not authorized for use in patients hospitalized due to COVID-19 *[see Warnings and Precautions (5.1, 5.3)]*.

The most common treatment-emergent adverse events observed in the sotrovimab treatment group in COMET-ICE were rash (2%) and diarrhea (1%), all of which were Grade 1 (mild) or Grade 2 (moderate). No other treatment-emergent adverse events were reported at a higher rate with sotrovimab compared to placebo.

7 PATIENT MONITORING RECOMMENDATIONS

Clinically monitor patients during infusion and observe patients for at least 1 hour after infusion is complete.

8 ADVERSE REACTIONS AND MEDICATION ERRORS REPORTING REQUIREMENTS AND INSTRUCTIONS

Clinical trials evaluating the safety of sotrovimab are ongoing *[see Overall Safety Summary (6)]*.

Completion of an FDA MedWatch Form to report all medication errors and serious adverse events* occurring during sotrovimab use and considered to be potentially related to sotrovimab is mandatory and must be done by the prescribing healthcare provider and/or the provider's designee. These adverse events must be reported within 7 calendar days from the onset of the event:

*Serious adverse events are defined as:

- death;
- a life-threatening adverse event;
- inpatient hospitalization or prolongation of existing hospitalization;
- a persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions;
- a congenital anomaly/birth defect;
- a medical or surgical intervention to prevent death, a life-threatening event, hospitalization, disability, or congenital anomaly.

If a serious and unexpected adverse event occurs and appears to be associated with the use of sotrovimab, the prescribing healthcare provider and/or the provider's designee should complete and submit a MedWatch form to FDA using one of the following methods:

- Complete and submit the report online at www.fda.gov/medwatch/report.htm, or

- Complete and submit a postage-paid FDA Form 3500 (https://www.fda.gov/media/76299/download) and return by:
  - Mail to MedWatch, 5600 Fishers Lane, Rockville, MD 20852-9787, or
  - Fax (1-800-FDA-0178), or
- Call 1-800-FDA-1088 to request a reporting form.

IMPORTANT: When reporting adverse events or medication errors to MedWatch, please complete the entire form with detailed information. It is important that the information reported to FDA be as detailed and complete as possible. Information should include:

- Patient demographics (e.g., patient initials, date of birth),
- Pertinent medical history,
- Pertinent details regarding admission and course of illness,
- Concomitant medications,
- Timing of adverse event(s) in relationship to administration of sotrovimab,
- Pertinent laboratory and virology information,
- Outcome of the event and any additional follow-up information if it is available at the time of the MedWatch report. Subsequent reporting of follow-up information should be completed if additional details become available.

The following steps are highlighted to provide the necessary information for safety tracking:

1. In Section A, Box 1, provide the patient's initials in the Patient Identifier.
2. In Section A, Box 2, provide the patient's date of birth.
3. In Section B, Box 5, description of the event:
   a. Write "Sotrovimab use for COVID-19 under Emergency Use Authorization (EUA)" as the first line.
   b. Provide a detailed report of medication error and/or adverse event. It is important to provide detailed information regarding the patient and adverse event/medication error for ongoing safety evaluation of this unapproved drug. Please see information to include listed above.
4. In Section G, Box 1, name and address:
   a. Provide the name and contact information of the prescribing healthcare provider or institutional designee who is responsible for the report.
   b. Provide the address of the treating institution (NOT the healthcare provider's office address).

9 OTHER REPORTING REQUIREMENTS

- In addition, please provide a copy of all FDA MedWatch forms to:

  GlaxoSmithKline, Global Safety
  Fax: 919-287-2902
  Email: WW.GSKAEReportingUS@gsk.com
  Or call the GSK COVID Contact Center at 1-866-GSK-COVID (866-475-2684) to report adverse events.

10 DRUG INTERACTIONS

Clinical drug-drug interaction studies have not been performed with sotrovimab. Sotrovimab is not renally excreted or metabolized by cytochrome P450 (CYP) enzymes; therefore, interactions with concomitant medications that are renally excreted or that are substrates, inducers, or inhibitors of CYP enzymes are unlikely.

11 USE IN SPECIFIC POPULATIONS

11.1 Pregnancy

Risk Summary

There are insufficient data to evaluate a drug-associated risk of major birth defects, miscarriage, or adverse maternal or fetal outcome. Sotrovimab should be used during pregnancy only if the potential benefit justifies the potential risk for the mother and the fetus.

Nonclinical reproductive toxicity studies have not been conducted with sotrovimab. In a cross-reactive binding assay using a protein array enriched for human embryofetal proteins, no off-target binding was detected for sotrovimab. Since sotrovimab is an Fc-enhanced human immunoglobulin G (IgG), it has the potential for placental transfer from the mother to the developing fetus. The potential treatment benefit or risk of placental transfer of sotrovimab to the developing fetus is not known.

The estimated background risk of major birth defects and miscarriage for the indicated population is unknown. All pregnancies have a background risk of birth defect, loss, or other adverse outcomes. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2% to 4% and 15% to 20%, respectively.

11.2 Lactation

Risk Summary

There are no available data on the presence of sotrovimab in human or animal milk, the effects on the breastfed infant, or the effects on milk production. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for sotrovimab and

any potential adverse effects on the breastfed infant from sotrovimab or from the underlying maternal condition. Individuals with COVID-19 who are breastfeeding should follow practices according to clinical guidelines to avoid exposing the infant to COVID-19.

11.3 Pediatric Use

Sotrovimab is not authorized for use in pediatric patients under 12 years of age or weighing less than 40 kg. The safety and effectiveness of sotrovimab have not been assessed in pediatric patients. The recommended dosing regimen in patients 12 years to less than 18 years of age, weighing at least 40 kg, is expected to result in comparable serum exposures of sotrovimab as those observed in adults based on an allometric scaling approach (which accounted for effect of body weight changes associated with age on clearance and volume of distribution).

11.4 Geriatric Use

Of the 430 patients receiving sotrovimab in COMET-ICE, 20% were 65 years of age and older and 10% were over 70 years of age. The difference in pharmacokinetics (PK) of sotrovimab in geriatric patients compared to younger patients has not been quantified.

11.5 Renal Impairment

No clinical trials have been conducted to evaluate the effects of renal impairment on the PK of sotrovimab. Sotrovimab is not eliminated intact in the urine, thus renal impairment is not expected to affect the exposure of sotrovimab.

11.6 Hepatic Impairment

No clinical trials have been conducted to evaluate the effects of hepatic impairment on the PK of sotrovimab. The impact of hepatic impairment on the PK of sotrovimab is unknown.

12 OVERDOSAGE

There is no human experience of acute overdosage with sotrovimab.

There is no specific treatment for an overdose with sotrovimab. If overdose occurs, the patient should be treated supportively with appropriate monitoring as necessary.

13 PRODUCT DESCRIPTION

Sotrovimab is a human immunoglobulin G-1 (IgG1-kappa) monoclonal antibody consisting of 2 identical light chain (LC) polypeptides composed of 214 amino acids each and 2 identical heavy chain (HC) polypeptides, each composed of 457 amino acids. Sotrovimab is produced by a Chinese Hamster Ovary cell line and has a molecular weight of approximately 149 kDa.

Sotrovimab injection is a sterile, preservative-free, clear, colorless or yellow to brown solution supplied in a single-dose vial for intravenous infusion after dilution.

Each mL contains sotrovimab (62.5 mg), L-histidine (1.51 mg), L-histidine monohydrochloride (2.15 mg), L-methionine (0.75 mg), polysorbate 80 (0.4 mg), and sucrose (70 mg). The solution

of sotrovimab has a pH of 6.0.

14 CLINICAL PHARMACOLOGY

14.1 Mechanism of Action

Sotrovimab is a recombinant human IgG1-kappa mAb that binds to a conserved epitope on the spike protein receptor binding domain of SARS-CoV-2 with a dissociation constant (K_D = 0.21 nM) but does not compete with human ACE2 receptor binding (IC_{50} value >33.6 nM [5 µg/mL]). Sotrovimab inhibits an undefined step that occurs after virus attachment and prior to fusion of the viral and cell membranes. The Fc domain of sotrovimab includes M428L and N434S amino acid substitutions (LS modification) that extend antibody half-life, but do not impact wild-type Fc-mediated effector functions in cell culture.

14.2 Pharmacokinetics

It is expected that the half-life of sotrovimab is longer than Fc-unmodified IgG due to the LS modification, but data are not available. Based on noncompartmental analysis, the mean (geomean) C_{max} following a 1 hour IV infusion was 137 µg/mL (N = 129, CV% 40), and the mean (geomean) Day 29 concentration was 34 µg/mL (N = 78, CV% 23) from all subjects with an available Day 29 sample.

Specific Populations

The effect of different covariates (e.g., age, sex, race, body weight, disease severity, hepatic impairment) on the PK of sotrovimab is unknown. Renal impairment is not expected to impact the PK of sotrovimab since mAbs with molecular weight >69 kDa do not undergo renal elimination. Similarly, dialysis is not expected to impact the PK of sotrovimab.

15 MICROBIOLOGY/RESISTANCE INFORMATION

Antiviral Activity

The neutralization activity of sotrovimab against SARS-CoV-2 (isolate USA WA1/2020) was measured in a concentration response model using cultured Vero E6 cells. Sotrovimab neutralized SARS-CoV-2 with an average EC_{50} value of 0.67 nM (100.1 ng/mL) and an average EC_{90} value of 1.2 nM (186.3 ng/mL).

Sotrovimab demonstrated cell culture FcγR activation using Jurkat reporter cells expressing FcγRIIa (low-affinity R131 and high affinity H131 alleles), FcγRIIIa (low-affinity F158 and high-affinity V158 alleles) and FcγRIIb. Sotrovimab exhibited antibody-dependent cell-mediated cytotoxicity (ADCC) in cell culture using isolated human natural killer (NK) cells following engagement with target cells expressing spike protein. Sotrovimab also elicited antibody-dependent cellular phagocytosis (ADCP) in cell-based assays using $CD14^+$ monocytes targeting cells expressing spike protein.

Antibody Dependent Enhancement (ADE) of Infection

The risk that sotrovimab could mediate viral uptake and replication by immune cells was studied in U937 cells, primary human monocytic dendritic cells, and peripheral blood mononuclear cells. This experiment did not demonstrate productive viral infection in immune cells exposed to SARS CoV-2 in the presence of concentrations of sotrovimab from 1-fold down to 1000-fold below the EC_{50} value.

The potential for ADE was also evaluated in a hamster model of SARS-CoV-2 using sotrovimab. Intraperitoneal administration prior to inoculation resulted in a dose-dependent improvement in all measured outcomes (body weight, lung weight, total viral RNA in the lungs, or infectious virus levels based on $TCID_{50}$ measurements). No evidence of enhancement of disease was observed at any dose evaluated, including sub-neutralizing doses down to 0.05 mg/kg.

Antiviral Resistance

There is a potential risk of treatment failure due to the development of viral variants that are resistant to sotrovimab. Prescribing healthcare providers should consider the prevalence of SARS-CoV-2 variants in their area, where data are available, when considering treatment options.

An E340A amino acid substitution in the spike protein emerged in cell culture selection of resistant virus and had a >100-fold reduction in activity in a pseudotyped virus-like particle (VLP) assay. This substitution is in the conserved epitope of sotrovimab, which is comprised of 23 amino acids. A pseudotyped VLP assessment in cell culture showed that epitope amino acid sequence polymorphisms P337H/L/R/T and E340A/K/G conferred reduced susceptibility to sotrovimab based on observed fold-increase in EC_{50} value shown in parentheses: E340K (>297), P337R (>276), P337L (180), E340A (>100), E340G (27), P337H (7.5), and P337T (5.4). The presence of the highly prevalent D614G variant, either alone or in combination, did not alter neutralization of sotrovimab. Pseudotyped VLP assessments indicate that sotrovimab retains activity against the UK (2.3-fold change in EC_{50} value; B.1.1.7: H69-, V70-, Y144-, N501Y, A570D, D614G, P681H, T716I, S982A, D1118H), South Africa (0.6-fold change in EC_{50} value; B.1.351: L18F, D80A, D215G, R246I, K417N, E484K, N501Y, D614G, A701V), Brazil (0.35-fold change in EC_{50} value; P.1: L18F, T20N, P26S, D138Y, R190S, K417T, E484K, N501Y, D614G, H655Y, T1027I, V1176F), California (0.7-fold change in EC_{50} value; CAL.20C: S13I, W152C, L452R, D614G), New York (0.6-fold change in EC_{50} value; B.1.526: L5F, T95I, D253G, E484K, D614G, A701V), and India (0.7-fold change in EC_{50} value; B.1.617; T95I, G142D, E154K, L452R, E484Q, D614G, P681R, and Q1071H) variant spike proteins (Table 1). Microneutralization data using authentic SARS-CoV-2 variant virus indicate that sotrovimab retains activity against the UK (3-fold change in EC_{50} value), South Africa (1.2-fold change in EC_{50} value) and Brazil (1.6-fold change in EC_{50} value) variants (Table 1).

Table 1: Authentic SARS-CoV-2 and Pseudotyped Virus-Like Particle Neutralization Data for SARS-CoV-2 Variant Substitutions with Sotrovimab

Lineage with Spike Protein Substitution	Key Substitutions Tested[a]	Fold Reduction in Susceptibility (Pseudotyped VLP)	Fold Reduction in Susceptibility (Authentic Virus)
B.1.1.7 (UK origin)	N501Y	No change[b]	No change[b]
B.1.351 (South Africa origin)	K417N + E484K + N501Y	No change[b]	No change[b]
P.1 (Brazil origin)	K417T + E484K + N501Y	No change[b]	No change[b]
B.1.427/B.1.429 (California origin)	L452R	No change[b]	nd[d]
B.1.526 (New York origin)[c]	E484K	No change[b]	nd[d]
B.1.617 (India origin)	L452R + E484Q	No change[b]	nd[d]

[a] For variants with more than one substitution of concern, only the one(s) with the greatest impact on activity is (are) listed.

[b] No change: <5-fold reduction in susceptibility

[c] Not all isolates of the New York lineage harbor the E484K substitution (as of February 2021).

[d] Not determined.

Limited nucleotide sequencing data from a total of 218 participants, at the time of authorization, indicated that 9 participants (5 placebo and 4 treated with sotrovimab) enrolled in COMET-ICE were infected with the CAL.20C variant (S13I, W152C, L452R), and one subject treated with sotrovimab progressed to require hospitalization. Two additional participants in the placebo group carried the L452R variant only. None of the participants were infected with SARS-CoV-2 that contained the full complement of spike substitutions characteristic of the UK (B.1.1.7), South African (B.1.351), or Brazilian (P.1) variants. One participant in the placebo group carried the N501Y variant at baseline.

In COMET-ICE, post-baseline epitope variants were detected in eight participants in the cohort receiving sotrovimab (spike protein substitutions E340K [4 subjects: ≥99.7% allele frequency]; A344V [6.2%]; K356R [7.5%]; S359G [2 subjects: 12.2% and 8.3%]). Of the variants detected at baseline and post-baseline, L335F, G339C, E340A, E340K, R346I, K356N, K356R, R357I, I358V and S359G substitutions have been assessed phenotypically using a pseudotyped VLP system. E340A and E340K substitutions confer reduced susceptibility to sotrovimab (>100-fold and >297-fold changes in EC_{50} value, respectively). Sotrovimab retains susceptibility against L335F (0.8-fold change in EC_{50} value), G339C (1.2-fold change in EC_{50} value), R346I (1.7-fold

change in EC_{50} value), K356N (1.1-fold change in EC_{50} value), K356R (0.8-fold change in EC_{50} value), R357I (1-fold change in EC_{50} value), I358V (0.7-fold change in EC_{50} value), and S359G (0.8-fold change in EC_{50} value) substitutions. The clinical impact of these variants is not yet known. Data collection and analysis is still ongoing.

Immune Response Attenuation

There is a theoretical risk that antibody administration may attenuate the endogenous immune response to SARS-CoV-2 and make patients more susceptible to re-infection.

16 NONCLINICAL TOXICOLOGY

Carcinogenesis, mutagenesis, and reproductive toxicology studies with sotrovimab have not been conducted.

In a toxicology study in monkeys, sotrovimab had no adverse effects when administered intravenously.

In tissue cross reactivity studies using human and monkey adult tissues, no binding of clinical concern was detected for sotrovimab.

In a cross-reactive binding assay using a protein array enriched for human embryofetal proteins, no off-target binding was detected for sotrovimab.

17 ANIMAL PHARMACOLOGIC AND EFFICACY DATA

In a Syrian Golden hamster model of SARS-CoV-2 infection, antiviral activity was demonstrated using a single dose of sotrovimab which was administered intraperitoneally at 24- or 48-hours prior to infection. Animals receiving 5 mg/kg or more of the antibody showed a significant improvement in body weight loss and significantly decreased total lung SARS-CoV-2 viral RNA compared to vehicle only and control antibody-treated animals. Levels of virus in the lung (as measured by $TCID_{50}$) were significantly decreased versus controls in hamsters receiving 0.5 mg/kg or more of the antibody.

18 CLINICAL TRIAL RESULTS AND SUPPORTING DATA FOR EUA

Clinical data supporting this EUA are based on an interim analysis from the Phase 1/2/3 COMET-ICE trial (NCT #04545060) that occurred after 583 randomized subjects had the opportunity to complete at least Day 29 of the trial. COMET-ICE is an ongoing, randomized, double-blind, placebo-controlled trial studying sotrovimab for the treatment of subjects with mild-to-moderate COVID-19 (subjects with COVID-19 symptoms who are not hospitalized). Eligible subjects were 18 years of age and older with at least one of the following comorbidities: diabetes, obesity (BMI >30), chronic kidney disease, congestive heart failure, chronic obstructive pulmonary disease, or moderate to severe asthma, or were 55 years of age and older regardless of comorbidities. The study included symptomatic patients with SARS-CoV-2 infection as confirmed by local laboratory tests and/or point of care tests and symptom onset within 5 days of

enrollment. Subjects with severe COVID-19 requiring supplemental oxygen or hospitalization and severely immunocompromised patients were excluded from the trial. Subjects were treated with a single 500-mg infusion of sotrovimab (n = 291) or placebo (n = 292) over 1 hour (Intent to Treat [ITT] population at interim analysis 1).

At baseline, the median age was 53 years (range:18 to 96); 22% of subjects were 65 years of age or older and 11% were over 70 years of age; 46% of subjects were male; 87% were White, 7% Black or African American, 6% Asian, 63% Hispanic or Latino. Fifty-eight percent of subjects received sotrovimab or placebo within 3 days of COVID-19 symptom onset and 42% within 4 to 5 days. The three most common pre-defined risk factors or comorbidities were obesity (63%), 55 years of age or older (47%), and diabetes requiring medication (23%). Overall, baseline demographic and disease characteristics were well balanced between the treatment arms.

The primary endpoint, progression of COVID-19 at Day 29, was reduced by 85% (adjusted relative risk reduction) in recipients of sotrovimab versus placebo (p = 0.002). Table 2 provides the results of the primary endpoint and a key secondary endpoint of COMET-ICE.

Table 2. Interim Efficacy Results in Adults with Mild-to-Moderate COVID-19

	Sotrovimab n = 291	**Placebo n = 292**
Progression of COVID-19 (defined as hospitalization for >24 hours for acute management of any illness or death from any cause) (Day 29)		
Proportion (n, %)	3 (1%)	21 (7%)
Adjusted Relative Risk Reduction (97.24% CI)	85% (44%, 96%)	
p-value	0.002	
All-cause mortality (up to Day 29)		
Proportion (n, %)	0	1 (<1%)

Analysis of change from baseline in viral load in COMET-ICE is not yet possible because data are not available in the majority of trial participants.

19 HOW SUPPLIED/STORAGE AND HANDLING

How Supplied

Sotrovimab injection 500 mg (62.5 mg/mL) is a sterile, preservative-free, clear, colorless or yellow to brown solution supplied in a carton containing one single-dose glass vial with a rubber vial stopper (not made with natural rubber latex) and a flip-off cap (NDC 0173-0901-86).

Storage and Handling

Sotrovimab is preservative-free. Discard unused portion.

Store unopened vials refrigerated at 2°C to 8°C (36°F to 46°F) in original carton. Do not freeze

or shake. Protect from light.

The solution of sotrovimab in the vial is preservative-free and requires dilution prior to administration. The diluted infusion solution of sotrovimab should be administered immediately. If immediate administration is not possible, store the diluted infusion solution for up to 24 hours at refrigerated temperature (2°C to 8°C [36°F to 46°F]) or up to 4 hours at room temperature (20°C to 25°C [68°F to 77°F]) including transportation and infusion time. If refrigerated, allow the infusion solution to equilibrate to room temperature for approximately 15 minutes prior to administration.

20 PATIENT COUNSELING INFORMATION

Patients treated with sotrovimab should continue to self-isolate and use infection control measures (e.g., wear mask, isolate, social distance, avoid sharing personal items, clean and disinfect "high touch" surfaces, and frequent handwashing) according to CDC guidelines. Also, see "Fact Sheet for Patients, Parents, and Caregivers".

21 CONTACT INFORMATION

For additional information visit www.sotrovimabinfo.com

If you have questions, please call the GSK COVID Contact Center at 1-866-GSK-COVID (866-475-2684).

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STR:XFS-HCP

Revised: Month 2021

Frequently Asked Questions on the Emergency Use Authorization for Actemra (Tocilizumab) for Treatment of COVID-19

Q. What is the difference between an Emergency Use Authorization (EUA) and an FDA approval?
A. Under section 564 of the Federal Food, Drug & Cosmetic Act (FD&C Act), the FDA may, pursuant to a declaration by the HHS Secretary based on one of four types of determinations, authorize an unapproved product or unapproved uses of an approved product for emergency use. In issuing an EUA, the FDA must determine, among other things, that based on the totality of scientific evidence available, including data from adequate and well-controlled clinical trials, if available, it is reasonable to believe that the product may be effective in diagnosing, treating, or preventing a serious or life-threatening disease or condition caused by a chemical, biological, radiological, or nuclear agent; that the known and potential benefits of the product, when used to diagnose, treat, or prevent such diseases or conditions, outweigh the known and potential risks for the product; and that there are no adequate, approved, and available alternatives. Emergency use authorization is NOT the same as FDA approval or licensure.

Q. What does this EUA authorize?
A. The EUA authorizes Actemra (tocilizumab), manufactured by Genentech, for emergency use by healthcare providers for the treatment of COVID-19 in hospitalized adults and pediatric patients (2 years of age and older) who are receiving systemic corticosteroids and require supplemental oxygen, non-invasive or invasive mechanical ventilation, or extracorporeal membrane oxygenation (ECMO).

Q. Is Actemra approved by the FDA to treat COVID-19?
A. No. Actemra is not FDA-approved for the treatment of COVID-19.

Actemra is currently FDA-approved for the treatment of:

- Adult patients with moderately to severely active rheumatoid arthritis who have had an inadequate response to one or more Disease-Modifying Anti-Rheumatic Drugs (DMARDs).
- Adult patients with giant cell arteritis.
- Slowing the rate of decline in pulmonary function in adult patients with systemic sclerosis-associated interstitial lung disease (SSc-ILD).
- Patients 2 years of age and older with active polyarticular juvenile idiopathic arthritis (PJIA).
- Patients 2 years of age and older with active systemic juvenile idiopathic arthritis (SJIA).
- Adults and pediatric patients 2 years of age and older with chimeric antigen receptor (CAR) T cell-induced severe or life-threatening cytokine release syndrome (CRS).

FDA has determined Actemra is safe and effective for these uses when used in accordance with the FDA-approved labeling.

Q. Can Actemra be used outside the hospital (i.e., for non-hospitalized patients)?
A. No. Under the EUA, Actemra is not authorized to treat COVID-19 patients outside of the hospital.

Q. Are there data showing Actemra might benefit patients with COVID-19?

A. The data supporting this EUA are from four clinical trials. These included one randomized, controlled, open-label, platform trial [Randomised Evaluation of COVID-19 Therapy (RECOVERY)] and three randomized, double-blind, placebo-controlled trials (EMPACTA, COVACTA, and REMDACTA). The largest trial, RECOVERY, showed a benefit in mortality and EMPACTA also showed a benefit for treatment with Actemra. While COVACTA and REMDACTA did not show a benefit of treatment with Actemra, these trials contributed to the assessment of safety.

Based on the totality of scientific evidence available, including data available from adequate and well-controlled clinical trials, FDA determined that it is reasonable to believe Actemra may be effective for the treatment of COVID-19 in hospitalized adults and pediatric patients (2 years of age and older) who are receiving systemic corticosteroids and require supplemental oxygen, non-invasive or invasive mechanical ventilation, or extracorporeal membrane oxygenation (ECMO).

- In the RECOVERY trial, 4116 hospitalized patients with severe COVID-19 pneumonia were randomized, 2022 patients received Actemra in addition to usual care and 2094 patients received usual care (the routine care patients receive for treatment of COVID-19) alone. The primary outcome evaluated death through 28 days of follow-up, and results of the primary analysis were statistically significant. The probability of death by day 28 was estimated to be 30.7% for patients receiving Actemra and 34.9% for patients receiving usual care alone. The median time to hospital discharge was 19 days for patients receiving Actemra and more than 28 days for patients receiving usual care alone.
- In the EMPACTA trial, 389 hospitalized patients with COVID-19 pneumonia were randomized, 249 patients received Actemra and 128 patients received a placebo. The primary endpoint was the cumulative proportion of patients who required mechanical ventilation or died through 28 days of follow-up. For patients receiving Actemra, there was an observed reduction in progression to mechanical ventilation or death compared to patients who received placebo, with the primary analysis results being statistically significant. The proportion of patients who required mechanical ventilation or died by day 28 was estimated to be 12.0% for Actemra and 19.3% for placebo.
- In the COVACTA trial, 452 hospitalized patients with severe COVID-19 pneumonia were randomized, 294 patients received Actemra and 144 patients received a placebo. The primary efficacy endpoint was clinical status through 28 days of follow-up assessed on a 7-category ordinal scale. While there was no statistically significant difference observed in clinical status on the 7-category ordinal scale between treatment groups, the COVACTA trial contributed to the assessment of the safety for Actemra when used for the treatment of COVID-19.
- In the REMDACTA trial, 649 hospitalized patients with severe COVID-19 pneumonia were randomized, 430 received Actemra in combination with remdesivir and 210 received a placebo in combination with remdesivir. The primary efficacy endpoint was time to hospital discharge or “ready for discharge” through 28 days of follow-up. While there were no statistically significant differences observed between treatment groups with respect to time to hospital discharge or “ready for discharge”

through 28 days of follow-up, the REMDACTA trial contributed to the assessment of the safety for Actemra when used for the treatment of COVID-19.

For additional information, please refer to section 14 of the authorized Fact Sheet for Healthcare Providers.

Q. Are there clinical trials underway evaluating Actemra for COVID-19?
A. Yes. Clinical trials remain ongoing to study Actemra for the treatment of COVID-19.

Q. Are side effects possible with Actemra?
A. Yes. Possible side effects of Actemra are:

- Serious infections leading to hospitalization or death including tuberculosis (TB), bacterial, invasive fungal, viral, and other opportunistic infections have occurred in patients receiving Actemra. In COVID-19 patients, Actemra should not be administered if patients have any other concurrent active infection, including localized infection.
- Increases in levels of liver enzymes. Actemra is not recommended in COVID-19 patients with elevated alanine aminotransferase (ALT) or aspartate aminotransferase (AST) above 10 times the upper limit of the reference range. When Actemra is used for treatment of COVID-19, ALT and AST should be monitored according to current standard clinical practice.
- Hypersensitivity reactions, including anaphylaxis. Actemra should only be infused by a healthcare professional with appropriate medical support to manage anaphylaxis.
- Common adverse reactions in COVID-19 patients include constipation, anxiety, diarrhea, insomnia, hypertension, and nausea.

See Warnings and Precautions in the FDA-approved full prescribing information for additional information on risks associated with longer-term treatment with Actemra.

Q. How can Actemra for use under the EUA be obtained?
A. Genentech and its authorized distributors distribute Actemra to hospitals for its authorized use under the EUA. Licensed healthcare providers interested in administering Actemra should contact Genentech or visit Genentech's website.

Q. Is there a requirement for providers to report side effects as part of the EUA?
A. Yes. As part of the EUA, FDA is requiring health care providers who prescribe Actemra to treat COVID-19 to report all medication errors and serious adverse events considered to be potentially related to Actemra through FDA's MedWatch Adverse Event Reporting program. Providers can complete and submit the report online; or download and complete the form, then submit it via fax at 1-800-FDA-0178. This requirement is outlined in the EUA's health care provider Fact Sheet. FDA MedWatch forms should also be provided to Genentech.

Q. Do patient outcomes need to be reported under the EUA?
A. No, reporting of patient outcomes is not required under the EUA. However, reporting of all medication errors and serious adverse events considered to be potentially related to the emergency use of Actemra occurring during treatment is required.

Q. Does the EUA authorize Actemra to be used to prevent COVID-19?

A. No. The EUA for Actemra does not authorize the emergency use of Actemra for the prevention of COVID-19.

Q. Can health care providers share the patient/caregiver Fact Sheet electronically?
A. The letter of authorization for Actemra requires that Fact Sheets be made available to healthcare providers and to patients, parents, and caregivers, "through appropriate means." Electronic delivery of the Fact Sheet is an appropriate means. For example, when the patient requests the Fact Sheet electronically, it can be delivered as a PDF prior to medication administration. Health care providers should confirm receipt of the Fact Sheet with the patient.

Q: Has Actemra been tested in children COVID-19?
A: Actemra is approved for the treatment of SJIA, PJIA, and CRS in patents 2 years of age and older. Actemra has not been studied in children with COVID-19. FDA authorized the emergency use of Actemra in certain children (2 years and older) hospitalized with COVID-19 based upon the similarity of the condition in children and extensive safety and dosing information with use of Actemra in pediatric patients for approved indications.

Q: Is there clinical data about the use of Actemra in people who are pregnant or breastfeeding?
A: The limited data available with Actemra in people who are pregnant is not sufficient to determine whether there is a drug-associated risk for major birth defects and miscarriage. No information is available on the presence of Actemra in human milk, the effects of the drug on the breastfed infant, or the effects of the drug on milk production. The lack of clinical data during lactation prevents a clear determination of the risk of Actemra to an infant during lactation; therefore the developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for Actemra and the potential adverse effects on the breastfed child from Actemra or from the underlying maternal condition. Breastfeeding individuals with COVID-19 should follow practices according to clinical guidelines to avoid exposing the infant to COVID-19.

Pause in the Distribution of bamlanivimab/etesevimab

June 25, 2021

The Assistant Secretary for Preparedness and Response (ASPR) and the Food and Drug Administration (FDA) within the U.S. Department of Health and Human Services are committed to ensuring timely and transparent communication regarding the COVID-19 monoclonal antibody treatments currently authorized for emergency use in certain patients with COVID-19.

Today, we are informing you that ASPR is immediately pausing all distribution of bamlanivimab and etesevimab together and etesevimab alone (to pair with existing supply of bamlanivimab at a facility for use under EUA 094) on a national basis until further notice. In addition, FDA recommends that health care providers nationwide use alternative authorized monoclonal antibody therapies, as described below, and not use bamlanivimab and etesevimab administered together at this time.

The Centers for Disease Control and Prevention (CDC) has identified that the combined frequencies of the SARS-CoV-2 P.1/Gamma variant (first identified in Brazil) and the B.1.351/Beta variant (first identified in South Africa) throughout the United States now exceed 11% and are trending upward (https://www.cdc.gov/coronavirus/2019-ncov/cases-updates/variant-proportions.html). Results from in vitro assays that are used to assess the susceptibility of viral variants to particular monoclonal antibodies suggest that bamlanivimab and etesevimab administered together are not active against either the P.1 or B.1.351 variants. These assays use “pseudotyped virus-like particles” that help determine likely susceptibility of the live SARS-CoV-2 variant viruses.

REGEN-COV and sotrovimab are alternative monoclonal antibody therapies that are currently authorized for the same use as bamlanivimab and etesevimab administered together. Based on similar in vitro assay data currently available, REGEN-COV and sotrovimab are likely to retain activity against the P.1 or B.1.351 variants. All treatment delivery sites can continue ordering REGEN-COV from the authorized distributer by following the existing ordering and reporting procedures. All treatment sites may also find information on the availability and ordering of sotrovimab by visiting GlaxoSmithKline’s website at www.sotrovimab.com.

Healthcare providers should review the Antiviral Resistance information in Section 15 of the authorized Fact Sheets for each monoclonal antibody therapy available under an EUA for details regarding specific variants and resistance. Health care providers should also refer to the CDC website (https://www.cdc.gov/coronavirus/2019-ncov/cases-updates/variant-proportions.html) and information from state and local health authorities regarding reports of viral variants of importance in their region to guide treatment decisions.

Monoclonal antibody therapies available under an EUA must be used in accordance with the terms and conditions for the respective authorization, including the authorized labeling. The Letters of Authorization may be accessed at: https://www.fda.gov/emergency-preparedness-and-response/mcm-legal-regulatory-and-policy-framework/emergency-use-authorization#coviddrugs.

ASPR and FDA will continue to work with the CDC and the National Institutes of Health on surveillance of variants that may impact the use of the monoclonal antibody therapies authorized for emergency use. We will provide further updates and consider additional action as new information becomes available.

Please contact COVID19Therapeutics@hhs.gov with any questions.

Related Resources

- Casirivimab/ imdevimab
- Bamlanivimab/ etesevimab
- SPEED: Special Projects for Equitable and Efficient Distribution of COVID-19 Outpatient Therapeutics

- Locating Sites for COVID-19 Antibody Treatments

COVID Antibody Testing
August 2021

Question: Should the current limitations on COVID antibody testing be expanded?

Question source: HSD, HERC staff

Issue: Currently, COVID antibody testing is limited to hospitalized patients being evaluated for possible multi-system inflammatory syndrome (MIS). Since the last HERC review of this topic, the CDC has updated their guidance on when antibody testing might be appropriate. Current CDC guidelines include more clinical situations than just MIS evaluation. HSD has requested a review by the HERC of antibody testing policy. Of note, new antibody tests that are administered at pharmacies are being rolled out and current policy only allows hospital-based testing.

Current Prioritized List status
DIAGNOSTIC GUIDELINE D27, SARS-COV-2 (COVID-19) TESTING
Testing for SARS-CoV-2 (COVID-19) virus RNA or viral antigen is a covered diagnostic service.

Antibody testing for SARS-CoV-2 (COVID-19; CPT 86413, 86328 or 86769) is covered as diagnostic only when such testing meets the following criteria:

A) Testing is done using tests that have FDA Emergency Use Authorization (EUA) or FDA approval; AND
B) Testing is used as part of the diagnostic work up of multisystem inflammatory syndrome in children (MIS-C) or multisystem inflammatory syndrome in adults (MIS-A) for hospitalized persons.

March 17, 2021 CDC Interim Guidelines for COVID-19 Antibody Testing
https://www.cdc.gov/coronavirus/2019-ncov/lab/resources/antibody-tests-guidelines.html

Key points:
• Serologic testing does not replace virologic testing and should not be used to establish the presence or absence of acute SARS-CoV-2 infection.
• Serologic tests can vary in their individual performance characteristics; tests that have received Emergency Use Authorization (EUA) should be used for public health and clinical purposes.
• Antibody testing is not currently recommended to assess for immunity to COVID-19 following COVID-19 vaccination or to assess the need for vaccination in an unvaccinated person
• Unvaccinated persons who have tested antibody positive within 3 months before or immediately following an exposure to someone with suspected or confirmed COVID-19 and who have remained asymptomatic since the current COVID-19 exposure do not need to quarantine, provided there is limited or no contact with persons at high risk for severe COVID-19 illness

• Antibody testing may be useful to support the diagnosis of COVID-19 illness or complications of COVID-19 in the following situations:
    - A positive antibody test at least 7 days following acute illness onset in persons with a previous negative antibody test (i.e., seroconversion) and who did not

receive a positive viral test may indicate SARS-CoV-2 infection between the dates of the negative and positive antibody tests.
- A positive antibody test can help support a diagnosis when patients present with complications of COVID-19 illness, such as multisystem inflammatory syndrome and other post-acute sequelae of COVID-19.

OHA SHA input:
The SHAs agreed with the HERC staff recommended changes. They agreed with not expanding coverage to the outpatient setting due to lack of evidence that this would change clinical management or isolation recommendations, particularly in light of the new COVID variants.

HERC staff summary:
The CDC has expanded their guidelines for use of COVID-19 antibody tests. The major change appears to be use of such testing to confirm illness in persons who test PCR negative and have symptoms consistent with COVID-19 and in persons with COVID complications other than MIS. No change in treatment would be achieved with knowing COVID-19 status for persons with mild sequelae. For persons with severe sequelae requiring hospitalization or who have COVID like illness requiring hospitalization, knowledge of COVID infection might change management. The current COVID antibody testing should be expanded to include other uses in hospitalized patients. However, expanding coverage outside of the hospital setting will not improve health outcomes. There is a strong CDC recommendation against routine testing to see if a vaccine has produced immunity or to determine whether a patient has had a past COVID infection.

HERC staff recommendation:
1) Modify Diagnostic Guideline D27 as shown below

DIAGNOSTIC GUIDELINE D27, SARS-COV-2 (COVID-19) TESTING
Testing for SARS-CoV-2 (COVID-19) virus RNA or viral antigen is a covered diagnostic service.

Antibody testing for SARS-CoV-2 (COVID-19; CPT 86413, 86328 or 86769) is covered as diagnostic only when such testing meets the following criteria:
A) Testing is done using tests that have FDA Emergency Use Authorization (EUA) or FDA approval; AND
B) Testing is used as part of the diagnostic work up in hospitalized patients of
   1) acute COVID-19 infection in a patient with a previous negative COVID-19 antibody test and a negative COVID-19 RNA or viral antigen test; OR
   2) complications of COVID-19 infection, such as myocarditis, coagulopathy, or multisystem inflammatory syndrome in children (MIS-C) or multisystem inflammatory syndrome in adults (MIS-A).

Section 5.0

New Codes

ICD10 Code	Code Description	Similar Codes	Recommended Placement	Further Information
A79.82	Anaplasmosis [A. phagocytophilum]	Other codes in the A79.8 familfy are on line 268	268 RICKETTSIAL AND OTHER ARTHROPOD-BORNE DISEASES	Tick bourne disease
C56.3	Malignant neoplasm of bilateral ovaries	C56.1 and C56.2 (malignant neoplasm of left/right ovary) are on line 238	238 CANCER OF OVARY	
C79.63	Secondary malignant neoplasm of bilateral ovaries	C79.61 and C79.62 (Secondary malignant neoplasm of left/right ovary) are on line 238	238 CANCER OF OVARY	
C84.7A	Anaplastic large cell lymphoma, ALK-negative, brea	Other codes in the C84.7 family are on lines 158 and 163	158 NON-HODGKIN'S LYMPHOMAS Treatment: MEDICAL THERAPY 163 NON-HODGKIN'S LYMPHOMAS Treatment: BONE MARROW TRANSPLANT	
D55.21	Anemia due to pyruvate kinase deficiency	Parent code (D55.2 Anemia due to disorders of glycolytic enzymes) was on line 194	194 HEREDITARY ANEMIAS, HEMOGLOBINOPATHIES, AND DISORDERS OF THE SPLEEN	
D55.29	Anemia due to other disorders of glycolytic enzyme	See above	194 HEREDITARY ANEMIAS, HEMOGLOBINOPATHIES, AND DISORDERS OF THE SPLEEN	
E75.244	Niemann-Pick disease type A/B	Other Niemann-Pick disease codes are on lines 60,71,99,292,345,377	60 METABOLIC DISORDERS 99 END STAGE RENAL DISEASE 71,292,345,377 Dysfunction lines	
F32.A	Depression, unspecified	Other F32 codes are on line 203	203 DEPRESSION AND OTHER MOOD DISORDERS, MILD OR MODERATE	Unspecified codes have traditionally been on uncovered lines; however, these codes have been frequently used with ICD-10 due to coding complexity

ICD10 Code	Code Description	Similar Codes	Recommended Placement	Further Information
F78.A1	SYNGAP1-related intellectual disability	F78 (Other intellectual disabilities) is on lines 71,292,345,377	71,292,345,377 Dysfunction lines	
F78.A9	Other genetic related intellectual disability	See above	71,292,345,377 Dysfunction lines	
G04.82	Acute flaccid myelitis	G04.89 (Other myelitis) is on lines 71,292,345,377,535	71,292,345,377 Dysfunction lines 535 VIRAL, SELF-LIMITING ENCEPHALITIS, MYELITIS AND ENCEPHALOMYELITIS	Acute disorder mainly in children. According to the CDC, there is no specific treatment. PT/OT may be used for symptoms
G92.8	Other toxic encephalopathy	Parent ICD-10 code G92 (Toxic encephalopathy) was on lines 71,292,345,377	71,292,345,377 Dysfunction lines	
G92.9	Unspecified toxic encephalopathy	See above	71,292,345,377 Dysfunction lines	
I5A	Non-ischemic myocardial injury (non-traumatic)		INFORMATIONAL DIAGNOSES	Per the CMS/CDC meeting minutes, I5A is a secondary code, and the primary condition (eg acute renal failure, acute myocarditis, paroxysmal tachycardia) must be coded first
K22.81	Esophageal polyp	Was previously coded with D13.0 (Benign neoplasm of esophagus) which is on line 638	638 BENIGN NEOPLASMS OF DIGESTIVE SYSTEM	
K22.82	Esophagogastric junction polyp	See above	638 BENIGN NEOPLASMS OF DIGESTIVE SYSTEM	

ICD10 Code	Code Description	Similar Codes	Recommended Placement	Further Information
K22.89	Other specified disease of esophagus	Parent code K22.8 (Other specified diseases of esophagus) was on line 56 ULCERS, GASTRITIS, DUODENITIS, AND GI HEMORRHAGE. This code's subdiagnoses include esophageal hemorrhage	56 ULCERS, GASTRITIS, DUODENITIS, AND GI HEMORRHAGE	
M31.10	Thrombotic microangiopathy, unspecified	Parent ICD-10 code M31.1 (Thrombotic microangiopathy) was on line 175	175 POLYARTERITIS NODOSA AND ALLIED CONDITIONS	
M31.19	Other thrombotic microangiopathy	Parent ICD-10 code M31.1 (Thrombotic microangiopathy) was on line 175	175 POLYARTERITIS NODOSA AND ALLIED CONDITIONS	
M35.05	Sjogren syndrome with inflammatory arthritis	Systemic Sjogren's syndrome is on line 330	330 SYSTEMIC SCLEROSIS; SJOGREN'S SYNDROME	
M35.06	Sjogren syndrome with peripheral nervous system involvement	Systemic Sjogren's syndrome is on line 330	330 SYSTEMIC SCLEROSIS; SJOGREN'S SYNDROME	
M35.07	Sjogren syndrome with central nervous system involvement	Systemic Sjogren's syndrome is on line 330	330 SYSTEMIC SCLEROSIS; SJOGREN'S SYNDROME	
M35.08	Sjogren syndrome with gastrointestinal involvement	Systemic Sjogren's syndrome is on line 330	330 SYSTEMIC SCLEROSIS; SJOGREN'S SYNDROME	
M35.0A	Sjogren syndrome with glomerular disease	Glomerular disease is on lines 59 and 99	59 END STAGE RENAL DISEASE Treatment MEDICAL THERAPY INCLUDING DIALYSIS 99 END STAGE RENAL DISEASE Treatment RENAL TRANSPLANT 330 SYSTEMIC SCLEROSIS; SJOGREN'S SYNDROME	

ICD10 Code	Code Description	Similar Codes	Recommended Placement	Further Information
M35.0B	Sjogren syndrome with vasculitis	Systemic Sjogren's syndrome is on line 330	330 SYSTEMIC SCLEROSIS; SJOGREN'S SYNDROME	
M45.A0	Non-radiographic axial spondyloarthritis of unspecified sites in spine	Similar conditions such as ankylosing spondilitis are on lines 402,529	402 CONDITIONS OF THE BACK AND SPINE 529 CONDITIONS OF THE BACK AND SPINE WITHOUT URGENT SURGICAL INDICATIONS	axial spondyloarthritis is an inflammatory disease of the spine
M45.A1	Non-radiographic axial spondyloarthritis of occipito-atlanto-axial region	See above	402 CONDITIONS OF THE BACK AND SPINE 529 CONDITIONS OF THE BACK AND SPINE WITHOUT URGENT SURGICAL INDICATIONS	
M45.A2	Non-radiographic axial spondyloarthritis of cervical region	See above	402 CONDITIONS OF THE BACK AND SPINE 529 CONDITIONS OF THE BACK AND SPINE WITHOUT URGENT SURGICAL INDICATIONS	
M45.A3	Non-radiographic axial spondyloarthritis of cervicothoracic region	See above	402 CONDITIONS OF THE BACK AND SPINE 529 CONDITIONS OF THE BACK AND SPINE WITHOUT URGENT SURGICAL INDICATIONS	
M45.A4	Non-radiographic axial spondyloarthritis of thoracic region	See above	402 CONDITIONS OF THE BACK AND SPINE 529 CONDITIONS OF THE BACK AND SPINE WITHOUT URGENT SURGICAL INDICATIONS	
M45.A5	Non-radiographic axial spondyloarthritis of thoracolumbar region	See above	402 CONDITIONS OF THE BACK AND SPINE 529 CONDITIONS OF THE BACK AND SPINE WITHOUT URGENT SURGICAL INDICATIONS	

ICD10 Code	Code Description	Similar Codes	Recommended Placement	Further Information
M45.A6	Non-radiographic axial spondyloarthritis of lumbar region	See above	402 CONDITIONS OF THE BACK AND SPINE 529 CONDITIONS OF THE BACK AND SPINE WITHOUT URGENT SURGICAL INDICATIONS	
M45.A7	Non-radiographic axial spondyloarthritis of lumbosacral region	See above	402 CONDITIONS OF THE BACK AND SPINE 529 CONDITIONS OF THE BACK AND SPINE WITHOUT URGENT SURGICAL INDICATIONS	
M45.A8	Non-radiographic axial spondyloarthritis of sacral and sacrococcygeal region	See above	402 CONDITIONS OF THE BACK AND SPINE 529 CONDITIONS OF THE BACK AND SPINE WITHOUT URGENT SURGICAL INDICATIONS	
M45.AB	Non-radiographic axial spondyloarthritis of multiple sites in spine	See above	402 CONDITIONS OF THE BACK AND SPINE 529 CONDITIONS OF THE BACK AND SPINE WITHOUT URGENT SURGICAL INDICATIONS	
M54.50	Low back pain, unspecified	Low back pain is on line 402	402 CONDITIONS OF THE BACK AND SPINE	
M54.51	Vertebrogenic low back pain		402 CONDITIONS OF THE BACK AND SPINE	
M54.59	Other low back pain		402 CONDITIONS OF THE BACK AND SPINE	
P00.82	Newborn affected by (positive) maternal group B streptococcus (GBS) colonization		2 BIRTH OF INFANT	
P09.1	Abnormal findings on neonatal screening for inborn errors of metabolism	Parent code P09 (Abnormal findings on neonatal screening) was on the DWF	DIAGNOSTIC WORKUP FILE (DWF)	

ICD10 Code	Code Description	Similar Codes	Recommended Placement	Further Information
P09.2	Abnormal findings on neonatal screening for congenital endocrine disease	See above	DIAGNOSTIC WORKUP FILE (DWF)	
P09.3	Abnormal findings on neonatal screening for congenital hematologic disorders	See above	DIAGNOSTIC WORKUP FILE (DWF)	
P09.4	Abnormal findings on neonatal screening for cystic fibrosis	See above	DIAGNOSTIC WORKUP FILE (DWF)	
P09.5	Abnormal findings on neonatal screening for critical congenital heart disease	See above	DIAGNOSTIC WORKUP FILE (DWF)	
P09.6	Abnormal findings on neonatal screening for neonatal hearing loss	See above	DIAGNOSTIC WORKUP FILE (DWF)	
P09.8	Other abnormal findings on neonatal screening	See above	DIAGNOSTIC WORKUP FILE (DWF)	
P09.9	Abnormal findings on neonatal screening, unspecified	See above	DIAGNOSTIC WORKUP FILE (DWF)	
R05.1	Acute cough	Parent code R05 (Cough) was on DWF	DIAGNOSTIC WORKUP FILE (DWF)	
R05.2	Subacute cough	See above	DIAGNOSTIC WORKUP FILE (DWF)	
R05.3	Chronic cough	See above	DIAGNOSTIC WORKUP FILE (DWF)	
R05.4	Cough syncope	See above	DIAGNOSTIC WORKUP FILE (DWF)	
R05.8	Other specified cough	See above	DIAGNOSTIC WORKUP FILE (DWF)	
R05.9	Cough, unspecified	See above	DIAGNOSTIC WORKUP FILE (DWF)	
R35.81	Nocturnal polyuria	Parent code R35.8 (Other polyuria) was on DWF	DIAGNOSTIC WORKUP FILE (DWF)	
R35.89	Other polyuria	See above	DIAGNOSTIC WORKUP FILE (DWF)	
R63.30	Feeding difficulties, unspecified	Parent code R63.3 (Feeding difficulties) was on DWF	DIAGNOSTIC WORKUP FILE (DWF)	
R63.39	Other feeding difficulties	See above	DIAGNOSTIC WORKUP FILE (DWF)	
R79.83	Abnormal findings of blood amino-acid level	Other R78.8 codes are on DWF	DIAGNOSTIC WORKUP FILE (DWF)	

ICD10 Code	Code Description	Similar Codes	Recommended Placement	Further Information
S06.A0XA	Traumatic brain compression without herniation, initial encounter	Similar codes are on line 196	196 SUBARACHNOID AND INTRACEREBRAL HEMORRHAGE/HEMATOMA; CEREBRAL ANEURYSM; COMPRESSION OF BRAIN	
S06.A0XD	Traumatic brain compression without herniation, subsequent encounter	See above	196 SUBARACHNOID AND INTRACEREBRAL HEMORRHAGE/HEMATOMA; CEREBRAL ANEURYSM; COMPRESSION OF BRAIN	
S06.A0XS	Traumatic brain compression without herniation, sequela	See above	INFORMATIONAL DIAGNOSES	
S06.A1XA	Traumatic brain compression with herniation, initial encounter	See above	196 SUBARACHNOID AND INTRACEREBRAL HEMORRHAGE/HEMATOMA; CEREBRAL ANEURYSM; COMPRESSION OF BRAIN	
S06.A1XD	Traumatic brain compression with herniation, subsequent encounter	See above	196 SUBARACHNOID AND INTRACEREBRAL HEMORRHAGE/HEMATOMA; CEREBRAL ANEURYSM; COMPRESSION OF BRAIN	
S06.A1XS	Traumatic brain compression with herniation, sequela	See above	INFORMATIONAL DIAGNOSES	
T40.711A	Poisoning by cannabis, accidental (unintentional), initial encounter	Other poisoning codes are on lines 71,102,292,345,377	71,292,345,377 Dysfunction lines 102 POISONING BY INGESTION, INJECTION, AND NON-MEDICINAL AGENTS	
T40.711D	Poisoning by cannabis, accidental (unintentional), subsequent encounter	See above	71,102,292,345,377	
T40.711S	Poisoning by cannabis, accidental (unintentional), sequela	See above	INFORMATIONAL DIAGNOSES	

ICD10 Code	Code Description	Similar Codes	Recommended Placement	Further Information
T40.712A	Poisoning by cannabis, intentional self-harm, initial encounter	See above	71,102,292,345,377	
T40.712D	Poisoning by cannabis, intentional self-harm, subsequent encounter	See above	71,102,292,345,377	
T40.712S	Poisoning by cannabis, intentional self-harm, sequela	See above	INFORMATIONAL DIAGNOSES	
T40.713A	Poisoning by cannabis, assault, initial encounter	See above	71,102,292,345,377	
T40.713D	Poisoning by cannabis, assault, subsequent encounter	See above	71,102,292,345,377	
T40.713S	Poisoning by cannabis, assault, sequela	See above	INFORMATIONAL DIAGNOSES	
T40.714A	Poisoning by cannabis, undetermined, initial encounter	See above	71,102,292,345,377	
T40.714D	Poisoning by cannabis, undetermined, subsequent encounter	See above	71,102,292,345,377	
T40.714S	Poisoning by cannabis, undetermined, sequela	See above	INFORMATIONAL DIAGNOSES	
T40.715A	Adverse effect of cannabis, initial encounter	Other "adverse effect" codes are on line 102	102 POISONING BY INGESTION, INJECTION, AND NON-MEDICINAL AGENTS	
T40.715D	Adverse effect of cannabis, subsequent encounter	Other "adverse effect" codes are on line 102	102 POISONING BY INGESTION, INJECTION, AND NON-MEDICINAL AGENTS	
T40.715S	Adverse effect of cannabis, sequela	Other "adverse effect" codes are on line 102	INFORMATIONAL DIAGNOSES	
T40.716A	Underdosing of cannabis, initial encounter	Other "underdosing" codes are DWF	DIAGNOSTIC WORKUP FILE (DWF)	
T40.716D	Underdosing of cannabis, subsequent encounter	Other "underdosing" codes are DWF	DIAGNOSTIC WORKUP FILE (DWF)	

ICD10 Code	Code Description	Similar Codes	Recommended Placement	Further Information
T40.716S	Underdosing of cannabis, sequela	Other "underdosing" codes are DWF	INFORMATIONAL DIAGNOSES	
T40.721A	Poisoning by synthetic cannabinoids, accidental (unintentional), initial encounter	Other poisoning codes are on lines 71,102,292,345,377	71,292,345,377 Dysfunction lines 102 POISONING BY INGESTION, INJECTION, AND NON-MEDICINAL AGENTS	
T40.721D	Poisoning by synthetic cannabinoids, accidental (unintentional), subsequent encounter	See above	71,102,292,345,377	
T40.721S	Poisoning by synthetic cannabinoids, accidental (unintentional), sequela	See above	INFORMATIONAL DIAGNOSES	
T40.722A	Poisoning by synthetic cannabinoids, intentional self-harm, initial encounter	See above	71,102,292,345,377	
T40.722D	Poisoning by synthetic cannabinoids, intentional self-harm, subsequent encounter	See above	71,102,292,345,377	
T40.722S	Poisoning by synthetic cannabinoids, intentional self-harm, sequela	See above	INFORMATIONAL DIAGNOSES	
T40.723A	Poisoning by synthetic cannabinoids, assault, initial encounter	See above	71,102,292,345,377	
T40.723D	Poisoning by synthetic cannabinoids, assault, subsequent encounter	See above	71,102,292,345,377	
T40.723S	Poisoning by synthetic cannabinoids, assault, sequela	See above	INFORMATIONAL DIAGNOSES	
T40.724A	Poisoning by synthetic cannabinoids, undetermined, initial encounter	See above	71,102,292,345,377	

ICD10 Code	Code Description	Similar Codes	Recommended Placement	Further Information
T40.724D	Poisoning by synthetic cannabinoids, undetermined, subsequent encounter	See above	71,102,292,345,377	
T40.724S	Poisoning by synthetic cannabinoids, undetermined, sequela	See above	INFORMATIONAL DIAGNOSES	
T40.725A	Adverse effect of synthetic cannabinoids, initial encounter	Other "adverse effect" codes are on line 102	102 POISONING BY INGESTION, INJECTION, AND NON-MEDICINAL AGENTS	
T40.725D	Adverse effect of synthetic cannabinoids, subsequent encounter	Other "adverse effect" codes are on line 102	102 POISONING BY INGESTION, INJECTION, AND NON-MEDICINAL AGENTS	
T40.725S	Adverse effect of synthetic cannabinoids, sequela	Other "adverse effect" codes are on line 102	INFORMATIONAL DIAGNOSES	
T40.726A	Underdosing of synthetic cannabinoids, initial encounter	Other "underdosing" codes are DWF	DIAGNOSTIC WORKUP FILE (DWF)	
T40.726D	Underdosing of synthetic cannabinoids, subsequent encounter	Other "underdosing" codes are DWF	DIAGNOSTIC WORKUP FILE (DWF)	
T40.726S	Underdosing of synthetic cannabinoids, sequela	Other "underdosing" codes are DWF	INFORMATIONAL DIAGNOSES	
T80.82XA	Complication of immune effector cellular therapy, initial encounter	Similar codes are on line 424	424 COMPLICATIONS OF A PROCEDURE USUALLY REQUIRING TREATMENT	
T80.82XD	Complication of immune effector cellular therapy, subsequent encounter	Similar codes are on line 424	424 COMPLICATIONS OF A PROCEDURE USUALLY REQUIRING TREATMENT	
T80.82XS	Complication of immune effector cellular therapy, sequela	Similar codes are on line 424	INFORMATIONAL DIAGNOSES	
Y35.899A	Legal intervention involving other specified means, unspecified person injured, initial encounter		INFORMATIONAL DIAGNOSES	

ICD10 Code	Code Description	Similar Codes	Recommended Placement	Further Information
Y35.899D	Legal intervention involving other specified means, unspecified person injured, subsequent encounter		INFORMATIONAL DIAGNOSES	
Y35.899S	Legal intervention involving other specified means, unspecified person injured, sequela		INFORMATIONAL DIAGNOSES	
Z55.5	Less than a high school diploma		INFORMATIONAL DIAGNOSES	
Z58.6	Inadequate drinking-water supply		INFORMATIONAL DIAGNOSES	
Z59.00	Homelessness unspecified		INFORMATIONAL DIAGNOSES	
Z59.01	Sheltered homelessness		INFORMATIONAL DIAGNOSES	
Z59.02	Unsheltered homelessness		INFORMATIONAL DIAGNOSES	
Z59.41	Food insecurity		INFORMATIONAL DIAGNOSES	
Z59.48	Other specified lack of adequate food		INFORMATIONAL DIAGNOSES	
Z59.811	Housing instability, housed, with risk of homelessness		INFORMATIONAL DIAGNOSES	
Z59.812	Housing instability, housed, homelessness in past 12 months		INFORMATIONAL DIAGNOSES	
Z59.819	Housing instability, housed unspecified		INFORMATIONAL DIAGNOSES	
Z59.89	Other problems related to housing and economic circumstances		INFORMATIONAL DIAGNOSES	
Z71.85	Encounter for immunization safety counseling	Immunization codes are on line 3	3 PREVENTION SERVICES WITH EVIDENCE OF EFFECTIVENESS	
Z91.014	Allergy to mammalian meats		INFORMATIONAL DIAGNOSES	
Z91.51	Personal history of suicidal behavior	Parent code Z91.5 (Personal history of self-harm) was on INFORMATIONAL DIAGNOSES	INFORMATIONAL DIAGNOSES	

ICD10 Code	Code Description	Similar Codes	Recommended Placement	Further Information
Z91.52	Personal history of nonsuicidal self-harm	Parent code Z91.5 (Personal history of self-harm) was on INFORMATIONAL DIAGNOSES	INFORMATIONAL DIAGNOSES	
Z92.850	Personal history of Chimeric Antigen Receptor T-cell therapy		INFORMATIONAL DIAGNOSES	
Z92.858	Personal history of other cellular therapy		INFORMATIONAL DIAGNOSES	
Z92.859	Personal history of cellular therapy, unspecified		INFORMATIONAL DIAGNOSES	
Z92.86	Personal history of gene therapy		INFORMATIONAL DIAGNOSES	

ICD10 Code	Code Description	Recommended Placement
D75.838	Other thrombocytosis	653 CARDIOVASCULAR CONDITIONS WITH NO OR MINIMALLY EFFECTIVE TREATMENTS OR NO TREATMENT NECESSARY
D75.839	Thrombocytosis, unspecified	653 CARDIOVASCULAR CONDITIONS WITH NO OR MINIMALLY EFFECTIVE TREATMENTS OR NO TREATMENT NECESSARY
D89.44	Hereditary alpha tryptasemia	652 ENDOCRINE AND METABOLIC CONDITIONS WITH NO OR MINIMALLY EFFECTIVE TREATMENTS OR NO TREATMENT NECESSARY
G44.86	Cervicogenic headache	540 TENSION HEADACHE
G92.00	Immune effector cell-associated neurotoxicity syndrome, grade unspecified	313 DISORDERS INVOLVING THE IMMUNE SYSTEM 71,292,345,377 Dysfunction lines
G92.01	Immune effector cell-associated neurotoxicity syndrome, grade 1	313 DISORDERS INVOLVING THE IMMUNE SYSTEM 71,292,345,377 Dysfunction lines
G92.02	Immune effector cell-associated neurotoxicity syndrome, grade 2	313 DISORDERS INVOLVING THE IMMUNE SYSTEM 71,292,345,377 Dysfunction lines
G92.03	Immune effector cell-associated neurotoxicity syndrome, grade 3	313 DISORDERS INVOLVING THE IMMUNE SYSTEM 71,292,345,377 Dysfunction lines
G92.04	Immune effector cell-associated neurotoxicity syndrome, grade 4	313 DISORDERS INVOLVING THE IMMUNE SYSTEM 71,292,345,377 Dysfunction lines
G92.05	Immune effector cell-associated neurotoxicity syndrome, grade 5	313 DISORDERS INVOLVING THE IMMUNE SYSTEM 71,292,345,377 Dysfunction lines
K31.A0	Gastric intestinal metaplasia, unspecified	528 DISORDERS OF FUNCTION OF STOMACH AND OTHER FUNCTIONAL DIGESTIVE DISORDERS
K31.A11	Gastric intestinal metaplasia without dysplasia, involving the antrum	528 DISORDERS OF FUNCTION OF STOMACH AND OTHER FUNCTIONAL DIGESTIVE DISORDERS
K31.A12	Gastric intestinal metaplasia without dysplasia, involving the body (corpus)	528 DISORDERS OF FUNCTION OF STOMACH AND OTHER FUNCTIONAL DIGESTIVE DISORDERS
K31.A13	Gastric intestinal metaplasia without dysplasia, involving the fundus	528 DISORDERS OF FUNCTION OF STOMACH AND OTHER FUNCTIONAL DIGESTIVE DISORDERS
K31.A14	Gastric intestinal metaplasia without dysplasia, involving the cardia	528 DISORDERS OF FUNCTION OF STOMACH AND OTHER FUNCTIONAL DIGESTIVE DISORDERS

ICD10 Code	Code Description	Recommended Placement
K31.A15	Gastric intestinal metaplasia without dysplasia, involving multiple sites	528 DISORDERS OF FUNCTION OF STOMACH AND OTHER FUNCTIONAL DIGESTIVE DISORDERS
K31.A19	Gastric intestinal metaplasia without dysplasia, unspecified site	528 DISORDERS OF FUNCTION OF STOMACH AND OTHER FUNCTIONAL DIGESTIVE DISORDERS
K31.A21	Gastric intestinal metaplasia with low grade dysplasia	528 DISORDERS OF FUNCTION OF STOMACH AND OTHER FUNCTIONAL DIGESTIVE DISORDERS
K31.A22	Gastric intestinal metaplasia with high grade dysplasia	528 DISORDERS OF FUNCTION OF STOMACH AND OTHER FUNCTIONAL DIGESTIVE DISORDERS
K31.A29	Gastric intestinal metaplasia with dysplasia, unspecified	528 DISORDERS OF FUNCTION OF STOMACH AND OTHER FUNCTIONAL DIGESTIVE DISORDERS
L24.A0	Irritant contact dermatitis due to friction or contact with body fluids, unspecified	533 CONTACT DERMATITIS AND NON-INFECTIOUS OTITIS EXTERNA
L24.A1	Irritant contact dermatitis due to saliva	533 CONTACT DERMATITIS AND NON-INFECTIOUS OTITIS EXTERNA
L24.A2	Irritant contact dermatitis due to fecal, urinary or dual incontinence	533 CONTACT DERMATITIS AND NON-INFECTIOUS OTITIS EXTERNA
L24.A9	Irritant contact dermatitis due friction or contact with other specified body fluids	533 CONTACT DERMATITIS AND NON-INFECTIOUS OTITIS EXTERNA
L24.B0	Irritant contact dermatitis related to unspecified stoma or fistula	71 EUROLOGICAL DYSFUNCTION IN BREATHING, EATING, SWALLOWING, BOWEL, OR BLADDER CONTROL CAUSED BY CHRONIC CONDITIONS; ATTENTION TO OSTOMIES
L24.B1	Irritant contact dermatitis related to digestive stoma or fistula	71 EUROLOGICAL DYSFUNCTION IN BREATHING, EATING, SWALLOWING, BOWEL, OR BLADDER CONTROL CAUSED BY CHRONIC CONDITIONS; ATTENTION TO OSTOMIES
L24.B2	Irritant contact dermatitis related to respiratory stoma or fistula	71 EUROLOGICAL DYSFUNCTION IN BREATHING, EATING, SWALLOWING, BOWEL, OR BLADDER CONTROL CAUSED BY CHRONIC CONDITIONS; ATTENTION TO OSTOMIES

ICD10 Code	Code Description	Recommended Placement
L24.B3	Irritant contact dermatitis related to fecal or urinary stoma or fistula	71 EUROLOGICAL DYSFUNCTION IN BREATHING, EATING, SWALLOWING, BOWEL, OR BLADDER CONTROL CAUSED BY CHRONIC CONDITIONS; ATTENTION TO OSTOMIES
M31.11	Hematopoietic stem cell transplantation-associated thrombotic microangiopathy [HSCT-TMA]	285 COMPLICATIONS OF A PROCEDURE ALWAYS REQUIRING TREATMENT
M35.0C	Sjogren syndrome with dental involvement	53 PREVENTIVE DENTAL SERVICES 330 SYSTEMIC SCLEROSIS; SJOGREN'S SYNDROME
R45.88	Nonsuicidal self-harm	203 DEPRESSION AND OTHER MOOD DISORDERS, MILD OR MODERATE
R63.31	Pediatric feeding disorder, acute	149 FEEDING AND EATING DISORDERS OF INFANCY OR CHILDHOOD
R63.32	Pediatric feeding disorder, chronic	149 FEEDING AND EATING DISORDERS OF INFANCY OR CHILDHOOD
U09.9	Post COVID-19 condition, unspecified	345 NEUROLOGICAL DYSFUNCTION IN COMMUNICATION CAUSED BY CHRONIC CONDITIONS 399 INFLUENZA, COVID-19 AND OTHER NOVEL RESPIRATORY VIRAL ILLNESS

2022 ICD-10 Code Placement Issues

1) **D75.838** Other thrombocytosis and **D75.839** Thrombocytosis, unspecified
    a. Thrombocytosis is defined as a platelet count greater than 400 × 109/L. Generally, thrombocytosis is much more likely to be reactive (> 80% of cases) than primary. Reactive or secondary thrombocytosis is usually associated with infections, inflammation, trauma, hemolysis, metastatic cancer, post-splenectomy sate, or iron deficiency anemia. Causes of primary thrombocytosis include myeloproliferative neoplasms, myelodysplastic syndromes, myelodysplastic syndrome, and other myeloid malignancies. Reactive or secondary thrombocytosis generally does not need to be treated, other than treating the underlying cause. Primary thrombocytosis generally also goes not require treatment if the patient is asymptomatic. If the patient has very high platelet counts (over a million) or is symptomatic with blood clots or bleeding, then the patient may be treated with aspirin, hydroxyurea, anagrelide or interferon alpha. Work up for this condition includes blood tests, screening for genetic mutations, and bone marrow biopsy.
    b. This is a new category of codes. Per the CDC/CMS meeting notes from September 2020, the new code D75.838 is intended to code for reactive thrombocytosis or secondary thrombocytosis. Essential thrombocytosis is intended to be coded by D47.2 Essential (hemorrhagic) thrombocythemia, which is on lines 158 NON-HODGKIN'S LYMPHOMAS and 179 ACUTE LEUKEMIA, MYELODYSPLASTIC SYNDROME Treatment: Bone Marrow Transplant. The code D75.839 is noted in the CDC/CMS minutes to be intended for coding non-neoplastic thrombocytosis that is not primary or secondary (note: no subdiagnoses are given and it is unclear what such a diagnosis might be)
    c. <u>HERC staff recommendation</u>:
        i. Place ICD-10-CM D75.838 (Other thrombocytosis) and D75.839 (Thrombocytosis, unspecified) on line 653 CARDIOVASCULAR CONDITIONS WITH NO OR MINIMALLY EFFECTIVE TREATMENTS OR NO TREATMENT NECESSARY
            1. No treatment is necessary for secondary or reactive thrombocytosis under than treatment of the underlying condition. It is unclear what D75.839 is intended to code for.

2) **D89.44** Hereditary alpha tryptasemia
    a. Daughter code of D89.4 (**Mast cell activation syndrome and related disorders**), all of the other daughter codes of which are on line 313 DISORDERS INVOLVING THE IMMUNE SYSTEM
    b. From the National Institute of Allergy and Infectious Disease (underline HERC staff):
        i. <u>Hereditary alpha tryptasemia</u> can be called a biochemical trait. A trait is simply a characteristic that is caused by a difference in the DNA. In the case of hereditary alpha tryptasemia, people with this trait have inherited extra copies of the alpha tryptase gene (*TPSAB1*), and this leads to increased levels of trypase protein detected in the blood, whether a reaction is happening or not.
            1. Very common in the general population and many people have no symptoms.
        ii. Several features that may be shared among those who have <u>hereditary alpha tryptasemia syndrome</u> are multiple symptoms affecting a variety of systems including (but not limited to) these:
            1. Chronic skin flushing, itching, or hives
            2. Bee sting allergy

3. Dizziness and/or difficulty maintaining a normal pulse and blood pressure
4. Chronic head, back, and joint pain
5. Skeletal abnormalities
6. GI disturbances including heartburn, IBS, and numerous food and drug reactions and intolerances
7. Sleep disturbances

iii. It is unclear if the syndrome involves activated mast cells or not
iv. There is currently no reason to test for hereditary alpha tryptasemia, as the treatment will not be different based on the result. Treatment is symptom based, and mainly includes antihistamines.

c. HERC staff summary:
   i. Hereditary alpha tryptasemia does not appear to be pathologic, and is common in the general population. The related syndrome is pathologic and is treated with antihistamines. There is no code currently for the related syndrome (hereditary alpha tryptasemia syndrome).
d. HERC staff recommendation:
   i. Place ICD-10-CM D89.44 (Hereditary alpha tryptasemia) on line 652 ENDOCRINE AND METABOLIC CONDITIONS WITH NO OR MINIMALLY EFFECTIVE TREATMENTS OR NO TREATMENT NECESSARY
      1. Alternative: line 313 DISORDERS INVOLVING THE IMMUNE SYSTEM

3) **G44.86** Cervicogenic headache
   a. Cervicogenic headache (CGH) occurs when pain is referred from a specific source in the neck up to the head. This pain is commonly a steady ache or dull feeling
   b. There has not previously been a specific ICD-10 code for cervicogenic headache. R51 (Headache) was placed on line 540 TENSION HEADACHES to represent this diagnosis with the following coding specification: Osteopathic manipulative treatment and chiropractic manipulative treatment (CPT 98926-98929, 98940- 98943) pair on this line only with cervicogenic headache (R51). Note: the code R51 no longer exists, and the daughter codes are on the DIAGNOSTIC WORKUP FILE (DWF)
   c. In March, 2021, the coding specification was removed from line 540 and a new guideline was created for this line.
   d. HERC staff recommendations:
      i. Place ICD-10-CM G44.86 (Cervicogenic headache) on line 540 TENSION HEADACHE
      ii. Modify the new guideline for line 540 as shown below:

GUIDELINE NOTE XXX CERVICOGENIC HEADACHE
Line 540
Osteopathic manipulative treatment and chiropractic manipulative treatment (CPT 98926-98929, 98940- 98943) pair on this line only with cervicogenic headache (~~R51~~ G44.86).

4) **G92.0X** Immune effector cell-associated neurotoxicity syndrome
   a. Immune effector cell-associated neurotoxicity syndrome (ICANS; often referred to as neurotoxicity) is a complication of CAR-T cell therapy. ICANS typically manifests as a toxic encephalopathy and starts with word-finding difficulty, confusion, dysphasia,

aphasia, impaired fine motor skills and somnolence. In more severe cases, seizures, motor weakness, cerebral edema and coma have been noted. ICANS is reversible in most patients with no permanent neurological deficits.

b. Similar to cytokine release syndrome (ICD-10 D89.83X) which is on line 313 DISORDERS INVOLVING THE IMMUNE SYSTEM
c. Treatment is typically corticosteroids. Other treatments being studies include other immune modulators such as ruxolitinib and itacitinib
d. The parent ICD-10 code G92 (Toxic encephalopathy) was on lines 71,292,345,377
e. HERC staff recommendations:
    i. Place ICD-10-CM G92.0X (Immune effector cell-associated neurotoxicity syndrome) on line 313 DISORDERS INVOLVING THE IMMUNE SYSTEM for treatment as the condition is similar to ICD10 D89.83X
    ii. Place ICD-10-CM G92.0X on the dysfunction lines (lines 71,292,345,377) for treatment of manifestations, similar to parent code G92

5) **K31.A1X** Gastric intestinal metaplasia without dysplasia and **K31.A2X** Gastric intestinal metaplasia with dysplasia
    a. Gastric intestinal metaplasia is a condition in which the gastric mucosa changes to tissue resembling intestinal tissue. It is related to H Pylori infection. It is unclear if this condition increases cancer risk or other outcomes.
    b. Previously, this condition was coded with K31.89 (Other diseases of stomach and duodenum) which was on line 528 DISORDERS OF FUNCTION OF STOMACH AND OTHER FUNCTIONAL DIGESTIVE DISORDERS
    c. Similar codes
        i. Barrett's esophagus without dysplasia (K22.70) is on line 380 ESOPHAGITIS; GERD
        ii. Barrett's esophagus with dysphasia (K22.71) is on line 314 CANCER OF ESOPHAGUS; BARRETT'S ESOPHAGUS WITH DYSPLASIA
        iii. Stomach cancer (C16.9 Malignant neoplasm of stomach, unspecified) is on line 215 CANCER OF STOMACH
        iv. Gastritis is on line 56 ULCERS, GASTRITIS, DUODENITIS, AND GI HEMORRHAGE
    d. Expert guideline
        i. **Gupta 2020**, American Gastroenterological Association Practice Guideline for Treatment of Gastric Intestinal Metaplasia
            1. Recommendation 1. In patients with GIM, the AGA recommends testing for H pylori followed by eradication over no testing and eradication. Strong recommendation, moderate quality of evidence.
            2. Recommendation 2. In patients with GIM the AGA suggests against routine use of endoscopic surveillance. Conditional recommendation, very low quality of evidence Comment: Patients with GIM at higher risk for gastric cancer who put a high value on potential but uncertain reduction in gastric cancer mortality, and who put a low value on potential risks of surveillance endoscopies, may reasonably elect for surveillance.
                a. Patients with GIM specifically at higher risk of gastric cancer include those with:
                    i. Incomplete vs complete GIM
                    ii. Extensive vs limited GIM

iii. Family history of gastric cancer

b. Patients at overall increased risk for gastric cancer include:

i. Racial/ethnic minorities

ii. Immigrants from high incidence regions

3. Recommendation 3. In patients with GIM, the AGA suggests against routine short-interval repeat endoscopy for the purpose of risk stratification. Conditional recommendation, very low quality of evidence. Comment: Based on shared decision-making, patients with GIM and high-risk stigmata, concerns about completeness of baseline endoscopy, and/or who are at overall increased risk for gastric cancer (racial/ethnic minorities, immigrants from regions with high gastric cancer incidence, or individuals with family history of first-degree relative with gastric cancer) may reasonably elect for repeat endoscopy within 1 year for risk stratification.

e. HERC staff summary

i. Gastric intestinal metaplasia is a condition that may increase the risk of cancer of the stomach. Treatment appears to be limited to H Pylori eradication if H Pylori is found to be present. Some patients with this condition may need repeat upper endoscopy for monitoring.

f. <u>HERC staff recommendation</u>:

i. Place ICD-10-CM K31.A1X (Gastric intestinal metaplasia without dysplasia) on line 528 DISORDERS OF FUNCTION OF STOMACH AND OTHER FUNCTIONAL DIGESTIVE DISORDERS

ii. Place ICD-10-CM K31.A2X (Gastric intestinal metaplasia with dysplasia) on line 528 DISORDERS OF FUNCTION OF STOMACH AND OTHER FUNCTIONAL DIGESTIVE DISORDERS

1. Note: repeat EGDs would be diagnostic and therefore available for surveillance even with the placement on a non-covered line

6) **L24.A and L24.B** Irritant contact dermatitis due to body fluids

a. Currently, all irritant contact dermatitis ICD-10-CM codes are on line 533 CONTACT DERMATITIS AND NON-INFECTIOUS OTITIS EXTERNA. These codes involve contact with metals, cosmetics, etc. The new codes involve contact with bodily fluids. Some of these codes involve digestive or respiratory stomas. Contact dermatitis around stomas can cause complications which can require extensive nursing care or revision of the stoma. These codes should be on a line with similar codes in the ICD-10-CM Z43 family (Encounter for attention to stomas) which are on line 71 EUROLOGICAL DYSFUNCTION IN BREATHING, EATING, SWALLOWING, BOWEL, OR BLADDER CONTROL CAUSED BY CHRONIC CONDITIONS; ATTENTION TO OSTOMIES

b. <u>HERC staff recommendations</u>

i. Place the following ICD-10-CM codes on line 533 CONTACT DERMATITIS AND NON-INFECTIOUS OTITIS EXTERNA

1. L24.A0 (Irritant contact dermatitis due to friction or contact with body fluids, unspecified)
2. L24.A1 (Irritant contact dermatitis due to saliva)
3. L24.A9 (Irritant contact dermatitis due friction or contact with other specified body fluids)

ii. Discuss placement of the following codes

1. L24.A2 (Irritant contact dermatitis due to fecal, urinary or dual incontinence)
    a. Staff recommendation: line 533 CONTACT DERMATITIS AND NON-INFECTIOUS OTITIS EXTERNA
    b. Alternative placement line 455 URINARY INCONTINENCE

iii. Place the following ICD-10-CM codes on line 71 NEUROLOGICAL DYSFUNCTION IN BREATHING, EATING, SWALLOWING, BOWEL, OR BLADDER CONTROL CAUSED BY CHRONIC CONDITIONS; ATTENTION TO OSTOMIES

1. L24.B0 (Irritant contact dermatitis related to unspecified stoma or fistula)
2. L24.B1 (Irritant contact dermatitis related to digestive stoma or fistula)
3. L24.B2 (Irritant contact dermatitis related to respiratory stoma or fistula)
4. L24.B3 (Irritant contact dermatitis related to fecal or urinary stoma or fistula)

7) **M31.11** Hematopoietic stem cell transplantation-associated thrombotic microangiopathy [HSCT-TMA]
    a. Transplant-associated thrombotic microangiopathy (TA-TMA) is an increasingly recognized complication of hematopoietic stem cell transplant (HSCT) with high morbidity and mortality. The triad of endothelial cell activation, complement dysregulation, and microvascular hemolytic anemia has the potential to cause end organ dysfunction, multiple organ dysfunction syndrome and death
    b. **Young 2021**, review of HSCT-TMA
        i. Treatment:
            1. Therapeutic plasma exchange: studies show response ranging from 60-66%
            2. Immunosuppressive medications such as rituximab, defibrotide, eculizumab, narsoplimab
    c. <u>HERC staff recommendation</u>:
        i. Place ICD-10-CM M31.11 (Hematopoietic stem cell transplantation-associated thrombotic microangiopathy [HSCT-TMA]) on line 285 COMPLICATIONS OF A PROCEDURE ALWAYS REQUIRING TREATMENT
            1. Contains therapeutic plasma exchange CPT codes and ICD-10 D89.813 (Graft-versus-host disease, unspecified) is also on this line

8) **M36.0C** Sjogren syndrome with dental involvement
    a. From the American Dental Association: Sjögren disease is an autoimmune disease that can result in the destruction of exocrine glandular epithelium. The most common symptoms are dry mouth and dry eyes. Specific oral manifestations associated with Sjögren disease may include increased risk of caries, gingivitis, oral candidiasis, enlarged salivary glands, and others. Treatment of Sjögren disease is primarily supportive/palliative, focusing on symptom relief and prevention.
    b. Expert input:
        i. Gary Allen, DMD**:** I do think it should be on a dental line and I would recommend Line 53, Preventive Dental Services. Guideline Note 17 is linked

with Line 53 and members with the diagnosis would qualify and should receive additional preventive services.

GUIDELINE NOTE 17, PREVENTIVE DENTAL CARE

Lines 3,53

Dental cleaning is limited to once per 12 months for adults and twice per 12 months for children up to age 19 (D1110, D1120). More frequent dental cleanings may be required for certain higher risk populations.

Fluoride varnish (99188) is included on Line 3 for use with children 18 and younger during well child preventive care visits. Fluoride treatments (D1206 and D1208) are included on Line 53 PREVENTIVE DENTAL SERVICES for use with adults and children during dental visits. The total number of fluoride applications provided in all settings is not to exceed four per twelve months for a child at high risk for dental caries and two per twelve months for a child not at high risk. The number of fluoride treatments is limited to once per 12 months for average risk adults and up to four times per 12 months for high-risk adults.

c. HERC staff recommendation:
    i. Place ICD-10-CM M36.0C (Sjogren syndrome with dental involvement) on line 53 PREVENTIVE DENTAL SERVICES

9) **R45.8** Nonsuicidal self-harm
    a. Non-suicidal self-injury (NSSI) is defined as deliberately injuring oneself without suicidal intent. The most common form of NSSI is self-cutting, but other forms include burning, scratching, hitting, intentionally preventing wounds from healing, and other similar behaviors. Generally, self-harm is done as an attempt to regulate emotions.
    b. Similar codes: there were no equivalent codes for this type of behavior. Other R45.8 codes (R45.851 suicidal ideation, R45.89 Other symptoms and signs involving emotional state, etc.) are on the Diagnostic Work Up File (DWF)
    c. Evidence
        i. **Bahji 2021**, Systematic review of psychotherapy for self-harm in children and adolescents
            1. N=44 RCTs (5406 patients)
            2. Dialectical behavioral therapies were associated with reductions in self-harm (OR, 0.28; 95%CI, 0.12-0.64) and suicidal ideation (Cohen *d* SMD, −0.71; 95%CI, −1.19 to −0.23) at the end of treatment, while mentalization-based therapies were associated with decreases in self-harm (OR, 0.38; 95%CI, 0.15-0.97) and suicidal ideation (Cohen *d* SMD, −1.22; 95%CI, −2.18 to −0.26) at the end of follow-up. The quality of evidence was downgraded because of high risk of bias overall, heterogeneity, publication bias, inconsistency, and imprecision.
        ii. **Witt 2021**, Cochrane review psychosocial interventions for self-harm in adults
            1. N=76 trials (21,414 patients)
            2. On the basis of data from four trials, individual cognitive behavioral therapy (CBT)-based psychotherapy may reduce repetition of SH as

compared to TAU or another comparator by the end of the intervention (OR 0.35, 95% CI 0.12 to 1.02; N = 238; k = 4; GRADE: low certainty evidence), although there was imprecision in the effect estimate. At longer follow-up time points (e.g., 6- and 12-months) there was some evidence that individual CBT-based psychotherapy may reduce SH repetition.

3. Whilst there may be a slightly lower rate of SH repetition for dialectical behavior therapy (DBT) (66.0%) as compared to TAU or alternative psychotherapy (68.2%), the evidence remains uncertain as to whether DBT reduces absolute repetition of SH by the post-intervention assessment.
4. On the basis of data from a single trial, mentalization-based therapy (MBT) reduces repetition of SH and frequency of SH by the post-intervention assessment (OR 0.35, 95% CI 0.17 to 0.73; N = 134; k = 1; GRADE: high-certainty evidence).
5. A group-based emotion regulation psychotherapy may also reduce repetition of SH by the post-intervention assessment based on evidence from two trials by the same author group (OR 0.34, 95% CI 0.13 to 0.88; N = 83; k = 2; moderate-certainty evidence). There is probably little to no effect for different variants of DBT on absolute repetition of SH, including DBT group-based skills training, DBT individual skills training, or an experimental form of DBT in which participants were given significantly longer cognitive exposure to stressful events. The evidence remains uncertain as to whether provision of information and support, based on the Suicide Trends in At-Risk Territories (START) and the Suicide-PREvention Multisite Intervention Study on Suicidal behaviors (SUPRE-MISS) models, have any effect on repetition of SH by the postintervention assessment.
6. There was no evidence of a difference for psychodynamic psychotherapy, case management, general practitioner (GP) management, remote contact interventions, and other multimodal interventions, or a variety of brief emergency department-based interventions.
7. **Authors' conclusions** Overall, there were significant methodological limitations across the trials included in this review. Given the moderate or very low quality of the available evidence, there is only uncertain evidence regarding a number of psychosocial interventions for adults who engage in SH. Psychosocial therapy based on CBT approaches may result in fewer individuals repeating SH at longer follow-up time points, although no such effect was found at the post-intervention assessment and the quality of evidence, according to the GRADE criteria, was low.

iii. **Witt 2021,** Cochrane review psychosocial interventions for self-harm in children and adolescents

1. N-17 trials (2280 patients)
2. There was a lower rate of SH repetition for DBT-A (30%) as compared to TAU, EUC, or alternative psychotherapy (43%) on repetition of SH at post-intervention in four trials (OR 0.46, 95% CI 0.26 to 0.82; N = 270; k = 4; high-certainty evidence). There may be no evidence of a difference

for individual cognitive behavioral therapy (CBT)-based psychotherapy and TAU for repetition of SH at post-intervention (OR 0.93, 95% CI 0.12 to 7.24; N = 51; k = 2; low-certainty evidence). We are uncertain whether mentalization based therapy for adolescents (MBT-A) reduces repetition of SH at post-intervention as compared to TAU (OR 0.70, 95% CI 0.06 to 8.46; N = 85; k = 2; very low-certainty evidence). Heterogeneity for this outcome was substantial (IR = 68%). There is probably no evidence of a difference between family therapy and either TAU or EUCon repetition of SH at post-intervention (OR 1.00, 95% CI 0.49 to 2.07; N = 191; k = 2; moderate-certainty evidence). However, there was no evidence of a difference for compliance enhancement approaches on repetition of SH by the six-month follow-up assessment, for group-based psychotherapy at the six- or 12-month follow-up assessments, for a remote contact intervention (emergency cards) at the 12-month assessment, or for therapeutic assessment at the 12- or 24-month follow-up assessments.

3. **Authors' conclusions:** Given the moderate or very low quality of the available evidence, and the small number of trials identified, there is only uncertain evidence regarding a number of psychosocial interventions in children and adolescents who engage in SH.

iv. **Witt 2021,** Cochrane review of pharmacological interventions for self-harm in adults

1. N=7 trials (574 patients)
2. It is uncertain if newer generation antidepressants reduce repetition of SH compared to placebo (OR 0.59, 95% CI 0.29 to 1.19; N = 129; k = 2; very low-certainty evidence). There may be a lower rate of SH repetition for antipsychotics (21%) as compared to placebo (75%) (OR 0.09, 95% CI 0.02 to 0.50; N = 30; k = 1; low-certainty evidence). However, there was no evidence of a difference between antipsychotics compared to another comparator drug/dose for repetition of SH (OR 1.51, 95% CI 0.50 to 4.58; N = 53; k = 1; low-certainty evidence). There was also no evidence of a difference for mood stabilizers compared to placebo for repetition of SH (OR 0.99, 95% CI 0.33 to 2.95; N = 167; k = 1; very low-certainty evidence), or for natural products compared to placebo for repetition of SH (OR 1.33, 95% CI 0.38 to 4.62; N = 49; k = 1; low certainty) evidence.
3. **Authors' conclusions** Given the low or very low quality of the available evidence, and the small number of trials identified, there is only uncertain evidence regarding pharmacological interventions in patients who engage in SH.

d. BHAP input: There was agreement that this code should be paired with psychotherapy CPT codes. The group agreed that this diagnosis is best not placed on DWF or on the Borderline Personality Disorder line. However, some BHAP members felt the Adjustment Disorder line was preferable, while others felt that either the Moderate Depression line or Anxiety Disorder line was more appropriate. More members suggested the Moderate Depression line that any other placement.

e. HERC staff summary: non-suicidal self harm is a clinical entity that has specific treatment modalities, rather than a sign or symptom like most other codes in the "R" series.

Evidence supports use of some types of psychotherapy. Insufficient evidence exists for pharmacologic therapy. Some articles link self harm to borderline personality disorder, while others link it to anxiety and/or depression.

f. HERC staff recommendation
    1. Place ICD-10-CM **R45.8** (Nonsuicidal self-harm) on line 203 DEPRESSION AND OTHER MOOD DISORDERS, MILD OR MODERATE
        a. Psychotherapy codes are present for pairing on this line
    2. Other placement options include line 414 OVERANXIOUS DISORDER; GENERALIZED ANXIETY DISORDER; ANXIETY DISORDER, UNSPECIFIED, 444 ADJUSTMENT DISORDERS or 462 OBSESSIVE-COMPULSIVE DISORDERS

10) **R63.31** and **R63.32** Pediatric feeding disorder
    a. Pediatric feeding disorder (also termed avoidant/restrictive food intake disorders) is a distinct clinical entity in which a child avoids eating or limits what or how much he or she will eat. This leads to problems including weight loss, nutritional deficiency, need for nutritional supplements, or problems with daily functioning. There are DSM-V diagnostic criteria for feeding disorders in infants or young children.
    b. Treatments include dietician visits, gastroenterology consultation and testing such as EGD or swallow studies, psychotherapy, speech and OT therapy
    c. Similar codes: this condition was previously coded with F98.29 (Other feeding disorders of infancy and early childhood) which is on line 149 FEEDING AND EATING DISORDERS OF INFANCY OR CHILDHOOD. Most "R" codes are on the Diagnostic Workup File (DWF). Staff suggestion for the other codes being broken out of R63.3 (R63.30 Feeding difficulties, unspecified and R36.39 Other feeing difficulties) are proposed for DWF in the straightforward section of this review
    d. HERC staff recommendation:
        i. Place ICD-10-CM R63.31 (Pediatric feeding disorder, acute) and R63.32 (Pediatric feeding disorder, chronic) on line 149 FEEDING AND EATING DISORDERS OF INFANCY OR CHILDHOOD

11) **U09.9** Post COVID-19 condition, unspecified
    a. From the CDC discussion at the CMS meeting for ICD-10 codes: If there is description of a sequela of COVID-19, a residual condition following COVID-19, or a post COVID-19 condition, then the new proposed code would be used. If there is a history of COVID-19, without a current related condition, then it would be appropriate to assign the code Z86.16, Personal history of COVID-19. If there is a current infection or recurrent infection with COVID-19, then it would be appropriate to assign the code U07.1, COVID-19.
    b. **CDC 2021**: https://www.cdc.gov/coronavirus/2019-ncov/hcp/clinical-care/post-covid-index.html
        i. Accessed July 20, 2021
        ii. The term "Post-COVID Conditions" is an umbrella term for the wide range of physical and mental health consequences experienced by some patients that are present four or more weeks after SARS-CoV-2 infection, including by patients who had initial mild or asymptomatic acute infection.

iii. Creating a comprehensive rehabilitation plan may be helpful for some patients and might include physical and occupational therapy, speech and language therapy, vocational therapy, as well as neurologic rehabilitation for cognitive symptoms. A conservative physical rehabilitation plan might be indicated for some patients (e.g., persons with post-exertional malaise); consultation with physiatry for cautious initiation of exercise and recommendations about pacing may be useful. Gradual return to exercise as tolerated could be helpful for most patients. Optimizing management of underlying medical conditions might include counseling on lifestyle components such as nutrition, sleep, and stress reduction (e.g., meditation).

c. Expert input
    i. Dr. Eric Herman, OHSU Long COVID Program
        1. Treatments recommended:
            a. PT is an essential component of managing fatigue, Post-exertional malaise, etc.
            b. OT, or perhaps SLT [speech language therapy] is a carefully constructed part of our program to help with cognitive blunting (brain fog). We are using speech language therapists, but other systems may use OT, etc.
            c. Clinically indicated specialty referrals of course, but perhaps the one that seems to be problematic in terms of authorization is Neuropsychiatric. For interest's sake our most referred specialties are: Neuro, Behavioral Health, neuropsych, cards, sleep medicine.

d. HERC staff summary: post-COVID conditions are poorly understood and are actively being researched. Treatments per the CDC and experts include PT, OT, speech therapy, and neurologic rehabilitation.

e. <u>HERC staff recommendation</u>:
    i. Place ICD-10-CM U09.9 (Post COVID-19 condition, unspecified) on line 399 INFLUENZA, COVID-19 AND OTHER NOVEL RESPIRATORY VIRAL ILLNESS and line 345 NEUROLOGICAL DYSFUNCTION IN COMMUNICATION CAUSED BY CHRONIC CONDITIONS
        1. Line 345 contains PT, OT, and speech therapy CPT codes. No other dysfunction line contains speech therapy codes
        2. Neuropsychological testing is diagnostic and governed by Diagnostic Guideline D26

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CLINICAL PRACTICE GUIDELINES

AGA Clinical Practice Guidelines on Management of Gastric Intestinal Metaplasia

Samir Gupta,[1,2] Dan Li,[3,4] Hashem B. El Serag,[5] Perica Davitkov,[6,7] Osama Altayar,[8] Shahnaz Sultan,[9] Yngve Falck-Ytter,[10,11] and Reem A. Mustafa[12]

[1]Department of Veterans Affairs San Diego Healthcare System, San Diego, California; [2]Division of Gastroenterology and the Moores Cancer Center, University of California San Diego, La Jolla, California; [3]Department of Gastroenterology, Kaiser Permanente Santa Clara Medical Center, Santa Clara, California; [4]Division of Research, Kaiser Permanente Northern California, Oakland, California; [5]Department of Medicine, Baylor College of Medicine, Houston, Texas; [6]Veterans Administration, Northeast Ohio Healthcare System, Cleveland, Ohio; [7]Case Western Reserve University School of Medicine, Cleveland, Ohio; [8]Division of Gastroenterology, Washington University School of Medicine, St Louis, Missouri; [9]Minneapolis Veterans Affairs Healthcare System, University of Minnesota, Minneapolis, Minnesota; [10]Department of Veterans Affairs Cleveland Medical Center, Cleveland, Ohio; [11]Case Western Reserve University, Cleveland, Ohio; [12]Department of Internal Medicine, University of Kansas Medical Center, Kansas

See editorial on page 473.

Gastric cancer is the third leading cause of cancer death worldwide.[1] In 2018, 1,033,701 incident cases were diagnosed globally,[1] including 26,240 nationally in the United States.[2] The majority of gastric cancers in the United States are non-cardia gastric cancers, arising from the antrum, incisura, body, and/or fundus.[3] Chronic infection with *Helicobacter pylori* is the primary risk factor for (intestinal-type) non-cardia gastric cancer, with at least 80% of the global gastric cancer burden attributable to this pathogen.[4] Non-cardia intestinal-type cancer, the most common histologic subtype of gastric cancer, has been shown to follow a pattern of stepwise progression (ie, the Correa cascade), from normal mucosa to non-atrophic gastritis to atrophic gastritis to intestinal metaplasia to gastric adenocarcinoma.[5] Ability to identify precursor lesions on gastric biopsies has led to interest in developing screening and surveillance strategies for early detection and prevention of gastric cancer. In East Asia, population-based screening programs have been implemented in countries with particularly high gastric cancer incidence and mortality, such as Japan and Korea. These programs have resulted in higher detection rates of early gastric cancer, with substantially reduced mortality.[6,7] In low-incidence countries, such as the United States, population-wide screening has not been endorsed. However, interest remains in determining whether screening and surveillance targeted to specific populations based on histologic risk factors, race/ethnicity, immigration from countries with high gastric cancer incidence, and other factors may be warranted.

Gastric intestinal metaplasia (GIM) may represent the histologic step just before development of dysplasia. GIM has been considered as one specific marker to identify patients who might benefit from surveillance because it has been associated with increased risk for gastric cancer and is routinely encountered in clinical practice.[5] Surveys of US endoscopists have found wide variation in practice patterns in the management of GIM, even among physicians regularly caring for populations that could be at increased risk based on race/ethnicity and/or immigration status.[8] An evidence-based guideline supported by a comprehensive literature review for management of patients with GIM has not been previously published in the United States. Accordingly, we aimed to develop evidence-based guidelines to inform management of patients with GIM incidentally detected on gastric biopsies in routine clinical practice. A reader's understanding of this guideline will be optimized and enhanced by reading the accompanying 2 technical reviews (TRs), which provide an overview and synthesis of the evidence used to inform this guideline.[9,10]

Scope, Target Audience, and Definitions

This guideline focuses on recommendations for management of patients with GIM detected as part of routine upper endoscopy for reasons including workup of endoscopically identified gastropathy/presumed gastritis, dyspepsia, or exclusion of *H pylori*. Screening for gastric cancer (either population-wide or in select populations) and management of patients with dysplasia of the gastric mucosa, gastric adenocarcinoma, and/or autoimmune gastritis are beyond the scope of the current guideline. This guideline is intended to aid decision-making for patients who are undergoing upper endoscopy in North America. GIM is

Abbreviations used in this paper: **AGA, American Gastroenterological Association; ASGE, American Society of Gastrointestinal Endoscopy; CI, confidence interval; ESGE, European Society of Gastrointestinal Endoscopy; GIM, gastric intestinal metaplasia; GRADE, Grading of Recommendations Assessment, Development and Evaluation; PICO, population, intervention, comparator, and outcome; RR, relative risk; TR, technical review.**

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linked mainly to risk for non-cardia gastric cancer. For ease of presentation, we refer to non-cardia gastric cancer as "gastric cancer" throughout this article.

Methods

The steps undertaken in the development of this guideline were guided by the AGA guideline development process, which has been outlined elsewhere.[11] Briefly, the AGA process for developing clinical practice guidelines incorporates the Grading of Recommendations Assessment, Development and Evaluation (GRADE) methodology[11] and best practices, as outlined by the Academy of Medicine, formerly Institute of Medicine.[12]

Guideline Panel Composition, Funding, and Conflict of Interest

The guideline panel included gastroenterologists (S.G., D.L., and H.E.), guideline methodologist trainees (P.D. and O.A.), and GRADE experts (S.S., Y.F.Y., and R.A.M.). The guideline panel worked closely with TR team members who reviewed the evidence used to inform this guideline. Development of this guideline was wholly funded by the AGA, with no other additional outside funding.

Conflict of interest of all guideline panel members was managed according to AGA Institute Clinical Guidelines Committee policy. Before appointment to the panel, individuals completed conflict of interest forms and disclosed any and all relevant conflicts for 3 years before appointment. All conflict of interest forms can be accessed at AGA's National Office in Bethesda, MD.

Formulating Specific Clinical Questions

As described in detail in the TR documents accompanying this guideline, we developed 4 clinically relevant questions for management of GIM detected at routine endoscopy using the PICO format. The PICO format frames clinical questions by defining a specific population, intervention, comparator, and outcome. Our PICO questions were:

1. Among patients with GIM, does testing and treating for *H pylori* vs no testing and treatment affect patient important outcomes?
2. Among patients with GIM who are identified as low risk, does subsequent surveillance upper endoscopy vs no follow-up affect patient important outcomes?
3. Among patients with GIM who are identified as high risk, does subsequent surveillance upper endoscopy vs no follow-up affect patient important outcomes?
4. Among patients with GIM without dysplasia, does short-term follow-up (<1 year) with biopsies to determine the extent of GIM vs no short-term follow-up affect patient-important outcomes?

After finalizing the PICO questions, the TR team and the guideline panel prioritized patient-important outcomes critical and important for decision-making. Patient-important outcomes of interest included both benefits and harms, such as early gastric cancer detection, reduced morbidity/mortality from gastric cancer, complications associated with endoscopy, psychological outcomes (eg, anxiety and stress related to endoscopic surveillance, coping with a precancerous condition), and resource implications.

Evidence Review

A comprehensive list of direct and indirect evidence needed to inform the questions was developed (Table 1). The desired evidence included incidence and prevalence data for GIM, incidence of gastric cancer in individuals with GIM, and risk factors associated with progression to gastric cancer in patients with GIM compared with individuals without GIM. This "wish list of needed evidence" guided the systematic literature search. Given the paucity of robust direct data on GIM in the United States, evidence from all regions of the world was considered relevant in the evidence-gathering phase. Details related to the management and natural progression of dysplasia were considered outside the scope of this TR unless there was clear discernible clinical relevance to outcomes of GIM.

Development of Recommendations

Upon completion of the evidence synthesis, the guideline panel (S.G., D.L., and H.E.) worked with the TR team to understand the evidence. The panel established the following decision threshold to support surveillance: rate of progression to gastric cancer among individuals with GIM that exceeds 0.5%–1% annually.

During a face-to-face meeting followed by online communication and conference calls, the guideline panel developed recommendations based on the following elements of the GRADE evidence to decision framework: quality or certainty in the evidence, balance of benefits and harms, assumptions about patient values and preferences, and resource implications.

For each guideline statement, the strength of the recommendation and the quality of evidence to support the recommendation are provided (summarized in Tables 2 and 3, respectively). The recommendations are labeled as "strong" or "conditional" according to the GRADE approach. The term *AGA recommends* is used for strong recommendations, and *AGA suggests* is used for conditional recommendations. Table 3 provides GRADE's interpretation of strong and conditional recommendations by patients, clinicians, health care policy makers, and researchers. Statements about the underlying values and preferences, as well as qualifying remarks accompanying each recommendation, are its integral parts and serve to facilitate more accurate interpretation.

External Review

Draft recommendations were reviewed by all members of the panel and were made available online for public comment and sent out for external review. Subsequently, the document was revised to address pertinent comments, but no changes were made to the recommendations.

Recommendations

A summary of all the recommendations in this guideline is provided in Table 4.

Recommendation 1. In patients with GIM, the AGA recommends testing for *H pylori* followed by eradication over no testing and eradication. *Strong recommendation, moderate quality of evidence.*

Rationale: *H pylori* is an established gastric carcinogen, accounting for up to 89% of non-cardia gastric cancers

Table 1. PICO Questions, Outcomes, and Evidence Needed to Inform PICO Questions

PICO question	Patient-important outcomes	Evidence needed to inform PICO questions
1. Among patients with GIM, does testing for *H pylori* and treating if positive vs no testing affect patient-important outcomes? 2. Among patients with GIM who are identified as low risk, does subsequent upper endoscopic surveillance vs no follow-up affect patient-important outcomes? 3. Among patients with GIM who are identified as high risk, does subsequent upper endoscopic surveillance vs no follow-up affect patient-important outcomes? 4. Among patients with GIM without dysplasia does short-term upper endoscopic follow-up (<1 year) to determine the extent (using biopsies) of GIM vs no short-term follow-up affect patient-important outcomes?	Early cancer detection Reduced gastric cancer morbidity/mortality Endoscopy complications Costs Psychological harms	Incidence and prevalence of GIM in the US population Incidence of stomach cancer in the general population Prevalence of concurrent gastric cancer in patients with GIM Incidence of gastric cancer in patients with GIM after GIM diagnosis Risk of progression to gastric cancer in patients with GIM Subgroups: Family history of gastric cancer, race/ethnicity, smoking status, histologic features, extent of GIM, biomarkers Potential adverse consequences of performing surveillance upper endoscopy for patients with GIM Benefits of performing surveillance upper endoscopy for patients with GIM

worldwide.[4] As outlined in the TR, 22 studies, including 7 randomized controlled trials and 3 cohort studies, were used to inform recommendations on whether *H pylori* diagnosed in the setting of histologically detected GIM should be eradicated.[9] The TR found that *H pylori* eradication (compared with placebo) among individuals with or without GIM in the absence of gastric neoplasia was associated with a 32% pooled relative risk (RR) reduction in incident gastric cancer risk (RR, 0.68; 95% confidence interval [CI], 0.48–0.96). *H pylori* eradication (compared with placebo) among individuals with or without GIM was also associated with a 33% pooled RR reduction in risk for gastric cancer mortality (RR, 0.67; 95% CI, 0.38–1.17). Analyses of gastric cancer among individuals with *H pylori* infection and confirmed GIM showed a qualitatively similar RR reduction for incident gastric cancer associated with eradication of *H pylori* (RR, 0.76; 95% CI, 0.36–1.61). Results from the studies identified in the TR's comprehensive systematic review were insufficient to assess the impact of *H pylori* eradication on gastric cancer mortality restricted to individuals with confirmed GIM (see Table 3 in Gawron et al,[9] for the this evidence profile summarizes the body and quality of evidence that informed this recommendation).

Overall, the known strong association of *H pylori* with risk for incident gastric cancer and the TR's findings, which reinforce the evidence of reduced risk for incident gastric cancer after *H pylori* eradication, supports the AGA recommendation to test for and eradicate *H pylori* in individuals with incidentally detected GIM. The quality of evidence to support this recommendation was rated as moderate, in part because of the lack of data on impact of *H pylori* eradication in individuals with confirmed GIM. In addition, the trial that had the largest influence on the pooled estimate was limited by attrition bias and was conducted in an indigenous Chinese population, which may have different risk of gastric cancer. Confirming eradication of *H pylori* is recommended, given high known *H pylori* eradication failure rates using current therapies, but the method of testing for *H pylori* and strategies for confirming eradication are outside scope of the current guideline and are covered elsewhere.[13]

Recommendation 2. In patients with GIM the AGA suggests against routine use of endoscopic surveillance. *Conditional recommendation, very low quality of evidence*
Comment: Patients with GIM at higher risk for gastric cancer who put a high value on potential but uncertain reduction in gastric cancer mortality, and who put a low value on potential risks of surveillance endoscopies, may reasonably elect for surveillance.
Patients with GIM specifically at higher risk of gastric cancer include those with:

- **Incomplete vs complete GIM**
- **Extensive vs limited GIM**
- **Family history of gastric cancer**

Patients at overall increased risk for gastric cancer include:

- **Racial/ethnic minorities**
- **Immigrants from high incidence regions**

Comment: Patients with GIM who put a high value on potential reduction in gastric cancer mortality, despite a lack of direct supporting evidence, in the context of an approximate 0.16% annual and an approximate 1.6% ten-year cumulative risk for incident gastric cancer, and who put a low value on the potential risks of repeat surveillance endoscopies may reasonably select to enroll in endoscopic surveillance. Patients with GIM who could be at higher risk

Table 2. Interpretation of the Certainty in Evidence of Effects Using the GRADE Framework

GRADE	Description
High	We are very confident that the true effect lies close to that of the estimate of the effect.
Moderate	We are moderately confident in the effect estimate. The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
Low	Our confidence in the effect estimate is limited. The true effect may be substantially different from the estimate of the effect.
Very low	We have very little confidence in the effect estimate. The true effect is likely to be substantially different from the estimate of effect

for gastric cancer (≥1.6% ten-year risk), who put a high value on potentially reducing gastric cancer mortality despite a lack of direct supporting evidence, and who put a low value on the potential risks of surveillance endoscopies may also reasonably select endoscopic surveillance. Similarly, patients who are at overall increased risk for gastric cancer may also reasonably select endoscopic surveillance. Risk assessment should be individualized. Patients with GIM at higher risk of gastric cancer include those with incomplete (at least partial colonic type) vs complete (small intestinal type) intestinal metaplasia (3.3-fold RR based on low quality of evidence); family history of gastric cancer (4.5-fold RR based on very low quality of evidence); and extensive (involving the gastric body plus either antrum and/or incisura) vs limited GIM (involving the gastric antrum and/or incisura only; 2.1-fold RR based on very low quality of evidence (see Table 2 in Altayar et al,[10]). Although the TR did not find evidence supporting increased risk for gastric cancer among racial/ethnic minorities or immigrants with documented GIM, an overall increased risk for gastric cancer (irrespective of presence/absence of GIM) has been established among these groups, and may be considered as part of decision-making regarding surveillance.[3,14]

There are insufficient data to guide recommendations on the optimal surveillance interval. Based on indirect evidence of cumulative gastric cancer incidence among patients with GIM, repeat upper endoscopy every 3–5 years with careful mucosal visualization and gastric biopsies of the antrum, body, and any concerning lesions could be considered in patients with incidental GIM, if shared decision-making favors surveillance.

Rationale: Based on the comprehensive TR systematic review, there was no direct evidence to inform recommendations for or against endoscopic surveillance after *H pylori* eradication. Specifically, the TR found no randomized controlled trial, cohort study, or case–control study comparing impact of endoscopic surveillance vs no surveillance on gastric cancer risk among patients with GIM. Based on the lack of comparative evidence to support altered gastric cancer incidence or mortality among patients with GIM enrolled in surveillance vs no surveillance, the AGA recommends shared decision-making regarding use of endoscopic surveillance over routine use of surveillance. The TR identified indirect evidence that could inform decision-making on whether to consider endoscopic surveillance in select cases, including prevalence of GIM on routine gastric biopsies; longitudinal risk for incident gastric cancer among individuals with GIM; and factors that may be associated with increased gastric cancer risk among individuals with GIM.

Pooled prevalence of GIM among 897,371 individuals with gastric biopsies was estimated to be 4.8% (95% CI, 4.8%–4.9%).[10] As such, the panel recognizes that any recommendations for surveillance of GIM could impact a significant proportion of individuals undergoing endoscopy with biopsy. A limitation of this meta-analysis is that most of the data were from a single study reporting on prevalence of GIM among gastric biopsies routinely submitted for

Table 3. Interpretation of Strong and Conditional Recommendations Using the GRADE Framework

Implications	Strong recommendation[a]	Conditional recommendation[b]
For patients	Most individuals in this situation would want the recommended course of action and only a small proportion would not.	The majority of individuals in this situation would want the suggested course of action, but many would not.
For clinicians	Most individuals should receive the intervention. Formal decision aids are not likely to be needed to help individuals make decisions consistent with their values and preferences.	Different choices will be appropriate for individual patients consistent with his or her values and preferences. Use shared decision-making. Decision aids may be useful in helping patients make decisions consistent with their individual risks, values, and preferences.
For policy-makers	The recommendation can be adapted as policy or performance measure in most situations.	Policy-making will require substantial debate and involvement of various stakeholders. Performance measures should assess whether decision-making is appropriate.

[a]Strong recommendations are indicated by statements that lead with "we recommend."
[b]Conditional recommendations are indicated by statements that lead with "we suggest."

Table 4. AGA Recommendations for Management of Gastric Intestinal Metaplasia

Statement	Strength of recommendation	Quality of evidence
1. In patients with GIM, the AGA recommends testing for *H pylori*, followed by eradication over no testing and eradication	Strong	Moderate
2. In patients with GIM, the AGA suggests against routine use of endoscopic surveillance	Conditional	Very Low
Comments: Patients with GIM at higher risk for gastric cancer who put a high value on potential but uncertain reduction in gastric cancer mortality, and who put a low value on potential risks of surveillance endoscopies, may reasonably elect for surveillance.[a]		
Patients with GIM specifically at higher risk of gastric cancer include those with:		
• Incomplete vs complete GIM		
• Extensive vs limited GIM		
• Family history of gastric cancer		
Patients at overall increased risk for gastric cancer include:		
• Racial/ethnic minorities		
• Immigrants from high incidence regions		
3. In patients with GIM, the AGA suggests against routine repeat short-interval endoscopy with biopsies for the purpose of risk stratification	Conditional	Very Low
Comments: Based on shared decision-making, patients with GIM and high-risk stigmata, concerns about completeness of baseline endoscopy, and/or who are at overall increased risk for gastric cancer (racial/ethnic minorities, immigrants from regions with high gastric cancer incidence, or individuals with family history of first-degree relative with gastric cancer) may reasonably elect for repeat endoscopy within 1 year for risk stratification.		

[a]There are insufficient data to guide optimal surveillance interval. Based on indirect evidence regarding cumulative gastric cancer incidence among patients with GIM, repeat upper endoscopy with careful mucosal visualization and gastric biopsies of the antrum and body and any concerning lesions may be considered in 3–5 years among patients with incidentally detected GIM, if shared decision-making favors surveillance.

pathologic review to a single national gastrointestinal pathology service company in the United States.

The 3-, 5-, and 10-year pooled cumulative rates of incident gastric cancer among patients with GIM were estimated to be 0.4% (95% CI, 0.1%–0.8% based on 4 studies); 1.1% (95% CI, 1.0%–1.2% based on 7 studies); and 1.6% (95% CI, 1.5%–1.7% based on 4 studies), respectively.[9] Just 2 of the studies included to estimate cumulative gastric cancer risk were from the United States. For example, among individuals from a large integrated health care plan in Southern California, the cumulative 5-year risk for gastric cancer was estimated to be 0.9% (95% CI, 0.3%–1.6%).[15] The pooled annual rate of progression to gastric cancer among individuals with GIM was estimated to be 0.16% per year. This estimate is lower than the previously reported pooled annual cumulative risk of 0.33% for esophageal adenocarcinoma among patients with non-dysplastic Barrett's esophagus, a condition for which endoscopic surveillance is often routinely recommended.[16] The TR also was able to estimate cumulative rate of progression to dysplasia among individuals with GIM as being 15% at 3 years (95% CI, 13%–17%) and 15% at 5 years (95% CI, 12%–19%), based on 7 total studies with nearly 3000 patients with GIM; all studies contributing data to these estimates were from outside the United States.[9]

The TR also summarized evidence informing differential risk for gastric cancer according to several prespecified potential risk factors for gastric cancer, including race/ethnicity, family history of gastric cancer, smoking, autoimmune gastritis/pernicious anemia, histologic features (incomplete vs complete GIM), extent of GIM (extensive vs limited) and biomarkers (eg, CagA positivity).[10] Assessment of differential risk by race/ethnicity was performed only for North American studies. Meta-analysis of the 3 studies identified showed that among patients with confirmed GIM, cumulative risk for gastric cancer was not statistically significantly different for Hispanics (1.0%; 95% CI, 0.4%–1.7%), Asians (0.3%; 95% CI, 0.1%–0.8%), blacks (0.4%; 95% CI, 0.0%–1.4%), and non-Hispanic whites (0.3%; 95% CI, 0.1%–0.6%) (see Table 2 in Altayar et al,[10]). Although no statistically significant difference across racial/ethnic groups was observed, the wide CIs and varying point estimates (eg, 1.0% for Hispanics vs 0.3% for non-Hispanic whites) do not rule out the possibility of clinically meaningful differences. Thus, while evidence clearly demonstrates that minority populations have overall higher risk for gastric cancer in the United States, current evidence does not support increased risk among racial/ethnic minorities once GIM is established. The TR did not identify higher prevalence of GIM among racial/ethnic minorities, and did not find racial/ethnic minorities with GIM have increased risk for gastric cancer compared to non-Hispanic whites with GIM, but based on the very low quality of evidence available we could not exclude the possibility of increased risk for GIM and progression of GIM among racial/ethnic minorities.

Seven studies assessing risk for gastric cancer among patients with GIM based on presence of incomplete (at least

partial areas of colonic type) vs complete (small intestinal type) GIM were identified. Based on meta-analysis, having incomplete vs complete GIM was associated with a 3-fold increased risk for incident gastric cancer on follow-up (RR, 3.33; 95% CI, 1.96–5.64).[9] None of these studies were from the United States. Anecdotally, US pathologists rarely report presence of incomplete vs complete GIM as part of routine GIM diagnosis. This observation raises concerns as to whether the histologic subtype of GIM can be feasibly utilized as part of risk stratification in the United States without a substantial educational initiative for pathologists.

Among patients with GIM, having a family history of a first-degree relative with gastric cancer was associated with 4.5-fold increased risk for incident gastric cancer based on 3 studies (RR, 4.53; 95% CI, 1.33–15.46).[9]

Among patients with GIM who had biopsies obtained from both the gastric antrum/incisura and body, extensive GIM vs limited involvement (ie, including involvement of at least the gastric body vs GIM of the antrum and/or incisura, respectively) was associated with a 2-fold higher pooled RR of incident gastric cancer (RR, 2.07; 95% CI, 0.97–4.42) based on 2 studies.[9] In the United States, the anecdotally reported routine practice of submitting gastric biopsies without specifying the total number of biopsies or separating biopsies taken into separate specimen jars labeled with specific anatomic locations could challenge the ability to use the anatomic extent of GIM for risk stratification unless a shift away from this practice occurs.

Little to no evidence was available to assess the risk for gastric cancer among patients with GIM based on personal history of concurrent smoking, pernicious anemia, autoimmune gastritis, or potential risk biomarkers.

Overall, indirect evidence summarized by the TR suggests GIM is diagnosed commonly (prevalence of 5%) and is associated with a cumulative risk for incident gastric cancer (1.6% at 10 years). Risk for cancer among individuals with GIM may be higher among individuals with incomplete vs complete histology, extensive vs limited GIM, and those with a family history of gastric cancer in a first-degree relative. Taken together, the AGA recommends these factors could be considered as part of the decision on whether to pursue surveillance upper endoscopy among individuals with GIM as part of the shared decision-making process.

Recommendation 3. In patients with GIM, the AGA suggests against routine short-interval repeat endoscopy for the purpose of risk stratification. *Conditional recommendation, very low quality of evidence.*
Comment: Based on shared decision-making, patients with GIM and high-risk stigmata, concerns about completeness of baseline endoscopy, and/or who are at overall increased risk for gastric cancer (racial/ethnic minorities, immigrants from regions with high gastric cancer incidence, or individuals with family history of first-degree relative with gastric cancer) may reasonably elect for repeat endoscopy within 1 year for risk stratification.

Patients with GIM who put a high value on the possible increased risk of gastric cancer associated with extensive GIM, and a low value on the risks associated with repeat endoscopy, could reasonably choose repeat endoscopy to establish the anatomic extent (sometimes referred to as "gastric mapping"), establish histologic subtype of GIM (if local pathologist expertise permits), and exclude prevalent cancer. Patients with GIM and high-risk stigmata (eg, visually detected abnormalities such as nodularity) or concerns about completeness of baseline endoscopy may also elect to undergo endoscopy within 1 year to detect prevalent cancer and/or for gastric biopsies to characterize the anatomic extent and histologic subtype of GIM. Patients with GIM at overall increased risk for gastric cancer (such as Hispanics, Asians, African Americans, and Native Americans/Alaska Natives;[3] immigrants from regions with high gastric cancer incidence[14]; or individuals with family history of first-degree relative with gastric cancer) may elect for repeat endoscopy within 1 year to detect prevalent cancer through targeted biopsies of any visible abnormalities, and to perform untargeted biopsies (at minimum of the antrum and body, submitted in separate specimen jars for pathology)[17] to better define risk for subsequent gastric cancer based on the anatomic extent of GIM and histologic subtype (incomplete vs complete).

Rationale: The TR found no direct evidence to support the impact of short-interval (<12 months) repeat upper endoscopy among patients with incidental GIM on patient-important outcomes. Specifically, no cohort study or case series of patients with incidentally found GIM systematically subjected to short-interval repeat endoscopy was identified. Thus, there was no direct evidence to inform frequency of detection of higher-risk GIM features or prevalent gastric cancer not appreciated at the initial endoscopy where GIM was diagnosed. Accordingly, based on a lack of data on the yield of short-interval repeat endoscopy and the impact on risk stratification or prevalent cancer detection, the AGA suggests shared decision-making regarding surveillance over routine use of endoscopic surveillance after GIM diagnosis and *H pylori* eradication if present.

The TR did identify indirect evidence that can be used to engage patients with incidentally detected GIM in shared decision-making on whether to consider a short-interval repeat endoscopy. Concern for undetected prevalent cancer could also justify short-interval repeat endoscopy. As mentioned previously, the TR did not identify any studies characterizing the endoscopic miss rate for gastric cancer among patients with GIM. As indirect evidence, the TR estimated the risk for gastric cancer within 1 year of GIM diagnosis, assuming that cancers diagnosed within 1 year of GIM follow-up are more likely to have been missed prevalent cases as opposed to incident cancers. Based on 4 cohort studies, the cumulative incidence of gastric cancer within 1 year of GIM diagnosis was estimated to be 0.5% (95% CI, 0.4%–0.6%),[9] suggesting the overall risk of missed cancer is low. Nonetheless, the AGA recognizes that individuals with any concerns for quality or completeness of the baseline endoscopy, and/or assessment of visually detected abnormalities, may reasonably elect to undergo a short-interval repeat upper endoscopy to exclude prevalent cancer.

As reported previously, the TR found evidence suggesting a 3-fold increased risk for incident gastric cancer among individuals with incomplete (at least partial colonic type) vs complete (small intestinal type) GIM, and a 2-fold increased risk for cancer among individuals with extensive vs limited GIM. Because GIM is often diagnosed based on an unspecified number of "random" biopsies submitted in a single pathology jar in clinical practice, the ability to confidently rule out the presence of incomplete GIM and extensive GIM could be limited. Accordingly, patients and providers who put a high value on these factors for determining the need for subsequent longitudinal endoscopic surveillance, may reasonably elect to undergo a short-interval repeat upper endoscopy to assess anatomic extent and histologic characteristics of GIM.

In the United States, racial/ethnic minorities have a much higher risk for incident and fatal gastric cancer than non-Hispanic whites.[3] While the TR did not identify substantially different rates of incident gastric cancer among individuals with previously established GIM across racial/ethnic groups, the AGA recognizes that groups with overall increased risk for gastric cancer may also reasonably elect for a short-interval repeat endoscopy for gastric biopsies to characterize anatomic extent and histologic subtype of GIM (if a decision favoring surveillance has not yet been made) and to exclude prevalent cancer.

Discussion

GIM is often detected as part of routine endoscopy, frequently when the original indication for the endoscopy was not screening for gastric cancer. As such, when GIM is detected as part of routine endoscopy, questions arise regarding whether *H pylori* should be identified and treated, whether endoscopic surveillance is indicated, whether an area with more advanced histology may not have been identified, and whether short-interval repeat endoscopy is needed for more precise risk stratification and/or to rule out prevalent gastric cancer. Based on an extensive TR of evidence to support management of patients with incident GIM, the AGA has made recommendations for management and surveillance (Table 4). Based on moderate-quality evidence, the AGA recommends testing for *H pylori* and eradication among individuals with GIM. Based on a very low quality of evidence, mainly due to a lack of studies specifically addressing clinical impact of short-interval repeat endoscopy and longitudinal endoscopic surveillance, the AGA suggests against routine short-interval repeat endoscopy and longitudinal surveillance.

Recognizing that the lack of evidence could put some patients at risk for adverse outcomes pending the generation of new, rigorous evidence, we investigated evidence that could help guide shared decision-making between patients and providers on whether to elect to undergo longitudinal surveillance or short-interval repeat endoscopy. Because we found incomplete (vs complete) GIM and extensive vs limited (involving the antum/incisura only) GIM were associated with increased risk for incident gastric cancer among patients with GIM, patients and providers may reasonably elect to undergo short-interval upper endoscopy to characterize presence/absence of these features, or commit to longitudinal surveillance if these features are known to be present. Similarly, because we found evidence supporting increased risk for gastric cancer among patients with GIM and a first-degree relative with gastric cancer, patients with GIM and a family history could reasonably elect for longitudinal endoscopic surveillance. Identifying the best management strategies for racial/ethnic minorities with GIM remains a challenge. The TR found, based on limited evidence, no statistically significant variation across racial/ethnic groups in cumulative gastric cancer risk among individuals with GIM. As noted previously, the wide CIs and varying point estimates for rate of incident gastric cancer (eg, 1.0% for Hispanics vs 0.3% for non-Hispanic whites) do not rule out the possibility of clinically meaningful differences. The overall higher risk for gastric cancer among racial/ethnic minorities in the United States, and for individuals in high-incidence regions, is well established. Further, data on variation in risk by racial/ethnic groups came from just 3 studies, and those studies did not account for whether minorities were from the United States or foreign-born, or the duration of their residence in countries with high gastric cancer incidence. New immigrants from high-incidence geographic areas (such as East Asia or South America) have higher risk of gastric cancer, likely due to shared risk factors, such as *H pylori* infection and other exposures.[14] Recognizing the uncertainty in risk, racial/ethnic minorities with GIM may reasonably elect to undergo short-interval repeat endoscopy to characterize anatomic extent of GIM, histologic subtype of GIM, exclude prevalent cancer, and/or to undergo longitudinal surveillance endoscopy until new evidence is generated. A suggested algorithm for management of patients with GIM is provided in a Clinical Decision Support Tool.

What Do Other Guidelines Say?

Compared to the AGA guidelines, the recommendations from other professional societies in the United States and Europe specific to patients with GIM within the scope of AGA recommendations are generally similar. The American Society of Gastrointestinal Endoscopy (ASGE) 2015 guidelines state: "We suggest surveillance endoscopy for patients with GIM who are at increased risk for gastric cancer due to ethnic background or family history. Optimal surveillance intervals have not been extensively studied and should be individualized."[18] ASGE guidelines also suggest surveillance may be suspended when 2 consecutive endoscopies are negative for dysplasia, and recommend eradication of *H pylori* if identified. Thus, ASGE guidelines are consistent with the AGA's recommendation against routine surveillance, and similar to our suggestion that surveillance may be considered based on shared decision-making between patients and providers for

patients with family history of gastric cancer or increased background risk for gastric cancer; duration of surveillance was not within the scope of the current AGA guideline. Further, the AGA recommendations to test and eradicate *H pylori* complement and extend the ASGE recommendation to eradicate *H pylori* if identified.

The European Society of Gastrointestinal Endoscopy (ESGE) recently published guidelines for management of epithelial precancerous conditions and lesions in the stomach, including GIM.[19] ESGE recommendations were based on updating the literature search for key questions of interest since their 2012 guidelines,[20] rating available evidence using a GRADE framework, and achieving consensus statements using a Delphi process. ESGE recommends consideration of *H pylori* eradication in patients with GIM, similar to the AGA's outright recommendation to test and eradicate *H pylori* for this group. With regard to endoscopic surveillance, ESGE highlighted increased risk associated with GIM at a single anatomic location (GIM of limited extent), but, with respect to having GIM at a single anatomic location alone, judged that the "increased risk does not justify surveillance in most cases, particularly if a high quality endoscopy with biopsies has excluded advanced stages of atrophic gastritis," citing this as a strong recommendation based on moderate-quality evidence. ESGE did recommend that surveillance 3 years from baseline could be considered for individuals with GIM at a single location but with family history of gastric cancer, incomplete GIM, persistent *H pylori* gastritis, citing this as a weak recommendation based on low-quality evidence. ESGE made a strong recommendation based on low-quality evidence in favor of surveillance endoscopy every 3 years among individuals with severe gastric atrophy or GIM in both the antrum and body, and/or (OLGA) Operative Link on Gastritis Assessment/OLGIM (Operative Link on Gastritis Assessment based on Intestinal Metaplasia) stage III/IV. ESGE also suggested that those with a family history plus these findings might consider even more intense 1- to 2-year surveillance endoscopy, citing this as a weak recommendation based on low-quality evidence. Taken together, ESGE and AGA recommendations are consistent in not recommending routine surveillance for patients with GIM in the absence of increased extent (antrum and body), family history of gastric cancer, and incomplete GIM. While AGA recommends shared decision-making to discuss pros and cons of surveillance in patients with risk factors, such as increased extent, family history, and incomplete GIM, ESGE explicitly recommends surveillance for individuals with increased extent and, similar to AGA, recommends consideration of surveillance for those with family history of gastric cancer and incomplete GIM. If surveillance is planned, whereas AGA recommends consideration of a 3- to 5-year interval for surveillance, ESGE recommends 3 years, with consideration for more intense surveillance in the setting of extensive GIM plus a family history of gastric cancer. ESGE did not explicitly make a recommendation for or against short-interval repeat endoscopy for characterizing extent of GIM or presence of GIM if not done at baseline, although all of its recommendations imply knowledge of biopsy findings from at least the antrum and body of the stomach.

Future Research Needs and Evidence Gaps

Our recommendations highlight several areas of uncertainty ripe for future research. Key evidence gaps include a lack of observational studies and randomized trials on impact of surveillance vs no surveillance on outcomes, such as early detection and prevention of gastric cancer. More data are needed to understand the importance of extensive vs limited (antral/incisura only) GIM on risk for gastric cancer. The yield of systematically repeating baseline endoscopy to characterize the anatomic extent and histologic subtype of GIM (eg, short-interval endoscopy with gastric mapping) requires study. Studies on the yield of repeat baseline endoscopy for patients with GIM detected on routine endoscopy should pay specific attention to the number of additional individuals identified as potentially at increased risk for progression to cancer based on findings at the repeat examination to clarify whether repeat examinations might change decisions on surveillance. Our TR suggests the most robust evidence base for a risk factor linked to gastric cancer among individuals with GIM is presence of incomplete vs complete metaplasia. As such, studies should investigate the potential benefit of implementing routine characterization of incomplete vs complete intestinal metaplasia by pathologists, particularly in the United States. Additional natural history studies are required, such as investigation of differences based on race, ethnicity, or country of origin, and whether risk of GIM detected as part of routine endoscopy differs from patients who are engaged in a specific screening program for gastric cancer. Additionally, there have been conflicting reports with respect to whether GIM continues to progress after *H pylori* eradication. Although some studies observed improvement or reversal of GIM after *H pylori* eradication,[21–23] others suggested that GIM may persist or continue to progress (ie, "a point of no return") after *H pylori* treatment.[24,25] The optimal protocol for obtaining gastric biopsies to increase the yield of GIM detection in clinical practice remains to be determined. Prior studies using the OLGA and OLGIM classifications have shown benefits in identifying patients with more extensive disease and at increased risk for disease progression, but adopting these systems in daily clinical practice may be challenging.[26,27] Using image-enhanced technologies (or virtual chromoendoscopy, such as narrow band imaging) to perform targeted gastric biopsy has been reported to improve detection of GIM.[28,29] Application of these techniques in routine practice and whether it translates to improved outcomes warrant further investigation. In addition, biomarkers such as pepsinogen (I and II) levels are commonly used in Asian countries for gastric cancer risk-stratification but have not been well studied in the United States.[30–32] Such studies may generate useful information in selecting patients with increased risk for gastric cancer who may benefit most from screening and

surveillance endoscopy. Studies are also required to place the effectiveness and cost-effectiveness of GIM management within the larger context of gastric prevention that may include screening for *H pylori* and screening endoscopy.

Several limitations should be considered when interpreting these recommendations. The recommendations were based on a paucity of evidence. In particular, the strength of recommendations was conditional for our recommendations on surveillance endoscopy, and the overall quality of evidence to support these recommendations was judged to be very low. Thus, it is highly possible that new studies addressing current evidence gaps may markedly impact future recommendations regarding the management of individuals with GIM.

In conclusion, the AGA recommends patients with GIM be tested and treated for *H pylori* to reduce risk for gastric cancer. In light of current evidence gaps, the AGA suggests against routine use of short-interval repeat endoscopy with biopsies for the purpose of risk stratification and routine endoscopic surveillance, but encourages patients and physicians to participate in shared decision-making regarding potential pros and cons of these strategies in light of current evidence gaps. The AGA recognizes that new evidence may emerge in the future that might more strongly support short-interval repeat endoscopy with biopsies for risk stratification, and/or endoscopic surveillance for gastric cancer risk reduction.

Plans for Updating This Guideline

Guidelines are living products. To remain useful, they need to be updated regularly as new information accumulates. This document will be updated when major new research is published. The need for update will be determined no later than in 2022.

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Correspondence
Address correspondence to: Chair, Clinical Guidelines Committee, American Gastroenterological Association National Office, 4930 Del Ray Avenue, Bethesda, Maryland 20814. e-mail: clinicalpractice@gastro.org.

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Conflicts of interest
The authors disclose no conflicts.

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REVIEW ARTICLE

Transplant-associated thrombotic microangiopathy: theoretical considerations and a practical approach to an unrefined diagnosis

Joanna A. Young[1] · Christopher R. Pallas[1] · Mary Ann Knovich[1]

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Abstract

Transplant-associated thrombotic microangiopathy (TA-TMA) is an increasingly recognized complication of hematopoietic stem cell transplant (HSCT) with high morbidity and mortality. The triad of endothelial cell activation, complement dysregulation, and microvascular hemolytic anemia has the potential to cause end organ dysfunction, multiple organ dysfunction syndrome and death, but clinical features mimic other disorders following HSCT, delaying diagnosis. Recent advances have implicated complement as a major contributor and the therapeutic potential of complement inhibition has been explored. Eculizumab has emerged as an effective therapy and narsoplimab (OMS721) has been granted priority review by the FDA. Large studies performed mostly in pediatric patients suggest that earlier recognition and treatment may lead to improved outcomes. Here we present a clinically focused summary of recently published literature and propose a diagnostic and treatment algorithm.

Introduction

Thrombotic microangiopathy is a well-recognized complication of hematopoietic stem cell transplant (HSCT), however, diagnosis can be delayed and confounded by expected cytopenias and end organ toxicities. Transplant-related factors prompt endothelial cell activation, complement dysregulation, and microvascular hemolytic anemia that can lead to end organ dysfunction and even death. Transplant-associated thrombotic microangiopathy (TA-TMA) resides within a spectrum of transplant-associated endothelial cell activation syndromes, including capillary leak syndrome, engraftment syndrome, and idiopathic pneumonia syndrome [1]. Whether hepatic veno-occlusive disease/sinusoidal obstructive syndrome (VOD/SOS) should be included within this spectrum is debated. Some exclude VOD/SOS because pathogenesis is not solely endothelial mediated. Others argue that the historical classification remains valuable [2]. The gold standard for diagnosis of TA-TMA is based on characteristic histologic findings, although bleeding risk often precludes tissue diagnosis. Due to the lack of a consensus definition for TA-TMA, the syndrome's incidence and impact is difficult to quantify [2–8]. However, TA-TMA has a consistently reported adverse impact on non-relapse mortality (NRM) and overall survival (OS) [3–5], and the clinical presentation ranges from self-limited disease to multi-organ dysfunction and death. It impacts the kidneys, gastrointestinal tract, central nervous system, heart, lungs, and serosal surfaces [6, 7]. Treatments with wide ranging mechanisms have been implemented with variable efficacy and survival benefit. Recent focus on terminal complement blockade with eculizumab has emerged as a widely accepted therapy [8–11]. Narsoplimab (OMS721) was recently granted FDA priority review [12, 13]. Lack of consensus on diagnostic criteria and treatment approach presents significant challenges.

Epidemiology

The incidence and mortality of TA-TMA varies widely due to heterogeneous diagnostic criteria, under-recognition, and the wide variety of treatments that are used. The incidence was estimated to be 8.2% in a comprehensive literature review published in 2004 aggregating the

These authors contributed equally: Joanna A. Young, Christopher R. Pallas

✉ Christopher R. Pallas
christopher.pallas@atriumhealth.org

[1] Levine Cancer Institute, Atrium Health, Charlotte, NC, USA

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Comparative Efficacy and Acceptability of Psychotherapies for Self-harm and Suicidal Behavior Among Children and Adolescents

A Systematic Review and Network Meta-analysis

Anees Bahji, MD; Matthew Pierce, MD; Jennifer Wong, MD; Johanne N. Roberge, MD; Iliana Ortega, MD; Scott Patten, MD, PhD

Abstract

IMPORTANCE Self-harm and suicidal behavior are associated with substantial morbidity and mortality among children and adolescents. The comparative performance of psychotherapies for suicidality is unclear because few head-to-head clinical trials have been conducted.

OBJECTIVE To compare the efficacy of psychotherapies for the treatment of self-harm and suicidality among children and adolescents.

DATA SOURCES Four major bibliographic databases (PubMed, MEDLINE, PsycINFO, and Embase) were searched for clinical trials comparing psychotherapy with control conditions from inception to September 2020.

STUDY SELECTION Randomized clinical trials comparing psychotherapies for suicidality and/or self-harm with control conditions among children and adolescents were included after a blinded review by 3 independent reviewers (A.B., M.P., and J.W.).

DATA EXTRACTION AND SYNTHESIS The Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) reporting guideline was followed for data abstraction, and the Cochrane risk of bias tool was used to evaluate study-level risk of bias. Data abstraction was performed by 1 reviewer (A.B.) and confirmed by 2 independent blinded reviewers (J.W. and M.P.). Data were analyzed from October 15, 2020, to February 15, 2021.

MAIN OUTCOMES AND MEASURES The primary outcomes were dichotomized self-harm and retention in treatment. The secondary outcomes were dichotomized all-cause treatment discontinuation and scores on instruments measuring suicidal ideation and depressive symptoms. Effect sizes were pooled using frequentist random-effects network meta-analysis models to generate summary odds ratios (ORs) and Cohen *d* standardized mean differences (SMDs). Negative Cohen *d* SMDs or ORs less than 1 indicated that the treatment reduced the parameter of interest relative to the control condition (eg, signifying a beneficial association with suicidal ideation).

RESULTS The systematic search generated 1272 unique records. Of those, 44 randomized clinical trials (5406 total participants; 4109 female participants [76.0%]) from 49 articles were selected (5 follow-up studies were merged with their primary clinical trials to avoid publication bias). The selected clinical trials spanned January 1, 1995, to December 31, 2020. The median duration of treatment was 3 months (range, 0.25-12.00 months), and the median follow-up period was 12 months (range, 1-36 months). None of the investigated psychotherapies were associated with increases in study withdrawals or improvements in retention in treatment compared with treatment as usual. Dialectical behavioral therapies were associated with reductions in self-harm (OR, 0.28;

(continued)

Key Points

Question What are the comparative efficacies and acceptability of psychosocial interventions for the treatment of self-harm and suicidality among children and adolescents?

Findings In this systematic review and network meta-analysis of pooled data from 44 randomized clinical trials of psychotherapies for children and adolescents that involved 5406 total participants, the investigated psychotherapies were found to be acceptable to patients, but the evidence was inconsistent with regard to self-harm and suicidality measures across therapeutic modalities.

Meaning The findings indicate that, although some psychotherapeutic modalities appeared to be acceptable and efficacious for reducing self-harm and suicidality among children and adolescents, methodological issues and high risk of bias suggest a need for additional randomized clinical trials.

+ Supplemental content

Author affiliations and article information are listed at the end of this article.

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Psychosocial interventions for self-harm in adults (Review)

Witt KG, Hetrick SE, Rajaram G, Hazell P, Taylor Salisbury TL, Townsend E, Hawton K

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[Intervention Review]

Psychosocial interventions for self-harm in adults

Katrina G Witt[1,2], Sarah E Hetrick[3], Gowri Rajaram[1,2], Philip Hazell[4], Tatiana L Taylor Salisbury[5], Ellen Townsend[6], Keith Hawton[7]

[1]Orygen, Parkville, Melbourne, Australia. [2]Centre for Youth Mental Health, The University of Melbourne, Melbourne, Australia. [3]Department of Psychological Medicine, Faculty of Medical and Health Sciences, The University of Auckland, Auckland, New Zealand. [4]Speciality of Psychiatry, University of Sydney School of Medicine, Sydney, Australia. [5]Health Service and Population Research Department, Institute of Psychiatry, Psychology and Neuroscience, King's College London, London, UK. [6]Self-Harm Research Group, School of Psychology, University of Nottingham, Nottingham, UK. [7]Centre for Suicide Research, Department of Psychiatry, University of Oxford, Oxford, UK

Contact address: Katrina G Witt, katrina.witt@orygen.org.au.

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ABSTRACT

Background

Self-harm (SH; intentional self-poisoning or self-injury regardless of degree of suicidal intent or other types of motivation) is a growing problem in most counties, often repeated, and associated with suicide. There has been a substantial increase in both the number of trials and therapeutic approaches of psychosocial interventions for SH in adults. This review therefore updates a previous Cochrane Review (last published in 2016) on the role of psychosocial interventions in the treatment of SH in adults.

Objectives

To assess the effects of psychosocial interventions for self-harm (SH) compared to comparison types of care (e.g. treatment-as-usual, routine psychiatric care, enhanced usual care, active comparator) for adults (aged 18 years or older) who engage in SH.

Search methods

We searched the Cochrane Common Mental Disorders Specialised Register, the Cochrane Library (Central Register of Controlled Trials [CENTRAL] and Cochrane Database of Systematic reviews [CDSR]), together with MEDLINE, Ovid Embase, and PsycINFO (to 4 July 2020).

Selection criteria

We included all randomised controlled trials (RCTs) comparing interventions of specific psychosocial treatments versus treatment-as-usual (TAU), routine psychiatric care, enhanced usual care (EUC), active comparator, or a combination of these, in the treatment of adults with a recent (within six months of trial entry) episode of SH resulting in presentation to hospital or clinical services. The primary outcome was the occurrence of a repeated episode of SH over a maximum follow-up period of two years. Secondary outcomes included treatment adherence, depression, hopelessness, general functioning, social functioning, suicidal ideation, and suicide.

Data collection and analysis

We independently selected trials, extracted data, and appraised trial quality. For binary outcomes, we calculated odds ratio (ORs) and their 95% confidence intervals (CIs). For continuous outcomes, we calculated mean differences (MDs) or standardised mean differences (SMDs) and 95% CIs. The overall quality of evidence for the primary outcome (i.e. repetition of SH at post-intervention) was appraised for each intervention using the GRADE approach.

Main results

We included data from 76 trials with a total of 21,414 participants. Participants in these trials were predominately female (61.9%) with a mean age of 31.8 years (standard deviation [SD] 11.7 years). On the basis of data from four trials, individual cognitive behavioural therapy (CBT)-based psychotherapy may reduce repetition of SH as compared to TAU or another comparator by the end of the intervention (OR 0.35, 95% CI 0.12 to 1.02; N = 238; k = 4; GRADE: low certainty evidence), although there was imprecision in the effect estimate. At longer follow-up time points (e.g., 6- and 12-months) there was some evidence that individual CBT-based psychotherapy may reduce SH repetition. Whilst there may be a slightly lower rate of SH repetition for dialectical behaviour therapy (DBT) (66.0%) as compared to TAU or alternative psychotherapy (68.2%), the evidence remains uncertain as to whether DBT reduces absolute repetition of SH by the post-intervention assessment. On the basis of data from a single trial, mentalisation-based therapy (MBT) reduces repetition of SH and frequency of SH by the post-intervention assessment (OR 0.35, 95% CI 0.17 to 0.73; N = 134; k = 1; GRADE: high-certainty evidence). A group-based emotion-regulation psychotherapy may also reduce repetition of SH by the post-intervention assessment based on evidence from two trials by the same author group (OR 0.34, 95% CI 0.13 to 0.88; N = 83; k = 2; moderate-certainty evidence). There is probably little to no effect for different variants of DBT on absolute repetition of SH, including DBT group-based skills training, DBT individual skills training, or an experimental form of DBT in which participants were given significantly longer cognitive exposure to stressful events. The evidence remains uncertain as to whether provision of information and support, based on the Suicide Trends in At-Risk Territories (START) and the SUicide-PREvention Multisite Intervention Study on Suicidal behaviors (SUPRE-MISS) models, have any effect on repetition of SH by the post-intervention assessment. There was no evidence of a difference for psychodynamic psychotherapy, case management, general practitioner (GP) management, remote contact interventions, and other multimodal interventions, or a variety of brief emergency department-based interventions.

Authors' conclusions

Overall, there were significant methodological limitations across the trials included in this review. Given the moderate or very low quality of the available evidence, there is only uncertain evidence regarding a number of psychosocial interventions for adults who engage in SH. Psychosocial therapy based on CBT approaches may result in fewer individuals repeating SH at longer follow-up time points, although no such effect was found at the post-intervention assessment and the quality of evidence, according to the GRADE criteria, was low. Given findings in single trials, or trials by the same author group, both MBT and group-based emotion regulation therapy should be further developed and evaluated in adults. DBT may also lead to a reduction in frequency of SH. Other interventions were mostly evaluated in single trials of moderate to very low quality such that the evidence relating to the use of these interventions is inconclusive at present.

PLAIN LANGUAGE SUMMARY

Psychosocial interventions for adults who self-harm

We have reviewed the interventional literature regarding psychosocial intervention treatment trials in the field. A total of 76 trials meeting our inclusion criteria were identified. There may be beneficial effects for psychological therapy based on cognitive behavioural therapy (CBT) approaches at longer follow-up time points, and for mentalisation-based therapy (MBT), and emotion-regulation psychotherapy at the post-intervention assessment. There may also be some evidence of effectiveness of standard dialectical behaviour therapy (DBT) on frequency of SH repetition. There was no clear evidence of effect for case management, information and support, remote contact interventions (e.g. emergency cards, postcards, telephone-based psychotherapy), provision of information and support, and other multimodal interventions.

Why is this review important?

Self-harm (SH), which includes intentional self-poisoning/overdose and self-injury, is a major problem in many countries and is strongly linked with suicide. It is therefore important that effective treatments are developed for people who engage in SH. There has been an increase in both the number of trials and the diversity of therapeutic approaches for SH in adults in recent years. It is therefore important to assess the evidence for their effectiveness.

Who will be interested in this review?

Hospital administrators (e.g. service providers), health policy officers and third party payers (e.g. health insurers), clinicians working with people who engage in SH, the people themselves, and their relatives.

What questions does this review aim to answer?

This review is an update of a previous Cochrane review from 2016 which found that CBT-based psychological therapy can result in fewer individuals repeating SH whilst DBT may lead to a reduction in frequency of repeated SH. This updated review aims to further evaluate the evidence for effectiveness of psychosocial interventions for people engaging in SH with a broader range of outcomes.

Which studies were included in the review?

To be included in the review, studies had to be randomised controlled trials of psychosocial interventions for adults who had recently engaged in SH.

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Interventions for self-harm in children and adolescents (Review)

Witt KG, Hetrick SE, Rajaram G, Hazell P, Taylor Salisbury TL, Townsend E, Hawton K

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[Intervention Review]

Interventions for self-harm in children and adolescents

Katrina G Witt[1,2], Sarah E Hetrick[3,4], Gowri Rajaram[1,2], Philip Hazell[5], Tatiana L Taylor Salisbury[6], Ellen Townsend[7], Keith Hawton[8]

[1]Orygen, Parkville, Melbourne, Australia. [2]Centre for Youth Mental Health, The University of Melbourne, Melbourne, Australia. [3]Department of Psychological Medicine, Faculty of Medical and Health Sciences, The University of Auckland, Auckland, New Zealand. [4]Children and Young People Satellite, Cochrane Common Mental Disorders, The University of Auckland, Auckland, New Zealand. [5]Speciality of Psychiatry, University of Sydney School of Medicine, Sydney, Australia. [6]Health Service and Population Research Department, Institute of Psychiatry, Psychology and Neuroscience, King's College London, London, UK. [7]Self-Harm Research Group, School of Psychology, University of Nottingham, Nottingham, UK. [8]Centre for Suicide Research, Department of Psychiatry, University of Oxford, Oxford, UK

Contact address: Katrina G Witt, katrina.witt@orygen.org.au.

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ABSTRACT

Background

Self-harm (SH; intentional self-poisoning or self-injury regardless of degree of suicidal intent or other types of motivation) is a growing problem in most countries, often repeated, and associated with suicide. Evidence assessing the effectiveness of interventions in the treatment of SH in children and adolescents is lacking, especially when compared with the evidence for psychosocial interventions in adults. This review therefore updates a previous Cochrane Review (last published in 2015) on the role of interventions for SH in children and adolescents.

Objectives

To assess the effects of psychosocial interventions or pharmacological agents or natural products for SH compared to comparison types of care (e.g. treatment-as-usual, routine psychiatric care, enhanced usual care, active comparator, placebo, alternative pharmacological treatment, or a combination of these) for children and adolescents (up to 18 years of age) who engage in SH.

Search methods

We searched the Cochrane Common Mental Disorders Specialized Register, the Cochrane Library (Central Register of Controlled Trials [CENTRAL] and Cochrane Database of Systematic Reviews [CDSR]), together with MEDLINE, Ovid Embase, and PsycINFO (to 4 July 2020).

Selection criteria

We included all randomised controlled trials (RCTs) comparing specific psychosocial interventions or pharmacological agents or natural products with treatment-as-usual (TAU), routine psychiatric care, enhanced usual care (EUC), active comparator, placebo, alternative pharmacological treatment, or a combination of these, in children and adolescents with a recent (within six months of trial entry) episode of SH resulting in presentation to hospital or clinical services. The primary outcome was the occurrence of a repeated episode of SH over a maximum follow-up period of two years. Secondary outcomes included treatment adherence, depression, hopelessness, general functioning, social functioning, suicidal ideation, and suicide.

Data collection and analysis

We independently selected trials, extracted data, and appraised trial quality. For binary outcomes, we calculated odds ratios (ORs) and their 95% confidence internals (CIs). For continuous outcomes, we calculated the mean difference (MD) or standardised mean difference (SMD)

and 95% CIs. The overall quality of evidence for the primary outcome (i.e. repetition of SH at post-intervention) was appraised for each intervention using the GRADE approach.

Main results

We included data from 17 trials with a total of 2280 participants. Participants in these trials were predominately female (87.6%) with a mean age of 14.7 years (standard deviation (SD) 1.5 years). The trials included in this review investigated the effectiveness of various forms of psychosocial interventions. None of the included trials evaluated the effectiveness of pharmacological agents in this clinical population. There was a lower rate of SH repetition for DBT-A (30%) as compared to TAU, EUC, or alternative psychotherapy (43%) on repetition of SH at post-intervention in four trials (OR 0.46, 95% CI 0.26 to 0.82; N = 270; k = 4; high-certainty evidence). There may be no evidence of a difference for individual cognitive behavioural therapy (CBT)-based psychotherapy and TAU for repetition of SH at post-intervention (OR 0.93, 95% CI 0.12 to 7.24; N = 51; k = 2; low-certainty evidence). We are uncertain whether mentalisation based therapy for adolescents (MBT-A) reduces repetition of SH at post-intervention as compared to TAU (OR 0.70, 95% CI 0.06 to 8.46; N = 85; k = 2; very low-certainty evidence). Heterogeneity for this outcome was substantial (I^2 = 68%). There is probably no evidence of a difference between family therapy and either TAU or EUC on repetition of SH at post-intervention (OR 1.00, 95% CI 0.49 to 2.07; N = 191; k = 2; moderate-certainty evidence). However, there was no evidence of a difference for compliance enhancement approaches on repetition of SH by the six-month follow-up assessment, for group-based psychotherapy at the six- or 12-month follow-up assessments, for a remote contact intervention (emergency cards) at the 12-month assessment, or for therapeutic assessment at the 12- or 24-month follow-up assessments.

Authors' conclusions

Given the moderate or very low quality of the available evidence, and the small number of trials identified, there is only uncertain evidence regarding a number of psychosocial interventions in children and adolescents who engage in SH. Further evaluation of DBT-A is warranted. Given the evidence for its benefit in adults who engage in SH, individual CBT-based psychotherapy should also be further developed and evaluated in children and adolescents.

PLAIN LANGUAGE SUMMARY

Interventions for children and adolescents who self-harm

We have reviewed the international literature regarding psychosocial interventions, pharmacological (drug), and natural product (dietary supplementation) treatment trials in the field. A total of 17 trials meeting our inclusion criteria were identified. There is little evidence of beneficial effects for individual cognitive behavioural therapy (CBT)-based psychotherapy, mentalisation-based therapy for adolescents (MBT-A), group-based psychotherapy, enhanced assessment approaches, compliance enhancement approaches, family interventions, or remote contact interventions. There is some evidence of effectiveness for dialectical behaviour therapy (DBT-A) for adolescents. However, few trials have been conducted and those that have are generally small, meaning that possible beneficial effects of some of these therapies cannot be ruled out.

Why is this review important?

Self-harm (SH), which includes intentional self-poisoning/overdose and self-injury, is a major problem in many countries and is strongly linked with suicide. It is therefore important that effective treatments for SH patients are developed. There has been an increase in the use of interventions for SH in children and adolescents. It is therefore important to assess the evidence for their effectiveness.

Who will be interested in this review?

Hospital administrators (e.g. service providers), health policy officers and third party payers (e.g. health insurers), clinicians working with patients who engage in SH, patients themselves, and their relatives.

What questions does this review aim to answer?

This review is an update of a previous Cochrane Review from 2015 which found little evidence of beneficial effects of interventions for SH in children and adolescents. This updated review aims to further evaluate the evidence for effectiveness of interventions for children and adolescents with SH with a broader range of outcomes.

Which studies were included in the review?

To be included in the review, studies had to be randomised controlled trials of either psychosocial or drug treatments for children and adolescents up to 18 years of age who had recently engaged in SH.

What does the evidence from the review tell us?

There have been surprisingly few investigations of treatments for SH in children and adolescents, despite the size of this problem in many countries. We found positive effects of DBT-A on repetition of SH. There is currently no clear evidence for the effectiveness of individual CBT-based psychotherapy, MBT-A, group-based psychotherapy, enhanced assessment approaches, compliance enhancement approaches, family interventions, or remote contact interventions in preventing repetition of SH.

What should happen next?

We recommend further trials of DBT-A. Given the evidence for its benefit for adults who engage in SH, individual CBT-based psychotherapy should also be further developed and evaluated in children and adolescents. Given the extent of SH in children and adolescents, greater attention should be paid to the development and evaluation of specific therapies for this population.

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Pharmacological interventions for self-harm in adults (Review)

Witt KG, Hetrick SE, Rajaram G, Hazell P, Taylor Salisbury TL, Townsend E, Hawton K

Witt KG, Hetrick SE, Rajaram G, Hazell P, Taylor Salisbury TL, Townsend E, Hawton K.
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[Intervention Review]

Pharmacological interventions for self-harm in adults

Katrina G Witt[1,2], Sarah E Hetrick[3], Gowri Rajaram[1,2], Philip Hazell[4], Tatiana L Taylor Salisbury[5], Ellen Townsend[6], Keith Hawton[7]

[1]Orygen, Parkville, Melbourne, Australia. [2]Centre for Youth Mental Health, The University of Melbourne, Melbourne, Australia. [3]Department of Psychological Medicine, Faculty of Medical and Health Sciences, The University of Auckland, Auckland, New Zealand. [4]Speciality of Psychiatry, University of Sydney School of Medicine, Sydney, Australia. [5]Health Service and Population Research Department, Institute of Psychiatry, Psychology and Neuroscience, King's College London, London, UK. [6]Self-Harm Research Group, School of Psychology, University of Nottingham, Nottingham, UK. [7]Centre for Suicide Research, Department of Psychiatry, University of Oxford, Oxford, UK

Contact address: Katrina G Witt, katrina.witt@orygen.org.au.

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ABSTRACT

Background

Self-harm (SH; intentional self-poisoning or self-injury regardless of degree of suicidal intent or other types of motivation) is a growing problem in most countries, often repeated, and associated with suicide. Evidence assessing the effectiveness of pharmacological agents and/or natural products in the treatment of SH is lacking, especially when compared with the evidence for psychosocial interventions. This review therefore updates a previous Cochrane Review (last published in 2015) on the role of pharmacological interventions for SH in adults.

Objectives

To assess the effects of pharmacological agents or natural products for SH compared to comparison types of treatment (e.g. placebo or alternative pharmacological treatment) for adults (aged 18 years or older) who engage in SH.

Search methods

We searched the Cochrane Common Mental Disorders Specialised Register, the Cochrane Library (Central Register of Controlled Trials [CENTRAL] and Cochrane Database of Systematic Reviews [CDSR]), together with MEDLINE. Ovid Embase and PsycINFO (to 4 July 2020).

Selection criteria

We included all randomised controlled trials (RCTs) comparing pharmacological agents or natural products with placebo/alternative pharmacological treatment in individuals with a recent (within six months of trial entry) episode of SH resulting in presentation to hospital or clinical services. The primary outcome was the occurrence of a repeated episode of SH over a maximum follow-up period of two years. Secondary outcomes included treatment acceptability, treatment adherence, depression, hopelessness, general functioning, social functioning, suicidal ideation, and suicide.

Data collection and analysis

We independently selected trials, extracted data, and appraised trial quality. For binary outcomes, we calculated odds ratios (ORs) and their 95% confidence internals (CIs). For continuous outcomes we calculated the mean difference (MD) or standardised mean difference (SMD) and 95% CI. The overall certainty of evidence for the primary outcome (i.e. repetition of SH at post-intervention) was appraised for each intervention using the GRADE approach.

Main results

We included data from seven trials with a total of 574 participants. Participants in these trials were predominately female (63.5%) with a mean age of 35.3 years (standard deviation (SD) 3.1 years). It is uncertain if newer generation antidepressants reduce repetition of SH compared to placebo (OR 0.59, 95% CI 0.29 to 1.19; N = 129; k = 2; very low-certainty evidence). There may be a lower rate of SH repetition for antipsychotics (21%) as compared to placebo (75%) (OR 0.09, 95% CI 0.02 to 0.50; N = 30; k = 1; low-certainty evidence). However, there was no evidence of a difference between antipsychotics compared to another comparator drug/dose for repetition of SH (OR 1.51, 95% CI 0.50 to 4.58; N = 53; k = 1; low-certainty evidence). There was also no evidence of a difference for mood stabilisers compared to placebo for repetition of SH (OR 0.99, 95% CI 0.33 to 2.95; N = 167; k = 1; very low-certainty evidence), or for natural products compared to placebo for repetition of SH (OR 1.33, 95% CI 0.38 to 4.62; N = 49; k = 1; lo- certainty) evidence.

Authors' conclusions

Given the low or very low quality of the available evidence, and the small number of trials identified, there is only uncertain evidence regarding pharmacological interventions in patients who engage in SH. More and larger trials of pharmacotherapy are required, preferably using newer agents. These might include evaluation of newer atypical antipsychotics. Further work should also include evaluation of adverse effects of pharmacological agents. Other research could include evaluation of combined pharmacotherapy and psychological treatment.

PLAIN LANGUAGE SUMMARY

Drugs and natural products for self-harm in adults

We have reviewed the international literature regarding pharmacological (drug) and natural product (dietary supplementation) treatment trials in the field. A total of seven trials meeting our inclusion criteria were identified. There is little evidence of beneficial effects of either pharmacological or natural product treatments. However, few trials have been conducted and those that have are small, meaning that possible beneficial effects of some therapies cannot be ruled out.

Why is this review important?

Self-harm (SH), which includes intentional self-poisoning/overdose and self-injury, is a major problem in many countries and is strongly linked with suicide. It is therefore important that effective treatments for SH patients are developed. Whilst there has been an increase in the use of psychosocial interventions for SH in adults (which is the focus of a separate review), drug treatments are frequently used in clinical practice. It is therefore important to assess the evidence for their effectiveness.

Who will be interested in this review?

Hospital administrators (e.g. service providers), health policy officers and third party payers (e.g. health insurers), clinicians working with patients who engage in SH, patients themselves, and their relatives.

What questions does this review aim to answer?

This review is an update of a previous Cochrane Review from 2015 which found little evidence of beneficial effects of drug treatments on repetition of SH. This updated aims to further evaluate the evidence for effectiveness of drugs and natural products for patients who engage in SH with a broader range of outcomes.

Which studies were included in the review?

To be included in the review, studies had to be randomised controlled trials of drug treatments for adults who had recently engaged in SH.

What does the evidence from the review tell us?

There is currently no clear evidence for the effectiveness of antidepressants, antipsychotics, mood stabilisers, or natural products in preventing repetition of SH.

What should happen next?

We recommend further trials of drugs for SH patients, possibly in combination with psychological treatment.

OPEN

Pediatric Feeding Disorder—Consensus Definition and Conceptual Framework

*Praveen S. Goday, †‡Susanna Y. Huh, *Alan Silverman, §Colleen T. Lukens, ||Pamela Dodrill, ¶Sherri S. Cohen, *Amy L. Delaney, #Mary B. Feuling, **Richard J. Noel, ††Erika Gisel, ‡‡Amy Kenzer, §§Daniel B. Kessler, ||||Olaf Kraus de Camargo, ¶¶Joy Browne, and ##James A. Phalen

ABSTRACT

Pediatric feeding disorders (PFDs) lack a universally accepted definition. Feeding disorders require comprehensive assessment and treatment of 4 closely related, complementary domains (medical, psychosocial, and feeding skill-based systems and associated nutritional complications). Previous diagnostic paradigms have, however, typically defined feeding disorders using the lens of a single professional discipline and fail to characterize associated functional limitations that are critical to plan appropriate interventions and improve quality of life. Using the framework of the World Health Organization *International Classification of Functioning, Disability, and Health*, a unifying diagnostic term is proposed: ''Pediatric Feeding Disorder'' (PFD), defined as impaired oral intake that is not age-appropriate, and is associated with medical, nutritional, feeding skill, and/or psychosocial dysfunction. By incorporating associated functional limitations, the proposed diagnostic criteria for PFD should enable practitioners and researchers to better characterize the needs of heterogeneous patient populations, facilitate inclusion of all relevant disciplines in treatment planning, and promote the use of common, precise, terminology necessary to advance clinical practice, research, and health-care policy.

Key Words: dysphagia, failure to thrive, feeding disorder

(*JPGN* 2019;68: 124–129)

What Is Known

- Pediatric feeding disorders lack a universally accepted definition.
- Previous diagnostic paradigms have defined feeding disorder from the perspective of a single medical discipline.

What Is New

- A unifying diagnostic term, ''Pediatric Feeding Disorder'', using the framework of the World Health Organization International Classification of Functioning, Disability, and Health is proposed.
- This term unifies the medical, nutritional, feeding skill, and/or psychosocial concerns associated with feeding disorders.
- The proposed diagnostic criteria should promote the use of common, precise, terminology necessary to advance clinical practice, research, and health care policy.

Feeding is a complex process that requires interaction of the central and peripheral nervous systems, oropharyngeal mechanism, cardiopulmonary system, and gastrointestinal (GI) tract with support from craniofacial structures and the musculoskeletal system. This coordinated interaction requires acquisition and mastery of skills appropriate for a child's physiology and developmental stage. In children, feeding occurs in the context of the caregiver-child dyad. A disruption in any of these systems places a child at risk

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From the *Feeding, Swallowing and Nutrition Center, Children's Hospital of Wisconsin, Medical College of Wisconsin, Milwaukee, WI, the †Growth and Nutrition Program, Division of Gastroenterology, Hepatology and Nutrition, Boston Children's Hospital, the ‡Department of Pediatrics, Harvard Medical School, Boston, MA, the §Pediatric Feeding and Swallowing Center, The Children's Hospital of Philadelphia, Philadelphia, PA, the ||Feeding and Developmental Therapy Team, Brigham & Women's Hospital NICU, Boston, MA, the ¶Pediatric Feeding and Swallowing Center, Perelman School of Medicine at the University of Pennsylvania, The Children's Hospital of Philadelphia, Philadelphia, PA, the #Feeding, Swallowing and Nutrition Center, Children's Hospital of Wisconsin, Milwaukee, WI, the **Pediatric Gastroenterology, Hepatology, and Nutrition, Duke University Medical Center, Durham, NC, the ††Department of Pediatrics and CanChild Centre for Childhood Disability Research McGill University, School of Physical & Occupational Therapy, Montreal, Quebec, Canada, the ‡‡Southwest Autism Research & Resource Center, Phoenix, AZ, the §§Developmental and Behavioral Pediatrics, University of Arizona College of Medicine-Phoenix, Phoenix, AZ, the ||||Ron Joyce Children's Health Centre, McMaster University, Hamilton, Ontario, Canada, the ¶¶University of Colorado School of Medicine, Anschutz Medical Campus, Fielding Graduate University, Aurora, CO, and the ##Developmental-Behavioral Pediatrics University Health System, Uniformed Services University, San Antonio, TX.

Address correspondence and reprint requests to Praveen S. Goday, MBBS, CNSC, Pediatric Gastroenterology and Nutrition, Medical College of Wisconsin, 8701 Watertown Plank Rd, Milwaukee, WI 53226 (e-mail: pgoday@mcw.edu).

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Dr Goday serves as consultant to Nutricia and serves on a Data Safety and Monitoring Board for Shire Pharmaceuticals. The remaining authors have no financial relationships relevant to this article to disclose.

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Section 6.0

Previously Discussed Items

Breast Cancer Index
Re-Review August 2021

Question: Should Breast Cancer Index be added to the covered biomarkers for determination of chemotherapy use as well as extended endocrine therapy use in breast cancer?

Question source: Biotheranostics, VBBS/HERC

Issue: At the May 2021 VBBS/HERC meetings, Breast Cancer Index (BCI) was reviewed. New coverage was added for BCI for use in determining extended endocrine therapy for breast cancer patients. This coverage was limited to node negative disease. The manufacturer requested further review of the utility of BCI for 1) planning adjuvant chemotherapy and 2) requested consideration of coverage for node-positive patients for both adjuvant endocrine and chemotherapy.

Staff summary from the May 2021 meeting:

> New evidence has been published since the coverage guidance review of Breast Cancer Index. Based on new secondary trial analysis, NCCN has determined that Breast Cancer Index was found to determine whether a patient would achieve disease free survival benefit from prolonged adjuvant endocrine therapy to prevent cancer recurrence if they have HR+, HER2-, node negative breast cancer. Therefore this test has clinical utility in determining which patients should be offered prolonged adjuvant endocrine therapy. This test would only be helpful in the population of women with this type of cancer who are willing to take prolonged adjuvant endocrine therapy, given its known side effects. NCCN has changed their recommendations to include use of BCI in this population. NCCN stated that there was not enough clinical data to determine utility in node positive patients. The American Society of Clinical Oncology (ASCO) recommendations agree with NCCN, with a moderate strength recommendation to the use of BCI in patients with ER/PgR-positive, HER2-negative, node-negative breast cancer to guide decisions for adjuvant systemic therapy.

Discussion at the May meeting centered around whether BCI should also be covered for decisions regarding extended endocrine therapy in node positive patients. VBBS/HERC voted to add coverage for BCI for decisions for endocrine therapy only in node negative patients. The question of the use of BCI for determination of adjuvant chemotherapy was referred back to HERC staff for additional review

The decision at the May meeting was to add the CPT code for BCI (81518) to line 191 CANCER OF BREAST; AT HIGH RISK OF BREAST CANCER, remove the entry for CPT 81518 from Guideline Note 173, and add the following clause to GUIDELINE NOTE 148, BIOMARKER TESTS OF CANCER TISSUE:
For early stage breast cancer that is estrogen receptor positive, HER2 negative, and lymph node negative, Breast Cancer Index (CPT 81518) is included on line 191 when the patient is willing to use the test results in a shared decision-making process regarding prolonged adjuvant endocrine therapy.

Since the May meeting, HERC staff has become aware that NCCN has updated their breast cancer guidelines, and now have a substantially reworked guideline that was published in late April, 2021 and were further edited and published in late June, 2021. In this revised guideline, Oncotype Dx is listed as the preferred test for all decisions related to decisions regarding adjuvant chemotherapy (systemic chemotherapy after surgical resection). Per NCCN: "Gene expression assays provide prognostic and therapy-predictive information that complements T,N,M and biomarker information. The use of these assays is not required for staging. The 21-gene assay (Oncotype Dx) is preferred by the NCCN Breast

Cancer Panel for prognosis and prediction of chemotherapy benefit. Other prognostic gene expression assays can provide prognostic information but the ability to predict chemotherapy benefit is unknown."

Expert guidelines

1) **NCCN 5.2021**, Breast Cancer (updated since the May meeting)
    a. For patients with HR+, HER2- disease, there are few data regarding the role of gene expression assays in those with ≥ 4 ipsilateral axillary lymph nodes
    b. In the treatment algorithm for HR+, HER2-, node negative, premenopausal patients, with tumors >0.5 cm: "strongly consider 21-gene RT-PCR (i.e. Oncotype DX) if candidate for chemotherapy (category 1)"
        i. Footnote: Other prognostic gene expression assays may be considered to help assess risk of recurrence but have not been validated to predict response to chemotherapy
    c. In the treatment algorithm for HR+, HER2-, node positive, premenopausal patients: "if candidate for chemotherapy consider gene expression assay to assess prognosis"
    d. There is a new algorithm for adjuvant endocrine therapy
        i. Premenopausal at diagnosis: the algorithm recommends 5 years of adjuvant endocrine therapy, followed by definitely do or consider an additional 5 years of adjuvant endocrine therapy depending on initial drug chosen and whether menopausal after the initial 5 year therapy is completed
        ii. Postmenopausal at diagnosis: the algorithm recommends 2-5 years of initial adjuvant endocrine therapy with consideration of 10 years of therapy in many situations
    e. In the table of recommended gene expression assays for consideration of adjuvant systemic therapy (page BINV-N 1 of 5):
        i. Only Oncotype Dx is listed as predictive for outcomes of adjuvant systemic therapy. Mammaprint, Prosigna, and Endopredict are listed as "not determined" whether they are predictive while BCI is only listed as predictive of extended adjuvant endocrine therapy.
        ii. For prognostic information regarding adjuvant systemic therapy, Oncotype DX and Mammaprint are listed as a category 1 recommendation. Prosigna, Endopredict, and BCI are listed at category 2A recommendations
        iii. Note: Oncotype Dx is listed as the preferred test, category 1, with a footnote stating "Gene expression assays provide prognostic and therapy-predictive information that complements T,N,M and biomarker information. The use of these assays is not required for staging. The 21-gene assay (Oncotype Dx) is preferred by the NCCN Breast Cancer Panel for prognosis and prediction of chemotherapy benefit. Other prognostic gene expression assays can provide prognostic information but the ability to predict chemotherapy benefit is unknown."
    f. In the table on gene expression assays for consideration of adjuvant systemic therapy, BCI has the following entries (page BINV-N 4 of 5):
        i. BCI low

1. For patients with T2 and T2 HR+ HER2- pN0 (node-negative) tumors, a BCI in the low-risk range (0-5), regardless of T size, places the tumor into the same prognostic category as T1a-T1b, N0, M0
2. Patients with BCI low demonstrated a lower risk of distant recurrence (compared to BCI high) and no significant improvement in DFS or OS compared to the control arm in terms of extending endocrine therapy duration

ii. BCI high

1. For patients with T1 HR+ HER2- pN0 tumors, a BCI high (5.1-10) demonstrated significant rates of late distant recurrence
2. In secondary analysis of the MA17, Trans-a TTom, and IDEAL trials, patients with HR+, T1-T3, pN0 or pN+ who had a BCI high demonstrated significant improvements in DFS when adjuvant endocrine therapy was extended compared to the control arm
3. In contrast BCI low patients derived no benefit from extended adjuvant therapy

Evidence

1) **Noordhoek 2021**: Breast Cancer Index Predicts Extended Endocrine Benefit to Individualize Selection of Patients with HRþ Early-stage Breast Cancer for 10 Years of Endocrine Therapy
   a. In patients with clinically high-risk features (pN+ pT2+), the 46% (N = 162) that were classified as BCI (H/I)-high experienced a statistically significant benefit from 5 years versus 2.5 years of letrozole (HR 0.32; 95% CI, 0.10–0.98; absolute benefit 12.5%; P ¼ 0.035), whereas the 54% of clinically high-risk patients classified as BCI (H/I)- low (N = 191) did not show significant benefit (P ¼ 0.742; HR 1.13; 95% CI, 0.55–2.31)
   b. Conversely, the 48% of patients (N = 220) in a clinically low-risk subset (pT1 or grade 1) that were classified as BCI (H/I)-high demonstrated a statistically significant benefit from 5 years versus 2.5 years of letrozole (HR 0.23; 95% CI, 0.07–0.81) and absolute benefit of 11.9% (P = 0.013), whereas the 52% of clinically low-risk patients (N = 239) classified as BCI (H/I)-low did not show significant benefit (HR 0.62; 95% CI, 0.27–1.38; P = 0.235

Breast Cancer Index
Re-Review August 2021

HERC staff summary

Based on the updated NCCN breast cancer guideline and new evidence, HERC staff recommends extending coverage for BCI testing to decision making regarding adjuvant chemotherapy to node positive patients with 1-3 involved nodes. Based on the NCCN recommendation to use Oncotype Dx preferentially for decisions regarding adjuvant chemotherapy, HERC staff does not recommend coverage for BCI in this situation.

HERC staff recommendations:

1) Modify GN148 as shown below
    a. May 2021 changes shown in purple

GUIDELINE NOTE 148, BIOMARKER TESTS OF CANCER TISSUE

Lines 157,184,191,229,262,271,329

The use of tissue of origin testing (e.g. CPT 81504) is included on Line 662 CONDITIONS FOR WHICH CERTAIN INTERVENTIONS ARE UNPROVEN, HAVE NO CLINICALLY IMPORTANT BENEFIT OR HAVE HARMS THAT OUTWEIGH BENEFITS.

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

- Oncotype DX Breast Recurrence Score (CPT 81519) for breast tumors that are estrogen receptor positive, HER2 negative, and either lymph node negative, or lymph node positive with 1-3 involved nodes.
- EndoPredict (CPT 81522) and Prosigna (CPT 81520 or PLA 0008M) for breast tumors that are estrogen receptor positive, HER2 negative, and lymph node negative.
- MammaPrint (using CPT 81521 or HCPCS S3854) for breast tumors that are estrogen receptor or progesterone receptor positive, HER2 negative, lymph node negative, and only in those cases categorized as high clinical risk.

For early stage breast cancer that is estrogen receptor positive, HER2 negative, and either lymph node negative or lymph node positive with 1-3 involved nodes, Breast Cancer Index (CPT 81518) is included on line 191 when the patient is willing to use the test results in a shared decision-making process regarding prolonged adjuvant endocrine therapy.

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

Oncotype DX Breast DCIS Score (CPT 81479) is ~~and Breast Cancer Index (CPT 81518) are~~ included on Line 662 CONDITIONS FOR WHICH CERTAIN INTERVENTIONS ARE UNPROVEN, HAVE NO CLINICALLY IMPORTANT BENEFIT OR HAVE HARMS THAT OUTWEIGH BENEFITS.

For melanoma, BRAF gene mutation testing (CPT 81210) is included on Line 229. DecisionDx-Melanoma (CPT 81529) is included on Line 662.

For lung cancer, epidermal growth factor receptor (EGFR) gene mutation testing (CPT 81235) is included on Line 262 only for non-small cell lung cancer. KRAS gene mutation testing (CPT 81275) is not included on this line.

For colorectal cancer, KRAS gene mutation testing (CPT 81275) is included on Line 157. BRAF (CPT 81210) and Oncotype DX are not included on this line. Microsatellite instability (MSI) is included on the Line 662.

For bladder cancer, Urovysion testing is included on Line 662.

For prostate cancer, Oncotype DX Genomic Prostate Score, Prolaris Score Assay (CPT 81541), and Decipher Prostate RP (CPT 81542) are included on Line 662.

For thyroid cancer, Afirma gene expression classifier (CPT 81546) is included on Line 662.

The development of this guideline note was informed by a HERC coverage guidance on Biomarkers Tests of Cancer Tissue for Prognosis and Potential Response to Treatment; the prostate-related portion of that coverage guidance was superseded by a Coverage Guidance on Gene Expression Profiling for Prostate Cancer. See https://www.oregon.gov/oha/HPA/DSI-HERC/Pages/Evidence-based-Reports.aspx

PET Scan for Breast Cancer
Re-Review 2021

Question: Should PET scans be covered for staging of breast cancer or monitoring of breast cancer therapy? If so, in what situations?

Question source: patient testimony

Issue: In May, 2021, VBBS and HERC heard testimony from a patient requesting re-review of lack of coverage for stage IV breast cancer therapy monitoring.

PET scans for breast cancer were reviewed through the Coverage Guidance process in 2013 and reaffirmed in 2016. Based on Choosing Wisely recommendations, PET scans were not recommended for:

1) initial staging of breast cancer at low risk for metastasis (asymptomatic individuals with newly identified ductal carcinoma in situ, or clinical stage I or II disease).
2) coverage as a modality to monitor response to treatment of breast cancer.
3) coverage for surveillance testing for asymptomatic individuals who have been treated for breast cancer with curative intent.

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In March 2018, PET scans for use in higher stage breast cancer was reviewed. The HERC staff summary read "PET scans are listed as a work up option (category 2B) by NCCN for initial staging of operable stage IIIA, T3, N1, M0 disease; stage IV disease; recurrent disease when other staging studies are equivocal or suspicious; and inflammatory breast cancer. Other work up options, such as CT or MRI with contrast or bone scans are available and are generally category 2A. NCCN panel members had reservations about the use of PET scans for recurrent disease work up. The medical literature indicates that PET scans have limited utility in stage III and IV breast cancer." At that meeting, the HCPCS code (G0252) for PET imaging of the breast was added to line 662/GN173 as "not a recommended test." Previously, this code was on the Services Recommended for Non-Coverage List. During that meeting, Olson stated that PET was not used in breast cancer patients routinely. He noted that lack of coverage for PET in stage IV disease went against standard of care, as it can show if bone lesions are actually active cancer metastases. Olson also noted that PET scans have a large radiation dose.

NCCN recently updated their breast cancer treatment guideline (most recent update is June 28, 2021). This guideline is substantially different that previous guidelines and has many updated treatment algorithms.

PET Scan for Breast Cancer
Re-Review 2021

Current Prioritized List status
Breast cancer is on line 191 CANCER OF BREAST; AT HIGH RISK OF BREAST CANCER

DIAGNOSTIC GUIDELINE D9, MRI FOR BREAST CANCER DIAGNOSIS

In women with recently diagnosed breast cancer, preoperative or contralateral MRI of the breast is not a covered service.

DIAGNOSTIC GUIDELINE D22, PET SCAN GUIDELINES

PET Scans are covered for diagnosis of the following cancers only:

- Solitary pulmonary nodules and non-small cell lung cancer
- Evaluation of cervical lymph node metastases when CT or MRI do not demonstrate an obvious primary tumor.

For diagnosis, PET is covered only when it will avoid an invasive diagnostic procedure, or will assist in determining the optimal anatomic location to perform an invasive diagnostic procedure.

PET scans are covered for the initial staging of the following cancers:

- Cervical cancer only when initial MRI or CT is negative for extra-pelvic metastasis
- Head and neck cancer when initial MRI or CT is equivocal
- Colon cancer
- Esophageal cancer
- Solitary pulmonary nodule
- Non-small cell lung cancer
- Lymphoma
- Melanoma

For staging, PET is covered when clinical management of the patient will differ depending on the stage of the cancer identified and either:

A) the stage of the cancer remains in doubt after standard diagnostic work up, OR
B) PET replaces one or more conventional imaging studies when they are insufficient for clinical management of the patient.

Restaging is covered only for cancers for which staging is covered and for thyroid cancer if recurrence is suspected and l131 scintography is negative. For restaging, PET is covered after completion of treatment for the purpose of detecting residual disease, for detecting suspected recurrence or to determine the extent of a known recurrence. PET is not covered to monitor tumor response during the planned course of therapy. PET scans are NOT indicated for routine follow up of cancer treatment or routine surveillance in asymptomatic patients.

PET scans are also indicated for preoperative evaluation of the brain in patients who have intractable seizures and are candidates for focal surgery. PET scans are NOT indicated for cardiac evaluation.

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**
G0252	Pet imaging, full and partial-ring pet scanners only, for initial diagnosis of breast cancer and/or surgical planning for breast cancer (e.g., initial staging of axillary lymph nodes)	Not a recommended test for axillary staging	March, 2018

PET Scan for Breast Cancer
Re-Review 2021

Expert guidelines

1) **NCCN 5.2021**:
    a. For non-metastatic invasive breast cancer
        i. Work up:
            1. Diagnostic bilateral mammogram with ultrasound as necessary
            2. Breast MRI (optional).
                a. Footnote: breast MRI may be useful for characterizing axillary and/or internal mammary nodal disease
                b. Further discussion: MRI has high sensitivity for evaluation of the extent of disease, but has a high percentage of false-positive findings resulting in further diagnostic workup up and increase in frequency of mastectomies. Two prospective RCTs have examined the utility of pre-operative MRI in determining disease extent, and neither demonstrated improvement in rates of post-lumpectomy re-excision.
            3. Consider additional imaging studies only in the presence of signs and symptoms of metastatic disease
                a. Discussion: the panel has re-iterated that routine systemic imaging is *not* indicated in patients with early breast cancer *in the absence* of signs/symptoms of metastatic disease [emphasis NCCN]. These recommendations are based on studies showing no additional value of these tests in patients with early-stage disease
                b. Discussion: **the use of PET or PET/CT scanning is not indicated in the staging of clinical stage I, II or operable III (T3 N1) breast cancer** [emphasis HERC staff]. The recommendation against PET is supported by the high false negative rate in the detection of lesions that are small (<1cm) and/or low grade, the low sensitivity for detection of axillary nodal metastases, the low prior probability of these patients having detectable metastatic disease, and the high rate of false positive scans.
                    i. FDG PET/CT is most helpful in situations where standard staging studies are equivocal or suspicious, especially in the setting of locally advanced or metastatic disease
                c. Post therapy surveillance with routine bone scans, CT scans, MRI scans, PET scans, etc. in the asymptomatic patient provide no advantage in survival or ability to palliate recurrent disease and are therefore not recommended
    b. For C≥T2 or cN+ (node positive) and M0 and considering preoperative systemic therapy:
        i. Additional tests to consider: chest/abdomen/pelvis CT or MRI with contrast (all 2A), PET (2B), FDG PET/CT (optional), breast MRI (optional)
        ii. Testing that should be performed includes axillary imaging with ultrasound or MRI
    c. Recurrent/stage IV (M1) disease
        i. Work up:
            1. Imaging:
                a. CT chest/abdomen/pelvis recommended as 2A

b. Bone scan or PET (2B)
c. FDG PET/CT (optional)
    i. FDG PET/CT is most helpful in situations where standard staging studies are equivocal or suspicious. FDG PET/CT may also be helpful in identifying unsuspected regional nodal disease and/or distant metastases when used in addition to standard staging studies
d. Discussion: **The NCCN Panel generally discourages the use of PET or PET/CT scan for the evaluation of patients with recurrent disease** [emphasis HERC staff]. There is limited evidence (mostly from retrospective studies) to support the use of PET/CT scanning to guide treatment planning through determination of the extent of disease in select patients with recurrent or metastatic disease. In general, the non-diagnostic CT scans used for PET under-evaluate the lungs and liver compared with contrast-enhanced diagnostic CT scans. The panel considers biopsy of equivocal or suspicious sites to be more likely than PET/CT scanning to provide accurate staging information in this population of patients. The consensus of the NCCN Panel is that FDG PET/CT is optional and most helpful in situations where standard imaging results are equivocal or suspicious. The NCCN Panel recommends bone scan or sodium fluoride PET/CT (category 2B) to detect bone metastases.

ii. Monitoring metastatic disease
    1. Monitoring the treatment of metastatic breast cancer involves a wide assortment of assessments…the information includes…functional imaging. The results of these evaluations generally are classified as response, continued response to treatment, stable disease, uncertainly regarding disease status, or progression of disease. The clinical typically must assess and balance multiple different forms of information to decide, along with the patient, whether disease is being controlled and the toxicity of treatment is acceptable.
    2. The panel…recommends using the same method of response assessment over time. For example, an abnormality initially found on diagnostic CT scan of the chest should be monitoring with repeat diagnostic CT scans of the chest.

2) **NICE 2009**: Advanced Breast Cancer, diagnosis and treatment
    a. Positron emission tomography fused with computed tomography (PET-CT) should only be used to make a new diagnosis of metastases for patients with breast cancer whose imaging is suspicious but not diagnostic of metastatic disease.
    b. Do not use PET-CT to monitor advanced breast cancer.

Other payer policies

1) **Aetna 2021**:
    a. Breast Cancer:
    b. FDG-PET scans are considered medically necessary for members with breast cancer for the following indications, where general medical necessity criteria for oncologic indications (II. A. listed above) are met:
        i. Initial staging of members with stage III or higher when conventional imaging is equivocal; *or*
        ii. Monitoring tumor response to treatment for persons with locally advanced and metastatic breast cancer when a change in therapy is contemplated; *or*
        iii. Restaging of members with known metastases; *or*
        iv. Evaluating suspected recurrence (new palpable lesions in axilla or adjacent area, rising tumor markers, changes in other imaging which are equivocal or suspicious).
    c. FDG-PET is considered experimental and investigational for the initial diagnosis of breast cancer and for the staging of axillary lymph nodes.
    d. II.A criteria:
        i. **Staging:** PET is considered medically necessary in situations in which clinical management of the member would differ depending on the stage of the cancer identified and *either*:
            1. The stage of the cancer remains in doubt after completion of a standard diagnostic work-up, including conventional imaging (computed tomography, magnetic resonance imaging, or ultrasound); *or*
            2. The use of PET would potentially replace one or more conventional imaging studies when it is expected that conventional study information is insufficient for the clinical management of the member.
        ii. Re-staging: PET is considered medically necessary for re-staging after completion of treatment for the purpose of detecting residual disease, for detecting suspected recurrence in persons with signs or symptoms of recurrence, or to determine the extent of recurrence. Use of PET is also considered medically necessary if it could potentially replace one or more conventional imaging studies when it is expected that conventional study information is insufficient for the clinical management of the member. PET for post-treatment surveillance is considered experimental and investigational, where surveillance is defined as use of PET beyond the completion of treatment, in the absence of signs or symptoms of cancer recurrence or progression, for the purpose of detecting recurrence or progression or predicting outcome.
        iii. Monitoring: PET for monitoring tumor response during the planned course of therapy is not considered medically necessary except for breast cancer. Re-staging occurs only after a course of treatment is completed.
    e. **Note:** HCPCS G0252 is specifically listed as non-covered
2) **Cigna 2020**
    a. PET is not medically necessary for the following:
        i. Non-invasive breast cancers
        ii. Prior to lymph node sampling in an individual with clinical Stage I, II, or operable IIIA disease
        iii. Obvious multi-organ metastatic disease is present on recent CT or MRI

b. PET is covered for
    i. Clinical Stage III and Stage IV disease or for signs or symptoms of systemic disease (including elevated liver function tests or tumor markers) when there is
        1. Inconclusive CT and bone scan
    ii. Evaluation of bone pain
        1. PET/CT (CPT® 78815) with Sodium Fluoride radiotracer may be obtained if CT, MRI, Bone scan and FDG PET/CT scan are inconclusive for bone metastases
    iii. Treatment response in individuals with metastatic disease and measurable disease on imaging:
        1. For individuals receiving chemotherapy, imaging is indicated after every 2 cycles
        2. For individuals receiving hormonal or endocrine therapy, imaging is indicated every 3 months
            a. PET/CT (CPT® 78815) with Sodium Fluoride radiotracer may be obtained if CT, MRI, Bone scan and FDG PET/CT scan are inconclusive for bone metastases
        3. ANY of the following:
            a. Elevated LFTs
            b. Rising tumor markers
            c. Signs or symptoms of recurrence
            d. Biopsy proven recurrence
                i. PET/CT (CPT® 78815) with Sodium Fluoride radiotracer may be obtained if CT, MRI, Bone scan and FDG PET/CT scan are inconclusive for bone metastases
        4. Bone metastasis as the only site of stage IV disease (excluding brain metastases) and a prior bone scan has not been performed for serial comparison OR Inconclusive findings on CT/MRI scan
            a. PET/CT (CPT® 78815)
        5. Neither PET nor CT are indicated to assess response to neoadjuvant chemotherapy
        6. PET not covered for surveillance or follow up

PET Scan for Breast Cancer
Re-Review 2021

HERC staff summary:
The latest NCCN breast cancer update does not recommend PET scans for initial evaluation of stage I, II, or operable stage III breast cancer. The NCCN panel generally discourages the use of PET scans in the diagnosis or monitoring of higher stage disease, recommending CT with contrast as a more reliable imaging method. Per the NCCN panel, the most likely helpful use of PET/CT is in situations where metastatic disease is suspected clinically and standard staging studies are equivocal or suspicious. This agrees with the NICE recommendation to use PET/CT only when standard imaging is suspicious but not diagnostic of metastatic disease. NCCN recommends using the same imaging modality which found the abnormality of interest to monitor disease when a change of therapy is being considered (new recommendation).

All major insurers cover PET scans for breast cancer with some restrictions. This coverage varies by insurer. The literature and guidelines in this area are rapidly changing.

HERC staff recommendation:

1) Modify Diagnostic Guideline D22 as shown below
    a. Adds limited coverage for evaluation of patients with suspected metastatic disease when standard imaging is suspicious or equivocal
        i. Consistent with the option allowed by NCCN and by NICE
    b. Allows monitoring of metastatic disease when the initial imaging modality to find the metastatic abnormality was PET scan and when a change of therapy is being contemplated
        i. Consistent with current NCCN recommendations and private payer policies
    c. See blue wording below (purple wording are changes adopted in May, 2021)

DIAGNOSTIC GUIDELINE D22, PET SCAN GUIDELINES
PET Scans are covered for diagnosis of the following cancers only:

- Solitary pulmonary nodules and non-small cell lung cancer
- Evaluation of cervical lymph node metastases when CT or MRI do not demonstrate an obvious primary tumor.

For diagnosis, PET is covered only when it will avoid an invasive diagnostic procedure, or will assist in determining the optimal anatomic location to perform an invasive diagnostic procedure.

PET scans are covered for the initial staging of the following cancers:

- Cervical cancer only when initial MRI or CT is negative for extra-pelvic metastasis
- Head and neck cancer when initial MRI or CT is equivocal
- Colon cancer
- Esophageal cancer
- Solitary pulmonary nodule
- Non-small cell lung cancer
- Lymphoma
- Melanoma
- Breast cancer ONLY when metastatic disease is suspected AND standard imaging results are equivocal or suspicious

PET Scan for Breast Cancer
Re-Review 2021

For initial staging, PET is covered when clinical management of the patient will differ depending on the stage of the cancer identified and either:

A) the stage of the cancer remains in doubt after standard diagnostic work up, OR
B) PET replaces one or more conventional imaging studies when they are insufficient for clinical management of the patient.

For monitoring tumor response during active therapy for purposes of treatment planning, PET is covered for

1) classic Hodgkin's lymphoma treatment ~~only~~.
2) metastatic breast cancer ONLY when a change in therapy is contemplated AND PET scan was the imaging modality initially used to find the tumor being monitored.

~~For monitoring tumor response during active therapy for purposes of treatment planning, PET is covered for classic Hodgkin's lymphoma treatment only. PET is not covered to monitor tumor response during the planned course of therapy for any other cancer.~~

Restaging is covered only for cancers for which staging is covered and for thyroid cancer if recurrence is suspected and l131 scintography is negative. For restaging, PET is covered after completion of treatment for the purpose of detecting residual disease, for detecting suspected recurrence or to determine the extent of a known recurrence. ~~PET is not covered to monitor tumor response during the planned course of therapy.~~ PET scans are NOT indicated for routine follow up of cancer treatment or routine surveillance in asymptomatic patients.

PET scans are also indicated for preoperative evaluation of the brain in patients who have intractable seizures and are candidates for focal surgery. PET scans are NOT indicated for cardiac evaluation.

Aduhelm Imaging Requirements

Issue: the FDA recently approved a new medication for treatment of Alzheimer's dementia, aducanumab (Aduhelm). The FDA labeling for this medication requires a brain MRI within one year of initiating treatment and then again prior to the 7th and 12 infusions to look for microhemorrhages (Amyloid Related Imaging Abnormalities (ARIA), and whenever a patient's symptoms are suggestive of ARIA. The studies which led to the approval of this medication all used a PET scan positive for amyloid as an inclusion criterion. The pharmacy group at OHA is requiring a PET scan as part of their PA criteria for this medication as they feel such a requirement will allow the most appropriate and focused utilization of this drug. The only other option for definitive identification of amyloid plaque is a lumbar puncture.

Currently, there are two guidelines on the Prioritized List that do not allow PET scans or MRIs for imaging in dementia that need to be modified to allow a pathway to coverage for aducanumab.

Note: multiple medications similar to aducanumab are in development and are anticipated to be under FDA review in the near future.

Evidence

1) **AHRQ 2020,** Diagnosis and Treatment of Clinical Alzheimer's-Type Dementia: A Systematic Review
    a. N=24 studies on accuracy of biomarkers for Alzheimer's disease (15 brain imaging, 9 CSF testing)
        i. The 15 imaging studies included 1,362 patients
    b. Summary statement: compared with clinical evaluation alone, amyloid positron emission tomography (PET), fluorodeoxyglucose (FDG)-PET, and combinations of CSF tests added to clinical evaluation may improve accuracy for distinguishing AD from non-AD dementia.
    c. For distinguishing between neuropathologically-confirmed Alzheimer's disease (AD) and non-AD, studies report:
        i. Amyloid positron emission tomography (PET) was highly sensitive and specific for beta-amyloid neuropathology of AD and, based on a single study, may increase classification accuracy when added to clinical evaluation.
        ii. Fluorodeoxyglucose (FDG)-PET was highly sensitive and moderately specific and, based on a single study, may increase classification accuracy when added to clinical evaluation.
        iii. Magnetic resonance imaging (MRI) medial temporal atrophy was highly sensitive and specific, and single-photon emission computerized tomography (SPECT) cerebral blood flow had variable accuracy; whereas SPECT plus clinical evaluation had lower sensitivity and higher specificity than clinical evaluation alone in two studies, no studies compared MRI plus clinical evaluation versus clinical evaluation alone.
    d. For distinguishing neuropathologically-confirmed AD from individual types of non-Alzheimer's dementia, studies report:
        i. FDG-PET had high sensitivity and moderate specificity for distinguishing AD from neuropathologically-confirmed frontotemporal lobar degeneration (FTLD) and,

based on a single study, may increase classification accuracy when added to a clinical evaluation.

ii. MRI medial temporal atrophy had moderate to high sensitivity and low to moderate specificity for distinguishing AD from neuropathologically-confirmed Lewy body disease (LBD) or FTLD.

e. Data on classification accuracy of brain imaging for neuropathologically-confirmed AD are limited by:
    i. Few studies, small sample sizes, and study heterogeneity (including criteria for AD neuropathology and composition of non-AD comparison group, interval between imaging and autopsy, methods of image acquisition and analysis, and cut points for defining abnormal scans).

f. Studies specifically on PET diagnostic accuracy
    i. N=4 studies (426 patients)
        1. Compared PET results to autopsy results
    ii. Median amyloid PET sensitivity from all four studies was 0.91 (range 0.79-0.98) and median specificity was 0.92 (range 0.76-1.0). Two of these studies also reported accuracy of clinical evaluation. In the first of these two studies (n=59), clinical evaluation had sensitivity of 0.72 and specificity of 0.95 for neuropathologically confirmed AD and amyloid PET corrected 10 of 11 clinical false negatives and the one clinical false positive but miscategorized 2 of 28 clinical true positives. In the second study, clinical evaluation had sensitivity of 0.94 and specificity of 0.52, and amyloid PET had sensitivity of 0.98 and specificity of 0.89.

HERC staff summary

PET has higher sensitivity and specificity for determining if a patient has Alzheimer's dementia versus other forms of dementia compared to brain MRI. The studies of Aduhelm used PET positive for AD as an entrance criterion. To most accurately determine the patients who might benefit from Aduhelm or similar future medications, HERC staff recommends allowing PET scans for patients who are being evaluated for eligibility for this medication. MRI is required by FDA labeling for monitoring during Aduhelm therapy.

HERC staff recommendations

1) Modify Diagnostic Guideline D7 as shown below
2) Modify Diagnostic Guideline D22 as shown below
    a. Note other changes to this guideline are recommended with other topics at this meeting

DIAGNOSTIC GUIDELINE D7, NEUROIMAGING IN DEMENTIA

Neuroimaging is covered:

A) To rule out reversible causes of dementia (tumors, normal pressure hydrocephalus and chronic subdural hematoma) via structural neuroimaging only
B) MRI is covered for monitoring for adverse effects of aducanumab or similar FDA approved medications for treatment of Alzheimer's disease

Neuroimaging is not covered:

A) For screening of asymptomatic patients for dementia
B) To predict progression of the risk of developing dementia in patients with mild cognitive impairment
C) For screening, diagnosis, or monitoring of dementia, with functional neuroimaging (PET, SPECT or fMRI)
    1) PET scans are covered for patients being considered for treatment with aducanumab or similar FDA approved medications for treatment of Alzheimer's disease.

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 D22, PET SCAN GUIDELINES

PET Scans are covered for diagnosis of the following cancers only:

- Solitary pulmonary nodules and non-small cell lung cancer
- Evaluation of cervical lymph node metastases when CT or MRI do not demonstrate an obvious primary tumor.

For diagnosis, PET is covered only when it will avoid an invasive diagnostic procedure, or will assist in determining the optimal anatomic location to perform an invasive diagnostic procedure.

PET scans are covered for the initial staging of the following cancers:

- Cervical cancer only when initial MRI or CT is negative for extra-pelvic metastasis
- Head and neck cancer when initial MRI or CT is equivocal
- Colon cancer
- Esophageal cancer

- Solitary pulmonary nodule
- Non-small cell lung cancer
- Lymphoma
- Melanoma

For staging, PET is covered when clinical management of the patient will differ depending on the stage of the cancer identified and either:

A) the stage of the cancer remains in doubt after standard diagnostic work up, OR
B) PET replaces one or more conventional imaging studies when they are insufficient for clinical management of the patient.

Restaging is covered only for cancers for which staging is covered and for thyroid cancer if recurrence is suspected and l131 scintography is negative. For restaging, PET is covered after completion of treatment for the purpose of detecting residual disease, for detecting suspected recurrence or to determine the extent of a known recurrence. PET is not covered to monitor tumor response during the planned course of therapy. PET scans are NOT indicated for routine follow up of cancer treatment or routine surveillance in asymptomatic patients.

PET scans are also indicated 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. PET scans are indicated PET scans are NOT indicated for cardiac evaluation.

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

ADUHELM™ (aducanumab-avwa) injection, for intravenous use
Initial U.S. Approval: 2021

RECENT MAJOR CHANGES

Indications and Usage (1) 7/2021

INDICATIONS AND USAGE

ADUHELM is an amyloid beta-directed antibody indicated for the treatment of Alzheimer's disease. Treatment with ADUHELM should be initiated in patients with mild cognitive impairment or mild dementia stage of disease, the population in which treatment was initiated in clinical trials. There are no safety or effectiveness data on initiating treatment at earlier or later stages of the disease than were studied. This indication is approved under accelerated approval based on reduction in amyloid beta plaques observed in patients treated with ADUHELM. Continued approval for this indication may be contingent upon verification of clinical benefit in confirmatory trial(s). (1)

DOSAGE AND ADMINISTRATION

- Titration is required for treatment initiation. (2.1)
- The recommended maintenance dosage is 10 mg/kg administered as an intravenous infusion over approximately one hour every four weeks. (2.1)
- Obtain a recent (within one year) brain MRI prior to initiating treatment. (2.2, 5.1)
- Obtain MRIs prior to the 7th and 12th infusions. If radiographic severe ARIA-H is observed, treatment may be continued with caution only after a clinical evaluation and a follow-up MRI demonstrates radiographic stabilization (i.e., no increase in size or number of ARIA-H). (2.2, 5.1)
- Dilution in 100 mL of 0.9% Sodium Chloride Injection, USP, is required prior to administration. (2.4)
- Administer as an intravenous infusion over approximately one hour via a 0.2 or 0.22 micron in-line filter. (2.5)

DOSAGE FORMS AND STRENGTHS

Injection:

- 170 mg/1.7 mL (100 mg/mL) solution in a single-dose vial (3)
- 300 mg/3 mL (100 mg/mL) solution in a single-dose vial (3)

CONTRAINDICATIONS

None. (4)

WARNINGS AND PRECAUTIONS

- Amyloid Related Imaging Abnormalities (ARIA): Enhanced clinical vigilance for ARIA is recommended during the first 8 doses of treatment with ADUHELM, particularly during titration. If a patient experiences symptoms which could be suggestive of ARIA, clinical evaluation should be performed, including MRI testing if indicated. (2.2, 5.1)
- Hypersensitivity Reactions: Angioedema and urticaria have occurred. If a hypersensitivity reaction occurs, promptly discontinue the infusion of ADUHELM and initiate appropriate therapy. (5.2)

ADVERSE REACTIONS

Most common adverse reactions (at least 10% and higher incidence compared to placebo): ARIA-Edema, headache, ARIA-H microhemorrhage, ARIA-H superficial siderosis, and fall. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Biogen at 1-833-425-9360 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

See 17 for PATIENT COUNSELING INFORMATION and Medication Guide.

Revised: 7/2021

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FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

ADUHELM is indicated for the treatment of Alzheimer's disease. Treatment with ADUHELM should be initiated in patients with mild cognitive impairment or mild dementia stage of disease, the population in which treatment was initiated in clinical trials. There are no safety or effectiveness data on initiating treatment at earlier or later stages of the disease than were studied. This indication is approved under accelerated approval based on reduction in amyloid beta plaques observed in patients treated with ADUHELM *[see Clinical Studies (14)]*. Continued approval for this indication may be contingent upon verification of clinical benefit in confirmatory trial(s).

2 DOSAGE AND ADMINISTRATION

2.1 Dosing Instructions

After an initial titration, the recommended dosage of ADUHELM is 10 mg/kg (see Table 1). ADUHELM is administered as an intravenous (IV) infusion over approximately one hour every four weeks and at least 21 days apart.

Table 1: Dosing Schedule

IV Infusion (every 4 weeks)	ADUHELM Dosage (administered over approximately one hour)
Infusion 1 and 2	1 mg/kg
Infusion 3 and 4	3 mg/kg
Infusion 5 and 6	6 mg/kg
Infusion 7 and beyond	10 mg/kg

2.2 Monitoring for Amyloid Related Imaging Abnormalities

Obtain recent (within one year) brain magnetic resonance imaging (MRI) prior to initiating treatment. Obtain MRIs prior to the 7th infusion (first dose of 10 mg/kg) and 12th infusion (sixth dose of 10 mg/kg). If 10 or more new incident microhemorrhages or > 2 focal areas of superficial siderosis (radiographic severe ARIA-H) is observed, treatment may be continued with caution only after a clinical evaluation and a follow-up MRI demonstrates radiographic stabilization (i.e., no increase in size or number of ARIA-H) *[see Warnings and Precautions (5.1)]*.

2.3 Resuming ADUHELM After Missed Dose

If an infusion is missed, resume administration at the same dose as soon as possible *[see Dosage and Administration (2.1)]*. Infusions are to be administered every 4 weeks and at least 21 days apart.

2.4 Dilution Instructions

- Use aseptic technique when preparing the ADUHELM diluted solution for intravenous infusion. Each vial is for single-dose only. Discard any unused portion.
- Calculate the dose, total volume of ADUHELM solution required, and the number of vials needed based on the patient's actual body weight. Each vial contains an ADUHELM concentration of 100 mg per mL. More than one vial may be needed for a full dose.
- Select the correct vial(s) for the required volume *[see Dosage Forms and Strengths (3)]*.
- Check that the ADUHELM solution is clear to opalescent and colorless to yellow solution. Do not use if opaque particles, discoloration, or other foreign particles are present.
- Remove the flip-off cap from the vial. Insert the syringe needle into the vial through the center of the rubber stopper.
- Withdraw the required volume of ADUHELM from the vial(s) and add to an infusion bag of 100 mL of 0.9% Sodium Chloride Injection, USP. Do not use other intravenous diluents to prepare the ADUHELM diluted solution.
- Gently invert the infusion bag containing the ADUHELM diluted solution to mix completely. Do not shake.
- After dilution, immediate use is recommended. If not administered immediately, store the diluted solution of ADUHELM in 0.9% Sodium Chloride Injection, USP refrigerated at 2°C to 8°C (36°F to 46°F) for up to 3 days, or at room temperature up to 30°C (86°F) for up to 12 hours.
- Prior to infusion, allow the ADUHELM diluted solution to warm to room temperature.

2.5 Administration Instructions

- Visually inspect the ADUHELM diluted solution for particles or discoloration prior to administration. Do not use if it is discolored, or opaque or foreign particles are seen.
- Infuse ADUHELM diluted solution intravenously over approximately one hour through an intravenous line containing a sterile, low-protein binding, 0.2 or 0.22 micron in-line filter.
- Promptly discontinue the infusion upon the first observation of any signs or symptoms consistent with a hypersensitivity-type reaction *[see Warnings and Precautions (5.2)]*.

3 DOSAGE FORMS AND STRENGTHS

ADUHELM is a clear to opalescent and colorless to yellow solution, available as:

- Injection: 170 mg/1.7 mL (100 mg/mL) in a single-dose vial
- Injection: 300 mg/3 mL (100 mg/mL) in a single-dose vial

4 CONTRAINDICATIONS

None.

5 WARNINGS AND PRECAUTIONS

5.1 Amyloid Related Imaging Abnormalities

ADUHELM can cause amyloid related imaging abnormalities-edema (ARIA-E), which can be observed on MRI as brain edema or sulcal effusions, and amyloid related imaging abnormalities-hemosiderin deposition (ARIA-H), which includes microhemorrhage and superficial siderosis.

Obtain recent (within one year) brain magnetic resonance imaging (MRI) prior to initiating treatment *[see Dosage and Administration (2.2)]*. The safety of ADUHELM in patients with any pre-treatment localized superficial siderosis, 10 or more brain microhemorrhages, and/or with a brain hemorrhage greater than 1 cm within one year of treatment initiation has not been established.

In clinical studies of ADUHELM, the severity of ARIA was classified by radiographic criteria, as shown in Table 2.

Table 2: ARIA MRI Classification Criteria

ARIA Type	Radiographic Severity		
	Mild	**Moderate**	**Severe**
ARIA-E	FLAIR hyperintensity confined to sulcus and or cortex/subcortical white matter in one location < 5 cm	FLAIR hyperintensity 5 to 10 cm, or more than 1 site of involvement, each measuring < 10 cm	FLAIR hyperintensity measuring > 10 cm, often with significant subcortical white matter and/or sulcal involvement. One or more separate sites of involvement may be noted.
ARIA-H microhemorrhage	≤ 4 new incident microhemorrhages	5 to 9 new incident microhemorrhages	10 or more new incident microhemorrhages
ARIA-H superficial siderosis	1 focal area of superficial siderosis	2 focal areas of superficial siderosis	> 2 focal areas of superficial siderosis

In Studies 1 and 2, ARIA (-E and/or -H) was observed in 41% of patients treated with ADUHELM with a planned dose of 10 mg/kg (454 out of 1105), compared to 10% of patients on placebo (111 out of 1087).

ARIA-E was observed in 35% of patients treated with ADUHELM 10 mg/kg, compared to 3% of patients on placebo. The incidence of ARIA-E was higher in apolipoprotein E ε4 (ApoE ε4) carriers than in ApoE ε4 non-carriers (42% and 20%, respectively). The majority of ARIA-E radiographic events occurred early in treatment (within the first 8 doses), although ARIA can occur at any time. Among patients treated with a planned dose of ADUHELM 10 mg/kg who had ARIA-E, the maximum radiographic severity was mild in 30%, moderate in 58%, and severe

in 13% of patients. Resolution occurred in 68% of ARIA-E patients by 12 weeks, 91% by 20 weeks, and 98% overall after detection. 10% of all patients who received ADUHELM 10 mg/kg had more than one episode of ARIA-E.

ARIA-H in the setting of ARIA-E associated with the use of ADUHELM 10 mg/kg was observed in 21% of patients treated with ADUHELM 10 mg/kg, compared to 1% of patients on placebo. There was no imbalance in isolated ARIA-H (i.e., ARIA-H in patients who did not also experience ARIA-E) between ADUHELM and placebo. There was no imbalance in hemorrhage greater than 1 cm between ADUHELM and placebo.

Clinical symptoms were present in 24% of patients treated with ADUHELM 10 mg/kg who had an observation of ARIA (-E and/or -H), compared to 5% of patients on placebo. The most common symptom in patients treated with ADUHELM 10 mg/kg with ARIA was headache (13%). Other frequent symptoms were confusion/delirium/altered mental status/disorientation (5%), dizziness/vertigo (4%), visual disturbance (2%), and nausea (2%). Serious symptoms associated with ARIA were reported in 0.3% of patients treated with ADUHELM 10 mg/kg. Clinical symptoms resolved in the majority of patients (88%) during the period of observation.

Enhanced clinical vigilance for ARIA is recommended during the first 8 doses of treatment with ADUHELM, particularly during titration, as this is the time the majority of ARIA was observed in Studies 1 and 2. If a patient experiences symptoms which could be suggestive of ARIA, clinical evaluation should be performed, including MRI testing if indicated. If ARIA is observed on MRI in the presence of clinical symptoms, careful clinical evaluation should be performed prior to continuing treatment.

Obtain brain MRIs prior to the 7^{th} infusion (first dose of 10 mg/kg) and 12^{th} infusion (sixth dose of 10 mg/kg) of ADUHELM to evaluate for the presence of asymptomatic ARIA. For patients with radiographic findings of ARIA, enhanced clinical vigilance is recommended. Additional MRIs may be considered if clinically indicated. If radiographically severe ARIA-H is observed, treatment may be continued with caution only after a clinical evaluation and a follow-up MRI demonstrates radiographic stabilization (i.e., no increase in size or number of ARIA-H). For ARIA-E or mild/moderate ARIA-H, treatment may continue with caution. If dosing is temporarily suspended, dosing may resume at that same dose and titration schedule. There are no systematic data on continued dosing with ADUHELM following detection of radiographically moderate or severe ARIA. In Studies 1 and 2, temporary dose suspension was required for radiographically moderate or severe ARIA-E and radiographically moderate ARIA-H. In Studies 1 and 2, permanent discontinuation of dosing was required for radiographically severe ARIA-H. The benefits of reaching and maintaining the 10 mg/kg dose should be considered when evaluating a potential dose suspension.

5.2 Hypersensitivity Reactions

Angioedema and urticaria were reported in one patient in the placebo-controlled period of Studies 1 and 2, and occurred during the ADUHELM infusion. Promptly discontinue the infusion upon the first observation of any signs or symptoms consistent with a hypersensitivity reaction, and initiate appropriate therapy.

6 ADVERSE REACTIONS

The following adverse reactions are described elsewhere in the labeling:

- Amyloid Related Imaging Abnormalities *[see Warnings and Precautions (5.1)]*
- Hypersensitivity Reactions *[see Warnings and Precautions (5.2)]*

6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in 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 clinical practice.

The safety of ADUHELM has been evaluated in 3,078 patients who received at least one dose of ADUHELM. In two placebo-controlled studies (Studies 1 and 2) in patients with Alzheimer's disease, a total of 1105 patients received ADUHELM 10 mg/kg *[see Clinical Studies (14)]*. Of these 1105 patients, approximately 52% were female, 76% were White, 10% were Asian, and 3% were of Hispanic or Latino ethnicity. The mean age at study entry was 70 years (range from 50 to 85).

In the combined placebo-controlled and long-term extension periods of Studies 1 and 2, 834 patients received at least one dose of ADUHELM 10 mg/kg once monthly for at least 6 months, 551 patients for at least 12 months, and 309 patients for at least 18 months. In the combined placebo-controlled and long-term extension periods, 5% (66 out of 1386) of patients in the 10 mg/kg dose group withdrew from the study because of an adverse reaction. The most common adverse reaction resulting in study withdrawal in the combined placebo-controlled and long-term extension periods was ARIA-H superficial siderosis. Table 3 shows adverse reactions that were reported in at least 2% of patients treated with ADUHELM and at least 2% more frequently than in patients on placebo.

Table 3: Adverse Reactions Reported in at Least 2% of Patients Treated with ADUHELM 10 mg/kg and at Least 2% Higher Than Placebo in Studies 1 and 2

Adverse Reaction	**ADUHELM 10 mg/kg N=1105 %**	**Placebo N=1087 %**
ARIA-E	35	3
Headache[a]	21	16
ARIA-H microhemorrhage	19	7
ARIA-H superficial siderosis	15	2
Fall	15	12
Diarrhea[b]	9	7
Confusion/Delirium/Altered Mental Status/Disorientation[c]	8	4

[a]*Headache includes the adverse reaction related terms headache, head discomfort, migraine, migraine with aura, and occipital neuralgia.*
[b]*Diarrhea includes the adverse reaction related terms diarrhea and infectious diarrhea.*
[c]*Confusion/Delirium/Altered Mental Status/Disorientation includes the adverse reaction related terms confusional state, delirium, altered state of consciousness, disorientation, depressed level of consciousness, disturbance in attention, mental impairment, mental status changes, postoperative confusion, and somnolence.*

6.2 Immunogenicity

As with all therapeutic proteins, there is potential for immunogenicity. The detection of antibody formation is highly dependent on the sensitivity and specificity of the assay. Additionally, the observed incidence of antibody (including neutralizing antibody) positivity in an assay may be influenced by several factors including assay methodology, sample handling, timing of sample collection, concomitant medications, and underlying disease. For these reasons, comparison of the incidence of antibodies in the studies described below with the incidence of antibodies in other studies or to other aducanumab products may be misleading.

The immunogenicity of ADUHELM has been evaluated using an in vitro assay for the detection of binding anti-aducanumab-avwa antibodies.

In up to 41 months of treatment in the combined placebo-controlled and long-term extension periods of Studies 1 and 2, up to 0.6% (15/2689) of patients receiving ADUHELM once monthly developed anti-aducanumab-avwa antibodies.

Based on the limited number of patients who tested positive for anti-aducanumab-avwa antibodies, no observations were made concerning a potential effect of neutralizing activity of anti-aducanumab-avwa antibodies on exposure or efficacy; however, the available data are too limited to make definitive conclusions regarding an effect on pharmacokinetics, safety, or efficacy of ADUHELM. Quantification of neutralizing anti-aducanumab-avwa antibodies has not been assessed.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

There are no adequate data on ADUHELM use in pregnant women to evaluate for a drug-associated risk of major birth defects, miscarriage, or other adverse maternal or fetal outcomes. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2 to 4% and 15 to 20%, respectively. The background risk of major birth defects and miscarriage for the indicated population is unknown.

Data

Animal Data

Intravenous administration of aducanumab-avwa (0, 100, 300, or 1000 mg/kg/week) to female rats through organogenesis had no adverse effect on embryofetal development.

Intravenous administration of aducanumab-avwa (0, 100, 300, or 1000 mg/kg/week) to female rats throughout pregnancy and lactation had no adverse effects on pre- or postnatal development.

The relevance of these data to humans is limited because aggregated amyloid beta, the pharmacological target of aducanumab-avwa, is not present in rat.

8.2 Lactation

Risk Summary

There are no data on the presence of aducanumab-avwa in human milk, the effects on the breastfed infant, or the effects of the drug on milk production. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for ADUHELM and any potential adverse effects on the breastfed infant from ADUHELM or from the underlying maternal condition.

8.4 Pediatric Use

Safety and effectiveness in pediatric patients have not been established.

8.5 Geriatric Use

In Studies 1 and 2, the age of patients ranged from 50 to 85 years, with a mean age of 70 years; 79% were 65 and older, and 32% were 75 and older. There were no notable differences in the incidence of adverse reactions between these age groups, and no additional safety concerns in patients 65 years of age and older compared to younger patients.

11 DESCRIPTION

Aducanumab-avwa is a recombinant human immunoglobulin gamma 1 (IgG1) monoclonal antibody directed against aggregated soluble and insoluble forms of amyloid beta, and is expressed in a Chinese hamster ovary cell line. Aducanumab-avwa has an approximate molecular weight of 146 kDa.

ADUHELM (aducanumab-avwa) injection is a preservative-free, sterile, clear to opalescent, and colorless to yellow solution for intravenous infusion after dilution supplied in single-dose vials available in concentrations of 170 mg/1.7 mL (100 mg/mL) or 300 mg/3 mL (100 mg/mL) of ADUHELM.

Each mL of solution contains 100 mg of aducanumab-avwa and L-arginine hydrochloride (31.60 mg), L-histidine (0.60 mg), L-histidine hydrochloride monohydrate (3.39 mg), L-methionine (1.49 mg), polysorbate 80 (0.50 mg), and Water for Injection at an approximate pH of 5.5.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Aducanumab-avwa is a human, immunoglobulin gamma 1 (IgG1) monoclonal antibody directed against aggregated soluble and insoluble forms of amyloid beta. The accumulation of amyloid beta plaques in the brain is a defining pathophysiological feature of Alzheimer's disease. ADUHELM reduces amyloid beta plaques, as evaluated in Studies 1, 2, and 3 *[see Clinical Studies (14)]*.

12.2 Pharmacodynamics

Effect of ADUHELM on Amyloid Beta Pathology

ADUHELM reduced amyloid beta plaque in a dose- and time-dependent manner in Study 1, Study 2, and Study 3, compared with placebo *[see Dosage and Administration (2.1) and Clinical Studies (14)]*.

The effect of ADUHELM on amyloid beta plaque levels in the brain was evaluated using PET imaging (^{18}F-florbetapir tracer). The PET signal was quantified using the Standard Uptake Value Ratio (SUVR) method to estimate brain levels of amyloid beta plaque in composites of brain areas expected to be widely affected by Alzheimer's disease pathology (frontal, parietal, lateral temporal, sensorimotor, and anterior and posterior cingulate cortices), compared to a brain region expected to be spared of such pathology (cerebellum). The SUVR was also expressed on the Centiloid scale.

In substudies of Study 1 and Study 2, ADUHELM reduced amyloid beta plaque levels in the brain, producing reductions at both ADUHELM low dose and high dose levels and at both Weeks 26 and 78 ($p < 0.0001$), compared to placebo. The magnitude of reduction was time- and dose-dependent. In the long-term extension of Study 1 and Study 2, a continued decrease in brain amyloid beta plaque levels was observed at Week 132 in patients initially randomized to ADUHELM.

In Study 3, ADUHELM reduced amyloid beta plaque levels in the brain, producing statistically significant dose- and time-dependent reductions compared to placebo in the 3 mg/kg, 6 mg/kg, and 10 mg/kg ADUHELM treatment groups at Week 26, and in all ADUHELM treatment groups at Week 54. Among those dosed with ADUHELM during the placebo-controlled period in Study 3, amyloid beta plaque levels in the brain continued to decline in a time- and dose-dependent manner in the long-term extension period through Week 222.

Effect of ADUHELM on Tau Pathophysiology

ADUHELM reduced markers of tau pathophysiology (CSF p-Tau and Tau PET) and neurodegeneration (CSF t-Tau) in Study 1 and Study 2 *[see Clinical Studies (14)]*.

ADUHELM reduced CSF levels of p-Tau in substudies conducted in Study 1 and Study 2. The adjusted mean change from baseline in CSF p-Tau levels relative to placebo was in favor of the ADUHELM low ($p<0.01$) and high ($p<0.001$) dose groups at Week 78 in Study 1. Results in Study 2 numerically favored ADUHELM but were not statistically significant.

ADUHELM reduced CSF levels of t-Tau in substudies conducted in Study 1 and Study 2. The adjusted mean change from baseline in CSF t-Tau levels relative to placebo was in favor of the ADUHELM low ($p<0.05$) and high ($p<0.01$) dose groups at Week 78 in Study 1. Results in Study 2 numerically favored ADUHELM but were not statistically significant.

Substudies were conducted in both Study 1 and Study 2 to evaluate the effect of ADUHELM on neurofibrillary tangles composed of tau protein using PET imaging (^{18}F-MK6240 tracer). The PET signal was quantified using the SUVR method to estimate brain levels of tau in brain regions expected to be affected by Alzheimer's disease pathology (medial temporal, temporal, frontal, cingulate, parietal, and occipital cortices) in the study population compared to a brain region expected to be spared of such pathology (cerebellum). Data from the substudies were

pooled, comprising 37 patients with longitudinal follow-up. The adjusted mean change from baseline in tau PET SUVR relative to placebo at follow-up was in favor of ADUHELM high dose in the medial temporal ($p<0.001$), temporal ($p<0.05$), and frontal ($p<0.05$) brain regions. No statistically significant differences were observed for the cingulate, parietal, or occipital cortices.

Exposure-Response Relationships

Model based exposure-response analyses for Studies 1 and 2 demonstrated that higher exposures to ADUHELM were associated with greater reduction in clinical decline on CDR-SB, ADAS-Cog13, and ADCS-ADL-MCI. In addition, higher exposures to ADUHELM were associated with greater reduction in amyloid beta plaque in Studies 1 and 2. An association between reduction in amyloid beta plaque and clinical decline on CDR-SB was also observed.

12.3 Pharmacokinetics

The pharmacokinetics (PK) of ADUHELM were characterized using a population PK analysis with concentration data collected from 2961 subjects with Alzheimer's disease who received ADUHELM in single or multiple doses.

Steady-state concentrations of ADUHELM were reached by 16 weeks of repeated dosing with an every 4-week regimen, and the systemic accumulation was 1.7-fold. The peak concentration (C_{max}), trough concentration (C_{min}), and area under the plasma concentration versus time curve at steady state (AUC_{ss}) of ADUHELM increased dose proportionally in the dose range of 1 to 10 mg/kg every 4 weeks.

Distribution

The mean value (95% CI) for volume of distribution at steady state is 9.63 L (9.48, 9.79).

Elimination

ADUHELM is expected to be degraded into small peptides and amino acids via catabolic pathways in the same manner as endogenous IgG. ADUHELM clearance (95% CI) is 0.0159 (0.0156, 0.0161) L/hr. The terminal half-life is 24.8 (14.8, 37.9) days.

Specific Populations

Body weight, age, sex, and race were found to impact exposure to ADUHELM. However, none of these covariates were found to be clinically significant.

Patients with Renal or Hepatic Impairment

No studies were conducted to evaluate the pharmacokinetics of ADUHELM in patients with renal or hepatic impairment. ADUHELM is not expected to undergo renal elimination or metabolism by hepatic enzymes.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenesis

Carcinogenicity studies have not been conducted.

Mutagenesis

Genotoxicity studies have not been conducted.

Impairment of Fertility

Intravenous administration of aducanumab-avwa (0, 100, 300, or 1000 mg/kg/week) to male and female rats prior to and during mating and continuing in females to gestation day 7 resulted in no adverse effects on fertility or reproductive performance.

The relevance of these data to humans is limited because aggregated amyloid beta, the pharmacological target of aducanumab-avwa, is not present in rat.

14 CLINICAL STUDIES

The efficacy of ADUHELM was evaluated in two double-blind, randomized, placebo-controlled, parallel group studies (Study 1, NCT 02484547 and Study 2, NCT 02477800) in patients with Alzheimer's disease (patients with confirmed presence of amyloid pathology and mild cognitive impairment or mild dementia stage of disease, consistent with Stage 3 and Stage 4 Alzheimer's disease, stratified to include 80% Stage 3 patients and 20% Stage 4 patients). The effects of ADUHELM were also supported by a double-blind, randomized, placebo-controlled, dose-ranging study (Study 3, NCT 01677572) in patients with Alzheimer's disease (patients with confirmed presence of amyloid pathology and prodromal or mild dementia stage of disease, consistent with Stage 3 and Stage 4 Alzheimer's disease, with an enrolled distribution of 43% Stage 3 patients and 57% Stage 4 patients), followed by an optional, dose-blind, long-term extension period.

In Studies 1 and 2, patients were randomized to receive ADUHELM low dose (3 or 6 mg/kg for ApoE ε4 carriers and noncarriers, respectively), ADUHELM high dose (10 mg/kg), or placebo every 4 weeks for 18 months, followed by an optional, dose-blind, long-term extension period. Both studies included an initial titration period of up to 6 months to the maximum target dose. At the beginning of the study, ApoE ε4 carriers were initially titrated up to a maximum of 6 mg/kg in the high dose group, which was later adjusted to 10 mg/kg.

In Studies 1 and 2, patients were enrolled with a Clinical Dementia Rating (CDR) global score of 0.5, a Repeatable Battery for Assessment of Neuropsychological Status (RBANS) delayed memory index score $\leq$ 85, and a Mini-Mental State Examination (MMSE) score of 24-30. In Study 3, patients were enrolled with a global CDR score of 0.5 or 1.0 and an MMSE score of 20-30. Patients were enrolled with or without concomitant approved therapies (cholinesterase inhibitors and the N-methyl-D-aspartate antagonist memantine) for Alzheimer's disease.

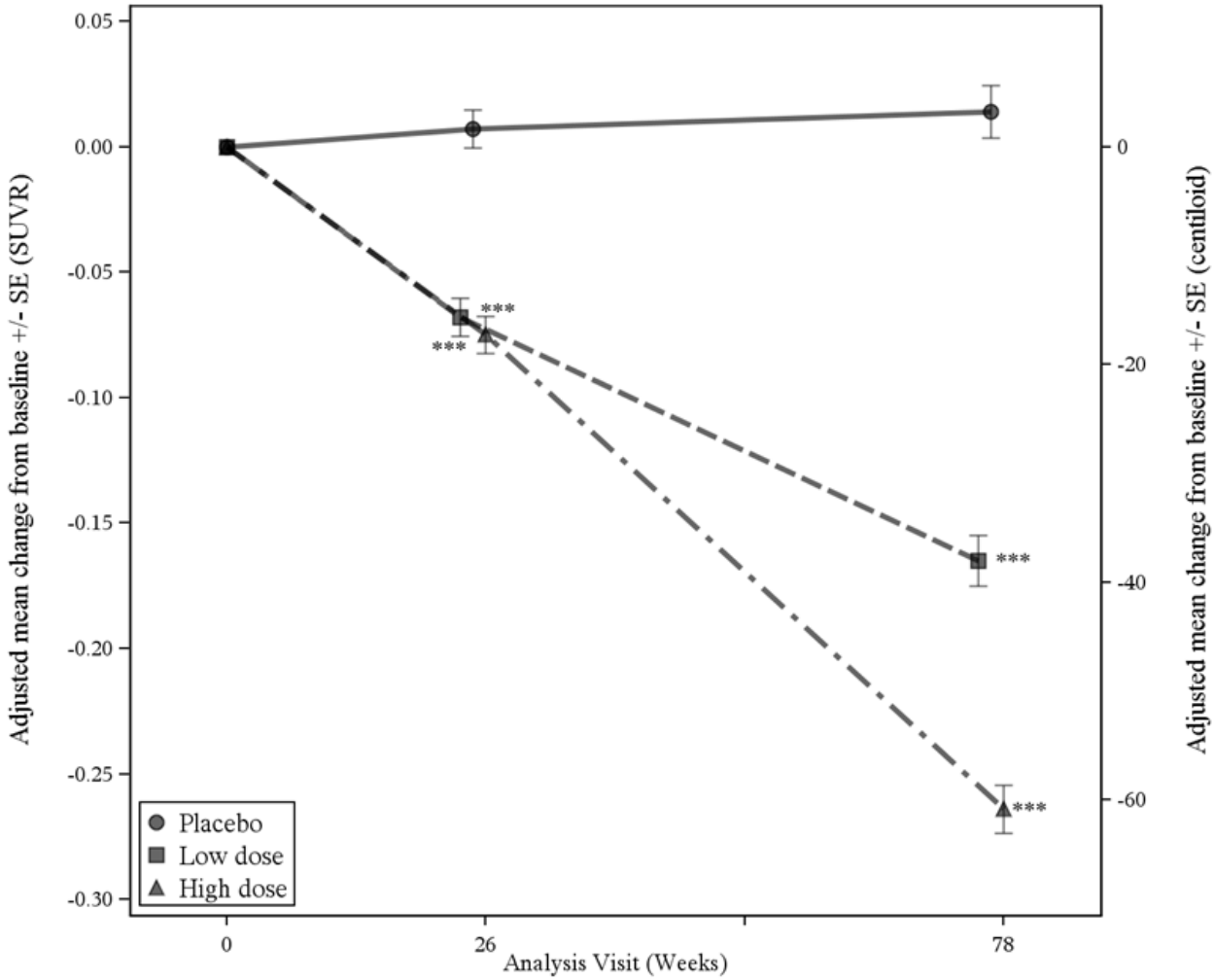
Studies 1 and 2 were terminated prior to their planned completion. Study endpoints were analyzed based on the prespecified statistical analysis plan.

Study 1

In Study 1, 1638 patients were randomized 1:1:1 to receive ADUHELM low dose, ADUHELM high dose, or placebo. At baseline, the mean age of patients was 71 years, with a range of 50 to 85 years.

A subgroup of 488 patients were enrolled in the amyloid PET substudy; of these, 302 were evaluated at week 78. Results from the amyloid beta PET and CSF biomarker substudies are described in Figure 1 and Table 4.

Figure 1: Reduction in Brain Amyloid Beta Plaque (Change from Baseline in Amyloid Beta PET Composite, SUVR and Centiloids) in Study 1



Number of subjects

Placebo	159	129	93
Low dose	159	129	100
High dose	170	138	109

*** p<0.001

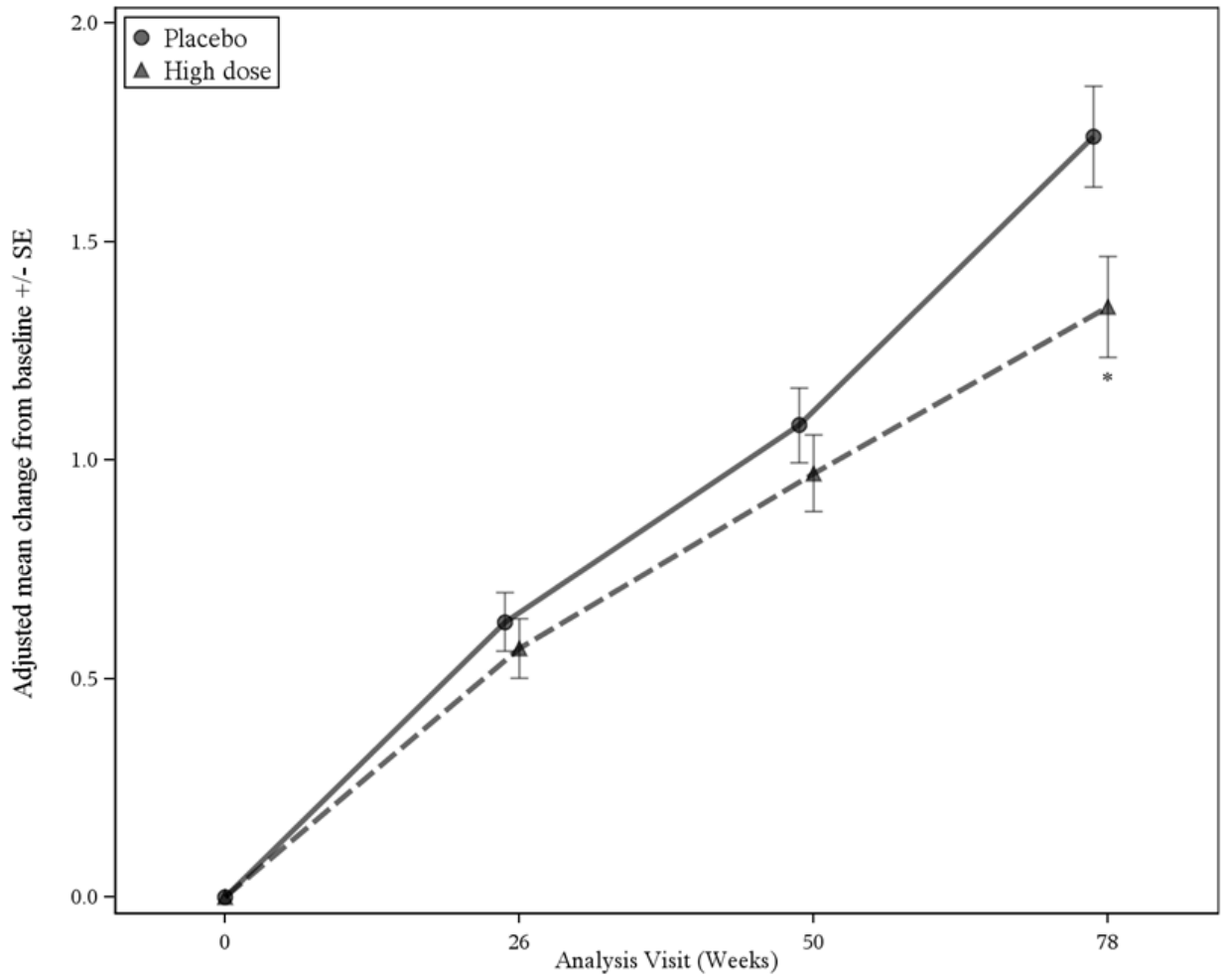
Table 4: Biomarker Results of ADUHELM in Study 1

Biomarker Endpoint at Week 78[1]	**ADUHELM High dose**	**Placebo**
Amyloid Beta PET Composite SUVR	N=170	N=159
Mean baseline	1.383	1.375
Change from baseline Difference from placebo	-0.264 -0.278, p<0.0001	0.014
Amyloid Beta PET Centiloid	N=170	N=159
Mean baseline	85.3	83.5
Change from baseline (%) Difference from placebo	-60.8 (-71%) -64.2, p<0.0001	3.4
CSF p-Tau (pg/mL)	N=17	N=28
Mean baseline	100.11	72.55
Change from baseline Difference from placebo	-22.93 -22.44, p=0.0005	-0.49
CSF t-Tau (pg/mL)	N=17	N=28
Mean baseline	686.65	484.00
Change from baseline Difference from placebo	-112.44 -112.05, p=0.0088	-0.39

[1]P-values were not statistically controlled for multiple comparisons.

The primary efficacy endpoint was the change from baseline on the CDR-Sum of Boxes (CDR-SB) at Week 78. In Study 1, treatment with ADUHELM high dose demonstrated reduced clinical decline, as evidenced by a statistically significant treatment effect on change from baseline in CDR-SB compared to placebo (-0.39 [-22%], p = 0.0120), as shown in Figure 2 and Table 5. The estimate of the treatment effect favored ADUHELM across all prespecified subgroups of interest.

Figure 2: Line Plot of Primary Efficacy Endpoint (Change From Baseline in CDR Sum of Boxes) in Study 1



Number of subjects

Placebo	548	532	430	288
High dose	547	513	431	299

* $p<0.05$

Secondary efficacy endpoints included the change from baseline in MMSE score at Week 78, the change from baseline in the Alzheimer's Disease Assessment Scale-Cognitive Subscale (13 items) (ADAS-Cog 13) at Week 78, and the change from baseline in the Alzheimer's Disease Cooperative Study – Activities of Daily Living Inventory (Mild Cognitive Impairment version) (ADCS-ADL-MCI) score at Week 78. In Study 1, statistically significant differences from placebo were observed in the ADUHELM high dose group on all secondary efficacy endpoints evaluated. The estimate of the treatment effect favored ADUHELM across most prespecified subgroups of interest for the secondary efficacy endpoints. The Neuropsychiatric Inventory-10 item (NPI-10) was the only tertiary endpoint that assessed efficacy. The results of the high dose group, compared to placebo, are presented in Table 5.

Differences from placebo observed in the ADUHELM low dose group numerically favored ADUHELM but were not statistically significant.

Table 5: Clinical Results of ADUHELM in Study 1

Clinical Endpoint at Week 78	ADUHELM High dose (N=547)	Placebo (N=548)
CDR-SB		
Mean baseline	2.51	2.47
Change from baseline	1.35	1.74
Difference from placebo (%)	-0.39 (-22%)	
	p=0.0120	
MMSE		
Mean baseline	26.3	26.4
Change from baseline	-2.7	-3.3
Difference from placebo (%)	0.6 (-18%)	
	p=0.0493	
ADAS-Cog 13		
Mean baseline	22.246	21.867
Change from baseline	3.763	5.162
Difference from placebo (%)	-1.400 (-27%)	
	p=0.0097	
ADCS-ADL-MCI		
Mean baseline	42.5	42.6
Change from baseline	-2.5	-4.3
Difference from placebo (%)	1.7 (-40%)	
	p=0.0006	
NPI-10[1]		
Mean baseline	4.5	4.3
Change from baseline	0.2	1.5
Difference from placebo (%)	-1.3 (-87%)	
	p=0.0215	

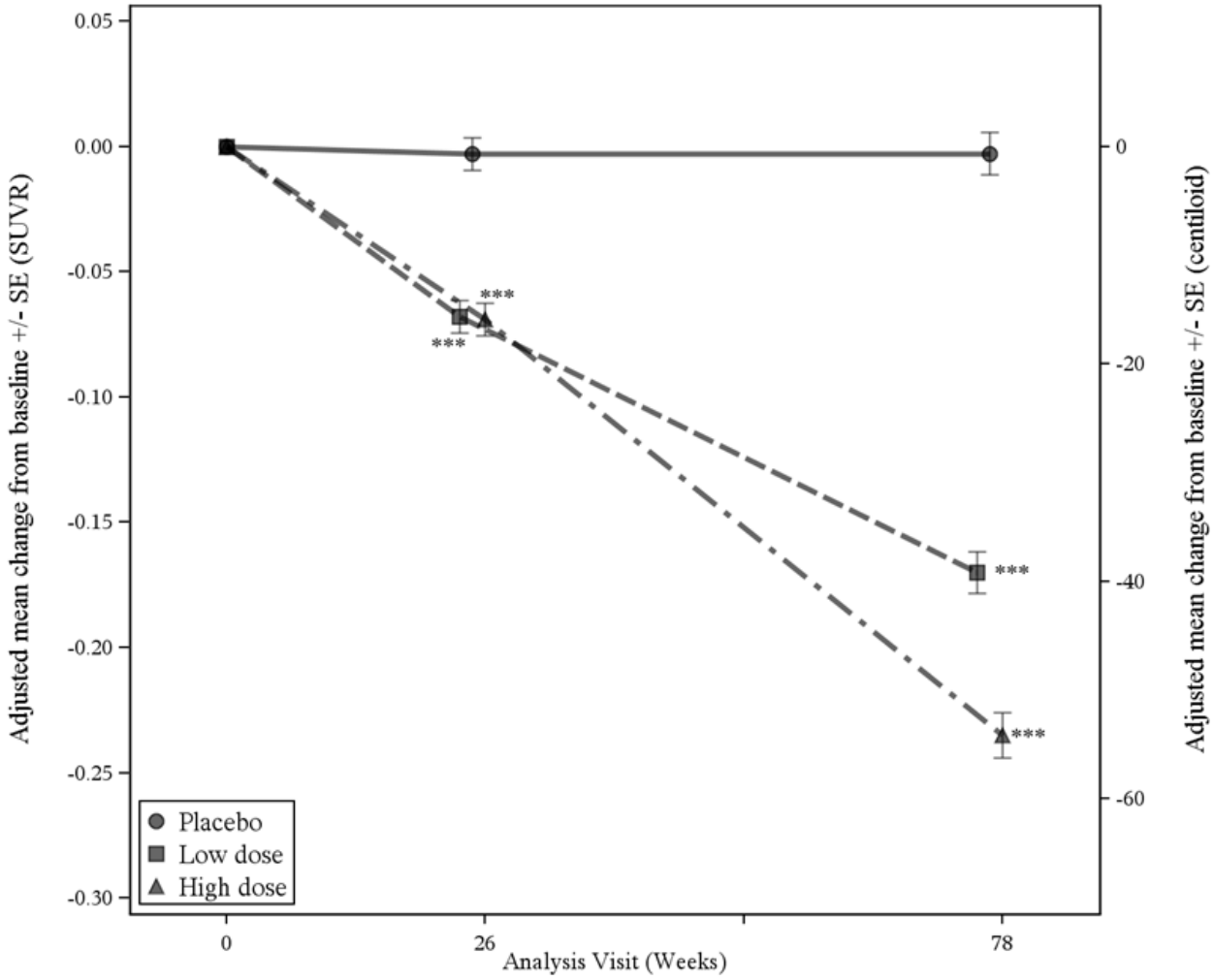
[1]P-value was not statistically controlled for multiple comparisons.

Study 2

In Study 2, 1647 patients were randomized 1:1:1 to receive ADUHELM low dose, ADUHELM high dose, or placebo. At baseline, the mean age of patients was 71 years, with a range of 50 to 85 years.

A subgroup of 585 patients were enrolled in the amyloid PET subgroup; of these, 374 were evaluated at week 78. Results from the amyloid beta PET and CSF biomarker substudies are described in Figure 3 and Table 6.

Figure 3: Reduction in Brain Amyloid Beta Plaque (Change from Baseline in Amyloid Beta PET Composite, SUVR and Centiloids) in Study 2



Number of subjects

Placebo	204	168	124
Low dose	198	169	138
High dose	183	156	112

*** p<0.001

Table 6: Biomarker Results of ADUHELM in Study 2

Biomarker Endpoint at Week 78[1]	**ADUHELM High dose**	**Placebo**
Amyloid Beta PET Composite SUVR	N=183	N=204
Mean baseline	1.407	1.376
Change from baseline Difference from placebo	-0.235 -0.232, p<0.0001	-0.003
Amyloid Beta PET Centiloid	N=183	N=204
Mean baseline	90.8	83.8
Change from baseline (%) Difference from placebo	-54.0 (-59%) -53.5, p<0.0001	-0.5
CSF p-Tau (pg/mL)	N=18	N=15
Mean baseline	121.81	94.53
Change from baseline Difference from placebo	-13.19 -10.95, p=0.3019	-2.24
CSF t-Tau (pg/mL)	N=16	N=14
Mean baseline	618.50	592.57
Change from baseline Difference from placebo	-102.51 -69.25, p=0.3098	-33.26

[1]P-values were not statistically controlled for multiple comparisons.

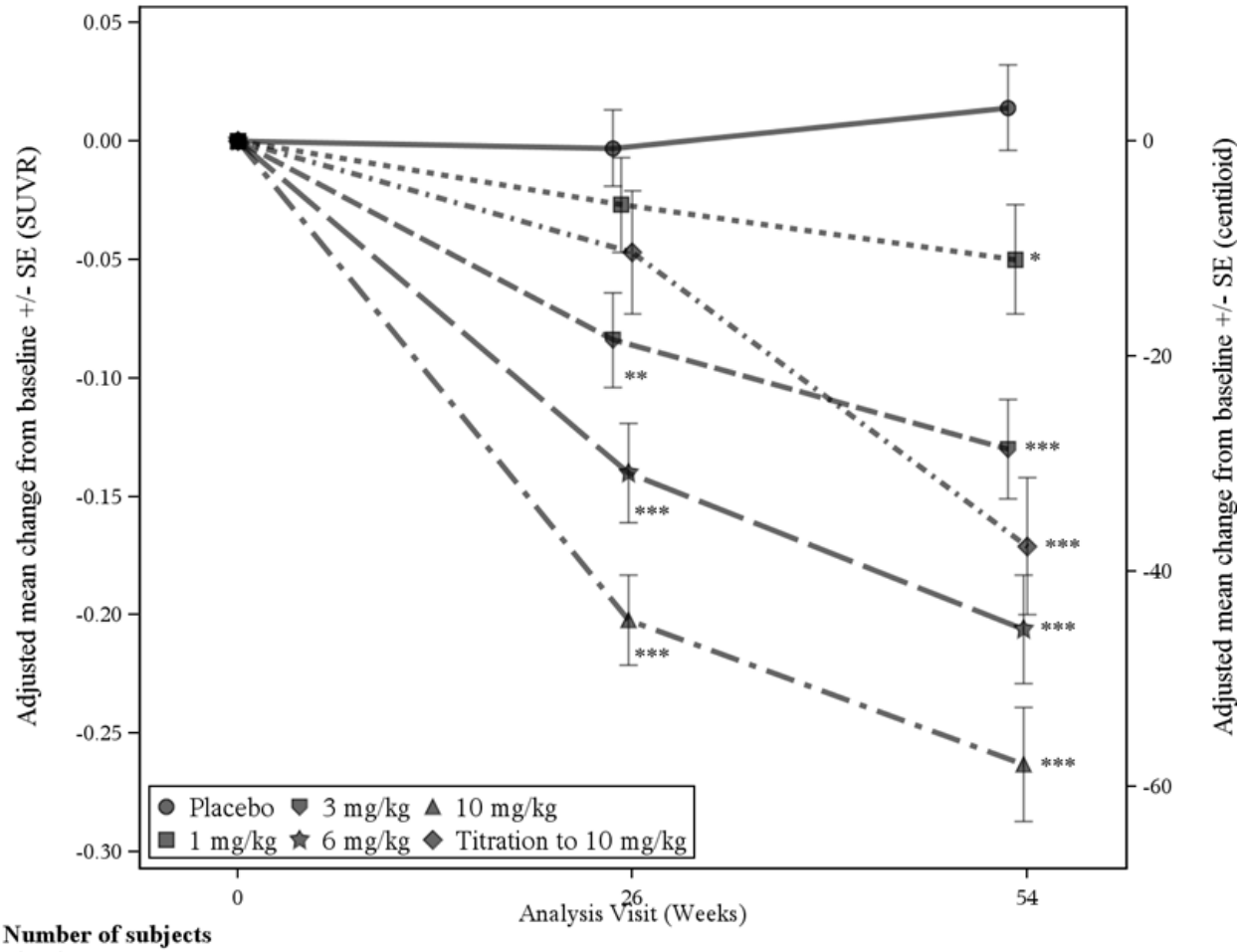
No statistically significant differences were observed between the ADUHELM-treated and placebo-treated patients on the primary efficacy endpoint, the change from baseline in CDR-SB score at 78 weeks.

Study 3

In Study 3, 197 patients were randomized to receive a fixed dose of ADUHELM 1 mg/kg (n=31), 3 mg/kg (n=32), 6 mg/kg (n=30), 10 mg/kg (n=32), titration of ADUHELM to 10 mg/kg over 44 weeks (n=23), or placebo (n=48) for 12 months. At baseline, the mean age of patients was 73 years, with a range of 51-91 years.

Results from the amyloid beta PET substudy are described in Figure 4 and Table 7.

Figure 4: Reduction in Brain Amyloid Beta Plaque (Change from Baseline in Amyloid Beta PET Composite, SUVR and Centiloids) in Study 3



Number of subjects

Placebo	42	42	38
1 mg/kg	26	26	21
3 mg/kg	29	27	26
6 mg/kg	24	23	23
10 mg/kg	28	27	21
Titration to 10 mg/kg	18	17	16

* p<0.05, ** p<0.01, *** p<0.001

Table 7: Biomarker Results of ADUHELM in Study 3

Biomarker Endpoint at Week 54[1]	**ADUHELM 10 mg/kg**	**Placebo**
Amyloid Beta PET Composite SUVR	N=28	N=42
Mean baseline	1.432	1.441
Change from baseline Difference from placebo	-0.263 -0.277, p<0.0001	0.014
Amyloid Beta PET Centiloid	N=28	N=42
Mean baseline	94.5	96.5

Change from baseline (%) Difference from placebo	-58.0 (-61%) -61.1, p<0.0001	3.1

[1]P-values were not statistically controlled for multiple comparisons.

Clinical assessments in Study 3 were exploratory. Results for clinical assessments were directionally aligned with the findings from Study 1, with less change from baseline in CDR-SB and MMSE scores at 1 year in the ADUHELM 10 mg/kg fixed-dose group than in patients on placebo (CDR-SB: -1.26, 95% CI [-2.356, -0.163]; MMSE: 1.9, 95% CI [0.06, 3.75]).

16 HOW SUPPLIED/STORAGE AND HANDLING

16.1 How Supplied

ADUHELM (aducanumab-avwa) injection is a preservative-free, sterile, clear to opalescent, and colorless to yellow solution. ADUHELM is supplied one vial per carton as follows:

170 mg/1.7 mL (100 mg/mL) single-dose vial (with red flip cap) – NDC 64406-101-01

300 mg/3 mL (100 mg/mL) single-dose vial (with blue flip cap) – NDC 64406-102-02

16.2 Storage and Handling

Unopened Vial

- Store in original carton until use to protect from light.
- Store in a refrigerator at 2°C to 8°C (36°F to 46°F).
- Do not freeze or shake.
- If no refrigeration is available, ADUHELM may be stored unopened in its original carton to protect from light at room temperature up to 25°C (77°F) for up to 3 days.
- Prior to dilution, unopened vials of ADUHELM may be removed from and returned to the refrigerator if necessary, when kept in the original carton. Total combined time out of refrigeration with protection from light should not exceed 24 hours at room temperature up to 25°C (77°F).

17 PATIENT COUNSELING INFORMATION

Advise the patient and/or caregiver to read the FDA-approved patient labeling (Medication Guide).

Amyloid Related Imaging Abnormalities

Inform patients that ADUHELM may cause Amyloid Related Imaging Abnormalities or "ARIA". ARIA most commonly presents as temporary swelling in areas of the brain that usually resolves over time. Some people may also have small spots of bleeding in or on the surface of the brain. Inform patients that most people with swelling in areas of the brain do not experience symptoms, however, some people may experience symptoms such as headache, confusion, dizziness, vision changes, or nausea. Instruct patients to notify their healthcare provider if these

symptoms occur. Notify patients that their healthcare provider will perform MRI scans to monitor for ARIA *[see Warnings and Precautions (5.1)]*.

Hypersensitivity Reactions

Inform patients that ADUHELM may cause hypersensitivity reactions, including angioedema and urticaria, and to contact their healthcare provider if hypersensitivity reactions occur *[see Warnings and Precautions (5.2)]*.

55093-02

Manufactured by:
Biogen Inc.
Cambridge, MA 02142
US License #1697

ADUHELM is a trademark of Biogen.

MEDICATION GUIDE

ADUHELM™ (AD-yew-helm)
(aducanumab-avwa)
injection, for intravenous use

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

ADUHELM can cause serious side effects, including:

Amyloid Related Imaging Abnormalities or "ARIA". ARIA is a common side effect that does not usually cause any symptoms but can be serious. It is most commonly seen as temporary swelling in areas of the brain that usually resolves over time. Some people may also have small spots of bleeding in or on the surface of the brain with the swelling. Although most people with swelling in areas of the brain do not have symptoms, some people may have symptoms, such as:

- headache
- dizziness
- nausea
- confusion
- vision changes

Your healthcare provider will do magnetic resonance imaging (MRI) scans before and during your treatment with ADUHELM to check you for ARIA.

Call your healthcare provider or go to the nearest hospital emergency room right away if you have any of the symptoms listed above.

What is ADUHELM?

- ADUHELM is a prescription medicine used to treat people with Alzheimer's disease.

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

Before receiving ADUHELM, tell your healthcare provider about all of your medical conditions, including if you:

- are pregnant or plan to become pregnant. It is not known if ADUHELM will harm your unborn baby. Tell your healthcare provider if you become pregnant during your treatment with ADUHELM.
- are breastfeeding or plan to breastfeed. It is not known if aducanumab-avwa (the active ingredient in ADUHELM) passes into your breast milk. Talk to your healthcare provider about the best way to feed your baby while receiving ADUHELM.

Tell your healthcare provider about all of the medicines you take, including prescription and over-the-counter medicines, vitamins, and herbal supplements.

How will I receive ADUHELM?

- ADUHELM is given through a needle placed in your vein (intravenous (IV) infusion) in your arm.
- ADUHELM is given every 4 weeks. Each infusion will last about 1 hour.

What are the possible side effects of ADUHELM?

ADUHELM can cause serious side effects, including:

- **See above "What is the most important information I should know about ADUHELM?"**
- **Serious allergic reactions.** Swelling of the face, lips, mouth, or tongue and hives have happened during an ADUHELM infusion. **Tell your healthcare provider if you have any of the symptoms of a serious allergic reaction during or after ADUHELM infusion.**

The most common side effects of ADUHELM include:

- swelling in areas of the brain, with or without small spots of bleeding in or on the surface of the brain (ARIA)
- headache
- fall

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

General Information about the safe and effective use of ADUHELM.

Medicines are sometimes prescribed for purposes other than those listed in this Medication Guide. You can ask your pharmacist or healthcare provider for more information about ADUHELM that is written for health professionals. For more information, go to www.aduhelm.com or call at 1-833-425-9360.

What are the ingredients in ADUHELM?

Active ingredient: aducanumab-avwa
Inactive ingredients: L-arginine hydrochloride, L-histidine, L-histidine hydrochloride monohydrate, L-methionine, polysorbate 80, and water for injection

Manufactured by: Biogen Inc., Cambridge, MA 02142, U.S. License #1697

This Medication Guide has been approved by the U.S. Food and Drug Administration Approved: 6/2021

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

ERIC P BASTINGS on behalf of TERESA J BURACCHIO
07/07/2021 08:25:55 PM

Comparative Effectiveness Review
Number 223

Diagnosis and Treatment of Clinical Alzheimer's-Type Dementia: A Systematic Review

AHRQ
Agency for Healthcare
Research and Quality

Comparative Effectiveness Review

Number 223

Diagnosis and Treatment of Clinical Alzheimer's-Type Dementia: A Systematic Review

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Prepared by:
Minnesota Evidence-based Practice Center
Minneapolis, MN

Investigators:
Howard A. Fink, M.D., M.P.H.
Laura S. Hemmy, Ph.D.
Eric J. Linskens, B.S.
Pombie C. Silverman, B.A.
Roderick MacDonald, M.S.
J. Riley McCarten, M.D.
Kristine M.C. Talley, Ph.D., R.N., G.N.P.-B.C., FGSA
Priyanka J. Desai, M.S.P.H.
Mary L. Forte, Ph.D., D.C.
Margaret A. Miller, M.A.
Michelle Brasure, Ph.D., M.S.P.H., M.L.I.S.
Victoria A. Nelson, M.Sc.
Brent C. Taylor, Ph.D., M.P.H.
Weiwen Ng, M.P.H.
Jeannine M. Ouellette, M.F.A.
Nancy L. Greer, Ph.D.
Kerry M. Sheets, M.D.
Timothy J. Wilt, M.D., M.P.H.
Mary Butler, Ph.D., M.B.A.

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April 2020

Structured Abstract

Objective. To summarize evidence on: (1) the accuracy of brief cognitive tests for identifying clinical Alzheimer's-type dementia (CATD) in individuals with suspected cognitive impairment; (2) the accuracy of biomarkers for identifying Alzheimer's disease (AD) in individuals with dementia; and (3) the benefits and harms of prescription drugs and supplements for cognition, function, and behavioral and psychological symptoms of dementia (BPSD) in patients with CATD.

Data sources. Electronic bibliographic databases to March 2019, ClinicalTrials.gov, systematic review bibliographies.

Review methods. Cognitive test accuracy studies must have used explicit CATD diagnostic criteria and a non-CATD control group. Biomarker accuracy studies must have used neuropathologic criteria to define AD cases and non-AD controls. All treatment trials must have enrolled participants with CATD; those evaluating BPSD enrolled individuals with CATD and BPSD. Minimum trial duration was 2 weeks for agitation, aggression, psychosis, and disinhibited sexual behavior, and 24 weeks for other outcomes. Two reviewers rated risk of bias (ROB) and strength of evidence. One reviewer extracted data; a second checked accuracy. We analyzed English-language studies with low or medium ROB.

Results. We analyzed 56 unique studies on the accuracy of brief cognitive tests for CATD, 24 on accuracy of biomarkers for AD (15 brain imaging, nine cerebrospinal fluid [CSF] testing), and 67 trials of CATD treatment (54 reporting cognition or function, 13 reporting BPSD). Multiple brief cognitive tests were highly sensitive and specific ($\geq$0.8) for distinguishing CATD from normal cognition, but less so for distinguishing mild CATD from normal cognition or CATD from mild cognitive impairment (MCI). Based on few studies, compared with clinical evaluation alone, amyloid positron emission tomography (PET), fluorodeoxyglucose (FDG)-PET, and combinations of CSF tests added to clinical evaluation may improve accuracy for distinguishing AD from non-AD dementia. Regardless of CATD severity, cholinesterase-inhibitors produced small improvements in cognition and function compared with placebo but may increase serious adverse events and withdrawals due to adverse events. For moderate to severe CATD, memantine plus a cholinesterase inhibitor slightly improved global change and inconsistently improved cognition, but not function, compared with a cholinesterase inhibitor alone. Evidence was mostly insufficient about the effects of prescription drugs and supplements on agitation, aggression, psychosis, or disinhibited sexual behavior.

Conclusions. Brief cognitive tests accurately distinguished CATD from normal cognition, but were less accurate distinguishing smaller clinical differences. Whether biomarkers improve diagnostic accuracy when added to clinical evaluation needs further verification, but potential benefits of testing are limited by lack of effective treatments for AD and non-AD dementias. Cholinesterase-inhibitors slightly outperformed placebo for cognition and function, but evidence of whether any drug treatments improved BPSD was largely insufficient.

PET Scan Guideline Revisions for Clarity

Issue: At the May 2021 VBBS meeting, the subcommittee members asked that the PET scan guideline be brought back to the August meeting with suggested revisions to improve its clarity. HERC staff have worked with CCO medical directors to improve the clarity of the guideline.

Current Guideline as of May 2021:

DIAGNOSTIC GUIDELINE D22, PET SCAN GUIDELINES

PET Scans are covered for diagnosis of the following cancers only:

- Solitary pulmonary nodules and non-small cell lung cancer
- Evaluation of cervical lymph node metastases when CT or MRI do not demonstrate an obvious primary tumor.

For diagnosis, PET is covered only when it will avoid an invasive diagnostic procedure, or will assist in determining the optimal anatomic location to perform an invasive diagnostic procedure.

PET scans are covered for the initial staging of the following cancers:

- Cervical cancer only when initial MRI or CT is negative for extra-pelvic metastasis
- Head and neck cancer when initial MRI or CT is equivocal
- Colon cancer
- Esophageal cancer
- Solitary pulmonary nodule
- Non-small cell lung cancer
- Lymphoma
- Melanoma

For initial staging, PET is covered when clinical management of the patient will differ depending on the stage of the cancer identified and either:

A) the stage of the cancer remains in doubt after standard diagnostic work up, OR
B) PET replaces one or more conventional imaging studies when they are insufficient for clinical management of the patient.

For monitoring tumor response during active therapy for purposes of treatment planning, PET is covered for classic Hodgkin's lymphoma treatment only. PET is not covered to monitor tumor response during the planned course of therapy for any other cancer.

Restaging is covered only for cancers for which staging is covered and for thyroid cancer if recurrence is suspected and l131 scintography is negative. For restaging, PET is covered after completion of treatment for the purpose of detecting residual disease, for detecting suspected recurrence or to determine the extent of a known recurrence. PET scans are NOT indicated for routine follow up of cancer treatment or routine surveillance in asymptomatic patients.

PET scans are also indicated for preoperative evaluation of the brain in patients who have intractable seizures and are candidates for focal surgery. PET scans are NOT indicated for cardiac evaluation.

HERC staff recommendation

1) Revise the PET scan guideline as shown below
    a. Shown first without mark up for ease of review; shown second with marked up changes
    b. Purple wording reflects the wording changes from the separate summary on PET for breast cancer. There is additional changes in blue and red which would also be needed if the PET scan for breast cancer changes from that summary are moved forward

DIAGNOSTIC GUIDELINE D22, PET SCANS

Diagnosis:

PET scans are covered for diagnosis only when:

1) the PET scan is for evaluation of either
    a. Solitary pulmonary nodules and non-small cell lung cancer, OR
    b. Evaluation of cervical lymph node metastases when CT or MRI do not demonstrate an obvious primary tumor, AND
2) the PET scan will
    a. avoid an invasive diagnostic procedure, OR
    b. assist in determining the optimal anatomic location to perform an invasive diagnostic procedure.

Initial staging:

PET scans are covered for initial staging only when:

1) The staging is for one of the following cancers/situations:
    a. Cervical cancer only when initial MRI or CT is negative for extra-pelvic metastasis
    b. Head and neck cancer when initial MRI or CT is equivocal
    c. Colon cancer
    d. Esophageal cancer
    e. Solitary pulmonary nodule
    f. Non-small cell lung cancer
    g. Lymphoma
    h. Melanoma
    i. Breast cancer ONLY when metastatic disease is suspected AND standard imaging results are equivocal or suspicious; AND
2) Clinical management of the patient will differ depending on the stage of the cancer identified and either:
    a. the stage of the cancer remains in doubt after standard diagnostic work up, OR
    b. 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

1) classic Hodgkin's lymphoma treatment ~~only~~.
2) metastatic breast cancer ONLY when a change in therapy is contemplated AND PET scan was the imaging modality initially used to find the tumor being monitored.

Restaging:

Restaging is covered only when:

1) the cancer has staging covered above OR for thyroid cancer if recurrence is suspected and l131 scintography is negative, AND
2) initial therapy has been completed, AND
3) the PET scan is conducted for
    a. detecting residual disease, or
    b. detecting suspected recurrence, or
    c. determining the extent of a known recurrence.

Other indications:

1) PET scans are covered for preoperative evaluation of the brain in patients who have intractable seizures and are candidates for focal surgery.
2) 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:

1) 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.
2) PET scans are NOT covered for routine follow up of cancer treatment or routine surveillance in asymptomatic patients.
3) PET scans are NOT covered for cardiac evaluation.

DIAGNOSTIC GUIDELINE D22, PET SCANS ~~GUIDELINES~~

Diagnosis:

PET Scans are covered for diagnosis ~~of the following cancers~~ only when:

1) The PET scan is for evaluation of either
    a. Solitary pulmonary nodules and non-small cell lung cancer, OR
    b. Evaluation of cervical lymph node metastases when CT or MRI do not demonstrate an obvious primary tumor~~.~~, AND
2) the PET scan will
    a. ~~For diagnosis, PET is covered only when it will~~ avoid an invasive diagnostic procedure, OR
    b. will assist in determining the optimal anatomic location to perform an invasive diagnostic procedure.

Initial staging:

PET scans are covered for the initial staging when ~~of the following cancers~~:

1) The staging is for one of the following cancers/situations:
    a. Cervical cancer only when initial MRI or CT is negative for extra-pelvic metastasis
    b. Head and neck cancer when initial MRI or CT is equivocal
    c. Colon cancer
    d. Esophageal cancer
    e. Solitary pulmonary nodule
    f. Non-small cell lung cancer
    g. Lymphoma

h. Melanoma,
i. Breast cancer ONLY when metastatic disease is suspected AND standard imaging results are equivocal or suspicious; AND

2) ~~For initial staging, PET is covered when~~ clinical management of the patient will differ depending on the stage of the cancer identified and either:
   a. the stage of the cancer remains in doubt after standard diagnostic work up, OR
   b. PET replaces one or more conventional imaging studies when they are insufficient for clinical management of the patient.

Monitoring:

1) For monitoring tumor response during active therapy for purposes of treatment planning, PET is covered for classic Hodgkin's lymphoma treatment ~~only~~.
2) metastatic breast cancer ONLY when a change in therapy is contemplated AND PET scan was the imaging modality initially used to find the tumor being monitored.

~~PET is not covered to monitor tumor response during the planned course of therapy for any other cancer~~.

Restaging:

Restaging is covered only when:

1) ~~for cancers for which staging is covered and~~ the cancer has staging covered above OR for thyroid cancer if recurrence is suspected and I131 scintography is negative, AND
2) ~~For restaging, PET is covered after completion of treatment~~ Initial therapy has been completed, AND
3) ~~for the purpose of~~ The PET scan is conducted for
   a. detecting residual disease, or
   b. ~~for~~ detecting suspected recurrence, or
   c. ~~to~~ determine~~ing~~ the extent of a known recurrence.

~~PET scans are NOT indicated for routine follow up of cancer treatment or routine surveillance in asymptomatic patients~~.

Other indications:

PET scans are ~~also indicated~~ 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. ~~PET scans are NOT indicated for cardiac evaluation.~~

Non-covered conditions/situations:

1) 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.
2) PET scans are NOT covered for routine follow up of cancer treatment or routine surveillance in asymptomatic patients.
3) PET scans are NOT covered for cardiac evaluation.

Section 7.0

New Discussion Items

USPSTF Updates
Screening for Colon Cancer

Issue: The USPSTF updated their colon cancer screening recommendations on May 18, 2021. There was one major change and one minor change in the recommendations.

The major change in the recommendation is lowering the age for initiating screening to age 45. The drop in the recommended age for starting screening down to age 45 was based on both "the incidence of CRC has been increasing among adults younger than 50 years" and the USPSTF modeling study that showed "when the benefits of screening are measured by the number of LYG [life years gained], most of the efficient screening strategies identified by all 3 models specified screening starting at age 45." Screening persons aged 45 to 50 years is a "B" recommendation due to moderate net benefit, and screening persons aged 50 to 75 years is an "A" recommendation due to substantial net benefit.

The minor change was in the recommendation wording for screening persons 76-85 years of age. The 2016 wording for this recommendation was "The decision to screen for colorectal cancer in adults aged 76 to 85 years should be an individual one, taking into account the patient's overall health and prior screening history. Adults in this age group who have never been screened for colorectal cancer are more likely to benefit. Screening would be most appropriate among adults who 1) are healthy enough to undergo treatment if colorectal cancer is detected and 2) do not have comorbid conditions that would significantly limit their life expectancy." The 2020 wording is "The USPSTF recommends that clinicians selectively offer screening for colorectal cancer in adults aged 76 to 85 years. Evidence indicates that the net benefit of screening all persons in this age group is small. In determining whether this service is appropriate in individual cases, patients and clinicians should consider the patient's overall health, prior screening history, and preferences." The screening recommendation for this age group remains a "C" recommendation due to a small net benefit.

The USPSTF continues to list a menu of screening options without comment about which options should be preferred. The options listed include fecal occult blood testing/FIT test, flexible sigmoidoscopy, colonoscopy, CT colonoscopy, fecal DNA (Cologuard), and a blood test called Epi pro-Colon. Currently, per Guideline Note 106 PREVENTIVE SERVICES, colonoscopy, flexible sigmoidoscopy, fecal occult blood testing and FIT testing are covered as colorectal cancer screening modality. HERC staff did not find compelling evidence that the modalities for screening currently covered in GN106 should be modified. Per the USPSTF review, colonoscopy, flexible sigmoidoscopy, hemoccult and FIT testing remain the only modalities for which use has shown both significant reduction in colorectal cancer incidence and morality.

Looking at subgroups including sex, race, and ethnicity, the USPSTF was not able to find data that was broken out by race or ethnicity regarding the effectiveness of different screening strategies or regarding the age of initiation of screening. Of note, the 2017 USPSTF colon cancer update recommending initiation of screening at age 45 for African Americans.

Currently, Guideline Note 106 PREVENTIVE SERVICES has details regarding colon cancer screening coverage. These details need to be updated given the updated USPSTF recommendations. Cologuard, CT colonoscopy, and serum screening tests are listed in GN172 as non-covered. Current OHA rule allows health plans to determine how a USPSTF A or B recommendation is implemented.

USPSTF Updates
Screening for Colon Cancer

45 CFR 147.130 (a)(4) says:

> (4) Reasonable medical management. Nothing prevents a plan or issuer from using reasonable medical management techniques to determine the frequency, method, treatment, or setting for an item or service described in paragraph (a)(1) of this section to the extent not specified in the relevant recommendation or guideline. To the extent not specified in a recommendation or guideline, a plan or issuer may rely on the relevant clinical evidence base and established reasonable medical management techniques to determine the frequency, method, treatment, or setting for coverage of a recommended preventive health service.

Of note, a new HCPCS code was released in June 2021 for the serum screening test (Epi proColon, also known as mSEPT9): HCPCS G0327 Colorectal cancer screening; blood-based biomarker.

At the May, 2021 meeting, two guidelines that included USPSTF specific recommendations were removed from the Prioritized List as redundant to GN106 (asymptomatic carotid artery screening and lung cancer screening), and requiring frequent changes to mirror USPSTF.

USPSTF Updates
Screening for Colon Cancer

HERC staff recommendations:

1) Modify GN106 as shown below:
    a. Updates USPSTF age specific information; removal not feasible as the 76-85 year old age group is a "C" recommendation and therefore not included in the "A" and "B" coverage requirement
    b. Modifies the requirements for coverage of screening for ages 76-85 years to align with current USPSTF recommendations
    c. Continues to specify the screening modalities which are covered
    d. Calls out non-covered screening modalities
2) Add HCPCS G0327 (Colorectal cancer screening; blood-based biomarker) to line 502 CONDITIONS FOR WHICH INTERVENTIONS RESULT IN MARGINAL CLINICAL BENEFIT OR LOW COST-EFFECTIVENESS
    a. Modify the entry in GN172 to include the new HCPCS code for the serum CRC screening test
        i. Note: mSEPT9 is the generic name for Epi proColon

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, 2020.
    1) http://www.uspreventiveservicestaskforce.org/Page/Name/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 http://www.aap.org/en-us/professional-resources/practice-support/Periodicity/Periodicity Schedule_FINAL.pdf.
    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 a**s updated by HRSA in December 2019. Available at https://www.hrsa.gov/womens-guidelines-2019 as of September 4, 2020.

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.

USPSTF Updates
Screening for Colon Cancer

Colorectal cancer screening is included on Line 3 for average-risk adults aged ~~50~~ 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 only ~~for those who~~ after informed decision making between patients and clinicians which includes consideration of the patient's overall health, prior screening history, and preferences.

~~A) Are healthy enough to undergo treatment if colorectal cancer is detected, and~~
~~B) Do not have comorbid conditions that would significantly limit their life expectancy.~~

Note: CPT code 96110 (Developmental screening (eg, 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 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 ~~September, 2017~~ ; ~~August 2020 (Cologuard)~~

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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Author Affiliations: Kaiser Permanente Evidence-based Practice Center, Center for Health Research, Kaiser Permanente, Portland, Oregon.

Corresponding Author: Jennifer S. Lin, MD, MCR, Kaiser Permanente Evidence-based Practice Center, The Center for Health Research, Kaiser Permanente Northwest, 3800 N Interstate Ave, Portland, OR 97227 (jennifer.s.lin@kpchr.org).

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Although the incidence of colorectal cancer (CRC) has declined over time, it remains a significant cause of morbidity and mortality in the US. Among all cancers, it is third in incidence and cause of cancer death for both men and women.[1] In addition, cohort trends indicate that CRC incidence is decreasing only for persons 55 years or older.[2] From the mid-1990s until 2013 the incidence of CRC had increased annually by 0.5% to 1.3% in adults aged 40 to 54 years.[2]

In 2016, the US Preventive Services Task Force (USPSTF) recommended screening for CRC starting at age 50 years and continuing until age 75 years (A recommendation). The task force recommended that the decision to screen for CRC in adults aged 76 to 85 years should be based on the individual, accounting for the patient's overall health and prior screening history (C recommendation).[3] To complete screening, this recommendation offered a number of stool-based and direct visualization tests.

This systematic review was conducted to update the previous review[4,5] on the effectiveness, test accuracy, and harms of CRC screening as well as to inform a separate modeling report,[6,7] which together were used by the USPSTF in the process of updating its CRC screening recommendation.

Methods

Scope of Review

This review addressed 3 key questions (KQs), which are listed in **Figure 1**. No major changes were made to the scope of the previous review for the conduct of the current review except for the addition of 2 screening modalities (ie, capsule endoscopy, urine testing), which are not discussed in this article. The full report[9] provides additional details on the methods, results, and contextual issues addressed.

Data Sources and Searches

Ovid MEDLINE, PubMed (publisher-supplied records only), and the Cochrane Central Register of Controlled Trials were searched to locate primary studies informing the key questions (eMethods in the Supplement). Searches included literature published between January 1, 2015, and December 4, 2019. The searches were supplemented with expert suggestions and by reviewing reference lists from other relevant systematic reviews, including the 2016 USPSTF evidence report.[4] Ongoing surveillance was conducted through March 26, 2021, through article alerts and targeted searches of high-impact journals to identify major studies published in the interim that may affect the conclusions or understanding of the evidence. Two new studies were identified[10,11]; however, they did not substantively change the review's interpretation of findings or conclusions and are not discussed further.

Study Selection

Two independent reviewers screened the titles, abstracts, and relevant full-text articles to ensure consistency with a priori inclusion and exclusion criteria (eTable 1 in the Supplement). Included studies were English-language studies of asymptomatic screening populations of individuals 40 years or older who were either at average risk for CRC or not selected for inclusion based on CRC risk factors. Studies that evaluated direct visualization (ie, colonoscopy, flexible sigmoidoscopy, computed tomography [CT] colonography) or currently available stool-based (ie, guaiac fecal occult blood test [gFOBT], fecal immunochemical test [FIT], stool DNA with a FIT [sDNA-FIT]), or serum-based (ie, methylated *SEPT9* gene) tests were included.

For KQ1, randomized clinical trials (RCTs) or nonrandomized controlled intervention studies of CRC screening vs no screening or trials comparing screening tests were included. Included studies needed to report outcomes of CRC incidence, CRC-specific mortality, or all-cause mortality. For tests without trial-level evidence, well-conducted prospective cohort studies were included.

For KQ2, test accuracy studies that used colonoscopy as the reference standard were included. Well-conducted test accuracy studies that used robust registry follow-up for screen-negative participants were also included. Studies whose design was subject to a high risk of bias were excluded, including those studies subject to verification bias, spectrum bias, or both.[12-16]

For KQ3, all trials and observational studies that reported serious adverse events requiring unexpected or unwanted medical attention or resulting in death were included. These events included, but were not limited to, perforation, major bleeding, severe abdominal symptoms, and cardiovascular events. Studies designed to assess for extracolonic findings (ie, incidental findings on CT colonography) and the resultant diagnostic yield and harms of workup were also included.

Data Extraction and Quality Assessment

Two reviewers critically appraised all articles that met inclusion criteria using prespecified quality criteria (eTable 2 in the Supplement).[8] Disagreements about critical appraisal were resolved by consensus. Poor-quality studies (ie, those with methodological shortcomings resulting in a high risk of bias) were excluded. One reviewer extracted descriptive information and outcome data into standardized evidence tables and a second reviewer checked the data for accuracy.

Data Synthesis and Analysis

The results were synthesized by KQ, type of screening test, and study design. For KQ1, the syntheses were organized into 3 main categories: (1) trials designed to assess the effectiveness (intention to screen) of screening tests compared with no screening; (2) observational studies designed to assess the association of receipt of a screening test compared with no screening; and (3) comparative trials of one screening test vs another screening test. Many of the trials comparing screening tests that met inclusion criteria, however, were designed to determine the differential uptake of tests, determine the comparative yield between tests, or both. As such, they were not powered to detect differences in CRC outcomes or mortality (ie, comparative effectiveness) and are not discussed in this article. When data were available, random-effects meta-analyses were conducted using the restricted maximum likelihood method to estimate the pooled incidence rate ratio (IRR).

For KQ2, the analyses primarily focused on per-person test accuracy of a single test application to detect CRC, advanced adenomas, advanced neoplasia, and adenomas by size (≥6 mm or ≥10 mm). When possible, data from contingency tables was analyzed using a bivariate model, which modeled sensitivity and specificity simultaneously. Although studies evaluating stool-based tests using

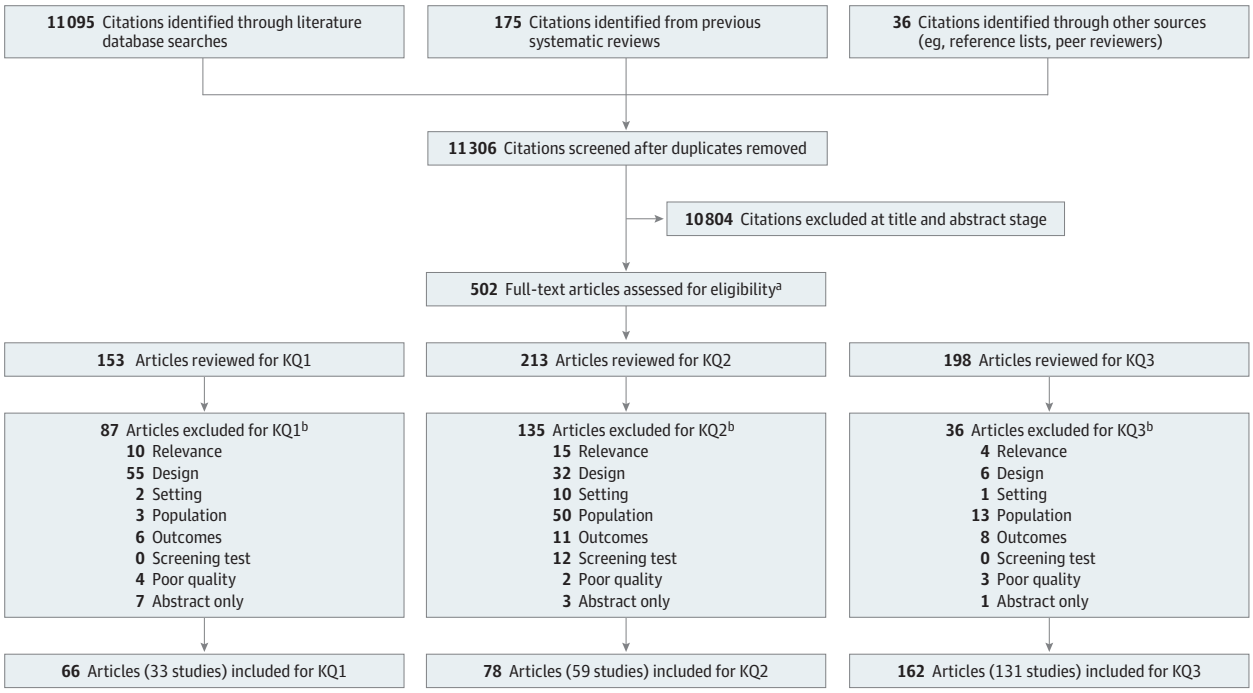
Figure 1. Analytic Framework: Screening for Colorectal Cancer

Evidence reviews for the US Preventive Services Task Force (USPSTF) use an analytic framework to visually display the key questions that the review will address to allow the USPSTF to evaluate the effectiveness and safety of a preventive service. The questions are depicted by linkages that relate interventions and outcomes. Additional Information available in the USPSTF Procedure Manual.[8] FIT indicates fecal immunochemical test; gFOBT, guaiac-based fecal occult blood test; m*SEPT9*, methylated septin 9 gene; sDNA test, stool DNA test; SSP, sessile serrated polyp.

[a] Screening technology with conditional approval from the US Food and Drug Administration for screening for colorectal cancer.

[b] Screening modality not discussed in this article.

Figure 2. Literature Search Flow Diagram: Screening for Colorectal Cancer



KQ indicates key question.

[a] Articles could be reviewed for more than 1 KQ.

[b] Reasons for exclusion: Relevance: Study aim not relevant. Design: Study did not use an included design. Setting: Study not conducted in a country relevant to US practice or not conducted in, recruited from, or feasible for primary care or a health system. Population: Study not conducted in an included population. Outcomes: Study did not have relevant outcomes or had incomplete outcomes. Screening test: Screening test was out of scope. Quality: Study was poor quality. Abstract only: Full-text publication not available.

a colonoscopy reference standard for all persons and studies using a registry follow-up for screen-negative persons were included, only results from the former study design are detailed in this article. For the FITs, random-effects meta-analyses were conducted by test "family" (ie, tests produced by the same manufacturer, using the same components and method and compatible automated analyzers) and by cutoff values (in μg Hb/g feces).

For KQ3, there were no hypothesized serious harms for stool-, blood-, or serum-based tests beyond test inaccuracy and harms accrued from subsequent colonoscopy. Harms for direct visualization tests were categorized by indication (ie, screening vs follow-up for an abnormal flexible sigmoidoscopy or stool test). For colonoscopy and flexible sigmoidoscopy, random-effects meta-analyses using the DerSimonian and Laird method were conducted to estimate rates of perforation and major bleeding.

All quantitative analyses were conducted in Stata version 16 (StataCorp). The presence of statistical heterogeneity was assessed among pooled studies using the I^2 statistic. All tests were 2-sided, with $P < .05$ indicating statistical significance.

The aggregate strength of evidence (ie, high, moderate, or low) was subsequently assessed for each KQ using the approach described in the Methods Guide for the Effectiveness and Comparative Effectiveness Reviews,[17] based on consistency, precision, reporting bias, and study quality.

Results

Investigators reviewed 11 306 unique citations and 502 full-text articles for all KQs (**Figure 2**). Overall, 196 studies reported in 255 publications were included, 70 of which were newly identified since the prior review. A full list of included studies by KQ is available in the Supplement.

Benefits of Screening

Key Question 1. What is the effectiveness or comparative effectiveness of screening in reducing colorectal cancer, mortality, or both?

Thirty-three unique fair- to good-quality studies (n = 10 776 276)[18-50] (published in 66 articles[18-83]) were included to assess the effectiveness or comparative effectiveness of screening tests on CRC incidence and mortality. These included 2 prospective cohort studies[37,47] (n = 436 927) that examined the effectiveness of screening colonoscopy, 4 RCTs[19,24,29,35] (n = 458 002) that examined the effectiveness of flexible sigmoidoscopy with or without a FIT, 6 trials[20,21,27,36,38,39] (n = 525 966) that examined the effectiveness of a gFOBT, and 1 prospective cohort study[46] (n = 5 417 699) that examined the effectiveness of a FIT. In addition to 1 screening RCT[19] (n = 98 678) that evaluated flexible sigmoidoscopy plus FIT vs flexible sigmoidoscopy alone, 20

Table 1. Key Question 1: Overall Summary of Impact of Screening vs No Screening on Colorectal Cancer Incidence and Mortality

Screening test (sample No.)	No. of studies (participants)	Rounds (intervals)	Follow-up, y	CRC incidence	CRC mortality
Colonoscopy[37,47]	2 cohort studies[a] (n = 436 927)	1	8-24[b]	With polypectomy: HR, 0.53 (95% CI, 0.40 to 0.71)[c] Negative colonoscopy result: HR, 0.47 (95% CI, 0.39 to 0.57)[c] Age 70-74 y: RD, −0.42% (95% CI, −0.24% to −0.63%)[d] Age 75-79 y: RD, −0.14% (95% CI, −0.41% to −0.16%)[d]	HR, 0.32 (95% CI, 0.24 to 0.45)[c]
Flexible sigmoidoscopy[19,24,29,35]	4 RCTs[a] (n = 458 002)	1-2 (every 3-5 y)	11-17	IRR, 0.78 (95% CI, 0.74 to 0.83)	IRR, 0.74 (95% CI, 0.68 to 0.80)
Hemoccult II[20,21,27,36,39]	5 RCTs[e] (n = 419 966)	2-9 (every 2 y)	11-30	RR range, 0.90 (95% CI, 0.77 to 1.04) to 1.02 (95% CI, 0.93 to 1.12)	RR range, 0.78 (95% CI, 0.65 to 0.93) to 0.91 (95% CI, 0.84 to 0.98)[f]
FIT[46]	1 cohort study[a] (n = 5.4 million)	Every 2 y	6 (mean, 3)	NR	RR, 0.90 (95% CI, 0.84 to 0.95)

Abbreviations: CRC, colorectal cancer; FIT, fecal immunochemical test; HR, hazard ratio; IRR, incidence rate ratio; NR, not reported; RCT, randomized clinical trial; RD, risk difference; RR, relative risk.

[a] Includes newly identified studies or newly identified articles with additional follow-up to a previously included study.

[b] Twenty-two–year follow-up for incidence; 24-year follow-up for mortality.

[c] Adjusted for age, body mass index, family history, smoking status, physical activity, diet, vitamin use, aspirin use, nonsteroidal anti-inflammatory drug use, cholesterol-lowering drug use, hormone replacement therapy.

[d] Standardized 8-year risk.

[e] One RCT in Finland that only has interim follow-up is not represented in this table (n = 360 492).

[f] Annual RR from 1 trial only, 0.68 (95% CI, 0.56-0.82); 11 rounds every 1 year, 30-year follow-up.

studies[18,22,23,25,26,28,30-34,40-45,48-50] (n = 471 860) that compared screening modalities were included. The magnitude of benefit in CRC mortality and cancer incidence among screening tests could not be directly compared because of major differences in the design of included studies for each test type (eg, trial vs observational study, intention to screen vs as screened, outcome metric reported). No studies were found evaluating the effectiveness of CT colonography, high-sensitivity gFOBT, sDNA with or without FIT, or serum tests on CRC incidence, CRC mortality, or both.

Colonoscopy

Two large, prospective observational studies[37,47] (n = 436 927) evaluating the association of receipt of screening colonoscopy with CRC incidence or mortality were included (**Table 1**). After 24 years of follow-up, 1 study among health professionals (n = 88 902) found that the CRC-specific mortality rate was lower in people who self-reported at least 1 screening colonoscopy compared with those who had never had a screening colonoscopy (adjusted hazard ratio, 0.32 [95% CI, 0.24-0.45]).[37] This study found that screening colonoscopies were associated with lower CRC mortality from both distal and proximal cancers. Another study conducted among Medicare beneficiaries (n = 348 025) with much shorter follow-up found that people aged 70 to 74 years who underwent a screening colonoscopy had a lower 8-year standardized risk for CRC (−0.42% [95% CI, −0.24% to −0.63%]) than those who did not undergo the test.[47]

Flexible Sigmoidoscopy

Four well-conducted trials[19,24,29,35] (n = 458 002) of 1- or 2-time flexible sigmoidoscopy screening that demonstrated a reduction in CRC incidence and mortality were included (Table 1). All 4 trials were included in the previous review. While 3 of these trials have published longer follow-up since the previous review,[19,24,29] the new data did not change the conclusions on screening effectiveness. Based on 4 RCTs that used intention-to-screen analyses, 1- or 2-time flexible sigmoidoscopy was consistently associated with a decrease in CRC incidence (IRR, 0.78 [95% CI, 0.74-0.83], with 28 to 47 fewer CRC cases per 100 000 person-years) and CRC-specific mortality (IRR, 0.74 [95% CI, 0.68-0.80], with 10 to 17 fewer CRC deaths per 100 000 person-years) when compared with no screening at 11 to 17 years of follow-up (eFigure 1 in the Supplement).

Guaiac Fecal Occult Blood Test

Six well-conducted trials[20,21,27,36,38,39] (n = 780 458) of biennial or annual gFOBT screening that demonstrated a reduction in CRC incidence and mortality were included (Table 1). Based on 5 RCTs[20,21,27,36,39] (n = 419 966) that used intention-to-screen analyses, biennial screening with Hemoccult II (Beckman Coulter) was associated with a reduction of CRC-specific mortality compared with no screening after 2 to 9 rounds of screening at 11 to 30 years of follow-up (relative risk [RR], 0.91 [95% CI, 0.84-0.98] at 19.5 years; RR, 0.78 [95% CI, 0.65-0.93] at 30 years) (eTable 3 in the Supplement). One additional trial[38] of screening with Hemoccult II in Finland (n = 360 492) reported only interim findings, with a follow-up of 4.5 years.

Fecal Immunochemical Test

Although many observational studies have evaluated national FIT screening programs, only 1 prospective observational study[46] (n = 5 417 699) that evaluated receipt of FIT on CRC incidence, CRC mortality, or both met the inclusion criteria (Table 1). This study found that 1 to 3 rounds of screening with a biennial FIT (OC-Sensor [Eiken Chemical] or HM JACK [Kyowa Medex]) were associated with lower CRC mortality at 6 years' follow-up, compared with no screening (adjusted RR, 0.90 [95% CI, 0.84-0.95]).[46]

Comparative Effectiveness

In 1 flexible sigmoidoscopy screening RCT (n = 98 678), compared with persons in the no screening group, persons in the flexible sigmoidoscopy plus FIT group had lower risk of CRC-specific mortality than those in the flexible sigmoidoscopy–only group (age-adjusted

Table 2. Key Question 2: Summary of Test Accuracy Results for Direct Visualization Screening Tests[a]

Screening test group	No. of studies	No. of participants	CRC Sensitivity (95% CI)	Adenomas ≥10 mm Sensitivity (95% CI)	Adenomas ≥10 mm Specificity (95% CI)	Adenomas ≥6 mm Sensitivity (95% CI)	Adenomas ≥6 mm Specificity (95% CI)
Flexible sigmoidoscopy	0	NA	NA	NA	NA	NA	NA
CT colonography[b]	7	5328	0.86-1.0 (0.21-1.0)	0.89 (0.83-0.96)	0.94 (0.89-1.0)	0.86 (0.78-0.95)	0.88 (0.83-0.95)
Colonoscopy	4	4821	0.18-1.0 (0.01-1.0)	0.89-0.95 (0.70-0.99)	0.89 (0.86-0.91)[c]	0.75-0.93 (0.63-0.96)	0.94 (0.92-0.96)[c]

Abbreviations: CRC, colorectal cancer; CT, computed tomography; NA, not available.

[a] Pooled estimates from meta-analysis when available; otherwise, range of values and range of the 95% CI reported.

[b] Test accuracy shown for CT colonography with bowel preparation only. Two additional studies without bowel preparation are not represented in this table.

[c] Only 1 study reported specificity.

hazard ratio, 0.62 [95% CI, 0.42-0.90] vs 0.84 [95% CI, 0.61-1.17]), although this difference was not statistically significant.[19] Additional included trials were primarily designed to evaluate the comparative uptake/adherence, test positivity, and initial cancer detection of one screening test vs another. Several adequately powered studies currently underway are evaluating the comparative effectiveness of direct visualization vs stool-based screening programs (eTable 4 in the Supplement).

Findings by Age, Sex, and Race/Ethnicity

Overall, age stratified analyses from flexible sigmoidoscopy and gFOBT trials did not demonstrate statistically significant differences in benefit in older vs younger adults, although age strata used were not consistent across trials. Only 3 gFOBT studies included adults younger than 50 years at recruitment, and none of these studies provided age-stratified analyses for this age group.[27,36,39] One study evaluating receipt of screening colonoscopy among Medicare beneficiaries did not find a benefit in 8-year standardized risk for CRC in those aged 75 to 79 years, in contrast to the benefit seen in those aged 70 to 74 years.[47] Reductions in CRC incidence (eFigure 2 in the Supplement) and mortality (eFigure 3 in the Supplement) from flexible sigmoidoscopy trials were greater for men than for women. This evidence, however, was less consistent in 3 trials that reported sex differences for gFOBT screening programs.

Accuracy of Screening

Key Question 2. What is the accuracy of direct visualization, stool-based, or serum-based screening tests for detecting colorectal cancer, advanced adenomas, or adenomatous polyps based on size?

Fifty-nine studies[84-142] (n = 3 491 045) (published in 78 articles[84-161]) that evaluated the accuracy of various screening tests were included. There were no new studies published since the prior review that would add to the understanding of screening sensitivity or specificity for colonoscopy, CT colonography, or flexible sigmoidoscopy. New studies were identified that evaluated the sensitivity and specificity of stool-based (ie, high-sensitivity gFOBT, FIT, sDNA-FIT) and serum-based tests for screening.

Colonoscopy and CT Colonography

Nine fair- to good-quality studies[102,105,110,111,114,117,121,128,138] (n = 6497) that evaluated screening CT colonography were included, 4 of which (n = 4821) also reported the test accuracy of colonoscopy (**Table 2**).[110,111,128,138] 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.

Based on 3 studies[111,128,138] (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.[138]

Based on 7 studies[105,110,111,114,117,121,128] (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) (eFigure 4 in the Supplement). 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) (eFigure 5 in the Supplement). Although there was some variation in estimates of sensitivity and specificity among included studies, it remains unclear whether the variation of test performance was due to differences in study design, populations, CT colonography imaging, reader experience, or reading of protocols.

High-Sensitivity gFOBT

Two[84,133] (n = 3503) of the 5 studies that evaluated Hemoccult Sensa (Beckman Coulter) applied a colonoscopy reference standard to all persons (**Table 3**). In these 2 studies, the sensitivity to detect CRC ranged from 0.50 to 0.75 (95% CI range, 0.09-1.0) and specificity ranged from 0.96 to 0.98 (95% CI range, 0.95-0.99). Hemoccult Sensa was not sensitive to detect advanced adenocarcinoma (sensitivity range, 0.06-0.17; 95% CI range, 0.02-0.23).

Fecal Immunochemical Test

There are a wide variety of FITs available. Those most commonly evaluated in this review were part of the OC-Sensor family (Eiken Chemical; includes tests OC FIT-CHEK, OC-Auto, OC-Micro, OC-Sensor, and OC-Sensor Micro) or the OC-Light test (by the same manufacturer but using a different methodology) (Table 3). Based on 9 studies[89,97,100,107,108,113,127,130,133] (n = 34 352) that used OC-Sensor tests to detect CRC with a colonoscopy reference standard

Table 3. Key Question 2: Summary of Test Accuracy Results From Studies With Colonoscopy Follow-up for Stool and Serum Screening Tests[a]

Screening test group	No. of studies	No. of participants	CRC		Advanced neoplasia		Advanced adenoma	
			Sensitivity (95% CI)	Specificity (95% CI)	Sensitivity (95% CI)	Specificity (95% CI)	Sensitivity (95% CI)	Specificity (95% CI)
High-sensitivity gFOBT: Hemoccult Sensa	2[b]	3503	0.50-0.75 (0.09-1.0)	0.96-0.98 (0.95-0.99)	0.07-0.21 (0.02-0.27)	0.96-0.99 (0.96-0.99)	0.06-0.17 (0.02-0.23)	0.96-0.99 (0.96-0.99)
FIT								
OC-Sensor	13[b,c]	44 887	0.74 (0.64-0.83)	0.94 (0.93-0.96)	0.25 (0.21-0.31)	0.96 (0.95-0.97)	0.23 (0.20-0.25)	0.96 (0.95-0.97)
OC-Light	4[b]	32 424	0.81 (0.70-0.91)	0.93 (0.91-0.96)	0.27 (0.16-0.38)	0.95 (0.92-0.98)	0.28 (0.19-0.37)	0.94 (0.91-0.97)
Other	12[b,c]	53 527	0.50-0.97 (0.09-1.00)	0.83-0.97 (0.82-0.97)	0.02-0.66 (0.01-0.99)	0.60-0.99 (0.58-1.0)	0.18-0.50 (0.13-0.56)	0.85-0.98 (0.84-0.98)
mtsDNA-FIT: Cologuard	4[b]	12 424	0.93 (0.87-1.0)	0.85 (0.84-0.86)	0.47 (0.44-0.50)	0.89 (0.87-0.92)	0.43 (0.40-0.46)	0.89 (0.86-0.92)
Serum: Epi proColon	1	6857	0.68 (0.53-0.80)	0.79 (0.77-0.81)	0.25 (0.22-0.28)	0.79 (0.76-0.82)	0.22 (0.18-0.24)	0.79 (0.76-0.82)

Abbreviations: CRC, colorectal cancer; FIT, fecal immunochemical test; gFOBT, guaiac fecal occult blood test; mtsDNA, multitargeted stool-based DNA.

[a] Pooled estimates and 95% CI from meta-analysis when available; otherwise, range of values and range of the 95% CIs reported.

[b] Includes newly identified studies.

[c] One nested case-control study[104] (n = 516) is not represented in this table.

and the manufacturer-recommended cutoff of 20 µg Hb/g feces, pooled sensitivity was 0.74 (95% CI, 0.64 to 0.83; I^2 = 31.6%) and pooled specificity was 0.94 (95% CI, 0.93-0.96; I^2 = 96.6%) (eFigure 6 in the Supplement). As expected at lower cutoffs (10 and 15 µg Hb/g feces), the sensitivity increased and the corresponding specificities decreased. Based on 10 studies[89,91,97,100,107,108,113,127,130,133] (n = 40 411) that used OC-Sensor tests to detect advanced adenocarcinoma with a colonoscopy reference standard, sensitivity using a cutoff of 20 µg Hb/g feces was 0.23 (95% CI, 0.20-0.25; I^2 = 47.4%) and specificity was 0.96 (95% CI, 0.95-0.97; I^2 = 94.8) (eFigure 7 in the Supplement). Based on 3 studies[95,96,98] (n = 31 803), OC-Light had similar sensitivity and specificity to detect CRC and advanced adenocarcinoma compared with OC-Sensor.

sDNA (With or Without FIT)

The only available sDNA screening test includes a FIT assay marketed as Cologuard (Exact Sciences), which is sometimes referred to as a multitarget stool DNA test. Based on 4 studies[99,108,130,142] (n = 12 424) to detect CRC using a colonoscopy, pooled sensitivity was 0.93 (95% CI, 0.87-1.0) and pooled specificity was 0.85 (95% CI, 0.84-0.86); to detect advanced adenoma, pooled sensitivity was 0.43 (95% CI, 0.40-0.46) and pooled specificity was 0.89 (95% CI, 0.86-0.92) (Table 3; eFigure 8 in the Supplement).

Serum Test

Currently, one serum test—Epi proColon (Epigenomics)—is available to screen average-risk adults for CRC through detection of circulating methylated *SEPT9* DNA. Based on 1 fair-quality nested case-control study[129] (n = 6857), sensitivity to detect CRC was 0.68 (95% CI, 0.53-0.80) and specificity was 0.79 (95% CI, 0.77-0.81) (Table 3). The sensitivity to detect advanced adenoma was 0.22 (95% CI, 0.18-0.24) and specificity was 0.79 (95% CI, 0.76-0.82).

Findings by Age, Sex, and Race/Ethnicity

While FIT studies that examined differences in test accuracy by age, sex, or race/ethnicity were limited, no consistent differences by subgroup were found. Overall, in 10 studies there were no significant differences in test accuracy by age strata, including 2 studies reporting stratified analyses for persons younger than 50 years; however, 2 studies suggested possible lower specificity to detect CRC in older persons (70 years or older). Six studies reported test accuracy by sex and produced inconsistent findings. One OC-Sensor study reported no difference in test accuracy for advanced neoplasia in Black vs White participants.[99]

The largest study[108,162] on sDNA-FIT reported test accuracy by age, sex, and race/ethnicity groups, although this study was not designed to examine these differences. This study found that the specificity to detect CRC and advanced adenoma decreases as age increases, but there was not a clear pattern for increasing sensitivity with increasing age. Findings were inconsistent in 2 studies that reported test accuracy for White participants compared with Black participants.

Harms of Screening

Key Question 3. What are the serious harms of the different screening tests?

One hundred thirty-one fair- or good-quality studies[18-29,33-36,43,47,49,102,105,110,114,117,128,131,138,163-266] (published in 162 articles[18-29,33-36,43,47,49,51-54,56-58,60,61,64,65,68,69,71-80,102,105,110,114,117,128,131,138,143,163-273]) were included. Among these, 18 studies[19,22,24,28,29,33-35,49,203,206,212,216,234,235,239,254,260] (n = 395 077) evaluated serious harms from screening flexible sigmoidoscopy; 67 studies[26,43,47,163,164,166,168,171,172,174,179,180,182-189,191-195,197-199,201,203-205,210,213,215-218,226,229,231,233,237-252,255,256,258,261-266] (n = 25 784 107) evaluated screening colonoscopy; 21 studies[19-21,24,26,27,29,34-36,49,169,172,173,175-177,181,225,227,236] (n = 903 872) evaluated colonoscopy following an abnormal result from a stool test, flexible sigmoidoscopy, or CT colonography; and 38 studies[18,23,43,102,105,110,114,117,128,138,165,167,170,178,189,190,196,200,202,203,207-211,214,219-224,228,230,232,253,257,259] (n = 140 607) evaluated CT colonography. Of the studies evaluating CT colonography, 7 studies[102,105,117,138,202,203,253] (n = 3365) provided estimates of radiation exposure and 27 studies[18,23,43,110,128,138,165,167,170,178,200,207-211,214,219-224,230,232,257,259] (n = 48 235) reported extracolonic findings. While no studies examined the harms of stool or serum testing, there are not hypothesized serious harms for these noninvasive tests

Table 4. Key Question 3: Summary of Serious Harms and Extracolonic Findings From Screening

Modality	Outcome	No. of studies	No. of participants	Events per 10 000 procedures (95% CI)
Screening flexible sigmoidoscopy	Serious bleeding	10	179 854	0.50 (0.0-1.30)
	Perforation	11	359 679	0.20 (0.10-0.40)
Screening colonoscopy	Serious bleeding	20	5 172 508	14.6 (9.4-19.9)
	Perforation	26	5 272 600	3.1 (2.3-4.0)
Colonoscopy following abnormal stool test result	Serious bleeding	11	78 793	17.5 (7.6-27.5)
	Perforation	12	341 922	5.4 (3.4-7.4)
Colonoscopy following abnormal flexible sigmoidoscopy result	Serious bleeding	4	5790	20.7 (8.2 to 33.2)
	Perforation	4	23 022	12.0 (7.5 to 16.5)
CT colonography	Radiation exposure	7	NA	≈1 to 5 mSv per examination
	ECF	27	48 235	E4: 3.4%-26.9% of CT colonography examinations; E3: 1.3%-11.4% of CT colonography examinations[a]

Abbreviations: CT, computed tomography; ECF, extracolonic finding; NA, not available.

[a] Based on CT Colonography Reporting and Data System categorization of ECFs, where E3 = likely unimportant or incompletely characterized finding for which workup may be required and E4 = potentially important finding requiring follow-up.[274]

other than diagnostic inaccuracy (ie, false-positive or false-negative test results) or downstream harms of follow-up tests.

Serious adverse events from colonoscopy among screening populations were estimated at 3.1 perforations (95% CI, 2.3-4.0) per 10 000 procedures (26 studies, n = 5 272 600) and 14.6 major bleeding events (95% CI, 9.4-19.9) per 10 000 procedures (20 studies, n = 5 172 508) (**Table 4**). Serious adverse events from screening flexible sigmoidoscopy alone were less common, with a pooled estimate of 0.2 perforations (95% CI, 0.1-0.4) per 10 000 procedures (11 studies, n = 359 679) and 0.5 major bleeding events (95% CI, 0-1.3) per 10 000 procedures (10 studies, n = 179 854). However, for colonoscopies following flexible sigmoidoscopy with abnormal findings, the pooled estimates were 12.0 perforations (95% CI, 7.5-16.5) per 10 000 colonoscopy procedures (4 studies, n = 23 022) and 20.7 major bleeding events (95% CI, 8.2-33.2) per 10 000 colonoscopy procedures (4 studies, n = 5790). Serious adverse events from colonoscopy following stool testing with an abnormal result were estimated at 5.4 perforations (95% CI 3.4-7.4) per 10 000 colonoscopy procedures (12 studies, n = 341 922) and 17.5 serious bleeding events (95% CI, 7.6-27.5) per 10 000 colonoscopy procedures (11 studies, n = 78 793). Other harms which may result from screening, such as cardiopulmonary events or infections, are best assessed using comparative study designs. Only 4 studies[47,187,191,262] (n = 4 173 949) reported harms in a cohort that received colonoscopy compared with a cohort that did not. These studies did not find a higher risk of serious harms associated with colonoscopy.

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 (eTable 5 in the Supplement) (27 studies, n = 48 234). Approximately 1.3% to 11.4% of CT colonographies had potentially important extracolonic findings (CT Colonography Reporting and Data System [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).

Findings by Age, Sex, and Race/Ethnicity

Twenty-three studies provided analyses of differential harms of colonoscopy by age. These studies generally found increasing rates of serious adverse events with increasing age, including perforation and bleeding. Sex differences in serious harms, when reported in 12 studies, suggested little differential risk between men and women. There were inconsistent findings in 4 studies that report harm stratified by race/ethnicity.

In 4 studies, extracolonic findings on CT colonography were more common with increasing age.[110,208,209,211] Three studies reported extracolonic findings by sex, finding similar rates of extracolonic findings in both groups.[207,219,221]

Discussion

This systematic review assessed the effectiveness, test accuracy, and harms of CRC screening. A summary of the identified evidence is shown in **Table 5**. Since the 2016 USPSTF recommendation, more evidence has been published on the effectiveness and test accuracy of newer stool tests (FIT and sDNA-FIT) and the test accuracy of a US Food and Drug Administration–approved serum test (Epi proColon) for use in persons declining colonoscopy, flexible sigmoidoscopy, gFOBT, or FIT. More data on colonoscopy harms have also been published that reported higher estimates of major bleeding than previously appreciated. Overall, the different screening tests evaluated have different levels of evidence to demonstrate their ability to reduce cancer mortality and to detect cancer, precursor lesions, or both as well as their risk of serious adverse events.

Table 5. Summary of Evidence

Instrument or treatment	Study design (No. of observations)	Summary of findings	Consistency and precision	Other limitations	Strength of evidence	Applicability
KQ1: Benefits of screening						
Flexible sigmoidoscopy	4 RCTs (n = 458 002)	One- or 2-time flexible sigmoidoscopy decreased CRC mortality compared with no screening at 11-17-y follow-up (IRR, 0.74 [95% CI, 0.68-0.80])	Consistent, precise	Only PLCO evaluated more than 1 round of screening Variation in referral criteria led to differing rates of follow-up colonoscopy	High	No longer widely used in the US No studies included people younger than 50 y
Colonoscopy	2 Cohort studies (n = 436 927)	One study found CRC mortality was lower in people with at least 1 screening colonoscopy vs those who never had a screening colonoscopy after 24-y follow-up (adjusted HR, 0.32 [95% CI, 0.24-0.45]) Another study in people aged 70-74 y found CRC incidence was lower in people who had a screening colonoscopy vs those who did not after 8 y (standardized risk, 0.42% [95% CI, 0.24%-0.63%])	Consistent, imprecise	Variation in underlying risk for CRC, length of follow-up, and outcomes reported (only 1 study reported CRC mortality)	Low	Studies limited to health professionals and older adults Based on subgroup analyses, findings not applicable to people with first-degree relatives with CRC or to adults aged 75-79 y One study included people younger than 50 y
gFOBT	6 RCTs (n = 780 458)	Biennial screening with Hemoccult II decreased CRC-specific mortality compared with no screening after 2-9 rounds of screening at 11-30 y of follow-up (RR range, 0.91 [95% CI, 0.84-0.98] at 19.5 y to 0.78 [95% CI, 0.65-0.93] at 30 y) One trial in Finland (n = 360 492) reported only interim findings, with a follow-up of 4.5 y	Consistent, precise	Variation in number of screening rounds, use of rehydrated samples, definition of test positive, and recommended follow-up	High	Hemoccult II no longer widely used in US Three trials included people younger than 50 y
FIT	1 Cohort study (n = 5 417 699)	One to 3 rounds of biennial FIT were associated with lower CRC mortality compared with no screening at up to 6 y follow-up (adjusted RR, 0.90 [95% CI, 0.84-0.95])	NA	Limited follow-up (mean, 3 y)	Low	Study conducted in Taiwan FITs used include OC-Sensor and HM JACK Did not include participants younger than 50 y
Comparative effectiveness	20 RCTs (n = 386 711) 1 Cohort study (n = 85 149)	Trials comparing different screening tests do not provide evidence of comparative benefit on CRC incidence or mortality outcomes[a] Limited data suggest that 4 rounds of FIT detects a similar number of cancers as 1-time colonoscopy or flexible sigmoidoscopy; FIT can detect more cancers than Hemoccult II; 2-sample FIT does not appear superior to 1-sample FIT; and no statistically significant differences in cancer detection after 1-2 rounds of testing between FITs, despite differences in test positivity	Inconsistent, imprecise	Few trials powered to detect effect of screening on mortality; limited to a single round of screening Overall low number of cancers detected, and few interval cancers reported	Insufficient	No studies evaluating comparative effectiveness of capsule endoscopy, sDNA, serum, or urine tests No studies included people younger than 50 y

(continued)

Table 5. Summary of Evidence (continued)

Instrument or treatment	Study design (No. of observations)	Summary of findings	Consistency and precision	Other limitations	Strength of evidence	Applicability
KQ2: Accuracy of screening						
Colonoscopy	4 Studies, colonoscopy + CT colonography reference standard (n = 4821)	CRC: Sensitivity range, 0.18 to 1.0 (95% CI range, 0.01 to 1.0) Adenoma ≥10 mm: Sensitivity range, 0.89 to 0.95 (95% CI range, 0.74 to 1.0); specificity, 0.89 (95% CI, 0.86-0.91) Adenoma ≥6 mm: Sensitivity range, 0.75 to 0.93 (95% CI range, 0.63 to 0.96); specificity, 0.94 (95% CI, 0.92-0.96)	Consistent, imprecise	Studies not designed to assess test accuracy to detect cancers Specificity could only be calculated from 1 study	Moderate	Colonoscopies were conducted or supervised by "experienced" specialists Two studies included people younger than 50 y (1 only if they had a family history)
CT colonography	9 Studies, colonoscopy + CT colonography reference standard (n = 6497)	CRC:[b] Sensitivity range, 0.86 to 1.0 (95% CI range, 0.21 to 1.0) Adenoma ≥10 mm:[b] Sensitivity, 0.89 (95% CI, 0.83-0.96; I^2 = 41.7%); specificity, 0.94 (95% CI, 0.89-1.0; I^2 = 98.3%) Adenoma ≥6 mm:[b] Sensitivity, 0.86 (95% CI, 0.78-0.95; I^2 = 87.4%); specificity, 0.88 (95% CI, 0.83-0.95; I^2 = 94.9%)	CRC: consistent, imprecise Adenomas: consistent, precise	Studies not designed to assess test accuracy to detect cancers Unclear if variation in test performance is attributable to differences in study design, population, CT colonography imaging, or reader experience or reading protocols	Moderate	Estimates apply to CT colonography with full bowel prep Mostly single-center studies using limited number of highly trained radiologists; current practice may use lower doses of radiation (and therefore different technology/protocols) Four studies included people younger than 50 y (2 only if they had a family history)
High-sensitivity gFOBT	2 Studies, colonoscopy reference standard (n = 3503) 3 Studies, registry reference standard (n = 15 969)	CRC: Sensitivity range, 0.50 to 0.75 (95% CI range, 0.09 to 1.0); specificity range, 0.96 to 0.98 (95% CI range, (0.95 to 0.99) Advanced adenoma: sensitivity range, 0.06 to 0.17 (95% CI range, 0.02 to 0.23); specificity range, 0.96 to 0.99 (95% CI range, 0.96 to 0.99) Estimates for sensitivity to detect CRC were slightly higher in studies using differential reference standard (registry follow-up)	Inconsistent, imprecise	Only 2 studies without verification bias, with varying estimates	Low	Estimates apply to Hemoccult SENSA; test is no longer widely used in the US and requires 3 stool samples and dietary restrictions Did not include people younger than 50 y
FIT	25 Studies, colonoscopy reference standard (n = 122 370) 18 Studies, registry reference standard (n = 2 824 358)	CRC:[c] Sensitivity, 0.74 (95% CI, 0.64-0.83); I^2 = 31.6%; specificity, 0.94 (95% CI, 0.93-0.96); I^2 = 96.6% Advanced adenoma:[c] Sensitivity, 0.23 (95% CI, 0.20-0.25); I^2 = 47.4%; specificity, 0.96 (95% CI, 0.95-0.97); I^2 = 94.8 Estimates for sensitivity to detect CRC were slightly higher in studies using differential reference standard (registry follow-up)	Consistent, precise	Other than OC-Sensor and OC-Light, FITs were not evaluated in more than a single study using colonoscopy reference standards	High	Estimates apply to OC-Sensor family of FITs using manufacturer recommended cutoff[d] OC-Light has similar sensitivity and specificity to OC-Sensor Ten studies included people younger than 50 y No differences in test accuracy by age

(continued)

Table 5. Summary of Evidence (continued)

Instrument or treatment	Study design (No. of observations)	Summary of findings	Consistency and precision	Other limitations	Strength of evidence	Applicability
sDNA	4 Studies, colonoscopy reference standard (n = 12 424)	CRC: Sensitivity, 0.93 (95% CI, 0.87-1.0); I^2 = 0%; specificity, 0.85 (95% CI, 0.84-0.86); I^2 = 37.7% Advanced adenoma: Sensitivity, 0.43 (95% CI, 0.40-0.46); I^2 = 0%); specificity, 0.89 (95% CI, 0.86-0.92); I^2 = 87.8%	Consistent, precise	Only 1 study adequately powered to detect cancers	Moderate	Estimates apply to Cologuard (sDNA-FIT) In the largest study, 6% of people had inadequate stool samples Two studies included people younger than 50 y
Serum test	1 Study, colonoscopy reference standard (n = 6857)	CRC: Sensitivity, 0.68 (95% CI, 0.53-0.80); specificity, 0.79 (95% CI, 0.77-0.81) Advanced adenoma: Sensitivity, 0.22 (95% CI, 0.18-0.24); specificity, 0.79 (95% CI, 0.76-0.82)	Consistency NA, precise	Single nested case-control study	Low	Estimates apply to Epi proColon, evaluating the m*SEPT9* marker Currently only FDA-approved for people unwilling or unable to be screened by gFOBT, FIT, flexible sigmoidoscopy, or colonoscopy Did not include people younger than 50 y
KQ3: Harms of screening						
Flexible sigmoidoscopy	18 Observational studies (n = 395 077)	Major bleeding: 0.5 (95% CI, 0-1.3) events per 10 000 procedures Perforation: 0.2 (95% CI, 0.1-0.4) events per 10 000 procedures Other serious harms: not routinely reported but cannot be attributed to flexible sigmoidoscopy procedure	Consistent, precise	No studies with control group (no flexible sigmoidoscopy) Possible reporting bias of harms other than bleeding and perforation	Moderate	Reflects community practice, but flexible sigmoidoscopy no longer widely used in US practice No studies included people younger than 50 y
Screening colonoscopy	67 Observational studies (n = 27 746 669)	Major bleeding: 14.6 (95% CI, 9.4-19.9) events per 10 000 procedures Perforation: 3.1 (95% CI, 2.3-4.0) events per 10 000 procedures Other serious harms: in 4 studies with comparator groups, similar or less frequent adverse events in screened vs unscreened group	Consistent, precise	Only 4 studies with unscreened comparison	Moderate	Reflects community practice Twenty-one studies included people younger than 50 y Risk of serious harms appears to increase with age
Colonoscopy after an abnormal CT colonography, flexible sigmoidoscopy, or stool test result	21 Observational studies (n = 903 872)	After abnormal stool test result: Major bleeding: 17.5 (95% CI, 7.6-27.5) events per 10 000 procedures Perforation: 5.4 (95% CI, 3.4-7.4) events per 10 000 procedures Other serious harms: No estimate After abnormal flexible sigmoidoscopy result: Major bleeding: 20.7 (95% CI, 8.2-33.2) events per 10 000 procedures Perforation: 12.0 (95% CI, 7.5-16.5) events per 10 000 procedures Other serious harms: No estimate	Consistent, precise	No studies with unscreened comparison	Moderate	Reflects community practice Two studies after abnormal stool testing included people younger than 50 y

(continued)

Table 5. Summary of Evidence (continued)

Instrument or treatment	Study design (No. of observations)	Summary of findings	Consistency and precision	Other limitations	Strength of evidence	Applicability
CT colonography						
Harms	19 Observational studies (n = 90 133)	Serious harms from CT colonography in asymptomatic people are uncommon The effective dose of radiation per examination ranged from 0.8 to 5.3 mSv	Consistent, imprecise	No studies with control group (no CT colonography) More limited evidence in screening populations at true average risk Possible reporting bias of harms other than perforation	Moderate	Reflects community practice No studies included people younger than 50 y
ECF	27 Observational studies (n = 48 235)	ECFs requiring workup of potentially important findings (E4) occurred in 1.3% to 11.4% of examinations A minority of findings (≤3%) required definitive medical or surgical treatment, and extracolonic cancers were rarely detected (0.35%)	Consistent, imprecise	No studies able to quantify net benefit or harm Studies with varying levels of follow-up, few studies with final disposition of ECF	Low	ECF can be a benefit or a harm Prevalence of ECF appears to increase with age One study included people younger than 50 y

Abbreviations: CRC, colorectal cancer; CT, computed tomography; ECF, extracolonic finding; FDA, US Food and Drug Administration; FIT, fecal immunochemical test; gFOBT, guaiac fecal occult blood test; HR, hazard ratio; IRR, incidence rate ratio; KQ, key question; m*SEPT9*, methylated septin 9 gene; NA, not applicable; PLCO, Prostate, Lung, Colorectal, and Ovarian Cancer Screening Trial; RCT, randomized clinical trial; RR, relative risk; sDNA, stool DNA.

[a] Several adequately powered comparative effectiveness studies are currently underway will evaluate the comparative effectiveness of direct visualization vs stool-based screening programs.

[b] CT colonography with bowel prep results, 7 studies (n = 5328).

[c] FN: OC-Sensor results, 13 studies (n = 44 597).

[d] At lower cutoffs (15 and 10 µg Hb/g feces), the sensitivity for CRC increased (0.92 and 0.99, respectively) and the corresponding specificities decreased (0.92 and 0.90, respectively).

Data from well-conducted population-based screening RCTs demonstrate that intention to screen with Hemoccult II or flexible sigmoidoscopy can reduce CRC mortality. Hemoccult II and flexible sigmoidoscopy, however, are no longer widely used for screening in the US. Newer screening tests with similar sensitivity may result in CRC mortality reductions similar to reductions shown in existing trials. If sensitivity is better, without a trade-off in specificity (eg, various FITs), mortality reductions could be greater.[275] Decision analyses can help understand the trade-offs of false-positive results and optimal intervals of testing for tests that maximize sensitivity with a reduction in specificity (eg, sDNA-FIT). To date, while serum testing has more limited evidence around test accuracy, it has better patient acceptability and adherence than stool-based testing.[276] While CT colonography has evidence to support the adequate detection for precursor lesions greater than or equal to 6 mm (similar to colonoscopy), it may have harms associated with the cumulative exposure of radiation with repeated examinations, the detection of incidental findings, or both.

Adherence to screening remains the biggest challenge to implementation of screening and has consistently lagged behind recommended screenings for other cancers.[277] Adherence to a single round of screening, repeated screening, and follow-up colonoscopy vary across studies, setting, and populations.[278] Differential adherence to screening tests influences the benefits and harms of screening program and may influence the selection of a preferred strategy.

Although the incidence of CRC has been increasing among adults younger than 50 years, there is little empirical evidence evaluating potential differences in the effectiveness of screening, test performance of screening tests, and the harms of screening in adults younger than 50 years. Any differences in the effectiveness of screening at younger ages would be attributable to varying the underlying risk or incidence of CRC, the natural history of disease, or both, as well as differences in test accuracy by age. Limited studies demonstrate no difference in test accuracy of stool testing or harms of colonoscopy in people younger than 50 years. Although it is not hypothesized that colonoscopy or CT colonography are more harmful in younger adults than older adults, initiating screening at an earlier age will accrue more procedural harms and extracolonic findings, which should be weighed against any incremental benefit of earlier start to screening.

Systematic reviews have identified multivariable risk prediction models with adequate discrimination,[279,280] many of which have been externally validated[281,282]; however, they are not commonly used in clinical practice.[279,283] In theory, multivariable risk assessment can identify persons at higher risk for CRC and tailor when to initiate screening.

While several CRC screening trials evaluating colonoscopy, CT colonography, and FIT are underway, future research should also include trials or well-designed cohort studies in average-risk populations to evaluate the effects of new serum- and urine-based tests on cancer mortality and incidence. In addition, future research should include adequate sampling of different populations (by age, family risk, and race/ethnicity) to allow for robust subgroup analyses, use multivariable risk assessment to guide screening, or both. Studies to confirm the screening test performance of FITs with thus-far limited reproducibility would be helpful to offer other FIT alternatives to OC-Sensor and OC-Light. Likewise, test accuracy studies adequately powered for cancer detection to establish or confirm the

screening test performance of promising serum- and urine-based tests are needed to bolster a menu of options for screening that may have greater acceptability and feasibility. In general test accuracy studies to clarify any differential in detection of proximal vs distal test accuracy, and the detection of precursor lesions with more potential for malignant transformation (eg, serrated sessile lesions), would also be informative. In addition, understanding the overall net effect of detection of extracolonic findings may be helped by reporting of the downstream benefits and harms of extracolonic findings in randomized or nonrandomized studies with longer-term follow-up.

Limitations

This review has several limitations. First, it excluded studies in symptomatic people and people with the highest hereditary risk. Second, it included only trials or prospective cohort studies designed to evaluate the association of screening with CRC incidence or mortality. It is possible that excluded well-designed nested case-control studies of colonoscopy or FIT may have lower risk of bias than included prospective cohort studies. Third, although this review addressed some important contextual issues related to screening (eg, adherence to testing, risk assessment to tailor screening, test acceptability and availability), it did not include an assessment of the mechanism of benefit of the different screening tests (primary prevention vs early detection), methods to increase screening adherence, prevalence of interval cancers between screenings, potential harms of overdetection of adenomas or unnecessary polypectomy, technological enhancements to improve the test accuracy of direct visualization, and surveillance after screening.

Conclusions

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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Concept and design: All authors.
Acquisition, analysis, or interpretation of data: All authors.
Drafting of the manuscript: All authors.
Critical revision of the manuscript for important intellectual content: Perdue, Henrikson, Blasi.
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Technical Report

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Prepared by:
The Cancer Intervention and Surveillance Modeling Network (CISNET)
Colorectal Cancer Working Group

Investigators:
Amy B. Knudsen, PhD
Carolyn M. Rutter, PhD
Elisabeth F. P. Peterse, PhD
Anna P. Lietz, BA
Claudia L. Seguin, BA
Reinier G. S. Meester, PhD
Leslie A. Perdue, MPH
Jennifer S. Lin, MD
Rebecca L. Siegel, MPH
V. Paul Doria-Rose, DVM, PhD
Eric J. Feuer, PhD
Ann G. Zauber, PhD
Karen M. Kuntz, ScD
Iris Lansdorp-Vogelaar, PhD

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Structured Abstract

Importance: The U.S. Preventive Services Task Force (USPSTF) is updating its 2016 recommendations for screening for colorectal cancer.

Objective: To provide the USPSTF updated model-based estimates of the benefits, burden, and harms of colorectal cancer screening strategies that vary by the ages to begin and end screening, screening modality, and screening interval. Analyses also identify strategies that may provide an efficient balance of the colonoscopy burden and the life-years gained (LYG) from screening.

Design: Comparative modeling using 3 microsimulation models that simulate outcomes with and without colorectal cancer screening in a hypothetical cohort of previously unscreened average-risk U.S. 40-year-olds with no prior colorectal cancer diagnosis.

Exposures: Screening from ages 45, 50 or 55 years to ages 70, 75, 80, or 85 years with fecal immunochemical testing (FIT), multitarget stool DNA testing (FIT-DNA), flexible sigmoidoscopy (SIG) alone or in conjunction with interval FIT, computed tomographic colonography (CTC), or colonoscopy. Screening intervals varied by modality. All persons with an abnormal non-colonoscopy screening test were assumed to undergo follow up colonoscopy. Full adherence with all screening, follow up, and surveillance procedures was assumed.

Main Outcome and Measures: Estimated LYG relative to no screening (benefit), lifetime number of colonoscopies (burden), lifetime number of complications from screening (harms), and balance of incremental burden and benefit (efficiency ratios). Efficient strategies were those that required fewer additional colonoscopies per LYG, relative to other strategies.

Results: Estimated LYG from screening ranged from 171 to 381 per 1000 40-year-olds. Lifetime colonoscopy burden ranged from 624 to 6817 per 1000 individuals, and screening complications ranged from 5 to 22 per 1000 individuals. Forty-nine screening strategies were found to be efficient options by all 3 models; in 41 of these strategies, screening began at age 45. No single age to end screening was predominant among the efficient strategies, although the estimated increases in LYG from continuing screening after age 75 were generally small. With the exception of a 5-year interval for CTC, no screening interval was predominant among the efficient strategies for each modality. Among the screening strategies highlighted in the 2016 USPSTF colorectal cancer screening recommendations, lowering the age to begin screening from 50 to 45 was estimated to result in 22 to 27 additional LYG, 2 to 3 fewer colorectal cancer cases, and 0.9 to 1 fewer colorectal cancer death, but it was also estimated to result in 0.1 to 2 additional complications, 161 to 784 additional colonoscopies, and 0 (with colonoscopy) to 3553 additional non-colonoscopy tests over the lifetimes of 1000 persons (ranges are across screening strategies, based on mean estimates across the 3 models).

Sensitivity analyses indicated that there was little advantage to customizing screening by race and sex; the estimated numbers of LYG, colonoscopies, and complications were similar across race-sex groups, as were the efficient strategies and their ratios. Scenario analyses demonstrated that efficient strategies were similar across 3 scenarios for the population risk of colorectal cancer, including one in which the assumed risk increase was less conservative than the assumption for the base-case analysis.

The effect of imperfect adherence on outcomes was estimated by comparing strategies with different ages to begin screening (to examine delays in uptake) or with strategies with different screening intervals (to examine delays in rescreening). For example, the models estimated that extending the interval of repeat colonoscopy screening from 10 to 15 years would result in a loss of 22 to 38 life years per 1000, and extending the interval of FIT screening from annual to triennial testing would result in a loss of 28 to 41 life years per 1000.

Limitations: The models do not simulate the serrated polyp pathway to CRC. The models assume that the observed increase in colorectal cancer incidence among 20- to 44-year-olds in recent years is a cohort effect, and that the increase in risk will be carried forward as individuals age. They further assume that the increase in incidence is driven by an increased risk of developing adenomas, as opposed to faster or more frequent progression of adenomas to malignancy.

Conclusions: This comparative modeling study suggests that colorectal cancer screening may lead to sizable reductions in the lifetime risks of developing and dying from colorectal cancer. Many screening strategies are estimated to provide an efficient balance of the burden and benefit of screening; these strategies encompass a range of screening modalities, intervals, and ages. However, when the benefits of screening are measured by the number of LYG, most of the efficient screening strategies identified by all 3 models specified screening starting at age 45. Starting screening at age 45 was generally estimated to result in more LYG and fewer colorectal cancer cases and deaths than similar strategies with screening starting at age 50 or age 55, albeit with a higher lifetime burden of both colonoscopy and non-colonoscopy testing and slightly higher lifetime risks of complications.

Bright Futures as the EPSDT Periodicity Schedule for OHP

Issue: Medicaid programs must provide Early and Periodic Screening, Diagnostic and Treatment (EPSDT) benefits by federal rule. EPSDT provides comprehensive and preventive health care services for children under age 21 who are enrolled in Medicaid. EPSDT is key to ensuring that children and adolescents receive appropriate preventive, dental, mental health, and developmental, and specialty services.

Screening services required under EPSDT include

1) Comprehensive health and developmental history
2) Comprehensive unclothed physical exam
3) Appropriate immunizations (according to the Advisory Committee on Immunization Practices)
4) Laboratory tests (including lead toxicity screening)
5) Health Education (anticipatory guidance including child development, healthy lifestyles, and accident and disease prevention)

Currently, OHA does not have the required periodicity schedule for screening as required for a Medicaid program. HSD plans to adopt a rule which states in part: "Specifies screening services applicable at each stage of the beneficiary's life, beginning with a neonatal examination, up to the age at which an individual is no longer eligible for EPSDT services." HSD has requested that HERC add a reference to GN106 that specifies that Bright Futures is our EPSDT periodicity schedule for the screening portion of EPSDT.

HERC staff recommendation:

1) Modify GN106 to specify that Bright Futures is OHA's periodicity schedule for EPSDT
    a. See modified wording below
    b. Note: proposed wording changes for colon cancer screening from a separate issue are shown 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, 2020.
    1) http://www.uspreventiveservicestaskforce.org/Page/Name/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 http://www.aap.org/en-us/professional-resources/practice-support/Periodicity/Periodicity Schedule_FINAL.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 a**s updated by HRSA in December 2019. Available at https://www.hrsa.gov/womens-guidelines-2019 as of September 4, 2020.

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 ~~50~~ 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 colonoscopy (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 only for those who have a documented share decision making discussion with their clinician which takes into account the patient's overall health, prior screening history, and preferences.

~~A) Are healthy enough to undergo treatment if colorectal cancer is detected, and~~
~~B) Do not have comorbid conditions that would significantly limit their life expectancy.~~

Note: CPT code 96110 (Developmental screening (eg, 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

Smoking Cessation Prior to Elective Surgery
2021 Review

Questions:

1) Should an exception be made to the ancillary guideline A4 requirement for smoking cessation prior to elective procedures for cataract surgery and similar "bloodless surgeries"?
2) Should the smoking cessation prior to elective surgery guideline be removed entirely?
3) Should the location, types of procedures, and anesthesia type used be clarified in anxillary guideline A4?

Question sources:

1) Dr. Julie Falardeau, President, Oregon Academy of Ophthalmology; Dr. Michael Repka, AAO Medical Director for Governmental Affairs
2) Dr. Mark Pasternak, family physician in Coos Bay
3) Providence Health Plan

Issues:

1) Ancillary Guideline A4 requires smoking cessation for 4 weeks prior to elective procedures, other than a few types of procedures specified in the guideline (cancer surgery, reproductive surgery, diagnostic procedures). Cataract removal falls under this guideline and therefore patients must not smoke for 4 weeks prior to undergoing this procedure.

From Dr. Falardeau:

> Several Oregon Academy of Ophthalmology members have reached out to OAO leadership this past week regarding denials of cataract surgery for patients who smoke…While we recognize that smoking cessation is important, OAO believes that patients should not be denied vision-saving procedures based on their smoking habits. Patients with cataracts often experience difficulty safely performing daily activities like driving, managing medication, shopping, and even walking. Our surgeons also recognize that although there are many good reasons for smoking cessation prior to most surgeries, they do not pertain to cataract surgery. Cataract surgery is a bloodless surgery, meaning that the risks associated with smoking and wound healing and blood clots do not apply. As well, there is a lack of evidence linking increased pain and inflammation for smokers who have had cataract surgery.

2) Dr. Pasternak raised concerns about requiring smoking cessation prior to necessary procedures as a bias against smokers and his concerns with the withholding of needed care as leverage for smoking cessation

From Dr. Pasternak

> I was…intrigued by the meaning of "elective surgery" which we have had several discussion of but so far as I can see it simply refers to surgery which is scheduled rather than done on and emergency basis so I asked [ ] to send me a link to guidelines regarding smoking and the abstinence requirement for other procedures such as elective peripheral artery bypass surgery (where most of us know smoking is absolutely critical and cessation can relieve symptom and prevent recurrence before and after) or coronary artery bypass grafting where patient have selected it as an option over stenting or hysterectomy for severe intractable endometriosis. It's odd to see the changing social mores where we are coming to accept active methamphetamine

or heroin use as addictions so users don't have to demonstrate abstinence to treat hepatitis c but smoking is becoming the object of a new temperance movement. Frankly I don't think we should use delay of needed, albeit elective, medical treatment as leverage to enforce healthy habits beyond what is medically supportable.

From the CCO medical directors
The CCO medical directors were unanimous in their desire to see Ancillary Guideline A4 continue. Specific comments include:

> A4 is the single most important decision made by the HERC in the past 4 years…We do deny elective CABG/PCI and PVD interventions and almost universally get patients to quit. Providers/surgeons/cardiologists now mostly appreciate having the insurance company be the bad guy. Several Orthopedic surgeons have adopted this stance for all of their patients as they have seen lower infection rates and better healing.
>
> I have seen this guideline implemented in multiple organizations, and all have an exception process in situations where surgery is clearly necessary and the member is unable to quit despite reasonable attempts. I have seen a lot of providers say that they appreciate the guideline as a backstop to support their recommendations to patients to quit.

Of note, some CCOs noted that they do not enforce the smoking cessation requirement in surgeries that they do not prior authorize, which in some cases include cataract surgery. This may be leading to uneven provider requirements around the state.

3) From Providence Medical Plans:
   I have questions about Ancillary Guideline A4 Smoking Cessation and Elective Surgical Procedures. The guideline does not specify location of surgical procedures.
   1. Would this apply to **any** surgical procedure in a provider's office?
   2. Is this GN intended for those receiving general anesthesia, regional anesthesia or sedation in an ASC or hospital setting?
   If you could clarify the intent of this Guideline, I would be very appreciative.

Current Prioritized List status:

ANCILLARY GUIDELINE A4, SMOKING CESSATION AND ELECTIVE SURGICAL PROCEDURES

Smoking cessation is required prior to elective surgical procedures for active tobacco users. Cessation is required for at least 4 weeks prior to the procedure and requires objective evidence of abstinence from smoking prior to the procedure.

Elective surgical procedures in this guideline are defined as surgical procedures which are flexible in their scheduling because they do not pose an imminent threat nor require immediate attention within 1 month. Procedures for contraceptive/sterilization purposes, procedures targeted to active cancers (i.e. when a delay in the procedure could lead to cancer progression) and diagnostic procedures are not subject to the limitations in this guideline note.

The well-studied tests for confirmation of smoking cessation include cotinine levels and exhaled carbon monoxide testing. However, cotinine levels may be positive in nicotine replacement therapy (NRT) users, smokeless tobacco and e-cigarette users (which are not contraindications to elective surgery coverage). In patients using nicotine products aside from combustible cigarettes the following alternatives to urine cotinine to demonstrate smoking cessation may be considered:

- Exhaled carbon monoxide testing
- Anabasine or anatabine testing (NRT or vaping)

Certain procedures, such as lung volume reduction surgery, bariatric surgery, erectile dysfunction surgery, and spinal fusion have 6 month tobacco abstinence requirements. See Guideline Notes 8, 100, 112 and 159.

Evidence

Smoking cessation and cataract surgery

Searches for cataract surgery and smoking or nicotine found articles identifying smoking as a risk factor for cataract development. No literature was found on smoking as a risk factor for adverse outcomes in cataract surgery.

Smoking as a cause of surgical complications for elective surgeries

1) **MED 2015**, Tobacco Use and Outcomes for Elective Surgery
    a. The preponderance of evidence suggests that preoperative smoking increases the risk of poor surgical outcomes following common elective surgeries. The main findings and overall strength of evidence for the finding are listed below.
        i. Smokers have an increased risk of general morbidity, wound complications, general infections, pulmonary complications, neurological complications, and admission to the intensive care unit (ICU) after undergoing various types of elective surgery (moderate strength of evidence).
        ii. Smokers have an increased risk of dental implant failure following maxillary sinus floor augmentation (moderate strength of evidence).
        iii. Smokers have a higher risk of developing postoperative complications for the following types of dental surgery procedures: subepithelial connective-tissue grafts; guided tissue regeneration; and periodontal flap surgery (low strength of evidence).
        iv. Smokers experience more postoperative complications up to two years after rotator cuff surgery (moderate strength of evidence).
        v. Smokers have higher failure rates following glenoid labrum surgery (very low strength of evidence).
        vi. Smokers experience greater general postoperative complications following total hip arthroplasty (moderate strength of evidence).
        vii. Smokers experience greater long-term failure, cardiac and pulmonary complications, risk of infection, and mortality following total knee arthroplasty (low strength of evidence).
        viii. Smokers have significantly worse postoperative outcomes following coronary artery bypass graft surgery, general elective cardiac surgery, and transplant surgery (moderate strength of evidence).
    b. While the evidence does not clearly identify an optimal duration for preoperative smoking cessation, patients should be encouraged, using the most effective cessation methods available, to stop smoking at least one month prior to surgery in order to decrease the risk of developing postoperative complications.
    c. The literature search was limited to SRs, technology assessments, and meta-analyses. Multiple SRs, across a variety of surgical procedures, had relatively consistent findings. However, if specific types of surgery are not included in this report

Expert guidelines—cataract surgery and smoking

1) **NICE 2017**: Cataracts in Adults: Management https://www.nice.org.uk/guidance/ng77/resources/cataracts-in-adults-management-pdf-1837639266757
    a. No mention of smoking cessation
2) **American Academy of Ophthalmology 2016**: Cataract in the Adult Eye Preferred Practice Pattern
    a. Smoking cessation is discussed as a method of reducing patient risk for developing cataracts
    b. Smoking cessation is not mentioned in the pre-operative assessment or recommendations

HERC staff summary

There is no literature addressing the impact of smoking cessation on cataract surgery. Based on expert opinion, outcomes of this type of "bloodless surgery" are not affected by smoking cessation. Cataract surgery and similar bloodless surgeries should be included as exceptions in the current smoking cessation guideline.

Some providers are advocating for deletion of the guideline as a large barrier for care in certain populations. However, the CCO medical directors are strongly in favor of keeping this guideline.

Some edits for clarifying surgical location, anesthesia type, etc. should be made to the current guideline.

HERC staff recommendations:

1) Modify Ancillary Guideline A4 as shown below
    a. Bloodless surgery like cataract removal will be exempted from the requirement for smoking cessation due to lack of evidence of harm from smoking
    b. Clarifies that this guideline applies to all procedures regardless of location or anesthesia type

ANCILLARY GUIDELINE A4, SMOKING CESSATION AND ELECTIVE SURGICAL PROCEDURES

Smoking cessation is required prior to elective surgical procedures for active tobacco users. Cessation is required for at least 4 weeks prior to the procedure and requires objective evidence of abstinence from smoking prior to the procedure.

Elective surgical procedures in this guideline are defined as surgical procedures which are flexible in their scheduling because they do not pose an imminent threat nor require immediate attention within 1 month. Procedures for contraceptive/sterilization purposes, procedures targeted to active cancers (i.e. when a delay in the procedure could lead to cancer progression), ~~and~~ diagnostic procedures, and bloodless surgery (e.g. cataract surgery, certain skin procedures) are not subject to the limitations in this guideline note. This guideline applies regardless of procedure location and anesthesia type.

The well-studied tests for confirmation of smoking cessation include cotinine levels and exhaled carbon monoxide testing. However, cotinine levels may be positive in nicotine replacement therapy (NRT) users, smokeless tobacco and e-cigarette users (which are not contraindications to elective surgery coverage). In patients using nicotine products aside from combustible cigarettes the following alternatives to urine cotinine to demonstrate smoking cessation may be considered:

- Exhaled carbon monoxide testing
- Anabasine or anatabine testing (NRT or vaping)

Certain procedures, such as lung volume reduction surgery, bariatric surgery, erectile dysfunction surgery, and spinal fusion have 6 month tobacco abstinence requirements. See Guideline Notes 8, 100, 112 and 159.

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American Academy of Ophthalmology®
P. O. Box 7424
San Francisco, CA 94120-7424
415.561.8500

HIGHLIGHTED FINDINGS AND RECOMMENDATIONS FOR CARE

Symptomatic cataract is a surgical disease. Dietary intake and nutritional supplements have demonstrated minimal to no effect in the prevention or treatment of cataract. *(III, good quality, strong recommendation)*

The standard of care in cataract surgery in the United States is a small-incision phacoemulsification with foldable intraocular lens (IOL) implantation. It is a standard of care that has withstood the test of time.

Refractive cataract surgery has the potential to reduce a patient's dependence on eyeglasses and contact lenses for distance, intermediate, and near vision.

Intraocular lens technologies and surgical approaches to implanting lenses continue to improve.

Femtosecond laser-assisted cataract surgery (FLACS) increases the circularity and centration of the capsulorrhexis and reduces the amount of ultrasonic energy required to remove a cataract. However, the technology may not yet be cost-effective, and the overall risk profile has not yet been shown to be superior to that of standard phacoemulsification.

The use of topical nonsteroidal anti-inflammatory drugs (NSAIDs) is controversial, with evidence suggesting that NSAIDs only be used for the prevention of cystoid macular edema (CME) in patients with diabetic retinopathy or other high-risk ocular comorbidities.

Increasing evidence demonstrates that intracameral antibiotics reduce the risk of postoperative bacterial endophthalmitis.

Surgeons should recognize and prepare to manage high-risk characteristics that may complicate cataract surgery. New risks may become apparent as new technologies come to market. One example is capsular damage with rapid development of a complicated cataract associated with intravitreal injections.

Toxic anterior segment syndrome (TASS) may be confused with infectious endophthalmitis. However, TASS has an earlier onset, is associated with limbus-to-limbus corneal edema, and responds to corticosteroids.

Rhinoplasty and Septoplasty Coverage Clarification

Question: How can coverage of rhinoplasty and septoplasty on the Prioritized List be clarified?

Question source: VBBS

Issue: At the May 2021 VBBS meeting, members requested that HERC staff review the medical necessary indications for rhinoplasty and/or septoplasty. Rhinoplasty and septoplasty appear on several covered and multiple uncovered lines on the Prioritized List. The two covered lines containing non-cleft lip related rhinoplasty CPT codes are line 228 FRACTURE OF FACE BONES; INJURY TO OPTIC AND OTHER CRANIAL NERVES and line 465 CHRONIC SINUSITIS.

In May 2021, HERC staff brought recommendations for clarifying when rhinoplasty and/or septoplasty would be included as part of surgery for chronic sinusitis. The VBBS members felt that these procedures are rarely medically necessary. The members felt that rhinoplasty as part of larger facial reconstruction for conditions like cleft lip would be an example of a medically necessary indication. Note: cleft lip/palate rhinoplasty has a unique CPT code. Also, members requested clarification on the medical necessity criteria for septoplasty. VBBS members requested that HERC staff consult other payer policies, as well as sleep medicine, plastics, and ENT experts.

Reconstructive rhinoplasty is surgery of the nose to correct an external nasal deformity, damaged nasal structures or to replace lost tissue, while maintaining or improving the physiological function of the nose. Reconstructive septoplasty is the surgical correction of defects and deformities of the nasal septum (partition between the nostrils) by altering, splinting or removing obstructive tissue while maintaining or improving the physiological function of the nose. Cosmetic rhinoplasty and/or septoplasty are performed solely to enhance appearance.

Rhinoplasty and Septoplasty Coverage Clarification

Current Prioritized List status

Code	Code Description	Current Placement
30400	Rhinoplasty, primary; lateral and alar cartilages and/or elevation of nasal tip	465 CHRONIC SINUSITIS 506 NASAL POLYPS, OTHER DISORDERS OF NASAL CAVITY AND SINUSES 576 DEVIATED NASAL SEPTUM, ACQUIRED DEFORMITY OF NOSE, OTHER DISEASES OF UPPER RESPIRATORY TRACT
30410	Rhinoplasty, primary; complete, external parts including bony pyramid, lateral and alar cartilages, and/or elevation of nasal tip	465,506,576
30420	Rhinoplasty, primary; including major septal repair	228 FRACTURE OF FACE BONES; INJURY TO OPTIC AND OTHER CRANIAL NERVES 465, 506 561 ALLERGIC RHINITIS AND CONJUNCTIVITIS, CHRONIC RHINITIS 576
30430	Rhinoplasty, secondary; minor revision (small amount of nasal tip work)	Excluded
30435	Rhinoplasty, secondary; intermediate revision (bony work with osteotomies)	465,506
30450	Rhinoplasty, secondary; major revision (nasal tip work and osteotomies)	228,465,506
30460-30462	Rhinoplasty for nasal deformity secondary to congenital cleft lip and/or palate	300 CLEFT PALATE AND/OR CLEFT LIP
30465	Repair of nasal vestibular stenosis (eg, spreader grafting, lateral nasal wall reconstruction)	465,506,576
30468	Repair of nasal valve collapse with subcutaneous/submucosal lateral wall implant(s)	465,506,576
30520	Septoplasty or submucous resection, with or without cartilage scoring, contouring or replacement with graft	42 CLEFT PALATE WITH AIRWAY OBSTRUCTION 119 CHOANAL ATRESIA 202 SLEEP APNEA, NARCOLEPSY AND REM BEHAVIORAL DISORDER 246 LIFE-THREATENING EPISTAXIS 287 CANCER OF ORAL CAVITY, PHARYNX, NOSE AND LARYNX 465 CHRONIC SINUSITIS 506 NASAL POLYPS, OTHER DISORDERS OF NASAL CAVITY AND SINUSES 525 BENIGN NEOPLASM OF NASAL CAVITIES, MIDDLE EAR AND ACCESSORY SINUSES

GUIDELINE NOTE 27, SLEEP APNEA

Line 202

CPAP is covered initially when all of the following conditions are met:

- 12 week 'trial' period to determine benefit. This period is covered if apnea-hypopnea index (AHI) or respiratory disturbance index (RDI) is greater than or equal to 15 events per hour; or if between 5 and 14 events with additional symptoms including one or more of the following:
    - excessive daytime sleepiness defined as either an Epworth Sleepiness Scale score>10 or daytime sleepiness interfering with ADLs that is not attributable to another modifiable sedating condition (e.g. narcotic dependence), or
    - documented hypertension, or
    - ischemic heart disease, or
    - history of stroke;
- Providers must provide education to patients and caregivers prior to use of CPAP machine to ensure proper use; and
- Positive diagnosis through polysomnogram (PSG) or Home Sleep Test (HST).

CPAP coverage subsequent to the initial 12 weeks is based on documented patient tolerance, compliance, and clinical benefit. Compliance (adherence to therapy) is defined as use of CPAP for at least four hours per night on 70% of the nights during a consecutive 30-day period.

Mandibular advancement devices (oral appliances) are covered for those for whom CPAP fails or is contraindicated.

Surgery for sleep apnea in adults is not included on this line (due to lack of evidence of efficacy). Surgical codes are included on this line only for children who meet criteria according to Guideline Note 118 OBSTRUCTIVE SLEEP APNEA DIAGNOSIS AND TREATMENT FOR CHILDREN.

Hypoglossal nerve stimulation for treatment of obstructive sleep apnea is not included on this line due to insufficient evidence of effectiveness and evidence of harm.

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 35, SINUS SURGERY

Lines 287,465,506

Sinus surgery (other than adenoidectomy) is indicated when at least one of the following circumstances occur (A-G):

A) Recurrent acute rhinosinusitis, defined as 4 or more episodes of acute bacterial rhinosinusitis in one year without signs or symptoms of rhinosinusitis between episodes and have failed optimal medical management defined as nasal steroid therapy and nasal saline therapy, in patients who are compliant with oral antibiotics and/or oral corticosteroids for management of acute episodes of rhinosinusitis

OR

B) Chronic sinusitis defined as 12 weeks of continuous symptoms without improvement with one of the following (1-3):

1) Findings of obstruction of active infection on CT scan OR

2) Symptomatic mucocele OR
3) Negative CT scan but significant disease found on nasal endoscopy
AND
Failure of medical therapy defined as (1-2)
4) Two or more courses of antibiotics with adequate doses AND
5) Trial of inhaled and/or oral steroids (2 or more courses of adequate doses of one or both)

OR

C) Nasal polyposis causing or contributing to sinusitis

OR

D) Complications of sinusitis including subperiosteal or orbital abscess, Pott's puffy tumor, brain abscess or meningitis

OR

E) Invasive or allergic fungal sinusitis

OR

F) Tumor of nasal cavity or sinuses

OR

G) CSF rhinorrhea

Adenoidectomy (CPT 42830, 42835) is included on Line 465 only for treatment of children with chronic sinusitis who fail appropriate medical therapy.

GUIDELINE NOTE 118, OBSTRUCTIVE SLEEP APNEA DIAGNOSIS AND TREATMENT FOR CHILDREN

Line 202

Obstructive sleep apnea (OSA) in children (18 or younger) must be diagnosed by

A) nocturnal polysomnography with an AHI >5 episodes/h or AHI>1 episodes/h with history and exam consistent with OSA, OR
B) nocturnal pulse oximetry with 3 or more SpO2 drops <90% and 3 or more clusters of desaturation events, or alternatives desaturation (>3%) index >3.5 episodes/h, OR
C) use of a validated questionnaire (such as the Pediatric Sleep Questionnaire or OSA 18), OR
D) consultation with a sleep medicine specialist.

Polysomnography and/or consultation with a sleep medicine specialist to support the diagnosis of OSA and/or to identify perioperative risk is recommended for

A) high-risk children (i.e. children with cranio-facial abnormalities, neuromuscular disorders, Down syndrome, etc.)
B) children with equivocal indications for adenotonsillectomy (such as discordance between tonsillar size on physical examination and the reported severity of sleep-disordered breathing),
C) children younger than three years of age

Adenotonsillectomy is an appropriate first line treatment for children with OSA. Weight loss is recommended in addition to other therapy in patients who are overweight or obese. Adenoidectomy without tonsillectomy is only covered when a child with OSA has previously had a tonsillectomy, when

tonsillectomy is contraindicated, or when tonsillar hypertrophy is not present. More complex surgical treatments are only included on this line for children with craniofacial anomalies.

Intranasal corticosteroids are an option for children with mild OSA in whom adenotonsillectomy is contraindicated or for mild postoperative OSA.

CPAP is covered for a 3 month trial for children through age 18 who have

A) undergone surgery or are not candidates for surgery, AND
B) have documented residual sleep apnea symptoms (sleep disruption and/or significant desaturations) with residual daytime symptoms (daytime sleepiness or behavior problems)

CPAP will be covered for children through age 18 on an ongoing basis if:

- There is documentation of improvement in sleep disruption and daytime sleepiness and behavior problems with CPAP use
- Annual re-evaluation for CPAP demonstrates ongoing clinical benefit and compliance with use, defined as use of CPAP for at least four hours per night on 70% of the nights in a consecutive 30 day period

Other payer policies

1) **Aetna 2021**
    a. Aetna considers **septoplasty** medically necessary when *any* of the following clinical criteria is met:
        i. Asymptomatic septal deformity that prevents access to other intranasal areas when such access is required to perform medical necessary surgical procedures (e.g., ethmoidectomy); *or*
        ii. Documented recurrent sinusitis felt to be due to a deviated septum not relieved by appropriate medical and antibiotic therapy; *or*
        iii. Recurrent epistaxis (nosebleeds) related to a septal deformity; *or*
        iv. Septal deviation causing continuous nasal airway obstruction resulting in nasal breathing difficulty not responding to 4 or more weeks of appropriate medical therapy; *or*
        v. When done in association with cleft palate repair.
    b. Aetna considers **rhinoplasty** a cosmetic surgical procedure. Rhinoplasty may be considered medically necessary *only* in the following limited circumstances:
        i. When it is being performed to correct a nasal deformity secondary to congenital cleft lip and/or palate or for removal of a nasal dermoid; *or*
        ii. Upon individual case review, to correct chronic non-septal nasal airway obstruction from vestibular stenosis (collapsed internal valves) due to trauma, disease, or congenital defect[Footnote1*], when all of the following criteria are met:
            1. Prolonged, persistent obstructed nasal breathing; *and*
            2. Physical examination confirming moderate to severe vestibular obstruction; *and*
            3. Airway obstruction will not respond to septoplasty and turbinectomy alone; *and*
            4. Nasal airway obstruction is causing significant symptoms (e.g., chronic rhinosinusitis, difficulty breathing); *and*
            5. Obstructive symptoms persist despite conservative management for 4 weeks or greater, which includes, where appropriate, nasal steroids or immunotherapy; *and*
            6. Photographs demonstrate an external nasal deformity; *and*
            7. There is significant obstruction of one or both nares), documented by nasal endoscopy, computed tomography (CT) scan or other appropriate imaging modality; *or*
        iii. When rhinoplasty for nasal airway obstruction is performed as an integral part of a medically necessary septoplasty and there is documentation of gross nasal obstruction on the same side as the septal deviation[Footnote1*].
        iv. Footnote1=Documentation of criterion B or C should include:
            1. The duration and degree of symptoms related to nasal obstruction, such as chronic rhinosinusitis, mouth breathing, etc.; *and*
            2. The results of conservative management of symptoms; *and*
            3. If there is an external nasal deformity, pre-operative photographs showing the standard 4-way view: anterior-posterior, right and left lateral views, and base of nose (also known as worm's eye view confirming vestibular stenosis; this view is from the bottom of nasal septum pointing upwards); *and*

4. Relevant history of accidental or surgical trauma, congenital defect, or disease (e.g., Wegener's granulomatosis, choanal atresia, nasal malignancy, abscess, septal infection with saddle deformity, or congenital deformity); *and*
5. Results of nasal endoscopy, CT or other appropriate imaging modality documenting degree of nasal obstruction.

2. Cigna 2021

a. **Rhinoplasty** is considered medically necessary for ANY of the following indications:
   i. Correction or repair of a nasal deformity secondary to a cleft lip/palate or other severe congenital craniofacial deformity (e.g., deformity (e.g., maxillonasal dysplasia, Binder's syndrome, facial clefts) in a child five years of age or younger.
   ii. Correction or repair of a nasal deformity secondary to a cleft lip/palate or other severe congenital craniofacial deformity (e.g., maxillonasal dysplasia, Binder's syndrome, facial clefts) in a child that is age six years of age or older that is causing a functional impairment (i.e., nasal obstruction, inadequate airflow, feeding difficulties) when BOTH of the following criteria are met:
      1. photographic evidence of the anatomical abnormality including frontal, lateral and worm's eye view (e.g., nasal base)
      2. the functional impairment is expected to be resolved by the rhinoplasty
   iii. Correction or repair of a nasal deformity secondary to trauma that is causing a functional impairment (i.e., nasal obstruction, inadequate airflow) and ALL of the following criteria are met:
      1. nasal airway obstruction is poorly responsive to a recent six week trial of conservative medical management (e.g., topical/nasal corticosteroids, antihistamines)
      2. photographic evidence of the anatomical abnormality including frontal, lateral and worm's eye view (e.g., nasal base)
      3. the functional impairment has either not resolved after previous septoplasty/turbinectomy or would not be expected to resolve with a septoplasty/turbinectomy alone
      4. the functional impairment is expected to be resolved by the rhinoplasty
   iv. Rhinoplasty or vestibular stenosis repair when performed for EITHER of the following indications is considered cosmetic in nature and/or not medically necessary:
      1. solely for the purpose of changing appearance
      2. as a primary treatment for an obstructive sleep disorder when the above criteria for approval have not been met

b. **Septoplasty** is considered medically necessary when performed for ANY of the following indications:
   i. septal deviation causing nasal airway obstruction resulting in prolonged or chronic nasal breathing difficulty or mouth breathing that has proved poorly responsive to a recent trial of conservative medical management (e.g., topical/nasal corticosteroids, antihistamines)
   ii. recurrent epistaxis related to a septal deformity
   iii. performed in association with a covered cleft lip or cleft palate repair
   iv. obstructed nasal breathing due to septal deformity or deviation that has proved poorly responsive to medical management lasting at least six weeks and is interfering with the effective use of medically necessary continuous positive

airway pressure (CPAP) for the treatment of an obstructive sleep disorder (i.e., obstructive sleep apnea with an apnea/hypopnea index (AHI) ≥ 15 as documented by polysomnography or home/portable sleep study)

c. Anthem Blue Cross Blue Shield 2021

i. **Rhinoplasty** is considered medically necessary when **both** of the following criteria are met:
   1. the medical record documentation includes evidence of the failure of conservative medical therapy for severe airway obstruction from deformities due to disease, structural abnormality, or previous therapeutic process that will not respond to septoplasty alone; **and**
   2. the procedure can be reasonably expected to improve the functional impairment.
   3. **Note:** Only the initial restorative repair is medically necessary, unless the procedure is completed in stages with healing periods, then all stages are medically necessary.
   4. **Note:** Rhinoseptoplasty is considered medically necessary when the criteria above for rhinoplasty are met and medically necessary criteria in CG-SURG-18 Septoplasty **[see vi and vii below]** are also met.

ii. Rhinoplasty is considered reconstructive if there is documented evidence (that is, radiographs or appropriate imaging studies) of nasal fracture resulting in significant variation from normal without functional impairment. The intent of the surgery is to correct the deformity caused by the nasal fracture.

iii. Rhinoseptoplasty is considered reconstructive if there is documented evidence (that is, radiographs or appropriate imaging studies) of nasal and septal fracture resulting in significant variation from normal without functional impairment. The intent of the surgery is to correct the deformity caused by the nasal and septal fracture.

iv. Rhinoplasty or rhinoseptoplasty to modify the shape or size of the nose is considered cosmetic and not medically necessary when the medically necessary or reconstructive criteria in this section are not met.

v. Nasal **septoplasty** is considered medically necessary for either of the following conditions when an appropriate and reasonable trial of conservative management (which might include use of topical nasal corticosteroids, decongestants, antibiotics, allergy evaluation and therapy, etc.) has failed.
   1. Symptomatic septal deviation or deformity resulting in **one or more** of the following:
      a. Distressing symptoms of nasal obstruction with documented absence of other causes of obstruction likely to be responsible for the symptoms (for example, nasal polyps, tumor, etc.); **or**
      b. Persistent or recurrent epistaxis; **or**
      c. Chronic recurrent sinusitis **or**
      d. Asymptomatic deformity that prevents surgical access to other intranasal or paranasal areas (for example, sinuses, turbinates).

vi. Septoplasty is considered not medically necessary when the above criteria are not met and for all other indications including, but not limited to, the following:
   1. For asymptomatic septal deviation when there is no need for surgical access; **or**

2. In the absence of an appropriate and reasonable trial of conservative medical management of symptoms; **or**
3. When another condition likely to be causing the obstruction is present (for example, nasal polyp, tumor, etc.); **or**
4. For snoring, in the absence of one or more symptoms or conditions indicated as medically necessary.

Rhinoplasty and Septoplasty Coverage Clarification

HERC staff summary

All major insurers surveyed had detailed criteria for coverage of rhinoplasty and septoplasty. There currently are no such criteria on the Prioritized List. Due to confusion with HSD and CCO reviewers over HERC intent, addition of a guideline regarding these procedures would be valuable.

HERC staff recommendations:

1) Adopt a new guideline regarding coverage of septoplasty as shown below and add to lines
    a. 42 CLEFT PALATE WITH AIRWAY OBSTRUCTION
    b. 119 CHOANAL ATRESIA
    c. 246 LIFE-THREATENING EPISTAXIS
    d. 287 CANCER OF ORAL CAVITY, PHARYNX, NOSE AND LARYNX
    e. 465 CHRONIC SINUSITIS
    f. 506 NASAL POLYPS, OTHER DISORDERS OF NASAL CAVITY AND SINUSES
    g. 525 BENIGN NEOPLASM OF NASAL CAVITIES, MIDDLE EAR AND ACCESSORY SINUSES
2) Remove CPT 30520 (Septoplasty or submucous resection, with or without cartilage scoring, contouring or replacement with graft) from line 202 SLEEP APNEA, NARCOLEPSY AND REM BEHAVIORAL DISORDER
    a. Surgery is only covered for children with sleep apnea, and then the only covered procedures are tonsillectomy and adenoidectomy per the sleep apnea guideline
3) Adopt a new guideline regarding coverage of rhinoplasty as shown below and add to lines
    a. 228 FRACTURE OF FACE BONES; INJURY TO OPTIC AND OTHER CRANIAL NERVES
    b. 300 CLEFT PALATE AND/OR CLEFT LIP
    c. 465 CHRONIC SINUSITIS
    d. 506 NASAL POLYPS, OTHER DISORDERS OF NASAL CAVITY AND SINUSES
    e. 576 DEVIATED NASAL SEPTUM, ACQUIRED DEFORMITY OF NOSE, OTHER DISEASES OF UPPER RESPIRATORY TRACT
4) Remove CPT 30420 (Rhinoplasty, primary; including major septal repair) from line 561 ALLERGIC RHINITIS AND CONJUNCTIVITIS, CHRONIC RHINITIS
    a. Rhinoplasty is not indicated for allergic rhinitis
    b. Line 561 is missing all other rhinoplasty codes

GUIDELINE NOTE XXX SEPTOPLASTY

Lines 42,119,246,287,465,506,525

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 506]; 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 involving the nose.

Septoplasty is not covered for obstructive sleep apnea.

GUIDELINE NOTE XXX RHINOPLASTY

Lines 42,119,202,246,287,465,506,525

Rhinoplasty is included on these lines when

A) It is performed to correct a nasal deformity secondary to congenital cleft lip and/or palate or other severe congenital craniofacial anomaly; OR

B) It is performed as part of reconstruction after accidental or surgical trauma or disease (e.g., Wegener's granulomatosis, choanal atresia, nasal malignancy, abscess, septal infection with saddle deformity, or congenital deformity) AND
   1) There is prolonged, persistent obstructed nasal breathing unresponsive to a six week trial of conservative management (e.g. nasal corticosteroids, decongestants, antibiotics); AND
   2) Airway obstruction will not respond to septoplasty and turbinectomy alone; AND
   3) Physical examination confirming moderate to severe vestibular obstruction; AND
   4) Photographs demonstrate an external nasal deformity; AND
   5) 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) Physical examination confirming moderate to severe vestibular obstruction; AND
   4) Photographs demonstrate an external nasal deformity; AND
   5) There is significant obstruction of one or both nares), documented by nasal endoscopy, computed tomography (CT) scan or other appropriate imaging modality

Radiofrequency Ablation of Uterine Fibroids

Question: should radiofrequency ablation of uterine fibroids be removed from line 662/GN173 and added to a covered line?

Question source: Hologic, Inc.

Issue: Radiofrequency ablation of uterine fibroids was reviewed as a new code in November 2016 and was placed on line 662/GN173 as lacking evidence of effectiveness. The 2016 evidence review included 2 studies: 1 RCT (published in two separate articles: Brucker 2014 and Hahn 2013, N=50) and 1 prospective cohort study (the HALT study: Chudnoff 2013/Guido 2013/Berman 2014, N=135). An additional cohort study (Bongers 2014, N=50) was submitted as testimony but included only an endpoint of fibroid volume. Given the very limited amount of evidence, the HERC decided to place this procedure on line 662/GN173.

Hologic is requesting a re-review of radiofrequency ablation of uterine fibroids based on the recent ACOG practice guideline update on treatment of fibroids which included this procedure as one option that can be considered in women who do not desire a hysterectomy.

Radiofrequency ablation is a minimally invasive destruction of uterine fibroids with radiofrequency waves. Alternative treatments include oral contraceptives, Mirena IUD, hysterectomy, myomectomy, endometrial ablation, uterine artery embolization. Currently, vascular embolization, myomectomy, and hysterectomy are included on line 404 UTERINE LEIOMYOMA AND POLYPS for treatment of uterine fibroids, with a guideline.

Since the 2016 review, several systematic reviews / meta-analyses have been published, in addition to the 2021 ACOG practice guideline on leiomyomas.

Current Prioritized List status

58674 Laparoscopy, surgical, ablation of uterine fibroid(s) including intraoperative ultrasound guidance and monitoring, radiofrequency: Line 662 CONDITIONS FOR WHICH CERTAIN INTERVENTIONS ARE UNPROVEN, HAVE NO CLINICALLY IMPORTANT BENEFIT OR HAVE HARMS THAT OUTWEIGH BENEFITS:

0404T Transcervical uterine fibroid(s) ablation with ultrasound guidance, radiofrequency: Never Reviewed

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
58674	Laparoscopy, surgical, ablation of uterine fibroid(s)	Insufficient evidence of effectiveness	November, 2016

GUIDELINE NOTE 40, UTERINE LEIOMYOMA

Line 404

Hysterectomy, myomectomy, or uterine artery embolization for leiomyomata may be indicated when all of the following are documented (A-D):

A) One of the following (1 or 2):
   1) Patient history of 2 out of 3 of the following (a, b and c):
      a. Leiomyomata enlarging the uterus to a size of 12 weeks or greater gestation
      b. Pelvic discomfort cause by myomata (i or ii or iii):
         i) Chronic lower abdominal, pelvic or low backpressure
         ii) Bladder dysfunction not due to urinary tract disorder or disease
         iii) Rectal pressure and bowel dysfunction not related to bowel disorder or disease
      c. Rapid enlargement causing concern for sarcomatous changes of malignancy
   2) Leiomyomata as probable cause of excessive uterine bleeding evidenced by (a, b, c and d):
      a. Profuse bleeding lasting more than 7 days or repetitive periods at less than 21-day intervals
      b. Anemia due to acute or chronic blood loss (hemoglobin less than 10 or hemoglobin less than 11 g/dL if use of iron is documented)
      c. Documentation of mass by sonography
      d. Bleeding causes major impairment or interferes with quality of life
B) Nonmalignant cervical cytology, if cervix is present
C) Assessment for absence of endometrial malignancy in the presence of abnormal bleeding
D) Negative preoperative pregnancy test result unless patient is postmenopausal or has been previously sterilized

Evidence

1) **NICE 2021** Transcervical ultrasound-guided radiofrequency ablation for symptomatic uterine fibroids
    a. N=9 studies (1 RCT, 2 cohort studies reported in 6 publications, 1 case series, 1 case report)
    b. There is some evidence of efficacy but there were no high-quality comparative studies with sufficient numbers of patients to make a definitive evaluation
    c. NOTE: only transcervical radiofrequency ablation was included in this report (i.e. no laparoscopic procedures)
2) **AHRQ 2017,** Management of Uterine Fibroids
    a. N=2 RCTs of radiofrequency fibroid ablation (N-76 patients)
        i. Both RCTs assessed as poor quality
    b. Studies provided limited data on effects of ablation on bleeding, quality of life, and subsequent pregnancies, but did not report pain outcomes and noted no major complications.
    c. Summary/SOE: The strength of evidence for radiofrequency ablation is insufficient to inform care
3) **Bradley 2019**, Clinical Performance of Radiofrequency Ablation for Treatment of Uterine Fibroids: Systematic Review and Meta-Analysis of Prospective Studies
    a. Gynesonics, Inc., provided funding for this study.
    b. N= 32 articles of 1283 unique patients treated with laparoscopic RFA (19 articles), transvaginal RFA (8 articles), or transcervical fibroid ablation (5 articles)
        i. These 32 articles reported on 20 prospective studies
            1. Study quality was rated as good or fair for 19 of 20 studies.
            2. The study design elements that were most frequently missing from published reports were interrupted time-series design (20 of 20 studies), blinded outcome assessors (20 of 20 studies), analyses that failed to adjust for attrition (19 of 20 studies), and no justification for sample size (15 of 20 studies)
    c. Following RFA, mean fibroid volume decreased by 47% at 3 months, 55% at 6 months, 66% at 12 months, and 71% at >12 months follow-up
    d. Quality of life, where higher health-related quality of life (HRQL) scores indicate better quality of life, improved relative to baseline by 30 points at 3 months, 37 points at 6 months, 39 points at 12 months, and 31 points at >12 months follow-up (all $P < .001$ versus baseline).
    e. Fibroid symptoms, where lower symptom severity score (SSS) scores indicate lower symptom severity, decreased by 29, 36, 42, and 40 points relative to baseline over this same period (all $P < .001$ versus baseline)
    f. The cumulative rate of surgical reinterventions for fibroid related symptoms was 4.2%, 8.2%, and 11.5% at annual follow-up intervals through 3 years
    g. Complication reporting was highly inconsistent and inadequate such that any attempts at reporting these data would have led to inaccurate and misleading results. Regardless, no serious procedural complications such as death or iatrogenic injury to the bowel, bladder, or ureter were reported in any study.
    h. Conclusion: RFA of uterine fibroids significantly reduces fibroid volume, provides significant improvements in fibroid-related quality of life, and is associated with favorable reintervention rates.

4) **Lin 2019**, Quality of Life, Adverse Events, and Reintervention Outcomes after Laparoscopic Radiofrequency Ablation for Symptomatic Uterine Fibroids: A Meta-Analysis
    a. N=8 studies (581 patients)
        i. All studies included in Bradley 2019 above
        ii. Most of the studies excluded International Federation of Gynecology and Obstetrics (FIGO) type 0, 5, 6, 7, and 8 fibroids, because these types could be contraindicated
    a. Based on validated questionnaires, quality of life improved significantly until 36 months after laparoscopic radiofrequency ablation therapy, with a maximum improvement (Health-Related Quality of Life [HRQL] questionnaire score of +41.64 [95% confidence interval (CI), 38.94−44.34] and a transformed Symptom Severity Score [tSSS] of -39.37 [95% CI, 34.70−44.04]) at 12 months after laparoscopic radiofrequency ablation. All subscales of quality of life improved significantly, and most of the changes remained stable in long-term follow-up.
    b. The overall reintervention rate was 4.39% (95% CI, 1.60% −8.45%)
    c. The median uterine volume reduction was 69.17 cm3 (95% CI, 35.87−102.46 cm3).
    d. The overall procedure-related adverse events rate was 1.78% (95% CI, 0.62%−3.53%),
    e. In conclusion, according to our meta-analysis, laparoscopic radiofrequency ablation therapy is efficacious for small-sized and nonpedunculated symptomatic uterine fibroids. After treatment, patients will gain stable long-term symptom relief and quality of life improvement. Meanwhile, the overall risks of adverse events and reintervention are low

<u>Expert guidelines</u>

1) **ACOG 2021** Management of Symptomatic Uterine Leiomyomas
    a. Although evidence exists regarding outcomes with specific therapies, comparative effectiveness data are lacking for leiomyoma management options
    b. Laparoscopic radiofrequency ablation can be considered as a minimally invasive treatment option for the management of symptomatic leiomyomas in patients who desire uterine preservation
    c. The only two minimally invasive interventions for leiomyomas that are recommended by ACOG are uterine artery embolization and laparoscopic radiofrequency ablation. Focused ultrasound and endometrial ablation both had insufficient evidence to make a clinical recommendation

<u>Other payer policies</u>

1) Aetna 2021
    a. Aetna considers radiofrequency ablation (open or laparoscopic (e.g., the Acessa System)) or transcatheter uterine artery embolization (UAE) medically necessary as an alternative to hysterectomy or myomectomy for the treatment of uterine fibroids when the member has persistence of one or more symptoms directly attributed to uterine fibroids (i.e., excessive menstrual bleeding (menorrhagia), bulk-related pelvic pain, pressure or discomfort, urinary symptoms referable to compression of the ureter or bladder, and/or dyspareunia).

2) Cigna 2021

a. Ultrasound guided radiofrequency ablation is considered medically necessary for the treatment of symptomatic uterine fibroids**.**
b. Symptoms related to uterine fibroids are classified into the following categories:
    i. Heavy or prolonged menstrual bleeding
    ii. Bulk-related symptoms, such as pelvic pressure
    iii. Reproductive dysfunction (i.e., infertility or obstetric complications)
    iv. Pain

3) Centene 2021

a. It is the policy of health plans affiliated with Centene Corporation® that there is insufficient evidence in the published peer-reviewed literature to support the safety and effectiveness of radiofrequency ablation and the use of the Acessa™ and Sonata® Systems for the treatment of uterine fibroids.

HERC staff summary

Over the past 5 years, the literature on the effectiveness of laparoscopic radiofrequency ablation for treatment of uterine fibroids has grown more robust. There is still a dearth of RCTs, which has resulted in one of our highly trusted evidence-based sources (AHRQ) finding insufficient evidence of effectiveness. Systematic reviews and meta-analyses which included other prospective study designs have found consistent results indicating that this procedure reduces fibroid volume and symptoms and increases fibroid related quality of life. This procedure is now recommended as a treatment option by ACOG and is now being covered by most private insurers.

Transcervical radiofrequency ablation has a much small evidence base and has been found by one of our highly trusted sources (NICE) to have insufficient evidence of effectiveness. This procedure has a different procedure code that laparoscopic radiofrequency ablation.

HERC staff recommendations:

1) Add CPT **58674** (Laparoscopy, surgical, ablation of uterine fibroid(s) including intraoperative ultrasound guidance and monitoring, radiofrequency) to line 404 UTERINE LEIOMYOMA AND POLYPS
2) Remove CPT 58674 from line 662 CONDITIONS FOR WHICH CERTAIN INTERVENTIONS ARE UNPROVEN, HAVE NO CLINICALLY IMPORTANT BENEFIT OR HAVE HARMS THAT OUTWEIGH BENEFITS and remove the related entry from Guideline Note 173
3) Modify Guideline Note 40 as shown below
4) Add transcervical radiofrequency ablation (CPT 0404T) to line 663/GN173 as shown below

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

Line 662

The following Interventions are prioritized on Line 662 CONDITIONS FOR WHICH CERTAIN INTERVENTIONS ARE UNPROVEN, HAVE NO CLINICALLY IMPORTANT BENEFIT OR HAVE HARMS THAT OUTWEIGH BENEFITS:

Procedure Code	Intervention Description	Rationale	Last Review
0404T	Transcervical uterine fibroid(s) ablation with ultrasound guidance, radiofrequency	Insufficient evidence of effectiveness	August 2021
~~58674~~	~~Laparoscopy, surgical, ablation of uterine fibroid(s)~~	~~Insufficient evidence of effectiveness~~	~~November, 2016~~

GUIDELINE NOTE 40, UTERINE LEIOMYOMA

Line 404

Hysterectomy, myomectomy, ~~or~~ uterine artery embolization, or laparoscopic radiofrequency ablation for leiomyomata may be indicated when all of the following are documented (A-D):

E) One of the following (1 or 2):
   3) Patient history of 2 out of 3 of the following (a, b and c):
      a. Leiomyomata enlarging the uterus to a size of 12 weeks or greater gestation

b. Pelvic discomfort cause by myomata (i or ii or iii):
   i) Chronic lower abdominal, pelvic or low backpressure
   ii) Bladder dysfunction not due to urinary tract disorder or disease
   iii) Rectal pressure and bowel dysfunction not related to bowel disorder or disease
c. Rapid enlargement causing concern for sarcomatous changes of malignancy

4) Leiomyomata as probable cause of excessive uterine bleeding evidenced by (a, b, c and d):
   a. Profuse bleeding lasting more than 7 days or repetitive periods at less than 21-day intervals
   b. Anemia due to acute or chronic blood loss (hemoglobin less than 10 or hemoglobin less than 11 g/dL if use of iron is documented)
   c. Documentation of mass by sonography
   d. Bleeding causes major impairment or interferes with quality of life

F) Nonmalignant cervical cytology, if cervix is present
G) Assessment for absence of endometrial malignancy in the presence of abnormal bleeding
H) Negative preoperative pregnancy test result unless patient is postmenopausal or has been previously sterilized

NICE guidance

Transcervical ultrasound-guided radiofrequency ablation for symptomatic uterine fibroids

Interventional procedures guidance
Published: 31 March 2021
www.nice.org.uk/guidance/ipg689

Your responsibility

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

Commissioners and/or providers have a responsibility to implement the guidance, in their local context, in light of their duties to have due regard to the need to eliminate unlawful discrimination, advance equality of opportunity, and foster good relations. Nothing in this guidance should be interpreted in a way that would be inconsistent with compliance with those duties.

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

1 Recommendations

1.1 Evidence on the safety of transcervical ultrasound-guided radiofrequency ablation for symptomatic uterine fibroids raises no major safety concerns. However, evidence on its efficacy is limited in quality. Therefore, this procedure should only be used with special arrangements for clinical governance, consent, and audit or research. Find out what special arrangements mean on the NICE interventional procedures guidance page.

1.2 Clinicians wishing to do transcervical ultrasound-guided radiofrequency ablation for symptomatic uterine fibroids should:

- Inform the clinical governance leads in their healthcare organisation.
- Give patients clear written information to support shared decision making, including NICE's information for the public.
- Ensure that patients (and their families and carers as appropriate) understand the procedure's safety and efficacy, and any uncertainties about these.
- Audit and review clinical outcomes of all patients having the procedure. The main efficacy and safety outcomes identified in this guidance can be entered into NICE's interventional procedure outcomes audit tool (for use at local discretion).
- Discuss the outcomes of the procedure during their annual appraisal to reflect, learn and improve.

1.3 Healthcare organisations should:

- Ensure systems are in place that support clinicians to collect and report data on outcomes and safety for every patient having this procedure.
- Regularly review data on outcomes and safety for this procedure.

1.4 During the consent process clinicians should tell patients that the procedure may not fully relieve their symptoms and further procedures may be needed.

1.5 Further research should include comparative studies, preferably randomised controlled trials. It should report details of patient selection, disease-specific quality of life and long-term outcomes.

2 The condition, current treatments and procedure

The condition

2.1 Uterine fibroids (also known as uterine leiomyomas or myomas) are benign tumours of the uterine wall. They can be asymptomatic or cause symptoms including menorrhagia, intermenstrual bleeding, pelvic pressure or pain, and urinary incontinence. They can be associated with fertility problems and miscarriage.

Current treatments

2.2 Treatment depends on whether the fibroids cause symptoms, and if the person would like to become pregnant in the future. For symptomatic fibroids, treatment options include medications, interventional radiology and surgery. Interventional radiology treatments include uterine artery embolisation and MRI-guided focused ultrasound. Surgery includes hysterectomy, myomectomy, endometrial ablation techniques and myolysis.

The procedure

2.3 Transcervical ultrasound-guided radiofrequency ablation for symptomatic uterine fibroids is done using general or regional anaesthesia, or sedation. A radiofrequency ablation device with an ultrasound probe at the tip is inserted through the cervix into the endometrial cavity. The ultrasound probe is used to visualise and target the fibroid, which is then ablated with radiofrequency energy. The aim is to shrink the fibroid and reduce symptoms.

3 Committee considerations

The evidence

3.1 NICE did a rapid review of the published literature on the efficacy and safety of this procedure. This comprised a comprehensive literature search and detailed review of the evidence from 9 sources, which was discussed by the committee. The evidence included 1 systematic review, 2 cohort studies (6 publications),

1 case series and 1 case report. It is presented in the summary of key evidence section in the interventional procedures overview. Other relevant literature is in the appendix of the overview.

3.2 The professional experts and the committee considered the key efficacy outcomes to be: quality of life, fibroid-related symptom score, fibroid volume, reintervention rates and future pregnancy.

3.3 The professional experts and the committee considered the key safety outcomes to be: haemorrhage, infection, uterine perforation and hospital readmission.

3.4 Patient commentary was sought but none was received.

Committee comments

3.5 There is some evidence of efficacy but there were no high-quality comparative studies with sufficient numbers of patients to make a definitive evaluation. Fibroids are a common condition. These considerations underpinned the committee's request for more data collection including disease-specific quality of life measures and rarer complications.

3.6 The committee was informed that the procedure may be an option for people who want to maintain their fertility but the evidence for successful pregnancy after the procedure is limited to case reports.

3.7 All the evidence reviewed was in women aged under 50.

3.8 All the evidence reviewed was on fibroid types 1, 2, 3 and 4, and 2 to 5 (transmural), using the International Federation of Gynecology and Obstetrics (FIGO) classification system.

3.9 The committee was informed that there is a limit to the size of fibroid that can be treated using this procedure.

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Endorsing organisation

This guidance has been endorsed by Healthcare Improvement Scotland.

Accreditation

Comparative Effectiveness Review
Number 195

Management of Uterine Fibroids

Management of Uterine Fibroids

Structured Abstract

Objectives. We assessed the evidence about management of uterine fibroids. Specifically, we sought to determine effectiveness of interventions, risks of harm, and whether individual or fibroid characteristics influence outcomes.

Data sources. We searched MEDLINE® via PubMed® and Embase® to identify publications, as well as reviewed the reference lists of included studies.

Methods. We included studies published in English from January 1985 to September 2016. We identified randomized clinical trials to assess outcomes and harms of interventions. We used data from trials in a meta-analysis to estimate probability and timing of subsequent interventions for fibroids based on initial type of intervention. To describe risk of unrecognized leiomyosarcoma, we included studies that allowed calculation of prevalence of leiomyosarcoma discovered at the time of surgery for masses believed to be fibroids. We also identified publications that indicated operative approaches to removal of leiomyosarcoma tissue and built models to estimate survival. We extracted data, assessed risk of bias, and rated the strength of evidence for informing care.

Results. Of 97 included randomized trials, 43 studies assessed medications, 28 assessed procedures, and 37 assessed surgeries. Gonadotropin-releasing hormone (GnRH) agonists, mifepristone, and ulipristal reduced fibroid size and improved fibroid-related symptoms, including bleeding and quality of life (moderate strength of evidence [SOE] except quality of life for GnRH agonist [low SOE]). Several other medications have promise but are not supported by sufficient evidence. Uterine artery embolization (UAE) (high SOE) as well as high intensity focused ultrasound (low SOE) are effective for decreasing fibroid size/volume. Few other outcomes are well investigated for high intensity focused ultrasound. UAE studies reported improved outcomes for bleeding (moderate SOE), and quality of life (moderate SOE). Myomectomy and hysterectomy improved quality of life (both low SOE). Few well-conducted trials directly compared different treatment options. No studies were designed to evaluate expectant management, and evidence is insufficient to guide clinical care. Subsequent intervention ranged from 0 to 44 percent in studies that followed women after initial fibroid treatment. At 2-year followup, subsequent intervention rates were lowest for initial medical management and higher for UAE and myomectomy, especially among younger women. No individual characteristics of women or their fibroids were definitely associated with likelihood of intervention benefits or patient satisfaction. These findings were limited by the number and size of available studies. Using data from 160 studies, we estimated that among 10,000 women having surgery for presumed fibroids, between 0 and 13 will have a leiomyosarcoma detected. Of the surgical approaches, the 5-year survival after leiomyosarcoma diagnosis was 30 percent with power morcellation (95% Bayesian credible interval [BCI]: 13% to 61%), 59 percent with scalpel morcellation (BCI: 33% to 84%), and 60 percent with intact removal (BCI: 24% to 98%).

Conclusion. A range of interventions are effective for reducing fibroid size and improving symptoms. Some medications and procedures also improve quality of life. Few studies directly compare interventions. The risk of encountering a leiomyosarcoma at the time of fibroid surgery is low, and the method of fibroid removal may influence survival. Evidence to guide choice of

intervention is likely best when applied in the context of individual patient needs and preferences.

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Clinical Performance of Radiofrequency Ablation for Treatment of Uterine Fibroids: Systematic Review and Meta-Analysis of Prospective Studies

Linda D. Bradley, MD,[1] Resad P. Pasic MD, PhD,[2] and Larry E. Miller, PhD[3]

Abstract

Background: Radiofrequency ablation (RFA) has emerged as a safe and effective treatment option for women with symptomatic uterine fibroids and can be delivered by laparoscopic, transvaginal, or transcervical approaches. The evidence regarding typical patient outcomes with RFA has not previously been examined in a comprehensive fashion.

Materials and Methods: We performed a systematic review of prospective studies for treatment of uterine fibroids with RFA. Main outcomes were procedure time, patient recovery metrics, change in fibroid volume, symptom severity score (SSS), health-related quality of life (HRQL), and reinterventions. Data were analyzed with random effects meta-analysis and metaregression.

Results: We identified 32 articles of 1283 unique patients (median age: 42 years) treated with laparoscopic RFA (19 articles), transvaginal RFA (8 articles), or transcervical fibroid ablation (5 articles). Mean procedure time was 49 minutes, time to discharge was 8.2 hours, time to normal activities was 5.2 days, and time to return to work was 5.1 days. At 12 months follow-up, fibroid volume decreased by 66%, HRQL increased by 39 points, and SSS decreased by 42 points (all $P < .001$ versus baseline). The annual cumulative rate of reinterventions due to fibroid-related symptoms was 4.2%, 8.2%, and 11.5% through 3 years.

Conclusions: RFA of uterine fibroids significantly reduces fibroid volume, provides significant durable improvements in fibroid-related quality of life, and is associated with favorable reintervention rates.

Keywords: laparoscopic, leiomyoma, myoma, radiofrequency, transcervical, transvaginal

Introduction

Uterine fibroids are the most common benign solid pelvic tumor in women, developing in ~70% to 80% of women by 50 years of age.[1] More than 1 in 3 women with uterine fibroids report symptoms that interfere with activities of daily living such as heavy menstrual bleeding and/or bulk symptoms.[2] Self-management with nonprescription medication or lifestyle modification is common, but often unsuccessful.[3] Several surgical and interventional treatments are available to women with persistent symptoms attributable to uterine fibroids, including hysterectomy, myomectomy, and uterine artery embolization. However, patient acceptance of these treatments may be limited due to the increasing demand for less invasive therapies that preserve the uterus.[3]

Radiofrequency ablation (RFA) has emerged as a safe and effective treatment alternative as the procedure can be delivered in a minimally invasive fashion. RFA may be delivered by a laparoscopic, transvaginal, or transcervical approach into the uterine fibroid to induce coagulative necrosis[4] with subsequent reduction in fibroid-related symptoms. Previous reviews, often limited to a single device or treatment route, have reported patient outcomes following

[1]Department of Obstetrics and Gynecology, Women's Health Institute, Center for Menstrual Disoders, Cleveland Clinic, Cleveland, Ohio.
[2]Department of Obstetrics and Gynecology, University of Louisville Hospital, Louisville, Kentucky.
[3]Miller Scientific Consulting, Inc., Asheville, North Carolina.

ELSEVIER

JMIG The Journal of Minimally Invasive Gynecology

Review Article

Quality of Life, Adverse Events, and Reintervention Outcomes after Laparoscopic Radiofrequency Ablation for Symptomatic Uterine Fibroids: A Meta-Analysis

Letao Lin, MD, Haocheng Ma, MD, Jian Wang, MD, Haitao Guan, MD, Min Yang, MD, Xiaoqiang Tong, MD, and Yinghua Zou, MD

From the Department of Interventional Radiology and Vascular Surgery, Peking University First Hospital, Beijing, China (all authors).

ABSTRACT In this review, we assessed the short-term (3 and 6 months) and long-term (12, 24, and 36 months) symptom relief and quality of life improvement, procedure-related adverse event rate, reintervention rate, and days missed from work after laparoscopic radiofrequency ablation. Using MeSH keywords "uterine fibroid" and "ablation technique," a systematic search was performed in PubMed, Ovid, Embase, Cochrane Library, and Clinicaltrials.gov. Studies consisting of uterine fibroid symptoms and quality of life scores were considered eligible. Both comparative and noncomparative studies were included. Using a random-effects model, a meta-analysis was performed. Eight studies with a total of 581 patients were finally included in our review. Based on validated questionnaires, quality of life improved significantly until 36 months after laparoscopic radiofrequency ablation therapy, with a maximum improvement (Health-Related Quality of Life [HRQL] questionnaire score of +41.64 [95% confidence interval (CI), 38.94−44.34] and a transformed Symptom Severity Score [tSSS] of -39.37 [95% CI, 34.70−44.04]) at 12 months after laparoscopic radiofrequency ablation. All subscales of quality of life improved significantly, and most of the changes remained stable in long-term follow-up. The overall reintervention rate was 4.39% (95% CI, 1.60% −8.45%), and the median uterine volume reduction was 69.17 cm^3 (95% CI, 35.87−102.46 cm^3).The overall procedure-related adverse events rate was 1.78% (95% CI, 0.62%−3.53%), and patients missed an average of 4.35 days (95% CI, 2.55−6.15 days) of work. In conclusion, laparoscopic radiofrequency ablation therapy is an efficacious way to treat small-sized and nonpedunculated symptomatic uterine fibroids, providing stable long-term symptom relief and quality of life improvement with a low risk of adverse events and reintervention and just a few days of missed work. Journal of Minimally Invasive Gynecology (2019) 26, 409−416. © 2018 AAGL. All rights reserved.

Keywords: Laparoscopic radiofrequency ablation; Meta-analysis; Quality of life; Symptomatic uterine fibroid

Uterine fibroids are the most common benign tumors of the female reproductive system, with a cumulative incidence of >70% [1,2]. Approximately 50% of uterine fibroids become symptomatic, resulting in abnormal uterine bleeding, heavy menstrual bleeding, bulk symptoms, and other complications [2]. Owing to these symptoms and the desire for uterine conservation, today more patients desire a uterine-sparing treatment for fibroids [3]. The Society of Obstetricians and Gynaecologists of Canada guideline on this topic recommends several uterine-sparing procedures, including laparoscopic radiofrequency ablation [4].

The methodology and outcomes of studies of laparoscopic radiofrequency ablation differ. Therefore, we conducted this meta-analysis to evaluate time-related postoperative uterine fibroid symptoms and quality of life in patients after laparoscopic radiofrequency ablation. In addition, subscales of quality of life, rates of adverse events and reintervention, days of work missed, and uterine volume changes were assessed to provide a more comprehensive assessment of laparoscopic radiofrequency ablation.

The authors declare that they have no conflicts of interest.

Drs. Letao Lin and Haocheng Ma contributed equally to this work.

Precis: Laparoscopic radiofrequency ablation is efficacious for symptomatic uterine fibroids, providing long-term symptom relief and quality of life improvement with a low risk of adverse events and reintervention and only a few days of missed work.

Corresponding author: Yinghua Zou, MD, Department of Interventional Radiology and Vascular Surgery, Peking University First Hospital, No. 8 Xishiku St, Xicheng District, Beijing, 100034.
E-mail: yinghzou@139.com

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ovarian failure, and pulmonary embolism (20, 57). Minor complications occur in 21–64% of cases and are variably defined among different UAE studies (57). Minor complications may include pain, fever, and nausea associated with postembolization syndrome; vaginal discharge; and pelvic infection. Uterine artery embolization can be performed as an ambulatory procedure and is associated with a shorter procedural time, shorter hospital stay, and faster recovery time compared with surgical interventions (54). However, the rates of unscheduled visits and readmission are higher with UAE than with surgical interventions (OR, 2.74; 95% CI, 1.42–5.26) (54).

Data are limited on the effects of UAE on fertility and future pregnancy (20), and there is conflicting evidence on the effects on ovarian reserve. Rates of ovarian failure after UAE (defined as a follicle stimulating hormone level greater than 40 IU/L at 1 year after treatment) have been reported to be as high as 12% and 18% at 12 and 24 months, respectively, which is comparable to the rates associated with hysterectomy (20). In contrast, a more recent meta-analysis of six studies and 353 participants demonstrated no effect on ovarian reserve, as measured by serum concentrations of antimüllerian hormone and follicle stimulating hormone at 12 months postprocedure, although antral follicle count in two of the studies demonstrated a significant decline at 3 months (58). Compared with expectant management, and matched for age and leiomyoma location, uterine leiomyoma treatment with UAE is associated with an increased risk of pregnancy loss (35.2% versus 16.5%; OR, 2.8; 95% CI, 2.0–3.8), cesarean delivery (66% versus 48.5%; OR, 2.1; 95% CI, 1.4–2.9), and postpartum hemorrhage (13.9% versus 2.5%; OR, 6.4; 95% CI, 3.5–11.7) (59). There is conflicting evidence on reproductive outcomes of UAE compared with myomectomy, and small sample sizes in the available studies make it difficult to draw comparative conclusions (54, 60).

Radiofrequency Ablation

Laparoscopic radiofrequency ablation can be considered as a minimally invasive treatment option for the management of symptomatic leiomyomas in patients who desire uterine preservation and are counseled about the limited available data on reproductive outcomes. Radiofrequency ablation (RFA) can be delivered by a laparoscopic, transvaginal, or transcervical approach, using ultrasound guidance to induce coagulative necrosis in targeted uterine leiomyomas. All of the approaches are similarly effective in reducing uterine leiomyoma volume and in improving quality of life metrics, but the laparoscopic approach has been studied the most rigorously (61). Although RFA is a reasonable option to consider for the treatment of symptomatic uterine leiomyomas, access to this technology is currently limited.

Although laparoscopic RFA with a leiomyoma-specific FDA-approved device has been studied primarily in nonrandomized trials (62), two recent meta-analyses summarize long-term data on the use of RFA to treat a wide variety of leiomyoma types and sizes (61, 63). In these two meta-analyses, which included over 1,800 patients, uterine leiomyoma volume reduction ranged from 32% to 66% at 12 months, and 77% at greater than 12 months follow up (61, 63). The cumulative rate of postoperative surgical reintervention for leiomyoma-related symptoms was 4.2%, 8.2%, and 11.5% at 1, 2, and 3 years, respectively (61). Statistically and clinically significant improvements were observed in health-related quality of life and symptom severity in long-term follow up (up to 36 months) (61). Complication reporting was highly inconsistent, but no serious procedural complications such as death or injury to visceral structures was reported in any of the included studies. Neither meta-analysis reported outcomes on menstrual bleeding.

In a case-series of 30 pregnancies after laparoscopic RFA, there were 26 full-term live births and four pregnancy losses (64). Although in this small case series there were no cases of preterm delivery, uterine rupture, placental abruption, placenta accreta, or intrauterine growth restriction (64), sample size precludes any definitive conclusions about risk or incidence of pregnancy complications.

Focused Ultrasound

Focused ultrasound surgery, guided by diagnostic ultrasound or magnetic resonance, is a noninvasive treatment modality that uses multiple high-intensity ultrasound waves to cause coagulative necrosis of uterine leiomyomas. Currently only magnetic resonance-guided focused ultrasound is FDA approved for the treatment of uterine leiomyomas. Limited, low-quality data suggest that magnetic resonance-guided focused ultrasound and high-intensity focused ultrasound are associated with a reduction in leiomyoma and uterine size (20, 65). However, small randomized comparative trial data suggest that compared with UAE, magnetic resonance-guided focused ultrasound is associated with less improvement in symptoms and quality-of-life measures and a higher risk of reintervention (66). In a recent meta-analysis, the rate of reintervention at 60 months was 53.9% (55). Additional data are needed before recommendations can be made regarding the use of this treatment for uterine leiomyomas.

Endometrial Ablation

Limited data suggest that AUB-L is improved with endometrial ablation and is maintained in the year

Radiofrequency Water Vaper Transurethral Destruction of Prostate Tissue

Question: Should radiofrequency water vapor transurethral destruction of prostate tissue be moved to a covered line?

Question source: Holly Jo Hodges, CCO medical director

Issue: Radiofrequency water vapor transurethral destruction of prostate tissue was reviewed in 2018 as a new CPT code. At that time, only one RCT of 197 patients and one pilot study of 30 patients were identified and the evidence was found to be insufficient. The CPT code for this procedure was placed on line 662/GN173. Dr. Hodges has received requests for this procedure and requested an updated evidence review. Since the 2018 review, Cochrane has published a systematic review on this technology and NICE has published guidance.

A minimally invasive treatment for lower urinary tract symptoms (LUTS) using steam energy to coagulate part of the prostate to decrease its size. This technique is known as the Rezum© system.

There was a coverage guidance review in 2016 of minimally invasive treatments for LUTS, but radiofrequency water vapor transurethral destruction of prostate tissue was not included in that review.

Current Prioritized List status
CPT **53854** Transurethral destruction of prostate tissue; by radiofrequency generated water vapor is o on line 662/GN173

Similar codes are on line 327 FUNCTIONAL AND MECHANICAL DISORDERS OF THE GENITOURINARY SYSTEM INCLUDING BLADDER OUTLET OBSTRUCTION

1) CPT 53850 Transurethral destruction of prostate tissue; by microwave thermotherapy
2) CPT 53852 Transurethral destruction of prostate tissue; by radiofrequency thermotherapy

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 enlargement, surgical procedures are included on these lines only if symptoms are severe, and if drug treatment and conservative management options have been unsuccessful or are not appropriate.

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
- International Prostate Symptom Score (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

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

Line 660

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

Procedure Code	Intervention Description	Rationale	Last Review
53854	Transurethral destruction of prostate tissue; by radiofrequency generated water vapor	Insufficient evidence of effectiveness	November, 2018

Evidence

1) **Kang 2020**, Cochrane review of radiofrequency water vapor thermal therapy for LUTS
    a. Identified single, industry-sponsored RCT, with 197 randomized men, that compared convective radiofrequency water vapor thermal therapy to a sham procedure [McVary (several publications), included in 2018 review]
        i. 3 month follow up data only
    b. Convective radiofrequency water vapor thermal therapy may improve urologic symptom scores more than a sham procedure, measured on a IPSS scale (0 to 35; higher score represents worse urological symptoms) by a mean difference (MD) of -6.9 (95% confidence interval (CI) -9.06 to -4.74; 195 men; low-certainty evidence), and likely improves quality of life (QoL), measured on a IPSS-QoL scale (0 to 6; higher score represents worse QoL), by a MD of -1.2 (95% CI -1.66 to -0.74; 195 men; moderate-certainty evidence).
    c. We are very uncertain about the effects of convective radiofrequency water vapor thermal therapy on major adverse events (risk ratio (RR) 6.79, 95% CI 0.39 to 117.00; 197 men; very low-certainty evidence)
    d. We are very uncertain about the effects of convective radiofrequency water vapor thermal therapy on retreatment (RR 1.36, 95% CI 0.06 to 32.86; 197 men; very low-certainty evidence).
    e. Convective radiofrequency water vapor thermal therapy may have little to no effect on erectile function (MD 0.4, 95% CI -1.91 to 2.71; 130 men; low-certainty evidence) and ejaculatory function (MD 0.5, 95% CI -0.83 to 1.83; 130 men; low-certainty evidence).
    f. We found no evidence for other comparisons, such as convective radiofrequency water vapor thermal therapy versus TURP or other minimal invasive procedures.
    g. **Authors' conclusions** Compared to a sham procedure, urologic symptom scores and quality of life appear to improve with convective radiofrequency water vapor thermal therapy, but we are very uncertain about major adverse events. The certainty of evidence ranged from moderate to very low, with study limitations and imprecision being the most common reasons for rating down. These findings are based on a single industry sponsored study, with three-month short-term follow-up. We did not find any studies comparing convective radiofrequency water vapor thermal therapy to any other active treatment form, such as TURP.
2) **NICE 2020,** Rezum for treating lower urinary tract symptoms secondary to benign prostatic hyperplasia https://www.nice.org.uk/guidance/mtg49/resources/rezum-for-treating-lower-urinary-tract-symptoms-secondary-to-benign-prostatic-hyperplasia-pdf-64372064176069
    a. N=4 studies
        i. 1 RCT [Rezum II study also known as McVary, 5 publications, including in Cochrane review above]
            1. Follow up data at 4 years included
        ii. 1 prospective observational study (Dixon, 3 publications)
        iii. 2 retrospective observational studies [Mollengarden 2018, Darson 2017]
    b. The Rezum II study showed that Rezum was associated with statistically significant improvements in lower urinary tract symptoms (LUTS) compared with sham at the 3-month follow up. These improvements were maintained throughout 4 years of follow up. The treatment benefits of Rezum in relieving LUTS were also seen consistently in the observational studies. The incidence of sexual dysfunction after treatment with Rezum was low, with a few people reporting a decrease in ejaculatory function but little change in erectile function. Overall, the evidence base shows that Rezum is an effective

treatment for LUTS in people with benign prostatic hyperplasia (BPH). Rezum also improved quality of life

c. None of the included studies compared Rezum with other commonly used treatments for BPH.
d. The Rezum II study reported 3 procedure-related serious adverse events in the 3-month follow up, including extended urinary retention, and nausea and vomiting, which were considered to be because of the sedative medication. An additional 3 procedure-related serious adverse events were reported with Rezum during the 3- to 12-month follow-up period, including bladder contracture, bladder stone and urosepsis after cystoscopy.
e. Coverage recommendation: Evidence supports the case for adopting Rezum for treating lower urinary tract symptoms (LUTS) caused by benign prostatic hyperplasia (BPH) in the NHS. Rezum relieves LUTS and improves quality of life.

Expert guidelines

1) **Parsons 2020**, Surgical Management of Lower Urinary Tract Symptoms Attributed to Benign Prostatic Hyperplasia: AUA Guideline Amendment 2020
    a. Water vapor thermal therapy may be offered to patients with LUTS attributed to BPH provided prostate volume <80g. (Moderate Recommendation; Evidence Level: Grade C).
    b. Water vapor thermal therapy may be offered to eligible patients who desire preservation of erectile and ejaculatory function. (Conditional Recommendation; Evidence Level: Grade C).

Other payer policies

1) Anthem Blue Cross Blue Shield 2021
    a. radiofrequency water vapor transurethral destruction of prostate tissue is not medically necessary

2) Cigna 2020
    a. Water vapor thermal therapy (e.g., Rezūm System) is considered medically necessary for the treatment of symptomatic benign prostatic hyperplasia (BPH) when ALL of the following criteria are met:
        i. age 50 years or above
        ii. estimated prostate volume ≥ 30 cm3 and ≤ 80 cm3
        iii. failure, contraindication or intolerance to a trial of conventional medical therapy for BPH (e.g., alpha blocker, PDE5 Inhibitor, finasteride/dutasteride)

3) Aetna 2021
    a. Water vapor thermal therapy (e.g., Rezūm System) is considered medically necessary

Expert input

Brian Duty, urologist at OHSU and VbBS member

I have reviewed the summary document that Ariel included and completely agree with the recommendations. As noted, the AUA BPH guidelines were recently updated to include Rezum. Rezum in properly selected patients is believed to be a viable alternative to the UroLift procedure, which I think is covered if I'm reading the document correctly. Botox, HIFU, TEAP, Laser coagulation, and Embolization are not, which I agree with

Radiofrequency Water Vaper Transurethral Destruction of Prostate Tissue

HERC staff summary

Additional studies have been published since the 2018 HERC review of radiofrequency water vapor transurethral destruction of prostate tissue, as well as additional follow up of the one RCT included in the 2018 review. Including only the one published RCT on this treatment, Cochrane concluded that this procedure improves quality of life (moderate certainty evidence) and improves urologic symptom scores (low certainty evidence). Based on this same RCT, as well as 3 additional studies, NICE has concluded that this technology has enough evidence to support its use.

This technology has a level 3 recommendation from the AUA and is covered by most private insurers

HERC staff recommendations:

1) Add CPT **53854** (Transurethral destruction of prostate tissue; by radiofrequency generated water vapor) to line 327 FUNCTIONAL AND MECHANICAL DISORDERS OF THE GENITOURINARY SYSTEM INCLUDING BLADDER OUTLET OBSTRUCTION
    a. Guideline Note 145 criteria would apply
2) Remove CPT 53854 from line 662 CONDITIONS FOR WHICH CERTAIN INTERVENTIONS ARE UNPROVEN, HAVE NO CLINICALLY IMPORTANT BENEFIT OR HAVE HARMS THAT OUTWEIGH BENEFITS /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
~~53854~~	~~Transurethral destruction of prostate tissue; by radiofrequency generated water vapor~~	~~Insufficient evidence of effectiveness~~	~~November, 2018~~

Cochrane Library

Cochrane Database of Systematic Reviews

Convective radiofrequency water vapour thermal therapy for lower urinary tract symptoms in men with benign prostatic hyperplasia (Review)

Kang TW, Jung JH, Hwang EC, Borofsky M, Kim MH, Dahm P

Kang TW, Jung JH, Hwang EC, Borofsky M, Kim MH, Dahm P.
Convective radiofrequency water vapour thermal therapy for lower urinary tract symptoms in men with benign prostatic hyperplasia.
Cochrane Database of Systematic Reviews 2020, Issue 3. Art. No.: CD013251.
DOI: 10.1002/14651858.CD013251.pub2.

www.cochranelibrary.com

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[Intervention Review]

Convective radiofrequency water vapour thermal therapy for lower urinary tract symptoms in men with benign prostatic hyperplasia

Tae Wook Kang[1], Jae Hung Jung[1,2], Eu Chang Hwang[3], Michael Borofsky[4], Myung Ha Kim[5], Philipp Dahm[6]

[1]Department of Urology, Yonsei University Wonju College of Medicine, Wonju, Korea, South. [2]Institute of Evidence Based Medicine, Yonsei University Wonju College of Medicine, Wonju, Korea, South. [3]Department of Urology, Chonnam National University Medical School, Chonnam National University Hwasun Hospital, Hwasun, Korea, South. [4]Department of Urology, University of Minnesota, Minneapolis, Minnesota, USA. [5]Yonsei Wonju Medical Library, Yonsei University Wonju College of Medicine, Wonju, Korea, South. [6]Urology Section, Minneapolis VA Health Care System, Minneapolis, Minnesota, USA

Contact address: Jae Hung Jung, Institute of Evidence Based Medicine, Yonsei University Wonju College of Medicine, 20 Ilsan-ro, Wonju, Gangwon, 26426, Korea, South. jungx563@gmail.com, geneuro95@yonsei.ac.kr.

Editorial group: Cochrane Urology Group.
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ABSTRACT

Background

New minimal invasive surgeries have been suggested as alternative options to transurethral resection of the prostate (TURP) for the management of lower urinary tract symptoms (LUTS) in men with benign prostatic hyperplasia (BPH). Convective radiofrequency water vapour thermal therapy is a new technology that uses targeted, controlled water vapour energy (steam) to create necrotic tissue in the prostate.

Objectives

To assess the effects of convective radiofrequency water vapour thermal therapy for the treatment of lower urinary tract symptoms in men with benign prostatic hyperplasia.

Search methods

We performed a comprehensive search of multiple databases (the Cochrane Library, MEDLINE, Embase, Latin American and the Caribbean Health Sciences Literature, Scopus, Web of Science), trials registries, other sources of grey literature, and conference proceedings published up to 18 February 2020, with no restriction on the language or status of publication.

Selection criteria

We included parallel-group randomised controlled trials (RCTs), cluster-RCTs, and non-randomised observational prospective studies with concurrent comparison groups, in which men with BPH underwent convective radiofrequency water vapour thermal therapy, another active therapy, or a sham procedure.

Data collection and analysis

Two review authors independently screened the literature, extracted data, and assessed risk of bias. We had planned to perform statistical analyses using a random-effects model, and interpret them according to the *Cochrane Handbook for Systematic Reviews of Interventions.* We rated the certainty of the evidence according to the GRADE approach.

Main results

We included a single, industry-sponsored RCT, with 197 randomised men, that compared convective radiofrequency water vapour thermal therapy to a sham procedure. The mean age 62.9 years, the International Prostate Symptom Score (IPSS) was 21.97, and the mean prostate volume was 45.4 mL. We only found short-term data, measured up to three months.

Primary outcomes

Convective radiofrequency water vapour thermal therapy may improve urologic symptom scores more than a sham procedure, measured on a IPSS scale (0 to 35; higher score represents worse urological symptoms) by a mean difference (MD) of -6.9 (95% confidence interval (CI) -9.06 to -4.74; 195 men; low-certainty evidence), and likely improves quality of life (QoL), measured on a IPSS-QoL scale (0 to 6; higher score represents worse QoL), by a MD of -1.2 (95% CI -1.66 to -0.74; 195 men; moderate-certainty evidence). We are very uncertain about the effects of convective radiofrequency water vapour thermal therapy on major adverse events (risk ratio (RR) 6.79, 95% CI 0.39 to 117.00; 197 men; very low-certainty evidence) assessed by the Clavien-Dindo classification system of III, IV, and V complications.

Secondary outcomes

We are very uncertain about the effects of convective radiofrequency water vapour thermal therapy on retreatment (RR 1.36, 95% CI 0.06 to 32.86; 197 men; very low-certainty evidence). Convective radiofrequency water vapour thermal therapy may have little to no effect on erectile function (MD 0.4, 95% CI -1.91 to 2.71; 130 men; low-certainty evidence) and ejaculatory function (MD 0.5, 95% CI -0.83 to 1.83; 130 men; low-certainty evidence). Convective radiofrequency water vapour thermal therapy may increase minor adverse events assessed by the Clavien-Dindo classification system of Grade I and II complications (RR 1.89, 95% CI 1.15 to 3.11; 197 men; low-certainty evidence). This would correspond to 434 minor adverse events per 1000 men (95% CI 264 more to 714 more). We are very uncertain about the effects of convective radiofrequency water vapour thermal therapy on acute urinary retention (RR 4.98, 95% CI 0.28 to 86.63; 197 men; very low-certainty evidence). It likely greatly increases the rate of men requiring indwelling urinary catheters (RR 35.58, 95% CI 15.37 to 82.36; 197 men; moderate-certainty evidence).

We were unable to perform any of the predefined secondary analyses.

We found no evidence for other comparisons, such as convective radiofrequency water vapour thermal therapy versus TURP or other minimal invasive procedures.

Authors' conclusions

Compared to a sham procedure, urologic symptom scores and quality of life appear to improve with convective radiofrequency water vapour thermal therapy, but we are very uncertain about major adverse events. The certainty of evidence ranged from moderate to very low, with study limitations and imprecision being the most common reasons for rating down. These findings are based on a single industry-sponsored study, with three-month short-term follow-up. We did not find any studies comparing convective radiofrequency water vapour thermal therapy to any other active treatment form, such as TURP.

PLAIN LANGUAGE SUMMARY

Convective radiofrequency water vapour thermal therapy for lower urinary tract symptoms in men with benign prostatic hyperplasia

Review Question

What are the effects of convective radiofrequency water vapour thermal therapy in men with bothersome urinary symptoms because of an enlarged prostate?

Background

Prostate enlargement is common in older men, and can cause bothersome urinary symptoms, such as having to pass their water (voiding) often, a weak stream while voiding, or dribbling. If lifestyle changes and medications don't help, a variety of surgical procedures, including transurethral resection of the prostate (TURP), can improve these symptoms. They may also cause unwanted effects, such as problems with ejaculation or erections. Recently, a new procedure called 'convective radiofrequency water vapour thermal therapy' has become available. It is unclear how it compares to other treatments, such as TURP.

Study characteristics

We found a single study, with 197 men, that compared convective radiofrequency water vapour thermal therapy to a sham procedure (men were made to believe they received treatment, while in reality, they did not), funded by the device company. The men's average age was 62.9 years, and most had a moderate degree of bothersome urinary symptoms.

We found no studies that compared convective radiofrequency water vapour thermal therapy to another form of active treatment, such as TURP that men with an enlarged prostate and bothersome symptoms might otherwise choose.

Key results

Compared to a sham procedure, and with a three-month follow-up, convective radiofrequency water vapour thermal therapy may improve urinary symptoms (low certainty of evidence). Convective radiofrequency water vapour thermal therapy also likely improves quality of life (moderate certainty of evidence). We are very uncertain whether serious unwanted side effects are more common or not (very low certainty of evidence). Men's erections and ejaculations may be similar in men who have convective radiofrequency water vapour thermal therapy and those who receive the sham procedure (low certainty of evidence).

Findings of this review are up to date until 18 February 2020.

Certainty of the evidence

We judged the certainty of the evidence for the outcomes to be moderate, low or very low. Reasons for not being so confident had to do with the study design and the study size.

Surgical Management of Lower Urinary Tract Symptoms Attributed to Benign Prostatic Hyperplasia: AUA Guideline Amendment 2020

J. Kellogg Parsons,* Philipp Dahm, Tobias S. Köhler, Lori B. Lerner and Timothy J. Wilt

From the UCSD School of Medicine, La Jolla, California

Purpose: The AUA Guideline panel provides evidence-based recommendations for the surgical management of male lower urinary tract symptoms (LUTS) secondary to benign prostatic hyperplasia (BPH).

Materials and Methods: The Panel amended the Guideline in 2020 to reflect additional literature published through September 2019. When sufficient evidence existed, the Panel assigned the body of evidence a strength rating of A (high), B (moderate), or C (low) for support of Strong, Moderate, or Conditional Recommendations. In the absence of sufficient evidence, the Panel provided additional information as Clinical Principles and Expert Opinions (See table 1).

Results: Amendments to these Guidelines include: 1) an amended statement (Guideline 1) to include conducting a physical examination; 2) a new statement (Guideline 6) discussing concepts of treatment failure and retreatment; 3) an amended statement (Guideline 15) with updated supporting text for prostatic urethral lift (PUL); 4) an amended statement (Guideline 16) for PUL; 5) an amended statement (Guideline 17) with updated supporting text for transurethral microwave therapy (TUMT); 6) an amended statement (Guideline 18) with updated supporting text for water vapor thermal therapy; 7) updated supporting text for water vapor thermal therapy (Guideline 19); 8) an amended statement (Guideline 21) with updated supporting text for laser enucleation; 9) an amended statement (Guideline 22) with updated supporting text for Aquablation; and 10) an amended statement (Guideline 23) with updated supporting text for Prostate Artery Embolization (PAE).

Conclusions: These evidence-based updates to the AUA Guidelines further inform the surgical management of LUTS/BPH.

Key Words: transurethral resection of the prostate, laser therapy, lower urinary tract symptoms, prostate

Abbreviations and Acronyms

AUA = American Urological Association

BPE = Benign Prostatic Enlargement

BPH = Benign Prostatic Hyperplasia

HoLEP = Holmium Laser Enucleation of the Prostate

LUTS = Lower Urinary Tract Symptoms

LUTS/BPH = Lower Urinary Tract Symptoms Attributed to Benign Prostatic Hyperplasia

PAE = Prostate Artery Embolization

PUL = Prostatic Urethral Lift

RCT = Randomized Control Trial

ThuLEP = Thulium Laser Enucleation of the Prostate

TURP = Transurethral Resection of the Prostate

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* Correspondence: UCSD School of Medicine, La Jolla, California (e-mail: k0parsons@health.ucsd.edu).

BPH is a histologic diagnosis that refers to the proliferation of glandular epithelial tissue, smooth muscle, and connective tissue within the prostatic transition zone.[1] BPH is common in the aging male. The prevalence increases with age.[2]

Asymptomatic BPH does not require treatment. However, BPH can lead to an enlargement of the prostate (benign prostatic enlargement [BPE]). BPE may cause functional obstruction of the bladder outlet (benign prostatic obstruction), which may induce lower urinary tract symptoms (LUTS), urinary infections, bladder stones, and other conditions. Lower urinary tract obstruction may also be caused by

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Thrush

Question: Should thrush be moved to a covered line?

Question source: Ben Hoffman, MD, pediatrician

Issue: Currently, thrush (ICD-10-CM B37.0 Candidal stomatitis) is on lines 137 OPPORTUNISTIC INFECTIONS IN IMMUNOCOMPROMISED HOSTS; CANDIDIASIS OF STOMA; PERSONS RECEIVING CONTINUOUS ANTIBIOTIC THERAPY, 275 UROLOGIC INFECTIONS, and 583 CANDIDIASIS OF MOUTH, SKIN AND NAILS. Dr. Hoffman is requesting that thrush be moved to a covered line to ensure that breastfeeding babies can receive treatment. Thrush can be one cause of pain with breastfeeding, and lack of treatment can lead to discontinuation of breastfeeding.

According to the Academy of Breastfeeding Medicine (2016), thrush is treated with topical miconazole, clotrimazole, or nystatin to the maternal nipple and nystatin suspension or gentian violet for the infant's mouth. These medications are generally covered as inexpensive medications; however, if a CCO or HSD wanted to PA these medications, they would not be covered for thrush unless the patient was immunocompromised.

Additionally, HERC staff noted that one line containing ICD-10-CM B37.0 (line 275 UROLOGIC INFECTIONS) is not an appropriate line for mouth infection diagnosis. Urologic thrush is coded with ICD-10-CM B37.4 (Candidal cystitis and urethritis).

Review of old HSC/HERC minutes found no mention of previous review of thrush.

HERC staff recommendations:

1) Add ICD-10-CM B37.0 (Candidal stomatitis) to line 18 FEEDING PROBLEMS IN NEWBORNS
2) Remove ICD-10-CM B37.0 from lines 275 UROLOGIC INFECTIONS and 583 CANDIDIASIS OF MOUTH, SKIN AND NAILS
    a. Change the line name of line 583 to CANDIDIASIS ~~OF MOUTH,~~ SKIN AND NAILS

BREASTFEEDING MEDICINE
Volume 11, Number 2, 2016

DOI: 10.1089/bfm.2016.29002.pjb

ABM Clinical Protocol #26: Persistent Pain with Breastfeeding

Pamela Berens,[1] Anne Eglash,[2] Michele Malloy,[2] Alison M. Steube,[3,4]
and the Academy of Breastfeeding Medicine

A central goal of The Academy of Breastfeeding Medicine is the development of clinical protocols for managing common medical problems that may impact breastfeeding success. These protocols serve only as guidelines for the care of breastfeeding mothers and infants and do not delineate an exclusive course of treatment or serve as standards of medical care. Variations in treatment may be appropriate according to the needs of an individual patient.

Purpose

TO PROVIDE EVIDENCE-BASED GUIDANCE in the diagnosis, evaluation, and management of breastfeeding women with persistent nipple and breast pain.

Definitions

Among breastfeeding women, it can be challenging to distinguish pathologic pain from discomfort commonly reported in the first few weeks of breastfeeding. In this protocol, we define persistent pain as breastfeeding-associated pain lasting longer than 2 weeks. We are not addressing acute or recurrent mastitis as it is covered in ABM Protocol #4 Mastitis, Revised March 2014.[1]

Background

Pain and discomfort associated with breastfeeding are common in the first few weeks postpartum.[2] (II-2) (Quality of evidence [levels of evidence I, II-1, II-2, II-3, and III] is based on the U.S. Preventive Services Task Force Appendix A Task Force Ratings[3] and is noted in parentheses.) Since this is a common cause for early breastfeeding cessation,[4] the mother–baby dyad should be evaluated by a lactation specialist. Beyond this early period, reports of pain generally decline, but as many as one in five women report persistent pain at 2 months postpartum.[5] While initial discomfort with early latch may be considered physiological, pain severe enough to cause premature weaning should not. In one study of 1323 mothers who stopped breastfeeding during the first month postpartum, 29.3% cited pain and 36.8% identified sore, cracked, or bleeding nipples as an important reason.[6] Several authors have found a relationship between breastfeeding-associated pain and postpartum depression.[7,8] (II-2, III)

These studies suggest that breastfeeding-associated pain is linked with significant psychological stress; thus, mothers presenting with pain should be evaluated for mood symptoms and followed closely for resolution or treatment as needed. Timely identification and appropriate management of persistent breastfeeding-associated pain are crucial to enable women to achieve their infant feeding goals.

Although the literature on persistent nipple and/or breast pain is limited and the differential diagnosis is extensive, a number of etiologies and management strategies are emerging, most of which are based on expert opinion. The highly individual nature of the breastfeeding relationship combined with the complexity of the lactating breast, including its anatomy, physiology, and dynamic microbiome, adds challenges to the clinicians' efforts.

History and Examination

Assessment of persistent pain begins with a careful history and physical examination of both mother and infant, with particular attention to the following:

- Breastfeeding history
  - Previous breastfeeding experiences/problems/pain
  - Nipple/breast sensitivity before pregnancy
  - Milk supply (ongoing engorgement, high supply versus low supply)
  - Pattern of breastfeeding (frequency, duration, one, or both breasts)

[1]Department of Obstetrics and Gynecology, University of Texas Health Sciences Center at Houston, Houston, Texas.
[2]Department of Family and Community Medicine, University of Wisconsin School of Medicine and Public Health, Madison, Wisconsin.
[3]Department of Obstetrics and Gynecology, University of North Carolina School of Medicine, Chapel Hill, North Carolina.
[4]Carolina Global Breastfeeding Institute, Department of Maternal and Child Health, Gillings School of Global Public Health, Chapel Hill, North Carolina.

Table 1. Conditions, Symptoms, and Management of Persistent Nipple/Breast Pain

Condition	*Symptoms/signs*	*Management*
Infant ankyloglossia	Ongoing nipple damage and an infant with restricted tongue movement due to a tight lingual frenulum	• Frenulotomy/frenulectomy using scissors or laser by a trained health professional[44–46] (I, II-2, 1).
Breast pump trauma/misuse	Nipple or soft tissue injury/bruising	• Observe a pumping session. • Adjust level of suction or fit of flange.
Eczematous conditions	Erythematous skin *Acute* episodes: blisters, erosions, weeping/oozing, and crust formation *Chronic* eruptions: dry, scaling, and lichenified (thickened) areas. Lesions can be pruritic, painful, or even burning.[18,20]	• Reduce identifiable triggers. • Apply an emollient. • Apply low/medium-strength steroid ointment twice daily for 2 weeks (immediately after a breastfeed to maximize contact time before the next breastfeed).[20] • Use second-generation antihistamines for pruritus.[20] • Consider a short course (less than 3 weeks) of oral prednisolone or prednisone in resistant cases.[20,47]
Psoriasis	Erythematous plaques Clearly demarcated borders Fine silvery overlying scale	• Apply an emollient.[20,48] (I) • Apply low/medium-strength steroid ointment twice daily (immediately after a breastfeed) as first-line treatment.[20,48] • Avoid prolonged topical steroid use to prevent thinning of the nipple epithelium and delayed healing. • Topical Vitamin D creams or gels and phototherapy (UVB) are safe to use.[20,48] • Immunomodulating agents should not be used on the nipple due to the risk of infant oral absorption.[47]
Superficial bacterial infection associated with skin trauma	Persistent cracks, fissures Weeping, yellow crusted lesions especially in conjunction with other skin conditions Cellulitis	• Topical mupirocin or bacitracin ointment. • Oral antibiotics such as a cephalosporin or penicillinase-resistant penicillin[18,49] (I)
Bacterial dysbiosis	Bilateral dull, deep aching bilateral breast pain±burning Pain during and after breastfeeds Breast tenderness (especially lower quadrants)[29]	• Consider oral antibiotics such as a cephalosporin, amoxicillin/clavulanate, dicloxacillin, or erythromycin for 2–6 weeks.[20,29] • Indirect evidence to support that breast probiotics may assist the restoration of normal breast flora.[50,51]
Candida infection	Pink nipple/areola area Shiny or flaky appearance of the nipple Nipple pain out of proportion to the clinical findings Burning nipple pain and pain radiating into the breast[20,23]	• Topical azole antifungal ointment or cream (miconazole and clotrimazole also inhibit the growth of *Staphylococcus sp*) on nipples.[20] • Nystatin suspension or miconazole oral gel for infant's mouth.[20] • Gentian violet (less than 0.5% aqueous solution) may be used daily for no more than 7 days. Longer durations and higher concentrations may cause ulcerations and skin necrosis.[20,52] • Oral fluconazole (200 mg once, then 100 mg daily for 7–10 days) may be used for resistant cases. • Before prescribing fluconazole, review all maternal medications and assess for drug interactions. Do not use fluconazole in combination with domperidone or erythromycin due to concern of prolonged QT intervals.
Herpes simplex	Small, clustered exquisitely tender vesicles with an erythematous, edematous base Solitary small ulcer[20,53] Axillary lymphadenopathy[53]	• Oral antiviral therapy such as acyclovir or valacyclovir should be used in doses recommended for treating primary or recurrent Herpes simplex infections. • Prevent contact between lesions and the infant. • Avoid breastfeeding or feeding expressed breast milk to infants from an affected breast/nipple until the lesions are healed to prevent neonatal herpes infection.

(*continued*)

Section 8.0

Coverage Guidances

Deep Brain Neurostimulators for Refractory Epilepsy

Draft Coverage Guidance for VbBS Review

August 12, 2021

Oregon Health Authority

Oregon Health & Science University

Center For Evidence-based Policy

Disclosures

- None of the authors have any conflicts of interest to disclose.
- This slide set is designed for a live presentation with commentary, to accompany the full report. For the full draft coverage guidance (CG), see the 4/8/2021 EbGS Meeting Materials.

Background

- Approximately 3.4 million individuals diagnosed with epilepsy in the US, and about 42,900 live in Oregon (per the CDC in 2015)
- First line treatment is antiseizure medications, but about a third of patients continue to have seizures
  - Refractory epilepsy associated with adverse outcomes, including brain damage from continued seizures
  - Among individuals who undergo resective surgery after failing to control seizures with medication, 37% to 70% continue to have seizures
- Individuals with poorly controlled epilepsy who are either ineligible for resective surgery or other treatments (e.g., vagal nerve stimulation) may consider deep brain stimulation (DBS)

Background

- DBS is approved by the US Food and Drug Administration (FDA) for use in individuals 18+ years of age diagnosed with epilepsy characterized by partial onset seizures, with or without secondary generalization, and who have failed 3 or more trials of antiepileptic medications
- FDA approved the Medtronic DBS system for epilepsy on April 27, 2018

See 4/8/2021 EbGS meeting materials for the complete draft report.

Scope Statement

Population

Adults with refractory epilepsy who:

- Have a diagnosis of epilepsy characterized by partial-onset seizures with or without secondary generalization; and
- Have not responded to adequate trials of 3 or more antiepileptic medications; and
- Have averaged 6 or more seizures per month during the previous 3 months, with no more than 30 days between seizures; and
- Have focal anterior thalamic nucleus targets; and
- Are not candidates for resective epilepsy surgery or have a history of failed resective epilepsy surgery; and
- Are not candidates for other treatments for refractory epilepsy (e.g., vagal nerve stimulation) or have a history of failed treatments.

See 4/8/2021 EbGS meeting materials for the complete draft report.

Intervention and Comparators

Interventions

- Deep brain stimulation of the anterior nucleus of the thalamus (ANT)

Comparators

- Antiseizure medications or other treatments

See 4/8/2021 EbGS meeting materials for the complete draft report.

Outcomes

Critical Outcomes

- Hospitalization
- Harms (e.g., depression, suicidality, memory loss, surgery-related adverse events)

Important Outcomes

- Clinically significant change in seizure frequency
- Clinically significant improvement in standardized seizure severity scale
- Clinically significant change in medication use

See 4/8/2021 EbGS meeting materials for the complete draft report.

Key Questions

KQ1: What is the comparative effectiveness of deep brain stimulation of the anterior nucleus of the thalamus to treat refractory epilepsy?

KQ2: Does the comparative effectiveness of deep brain stimulation of the anterior nucleus of the thalamus vary by:

- Type of epilepsy
- Patient characteristics
- Previous treatments
- Location of seizure focus

KQ3: What are the harms of deep brain stimulation of the anterior nucleus of the thalamus to treat refractory epilepsy?

See 4/8/2021 EbGS meeting materials for the complete draft report.

Evidence Review

Oregon Health Authority

OREGON HEALTH & SCIENCE UNIVERSITY

Center For Evidence-based Policy

Evidence Source Overview

- To answer the key questions, we identified:
  - 2 randomized controlled trials (RCTs)
  - Observational follow-ups of RCTs during unblinded phases
  - 2 narrative systematic reviews that included description of harms
  - 3 observational databases and registries
  - 2 ongoing trials from the Clinical Trials Registry

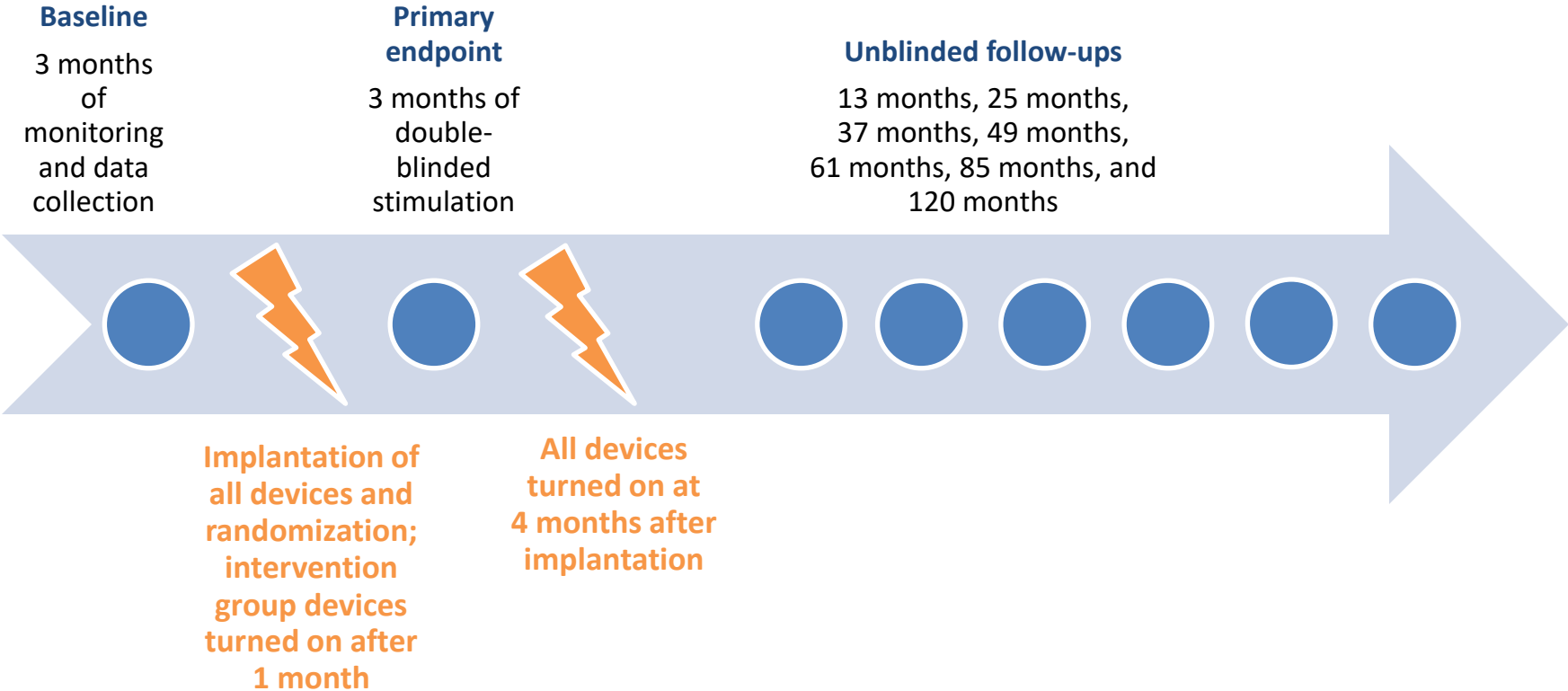
See 4/8/2021 EbGS meeting materials for the complete draft report.

KQ1: Effectiveness Sources

- Two RCTs with similar trial designs and samples (intervention, N = 62; control, N = 65)
  - Fisher et al., 2010 (CG ref# 11) and Herrman et al., 2019 (CG ref# 12)
- Adults with medically refractory partial seizures (mean age, 36.1 ± 11.2)
  - At least 6 seizures per month, but no more than 10 per day
  - Seizure frequency was 53.1 per month in the Herrman trial (N = 18)
- All were taking at least 1 antiseizure medication at baseline
  - 50% were taking 2 antiseizure medications
  - 37.5% were taking 3 antiseizure medications
  - 24.5% were taking 4 antiseizure medications
- 53% had tried resective surgery or vagal nerve stimulation

SANTE Trial Design (N = 109)

Intervention N = 54
Control N = 55



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Herrman Trial Design (N = 18)

Intervention N = 8
Control N = 10

Intended enrollment N = 40

Baseline

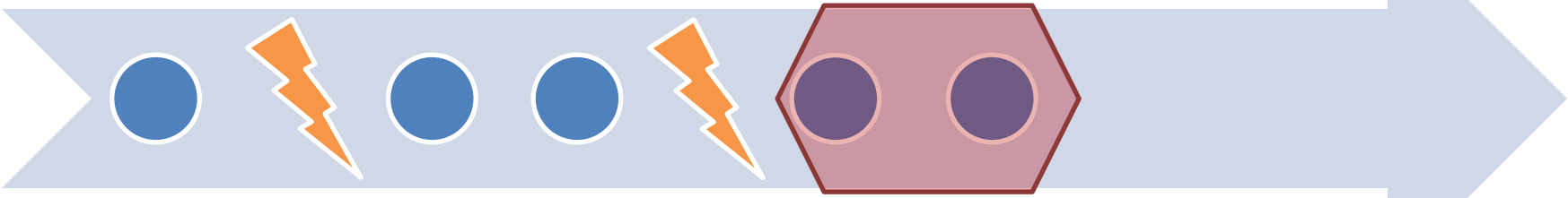
3 months of monitoring and data collection

Primary endpoints

3 and 6 months of double-blinded stimulation

Unblinded follow-ups

9 months and 12 months



Implantation and randomization; intervention group devices turned on after 1 month

All devices turned on at 7 months after implantation

Inclusion and enrollment discontinued after possible harm signal during halfway interim analysis

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Reporting Trial Results

Blinded: Only the intervention group had stimulation

- Follow-up at 3 months for SANTE trial
- Follow-up at 3 and 6 months for Herrman trial

Unblinded: Stimulators were turned on for both groups

- Follow-up at 13, 25, 37, 49, 61, 85, and 120 months for SANTE trial
- Follow-up at 9 and 12 months for Herrman trial

See 4/8/2021 EbGS meeting materials for the complete draft report.

KQ1: Seizure Frequency

- Blinded Phase
  - 29% greater reduction after 3 months in SANTE trial (54 of 109 received stimulation), but no significant difference at 6 months in Herrman trial (8 of 18 received stimulation)
- Unblinded Phase
  - 56% reduction after 2 years compared to baseline (N = 81), and a 69% median reduction after 5 years compared to baseline (N = 59) in SANTE study
    - At 7 years, the mean seizure frequency reduction was 75% compared to baseline (N = 50; $P < .05$)
  - 23% total seizure reduction compared to baseline after 6 months (N = 18) in Herrman study

KQ1: Seizure Severity

- Measured with Liverpool Seizure Severity Scale (LSSS)
  - Developed in Great Britain to assess the severity of seizure symptoms and has been validated in the US
  - Percept subscale (e.g., timing, ability to predict seizure, prevention of normal activities)
  - Ictal/postictal subscale (e.g., loss of consciousness, time to full recovery, perceived severity)

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KQ1: Seizure Severity

- Blinded Phase
  - No significant difference between intervention and control groups on LSSS (62 of 127 experienced stimulation)
- Unblinded Phase
  - Compared to baseline LSSS scores, there was an average improvement of 13.4 points (SD, 21.4; N = 103; *P* < .001) after 6 to 12 months, and an average improvement of 18.3 points after 5 years (SD, not reported; N = 81; *P* < .001) and remained stable through 7 years in SANTE study
  - Average improvement of 5 points after 6 months in the Herrman study (N = 18; SD, not reported)

KQ1: Hospitalizations

- No data from RCTs or associated follow-ups
- No data from systematic reviews
- Tafreshi et al., 2021: retrospective, noncomparative analysis of readmissions at 30-, 90-, and 180-day intervals (CG ref# 17)
  - Included 221 individuals with DBS device for refractory epilepsy from US Healthcare Cost and Utilization Project National Readmission Database
    - 4.4% were readmitted within 30 days
    - 14.9% within 90 days
    - 30.6% within 180 days

KQ1: Medication Use

- No data from blinded phases of the trials
- Unblinded phase of SANTE study
  - 61 of 83 participants (73.5%) had added a new antiseizure drug between implantation and 5-year follow-up
  - No comparison group
- No data from systematic reviews

KQ2: Effectiveness by Subpopulations

- No subgroup analyses for types of epilepsy or patient characteristics such as age or sex
- SANTE trial considered treatment history and seizure origin (CG ref# 11)
  - Similar patterns of improvement for participants with prior vagal nerve stimulation, resective surgery, or with neither of those prior treatments (no statistics reported)
  - Effectiveness might vary by location of seizure origin

KQ2: Effectiveness by Subpopulations

- Blinded phase of SANTE trial (CG ref# 11)
  - Of 62 participants who had seizure origins in one or both temporal regions, the intervention group (N = 33) reported greater median reduction in seizure frequency compared to baseline (intervention reduction, 44.2%; control reduction, 21.8%; *P* = .025)
  - No significant difference for participants with seizure origin in frontal, parietal, or occipital regions
  - Nonsignificant trend of median seizure reduction for 17 participants with multifocal or diffuse seizure origin (intervention reduction, 35.0%; control reduction, 14.1%)

KQ3: Harms Sources

- 2 RCTs with observational, noncomparative follow-ups (CG refs# 11-14)
- 2 systematic reviews with moderate risk of bias (CG refs# 15-16)
  - Narrative summaries of nonrandomized studies
  - 1 included 20 abstracts and publications for open-label studies of bilateral stimulation of the anterior nucleus of the thalamus, plus 2 publications of the SANTE trial
  - 1 included 66 studies of DBS-related surgical site infections, and included other DBS targets and indications
- Medtronic registry report (CG ref# 21)
- FDA MAUDE manufacturer and user facility device experience database (CG ref# 18)

KQ3: Depression Harms

- Blinded phase
  - 10 of 62 (16.1%) patients in stimulation group compared to 1 of 65 (1.5%) control group reported depression
    - 7 of those 10 from the intervention group had a history of preexisting depression
- Unblinded phase
  - 43 of 127 (33.9%) reported depression at 5 years
  - 19 of 50 (37.3%) reported depression at 7 years
  - 5 reported suicidality at 7 years

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KQ3: Memory Loss Harms

- Blinded phase
  - 7 of 54 (13%) of intervention group reported memory impairment, compared to 1 of 55 (2%) in control group
- Unblinded phase
  - 32 of 127 (25.2%) of all participants reported memory impairment
  - 5 of 50 (10%) reported memory impairment at 7 years

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KQ3: Surgery-related Harms

- Blinded phase
  - 14 of 109 (13%) participants had implant site infections; 9 of 109 (8.3%) had partial or full explants (did not report by study group, both groups had implantation)
- Systematic review: Kantzanou et al., 2021 (CG ref# 15)
  - 9.5% prevalence of surgical site infections (15 of 158 from 8 studies)

KQ3: Device-related Harms

- Unblinded phase
  - 6 of 127 reported an increase in seizure frequency of 50% or more during active stimulation
  - 7 of 127 (5.5%) experienced status epilepticus under active stimulation
  - 238 adverse events during first 13 months of SANTE study were considered device-related
    - 23% implant site pain
    - 22.7% paresthesia
    - 12.7% implant site infection
    - 10.0% ineffective device
    - Less than 10% experienced: lead misplacement, sensory disturbance, implant site inflammation, dizziness, lead misplacement, postprocedural pain, extensions fracture, or neurostimulator migration

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KQ3: Device-related Harms

- Systematic review: Zangiabadi et al., 2019 (CG ref# 16)
  - Wound infection
  - Lead or extension fracture
  - Erosion
  - Electrode migration
  - External interference with other devices
  - Equipment infection
  - Pain
  - Transient worsening or new seizures
  - Dizziness
  - Hardware discomfort
  - Ineffective product

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KQ3: Device-related Harms

- Medtronic Registry report did not disaggregate by DBS indication (N = 2,637; CG ref# 21)
  - High impedance (N = 187)
  - Lead migration or dislodgment (N = 44)
  - Device malfunction (N = 22)
  - Lead fracture (N = 21)
  - Low impedance (N = 20)
  - Extension migration (N = 19)
  - Neurostimulator failed to recharge (N = 11)
  - Extension fracture (N = 7)
  - Device breakage (N = 5)
  - Lead insulation failure (N = 4)
  - Premature battery depletion (N = 4)
  - Device connection issue (N = 2)
  - Device lead issue (N = 2)
  - Device material issue (N = 2)
  - Electromagnetic interference (N = 2)
  - Other event (N = 4)

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KQ3: Other Harms

- Unblinded phase
  - All 7 deaths (out of 127 participants) over 2 to 5 years of follow-up were judged to be unrelated to DBS implantation
  - Infrequent reported adverse events included paresthesia, partial seizures with secondary generalization, simple and complex partial seizures, anticonvulsant toxicity, dizziness, excoriation, contusion, nasopharyngitis, upper respiratory tract infection, injury, and headache

See 4/8/2021 EbGS meeting materials for the complete draft report.

KQ3: Other Harms

- Entries in the FDA MAUDE database for the 9 components of the Medtronic DBS system (CG ref# 21), not disaggregated by indication, included previously listed harms, plus:
  - Impaired vision or hearing
  - Intracranial hemorrhage
  - Painful swallowing
  - Numbness
  - Arrhythmia
  - Feeling of electrical shock or burning sensation

Ongoing Studies

- Ongoing open-label post-approval study to evaluate the long-term safety and effectiveness of the Medtronic system for DBS (CG ref# 20)
  - Estimated primary completion date of March 2027
  - Target enrollment of 216 adults with an average of 6 focal onset seizures per month and who have failed trials of at least 3 antiepileptic medications
  - Outcomes at 36 months post-implantation include percentage reduction in total seizure frequency and total seizure reduction stability

Ongoing Studies

- Ongoing RCT in France (CG ref# 19)
  - DBS for individuals with focal or multifocal epilepsy with or without secondary generalized seizure who have failed antiseizure drugs for at least 4 years, and who have failed vagal nerve stimulation
  - 62 participants aged 16 to 60 years
  - Primary completion date of December 2021
  - Seizure severity and quality of life 2 years after implantation, and cost-utility analyses for the payer and hospital

Evidence Summary

- Limited quantity and quality of evidence
  - 2 RCTs had moderate to high risk of bias during the blinded phases, and high risk of bias during unblinded follow-up periods
  - 2 systematic reviews with moderate risk of bias
  - Observational registries and databases had high risk of bias

See 4/8/2021 EbGS meeting materials for the complete draft report.

Evidence Summary

- Inconsistent evidence of reduction in seizure frequency and severity, and some participants had increased frequency of seizure activity
  - However, participants with seizure origin in one or both temporal regions likely had fewer seizures with DBS
  - No difference for participants with seizure origins in other regions
  - Prior treatment history was unrelated to seizure frequency during DBS
- Likely increased depression and memory loss with DBS
- Possibility of device malfunction and surgery-related infections

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GRADE Table

Outcomes	**Estimate of Effect for Outcome** ***Confidence in Estimate***
Hospitalizations *(Critical outcome)*	*No data*

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GRADE Table

Outcomes	Estimate of Effect for Outcome *Confidence in Estimate*
Harms *(Critical outcome)*	**Depression** Blinded Phase: 10/62 (16.1%) of patients in stimulation group compared to 1/65 (1.5%) control group reported depression Unblinded Phase: 43/127 (33.9%) reported depression **Memory Loss** Blinded Phase: 7/54 (13%) of stimulation group reported memory impairment, compared to 1/55 (2%) in control group Unblinded Phase: 32/127 (25.2%) of participants reported memory impairment **Surgery-related Harms** Blinded Phase: 14/109 (13%) participants had implant site infections; 9/109 (8.3%) had partial or full explants (did not report by study group) **Device-related Harms** Unblinded Phase: 6/127 reported an increase in seizure frequency of 50% or more during active stimulation; 7/127 (5.5%) experienced status epilepticus under active stimulation **Other Harms** Unblinded Phase: 7 deaths over 2 to 5 years of follow-up (out of 127 participants) were judged to be unrelated to DBS implantation; a total of 8 deaths between baseline and 10 years were judged to be unrelated to DBS implantation ●●○○ *(low confidence, based on 2 RCTs and 2 observational, noncomparative follow-ups, n = 127)*

GRADE Table

Outcomes	Estimate of Effect for Outcome *Confidence in Estimate*
Seizure Frequency *(Important outcome)*	Blinded Phase: 29% greater reduction after 3 months in 1 study (54/109 received stimulation), but no significant difference at 6 months in a second study (8/18 received stimulation). In subgroup analyses, 62 participants had seizure origins in 1 or both temporal regions, and the intervention group reported greater median reduction in seizure frequency compared to baseline (intervention reduction, 44.2%; control reduction, 21.8%; *P* = .025). There was no significant difference for participants with seizure origin in frontal, parietal, or occipital regions. There was a nonsignificant trend of median seizure reduction for 17 participants with multifocal or diffuse seizure origin (intervention reduction, 35.0%; control reduction, 14.1%; *P* > .05). There was no difference in reduction for participants with prior resective surgery, vagal nerve stimulation, or neither treatment. Unblinded Phase: 56% reduction after 2 years compared to baseline (N = 81), and a 69% median reduction after 5 years compared to baseline (N = 59) in 1 study. In a second study, there was a 23% total seizure reduction compared to baseline after 6 months (N = 18). In the 50 participants who remained in the study for 7 years, the mean seizure frequency reduction was 75% compared to baseline (*P* < .05) ●●○○ *(low confidence, based on 2 RCTs, n = 127, and 2 observational follow-ups of 2 RCTs)*

GRADE Table

Outcomes	Estimate of Effect for Outcome *Confidence in Estimate*
Seizure Severity *(Important outcome)*	Blinded Phase: no significant difference between intervention and control groups on Liverpool Seizure Severity Scale (62/127 experienced stimulation). Unblinded Phase: Compared to baseline scores on the Liverpool Seizure Severity Scale, there was an average improvement of 13.4 points (SD, 21.4; N = 103; *P* <. 001) after 6 to 12 months, and an average improvement of 18.3 points after 5 years (SD, not reported; N = 81; *P* < .001) in 1 study. There was an average improvement of 5 points after 6 months in a second study (N = 18; SD, not reported). ●●○○ *(low confidence, based on 1 blinded phase and 2 observational follow-ups of 2 RCTs)*

See 4/8/2021 EbGS meeting materials for the complete draft report.

GRADE Table

Outcomes	**Estimate of Effect for Outcome** ***Confidence in Estimate***
Medication Use *(Important outcome)*	Unblinded Phase: 61/83 participants (73.5%) had added a new antiseizure drug between implantation and 5-year follow-up. There was no comparison group. ●○○○ *(very low confidence, based on 1 observational follow-up of 1 RCT, n = 83)*

Payer Policies

Payer Policies

- Aetna considers bilateral stimulation of the ANT to be medically necessary for:
  - Patients aged 18 or older with partial onset seizures, with or without secondary generalization to tonic-clonic activity; and
  - Who have not responded to 3 or more antiepileptic medications.
- Aetna policy specifically names the Medtronic system as an example of a covered DBS system
  - Notes that DBS was evaluated in individuals with 6 or more seizures per month but was not evaluated in individuals with less frequent seizures.

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Payer Policies

- No coverage policy was found for DBS for refractory epilepsy for the following:
  - Washington Medicaid program
  - Medicare
  - Moda
- The following private payers consider DBS to be investigational for refractory epilepsy:
  - Cigna
  - Regence BlueCross BlueShield

Guidelines and Recommendations

Oregon Health Authority

OREGON HEALTH & SCIENCE UNIVERSITY

Center For Evidence-based Policy

Evidence-based Guidelines

- National Institute for Health and Care Excellence (NICE)
  - Individuals with refractory epilepsy who have anterior thalamic targets should only have DBS under special arrangements for clinical governance, consent, and audit or research
  - Special arrangements are recommended by NICE when the independent advisory committee judges that there is uncertainty about the safety and effectiveness of identified procedures, and this term also intends to highlight the essential role of informed consent to providers
  - Noted the limited quantity and quality of published evidence

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Evidence-based Guidelines

- Scottish Intercollegiate Guidelines Network (SIGN)
  - Patients who fail to respond to antiepileptic drugs should be assessed for neurosurgical treatment, and a very low strength of evidence supported consideration of curative resective surgery before consideration of palliative procedures such as vagus nerve stimulation
  - DBS is listed among the surgical treatment options considered during the literature review, but the authors noted the SANTE trial that presented evidence of possible seizure reduction in patients with drug-resistant epilepsy had substantial limitations and declined to provide an evidence rating for DBS

See 4/8/2021 EbGS meeting materials for the complete draft report.

Professional Society Guidelines

- National Association of Epilepsy Centers
  - Patients with intractable epilepsy should be treated at third- and fourth-level epilepsy centers, which have the resources and capability to offer surgical procedures, including the placement of intracranial electrodes and vagus nerve stimulators
- No guidelines were identified for:
  - American Academy of Neurology
  - American Epilepsy Society
  - Royal Australasian College of Surgeons

See 4/8/2021 EbGS meeting materials for the complete draft report.

Recommendations From Others

- European Expert Opinion Panel Convened by Medtronic
  - Medtronic paid travel, lodging, and honoraria for coming to Switzerland headquarters
  - 10 neurologists and 4 neurosurgeons
  - 71% of the Medtronic panel experts agreed on the patient selection criteria on the following slide

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Medtronic Panel Recommendations

- Patients with refractory epilepsy who are ineligible for resective surgery or vagus nerve stimulation
- Presurgical evaluation should include members from multiple disciplines to evaluate the patient's electroencephalograph video recordings of habitual seizures, magnetic resonance imaging, and neuropsychological evaluation
- Be cautious about selecting DBS for patients with a progressive etiology (e.g., tumor, dementia), history of suicide attempts, depression, psychogenic seizures, psychosis related to seizures, contraindications noted on the magnetic resonance imaging, or unreliable seizure diary

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Discussion

Discussion

Values and Preferences

- Patients who do not wish to have an invasive procedure would prefer medical management.
- Patients who have debilitating seizures despite optimal medical management would value the potential reduction in seizure frequency. These patients may be willing to accept the risk of harms, as they have few other treatment options.
- Continued uncontrolled seizures have known cognitive and neurological harms which need to be balanced against the risks of surgery.

Discussion

Resource Allocation

- Deep brain stimulation devices require expensive neurosurgery and regular follow-up for device management. However, DBS surgery is likely comparable in cost to resective surgery which is available to other populations with refractory epilepsy. In the RCTs of DBS, there was a significant rate of complications that required reintervention, raising the overall cost of the procedure.
- The population that qualifies for DBS have high-cost/high-frequency medical care. It is unclear from the literature whether DBS will decrease health care utilization in this group. There would need to be evidence of significant reduction in hospitalization, emergency department visits, etc., to offset the cost of the procedure.

Discussion

Other Considerations

- Deep brain stimulation is a highly technical procedure only available in a few centers. Prior to DBS, the patient may require highly technical diagnostic imaging and testing that might also only be available in a few centers.

Discussion

Balance of Benefits and Harms

- Based on low- and very low-certainty of evidence, there does not appear to be any reduction in medication use with deep brain stimulation for refractory epilepsy. We found no data on whether DBS reduces hospitalization. There may be a reduction in seizure frequency, but this finding is based on low certainty of evidence. However, data from the unblinded portion of the reviewed studies showed a cumulative reduction in seizure severity and frequency, with a subgroup achieving clinically meaningful benefits from DBS. There is a high rate of device-related complications, including infection, device migration, increase in depression, and memory loss. The balance of benefits for this population is at best uncertain and may vary based on patient characteristics and individual values and preferences.

Discussion

Rationale

- DBS for refractory epilepsy is recommended for coverage (*weak recommendation*) due to the reductions in seizure frequency observed by a subset of study participants in the reviewed literature. For some patients, this reduction may outweigh the risk of harms associated with the procedure when considered in conjunction with declines often associated with continued frequent seizures. In accordance with NAEC guidelines, such surgery should be performed at a Level 4 epilepsy center. It is a weak recommendation because of the significant harms as well as the low confidence in the estimate of effect for the benefit.

Discussion

Recommendation

Deep brain stimulation for treatment of refractory epilepsy is recommended for coverage (*weak recommendation*) when

1) the surgery is performed at a Level 4 epilepsy center, AND
2) the patient has failed multiple antiseizure medications, AND
3) the patient is ineligible for resective surgery OR has failed vagus nerve stimulation or resective surgery

See 4/8/2021 EbGS meeting materials for the complete draft report.

Discussion

See 4/8/2021 EbGS meeting materials for the complete draft report.

Evidence Sources

Randomized Controlled Trials

- Stimulation of the Anterior Nuclei of Thalamus for Epilepsy (SANTE) trial
  - Fisher R, Salanova V, Witt T, et al. Electrical stimulation of the anterior nucleus of thalamus for treatment of refractory epilepsy. *Epilepsia*. 2010;51(5):899-908. doi: 10.1111/j.1528-1167.2010.02536.x. (CG ref # 11)
  - Salanova V, Witt T, Worth R, et al. Long-term efficacy and safety of thalamic stimulation for drug-resistant partial epilepsy. *Neurology*. 2015;84:1017–1025. (CG ref # 13)
  - Troster AI, Meador KJ, Irwin CP, Fisher RS, Group SS. Memory and mood outcomes after anterior thalamic stimulation for refractory partial epilepsy. *Seizure*. 2017;45:133-141. doi: 10.1016/j.seizure.2016.12.014. (CG ref # 14)
  - Salanova V, Sperling MR, Gross RE, et al. The SANTE study at 10 years of follow-up: Effectiveness, safety, and sudden unexpected death in epilepsy. *Epilepsia.* 2021. doi: 10.1111/epi.16895. (CG ref # 34)
- Trial in Norway (inspired by SANTE)
  - Herrman H, Egge A, Konglund AE, Ramm-Pettersen J, Dietrichs E, Tauboll E. Anterior thalamic deep brain stimulation in refractory epilepsy: a randomized, double-blinded study. *Acta Neurol Scand.* 2019;139(3):294-304. doi: 10.1111/ane.13047. (CG ref # 12)

Systematic Reviews

- Kantzanou M, Korfias S, Panourias I, Sakas DE, Karalexi MA. Deep brain stimulation-related surgical site infections: a systematic review and meta-analysis. *Neuromodulation*. 2021. doi: 10.1111/ner.13354. (CG ref # 15)
- Zangiabadi N, Ladino LD, Sina F, Orozco-Hernandez JP, Carter A, Tellez-Zenteno JF. Deep brain stimulation and drug-resistant epilepsy: a review of the literature. *Front Neurol*. 2019;10:601. doi: 10.3389/fneur.2019.00601. (CG ref # 16)

Observational Registries and Databases

- Medtronic. Product performance report: summary of data from the Medtronic post-market registry. 2019; https://www.medtronic.com/content/dam/medtronic-com/products/product-performance/ppr-reports/2019-product-performance-report-combined.pdf?bypassIM=true. Accessed February 22, 2021. (CG ref # 21)
- Tafreshi AR, Shahrestani S, Lien BV, et al. Indication-based analysis of patient outcomes following deep brain stimulation surgery. Clin Neurol *Neurosurg*. 2021;200:106372. doi: 10.1016/j.clineuro.2020.106372. (CG ref # 17)
- US Food and Drug Administration. MAUDE manufacturer and use facility device experience. 2021; https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfmaude/search.cfm. Accessed March 3, 2021. (CG ref # 18)

Clinical Trial Registries

- Clinical Trials Registry. Medtronic deep brain stimulation (DBS) therapy for epilepsy post-approval study (EPAS). 2021; https://clinicaltrials.gov/ct2/show/NCT03900468. Accessed February 22, 2021. (CG ref # 20)
- Clinical Trials Registry. Deep brain stimulation of the anterior nucleus of the thalamus in epilepsy (FRANCE). 2020; www.clinicaltrials.gov/ct2/show/NCT02076698. Accessed March 3, 2021. (CG ref # 19)

Health Evidence Review Commission (HERC)

Coverage Guidance:

Deep Brain Neurostimulators for Refractory Epilepsy

DRAFT for VbBS/HERC Meetings 8/12/2021

HERC Coverage Guidance

Deep brain stimulation for treatment of refractory epilepsy is recommended for coverage (*weak recommendation*) when

1) the surgery is performed at a Level 4 epilepsy center, AND
2) the patient has failed multiple antiseizure medications, AND
3) the patient is ineligible for resective surgery OR has failed vagus nerve stimulation or resective surgery

Note: Definitions for strength of recommendation are in Appendix A. *GRADE Table Element Descriptions*. Rationales for each recommendation appear below in the GRADE table.

Oregon Health Authority

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Rationale for development of coverage guidances and multisector intervention reports

Coverage guidances are developed to inform coverage recommendations for public and private health plans in Oregon as plan administrators seek to improve patient experience of care, population health, and the cost-effectiveness of health care. In the era of public and private sector health system transformation, reaching these goals requires a focus on maximizing the benefits and minimizing the harms and costs of health interventions.

HERC uses the following principles in selecting topics for its reports to guide public and private payers:

- Represents a significant burden of disease or health problem
- Represents important uncertainty with regard to effectiveness or harms
- Represents important variation or controversy in implementation or practice
- Represents high costs or significant economic impact
- Topic is of high public interest

HERC bases its reports on a review of the best available research applicable to the intervention(s) in question. For coverage guidances, which focus on diagnostic and clinical interventions, evidence is evaluated using an adaptation of the GRADE methodology. For more information on coverage guidance methodology, see Appendix A.

Multisector interventions can be effective ways to prevent, treat, or manage disease at a population level. In some cases, HERC has reviewed evidence and identified effective interventions, but has not made formal coverage recommendations when these policies are implemented in settings other than traditional health care delivery systems because effectiveness may be dependent on the environment in which the intervention is implemented.

GRADE Table Description

HERC develops recommendations by using the concepts of the Grading of Recommendations, Assessment, Development, and Evaluation (GRADE) system. GRADE is a transparent and structured process for developing and presenting evidence and for performing the steps involved in developing recommendations. The table below lists the elements that determine the strength of a recommendation. HERC reviews the evidence and makes an assessment of each element, which in turn is used to develop the recommendations presented in the coverage guidance box. Estimates of effect are derived from the evidence presented in this document. The level of confidence in the estimate is determined by HERC based on the assessment of two independent reviewers from the Center for Evidence-based Policy.

In some cases, no systematic reviews or meta-analyses encompass the most current literature. In those cases, HERC may describe the additional evidence or alter the assessments of confidence in light of all available information. Such assessments are informed by clinical epidemiologists from the Center for Evidence-based Policy. Unless otherwise noted, statements regarding resource allocation, values and preferences, and other considerations are the assessments of HERC, as informed by the evidence reviewed, public testimony, and subcommittee discussion.

Recommendations for coverage are based on the balance of benefit and harms, resource allocation, values and preferences and other considerations. See Appendix A for more details about the factors that constitute the GRADE table.

GRADE Table

Should coverage of deep brain stimulation devices (DBS) be recommended for refractory epilepsy?

Outcomes	Estimate of Effect for Outcome *Confidence in Estimate*	Resource Allocation	Values and Preferences	Other Considerations
Hospitalizations *(Critical outcome)*	*No data*	DBS devices require expensive neurosurgery and regular follow-up for device management. However, DBS surgery is likely comparable in cost to resective surgery which is available to other populations with refractory epilepsy. In the RCTs of DBS, there was a significant rate of complications that required reintervention, which also raises the overall cost of the procedure. The population that qualifies for DBS have high-cost/high-	Patients who do not wish to have an invasive procedure would prefer medical management. Patients who have debilitating seizures despite optimal medical management would value the potential reduction in seizure frequency. These patients may be willing to accept the risk of harms, as they have few other treatment options. Continued uncontrolled seizures have known cognitive and neurological harms which need to be balanced against the risks of surgery.	DBS is a highly technical procedure only available in a few centers. Prior to DBS, the patient may require highly technical diagnostic imaging and testing that might also only be available in a few centers.
Harms *(Critical outcome)*	**Depression** Blinded Phase: 10/62 (16.1%) stimulation group participants compared to 1/65 (1.5%) control group participants reported depression Unblinded Phase: 43/127 (33.9%) participants reported depression by the end of 5 years; 19/50 (37.3%) reported depression, and 5/50 (10.0%) reported suicidality by the end of 7 years **Memory Loss** Blinded Phase: 7/54 (13%) stimulation group participants reported memory impairment, compared to 1/55 (2%) control group participants Unblinded Phase: 32/127 (25.2%) participants reported memory impairment by the end of 5 years; 5/50 (10.0%) reported memory impairment at 7 years **Surgery-Related Harms** Blinded Phase: 14/109 (13.0%) participants had implant site infections; 9/109 (8.3%) had partial or full explants (did not report by study group) Unblinded phase: 30.0% of participants had full			

Should coverage of deep brain stimulation devices (DBS) be recommended for refractory epilepsy?

Outcomes	Estimate of Effect for Outcome *Confidence in Estimate*	Resource Allocation	Values and Preferences	Other Considerations
	explants without reimplantation due to discontinuation by the end of 10 years after initial implant for the study **Device-Related Harms** Unblinded Phase: 6/127 participants reported an increase in seizure frequency of 50% or more during active stimulation; 7/127 (5.5%) experienced status epilepticus under active stimulation **Other Harms** Unblinded Phase: 7 deaths over 2 to 5 years of follow-up (out of 127 participants) were judged to be unrelated to DBS implantation; a total of 8 deaths between baseline and 10 years were judged to be unrelated to DBS implantation ●●○○ *(low confidence, based on 2 RCTs and 2 observational follow-ups, n = 127)*	frequency medical care. It is unclear from the literature whether DBS will decrease health care utilization in this group. There would need to be evidence of significant reduction in hospitalization, emergency department visits, etc., to offset the cost of the procedure, complications, and follow-up.		

Should coverage of deep brain stimulation devices (DBS) be recommended for refractory epilepsy?

Outcomes	Estimate of Effect for Outcome *Confidence in Estimate*	Resource Allocation	Values and Preferences	Other Considerations
Seizure Frequency *(Important outcome)*	Blinded Phase: 29% greater reduction after 3 months in 1 study (54/109 received stimulation), but no significant difference at 6 months in a second study (8/18 received stimulation). In subgroup analyses, 62 participants had seizure origins in 1 or both temporal regions, and the intervention group reported greater median reduction in seizure frequency compared to baseline (intervention reduction, 44.2%; control reduction, 21.8%; *P* = .025). There was no significant difference for participants with seizure origin in frontal, parietal, or occipital regions. There was a nonsignificant trend of median seizure reduction for 17 participants with multifocal or diffuse seizure origin (intervention reduction, 35.0%; control reduction, 14.1%; *P* > .05). There was no difference in reduction for participants with prior resective surgery, vagal nerve stimulation, or other treatment Unblinded Phase: 56% reduction after 2 years compared to baseline (N = 81), and a 69% median reduction after 5 years compared to baseline (N = 59) in 1 study. In a second study, there was a 23% total seizure reduction compared to baseline after 6 months (N = 18). In the 50 participants who remained in the study for 7 years, the mean seizure frequency reduction was 75% compared to baseline (*P* < .05) ●●○○ *(low confidence, based on 2 RCTs, n = 127, and 2 observational follow-ups of 2 RCTs)*			

Should coverage of deep brain stimulation devices (DBS) be recommended for refractory epilepsy?

Outcomes	Estimate of Effect for Outcome *Confidence in Estimate*	Resource Allocation	Values and Preferences	Other Considerations
Seizure Severity *(Important outcome)*	Blinded Phase: No significant difference between intervention and control groups on the LSSS (62/127 experienced stimulation) Unblinded Phase: Compared to baseline scores on the LSSS, there was an average improvement of 13.4 points (SD, 21.4; N = 103; *P* < .001) after 6 to 12 months, and an average improvement of 18.3 points after 5 years (SD, not reported; N = 81; *P* < .001) in 1 study. There was an average improvement of 5 points after 6 months in a second study (N = 18; SD, not reported). At the 7-year follow-up, the investigators reported that the improvement in LSSS score at 5 years remained stable at 7 years (no statistics reported) ●●○○ *(low confidence, based on 1 blinded phase and 2 observational follow-ups of 2 RCTs)*			
Medication Use *(Important outcome)*	Unblinded Phase: 61/83 participants (73.5%) had added a new antiseizure drug between implantation and 5-year follow-up. There was no comparison group. By the 7-year follow-up, 77% of participants had added at least 1 new antiseizure drug, and the investigators reported that the trajectory of improvement in seizure frequency was similar between participants with and without added antiseizure drugs (no statistics reported) ●○○○ *(very low confidence, based on 1 observational follow-up of 1 RCT, n = 83)*			

Should coverage of deep brain stimulation devices (DBS) be recommended for refractory epilepsy?

Outcomes	Estimate of Effect for Outcome *Confidence in Estimate*	Resource Allocation	Values and Preferences	Other Considerations
Balance of benefits and harms: Based on low- and very low-certainty of evidence, there does not appear to be any reduction in medication use with DBS for refractory epilepsy. We found no data on whether DBS reduces hospitalization. There may be a reduction in seizure frequency, but this finding is based on low-certainty evidence. However, data from the unblinded portion of the reviewed studies showed a cumulative reduction in seizure severity and frequency, with a subgroup achieving clinically meaningful benefits from DBS. There is a high rate of device-related complications, including infection, device migration, increase in depression, and memory loss. The balance of benefits for this population is at best uncertain and may vary based on patient characteristics and individual values and preferences.				
Rationale: DBS for refractory epilepsy is recommended for coverage *(weak recommendation*) due to the reductions in seizure frequency observed by a subset of study participants in the reviewed literature. For some patients, this reduction may outweigh the risk of harms associated with the procedure when considered in conjunction with declines often associated with continued frequent seizures. In accordance with NAEC guidelines, such surgery should be performed at a Level 4 epilepsy center. It is a weak recommendation because of the significant harms as well as the low confidence in the estimate of effect for the benefit.				
Recommendation: DBS for treatment of refractory epilepsy is recommended for coverage (*weak recommendation*) when 1) the surgery is performed at a Level 4 epilepsy center, AND 2) the patient has failed multiple antiseizure medications, AND 3) the patient is ineligible for resective surgery OR has failed vagus nerve stimulation or resective surgery				

Notes. GRADE table elements are described in Appendix A. The GRADE Evidence Profile is in Appendix B.

Abbreviations. DBS: deep brain stimulation; GRADE: Grading of Recommendations, Assessment, Development, and Evaluation system; LSSS: Liverpool Seizure Severity Scale; RCT: randomized controlled trial; SD: standard deviation.

Background

In 2015, the Centers for Disease Control and Prevention estimated that 3.4 million individuals in the US were diagnosed with and undergoing active treatment for epilepsy, with approximately 42,900 of these individuals residing in Oregon.[1] Antiseizure medications comprise the first course of treatment, but about a third of patients continue to have seizures while taking these medications.[2] Drug-resistant epilepsy is associated with an increased risk of adverse health outcomes for individuals with epilepsy, including hospitalization, decreased quality of life, and death.[3,4] Among individuals who fail to respond adequately to antiseizure medications, and who also undergo resective surgery, 37% to 70% continue to experience seizures.[5,6]

Individuals whose epilepsy has not responded to medications and resective surgery, or who are not candidates for resective surgery or other treatments (e.g., vagal nerve stimulation), may be eligible for deep brain stimulation (DBS).

Indications

DBS is approved by the US Food and Drug Administration (FDA) for use in individuals 18 years of age or older who are diagnosed with epilepsy characterized by partial onset seizures, with or without secondary generalization, and who have failed 3 or more trials of antiepileptic medications.[7]

Technology Description

The FDA approved the Medtronic DBS system for epilepsy on April 27, 2018.[7]

The Medtronic system uses constant electrical pulses from a generator implanted in the upper chest to activate electrodes implanted in specific areas of the brain through leads (i.e., a type of wire) that connect the generator to the electrodes.[8] The implantable system consists of 9 parts[9]:

- Model 37601 Activa PC Neurostimulator
- Model 3387S DBS Lead Kit
- Model 3389S DBS Lead Kit
- Model 37086 DBS Extension Kit
- Model 8840 N'Vision Programmer
- Model 8870 Software Application Card
- Model 37441 Intercept Patient Programmer
- Model 37022 External Neurostimulator
- Model 3353/3354 Lead Frame Kit

The FDA previously approved this Medtronic system in 1997 (Activa Tremor Control System) for unilateral thalamic stimulation to suppress tremor in patients with essential tremor or Parkinsonian tremor,[10] but the Medtronic system approved for DBS for epilepsy includes 1 additional element: the intercept patient programmer.[9]

Evidence Review

Risk of Bias for Identified Studies

Study designs and methodological quality of included publications are described first, and study results are then synthesized by study design within each outcome.

Randomized Controlled Trials

We identified 2 randomized controlled trials (RCTs) that evaluated DBS of the anterior nucleus of the thalamus (ANT) for adults with refractory epilepsy.[11,12]

Researchers in the Stimulation of the Anterior Nuclei of Thalamus for Epilepsy (SANTE) trial implanted Medtronic DBS devices with electrodes in the ANT in 109 adult patients with medically refractory partial seizures, including secondarily generalized seizures.[11] All participants were between 18 and 65 years of age (mean age, 36 years); half of the participants were female.[11] The trial was structured with a 3-month double-blinded phase, a subsequent 9-month open-label follow-up period, and additional data collection follow-ups at 2, 3, 4, 5, and 7 years. Prior to enrolling in the study, participants had failed trials of at least 3 antiseizure medications, and had recorded at least 6 seizures per month, but no more than 10 seizures per day, in a 3-month daily seizure diary.[11] Participants continued to use antiseizure medications after entering the study, and their medication was not adjusted during the first 12 months of the study (3-month blinded phase plus 9-month open-label phase); adjustment of antiseizure medication was permitted during the extended follow-up period of 5 years.[11] Potential participants were excluded if they had progressive neurologic or medical diseases, nonepileptic seizures, intelligence quotient of less than 70, an inability to take neuropsychological tests or complete seizure diaries, or were pregnant.[11] Participants who were randomized into the intervention condition experienced stimulation of 5 volts with 145 pulses per second, with 1 minute on and 5 minutes off stimulation (intervention, N = 54); participants who were randomized to the control condition did not experience any stimulation during the 3-month blinded phase of the trial (control, N = 54).[11]

We rated the blinded phase of the SANTE trial as having moderate risk of bias because of incomplete reporting of results, significant attrition between enrollment and implantation, potential conflicts of interest for several investigators (i.e., payments from Medtronic), and trial funding from the device manufacturer. We rated the observational follow-up study that gathered information about the SANTE participants during 7 years after implantation as having high risk of bias because of the noncomparative design; lack of blinding for participants, assessors, and investigators; and the same potential conflicts of interest described for blinded phase of the SANTE trial. Information about deaths of participants was collected through 10 years post-implantation. Results from the double-blinded phase and the open-label follow-ups were reported in 3 separate publications.[11,13,14,34]

In the second RCT, Herrman and colleagues conducted a prospective, randomized, double-blinded trial of the safety and effectiveness of DBS for adults with focal, drug-resistant epilepsy, with or without secondary generalization, who were not eligible for resective surgery (N = 18).[12] The average number of antiseizure drugs that participants had tried was 13 (range, 5 to 15), and participants had an average number of 53 seizures per month in the 3 months prior to implantation.[12] Exclusion criteria was the same as in the SANTE trial.[11,12] After DBS device implantation, participants were randomized to receive stimulation of 5 volts through the devices (intervention, N = 8), or to have no stimulation (control, N = 10), for a 6-month blinded phase.[12] All participants received stimulation of 5 volts during the

nonblinded open-label phase (months 7 through 12); data collected at 3, 6, 9, and 12 months focused on seizure frequency, seizure type, and adverse events.[12] Although the investigators intended to enroll 40 participants in this trial, they discontinued enrollment after results from an interim analysis suggested that there was a lack of significant reduction in seizures, and a possible increase in seizures for some participants receiving active stimulation.[12] We rated this study as having high risk of bias because characteristics were not balanced between groups (i.e., average number of seizures was higher in the intervention group, and types of seizures differed). We rated the 6-month open-label follow-up as having high risk of bias because of the of the noncomparative design, and lack of blinding for participants, assessors, and investigators.

Nonrandomized Studies

We described the unblinded phases of the SANTE trial and the Herrman trial above; outcomes from the unblinded phases and extended follow-ups are reported in the nonrandomized study portions of the evidence review in this report.

We identified 2 systematic reviews with moderate risk of bias that provided narrative summaries of nonrandomized studies, including adverse events and harms.[15,16] The reviews lacked adequate assessment of the methodological quality of component studies.

To assess harm outcomes and hospitalizations, we used these 2 systematic reviews, reports in the FDA Manufacturer and User Facility Device Experience database (MAUDE), the Medtronic product performance report, and a publication of a secondary analysis of patient outcomes following DBS surgery using the National Readmission Database to assess harm outcomes.[15-18] We rated the findings from these databases and registry as having high risk of bias because of the observational and noncomparative nature of the information.

We identified 2 ongoing studies registered on the Clinical Trials Registry related to DBS for refractory epilepsy which included individuals with targets in the ANT; we describe these in the final section of the evidence review.[19,20]

In the following sections, we report data for the selected critical and important outcomes based on the sources described above.

Hospitalizations

RCTs

Neither RCT reported hospitalizations for participants.[11,12]

Nonrandomized Studies

Neither systematic review reported hospitalizations for participants.[15,16]

We found no studies that compared hospitalizations before and after DBS implantation, or between individuals diagnosed with refractory epilepsy with and without DBS implants. No studies reported on hospitalizations due to seizures or complications of seizures.

Tafreshi and colleagues used the United States Healthcare Cost and Utilization Project National Readmission Database to identify patients being implanted with neurostimulators in 2016 through 2017, and analyzed complications from surgery and readmissions to hospital at 30-, 90- and 180-day intervals.[17] Of the 965 patients with epilepsy undergoing DBS implantation, 221 were propensity-score-

matched on age and sex with patients undergoing DBS implantation for Parkinson disease, essential tremor, and dystonia.[17] Compared with the other 3 groups, patients with epilepsy had the greatest average hospital length of stay (8.5 days), and highest average total inpatient cost (mean, $257,120.10; standard deviation [SD], $178,711.10).[17] Patients with epilepsy had similar incidence of infection within 30 days (8.2%), lowest frequency of DBS revision within 30 (1.64%) and 90 days (1.9%), and second-lowest frequency of DBS revision within 180 days (2.5%).[17] Frequency of readmission varied over time and by group; for patients with epilepsy, 4.4% were readmitted within 30 days, 14.9% within 90 days, and 30.6% within 180 days.[17] However, the retrospective analysis of the observational data in the readmission database in this study relies on a nonrepresentative sample. This study was not included in the GRADE Table because of its retrospective cohort study design.

Harms

Depression

RCTs

Statistically significant differences in the incidence of depression and memory impairment were reported during the blinded phase of the SANTE study: 14.8% (N = 8) participants in the intervention group reported symptoms of depression, compared to 1.8% (N = 1) in the control group (*P* = .016).[11] Seven participants in the intervention group who had depression during the blinded phase had a history of depression; 4 intervention group participants reported that these symptoms resolved within 76 days of onset.[11]

Nonrandomized Studies

Thirteen participants in the SANTE trial who participated in the 5-year follow-up phase of the study reported experiencing suicidal ideation.[13] One of these participants committed suicide; this death was not judged to be related to DBS, and is 1 of the 2 deaths that occurred between the 1- and 5-year follow-ups.[13] Forty-one participants reported having depression since the implantation of the DBS device, 27 of whom had a history of depression prior to implantation.[13] A 7-year follow-up with 67 of the participants reported no statistically significant change in depression, anxiety, or memory between measure collection at baseline and 7 years after implantation.[14] There was considerable loss to follow-up for both the 5-year (46% attritted) and 7-year (39% attritted) time points.[13] The publication that reported adverse events through 7 years reported that 37.3% of the participations reported depression between baseline and 7 years, and 10.0% reported suicidality.[34]

Herrman and colleagues indicated that 1 participant reported symptoms of depression at the 9-month follow-up.[12]

Memory Loss

RCTs

More participants report memory impairment in the intervention group of the SANTE study (13.0%; N = 7) than in the control group (1.8%; N = 1; *P* = .032).[11] Memory impairments resolved by the end of the follow-up period, ranging in time from 12 to 476 days after symptoms were first reported.[11] Experience of a confused mental state was only reported in the intervention group (7.4%; N = 4).[11]

Nonrandomized Studies

At the 5-year follow-up, 7.3% of SANTE participants reported memory impairment (N = 4).[13] The publication reporting adverse events through 7 years said 30.0% of participants reported memory loss between baseline and 7 years.[34]

Herrman and colleagues reported that 2 participants had experienced memory loss between implantation and the 12-month follow-up.[12]

Surgery-Related Harms

RCTs

During the blinded phase of the SANTE study, 13% (N = 14) participants had implant site infections; 1 patient had a meningeal reaction.[11] DBS hardware was removed from 9 patients (8.3%); 3 of these patients were later reimplanted with a DBS device.[11] Because all participants were implanted with DBS devices, infections were not reported by study arm. By the end of 10 years, 30.0% of the participants had their DBS systems explanted without reimplantation due to discontinuation of the therapy.[34]

Nonrandomized Studies

Kantzanou and colleagues reviewed 66 studies (12,258 total participants with DBS devices implanted for multiple indications) that reported surgical site infections; 8 studies with 158 total participants had DBS devices for refractory epilepsy.[15] Across all indications, the prevalence of surgical site infections was 4.6% (N = 569); for participants with DBS devices implanted for epilepsy, the prevalence was 9.5% (N = 15).[15]

Device-Related Harms

RCTs

Herrman and colleagues considered the following to be potentially adverse events: lack of significant between-group difference in seizure severity at the end of the 6-month blinded phase, absence of a consistent trend toward improvement in seizure frequency on average across participants at 12 months, and the return of general tonic seizures for 1 patient undergoing active stimulation.[12]

Nonrandomized Studies

There were 808 adverse events reported among 109 participants between implantation and 13-month follow-up of the SANTE trial, and 238 of these events were considered device-related. Five deaths were reported during the 3-year follow-up phase, and none were judged to be device-related.[11] Five participants had asymptomatic cerebral hemorrhages that were detected incidentally during neuroimaging.[11] Five participants (4.5%) experienced status epilepticus under active stimulation.[11] Three patients reported an average increase of 50% or more in seizure frequency during active stimulation.[11]

At the 5-year follow-up, SANTE participants reported experiencing the following adverse effects during the time between implantation and 5-year follow-up: implant site pain (23.6%), paresthesia (22.7%), implant site infection (12.7%), ineffective device (10.0%), discomfort (9.1%), lead misplacement (8.2%), sensory disturbance (8.2%), implant site inflammation (7.3%), dizziness (6.4%), postprocedural pain (6.4%), extensions fracture (5.5%), and neurostimulator migration (5.5%).[13]

Herrman and colleagues reported that 1 participant had a partial explant requiring reimplantation of an electrode, and 1 participant had dysarthria and left central facial nerve palsy that resolved within a

week.[12] After stimulation began, the following adverse effects were each experienced by a single individual: generalized tonic seizure, increased seizures, and cerebral stroke (judged to be unrelated to DBS).[12]

Zangiabadi and colleagues reviewed 20 small open-label, uncontrolled, pilot studies of DBS for refractory epilepsy with targets in the ANT (N = 127), and included the SANTE trial already discussed in this review.[16] Adverse events in these small studies included: wound infection; lead or extension fracture; erosion; electrode migration; external interference with other devices; equipment infection; pain; transient worsening or new seizures; dizziness; hardware discomfort; and ineffective product.[16]

The Medtronic product performance report from 2019 described reports of DBS device events from July 2009 through October 31, 2019 from 43 centers worldwide for selected devices.[21] Of the 2,637 individuals implanted with DBS devices being followed in the registry, 27 (1.0%) had an indication of epilepsy.[21] There were 364 product performance events for DBS devices for all indications as reported by physicians: high impedance (N = 187); lead migration or dislodgment (N = 44); device malfunction (N = 22); lead fracture (N = 21); low impedance (N = 20); extension migration (N = 19); neurostimulator failed to recharge (N = 11); extension fracture (N = 7); device breakage (N = 5); lead insulation failure (N = 4); premature battery depletion (N = 4); device connection issue (N = 2); device lead issue (N = 2); device material issue (N = 2); electromagnetic interference (N = 2); and other event (N = 4).[21] Out of these events, 107 resulted in surgical intervention.[21] The report did not disaggregate adverse events by indication.

Other Harms

RCTs

Other adverse events reported during the SANTE study in both groups, infrequently and without significant between-group difference, included paresthesia, partial seizures with secondary generalization, simple and complex partial seizures, anticonvulsant toxicity, dizziness, excoriation, contusion, nasopharyngitis, upper respiratory tract infection, injury, and headache.[11]

Nonrandomized Studies

About half of the participants in the SANTE trial participated in the 5-year follow-up phase of the study (54%; N = 59); 2 more deaths occurred between the 1-year and 5-year follow-ups, and neither was judged to be related to DBS.[13] Over the course of the study, from baseline through the end of 10 years, 8 participant deaths were found to be unrelated to DBS therapy or the study.[34] Four deaths were classified as possibly sudden unexpected death in epilepsy; 1 death was by suicide; 1 death was attributed to cardiorespiratory arrest from medication nonadherence; 1 death from a preexisting condition related to status epilepticus; and 1 death was due to liver cancer.[34]

Herrman and colleagues reported on the following adverse effects: headache, dizziness, vertigo, difficulty finding words, and altered perception of reality.[12]

We reviewed reports made to the FDA MAUDE database for all parts of the Medtronic DBS device; it was not possible to disaggregate reports by indication, and this device is also used in patients with Parkinson disease or essential tremor.[18] MAUDE entries include descriptions of patient problems that reporters think are associated with device problems.[18] In addition to the adverse events already discussed in this review, MAUDE reports included effects on patients such as impaired vision or hearing,

intracranial hemorrhage, painful swallowing, numbness, arrhythmia, and feeling of electrical shock or burning sensation.[18]

Seizure Frequency

RCTs

Both groups in the SANTE study experienced an unadjusted reduction in seizures between baseline and the end of the 3-month blinded phase: the intervention group had a median decrease of 40.4% and the control group had a median decrease of 14.5%.[11] After adjusting for age, the intervention group had a statistically significant adjusted mean percentage decrease of 29% in seizure frequency when compared to the control group (P = .002).[11] Post hoc subgroup analyses of the SANTE trial demonstrated that improvement in seizure frequency did not significantly vary by patient prior history of vagal nerve stimulation or resective surgery.[11] However, differences in reductions were reported by seizure onset site. Participants with seizure locations in one or both temporal regions had a greater reduction in seizure frequency from baseline in the stimulation group at 3 months (44.2%; N = 33) than the reduction for participants in the control group during the blinded phase of the study (21.8%; N = 29; P = .025).[11]

In subgroup analyses, 62 participants had seizure origins in one or both temporal regions, and the intervention group reported greater median reduction in seizure frequency compared to baseline (intervention reduction, 44.2%; control reduction, 21.8%; P = .025).[11] There was no significant difference for participants with seizure origin in frontal, parietal, or occipital regions. There was a nonsignificant trend of median seizure reduction for 17 participants with multifocal or diffuse seizure origin (intervention reduction, 35.0%; control reduction, 14.1%; P > .05).[11] There was no difference in reduction for participants with prior resective surgery, vagal nerve stimulation, or neither treatment.[11]

Herrman and colleagues reported that there was no significant difference between the intervention and control groups on seizure frequency at the end of the 6-month blinded phase.[12]

Nonrandomized Studies

During the open-label follow-ups for participants of the SANTE trial, some participants reported being seizure-free for 3 months (N = 6), 6 months (N = 14), 1 year (N = 8), 2 years (N = 6), and 1 participant had not reported a seizure for 4 years.[11,13] Thirteen participants reported that their seizure frequency was reduced by an average of 90% by the 2-year follow-up compared to seizure frequency at baseline.[11] In contrast, 3 patients reported an average increase of 50% or more in seizure frequency during active stimulation.[11] Participants analyzed in follow-ups reported significant average decreases in total seizure frequency compared to baseline of: 41% (N = 99) at 1 year post-implantation; 56% (N = 82) at 2 years; 53% (N = 75) at 3 years; 66% (N = 76) at 4 years; 69% (N = 59) at 5 years; 75% (N = 64) at 6 years; and 75% (N = 50) at 7 years.[11,13,34]

In subgroup analyses with the 50 remaining participants at the 7-year follow-up, participants with and without prior vagal nerve stimulation did not have significanly different median seizure reduction (median for group with prior vagal nerve stimulation, 75%; N = 21; median for group without prior vagal nerve stimulation, 78%; N = 29; between-group difference, P > .05).[34] Participants at the 7-year follow-up with temporal lobe seizures reported a significant median seizure reduction of 78% (N = 35) compared to baseline; participants with frontal lobe seizures reported a nonsignificant median reduction of 86% (N = 9) compared to baseline; and participants with seizures in other regions reported a significant median reduction of 39% (N = 11) compared to baseline.[34]

Herrman and colleagues reported that none of their participants were seizure-free at 12 months. Compared to baseline, 4 participants (22.2%) had reduction of less than 50% in seizure frequency, and 5 participants (27.8%) had a greater than 50% reduction in focal impaired awareness seizures.[12] One patient was judged to have an increase in seizure frequency related to the activation of the DBS devices, so this patient's stimulator was turned off during the open-label phase.[12]

Seizure Severity

RCTs

Investigators in the SANTE trial reported no difference in seizure severity with the Liverpool Seizure Severity Scale (LSSS) during the blinded phase of their trial, but greater reduction in complex partial seizures between baseline and 3 months in the stimulation group (36.3%) compared to the control group (12.1%; no sample size provided; $P = .047$).[11]

Herrman and colleagues reported that there was no significant difference in seizure severity, as measured by the LSSS, during the blinded phase of their trial (no estimates provided).[12]

Nonrandomized Studies

Fisher and colleagues reported that compared to baseline, SANTE study participants had an average improvement of 13.4 points on the LSSS at the 1-year follow-up when all participants had experienced stimulation for at least 6 months (SD, 21.4; N = 103; $P < .001$).[11] At the 2-year follow-up, participants reported an average decrease of 12.4 points on the LSSS compared to baseline (SD, 20.7; N = 99; $P < .001$).[11] Salanova and colleagues reported an improvement of 18.3 points on the LSSS at the 5-year follow-up compared to baseline (SD, not reported; N = 81; $P < .001$).[13] At the 7-year follow-up, the investigators reported that the improvement in seizure severity score on the LSSS found at 5 years remained stable (no statistics reported).[34]

Compared to baseline, Herrman and colleagues reported significant average improvement of 5 points on the LSSS after 6 months of stimulation (SD, not reported; $P = .004$).[12]

Medication Use

RCTs

Neither RCT reported changes in medication for participants as an outcome.[11,12]

Nonrandomized Studies

Salanova and colleagues reported that by the SANTE study 5-year follow-up, 61 participants with active DBS implants had begun taking at least 1 new antiseizure drug that they had not taken at baseline.[13] Salanova and colleagues noted that participants with less improvement in seizure frequency were more likely to add a medication, but that participants with added medications did not experience a quicker reduction in seizure frequency compared to participants who did not add medication.[13] They reported that approximately 6 to 8 participants per year decreased the number of antiseizure drugs or the dosage between years 1 and 5 of the SANTE open-label follow-up.[13] The authors stated that during the active stimulation follow-up, participants with new medications did not have a faster trajectory toward improvement compared to participants with stable medications.[13] However, no estimates were given for the statements that the authors made about patterns of medication use and relationship to improvement in seizure frequency. By the 7-year follow-up, 77% of the 50 remaining participants had

added at least 1 new antiseizure drug, and the investigators reported that the trajectory of improvement in seizure frequency was similar between participants with and without added antiseizure drugs (no statistics reported).[34]

Ongoing Studies of DBS for Refractory Epilepsy

In accordance with the requirements in the FDA premarket approval letter,[7] Medtronic is recruiting participants for an ongoing open-label post-approval study to evaluate the long-term safety and effectiveness of the Medtronic system for DBS, with an estimated primary completion date of March 2027.[20] This study has a target enrollment of 216 adults with an average of 6 focal onset seizures per month who have failed trials of at least 3 antiepileptic medications; the study will report primary outcomes at 36 months post-implantation for the percentage reduction in total seizure frequency and total seizure reduction stability.[20]

There is an ongoing RCT of DBS for individuals with focal or multifocal epilepsy with or without secondary generalized seizure who have failed antiseizure drugs for at least 4 years, and who have failed vagal nerve stimulation.[19] The trial sites in France have enrolled 62 participants aged 16 to 60 years, and the trial has a primary completion date of December 2021.[19] Assessed outcomes include effectiveness of DBS on seizure severity 2 years after implantation, quality of life for the participants, and cost-utility analyses for the payer and hospital.[19]

Evidence Summary

Results from the published comparative studies provided inconsistent information about whether DBS reduced seizure frequency and severity for people with refractory epilepsy. One study reported that DBS appeared to reduce seizures, because participants who experienced stimulation had fewer seizures after 3 or more months of stimulation than these same participants had had before the study started. However, a different study reported that some participants experienced more seizures after DBS than they had experienced before the study began, and that there was no difference in seizure frequency between the participants who experienced stimulation and those who did not. These studies also did not explore whether patterns of improvement might be related to patient characteristics such as age or sex. However, a single study reported that participants with seizures originating in one or both temporal regions had fewer seizures with DBS. Participants with seizures originating in the frontal, parietal, or occipital regions did not appear to have fewer seizures with DBS. It is not clear whether participants with multifocal or diffuse seizures have fewer seizures with DBS. A single study reported that participants had similar patterns of improvement whether they had previously tried vagal nerve stimulation, resective surgery, or neither of these treatments. DBS requires surgical implantation of a device, and participants in these studies experienced harms such as infections from the surgery or device, device malfunctions, pain, depression, and memory loss. However, people with uncontrolled seizures can also experience harms from injuries obtained during seizures, as well as memory impairment. Information from additional RCTs might clarify the risk of harms and the uncertain benefit of DBS for people with refractory epilepsy by comparing participants with and without DBS over a longer period to better understand the relationships between DBS effectiveness and harms.

We identified very few published comparative studies of DBS for refractory epilepsy, and only 1 ongoing RCT will assess comparative effectiveness and safety. The 2 blinded RCTs reviewed above were rated as having moderate to high risk of bias, and the unblinded follow-ups associated with those RCTs were rated as having high risk of bias; this resulted in low certainty of evidence for the effectiveness of DBS to

reduce seizure frequency and seizure severity. These studies plus 2 systematic reviews with moderate risk of bias were reviewed to assess harms and resulted in very low certainty of evidence for the safety of DBS (i.e., whether depression, memory loss, and surgical- and device-related harms were associated with DBS implantation and activation). One high-risk-of-bias observational follow-up reported on an aspect of medication use after DBS implantation, and resulted in very low certainty of evidence. None of the studies reported information about hospitalizations for participants implanted with DBS devices for refractory epilepsy.

Policy Landscape

Payer Coverage Policies

We identified policies related to covering DBS for refractory epilepsy from Aetna, Cigna, and Regence BlueCross BlueShield, but found no policies, guidance, or coverage determinations from Moda, the Washington Medicaid program, or Medicare.

Medicaid

The Washington State Health Care Authority Health Technology Clinical Committee has not made a coverage determination about DBS for refractory epilepsy, and no coverage policy was identified for Apple Health (Medicaid) related to DBS for refractory epilepsy.

Medicare

We did not identify any national or local coverage determinations for Medicare related to DBS for refractory epilepsy.

Private Payers

Aetna considers bilateral stimulation of the ANT to be medically necessary for patients aged 18 or older with partial onset seizures, with or without secondary generalization to tonic-clonic activity, and who have not responded to 3 or more antiepileptic medications.[22] Aetna's policy specifically names the Medtronic system as an example of a covered DBS system, and notes that DBS was evaluated in individuals with 6 or more seizures per month, but was not evaluated in individuals with less frequent seizures.[22] This policy was last reviewed in April 2021, with an anticipated next review date of February 2022.[22]

In a policy last reviewed November 15, 2020, Cigna considered DBS to be investigational for any condition apart from dystonia, Parkinson disease, and essential tremor.[23] This policy has an anticipated next review date of November 15, 2021.[23]

Regence BlueCross BlueShield does not cover DBS for epilepsy and intractable seizures, and lists these indications among those considered to be investigational; this DBS policy was last reviewed in May 2020 and has an anticipated next review date in March 2021.[24]

We did not identify any coverage policy from Moda about DBS for refractory epilepsy.

Evidence-based Recommendations

National Institute for Health and Care Excellence (NICE)

NICE published guidance for DBS for refractory epilepsy in adults in August 2020, and has an anticipated rereview date in 2023.[25] The committee based the recommendations on a rapid review completed in 2020.[26] As a result of the limited quantity and quality of published evidence, the recommendations included in this guidance state that individuals with refractory epilepsy who have anterior thalamic targets should only have DBS under special arrangements for clinical governance, consent, and audit or research.[25] Special arrangements are recommended by NICE when the independent advisory committee judges that there is uncertainty about the safety and effectiveness of identified procedures, and this term also intends to highlight the essential role of informed consent to providers.[27]

Scottish Intercollegiate Guidelines Network (SIGN)

In 2015, SIGN published a guideline for the diagnosis and management of epilepsy in adults, and updated the guideline in 2018 with an anticipated rereview date in 2022.[28] Key recommendations from the guideline state that patients who fail to respond to antiepileptic drugs should be assessed for neurosurgical treatment, and a very low strength of evidence supported consideration of curative resective surgery before consideration of palliative procedures such as vagus nerve stimulation.[28] DBS is listed among the surgical treatment options considered during the literature review, but the authors noted the SANTE trial that presented evidence of possible seizure reduction in patients with drug-resistant epilepsy had substantial limitations and declined to provide an evidence rating for DBS.[28] In contrast, the authors provided a low-strength-of-evidence rating for considering vagus nerve stimulation for patients with drug-resistant epilepsy who are ineligible for resective surgery.[28]

Recommendations from Professional Societies

American Academy of Neurology

We did not identify any guidelines from the American Academy of Neurology about DBS for treatment of epilepsy.[30]

American Epilepsy Society

We did not identify any guidelines from the American Epilepsy Society about DBS for treatment of epilepsy.[31]

National Association of Epilepsy Centers

The current guideline about levels of medical establishments for treating patients with epilepsy was published in 2010 by the National Association of Epilepsy Centers, and represents the third iteration of the guideline originally published in 1990.[32] This guideline notes that patients with intractable epilepsy should be treated at Level 3 and Level 4 epilepsy centers, which have the resources and capability to offer surgical procedures, including the placement of intracranial electrodes and vagus nerve stimulators.[32] At the time of publication of this guideline, DBS for refractory epilepsy was not yet FDA-approved.

Royal Australasian College of Surgeons

We did not identify any guidelines from the Royal Australasian College of Surgeons Australian Safety and Efficacy Register of New Interventional Procedures –Surgical publications and reports about DBS for treatment epilepsy.[33]

Recommendations from Others

European Expert Opinion Panel Convened by Medtronic

In response to a lack of guidelines for DBS for epilepsy, an expert panel was convened in Europe to review published literature and to publish a consensus statement about DBS to treat epilepsy in individuals with targets in the anterior nucleus of the thalamas.[29] The panel included 10 neurologists who were recognized as experts at managing drug-resistant epilepsy in patients with implanted DBS devices, and 4 neurosurgeons who were recognized as experts in implanting and managing DBS systems in patients with epilepsy.[29] The process for reaching consensus about patient selection and management included a literature review, web-based surveys completed by the experts about the content of the literature, an in-person analysis and debate of the survey results, and a final round of web-based survey to measure the final level of agreement among the experts.[29] Medtronic, the manufacturer of the only DBS system with FDA approval to treat epilepsy in the US, hosted the in-person meeting at their headquarters in Switzerland and gave each expert a speaker honoraria for their participation.[29]

The 2020 publication of this consensus reports that at least 71% of the experts agreed that each of the following criteria were important for patient selection[29]:

- Presurgical evaluation should include members from multiple disciplines to evaluate the patient's electroencephalograph video recordings of habitual seizures, magnetic resonance imaging, and neuropsychological evaluation. These elements assist in the assessment of the patient's preference, operability, history and prevalence of psychogenic seizures, and psychiatric history, including history of depression or memory deficits.
- Patients with drug-resistant temporal lobe epilepsy who were ineligible for resective surgery, and patients with failed vagus nerve stimulation or failed resective surgery were considered candidates for DBS.
- Multidisciplinary teams should be concerned about selecting DBS for patients with a progressive etiology (e.g., tumor, dementia), history of suicide attempts, depression, psychogenic seizures, psychosis related to seizures, contraindications noted on the magnetic resonance imaging, or unreliable seizure diary.
- Ability to monitor depression, anxiety, seizure frequency, quality of life, sleep quality, and incidence of infections in follow-up care on a regular basis.

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Coverage guidance is prepared by the Health Evidence Review Commission (HERC), HERC staff, and subcommittee members. The evidence summary is prepared by the Center for Evidence-based Policy at Oregon Health & Science University (Center). This document is intended to guide public and private purchasers in Oregon in making informed decisions about health care services.

The Center is not engaged in rendering any clinical, legal, business or other professional advice. The statements in this document do not represent official policy positions of the Center. Researchers involved in preparing this document have no affiliations or financial involvement that conflict with material presented in this document.

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Appendix A. GRADE Table Element Descriptions

Element	Description
Balance of benefits and harms	The larger the difference between the desirable and undesirable effects, the higher the likelihood that a strong recommendation is warranted. An estimate that is not statistically significant or has a confidence interval crossing a predetermined clinical decision threshold will be downgraded.
Quality of evidence	The higher the quality of evidence, the higher the likelihood that a strong recommendation is warranted
Resource allocation	The higher the costs of an intervention—that is, the greater the resources consumed in the absence of likely cost offsets—the lower the likelihood that a strong recommendation is warranted
Values and preferences	The more values and preferences vary, or the greater the uncertainty in values and preferences, the higher the likelihood that a weak recommendation is warranted
Other considerations	Other considerations include issues about the implementation and operationalization of the technology or intervention in health systems and practices within Oregon.

Strong recommendation

In Favor: The subcommittee concludes that the desirable effects of adherence to a recommendation outweigh the undesirable effects, considering the balance of benefits and harms, resource allocation, values and preferences and other factors.

Against: The subcommittee concludes that the undesirable effects of adherence to a recommendation outweigh the desirable effects, considering the balance of benefits and harms, resource allocation, values and preferences and other factors.

Weak recommendation

In Favor: The subcommittee concludes that the desirable effects of adherence to a recommendation probably outweigh the undesirable effects, considering the balance of benefits and harms, resource allocation, values and preferences and other factors., but further research or additional information could lead to a different conclusion.

Against: The subcommittee concludes that the undesirable effects of adherence to a recommendation probably outweigh the desirable effects, considering the balance of benefits and harms, cost and resource allocation, and values and preferences, but further research or additional information could lead to a different conclusion.

Confidence in estimate rating across studies for the intervention/outcome

Assessment of confidence in estimate includes factors such as risk of bias, precision, directness, consistency and publication bias.

High: The subcommittee is very confident that the true effect lies close to that of the estimate of the effect. Typical sets of studies are RCTs with few or no limitations and the estimate of effect is likely stable.

Moderate: The subcommittee is moderately confident in the estimate of effect: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different. Typical

sets of studies are RCTs with some limitations or well-performed nonrandomized studies with additional strengths that guard against potential bias and have large estimates of effects.

Low: The subcommittee's confidence in the estimate of effect is limited: The true effect may be substantially different from the estimate of the effect. Typical sets of studies are RCTs with serious limitations or nonrandomized studies without special strengths.

Very low: The subcommittee has very little confidence in the estimate of effect: The true effect is likely to be substantially different from the estimate of effect. Typical sets of studies are nonrandomized studies with serious limitations or inconsistent results across studies.

Appendix B. GRADE Evidence Profile

Quality Assessment (Confidence in Estimate of Effect)							
No. of Studies	**Study Design(s)**	**Risk of Bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other Factors**	**Quality**
Hospitalizations							
1	Observational	High	Not serious	Serious	Not serious	Secondary analysis of data collected for other purposes	Very low ●○○○
Harms							
4	2 RCTs with observational follow-ups and 2 systematic reviews	Moderate to high	Not serious	Serious	Not serious	Heterogenous patient populations; small sample sizes	Low ●●○○
Seizure frequency							
2	RCTs with observational follow-ups	Moderate to high	Not serious	Serious	Not serious	Heterogenous patient populations; small sample sizes	Low ●●○○
Seizure severity							
2	RCTs with observational follow-ups	Moderate to high	Not serious	Serious	Not serious	Heterogenous patient populations; small sample sizes	Low ●●○○
Medication use							
1	RCT with observational follow-up	Moderate to high	Unable to rate	Serious	Serious	Heterogenous patient populations; small sample sizes	Very low ●○○○

Appendix C. Methods

Scope Statement

Populations

Adults with refractory epilepsy who:

1) Have a diagnosis of epilepsy characterized by partial-onset seizures with or without secondary generalization; and
2) Have not responded to adequate trials of 3 or more antiepileptic medications; and
3) Have averaged 6 or more seizures per month during the previous 3 months, with no more than 30 days between seizures; and
4) Have focal anterior thalamic nucleus targets; and
5) Are not candidates for resective epilepsy surgery or have a history of failed resective epilepsy surgery; and
6) Are not candidates for other treatments for refractory epilepsy (e.g., vagal nerve stimulation) or have a history of failed treatments

Population scoping notes: None

Interventions

Deep brain stimulation of the anterior nucleus of the thalamus

Intervention exclusions: None

Comparators

Antiseizure medications or other treatments

Outcomes

Critical: Hospitalization, harms (for example, depression, suicidality, memory loss, surgery-related adverse events)

Important: Clinically significant change in seizure frequency, clinically significant improvement in Engel Epilepsy Surgery Outcome Scale (EESOS) scoring, clinically significant change in medication use

Considered but not selected for the GRADE table: Mortality from sudden death in epilepsy

Key Questions

KQ1: What is the comparative effectiveness of deep brain stimulation of the anterior nucleus of the thalamus to treat refractory epilepsy?

KQ2: Does the comparative effectiveness of deep brain stimulation of the anterior nucleus of the thalamus vary by:

a. Type of epilepsy
b. Patient characteristics
c. Previous treatments
d. Location of seizure focus

KQ3: What are the harms of deep brain stimulation of the anterior nucleus of the thalamus to treat refractory epilepsy?

Contextual Questions

None

Search Strategy

We conducted a full search of the core sources to identify systematic reviews, meta-analyses, and technology assessments that meet the criteria for the scope described above. Searches of core sources were limited to citations published after 2017.

The following core sources were searched:

Agency for Healthcare Research and Quality (AHRQ)
Canadian Agency for Drugs and Technologies in Health (CADTH)
Cochrane Library (Wiley Online Library)
Institute for Clinical and Economic Review (ICER)
Medicaid Evidence-based Decisions Project (MED)
National Institute for Health and Care Excellence (NICE)
Veterans Administration Evidence-based Synthesis Program (ESP)
Washington State Health Technology Assessment Program

An Ovid MEDLINE search was also conducted to identify systematic reviews, meta-analyses, and technology assessments, adapted from the NICE rapid review search strategy published in 2020.[26] The search was limited to publications in English published since 2010. After reviewing the systematic reviews and publications from NICE, we determined a review of component RCTs was needed to ensure inclusion of all publications resulting from the 2 completed RCTs on this topic. Therefore, an Ovid MEDLINE® search was conducted for RCTs published in 2010. The search was limited to publications in English.

Searches for clinical practice guidelines were limited to those published since 2017. A search for relevant clinical practice guidelines was also conducted using Ovid MEDLINE® and the following sources:

Australian Government National Health and Medical Research Council (NHMRC)
Canadian Agency for Drugs and Technologies in Health (CADTH)
Centers for Disease Control and Prevention (CDC), Community Preventive Services
National Institute for Health and Care Excellence (NICE)
Scottish Intercollegiate Guidelines Network (SIGN)
United States Preventive Services Task Force (USPSTF)
Veterans Administration/Department of Defense (VA/DoD) Clinical Practice Guidelines

A search of the US Food and Drug Administration manufacturer and user facility device experience (MAUDE) database for reports of harm using the model names and numbers associated with the neurostimulator system approved for use in patients with epilepsy. The manufacturer website was also searched for the most recent product performance report.

A search of the Clinical Trials Registry was conducted for completed and ongoing trials on this topic using the search terms *epilepsy*, *epileptic, seizure*, *neurostimulation, deep brain stimulation, stimulator,* and *stimulation.*

Inclusion/Exclusion Criteria

Studies were excluded if they were not published in English, did not address the scope statement, or were study designs other than systematic reviews, meta-analyses, technology assessments, randomized controlled trials, or clinical practice guidelines. However, because none of the includes RCTs and systematic reviews addressed the critical outcome of hospitalizations, a publication of a secondary analysis of hospital readmission data in a propensity score matched sample was included.

Appendix D. Applicable Codes

GROUP	CODES	DESCRIPTION
CPT Codes		
Diagnostic imaging and planning	70450	CT, head or brain without contrast material
	70551	MRI, brain (including brain stem), without contrast material
	76376	3D rendering with interpretation and reporting of computed tomography, magnetic resonance imaging, ultrasound, or other tomographic modality with image post-processing under concurrent supervision, not requiring image postprocessing on an independent workstation
	76377	3D rendering with interpretation and reporting of computed tomography, magnetic resonance imaging, ultrasound, or other tomographic modality with image post-processing under concurrent supervision, requiring image postprocessing on an independent workstation
Lead implantation or replacement	61863	Twist drill, burr hole, craniotomy, or craniectomy with stereotactic implantation of neurostimulator electrode array in subcortical site (eg, thalamus, globus pallidus, subthalamic nucleus, periventricular, periaqueductal gray), without use of intraoperative microelectrode recording; first array
	61864	Each additional array (List separately in addition to primary procedure)
	61867	Twist drill, burr hole, craniotomy, or craniectomy with stereotactic implantation of neurostimulator electrode array in subcortical site (eg, thalamus, globus pallidus, subthalamic nucleus, periventricular, periaqueductal gray), with use of intraoperative microelectrode recording; first array
	61868	Each additional array
Generator implantation or replacement	61885	Insertion or replacement of cranial neurostimulator pulse generator or receiver, direct or inductive coupling; with connection to a single electrode array
	61886	Insertion or replacement of cranial neurostimulator pulse generator or receiver, direct or inductive coupling; with connection to two or more electrode arrays
Revision or removal	61880	Revision or removal of intracranial neurostimulator electrodes
	61888	Revision or removal of cranial neurostimulator pulse generator or receiver
Intraoperative stimulation with microelectrode recording	95961	Functional cortical and subcortical mapping by stimulation and/or recording of electrodes on brain surface, or of depth electrodes, to provoke seizures or identify vital brain structures; initial hour of attendance by physician or other qualified healthcare professional
	95962	Functional cortical and subcortical mapping by stimulation and/or recording of electrodes on brain surface, or of depth electrodes, to provoke seizures or identify vital brain structures; each additional hour of attendance by physician or other qualified healthcare professional (List separately in addition to code for primary procedure)

Analysis and Programming	95970	Electronic analysis of implanted neurostimulator pulse generator/transmitter (e.g., contact group[s], interleaving, amplitude, pulse width, frequency [Hz], on/off cycling, burst, magnet mode, dose lockout, patient selectable parameters, responsive neurostimulation, detection algorithms, closed loop parameters, and passive parameters) by physician or other qualified health care professional, with brain, cranial nerve, spinal cord, peripheral nerve, or sacral nerve, neurostimulator pulse generator/transmitter, without programming
	95983	Electronic analysis of implanted neurostimulator pulse generator/transmitter (e.g., contact group[s], interleaving, amplitude, pulse width, frequency [Hz], on/off cycling, burst, magnet mode, dose lockout, patient selectable parameters, responsive neurostimulation, detection algorithms, closed loop parameters, and passive parameters) by physician or other qualified health care professional, with brain neurostimulator pulse generator/transmitter programming, first 15 minutes face-to-face time with physician or other qualified health care professional
	95984	With brain neurostimulator pulse generator/transmitter programming, each additional 15 minutes face-to-face time with physician or other qualified health care professional (List separately in addition to code for primary procedure)
HCPCS Level II Codes		
Pulse generator	C1767	Generator, neurostimulator (implantable), non-rechargeable
	C1820	Generator, neurostimulator (implantable), with rechargeable battery and charging system
	L8679	Implantable neurostimulator pulse generator, any type
	L8686	Implantable neurostimulator pulse generator, single array, non-rechargeable, includes extension
	L8687	Implantable neurostimulator pulse generator, dual array, rechargeable, includes extension
	L8688	Implantable neurostimulator pulse generator, dual array, non-rechargeable, includes extension
Extension	C1883	Adaptor/extension, pacing lead or neurostimulator lead (implantable)
Patient programmer	C1787	Patient programmer, neurostimulator
	L8681	Patient programmer (external) for use with implantable programmable neurostimulator pulse generator, replacement only
External recharger	L8689	External recharging system for battery (internal) for use with implantable neurostimulator, replacement only
ICD-10-CM Diagnosis Codes		
Epilepsy	G40.119	Localization-related (focal) (partial) symptomatic epilepsy and epileptic syndromes with simple partial seizures, intractable, without status epilepticus
	G40.219	Localization-related (focal) (partial) symptomatic epilepsy and epileptic syndromes with complex partial seizures, intractable, without status epilepticus
Device complications	T85.110A	Breakdown (mechanical) of implanted electronic neurostimulator of brain electrode (lead)

	T85.113A	Breakdown (mechanical) of implanted electronic neurostimulator, generator
	T85.120A	Displacement of implanted electronic neurostimulator of brain electrode (lead)
	T85.123A	Displacement of implanted electronic neurostimulator, generator
	T85.190A	Other mechanical complication of implanted electronic neurostimulator of brain electrode (lead)
	T85.193A	Other mechanical complication of implanted electronic neurostimulator, generator
	T85.731A	Infection and inflammatory reaction due to implanted electronic neurostimulator of brain, electrode (lead)
	T85.734A	Infection and inflammatory reaction due to implanted electronic neurostimulator generator
	T85.830A	Hemorrhage due to nervous system prosthetic devices, implants and grafts
	T85.840A	Pain due to nervous system prosthetic devices, implants and grafts
	T85.890A	Other specified complication of nervous system prosthetic devices, implants and grafts
Informational	Z45.42	Encounter for adjustment and management of neurostimulator
	Z96.82	Presence of neurostimulator

Note. Inclusion on this list does not guarantee coverage.

Abbreviations. 3D: three-dimensional; CPT: Current Procedural Terminology; HCPCS: Healthcare Common Procedure Coding System; ICD-10-CM: International Classification of Diseases, Tenth Revision, Clinical Modification; MRI: magnetic resonance imaging.

Coverage Guidance – Deep Brain Neurostimulators for Refractory Epilepsy

Question: How should the Coverage Guidance *Deep Brain Neurostimulators for Refractory Epilepsy* be applied to the Prioritized List?

Question source: EbGS

Issue: EbGS approved a coverage guidance regarding deep brain neurostimulators for refractory epilepsy at their June 2021 meeting. The "blue box" wording is shown below.

HERC Coverage Guidance

Deep brain stimulation for treatment of refractory epilepsy is recommended for coverage (*weak recommendation*) when

1) the surgery is performed at a Level 4 epilepsy center, AND
2) the patient has failed multiple anti-seizure medications, AND
3) the patient is ineligible for resective surgery OR has failed vagus nerve stimulation or resective surgery

Current Prioritized List status

GROUP	CODES	DESCRIPTION	
	CPT Codes		Current Placement
Lead implantation or replacement	61863	Twist drill, burr hole, craniotomy, or craniectomy with stereotactic implantation of neurostimulator electrode array in subcortical site (eg, thalamus, globus pallidus, subthalamic nucleus, periventricular, periaqueductal gray), without use of intraoperative microelectrode recording; first array	249 PARKINSON'S DISEASE
	61864	Each additional array (List separately in addition to primary procedure)	249
	61867	Twist drill, burr hole, craniotomy, or craniectomy with stereotactic implantation of neurostimulator electrode array in subcortical site (eg, thalamus, globus pallidus, subthalamic nucleus, periventricular, periaqueductal gray), with use of intraoperative microelectrode recording; first array	249
	61868	Each additional array	249
Generator implantation or replacement	61885	Insertion or replacement of cranial neurostimulator pulse generator or receiver, direct or inductive coupling; with connection to a single electrode array	174 GENERALIZED CONVULSIVE OR PARTIAL EPILEPSY WITHOUT MENTION OF IMPAIRMENT OF CONSCIOUSNESS 249

			285 COMPLICATIONS OF A PROCEDURE ALWAYS REQUIRING TREATMENT
	61886	Insertion or replacement of cranial neurostimulator pulse generator or receiver, direct or inductive coupling; with connection to two or more electrode arrays	249,285
Revision or removal	61880	Revision or removal of intracranial neurostimulator electrodes	249,285
	61888	Revision or removal of cranial neurostimulator pulse generator or receiver	174,285
Intraoperative stimulation with microelectrode recording	95961	Functional cortical and subcortical mapping by stimulation and/or recording of electrodes on brain surface, or of depth electrodes, to provoke seizures or identify vital brain structures; initial hour of attendance by physician or other qualified healthcare professional	DIAGNOSTIC PROCEDURES
	95962	Functional cortical and subcortical mapping by stimulation and/or recording of electrodes on brain surface, or of depth electrodes, to provoke seizures or identify vital brain structures; each additional hour of attendance by physician or other qualified healthcare professional (List separately in addition to code for primary procedure)	DIAGNOSTIC PROCEDURES
Analysis and Programming	95970	Electronic analysis of implanted neurostimulator pulse generator/transmitter (e.g., contact group[s], interleaving, amplitude, pulse width, frequency [Hz], on/off cycling, burst, magnet mode, dose lockout, patient selectable parameters, responsive neurostimulation, detection algorithms, closed loop parameters, and passive parameters) by physician or other qualified health care professional, with brain, cranial nerve, spinal cord, peripheral nerve, or sacral nerve, neurostimulator pulse generator/transmitter, without programming	DIAGNOSTIC PROCEDURES
	95983	Electronic analysis of implanted neurostimulator pulse generator/transmitter (e.g., contact group[s], interleaving, amplitude, pulse width, frequency [Hz], on/off cycling, burst, magnet mode, dose lockout, patient selectable parameters, responsive neurostimulation, detection	174,249,285

		algorithms, closed loop parameters, and passive parameters) by physician or other qualified health care professional, with brain neurostimulator pulse generator/transmitter programming, first 15 minutes face-to-face time with physician or other qualified health care professional	
	95984	With brain neurostimulator pulse generator/transmitter programming, each additional 15 minutes face-to-face time with physician or other qualified health care professional (List separately in addition to code for primary procedure)	174,249,285
ICD-10-CM Diagnosis Codes			
Epilepsy	G40.119	Localization-related (focal) (partial) symptomatic epilepsy and epileptic syndromes with simple partial seizures, intractable, without status epilepticus	30 EPILEPSY AND FEBRILE CONVULSIONS (medical line) 174 GENERALIZED CONVULSIVE OR PARTIAL EPILEPSY WITHOUT MENTION OF IMPAIRMENT OF CONSCIOUSNESS (surgical line) Dysfunction lines (71, 292, 345, 377)
	G40.219	Localization-related (focal) (partial) symptomatic epilepsy and epileptic syndromes with complex partial seizures, intractable, without status epilepticus	30,71,174,292,345,377

HERC staff recommendations:

1) Add the following CPT codes to line 174 GENERALIZED CONVULSIVE OR PARTIAL EPILEPSY WITHOUT MENTION OF IMPAIRMENT OF CONSCIOUSNESS
    a. CPT 61863-61868 Twist drill, burr hole, craniotomy, or craniectomy with stereotactic implantation of neurostimulator electrode array
    b. CPT 61880 Revision or removal of intracranial neurostimulator electrodes
    c. CPT 61886 Insertion or replacement of cranial neurostimulator pulse generator or receiver, direct or inductive coupling; with connection to two or more electrode arrays
2) Add a new guideline to line 174 as shown below

GUIDELINE NOTE XXX 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

1) the surgery is performed at a Level 4 epilepsy center, AND
2) the patient has failed multiple anti-seizure medications, AND
3) the patient is ineligible for resective surgery OR has failed vagus nerve stimulation or resective surgery

HERC Coverage Guidance: Deep Brain Neurostimulators for Refractory Epilepsy
Disposition of Public Comments

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Commenters

Identification	Stakeholder
A	David Spencer, MD, FAAN, Professor of Neurology and Director at OHSU Comprehensive Epilepsy Center [*Submitted April 15, 2021*]
B	Cyndy Novak, MBA, Senior Manager at Medtronic [*Submitted May 13, 2021*]

Public Comments

ID/#	Comment	Disposition
A1	Dear Commission, I am writing during this public comment period to express my support for the proposed coverage guidance recommendation of the HERC regarding DBS therapy for epilepsy. As the director of the OHSU epilepsy program, I personally provide care for (and also oversee our program's care for) patients with refractory epilepsy. While the majority of people with epilepsy respond well to treatment with anti-seizure medication, we see many in the substantial minority who do not and who have not responded to alternative approaches including resection/ablation or vagus nerve stimulation (or are not appropriate candidates for these). I believe it is critical to have alternative options such as deep brain stimulation for a small number of people who might substantially benefit and who may have few other options.	*Thank you for your comments. In the coverage guidance section titled Recommendations from Professional Societies we summarize the recommendation from the National Association of Epilepsy Centers Revised 2010 Guidelines for essential services, personnel, and facilities in specialized epilepsy centers.* *Some Level 3 centers offer noninvasive evaluation for epilepsy surgery, basic resective surgery, and implantation of vagal nerve stimulators. A Level 4 epilepsy center provides complex forms of neurodiagnostic monitoring, more extensive*

ID/#	Comment	Disposition
	I believe that patient selection is critical, and safeguards should be in place to prevent indiscriminate use of this therapy. For this reason, I would also advocate that coverage of DBS be limited to National Association of Epilepsy Center Level 4 programs. These are the programs that have undergone survey and have met criteria to be considered best equipped to manage patients with complex epilepsy needs, and this would ensure that there is careful vetting of candidates and a robust process of multidisciplinary review prior to DBS surgery for epilepsy. My concern is that the expertise for doing DBS surgery (the technical skill) exists outside of developed epilepsy programs because of the longstanding experience with DBS for Parkinson's disease (PD). I'd be concerned if centers without much experience treating complex epilepsy decided to start doing epilepsy DBS using their functional neurosurgeon who does PD DBS. Maybe they would inappropriately implant patients with depression and not monitor it, or implant patients who were actually better candidates for resection or other approach. Or those who did not truly have medication resistant epilepsy. The National Association of Epilepsy Centers (NAEC) is the accrediting body for epilepsy centers in the US. They designate programs as level 4, with personnel and technology that enables them to manage the most complex, including surgical cases, and level 3, who have expertise in epilepsy but that must be partnered with a level 4 program to do surgery. Thank you for your consideration of these comments.	*neuropsychological, and psychosocial treatment. The placement of intracranial electrodes, such as the implantation of DBS systems, is restricted to Level 4 centers.* *The National Association of Epilepsy Centers website indicates that there are 2 Level 4 epilepsy centers in Oregon (i.e., OHSU and Providence St. Vincent Medical Center, both located in Portland). There is a Level 3 epilepsy center in Boise, Idaho.* *Based on your comment, we have added a requirement for Level 4 epilepsy centers to the recommendation.*
B1	Hello- My name is Cyndy Novak and I am a Sr. Manager, Global Health Economics and Reimbursement, Brain Modulation at Medtronic. Our address is Medtronic, Inc. 7000 Central Ave NE, RCE 385 Minneapolis, MN 55432 and my email is cyndy.novak@medtronic.com.	*Thank you for your comments. We reviewed the publications and materials you attached to your comment. We have added the Salanova et al., 2021 publication to the coverage guidance, and the*

ID/#	Comment	Disposition
	I would like to provide some documents for your consideration in review of the proposed Guidelines for Deep Brain Stimulation for Refractory Epilepsy. We are pleased with your recommendation for coverage. We do feel that DBS for epilepsy should be treated equally to, and not only recommended, when VNS has failed. The attached documents provide additional information that you may not have reviewed and may be helpful as you look to finalize your guidance. Thank you so much for all that you are doing to help ensure that patients have access to life changing therapies.	*coverage guidance already included 4 of the publications that you provided.* *Of the publications you provided about DBS that we excluded from the coverage guidance, 1 was an abstract; 1 did not report outcomes relevant to our scope; and 21 reported results from study designs outside of the scope of our review. The other publications you provided were excluded because 7 focused on vagal nerve stimulation and 4 publications focused on responsive neurostimulation.* *Expert opinion from the 2020 European Expert Opinion Panel recommended DBS only for patients "with drug-resistant temporal lobe epilepsy who were ineligible for resective surgery, and patients with failed vagus nerve stimulation or failed resective surgery."*

References Provided by Commenters

ID	References
B	Already included in the coverage guidance: Fisher R, Salanova V, Witt T, et al. Electrical stimulation of the anterior nucleus of thalamus for treatment of refractory epilepsy. *Epilepsia*. 2010;51(5):899-908. doi: 10.1111/j.1528-1167.2010.02536.x Salanova V, Witt T, Worth R, et al. Long-term efficacy and safety of thalamic stimulation for drug-resistant partial epilepsy. *Neurology*. 2015;84(10):1017-1025. doi: 10.1212/WNL.0000000000001334 Troster AI, Meador KJ, Irwin CP, Fisher RS, Group SS. Memory and mood outcomes after anterior thalamic stimulation for refractory partial epilepsy. *Seizure*. 2017;45:133-141. doi: 10.1016/j.seizure.2016.12.014 Newly included in the coverage guidance: Salanova, V, Sperling, MR, Gross, RE, Irwin, CP, Vollhaber, J, Giftakis, JE, Fisher, RS; SANTÉ Study Group. The SANTÉ Study at 10 years of follow-up: Effectiveness, Safety and SUDEP. *Epilepsia*. 2021 Apr 8. doi: 10.1111/epi.16895. Online ahead of print. Not included in the coverage guidance: Annegers JF, Coan SP, Hauser WA, Leestma J. Epilepsy, vagal nerve stimulation by the NCP system, all-cause mortality, and sudden, unexpected, unexplained death. *Epilepsia*. 2000 May;41(5):549-53. Bergey GK, Morrell MJ, Mizrahi EM, et al. Long-term treatment with responsive brain stimulation in adults with refractory partial seizures. *Neurology.* 2015;84(8):810-817. Bouwens van der Vlis TAM, Schijns O, Schaper F, et al. Deep brain stimulation of the anterior nucleus of the thalamus for drug-resistant epilepsy. *Neurosurg Rev*. 2018. Dodrill CB, Morris GL. Effects of Vagal Nerve Stimulation on Cognition and Quality of Life in Epilepsy. *Epilepsy Behav*. 2001 Feb;2(1):46-53.

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