Health Evidence Review Commission's Value-based Benefits Subcommittee

May 19, 2022

8:00 AM - 1:00 PM

Online meeting

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Section 1.0

Call to Order

AGENDA
VALUE-BASED BENEFITS SUBCOMMITTEE
5/19/2022
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 **8:05 AM**
- **A.** Introductions
- **B.** General announcements/updates
- **C.** Errata
- **D.** Below the Line Review

III. New discussion items **8:10 AM**
- **A.** Visual field testing *(Eye tests for various conditions)*
- **B.** Adenoidectomy guideline update 2022 *(Adenoid removal for children with hearing loss related to ear infections)*
- **C.** Guideline revisions for bone anchored hearing aids (BAHA) *(A specific type of hearing aid for children)*

IV. Straightforward/consent agenda – Ariel Smits **9:15 AM**
- A. Consent table
- B. COVID coding update
- C. Items discussed with leadership and no changes recommended

V. New discussion items continued **9:20 AM**
- **A.** Temporary urethral stents 2022 *(Small tube inserted in the urine duct to treat a prostate condition)*
- **B.** Fecal lactoferrin *(A stool test to help diagnose the cause of bowel problems)*
- **C.** Gastric neurostimulators *(Implanted device used for diabetic stomach problems)*
- **D.** Routine monitoring MRIs in multiple sclerosis *(An imaging test for people with multiple sclerosis)*

BREAK **10:15 AM**

VI. New discussion items continued **10:30 AM**
- **A.** Coronary CT angiography *(An imaging test that looks at the arteries that supply blood to the heart)*
- **B.** Rhinophyma shaving *(Removing thickened skin from the nose due to a skin condition)*
- **C.** Spinal cord stimulators for diabetic peripheral neuropathy *(Spinal cord stimulation for lower body nerve issues for people with diabetes)*
- **D.** Shoulder arthroplasty with subacromial spacers *(Shoulder surgery with balloon implants to treat conditions such as severely torn rotator cuffs)*

VII. Previous discussion items **11:00 AM**

- **A.** Erythropoietin in chronic renal disease *(A drug to treat low blood count caused by kidney disease)*
- **B.** Orthodontia guideline update *(Braces for severely misaligned teeth that affect speech or eating)*

VIII. 2022 Below the Line review **11:15 AM**

- **A.** Benign gastrointestinal carcinoid tumors (*Surgery for an abnormal growth found in the stomach or intestines*)

IX. Coverage Guidances **11:30 PM**

- **A.** PANDAS/PANS *(Mental health symptoms developed after infection in children)*

X. Public comment on non-agenda items **12:55 PM**

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

Value-based Benefits Subcommittee Recommendations Summary
For Presentation to:
Health Evidence Review Commission on March 10, 2022

For specific coding recommendations and guideline wording, please see the text of the 3/10/2022 VbBS minutes.

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

- Move the diagnosis code for inflammatory joint diseases associated with autoimmune gut disease from an unfunded to a funded line
- Add the procedure code for platelet rich plasma injections to an unfunded line
- Add a procedure code to allow minimally invasive ablation of small renal tumors to the funded renal cancer line
- Add the CPT codes for gait analysis and surface electromyography to an unfunded line
- Delete the diagnosis code for extra toes from an unfunded line and left only on a funded line
- Add the procedure code for dorsal rhizotomy to a funded line to pair with spastic cerebral palsy
- Make a variety of straightforward coding changes

ITEMS CONSIDERED BUT NO RECOMMENDATIONS FOR CHANGES MADE

- No change was made in the non-coverage of mid-foot fusion for foot arthritis
- No change was made in the non-coverage of treatment of actinic keratoses
- No change was made to the non-coverage of sensory integration therapy

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

- Edit the chemodenervation guideline to include two additional lines with chemodenervation codes
- Add a new guideline indicating that pelvic congestion syndrome is a non-funded syndrome and does not pair with various vein procedures
- Edit the breast reconstruction after breast cancer surgery guideline to clarify that reconstruction is also covered after lumpectomy.
- Delete two guidelines regarding breast screening and extensively edit one guideline to indicate when breast MRI is a covered service
- Add a new guideline outlining when ablation of renal tumors is covered
- Edit the lower urinary tract symptoms guideline to clarify when procedures are covered
- Add a new guideline regarding dorsal rhizotomy
- Make several straightforward guideline note changes

2024 Biennial Review

- Delete the agenesis of lung line effective 1/1/2024
- Delete the spastic diplegia line effective 1/1/2024

VALUE-BASED BENEFITS SUBCOMMITTEE
Virtual Meeting
March 10, 2022
8:00 AM – 1:00 PM

Members Present: Kevin Olson, MD, Chair; Holly Jo Hodges, MD, MBA, Vice-chair; Cris Pinzon, MPH, BSN, BS, RN; Brian Duty, MD; Adriane Irwin, PharmD; David Saenger, MD.

Members Absent: Kathryn Schabel, MD; Mike Collins.

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

Also Attending: Dawn Mautner, MD; Kristty Zamora-Polanco and Senna Towner (Oregon Health Authority); Jenna Oh; l walker; Lisa Kouzes; Maria Gonzalez-Cress; Obinna Oleribe; Shauna Durbin and Val King MD MPH (Center for Evidence Based Health Policy); siobhan hess

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

  The meeting was called to order at 8:00 am and roll was called. A quorum of members was present at the meeting. Minutes from the November 18, 2021 VbBS meeting were reviewed and approved.

  Gingerich gave an update on Early and Periodic Screening, Diagnostic and Treatment (EPSDT) changes that are anticipated to be put into place on 1/1/2024, as well as the impact of recent changes to Statement of Intent 4 around allowing otherwise nonfunded services to be covered if they would benefit a child in terms of growth, development or ability to participate in school. He mentioned a recent CMS letter with requirements that treatments related to "long COVID" should be covered when medically necessary even if they wouldn't otherwise be covered, which is in some ways similar to the EPSDT changes coming in 2024.

  Gingerich made announcements of membership changes. He also introduced HERC staff trial of plain language summaries to certain issues summaries in today's meeting materials and asked for member and public feedback.

  Smits reviewed the errata document, as well as the January 1, 2022 placement of newly ACIP-approved pneumococcal vaccine CPT codes on a funded line per expressed HERC intent.

- **Topic: Straightforward/Consent Agenda**

Discussion: There was discussion on the following items:

1) CPT 87913 (COVID genotyping). Olson asked whether there was a pressing reason to add this code to the Diagnostic Procedure File as it is not currently required for clinical care and is subject to misuse. Smits noted that the code could be added to the COVID line to only pair with COVID infection. Gingerich noted that there were federal rules regarding COVID testing that would need to be consulted if this test was not covered. The group agreed to the staff recommended placement on the Diagnostic Procedure File, but requested that staff periodically audit use and bring this information to the HERC for possible action if overused.

2) Newborn home visits: Gingerich noted that these services are a carve-out and do not have cost to the CCOs.

Recommended Actions:

1) Add M62.81 (Muscle weakness (generalized)) to the dysfunction lines 71,292,345 and 377
2) Remove N96 (Recurrent pregnancy loss) from line 658 GENITOURINARY CONDITIONS WITH NO OR MINIMALLY EFFECTIVE TREATMENTS OR NO TREATMENT NECESSARY
    a. Advise HSD to add N96 to the Diagnostic Workup File
3) Remove H02.73 family (Vitiligo of eyelid and periocular area) from line 654 SENSORY ORGAN CONDITIONS WITH NO OR MINIMALLY EFFECTIVE TREATMENTS OR NO TREATMENT NECESSARY
    a. Add H02.73 family to lines 426 SEVERE INFLAMMATORY SKIN DISEASE and 656 DERMATOLOGICAL CONDITIONS WITH NO OR MINIMALLY EFFECTIVE TREATMENTS OR NO TREATMENT NECESSARY
4) Remove K22.10 (Ulcer of esophagus without bleeding) from line 513 ESOPHAGITIS AND GERD; ESOPHAGEAL SPASM; ASYMPTOMATIC DIAPHRAGMATIC HERNIA
    a. Add K22.10 to line 56 ULCERS, GASTRITIS, DUODENITIS, AND GI HEMORRHAGE
5) Remove M35.00 (Sjogren syndrome, unspecified) from line 510 DYSFUNCTION OF NASOLACRIMAL SYSTEM IN ADULTS; LACRIMAL SYSTEM LACERATION
    a. Add M35.00 to line 330 SYSTEMIC SCLEROSIS; SJOGREN'S SYNDROME
6) Remove L49.7 (Exfoliation due to erythematous condition involving 70-79 percent of body surface) from lines 57 SEVERE BURNS and 127 MODERATE BURNS
    a. Add L49.7 to line 504 ERYTHEMATOUS CONDITIONS
7) Remove H70.1 (Chronic mastoiditis) and H70.9 families (Unspecified mastoiditis) from line 476 CHRONIC OTITIS MEDIA; OPEN WOUND OF EAR DRUM
    a. Add H70.1 and H70.9 families to line 170 ACUTE MASTOIDITIS
8) Change the title of line 482 to MILD/MODERATE LICHEN PLANUS
9) Remove D78.02 (Intraoperative hemorrhage and hematoma of the spleen complicating other procedure) from line 529 DISORDERS OF FUNCTION OF STOMACH AND OTHER FUNCTIONAL DIGESTIVE DISORDERS
    a. Add D78.02 to line 285 COMPLICATIONS OF A PROCEDURE ALWAYS REQUIRING TREATMENT
10) Remove B33.2 family (Viral endocarditis, myocarditis, pericarditis, cardiomyopathy) from line 615 OTHER VIRAL INFECTIONS
    a. Add B33.2 family to line 81 MYOCARDITIS, PERICARDITIS, AND ENDOCARDITIS
11) Remove H16.31 (Corneal abscess) family from line 473 KERATOCONJUNCTIVITIS
    a. Add H16.31 family to line 244 CORNEAL ULCER; SUPERFICIAL INJURY OF EYE AND ADNEXA

12) Add HCPCS C9761 (Cystourethroscopy, with ureteroscopy and/or pyeloscopy, with lithotripsy, and ureteral catheterization for steerable vacuum aspiration of the kidney, collecting system, ureter, bladder, and urethra if applicable) to lines 49 CONGENITAL HYDRONEPHROSIS, 180 URETERAL STRICTURE OR OBSTRUCTION; HYDRONEPHROSIS; HYDROURETER, and 352 URINARY SYSTEM CALCULUS
13) Add 67515 (Injection of medication or other substance into Tenon's capsule) to lines 370 AMBLYOPIA and 393 STRABISMUS WITHOUT AMBLYOPIA AND OTHER DISORDERS OF BINOCULAR EYE MOVEMENTS; CONGENITAL ANOMALIES OF EYE; LACRIMAL DUCT OBSTRUCTION IN CHILDREN
14) Remove 17000 (Destruction (eg, laser surgery, electrosurgery, cryosurgery, chemosurgery, surgical curettement), premalignant lesions (eg, actinic keratoses); first lesion) from lines 373 ACNE CONGLOBATA AND ACNE FULMINANS, 453 SEVERE CYSTIC ACNE, 522 ROSACEA; MILD/MODERATE ACNE
15) Add N48.82 (Acquired torsion of penis) to line 424 COMPLICATIONS OF A PROCEDURE USUALLY REQUIRING TREATMENT
16) Modify GN73 as shown in Appendix A
17) Add the following CPT codes to line 3 PREVENTION SERVICES WITH EVIDENCE OF EFFECTIVENESS
    a. 91308 Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) (coronavirus disease [COVID-19]) vaccine, mRNA-LNP, spike protein, preservative free, 3 mcg/0.2 mL dosage, diluent reconstituted, tris-sucrose formulation, for intramuscular use
    b. 0081A Immunization administration by intramuscular injection of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) (coronavirus disease [COVID-19]) vaccine, mRNA-LNP, spike protein, preservative free, 3 mcg/0.2 mL dosage, diluent reconstituted, tris-sucrose formulation; first dose
    c. 0081B Second dose
    d. 91309 Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) (coronavirus disease [COVID-19]) vaccine, mRNA-LNP, spike protein, preservative free, 50 mcg/0.5 mL dosage, for intramuscular use
    e. 0094A Immunization administration by intramuscular injection of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) (coronavirus disease [COVID-19]) vaccine, mRNA-LNP, spike protein, preservative free, 50 mcg/0.5 mL dosage, booster dose
18) Add CPT 87913 (Infectious agent genotype analysis by nucleic acid (DNA or RNA); severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) (coronavirus disease [COVID-19]), mutation identification in targeted region(s)) to the Diagnostic Procedure File
19) Modify Diagnostic Guideline D27 as shown in Appendix A
20) Add CPT 99502 (Home visit for newborn care and assessment) to line 3 PREVENTION SERVICES WITH EVIDENCE OF EFFECTIVENESS
21) Add CPT 99501 (Home visit for postnatal assessment and follow-up care) to line 1 PREGNANCY
22) Add the S86.11 family (Strain of other muscle(s) and tendon(s) of posterior muscle group at lower leg level) to line 376 DISRUPTIONS OF THE LIGAMENTS AND TENDONS OF THE ARMS AND LEGS, EXCLUDING THE KNEE, RESULTING IN SIGNIFICANT INJURY/IMPAIRMENT
23) Add the S46.00 family (Unspecified injury of muscle(s) and tendon(s) of the rotator cuff of shoulder) to line 417 DISORDERS OF SHOULDER, INCLUDING SPRAINS/STRAINS GRADE 4 THROUGH 6 and 608 SPRAINS AND STRAINS OF ADJACENT MUSCLES AND JOINTS, MINOR
    a. Remove the S46.00 family from line 634 SUPERFICIAL WOUNDS WITHOUT INFECTION AND CONTUSIONS

24) Add the S46.09 family (Other injury of muscle(s) and tendon(s) of the rotator cuff of shoulder), S46.19 family (Other injury of muscle, fascia and tendon of long head of biceps), S46.29 family (Other injury of muscle, fascia and tendon of other parts of biceps), S46.39 family (Other injury of muscle, fascia and tendon of triceps), S46.89 family (Other injury of other muscles, fascia and tendons at shoulder and upper arm level), and S46.99 family (Other injury of unspecified muscle, fascia and tendon at shoulder and upper arm level) to lines 376, 417, and 608 and remove from line 634
25) Table:

Code	**Add to line**	**Delete from line**
S56.00 family (Unspecified injury of flexor muscle, fascia and tendon of right thumb at forearm level)	376 DISRUPTIONS OF THE LIGAMENTS AND TENDONS OF THE ARMS AND LEGS, EXCLUDING THE KNEE, RESULTING IN SIGNIFICANT INJURY/IMPAIRMENT 608 SPRAINS AND STRAINS OF ADJACENT MUSCLES AND JOINTS, MINOR	634 SUPERFICIAL WOUNDS WITHOUT INFECTION AND CONTUSIONS
S56.09 family (Other injury of flexor muscle, fascia and tendon of right thumb at forearm level)	376 608	634
S56.19 family (Other injury of flexor muscle, fascia and tendon of index finger at forearm level)	376 608	634
S56.20 family (Unspecified injury of other flexor muscle, fascia and tendon at forearm level)	376 608	634
S56.29 family (Other injury of other flexor muscle, fascia and tendon at forearm level)	376 608	634
S56.39 family (Other injury of extensor or abductor muscles, fascia and tendons of thumb at forearm level)	376 608	634
S56.49 family (Other injury of extensor muscle, fascia and tendon of middle finger at forearm level)	376 608	634
S56.59 family (Other injury of other extensor muscle, fascia and tendon at forearm level)	376 608	634
S56.89 family (Other injury of other muscles, fascia and tendons at forearm level)	376 608	634
S66.00 family (Unspecified injury of long flexor muscle, fascia and tendon of thumb at wrist and hand level)	376 608	634
S66.09 family (Other specified injury of long flexor muscle, fascia and tendon of thumb at wrist and hand level)	376 608	634

S66.10 family (Unspecified injury of flexor muscle, fascia and tendon of index finger at wrist and hand level)	376 608	634
S66.19 family (Other injury of flexor muscle, fascia and tendon of index finger at wrist and hand level)	376 608	634
S66.20 family (Unspecified injury of extensor muscle, fascia and tendon of thumb at wrist and hand level)	376 608	634
S66.29 family (Other specified injury of extensor muscle, fascia and tendon of thumb at wrist and hand level)	376 608	634
S66.30 family (Unspecified injury of extensor muscle, fascia and tendon of other finger at wrist and hand level)	376 608	634
S66.39 family (Other injury of extensor muscle, fascia and tendon of index finger at wrist and hand level)	376 608	634
S66.40 family (Unspecified injury of intrinsic muscle, fascia and tendon of thumb at wrist and hand level)	376 608	634
S66.49 family (Other specified injury of intrinsic muscle, fascia and tendon of thumb at wrist and hand level)	376 608	634
S66.50 family (Unspecified injury of intrinsic muscle, fascia and tendon of index finger at wrist and hand level)	376 608	634
S66.59 family (Other injury of intrinsic muscle, fascia and tendon of index finger at wrist and hand level)	376 608	634
S76.09 family (Other specified injury of muscle, fascia and tendon of hip)	376 608	634
S76.10 family (Unspecified injury of quadriceps muscle, fascia and tendon)	376 608	634
S76.20 family (Unspecified injury of adductor muscle, fascia and tendon of thigh)	376 608	634
S86.00 family (Unspecified injury of right Achilles tendon)	376 608	634
S86.09 (Other specified injury of Achilles tendon), S96.00 family (Unspecified injury of muscle and tendon of long flexor muscle of toe at ankle and foot level)	376 608	634
S96.09 family (Other injury of muscle and tendon of long flexor muscle of toe at ankle and foot level)	376 608	634

S96.10 family (Unspecified injury of muscle and tendon of long extensor muscle of toe at ankle and foot level)	376 608	634
S96.19 family (Other specified injury of muscle and tendon of long extensor muscle of toe at ankle and foot level)	376 608	634
S96.20 family (Unspecified injury of intrinsic muscle and tendon at ankle and foot level)	376 608	634
S96.29 family (Other specified injury of intrinsic muscle and tendon at ankle and foot level)	376 608	634

26) Add the S76.29 family (Other injury of adductor muscle, fascia and tendon of right thigh), S76.39 family (Other specified injury of muscle, fascia and tendon of the posterior muscle group at thigh level), S86.19 (Other injury of other muscle(s) and tendon(s) of posterior muscle group at lower leg level), S86.29 (Other injury of muscle(s) and tendon(s) of anterior muscle group at lower leg level) and S86.39 (Other injury of muscle(s) and tendon(s) of peroneal muscle group at lower leg level) to lines 376, 432 INTERNAL DERANGEMENT OF KNEE AND LIGAMENTOUS DISRUPTIONS OF THE KNEE, RESULTING IN SIGNIFICANT INJURY/IMPAIRMENT, and 608 and remove from line 634
27) Add HCPCS C97640-C9767 (Revascularization, endovascular, open or percutaneous, lower extremity artery(ies), except tibial/peroneal; with intravascular lithotripsy and transluminal stent placement) to line 662 CONDITIONS FOR WHICH CERTAIN INTERVENTIONS ARE UNPROVEN, HAVE NO CLINICALLY IMPORTANT BENEFIT OR HAVE HARMS THAT OUTWEIGH BENEFITS
    a. Modify GN173 as shown in Appendix A
28) Remove ICD-10-CM F98.3 (Pica of infancy and childhood) from line 631 PICA
29) Rename line 631 PICA IN ADULTS
30) Make no change in the non-pairing of mid-foot arthrosis with foot arthritis

MOTION: To approve the recommendations stated in the consent agenda. CARRIES 6-0.

- **Topic: Chemodenervation (botulinum toxin) guideline update**

Discussion: There was no discussion about this topic.

Recommended Actions:
1) Modify GN219 as shown in Appendix A

MOTION: To recommend the guideline note changes as presented. CARRIES 6-0.

- **Topic: Enteropathic arthropathies**

Discussion: There was no discussion about this topic.

Recommended Actions:

1) Remove ICD-10-CM M07.6 code family (enteropathic arthropathy) from line 659 MUSCULOSKELETAL CONDITIONS WITH NO OR MINIMALLY EFFECTIVE TREATMENTS OR NO TREATMENT NECESSARY.
2) Add ICD-10-CM M07.6 family (enteropathic arthropathy) to line 46 RHEUMATOID ARTHRITIS AND OTHER INFLAMMATORY POLYARTHROPATHIES

MOTION: To recommend the code changes as presented. CARRIES 6-0.

- **Topic: Erythropoietin in chronic kidney disease**

Discussion: There was concern about the proposed addition of coverage of ICD-10-CM D63.1 (Anemia in chronic kidney disease). This code is listed in coding guidelines as "epo resistant anemia." It also does not specify what level of renal dysfunction is required for treatment. Staff were instructed to clarify this topic and bring back to a future meeting.

- **Topic: Pelvic congestion syndrome**

Discussion: There was no discussion about this topic.

Recommended Actions:

1) Add a new guideline note to line 532 CHRONIC PELVIC INFLAMMATORY DISEASE, PELVIC PAIN SYNDROME, DYSPAREUNIA as shown in Appendix B

MOTION: To recommend the guideline note changes as presented. CARRIES 6-0.

- **Topic: Platelet rich plasma**

Discussion: Smits introduced the summary document. Olson requested that when prior coverage guidances are referenced in a review, that a link to or a copy of that coverage guidance be provided.

Recommended Actions:

1) Add CPT 0232T (Injection(s), platelet rich plasma, any site, including image guidance, harvesting and preparation when performed) to line 662 CONDITIONS FOR WHICH CERTAIN INTERVENTIONS ARE UNPROVEN, HAVE NO CLINICALLY IMPORTANT BENEFIT OR HAVE HARMS THAT OUTWEIGH BENEFITS
    a. Modify GN173 as shown in Appendix A

MOTION: To recommend the code and guideline note changes as presented. CARRIES 6-0.

- **Topic: Breast reconstruction after lumpectomy**

Discussion: There was no discussion about this topic.

Recommended Actions:

1) Modify Guideline Note 79 as shown in Appendix A

MOTION: To recommend the guideline note changes as presented. CARRIES 6-0.

- **Topic: Breast MRI guidelines**

Discussion: Smits introduced the summary document. Olson expressed concerns that situations recommended by NCCN and American Society of Breast Surgeons, such as multifocal disease, lobular breast cancer, extremely dense breasts or discrepancies in tumor size between imaging studies. In these cases, MRI can help determine whether a patient is a candidate for a lumpectomy rather than a mastectomy, or whether a patient requires a bilateral mastectomy. The new breast MRI guideline was modified to include such coverage.

Gingerich suggested deleting the reference to the breast MRI coverage guidance from the new guideline as the coverage guidance has been retired. This was accepted without discussion.

Recommended Actions:

1) Retire the following Coverage Guidances
    a. Breast Cancer Screening in Women at Above Average Risk
    b. PET For Breast Cancer (recently revised PET coverage criteria)
    c. MRI for Breast Cancer Diagnosis (last affirmed 2016)
    d. MRI for Breast Cancer Screening (outdated)
2) Delete Diagnostic Guideline D9 and Guideline Note 26
3) Revise Diagnostic Guideline D6 as shown in Appendix A

MOTION: To recommend the guideline note changes as amended. CARRIES 6-0.

- **Topic: Actinic keratoses**

Discussion: There was no discussion about this topic.

Recommended Actions:

1) Make no change in the placement of ICD-10 L57.0 (Actinic keratoses) on line 627 BENIGN NEOPLASMS OF SKIN AND OTHER SOFT TISSUES.

- **Topic: Radiofrequency ablation and cryotherapy for select renal cell cancers**

Discussion: Smits introduced the summary document. There was some discussion regarding whether to cover these procedures for renal cell cancers up to 4 cm. The group decided that the major guidelines recommended under 3cm and that size was kept in the proposed new guideline.

Recommended Actions:

1) Add CPT 50592 (Ablation, 1 or more renal tumor(s), percutaneous, unilateral, radiofrequency) and 50593 (Ablation, renal tumor(s), unilateral, percutaneous, cryotherapy) to line 214 CANCER OF KIDNEY AND OTHER URINARY ORGANS
    a. Advise HSD to remove CPT 50593 from the Ancillary Procedures File
    b. Delete CPT 50592 from line 662/GN173 as shown in Appendix A
2) Add a new guideline to line 214 as shown in Appendix B

MOTION: To recommend the code and guideline note changes as presented. CARRIES 6-0.

- **Topic: Clarification of the lower urinary tract symptoms (LUTS) guideline**

Discussion: There was no discussion about this topic.

Recommended Actions:

1) Modify GN145 as shown in Appendix A

MOTION: To recommend the guideline note changes as presented. CARRIES 6-0.

- **Topic: Sensory integration therapy**

Discussion: There was no discussion about this topic.

Recommended Actions:

1) Update the GN173 entry as shown in Appendix A

MOTION: To recommend the guideline note changes as presented. CARRIES 6-0.

- **Topic: Congenital foot deformity code review**

Discussion: Smits introduced the summary document. Hodges requested that staff consult with orthopedics or other subject matter experts to ensure that the coding changes proposed are appropriate. Staff will consult experts and bring this topic back to a future meeting for further discussion.

- **Topic: Gait analysis and surface electromyography**

Discussion: There was no discussion about this topic.

Recommended Actions:

1) Add CPT 96000-96004 (Comprehensive computer-based motion analysis by video-taping and 3D kinematics; Dynamic surface electromyography) to line 662 CONDITIONS FOR WHICH CERTAIN INTERVENTIONS ARE UNPROVEN, HAVE NO CLINICALLY IMPORTANT BENEFIT OR HAVE HARMS THAT OUTWEIGH BENEFITS
    a. Advise HSD to remove these codes from the Ancillary and Diagnostic Procedures files
2) Modify GN173 as shown in Appendix A

MOTION: To recommend the code and guideline note changes as presented. CARRIES 6-0.

- **Topic: Polydactyly clarification**

Discussion: There was no discussion about this topic.

Recommended Actions:

1) Remove ICD-10-CM Q69.9 (Polydactyly, unspecified) from line 579 CAVUS DEFORMITY OF FOOT; FLAT FOOT; POLYDACTYLY AND SYNDACTYLY OF TOES
2) Rename line 579 CAVUS DEFORMITY OF FOOT; FLAT FOOT; ~~POLYDACTYLY AND~~ SYNDACTYLY OF TOES

MOTION: To recommend the code changes as presented. CARRIES 6-0.

- **Topic: 2024 Biennial Review: agenesis of lung**

Discussion: There was no discussion about this topic.

Recommended Actions:

Effective 1/1/2024:

1) Delete Line 647 AGENESIS OF LUNG

MOTION: To recommend the biennial review change as presented. CARRIES 6-0.

- **Topic: 2024 Biennial Review: Dorsal rhizotomy for spastic diplegic cerebral palsy**

Discussion: There was no discussion about this topic.

Recommended Actions:

Effective October 1 2022:

1) Add CPT 63185 and 63190 (laminectomy with rhizotomy) to line 292 NEUROLOGICAL DYSFUNCTION IN POSTURE AND MOVEMENT CAUSED BY CHRONIC CONDITIONS
2) Adopt the new guideline shown in Appendix B for line 292
3) Strike through line 491 SPASTIC DIPLEGIA Treatment: RHIZOTOMY for the 10/1/22 Prioritized List

Effective 1/1/2024:

1) Delete Line 491 SPASTIC DIPLEGIA

MOTION: To recommend the code and guideline note changes and Biennial Review changes as presented. CARRIES 6-0.

- **Public Comment:**

  No additional public comment was received.

- **Issues for next meeting:**
  -Coding for erythropoietin in chronic kidney disease
  -Congenital foot deformity review

- **Next meeting:**

  May 19, 2022; Virtual meeting

- **Adjournment:**

  The meeting adjourned at 11:15 AM.

Appendix A

Revised Guideline Notes

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

~~Annual screening mammography and annual screening MRI are covered only for women at above-average risk of breast cancer. This coverage, beginning at 30 years of age, includes women who have one or more of the following:~~

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

~~For women with a history of high dose chest radiation (≥ 20 Gray) before the age of 30, annual screening MRI and annual screening mammography are covered beginning 8 years after radiation exposure or at age 25, whichever is later.~~

~~For women with both a personal history and a family history of breast cancer which give a greater than 20% lifetime risk of breast cancer, annual mammography, annual breast MRI and annual breast ultrasound are covered.~~

A) Annual breast MRI screening for high-risk patients
   1) For individuals with a genetic mutation known to confer a greater than 20% lifetime risk of breast cancer (e.g. BRCA1, BRCA2, Bannayan-Riley-Ruvalcaba syndrome, Cowden syndrome, or Li-Fraumeni syndrome), beginning 10 years prior to when the youngest family member was diagnosed with breast cancer (but not prior to age 25 years) or age 40 years, whichever comes first
   2) For individuals who received high dose chest radiation (≥ 20 Gray) between the ages of 10 and 30 years beginning 8 years after radiation exposure or at age 25, whichever is later
   3) For individuals with a lifetime risk of ≥ 20% as defined by models that are largely dependent on family history, beginning 10 years prior to when the youngest family member was diagnosed with breast cancer (but not prior to age 25 years) or age 40 years, whichever comes first

B) Evaluation of possible breast cancer
   1) To search for occult breast cancer in patients with Paget's disease of the nipple or in patients with axillary node metastasis when clinical examination and conventional breast imaging fail to detect a primary breast cancer
   2) For the further evaluation of suspicious clinical or imaging findings that remain indeterminate after complete mammographic and sonographic evaluations in lesions that do not meet criteria for breast biopsy

C) Preoperative breast MRI
   1) for patients with recently diagnosed breast cancer who qualify for MRI screening based on the high-risk criteria in section A above

2) For determining the extent of cancer or presence of multi-focal or multi-centric tumor or the presence of contralateral cancer, in patients with a proven breast cancer and associated clinical or conventional indeterminate imaging findings suspicious for malignancy. This may include patients with invasive lobular carcinoma or extremely dense breast tissue (limiting mammographic sensitivity), or when there are significant discrepancies in the estimated tumor size as measured on clinical exam, mammogram, and ultrasound

D) Evaluation of suspected breast implant rupture

3) Breast MRI is covered for evaluation of suspected breast implant rupture, if the MRI findings will aid the decision-making for implant removal or aid the diagnostic evaluation of indeterminate clinical or conventional imaging findings in patients with implants

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

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

~~For surveillance for a treated breast cancer, see Guideline Note 26 BREAST CANCER SURVEILLANCE.~~

~~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 D27, SARS-COV-2 (COVID-19) TESTING

Testing for SARS-CoV-2 (COVID-19) virus RNA or viral antigen is a covered diagnostic service. Testing for viral variants/mutations (CPT 87913) is only covered when required to guide patient treatment.

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).

~~**GUIDELINE NOTE 26, BREAST CANCER SURVEILLANCE**~~

~~*Line 191*~~

~~History and physical exam is indicated every 3 to 6 months for the first three years after primary therapy, then every 6-12 months for the next 2 years, then annually thereafter.~~

~~Mammography is indicated annually, and patients treated with breast-conserving therapy, initial mammogram of the affected breast should be 6 months after completion of radiotherapy.~~

Appendix A

~~No other surveillance testing is indicated.~~

~~For ongoing screening for a new breast cancer, see Guideline Note 2006 BREAST CANCER SCREENING IN ABOVE-AVERAGE RISK WOMEN.~~

GUIDELINE NOTE 73, PENILE ANOMALIES

Lines 424,433,571,658

Congenital anomalies of the penis (ICD-10-CM Q54.4, Q55.5 and Q55.6) are included on Line 434 only when they

A. Are associated with hypospadias, OR
B. Result in documented urinary retention, OR
C. Result in repeated urinary tract infections, OR
D. Result in recurrent infections such as meatitis or balanitis, OR
E. Involve 35 degrees of curvature or greater for conditions resulting in lateral or ventral curvature, OR
F. Involve 60 degrees of rotation or greater for conditions resulting in penile torsion, OR
G. Involve aplasia/congenital absence of the penis.

Otherwise, these diagnoses are included on Line 658.

Acquired anomalies of the penis (ICD-10-CM N48.82, N48.83, N48.89 or T81.9XXA) are included on Line 424 only when they are the result of a prior penile procedure AND either

A. Result in a skin bridge, OR
B. Result in a buried penis, OR
C. Are associated with hypospadias, OR
D. Result in documented urinary retention, OR
E. Result in repeated urinary tract infections, OR
F. Result in recurrent infections such as meatitis or balanitis, OR
G. Involve 35 degrees of curvature or greater for conditions resulting in lateral or ventral curvature, OR
H. Involve 60 degrees of rotation or greater for conditions resulting in penile torsion.

Otherwise, these diagnoses are included on Line 571 or Line 658.

GUIDELINE NOTE 79, BREAST RECONSTRUCTION

Line 191

Breast reconstruction is only covered after mastectomy, or lumpectomy that results in a significant deformity or asymmetry, as a treatment for breast cancer or as prophylactic treatment for the prevention of breast cancer in a woman who qualifies under Guideline Note 3, and must be completed within 5 years of initial mastectomy or lumpectomy.

Breast reconstruction may include contralateral reduction mammoplasty (CPT 19318) or contralateral mastopexy (CPT 19316). Mastopexy is only to be covered when contralateral reduction mammaplasty is inappropriate for breast reconstruction and mastopexy will accomplish the desired reconstruction result.

Appendix A

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.~~ hyperplasia (BPH), surgical procedures are included on this line for patients with one of the following:

A) Refractory urinary retention; OR
B) Recurrent urinary tract infections due to BPH; OR
C) Recurrent bladder stones or gross hematuria due to BPH; OR
D) Severe symptoms (International Prostate Symptom Score (IPSS) of 20-35) in patients who are not candidates for drug treatment due to intolerable side effects or have failed combination therapy with an alpha-blocker and 5-alpha reductase inhibitor for at least 3 months.

Prostatic urethral lift procedures (CPT 52441, 52442, HCPCS C9739, C9740) are included on Line 327 when the following criteria are met:

- Age 50 or older
- Estimated prostate volume < 80 cc
- IPSS ≥ 13
- No obstructive median lobe of the prostate identified on cystoscopy at the time of the procedure

The following interventions for benign prostate enlargement are not included on Line 327 due to lack of evidence of effectiveness:

- 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 219, CHEMODENERVATION

Lines 292,327,351,362,378,393,410,500,517,526

Inclusion of chemodenervation on the Prioritized List has the following limitations for the lines specified below:

Line 292 NEUROLOGICAL DYSFUNCTION IN POSTURE AND MOVEMENT CAUSED BY CHRONIC CONDITIONS

Chemodenervation with botulinum toxin injection (CPT 64642-64647) is included on this line for treatment of upper and lower limb spasticity (ICD-10-CM codes G24.02, G24.1, G35, G36.0, I69.03- I69.06 and categories G71, and G80-G83)

Line 327 FUNCTIONAL AND MECHANICAL DISORDERS OF THE GENITOURINARY SYSTEM INCLUDING BLADDER OUTLET OBSTRUCTION

Chemodenervation of the bladder (CPT 52287) is included on this line only for treatment of idiopathic detrusor over-activity or neurogenic detrusor over-activity (ICD-10-CM N32.81) in

patients who have not responded to or been unable to tolerate at least two urinary incontinence antimuscarinic therapies (e.g. fesoterodine, oxybutynin, solifenacin, darifenacin, tolterodine, trospium). Treatment is limited to 90 days, with additional treatment only if the patient shows documented positive response. Positive response to therapy is defined as a reduction of urinary frequency of 8 episodes per day or urinary incontinence of 2 episodes per day compared to baseline frequency.

Line 351 STRABISMUS DUE TO NEUROLOGIC DISORDER

Chemodenervation with botulinum toxin injection (CPT 67345) is included on this line for the treatment of strabismus due to other neurological disorders (ICD-10-CM H50.89).

Line 362 DYSTONIA (UNCONTROLLABLE); LARYNGEAL SPASM

Chemodenervation with botulinum toxin injection (CPT 64612, 64616) is included on this line only for treatment of blepharospasm (ICD-10-CM G24.5), spasmodic torticollis (ICD-10-CM G24.3), and other fragments of torsion dystonia (ICD-10-CM G24.9).

Line 378 ESOPHAGEAL STRICTURE; ACHALASIA

Chemodenervation with botulinum toxin injection (CPT 43201) is included on this line for treatment of achalasia (ICD-10 K22.0).

Line 393 STRABISMUS WITHOUT AMBLYOPIA AND OTHER DISORDERS OF BINOCULAR EYE MOVEMENTS; CONGENITAL ANOMALIES OF EYE; LACRIMAL DUCT OBSTRUCTION IN CHILDREN

Chemodenervation with botulinum toxin injection (CPT 67345) is included on this line for the treatment of strabismus due to other neurological disorders (ICD-10-CM H50.89).

Line 410 MIGRAINE HEADACHES

Chemodenervation for treatment of chronic migraine (CPT 64615) is included on this line for prophylactic treatment of adults who meet all of the following criteria:

A) have chronic migraine defined as headaches on at least 15 days per month of which at least 8 days are with migraine

B) has not responded to or have contraindications to at least three prior pharmacological prophylaxis therapies (e.g. beta-blocker, anticonvulsant or tricyclic antidepressant)

C) their condition has been appropriately managed for medication overuse

D) treatment is administered in consultation with a neurologist or headache specialist.

Treatment is limited to two injections given 3 months apart. Additional treatment requires documented positive response to therapy. Positive response to therapy is defined as a reduction of at least 7 headache days per month compared to baseline headache frequency.

Line 500 SIALOLITHIASIS, MUCOCELE, DISTURBANCE OF SALIVARY SECRETION, OTHER AND UNSPECIFIED DISEASES OF SALIVARY GLANDS

Chemodenervation with botulinum toxin injection (CPT 64611) is included on this line for the treatment of excessive salivation.

Line 517 DISORDERS OF SWEAT GLANDS

Chemodenervation with botulinum toxin injection (CPT 64650, 64653) is included on this line for the treatment of axillary hyperhidrosis and palmar hyperhidrosis (ICD-10-CM L74.52, R61).

Line 526 CHRONIC ANAL FISSURE

Chemodenervation with botulinum toxin injection (CPT 46505) is included on this line for the treatment of anal fissures.

Appendix A

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
0232T	Injection(s), platelet rich plasma, any site, including image guidance, harvesting and preparation when performed	Insufficient evidence of effectiveness	March 2022
C9764-C9767 C9772-C9775	Revascularization, endovascular, open or percutaneous, lower extremity artery(ies) ~~tibial/peroneal artery(ies),~~ with intravascular lithotripsy	Insufficient evidence of effectiveness	March 2022
~~50592~~	~~Radiofrequency ablation, 1 or more renal tumor(s)~~	~~Insufficient evidence of effectiveness~~	~~December 2005~~
97533	Sensory integrative techniques to enhance sensory processing and promote adaptive responses to environmental demands	Insufficient evidence of effectiveness	~~August 2010~~ March 2022
96000-96004	Comprehensive computer-based motion analysis by video-taping and 3D kinematics Dynamic surface electromyography	Insufficient evidence of effectiveness	March 2022

Appendix B

New Guideline Notes

GUIDELINE NOTE XXX PELVIC CONGESTION SYNDROME

Line 532

Pelvic congestion syndrome is included on this line using ICD-10-CM N94.89. This condition does not pair with any vein embolization procedures due to lack of evidence of effectiveness.

GUIDELINE NOTE XXX THERMAL ABLATION OF RENAL CELL CARCINOMA

Line 214

Thermal ablation (e.g., cryosurgery, radiofrequency ablation; CPT 50592, 50593) is included on this line only when:

1) The patient has biopsy-confirmed stage T1 renal cell cancer of <3 cm size; AND
2) The patient either has a surgically inoperable tumor(s) or is a poor candidate for standard treatments (i.e., nephrectomy).

GUIDELINE NOTE XXX DORSAL RHIZOTOMY FOR SPASTIC CEREBRAL PALSY

Line 292

Dorsal rhizotomy (CPT 63185 and 63190) is only included on this line for patients who meet ALL of the following criteria:

A) Has spastic diplegic cerebral palsy (ICD-10-CM G80.1); AND
B) Is a child aged 2 to 10 years; AND
C) Has good intrinsic lower extremity motor power, but is limited in ambulation by spasticity; AND
D) Has the functional capacity and motivation to participate in post-operative rehabilitation; AND
E) Has failed or been unable to tolerate other conservative treatment (e.g., pharmacotherapy, orthopedic management, physical therapy); AND
F) Has no contraindications to the procedure (e.g., significant scoliosis, progressive neurological disorders, severe fixed joint deformities)

Section 2.0

Staff Report

Errata
May 2022

1) On May 11, 2022, the following code placement corrections were made:

Code	Description	Initial placement	Corrected placement
S06.A0XA	Traumatic brain compression without herniation, initial encounter	INFORMATIONAL DIAGNOSIS	196 SUBARACHNOID AND INTRACEREBRAL HEMORRHAGE/HEMATOMA; CEREBRAL ANEURYSM; COMPRESSION OF BRAIN
S06.A0XD	Traumatic brain compression without herniation, subsequent encounter	INFORMATIONAL DIAGNOSIS	196 SUBARACHNOID AND INTRACEREBRAL HEMORRHAGE/HEMATOMA; CEREBRAL ANEURYSM; COMPRESSION OF BRAIN
S06.A1XA	Traumatic brain compression with herniation, initial encounter	INFORMATIONAL DIAGNOSIS	196 SUBARACHNOID AND INTRACEREBRAL HEMORRHAGE/HEMATOMA; CEREBRAL ANEURYSM; COMPRESSION OF BRAIN
S06.A1XD	Traumatic brain compression with herniation, subsequent encounter	INFORMATIONAL DIAGNOSIS	196 SUBARACHNOID AND INTRACEREBRAL HEMORRHAGE/HEMATOMA; CEREBRAL ANEURYSM; COMPRESSION OF BRAIN
M35.08	Sjogren syndrome with gastrointestinal involvement	59 END STAGE RENAL DISEASE 99 END STAGE RENAL DISEASE 330 SYSTEMIC SCLEROSIS; SJOGREN'S SYNDROME	330 SYSTEMIC SCLEROSIS; SJOGREN'S SYNDROME
P00.82	Newborn affected by (positive) maternal group B streptococcus (GBS) colonization	(Recommended for diagnostic workup file)	2 BIRTH OF INFANT

Below the Line Review Summary

Color Key	
	Topics under development
	Upcoming discussion topics
	Reviewed but no changes planned
	Already approved changes

Request source	Topic Description	Meeting Date	Planned Imp. Date	Summary of change (or recommended change, decision not to change)	Larger cost
Staff review	Deformities of upper body and all limbs	tbd		Review with orthopedics expert	
Staff review	Congenital anomalies of knee (Knee problems since birth)	tbd		Review with orthopedics expert	
Staff review	Genitourinary with minimal or no treatment required (genital and urinary organs)	tbd		Review with urology expert	
Staff review	Sleep disorders other than sleep apnea (including insomnia)	tbd		Consider adding insomnia above the funding line for cognitive behavioral therapy for insomnia (CBTi). Consider role of medication.	
Staff (Val King)	Temporomandibular Joint Syndrome (TMJ) (Pain and dysfunction in the jaw joint and muscles controlling jaw movement)	tbd		Needs evidence review for medical and surgical treatments	
HSD nurse reviewer	Median and radial nerve lesions	8/11/2022		Proposal to add to covered nerve lesion line with ulnar nerve lesions	
Staff review	Benign neoplasm of the digestive system (Surgery for an abnormal growth found in the stomach or intestines)	5/19/2022		Proposal to add benign carcinoid tumors to funded region	
HSD	Bilateral bone anchored hearing aids (BAHA) (A specific type of hearing aid for children)	5/19/2022		Proposal to expand coverage from unilateral to bilateral	
Staff review	Scrotal varices (An enlargement of the veins within the skin that holds the testicles (scrotum))	5/19/2022		Already on line 327 as well as line 548 with no guideline. Propose to remove from line 548 and change name of line	
Staff review	Other complications of a procedure	5/19/2022		Propose to rename line "Minor" as diagnoses are minor	

Request source	Topic Description	Meeting Date	Planned Imp. Date	Summary of change (or recommended change, decision not to change)	Larger cost
Staff review	Anemias due to kidney diseases (erythropoietin) (A drug to treat low blood count caused by kidney disease)	5/19/2022		Recommend clarifying coverage of erythropoietin for non-end stage kidney disease	
Dr. Hoffman	Conduct disorder/impulse disorders (A type of behavior disorder)	tbd		Working with partners, will review with Behavioral Health Advisory panel (BHAP).	
Staff review	Somatic symptoms line (Extreme feelings and anxiety about physical symptoms)	tbd		Review with BHAP for any need for reprioritization of one or more diagnoses or of entire line	
Staff review	Deformities of foot	tbd		Under review with ortho and podiatry, likely August 2022 review	
Staff review	Physical therapy for minor musculoskeletal conditions (Injuries and disorders that affect the human body's movement or muscles, tendons, ligaments, nerves, discs, blood vessels, etc.)			Limited benefit; would be very difficult to implement	
Dr. Hoffman	Allergic rhinitis (Nasal allergies/Hay fever)			No change; little impact on health except when comorbidity or growth/development/school exceptions apply	
Dr. Hoffman	Angiodema (Swelling (edema) of the lower layer of skin and tissue just under the skin)	11/18/2021	1/1/2022	Removed unfunded duplicate line (no substantive change, was already covered)	
Dr. Hoffman	Benign bone neoplasm			No change made; serious benign neoplasms are on line 401; Guideline 137 clarifies which are covered.	
Dr. Hoffman	Congenital anomalies of female genital tract excluding vagina			No change: Diagnoses on this line have no treatment. Other anomalies that require repair are on funded line(s)	
Dr. Hoffman	Dermatophytoses (ringworm, etc.)			No change; primary care and preferred medications should be sufficient for these conditions	
Dr. Hoffman	Diaper rash			No change: Primary care and preferred medications (nystatin) should be sufficient	

Request source	Topic Description	Meeting Date	Planned Imp. Date	Summary of change (or recommended change, decision not to change)	Larger cost
Dr. Hoffman	Dysmenorrhea			No change; primary care and preferred medications (NSAIDS, birth control) should be sufficient for these conditions	
Dr. Hoffman	Hodeolum/chalazeon			No change; primary care and preferred meds should be sufficient for these conditions. Rare exceptions can be considered through existing processes	
Dr. Hoffman	Mild eczema			No change; primary care and preferred medications should be sufficient for these conditions	
Dr. Hoffman	Mild psoriasis			No change; primary care and preferred medications should be sufficient for these conditions	
Dr. Hoffman	Minor burns			No change: Primary care and preferred medications should be sufficient	
Advocates	Pica (Persistent eating of non-food items (for example clay, wool, lead, wood) at an age when it is considered to be developmentally inappropriate)	3/10/2022	10/1/2022	No change: Removed ambiguity of coverage for pica in children (should have already been in funded region), renamed line to clarify that the unfunded line is "Pica in adults"	
Dr. Hoffman	Symptomatic urticaria			No change; primary care and preferred medications should be sufficient for these conditions	
Staff review	Angiosarcoma of liver; intrahepatic bile duct carcinoma			Liver angiosarcoma has a very poor prognosis with any treatment (6 months even with surgery). Per NIH, the only treatment of bile duct carcinoma is palliative care	
Staff review	Central retinal artery occlusion			Reviewed; no effective treatment is available	
Dr. Hoffman	Congenital ear anomalies without hearing impairment			Only microotia (ICD10 17.2) might be considered to move to funded line and most treatment recommendations are only to repair for costmetic reasons. Severe microotia (grade 3 and 4) would have hearing impairment and the hearing issues are addressed on line 311	
Dr. Hoffman	Conversion disorders F44.4-7, include non-epilectic seizures			Cognitive behavioral therapy would be available with another underlying disorder such as depression. No other treatment for actual disorder indicated	

Request source	Topic Description	Meeting Date	Planned Imp. Date	Summary of change (or recommended change, decision not to change)	Larger cost
Staff review	Cysts of Bartholin's gland and vulva			N75.1 (Abscess of Bartholin's gland) is included on line 205. Cysts typically have no symptoms and do not need treatment	
Staff review	Enophthalmos			Treatment is directed at underlying diseases, which appear in funded region	
Dr. Hoffman	Infectious mononucleosis			Primary care should be sufficient; there is no treatment for this condition	
Staff review	Miscellaneous rare congenital anomalies			Individual consideration will be required	
Staff review	Nasal polyps			and saline. Surgery indicated if causing chronic sinusitis due to blockage of sinus ostia (would be covered on chronic sinusitis line)	
Staff review	Personality disorders			No effective treatment	
Staff review	Secondary and ill-defined neoplasms			Treatment should be targeted to primary cancer, which would be covered.	
Staff review	Thrombosed and complicated hemorrhoids			Generally treated with fiber and observation. Could be addressed based on individual review	
Staff review	Tension headaches			Primary care and NSAIDs are effective treatments.	
Staff review	Esophageal ulcer	3/10/2022	10/1/2022	Added to funded region	
Dr. Hoffman	Foreign body in digestive tract	3/10/2022	1/1/2022	Had already been addressed prior to the concern raised, but implementation was pending	
Staff review	Generalized muscle weakness	3/10/2022	10/1/2022	Added to funded region	
HSD Staff	Handicapping malocclusion	11/18/2021	1/1/2023	Working on implementation issues; addition to funded region planned for 1/1/2023	x
CCO	Dorsal rhizotomy	3/10/2022	10/1/2022	Added to funded region	x
Staff review	Corneal abcess	3/10/2022	10/1/2022	Added to funded region	
Staff review	Lichen planus	3/12/2020	10/1/2022	Change name of line to reflect mild/moderate; severe forms on funded line as defined by Guideline Note 21	
Staff review	Mastoiditis	3/12/2020	10/1/2022	Added to funded region	
Dr. Hoffman	Nightmare disorder	11/18/2021	1/1/2022	Added to funded region	
Dr. Hoffman	Oral candidiasis (thrush)	8/12/2021	10/1/2021	Added to funded region for feeding problems in newborns line	

Request source	Topic Description	Meeting Date	Planned Imp. Date	Summary of change (or recommended change, decision not to change)	Larger cost
Dr. Hoffman	Phimosis (acquired penile complications, circumcision etc)	10/7/2021	1/1/2022	Clarified coverage criteria for acquired vs congenital anomalies of the penis. Added to funded region for acquired anomalies.	
Staff review	Polydactyly	3/12/2020	10/1/2022	Clarified earlier decision to confirm in funded region	
Public	Rhinoplasty/septoplasty/ deviated septum	8/12/2021	10/1/2022	Created new criteria for septoplasty, clarified conditions for coverage. Some new coverage and new limitations for services that would be cosmetic.	
Advocates	Selective mutism	11/18/2021	1/1/2022	Moved to funded anxiety line	
Staff review	Sjogren syndrome	3/10/2022	10/1/2022	Added to funded region	
Staff review	Tendon and ligament injuries	3/10/2022	10/1/2022	Added to funded region for full tears	
Staff review	Viral endocarditis, myocarditis, pericarditis, cardiomyopathy	3/10/2022	10/1/2022	Added to funded region	
Staff review	Vitiligo	10/7/2021	1/1/2022	Added vitiligo as a funded condition. Affects children's social function	x
Staff review	Acquired torsion of penis	3/10/2022	10/1/2022	Added to funded region	
Staff review	Agenesis of lung	3/10/2022	10/1/2022	Added to funded region for supportive care	
EPSDT	Child growth and development	11/18/2021	1/1/2022	Added path to coverage for treatments supporting growth, development and participation in school for children	x
Staff review	Chronic pancreatitis		1/1/2022	Already merged for 2022 before this review	
Staff review	Vitiligo of eyelid	3/10/2022	10/1/2022	Added to funded region	

Section 3.0

New Discussion Items

Visual Field Testing

Question: Should various diagnoses be paired with visual field testing or should visual field testing be made diagnostic?

Question source: Julie Falardeau, MD, OHSU Ophthalmology

Issue: Dr. Falardeau requested consideration of coverage/pairing of multiple diagnoses of visual field testing with a variety of ophthalmologic diseases. Visual field testing is used to determine if a patient has blind spots or visual limitations from eye or central nervous system disease. Visual field testing is coded with CPT 99201-99285, 92002-92014, 92081-92083, and 92133. Visual field testing is on 60+ ophthalmology lines. Evaluation and management and emergency room services (9920—99285) are already on the diagnostic procedures file, so should be covered regardless of the presenting diagnosis.

Dr. Falardeau's specific requests for consideration are listed below:

1) Optic neuritis: (ICD-10-CM H46.XX). These diagnoses are currently on line 650 INTRACRANIAL CONDITIONS WITH NO OR MINIMALLY EFFECTIVE TREATMENTS OR NO TREATMENT NECESSARY. These conditions result in loss of vision temporarily or permanently based on a variety of causes. Optic neuritis is a common presentation of multiple sclerosis.
    a. Evidence
        i. **De Lott 2022**, review of optic neuritis
            1. High-dose corticosteroids, both oral and intravenous (IV), are the most commonly used treatment for acute ON. A meta-analysis of three randomized controlled trials found no benefit in visual acuity recovery at 1 month, 6 months, and 1 year based on the dose or duration of oral treatment. A meta-analysis of two trials comparing placebo to IV corticosteroids of over 3000 mg total also found no significant improvement in visual acuity, contrast sensitivity, or visual field at 6 months
            2. the only benefit of corticosteroids was hastened visual recovery within the first 2 weeks, which is the primary indication for treatment. Secondary analyses of the trial data suggest that this early benefit is only about 1–2 lines of Snellen acuity
2) Pairing of visual field testing (CPT 92081-92083, 92133) with
    a. Papilledema (ICD-10-CM H47.1X) which is on line 650 INTRACRANIAL CONDITIONS WITH NO OR MINIMALLY EFFECTIVE TREATMENTS OR NO TREATMENT NECESSARY [Note ICD-10-CM H47.10 (Unspecified papilledema) is on the Diagnostic Workup File]. Dr. Falardeau writes that in about 10% of papilledema patients, surgery is required to prevent further vision loss. Such surgery would be for the underlying condition causing the papilledema (which would be covered). The most reliable way to monitor optic nerve function is with visual field testing.
    b. Optic disc atrophy (ICD-10-CM H47.2X) which is on line 654 SENSORY ORGAN CONDITIONS WITH NO OR MINIMALLY EFFECTIVE TREATMENTS OR NO TREATMENT NECESSARY. Dr. Falardeau also notes that optic atrophy may require visual field testing particularly for determination of whether vision is sufficient for driving. Optic atrophy has no treatment; treatment is aimed at the underlying condition (glaucoma, MS, etc.).
    c. Visual field defect (ICD-10-CM H53.4X) which is on the DIAGNOSTIC WORKUP FILE.

3) Pairing of visual field testing with optic nerve/chiasm tumors (ICD-10 C72.3X). Ophthalmology office visit CPT codes are already on line 294 CANCER OF BRAIN AND NERVOUS SYSTEM

HERC staff recommendation:

1) Remove visual field testing (CPT 92081-92083, 92133) from all current lines
    a. Advise HSD to add CPT 92081-92083, 92133) to the Diagnostic Procedure File (Codes 99203-99285 for evaluation and management and emergency visits are already on this file).
    b. There is a possibility for overutilization; however, these procedures are already found on 60+ ophthalmology lines

OHSU Casey Eye Institute

January 5, 2022

Mr. Patrick Allen
Director, Oregon Health Authority

RE: Prioritized List Addition Request

Dear Mr. Allen,

I am one of 4 neuro-ophthalmologists practicing in Oregon and 20% of my patients are receiving their insurance through Medicaid. Many of these patients are referred to my clinic for non-glaucomatous optic nerve disorders or unexplained vision loss/visual field loss. Visual field testing is considered standard of care for these patients and photograph of the optic nerve (optical coherence tomography) is greatly helpful in providing structural optic nerve information. For the majority of these patients, the diagnosis (or diagnoses) is considered "below-the-line". However, many of these conditions are serious and require neuro-ophthalmic monitoring. The challenge I am facing on a daily basis is that because so many of these diagnoses are considered "below-the-line", Medicaid does not cover the visual field testing **(CPT 92081-92083)** or the optical coherence tomography **(92133).** I believe that many of these diagnoses and the associated ancillary tests meet medical necessity criteria and are considered standard of care, not experimental.

Please consider the following for inclusion on the Prioritized List:

1. **Optic neuritis** (H46.00, H46.01, H46.02, H46.03, H46.10, H46.11, H46.12, H46.13, H46.8, H46.9)
   This condition affects patients of all ages and has a strong association with demyelinating disease such as multiple sclerosis. The diagnosis can be challenging and urgent evaluation in neuro-ophthalmology if often recommended. Prompt treatment with intravenous steroids can be needed to accelerate visual recovery, especially in patients with severe vision loss. Other types of optic neuritis can be autoimmune in nature and at higher risk of relapses. Patients with optic neuritis need to be closely monitored by ophthalmologists/neuro-ophthalmologists. Visual field testing is essential in patients with optic neuritis since many of them will remain with permanent optic nerve dysfunction. Optical coherence tomography obtained a few months after the initial event helps documenting the structural damage. CPT request: 99201-99285, 92002-92014, 92081-92083, 92133.

2. **Optic nerve/optic chiasm tumor** (C72.30, C72.31, C72.33, H47.42)
   I recently saw a child with optic chiasm tumor status-post surgical resection leaving him completely blind in one eye and significant peripheral visual field defect in the other eye. He is followed by neurosurgery with serial MRIs. However, his neurosurgeon and myself agree that as long as his visual field testing remains stable in his only seeing eye, additional surgery near the optic chiasm should be avoided. I am seeing him every 6 months. Because his diagnosis his considered "below-the-line", Medicaid will not to pay for his visual field testing, which is by far the most important test for this pediatric patient.
   The same applies for optic nerve tumor potentially treated with chemotherapy. Neuro-oncology relies just as much on the visual field test obtained in my clinic than the MRI.
   For any optic pathway tumor, visual field test is essential for visual function monitoring, as well as for evaluation of treatment response. CPT request: 99201-99285, 92002-92014, 92081-92083, 92133.

3. **Papilledema related to elevated intracranial pressure** (H47.11)
4. **Optic disc pallor/atrophy** (H47.20, H47.211, H47.212, H47.213, H47.219, H47.22, H47.291, H47.292, H47.293, H47.299)
5. **Visual field defect** (H53.40, H53.411, H53.412, H53.413, H53.431, H53.432, H53.433, H53.451, H53.452, H53.453, H53.461, H53.462, H53.463, H53.47, H53.481, H53.482, H53.483)

   For these diagnoses, visual field testing is also extremely important since it helps the clinician with the localization of the underlying pathological process and/or identifying the potential causes of vision loss or visual field defect. Again, these diagnoses are considered "below-the-line" and consequently are not covered by Medicaid. Unnecessary neuroimaging studies could be requested if we are not allowed to get a simple visual field test, which can be done on the same day as the patient's visit.

Thank you for your consideration of adding these conditions/treatments to the Prioritized List. Do not hesitate to contact me if further clarification is needed.

Sincerely,

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REVIEW

The changing landscape of optic neuritis: a narrative review

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Abstract

Optic neuritis (ON) is an inflammatory optic neuropathy that is often a harbinger of central nervous system (CNS) demyelinating disorders. ON is frequently misdiagnosed in the clinical arena, leading to either inappropriate management or diagnostic delays. As a result, patients may fail to achieve optimal recovery. The treatment response to corticosteroids and long term risk of multiple sclerosis was established in the first clinical trials conducted roughly 30 years ago. Spontaneous resolution was observed in the vast majority of patients and intravenous high-dose corticosteroids hastened recovery; half of the patients eventually developed multiple sclerosis. Over the ensuing decades, the number of inflammatory conditions associated with ON has significantly expanded exposing substantial variability in the prognosis, treatment, and management of ON patients. ON subtypes can frequently be distinguished by distinct clinical, serological, and radiological profiles allowing expedited and specialized treatment. Guided by an increased understanding of the immunopathology underlying optic nerve and associated CNS injuries, novel disease management strategies are emerging to minimize vision loss, improve long-term surveillance strategies, and minimize CNS injury and disability. Knowledge regarding the clinical signs and symptoms of different ON subtypes is essential to guide acute therapy, prognosticate recovery, accurately identify underlying CNS inflammatory disorders, and facilitate study design for the next generation of clinical and translational trials.

Keywords Optic neuritis · Multiple sclerosis · Demyelinating diseases · Optic nerve diseases

Introduction

Optic neuritis (ON) is a term used to describe any inflammatory condition affecting the optic nerve. Because ON is caused by a variety of central nervous system (CNS) and systemic disorders, incidence rates vary from 1.4 to 33 per 100,000 people, depending on diagnostic accuracy, efficient case capture, and population demographics [1–5]. ON, however, is frequently misdiagnosed because of errors in eliciting or interpreting the history and physical examination [6].

Distinguishing between subtypes of ON is both challenging and important in the current era, as serological and radiographic biomarkers can help refine diagnoses and tailor treatments. Clinical and radiologic features, such as older age, bilateral optic nerve involvement, and location of optic nerve inflammation may signal a specific etiology. Furthermore, treatment algorithms established by the Optic Neuritis Treatment Trial (ONTT) [7], conducted roughly 30 years ago, are not universally applicable.

This narrative review will focus on the salient features that distinguish ON from other common causes of optic neuropathy in adults. Moreover, we will highlight clinical phenotypes that characterize specific subtypes of autoimmune ON associated with CNS disease—multiple sclerosis and idiopathic (MS-ON; considered together as the phenotypes overlap), myelin oligodendrocyte glycoprotein (MOG-ON), and neuromyelitis optica spectrum disorder (NMOSD-ON). Although it does not seem to cause a retrobulbar ON, we have also included glial fibrillary acidic protein (GFAP-ON), because it is an autoimmune meningoencephalitis with inflammatory optic disc edema (papillitis) that should be considered when evaluating patients with optic disc edema

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Adenoidectomy Coverage 2022 Update

Plain Language Summary:
Background: An adenoidectomy is an operation done to remove your adenoids, which are a part of the immune system and are located in the back of the nose. The current guideline allows adenoid removal when a second set of ear tubes are placed in children 4 years and older. The proposed update allows for adenoid removal with the first set of ear tubes in some cases.
Should OHP cover this treatment? Yes, staff recommends adenoid removal should be allowed under certain conditions during initial ear tube placement because the benefits outweigh the risk of harms and concern for repeated surgery with anesthesia.

Question: Should the current guideline regarding coverage of adenoidectomy be updated to agree with the current American Academy of Otolaryngology-Head and Neck Surgery (AAO-HNS) guideline?

Question source: Peggy Kelley, MD, Director of Pediatric ENT at Providence Health Plans

Issue: The current guideline regarding adenoidectomy restricts this procedure to "Adenoidectomy is not indicated at the time of first pressure equalization tube insertion. It may be indicated in children aged 4 and older who are having their second set of tubes." This wording was based on the 2016 AAO guideline. AAO has updated their guideline for 2022 and includes indications for adenoidectomy with the first set of tympanostomy tubes in certain circumstances. Dr. Kelley is requesting that HERC reconsider our guideline wording.

From Dr. Kelley

> I would like to submit updated guidelines for the indication for adenoidectomy for children getting PE Tubes. The issue I would like to address is Guideline note 5. Guideline Note 51 states, "Adenoidectomy is not indicated at the time of first pressure equalization tube insertion. It may be indicated in children aged 4 and older who are having their second set of tubes." This information was the guideline more than 5 years ago.
>
> The 2016 guideline from the Academy of Otolaryngology Head & Neck surgery was: A new recommendation against adenoidectomy for a primary indication of OME in children <4 years old, including those with prior tympanostomy tubes, unless a distinct indication exists (nasal obstruction, chronic adenoiditis) This leaves in place the recommendation for adenoidectomy for children >age 4 years with nasal symptoms AND/Causing the otitis media with effusion.
>
> The most recent guideline link is Clinical Practice Guideline: Tympanostomy Tubes in Children - American Academy of Otolaryngology-Head and Neck Surgery (AAO-HNS) (entnet.org). This is the 2022 guideline. It confirms the indication for adenoidectomy with Tubes if there are nasal symptoms and clarifies that the purpose is to try to minimize the need for repeated surgery. From the executive Summary: A new option for the clinician to perform adenoidectomy as an adjunct to tympanostomy tube insertion for children with symptoms directly related to the adenoid (adenoid infection or nasal obstruction) or in children aged 4 years or older to reduce future incidence of recurrent otitis media or the need for repeat tube insertion.

Current Prioritized List status

CPT	Code description	Current Placement
42820	Tonsillectomy and adenoidectomy; younger than age 12	42 CLEFT PALATE WITH AIRWAY OBSTRUCTION 47 DEEP ABSCESSES, INCLUDING APPENDICITIS AND PERIORBITAL ABSCESS 64 CONGENITAL ANOMALIES OF UPPER ALIMENTARY TRACT, EXCLUDING TONGUE 202 SLEEP APNEA, NARCOLEPSY AND REM BEHAVIORAL DISORDER 368 STREPTOCOCCAL SORE THROAT AND SCARLET FEVER; VINCENT'S DISEASE; ULCER OF TONSIL; UNILATERAL HYPERTROPHY OF TONSIL 551 CHRONIC DISEASE OF TONSILS AND ADENOIDS
42821	Tonsillectomy and adenoidectomy; age 12 or over	42,47,64,202,368,551
42830	Adenoidectomy, primary; younger than age 12	42, 47, 202, 311 HEARING LOSS - AGE 5 OR UNDER 446 HEARING LOSS - OVER AGE OF FIVE 466 CHRONIC SINUSITIS 476 CHRONIC OTITIS MEDIA; OPEN WOUND OF EAR DRUM 551
42831	Adenoidectomy, primary; age 12 or over	42,47,202,476,551
42835	Adenoidectomy, secondary; younger than age 12	42,47,202,311,446,466,476,551
42836	Adenoidectomy, secondary; age 12 or over	42,47,202,476,551

GUIDELINE NOTE 51, CHRONIC OTITIS MEDIA WITH EFFUSION

Lines 311,446,476

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

Patients with specific higher risk conditions (including craniofacial anomalies, Down's syndrome, and cleft palate, or documented speech and language delay) along with hearing loss and chronic otitis media with effusion are intended to be included on Line 311 or Line 446 for children up to and including age 7. Otherwise hearing loss associated with chronic otitis media with effusion (without those specific higher risk conditions) is only included on Line 476.

For coverage to be considered on Line 311, Line 446 or Line 476, there should be a 3 to 6 month watchful waiting period after diagnosis of otitis media with effusion, and if documented hearing loss is greater than or equal to 25dB in the better hearing ear, tympanostomy surgery may be indicated, given short- but not long- term improvement in hearing. Formal audiometry is indicated for children with chronic OME present for 3 months or longer. Children with language delay, learning problems, or

significant hearing loss should have hearing testing upon diagnosis. Children with chronic OME who are not at risk for language delay (such as those with hearing loss <25dB in the better hearing ear) or developmental delay should be reexamined at 3- to 6-month intervals until the effusion is no longer present, significant hearing loss is identified, or structural abnormalities of the eardrum or middle ear are suspected.

Adenoidectomy is not indicated at the time of first pressure equalization tube insertion. It may be indicated in children aged 4 and older who are having their second set of tubes.

Removal of retained tympanostomy tubes requiring anesthesia (CPT code 69424) or as an office visit, is included on Line 424 as a complication, pairing with ICD-10-CM H74.8.

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

Practice guideline:

1) **Rosenfeld 2022**: Updated AAO clinical practice guideline for tympanostomy tubes in children
    a. Adjuvant adenoidectomy:
        i. Clinicians may perform adenoidectomy as an adjunct to tympanostomy tube insertion for children with symptoms directly related to the adenoids (adenoid infection or nasal obstruction) OR in children aged 4 years or older to potentially reduce future incidence of recurrent otitis media or the need for repeat tube insertion
        ii. Strength of recommendation: option based on randomized controlled trials, meta-analyses, and population-level studies, with a balance of benefits and harms.
        iii. Aggregate evidence quality: Grade B, based on RCTs for persistence of OME post-surgically, rate of repeat tube insertion, and hearing outcomes; observational studies regarding the rate of tube reinsertion and hearing outcomes; and meta-analyses on the benefit of adenoidectomy in patients greater than 4 years of age as compared with those younger than 4 years of age
        iv. Level of confidence in evidence: High for symptoms related to adenoids and children over the age of 4 years; medium for role as primary treatment in select populations and role in second tube insertion procedures in patients younger than 4 years
        v. Benefits: Optimize management of adenoid-related disease (nasal obstruction, bacterial infection, chronic rhinitis); reduce need for further surgery and anesthesia; optimize hearing outcomes; decreased persistence of MEE after surgery.
        vi. Risks, harms, costs: Surgical risks of adenoidectomy, additional anesthetic risk related to need for intubation during procedure, bleeding, hypernasality, velopharyngeal insufficiency, nasopharyngeal scarring/stenosis, Grisel's syndrome, longer recovery
        vii. Benefit-harm assessment: Equilibrium (balance) of benefits vs harms

HERC staff recommendation:

1) Modify GN51 as shown below
    a. Adds line 424 to the guideline as this line is mentioned in the guideline wording
    b. Modifies wording regarding adenoidectomy based on 2022 AAO guideline

GUIDELINE NOTE 51, CHRONIC OTITIS MEDIA WITH EFFUSION

Lines 311,424,446,476

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

Patients with specific higher risk conditions (including craniofacial anomalies, Down's syndrome, and cleft palate, or documented speech and language delay) along with hearing loss and chronic otitis media with effusion are intended to be included on Line 311 or Line 446 for children up to and including age 7. Otherwise hearing loss associated with chronic otitis media with effusion (without those specific higher risk conditions) is only included on Line 476.

For coverage to be considered on Line 311, Line 446 or Line 476, there should be a 3 to 6 month watchful waiting period after diagnosis of otitis media with effusion, and if documented hearing loss is greater than or equal to 25dB in the better hearing ear, tympanostomy surgery may be indicated, given short- but not long- term improvement in hearing. Formal audiometry is indicated for children with chronic OME present for 3 months or longer. Children with language delay, learning problems, or significant hearing loss should have hearing testing upon diagnosis. Children with chronic OME who are not at risk for language delay (such as those with hearing loss <25dB in the better hearing ear) or developmental delay should be reexamined at 3- to 6-month intervals until the effusion is no longer present, significant hearing loss is identified, or structural abnormalities of the eardrum or middle ear are suspected.

Adenoidectomy is ~~not indicated at the time of first pressure equalization tube insertion. It may be indicated in children aged 4 and older who are having their second set of tubes.~~ included on these lines at the time of tympanostomy tube insertion for children under age 4 with symptoms directly related to the adenoids (adenoid infection or nasal obstruction) OR in children aged 4 years or older.

Removal of retained tympanostomy tubes requiring anesthesia (CPT code 69424) or as an office visit, is included on Line 424 as a complication, pairing with ICD-10-CM H74.8.

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

AMERICAN ACADEMY OF OTOLARYNGOLOGY–HEAD AND NECK SURGERY FOUNDATION

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Clinical Practice Guideline: Tympanostomy Tubes in Children (Update)

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Sponsorships or competing interests that may be relevant to content are disclosed at the end of this article.

Abstract

Objective. Insertion of tympanostomy tubes is the most common ambulatory surgery performed on children in the United States. Tympanostomy tubes are most often inserted because of persistent middle ear fluid, frequent ear infections, or ear infections that persist after antibiotic therapy. All these conditions are encompassed by the term *otitis media* (middle ear inflammation). This guideline update provides evidence-based recommendations for patient selection and surgical indications for managing tympanostomy tubes in children. The guideline is intended for any clinician involved in managing children aged 6 months to 12 years with tympanostomy tubes or children being considered for tympanostomy tubes in any care setting as an intervention for otitis media of any type. The target audience includes specialists, primary care clinicians, and allied health professionals.

Purpose. The purpose of this clinical practice guideline update is to reassess and update recommendations in the prior guideline from 2013 and to provide clinicians with trustworthy, evidence-based recommendations on patient selection and surgical indications for managing tympanostomy tubes in children. In planning the content of the updated guideline, the guideline update group (GUG) affirmed and included all the original key action statements (KASs), based on external review and GUG assessment of the original recommendations. The guideline update was supplemented with new research evidence and expanded profiles that addressed quality improvement and implementation issues. The group also discussed and prioritized the need for new recommendations based on gaps in the initial guideline or new evidence that would warrant and support KASs. The GUG further sought to bring greater coherence to the guideline recommendations by displaying relationships in a new flowchart to facilitate clinical decision making. Last, knowledge gaps were identified to guide future research.

Methods. In developing this update, the methods outlined in the American Academy of Otolaryngology–Head and Neck Surgery Foundation's "Clinical Practice Guideline Development Manual, Third Edition: A Quality-Driven Approach for Translating Evidence Into Action" were followed explicitly. The GUG was convened with representation from the disciplines of otolaryngology–head and neck surgery, otology, pediatrics, audiology, anesthesiology, family medicine, advanced practice nursing, speech-language pathology, and consumer advocacy.

Action Statements. The GUG made *strong recommendations* for the following KASs: (14) clinicians should prescribe topical antibiotic ear drops only, without oral antibiotics, for children with uncomplicated acute tympanostomy tube otorrhea; (16) the surgeon or designee should examine the ears of a child within 3 months of tympanostomy tube insertion AND should educate families regarding the need for routine, periodic follow-up to examine the ears until the tubes extrude.

The GUG made *recommendations* for the following KASs: (1) clinicians should not perform tympanostomy tube insertion in children with a single episode of otitis media with effusion (OME) of less than 3 months' duration, from the date of onset (if known) or from the date of diagnosis (if onset is unknown); (2) clinicians should obtain a hearing evaluation if OME persists for 3 months or longer OR prior to surgery when a child becomes a candidate for tympanostomy tube insertion; (3) clinicians should offer bilateral tympanostomy tube insertion to children with bilateral OME for 3 months or longer AND documented hearing difficulties; (5) clinicians should

reevaluate, at 3- to 6-month intervals, children with chronic OME who do not receive tympanostomy tubes, until the effusion is no longer present, significant hearing loss is detected, or structural abnormalities of the tympanic membrane or middle ear are suspected; (6) clinicians should not perform tympanostomy tube insertion in children with recurrent acute otitis media who do not have middle ear effusion in either ear at the time of assessment for tube candidacy; (7) clinicians should offer bilateral tympanostomy tube insertion in children with recurrent acute otitis media who have unilateral or bilateral middle ear effusion at the time of assessment for tube candidacy; (8) clinicians should determine if a child with recurrent acute otitis media or with OME of any duration is at increased risk for speech, language, or learning problems from otitis media because of baseline sensory, physical, cognitive, or behavioral factors; (10) the clinician should not place long-term tubes as initial surgery for children who meet criteria for tube insertion unless there is a specific reason based on an anticipated need for prolonged middle ear ventilation beyond that of a short-term tube; (12) in the perioperative period, clinicians should educate caregivers of children with tympanostomy tubes regarding the expected duration of tube function, recommended follow-up schedule, and detection of complications; (13) clinicians should not routinely prescribe postoperative antibiotic ear drops after tympanostomy tube placement; (15) clinicians should not encourage routine, prophylactic water precautions (use of earplugs or headbands, avoidance of swimming or water sports) for children with tympanostomy tubes.

The GUG offered the following KASs as *options*: (4) clinicians may perform tympanostomy tube insertion in children with unilateral or bilateral OME for 3 months or longer (chronic OME) AND symptoms that are likely attributable, all or in part, to OME that include, but are not limited to, balance (vestibular) problems, poor school performance, behavioral problems, ear discomfort, or reduced quality of life; (9) clinicians may perform tympanostomy tube insertion in at-risk children with unilateral or bilateral OME that is likely to persist as reflected by a type B (flat) tympanogram or a documented effusion for 3 months or longer; (11) clinicians may perform adenoidectomy as an adjunct to tympanostomy tube insertion for children with symptoms directly related to the adenoids (adenoid infection or nasal obstruction) OR in children aged 4 years or older to potentially reduce future incidence of recurrent otitis media or the need for repeat tube insertion.

Keywords

otitis media, tympanostomy tubes, grommets, otorrhea, middle ear effusion, pediatric otolaryngology, developmental delay disorders

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Update Rationale and Scope

This clinical practice guideline (CPG) is an update and replacement for the earlier guideline ''Tympanostomy Tubes in Children,'' published in 2013 by the American Academy of Otolaryngology–Head and Neck Surgery Foundation (AAO-HNSF).[1] An update was necessitated by an >5-year lapse and by subsequent original research and systematic reviews that might modify existing recommendations or support new ones. Changes in content and methodology from the prior guideline include the following:

- New evidence from 6 CPGs, 18 systematic reviews, and 27 randomized controlled trials (RCTs)
- Emphasis on patient education and shared decision making with new tables of counseling opportunities and frequently asked questions
- Expanded key action statement (KAS) profiles to explicitly state quality improvement opportunities and implementation considerations
- New flowchart to clarify decision making and show the relationships among KAS recommendations
- A new strong recommendation that the surgeon or designee should examine the ears of a child within 3 months after tympanostomy tube insertion to assess outcomes and should educate families regarding the

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Bilateral BAHA

Plain Language Summary:
Background: Bone anchored hearing aids (BAHA) is a specific type of hearing aid who have "normal" hearing in one ear. This topic looks at covering this hearing aid for children who have hearing loss is both ears.

Should OHP cover BAHA for children who have hearing loss in both ears? Staff recommends OHP cover this treatment based on expert opinion.

Question: Should bone anchored hearing aids (BAHA) be covered for bilateral use in children?

Question source: Medical management committee as HSD

Issue: Currently, GN 103 limits coverage of bone-anchored hearing aid system (BAHA) to patients with normal hearing in one ear (with or without a hearing aid). Recently, MMC received a request for coverage for bilateral BAHA in a child with bilateral stenosis of the ear canal. Because GN 103 limited use to one ear and required the other ear to have normal hearing, the child was denied BAHA implantation. When coverage of BAHA was discussed in 2014 and 2015, only unilateral use was discussed based on the literature reviewed and on expert pediatric ENT opinion.

The BAHA is a hearing aid which uses the principle of bone conduction. In normal hearing, sound may be transmitted to the inner ear both by air (through the external ear canal) or through the bones of the skull. In individuals who are unable to hear using air conduction, either due to a congenital malformation of the ear canal or due to chronic ear infection, a hearing aid which utilizes bone conduction is the most appropriate.

Current Prioritized List status
The following codes are on lines 311 HEARING LOSS - AGE 5 OR UNDER and 446 HEARING LOSS - OVER AGE OF FIVE:
CPT **69714** (Implantation, osseointegrated implant, skull; with percutaneous attachment to external speech processor)
CPT **69716** (Implantation, osseointegrated implant, skull; with magnetic transcutaneous attachment to external speech processor)
CPT **69717** (Revision or replacement (including removal of existing device), osseointegrated implant, skull; with percutaneous attachment to external speech processor)
CPT **69719** (Revision or replacement (including removal of existing device), osseointegrated implant, skull; with magnetic transcutaneous attachment to external speech processor)

GUIDELINE NOTE 103, BONE ANCHORED HEARING AIDS

Lines 311,446

Bone anchored hearing aids (BAHA, CPT 69714, 69715; HCPCS L8690-L8694) are included on these lines when the following criteria are met:

A) The patient is aged 5-20 years for implanted bone anchored hearing aids; headband mounted BAHA devices may be used for children under age 5
B) Treatment is for unilateral severe to profound hearing loss when the contralateral ear has normal hearing with or without a hearing aid
C) Traditional air amplification hearing aids and contralateral routing of signal (CROS) hearing aid systems are not indicated or have been tried and are found to be not effective

D) Implantation is unilateral.

Use of BAHA for treatment of tinnitus is not covered.

GUIDELINE NOTE 143, TREATMENT OF UNILATERAL HEARING LOSS

Lines 311,446

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

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

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

Evidence

1) **Mandavia 2017,** systematic review on BAHA
   a) N=39 studies
      i) Eighteen articles were retrospective case series; three were case reports; eight were prospective case series; four were systematic reviews; four were narrative reviews; one was a Delphi study, one was a consensus document.
   b) Using the GRADE criteria, the quality of evidence was classified as of 'very low quality'
2) **Janssen 2012,** a systematic review of BAHA for bilateral permanent conductive hearing loss
   a) N=11 studies
      i) All observational
   b) In most studies, comparisons between unilateral and bilateral BAHA were intra-subject.
   c) Bilateral BAHA provided audiologic benefit compared to unilateral BAHA (improved thresholds for tones [2 studies], speech in quiet [5 studies] and in noise [3 studies], and improved localization/lateralization [3 studies]) and patients' perceived subjective benefit from bilateral BAHA (3 studies).
   d) Disadvantages of bilateral BAHAs included listening in noise in some conditions (3 studies), presumed additional cost, and presumed increase in adverse event risk.
   e) **Conclusion:** Bilateral BAHA provided additional objective and subjective benefit compared to unilateral BAHA; however, there was a limited number of studies available with good quality evidence.

Other payer policies

1) **NHS 2013**
   a) Criteria for unilateral implantation BAHA will be funded when assessment by a multidisciplinary team leads to a clear recommendation of a BAHA AND confirms all of the criteria below.
      i) The patient has one of the following:
         (a) Permanent bilateral conductive or mixed hearing loss.
         (b) Bilateral conductive or mixed hearing loss where one ear works better than the other, but clinicians would have considered two air conducting hearing aids (ACHAs) if the type of hearing loss had not precluded their use.
         (c) Unilateral conductive hearing loss with ear canal stenosis that is unlikely to benefit from meatoplasty; or who have had revision surgery and failed to tolerate ACHA.
         (d) Profound unilateral sensorineural hearing loss
      ii) AND The patient is clinically unsuitable for other medical or surgical treatments.
      iii) Otological indications supporting the use of BAHA include:
         (a) Congenital malformation of the middle/external or microtia.
         (b) Chronically draining ear that does not allow the use of an air conducting hearing aid.
         (c) Patients with bilateral conductive hearing loss due to ossicular disease (and not appropriate for surgical correction) or unable to be aided by conventional air conducting devices.
      iv) AND The following audiological criteria should be met: Conduction or mixed hearing loss with a bone conduction pure tone average (0.5, 1, 2, 3 kHz) threshold up to 45 dBHL for the Devino or BP 100,55dB for the Intenso and 70 dB for Cordelle II (Body

Processor). In the advent of new processors being released manufacturers audiological recommendations should be followed.

v) Air conduction pure tone average not better than 40 dB (for Adults).

vi) A maximum speech discrimination score better than 60% when using a phonetically balanced word list.

b) AND

i) The patient has had preoperative counselling, and has realistic expectations about the benefits and limitations of BAHA. They must be prepared to maintain their device in the long term.

ii) The patient will be able to keep the area around the fixture clean, either on their own or with help from other people.

iii) There are no contraindications for BAHA.

c) In children with binaural congenital hearing loss, intervention should take place as early in life as possible; BAHA may be provided on a headband until the child is old enough for surgery. The minimum age for first surgery, as identified by the equipment manufacturer, is three years. It is recommended that implant surgery be performed in two stages in children of up to 10 years of age. In children with bilateral conductive hearing loss; clinicians may consider bilateral BAHA if a decision is made that this would provide children with the best hearing environment in the classroom situation, following multidisciplinary clinical assessment by the BAHA team.

2) **Aetna 2022**:

a) Aetna considers fully or partially implantable bone-anchored hearing aids (BAHAs) or temporal bone stimulators medically necessary prosthetics for persons aged 5 years and older with a unilateral or bilateral conductive or mixed conductive and sensorineural hearing loss who have any of the following conditions, where the condition prevents restoration of hearing using a conventional air-conductive hearing aid and who meet the audiologic criteria below:

i) Congenital or surgically induced malformations of the external ear canal or middle ear (such as aural atresia); *or*

ii) Dermatitis of the external ear, including hypersensitivity reactions to ear moulds used in air conduction hearing aids; *or*

iii) Hearing loss secondary to otosclerosis in persons who can not undergo stapedectomy; *or*

iv) Severe chronic external otitis or otitis media; *or*

v) Tumors of the external ear canal and/or tympanic cavity; *or*

vi) Other conditions in which an air-conduction hearing aid is contraindicated.

b) Audiologic criteria:

i) Unilateral implant: Conductive or mixed (conductive and sensorineural) hearing loss with pure tone average bone conduction threshold values measured at 0.5, 1, 2, and 3 kHz less than or equal to 45 dB HL (BAHA Attract, BAHA Divino, BAHA BP100, Baha 4, Bonebridge Bone Conduction Implant, Cochlear Osia, Cochlear Osia 2, Cochlear Osia B1300 system, and Sophono Alpha System), 55 dB HL (BAHA 5 Power, Baha 5 Super Power Sound Processor, BAHA Intenso, Ponto Plus Power) or 65 dB HL (BAHA Cordelle II).

ii) Bilateral implant: Moderate-to-severe bilateral symmetric conductive or mixed (conductive and sensorineural) hearing loss, meeting above-listed bone conduction thresholds in both ears. Symmetric bone conduction threshold is defined as less than:

(a) 10 dB average difference between ears (measured at 0.5, 1, 2 and 4 kHz) or less than 15 dB difference at individual frequencies (BAHA Divino, Ponto Plus, Ponto Plus Power, Ponto Pro, Sophono Alpha System); *or*
(b) 10 dB average difference between ears (measured at 0.5, 1, 2, and 3 kHz), or less than a 15 dB difference at individual frequencies (BAHA Attract, BAHA BP100, BAHA 4, BAHA 5 Power, Baha 5 Super Power Sound Processor, BAHA Cordelle II, BAHA Intenso, Bonebridge Bone Conduction Implant, Cochlear Osia, Cochlear Osia 2, and Cochlear Osia B1300 system).

iii) Aetna considers an implantable BAHA for conductive or mixed hearing loss experimental and investigational when criteria are not met because of insufficient evidence in the peer-reviewed published medical literature.
iv) Aetna considers the use of an implantable BAHA medically necessary in persons with unilateral sensorineural hearing loss (single-sided deafness, i.e., deafness in one ear while the other ear has normal hearing).

3) **Idaho Medicaid 2022**
   a) Bone-Anchored Hearing Aid Bone-Anchored Hearing Aid (BAHA) is covered for participants under 21 with a prior authorization when medically necessary. It is recommended that participants over the age of five, trial a soft band BAHA before surgery is scheduled. The participant must meet one of the following criteria:
      i) The participant is diagnosed with ear canal atresia, no ear canals, and unable to wear an ear mold;
      ii) The participant is diagnosed with microtia, very small ear canal, and unable to wear an ear mold;
      iii) The participant has persistently discharging ears and is unable to use air conduction aid;
      iv) The participant has an ear condition made worse with ear molds; or
      v) Audiology test results indicate a pure tone average bone conduction threshold of up to 65 dB. Purchase of an auditory non-osseo integrated sound processor includes the headband in its reimbursement

Expert input:

Dr. Peggy Kelley, Providence pediatric ENT clinical director

I would request adding as in indication: Temporary bilateral conductive hearing loss in patients with cleft palate and middle ear effusions until their palate is repaired and PE Tubes can be placed. This would be BAHA on headband. (We no longer place PE tubes until the palate is closed as the ears just constantly drain until the palate is closed.) The BAHA is preferred over a traditional hearing aid in this type of patient. The BAHA corrects the conductive component only which means that there is no overcorrection or hearing damage that would result to the hearing nerve. It is possible for the native hearing to fluctuate with occasional clearing the middle ear and changes in the viscosity of the fluid in the middle ear until the palate is repaired. A traditional hearing aid is set for a specific hearing loss which may be too little or two much. The BAHA working across the bone is not influenced by the middle ear fluctuations.

HERC staff summary

The evidence for bilateral BAHA is very limited, with some benefits seen when compared to unilateral BAHA but increased cost and risk. Private payers and evidence based payers, such as NHS, are covering bilateral BAHA for children with bilateral conductive or mixed conductive/sensorineural hearing loss. The current requirement to have normal hearing in one ear for unilateral implantation is not reflected in any other payer policy reviewed, and per our expert is out of date. Experts recommend coverage of bilateral BAHA in certain situations.

HERC staff recommendation:

1) Modify GN103 as shown below

GUIDELINE NOTE 103, BONE ANCHORED HEARING AIDS

Lines 311,446

Bone anchored hearing aids (BAHA, CPT 69714, 69715; HCPCS L8690-L8694) are included on these lines when the following criteria are met:

A) The patient is aged 5-20 years for implanted bone anchored hearing aids; headband mounted BAHA devices may be used for children under age 5; AND

B) ~~Treatment is for unilateral severe to profound hearing loss when the contralateral ear has normal hearing with or without a hearing aid~~

C) ~~Traditional air amplification hearing aids and contralateral routing of signal (CROS) hearing aid systems are not indicated or have been tried and are found to be not effective~~

D) ~~Implantation is unilateral.~~

E) The patient has one of the following:

   1) Permanent bilateral conductive or mixed hearing loss (for example, congenital malformation of the middle/external ear, microtia, or ossicular disease) unable to be aided by conventional air conducting devices; OR

   2) Unilateral conductive hearing loss with ear canal stenosis or ear canal atresia that is unlikely to benefit from surgery; OR

   3) Profound unilateral sensorineural hearing loss when the contralateral ear has normal hearing with or without a hearing aid; OR

   4) Temporary bilateral conductive hearing loss in patients with cleft palate and middle ear effusions until their palate is repaired and tympanostomy tubes can be placed (for BAHA headband only); AND

F) The patient is clinically unsuitable for other medical or surgical treatments.

Use of BAHA for treatment of tinnitus is not covered.

ORIGINAL ARTICLE

An evaluation of the quality of evidence available to inform current bone conducting hearing device national policy

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Objectives: In 2016, NHS England published the commissioning policy on Bone Conducting Hearing Devices (BCHDs). This policy was informed by updated evidence on the clinical and cost-effectiveness of BCHDs as well as by the 2013 Bone Anchored Hearing Aid (BAHA) policy. Commissioning policies set the criteria for service delivery and therefore have a major impact on the care received by patients. It is important that stakeholders have a good appreciation of the available evidence informing policy, as this will promote engagement both with the policy and with future research leading on from the policy. In this article, we provide stakeholders with a transparent and pragmatic assessment of the quality of the body of evidence available to inform current BCHD national policy.

Method: (i) A systematic review of the literature on BCHDs published since the development of the 2013 policy was performed in September 2016, adhering to PRISMA recommendations. The search terms used were as follows bone conduction; bone conducting; bone anchor; BAHA; Bone Anchored Hearing Aid; Bone Conducting Hearing Device; BCHD; Bone Conducting Hearing Implant; BCHI; Sophono; Bonebridge; Soundbite; Ponto; Hearing aid; implant; device; hearing device. Publications that could inform current BCHD policy were included. The quality of included articles was assessed using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) system. (ii) The quality of evidence referenced by the 2013 BAHA policy was assessed using the GRADE system.

Results: (i) Of the 2576 publications on BCHDs identified by the systematic search, 39 met the inclusion criteria for further analysis. Using the GRADE criteria, the quality of evidence was classified as of 'very low quality'. (ii) The 2013 BAHA policy was informed by 14 references. The GRADE system classifies the quality of evidence that informed the policy as of 'very low quality'.

Conclusions: The GRADE system defines the body of evidence available to inform current national BCHD policy as of 'very low quality'. There is an urgent need for high-quality research to help make informed policy decisions about the care of patients with hearing loss. An (inter)-national registry of BCHDs could address this need.

NHS England issues commissioning policies that aim to ensure that the NHS delivers better outcomes for patients within its available resources.[1] Commissioning policies set the criteria for service delivery and therefore have a major impact on the care received by patients. It is important for commissioning policies to be based on strong evidence so that policy decisions are well informed. It is equally important that stakeholders have a good appreciation of the available evidence, as this will promote engagement both with the policy and with future research leading on from the policy.

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In July 2016, NHS England published the commissioning policy on Bone Conducting Hearing Implants (BCHI) with separate commissioning criteria for Bone Conducting Hearing Devices (BCHDs) and Middle Ear Implants.[2] Their policy criteria for BCHDs were informed by updated evidence on the clinical and cost-effectiveness of these devices,[2] as well as by the 2013 Bone Anchored Hearing Aid (BAHA) commissioning policy.[3] In this article, we provide stakeholders with a transparent and pragmatic assessment of the quality of the body evidence available to inform current BCHD policy.

Method

This study was conducted in two parts: (i) systematic review and critical assessment of the body of literature on BCHDs;

Systematic Review

AMERICAN ACADEMY OF OTOLARYNGOLOGY–HEAD AND NECK SURGERY FOUNDATION

Otolaryngology–Head and Neck Surgery
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SAGE

Bilateral Bone-Anchored Hearing Aids for Bilateral Permanent Conductive Hearing Loss: A Systematic Review

Renée M. Janssen, MSc[1], Paul Hong, MD, FRCS[2], and Neil K. Chadha, MBChB, MPHe, FRCS[3]

No sponsorships or competing interests have been disclosed for this article.

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Abstract

Objective. To systematically review the outcomes of bilateral versus unilateral bone-anchored hearing aids (BAHA) for individuals with bilateral permanent conductive hearing loss (CHL) with the goal of (1) deriving clinically oriented insights into the advantages and disadvantages of bilateral fitting and (2) identifying gaps in knowledge to stimulate future research.

Data Sources. Medline, EMBASE, and Cochrane databases were searched for studies of all languages published between 1977 and July 2011.

Review Methods. Studies were included if subjects of any age had permanent bilateral CHL and bilateral implanted BAHAs. Outcome measures of interest were any subjective or objective audiologic measures, quality of life indicators, or reports of adverse events.

Results. In all, 628 abstracts were generated from the literature searches; 11 studies met the criteria for data extraction and analysis. All 11 studies were observational. In most studies, comparisons between unilateral and bilateral BAHA were intra-subject. Bilateral BAHA provided audiologic benefit compared to unilateral BAHA (improved thresholds for tones [2 studies], speech in quiet [5 studies] and in noise [3 studies], and improved localization/lateralization [3 studies]) and patients' perceived subjective benefit from bilateral BAHA (3 studies). Disadvantages of bilateral BAHAs included listening in noise in some conditions (3 studies), presumed additional cost, and presumed increase in adverse event risk.

Conclusion. Bilateral BAHA provided additional objective and subjective benefit compared to unilateral BAHA; however, there was a limited number of studies available with good quality evidence. Aspects of bilateral BAHA that would benefit from further investigation are described, and recommendations for bilateral BAHA candidacy criteria are provided.

Keywords

bilateral, conductive hearing loss, BAHA, bone-anchored hearing aid, systematic review, bilateral BAHA

The purpose of this review was to consider original studies reporting on patients with bilateral permanent conductive hearing loss (CHL) and bilateral bone-anchored hearing aids (BAHA). This includes studies evaluating quality of life, patient reports of benefit, audiologic outcomes, and adverse events, with the purpose of deriving clinically oriented insights into the advantages and disadvantages of bilateral fitting. This study intends to aid clinicians who are considering bilateral BAHA implantation by providing an appraisal of the literature to date, as well as to identify gaps in knowledge in this area for the purpose of stimulating future research.

Brånemark first demonstrated in the 1950s that implanted titanium formed a strong connection with bone via a process that he termed *osseointegration*.[1] In 1977, Tjellström inserted titanium implants into the mastoid process of the temporal bone of 3 hearing-impaired patients who wore bone conduction hearing aids (BCHA) and provided them with a vibrator that attached to the percutaneous implant,[2] marking the first trial of the bone-anchored hearing aid.

The current BAHA consists of a titanium screw, percutaneous abutment, and sound processor/bone conductor that attaches to the abutment. A BAHA can compensate for any degree of air-bone gap; additionally, it can provide gain for a limited range of cochlear (ie, sensorineural) hearing loss. The BAHA is well suited to patients with significant conductive hearing losses and to patients who are unable to wear air conduction hearing aids (ACHA). Audiologic indications for the BAHA include bilateral permanent (or chronic) conductive hearing loss and, more recently, single-sided deafness.[3] Mixed hearing losses may also

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NHS Commissioning Board

Clinical Commissioning Policy: Bone Anchored Hearing Aids

April 2013

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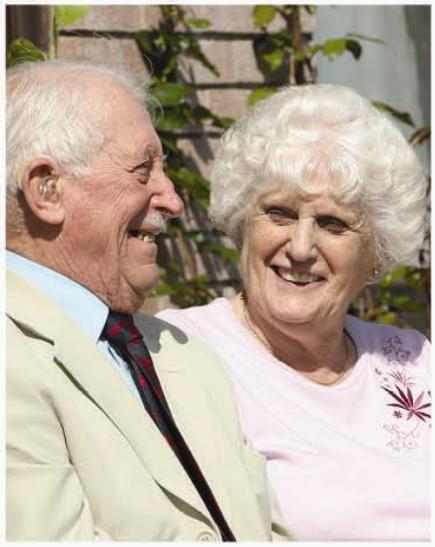

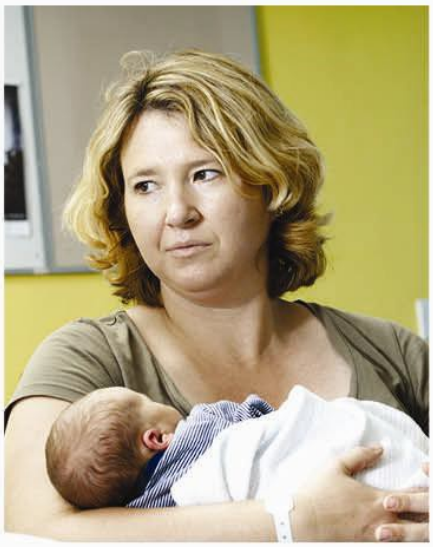

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NHS Commissioning Board

Clinical Commissioning Policy: Bone Anchored Hearing Aids

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Specialised Ear Surgery

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Contents

Policy Statement

The NHS Commissioning Board (NHS CB) will commission Bone Anchored Hearing Aids (BAHAs) for hearing loss in accordance with the criteria outlined in this document.

In creating this policy the NHS CB has reviewed this clinical condition and the options for its treatment. It has considered the place of this treatment in current clinical practice, whether scientific research has shown the treatment to be of benefit to patients, (including how any benefit is balanced against possible risks) and whether its use represents the best use of NHS resources.

This policy document outlines the arrangements for funding of this treatment for the population in England.

Equality Statement

The NHS CB has a duty to have regard to the need to reduce health inequalities in access to health services and health outcomes achieved as enshrined in the Health and Social Care Act 2012.The NHS CB is committed to ensuring equality of access and non-discrimination, irrespective of age, gender, disability (including learning disability), gender reassignment, marriage and civil partnership, pregnancy and maternity, race, religion or belief, sex (gender) or sexual orientation. In carrying out its functions, the NHS CB will have due regard to the different needs of protected equality groups, in line with the Equality Act 2010. This document is compliant with the NHS Constitution and the Human Rights Act 1998. This applies to all activities for which they are responsible, including policy development, review and implementation.

Plain Language Summary

The Bone-anchored hearing aid system (BAHA) is a hearing aid which uses the principle of bone conduction. In normal hearing sound may be transmitted to the inner ear both by air (through the external ear canal) or through the bones of the skull. In individuals who are unable to hear using air conduction, either due to a congenital malformation of the ear canal or due to chronic ear infection, a hearing aid which utilises bone conduction is the most appropriate.

There is evidence to support the use of bone anchored hearing devices in adults and children with hearing impairment that is not adequately corrected by conventional air conduction hearing aids. The intervention is safe and of proven benefit.

The care of children with congenital microtia MUST be coordinated by a multidisciplinary team that can provide appropriate hearing and reconstructive support.

Information on the outcome of treatments for these patients will be collected and considered when this policy is reviewed.

1. Introduction

There is evidence to support the use of bone anchored hearing devices in adults and children with hearing impairment that is not adequately corrected by conventional air conduction hearing aids. The intervention is safe and of proven benefit.

The care of children with microtia MUST be coordinated by a multidisciplinary team that can provide appropriate hearing and reconstructive support.

2. Definitions

The Bone-anchored hearing aid system (BAHA) is a hearing aid which uses the principle of bone conduction. In normal hearing sound may be transmitted to the inner ear both by air (through the external ear canal) or through the bones of the skull. In individuals who are unable to hear using air conduction, either due to a congenital malformation of the ear canal or due to chronic ear infection, a hearing aid which utilises bone conduction is the most appropriate.

The BAHA comprises a vibration transducer which is coupled to a titanium implant anchored to the temporal bone of the skull. Surgery is required for the placement of the titanium fixture. The BAHA system offers advantages over conventional bone conduction hearing aids. Conventional bone conduction aids require a transducer, placed on the opposite side of the head, to be held in place by a tight steel band and may cause problems with pressure effects (especially in children), an unnatural listening circumstance and loss of sound quality.[1,2]

3. Aim and objectives

The policy should ensure that patients who can be helped by a bone anchored hearing device are identified and carefully assessed. All patients for whom a conventional air conduction device is appropriate should be identified and not offered an implantable device.

It is the assessment of a patient to demonstrate that a hearing implant is the most effective clinical option that is of central importance. Alternative hearing implants for this patient group may also be considered when the patient is undergoing assessment.

4. Criteria for commissioning

Criteria for unilateral implantation

BAHA will be funded when assessment by a multidisciplinary team leads to a clear recommendation of a BAHA [1, 2] AND confirms all of the criteria below.

The patient has one of the following:

Permanent bilateral conductive or mixed hearing loss.

Bilateral conductive or mixed hearing loss where one ear works better than the other, but clinicians would have considered two air conducting hearing aids (ACHAs) if the type of hearing loss had not precluded their use.

Unilateral conductive hearing loss with ear canal stenosis that is unlikely to benefit from meatoplasty; or who have had revision surgery and failed to tolerate ACHA.[3, 4]

Profound unilateral sensorineural hearing loss

AND

The patient is clinically unsuitable for other medical or surgical treatments.

Otological indications supporting the use of BAHA include:

- Congenital malformation of the middle/external or microtia.
- Chronically draining ear that does not allow the use of an air conducting hearing aid.
- Patients with bilateral conductive hearing loss due to ossicular disease (and not appropriate for surgical correction) or unable to be aided by conventional air conducting devices.

AND

The following audiological criteria should be met:

Conduction or mixed hearing loss with a bone conduction pure tone average (0.5, 1, 2, 3 kHz) threshold up to 45 dBHL for the Devino or BP 100,55dB for the Intenso and 70 dB for Cordelle II (Body Processor). In the advent of new processors being released manufacturers audiological recommendations should be followed.

Air conduction pure tone average not better than 40 dB (for Adults).

A maximum speech discrimination score better than 60% when using a phonetically balanced word list.[2]

AND

The patient has had preoperative counselling, and has realistic expectations about the benefits and limitations of BAHA. They must be prepared to maintain their device in the long term.[2]

The patient will be able to keep the area around the fixture clean, either on their own or with help from other people.[5]

There are no contraindications for BAHA.

The following should be considered as contraindications to BAHA

Absolute

Having a bone disease that leaves the skull too thin to support a BAHA implant e.g. brittle bone disease (osteogenesis imperfecta)

Being younger than three years old.

Potential

Contraindications that may stop patients adequately maintaining their BAHA:

- Psychiatric disease
- Immature personality
- Alcohol or drug abuse

The NHS CB will not normally commission bilateral Bone Anchored Hearing Aid (BAHA) implantation. Such requests for funding will only be considered through an exceptions route.

Additional considerations for BAHA implantation in children:

In children with binaural congenital hearing loss, intervention should take place as early in life as possible; BAHA may be provided on a headband until the child is old enough for surgery. The minimum age for first surgery, as identified by the equipment manufacturer, is three years. It is recommended that implant surgery be performed in two stages in children of up to 10 years of age.

In children with bilateral conductive hearing loss; clinicians may consider bilateral BAHA if a decision is made that this would provide children with the best hearing environment in the classroom situation, following multidisciplinary clinical assessment by the BAHA team.

In children with unilateral hearing loss; BAHA would not normally be funded. Decisions should be taken on a case-by-case basis through the exceptional case process, centred on information regarding the child's development, audiometry results and communication needs.

5. Patient pathway

The patient pathway is described in detail in the Bone Anchored Hearing Aid specification.

6. Governance arrangements

Recommendations on standards for BAHA services come from a consensus statement of experts[1], which states that BAHA fitting should take place in a specialist centre performing at least 15 procedures per year. The team should include an otorhinolaryngologist surgeon, audiologist and, for children, paediatric anaesthetist and speech and language therapist.

7. Epidemiology and needs assessment

BAHAs are only appropriate for a very small sub-set of patients. The incidence of bilateral congenital ears is 'probably 1:10,000'.[1] The incidence of bilateral chronic suppurative otitis media is not known, though 'clinical observation would suggest this is a considerable problem'.[1] Gillett *et al* note that for a catchment area of circa 300,000, they 'implanted approximately eight to 10 patients per year.[7]

These figures suggest that between 1413 and 1766 BAHAs could be implanted per year in England (Census population 2011 = 53million (ONS)).

8. Evidence base

The reviews of BAHA all demonstrate evidence of clinical effectiveness. However this evidence is of a low quality; all the evidence comes from level 4 case series with relatively small sample sizes.[2]

BAHA is a safe intervention. In a study of 149 consecutive patients who underwent BAHA implantation, primarily for unilateral sensorineural hearing loss, the authors found no intra or perioperative complications. Post-operative complications occurred in 19/149 (12.8%) of the patients; these included skin overgrowth over the abutment, implant extrusion and local wound infections.[13]

There is currently insufficient evidence to justify commissioning bilateral implantation of BAHA. A Birmingham University review in 2005 found 5 small cases series; sample sizes ranging from 3 to 25. Methodological weaknesses encouraged positive results and the reviewers concluded that the use of bilateral BAHA was neither supported nor refuted.[14]

There is reasonable evidence to justify commissioning BAHA for unilateral hearing loss in specific circumstances.[3, 4, 6]

9. Rationale behind the policy statement

The BAHA consists of a permanent implant surgically inserted into the mastoid bone.

A vibrating part (permanent abutment) is then fitted onto this, and a small detachable sound processor clips onto the abutment.[5] The vibrating part then conducts sound through to the inner ear.

BAHAs are only appropriate for a very small sub-set of patients. It is appropriate to consider other treatment options before BAHA. The Canadian systematic review found no additional benefit in using BAHA for people previously using air conducting hearing aids (ACHA).[2] ACHA remains the first line treatment, and stapedectomy normally remains the second line treatment for otosclerosis[8] except in some older patients where BAHA is likely to be more effective than stapedectomy.[9]

The adult service requires a multi-disciplinary team dealing with otology and audiology within a specialised ENT service. The children's service should be located in a major paediatric centre because of the specialist anaesthetic needs.[6]

Cost effectiveness analysis of BAHA demonstrates an ICER of £17,610 per QALY gained. This falls within the NICE ICER threshold of £20,000- £30,000 per QALY.[11]

The selection criteria are based on the quality standards and good practice guidelines for BAHA for children and young people and current best available published evidence.

10. Mechanism for funding

From April 2013 the NHS CB will be responsible for commissioning in line with this policy on behalf of the population of England.

11. Audit requirements

There is currently no national database. The service specification records relevant outcome measures to be recorded. Service providers will be expected to collect and provide audit data on request

12. Documents which have informed this policy

The National Deaf Children's Society. Quality Standards in Bone Anchored Hearing Aids for Children and Young People. 2010

13. Links to other policies

This policy follows the principles set out in the ethical framework that governing the commissioning of NHS healthcare and those policies dealing with the approach to experimental treatments and processes for the management of individual funding requests (IFR).

14. Date of review

April 2014

15. Glossary

Term	Meaning
Atresia	Absence or closure of a tubular organ/ structure.
Audiology	Pertaining to the sense of hearing.
Binaural	Relating to or involving the use of both ears.
Bilateral	Relating to both sides of the body.
Congenital	Existing from birth or before.
Conductive Hearing Loss	Due to a defect in the conduction of sound from the external ear to the inner ear. This may be due to perforations of the eardrum, fluid or infection in the middle ear, or disorders of the small bones in the middle ear (ossicles).
Microtia	Congenital abnormally small ears.
Ossicular disease	Disease affecting the "ossicles", the small bones which conduct sound through the middle ear.

Sensorineural hearing loss	May be due to a lesion of the cochlea in the inner ear, the auditory nerve or the auditory centres in the brain.
Suppurative Otitis media	Infection of the middle ear which may lead to hearing loss, suppurative means with pus present.
Transducer	A device such as a microphone or electric motor that converts one form of energy into another.
Unilateral	Relating to one side of the body.

References

1. Proops D. Bone anchored hearing aids. British Association of Otorhinolaryngologists head & Neck Surgeons. Statements of clinical effectiveness. August 1998.
2. Bone anchored hearing aid. Health Technology Scientific Literature Review. Ontario. 2002.
3. Macnamara M, Phillips D, Proops DW. The bone anchored hearing aid (BAHA) in chronic suppurative otitis media (CSOM). *J Laryngol Otol Suppl.* 1996;**21**:38-40.
4. Wazen JJ, Spitzer J, Ghossaini SN, Kacker A, Zschommler A. Results of the bone-anchored hearing aid in unilateral hearing loss. *Laryngoscope.* 2001;**111**(6):955-8.
5. The National Deaf Children's Society. Quality Standards in Bone Anchored Hearing Aids for Children and Young People. 2010. Available at: http://www.ndcs.org.uk/document.rm?id=268 , Accessed 16/08/2012.
6. Personal communication Dr David Selvdurai Consultant Ear Nose and Throat Surgeon, St George's Hospital, Tooting, London.
7. Gillett D, Fairley JW, Chandrashaker TS, Bean A, Gonzales J. Bone-anchored hearing aids: results of the first eight years of a programme in a district general hospital, assessed by the Glasgow benefit inventory. *Journal of Laryngology and Otology*, 2006;**120**:537-542.
8. Burrell SP, Cooper HC, Proops DW. The bone anchored hearing aid: the third option for otosclerosis. *J Laryngol Otol Suppl* 1996;**21**:31-37.
9. Specialised services national definitions set (2nd Edition). http://www.specialisedcommissioning.nhs.uk/index.php/key-documents/specialised-servicesnational-definitions-set/ Accessed 08/01/10. (3rd Edition is due Spring 2010).
10. Bone-anchored hearing aids. Summary. Agence d'evaluation des technologies et des modes d'intervention en santé. Quebec AETMIS. May 2006.
11. Monksfield, P, Jowett S, Reid A, Proops D. Cost-effectiveness Analysis of the Bone-Anchored Hearing Device. *Otology & Neurotology*,2011;**32**(8):1192-1197.
12. RNID. Bone conducting hearing aids (factsheet). http://www.rnid.org.uk/information_resources/factsheets/hearing_aids/factsheets_leaflets/bone_conduction_hearing_aids.htm Accessed 08/01/10.
13. House JW & Kutz JW. Bone-anchored hearing aids: incidence and management of postoperative complications. *Otology and Neurotology, 2007;***28**:213-217.
14. Aggressive Research Intelligence Facility. Bone anchored hearing aids (bilateral): conductive hearing loss deafness. ARIF, 2005 http://www.arif.bham.ac.uk/b/bone-anchored-hearingaids.shtml Accessed 08/01/10.
15. Personal Communication, Dr Elwina Timehin, Mr David Selvadurai, BAHA Programme, St Georges Healthcare NHS Trust; "Patients with unilateral sensorineural deafness do benefit from using the device. At present we give them

a trial of a CROS (Contralateral Routing of Sound) aid when assessing their suitability for the device. In general if they benefit from its use then they definitely benefit from using the BAHA" and "The total number of patients is small, perhaps only 2-3 per year across all our PCTs"

Section 4.0

Consent Agenda-

Straightforward Items

Consent Agenda Issues—May 2022

Code	Code Description	Line(s) Involved	Issue	Recommendation(s)
11960 11971	Insertion of tissue expander(s) for other than breast, including subsequent expansion Removal of tissue expander without insertion of implant	Burn lines	OHSU plastic surgery requested that tissue expanders be paired with a variety of disfiguring diagnoses that might require extra tissue to close the wound from the repair. For example, patients with large congenital nevi frequently have tissue expanders placed to create extra normal tissue for use in closing the incision when the congenital nevi is excised. HERC staff recommend placing these codes on the Ancillary file to be used with various covered procedures as needed.	Remove 11960 and 11971 from all current Prioritized List lines. Advise HSD to add 11960 and 11971 to the Ancillary Procedures File
B4100	Food thickener, administered orally, per ounce		B4100 is not on any list. This is a standard treatment for dysphagia.	Advise HSD to add B4100 to the Ancillary Procedure File
58559-58563	Hysteroscopy with various surgical procedures	1 PREGNANCY	A series of CPT codes were added to line 1 in 2017 which were all thought to represent hysterectomy procedures. Five of these codes actually represent hysteroscopy with various procedures such as removal of fibroid or lysis of adhesions which are not appropriate during pregnancy. All of these codes are currently on other, appropriate lines.	Remove 58559-58563 from line 1

Consent Agenda Issues—May 2022

Code	Code Description	Line(s) Involved	Issue	Recommendation(s)
61538 61539 61781	Craniotomy with elevation of bone flap; for lobectomy, temporal lobe, with electrocorticography during surgery Craniotomy with elevation of bone flap; for lobectomy, other than temporal lobe, partial or total, with electrocorticography during surgery Stereotactic computer-assisted (navigational) procedure; cranial, intradural	174 GENERALIZED CONVULSIVE OR PARTIAL EPILEPSY WITHOUT MENTION OF IMPAIRMENT OF CONSCIOUSNESS	CPT 61537 (the same come without electrocorticography) appears on line 174. A CCO requested that 61538 be added to the epilepsy surgery line In addition, CPT 61539 is missing from line 174 when all similar codes (61540-61543) appear on that line Lastly, CPT 61781 appears on 6 other lines with intracranial surgery but not on line 174. The same CCO requested consideration of addition to line 174	Add 61538, 61539, and 61781 to line 174
		572 OTHER COMPLICATIONS OF A PROCEDURE	This line contains only diagnoses for minor complications. HERC staff recommends changing the line title to reflect this.	Change the name of line 572 to ~~OTHER~~ MINOR COMPLICATIONS OF A PROCEDURE
I86.1	Scrotal varices	327 FUNCTIONAL AND MECHANICAL DISORDERS OF THE GENITOURINARY SYSTEM INCLUDING BLADDER OUTLET OBSTRUCTION 548 SUBLINGUAL, SCROTAL, AND PELVIC VARICES	ICD-10 I86.1 is on both a covered and an uncovered line with no guideline. Staff recommends removing from lower line to reduce confusion.	Delete I86.1 from line 548 Rename line 548 SUBLINGUAL~~, SCROTAL,~~ AND PELVIC VARICES

Consent Agenda Issues—May 2022

Code	Code Description	Line(s) Involved	Issue	Recommendation(s)
90759	Hepatitis B vaccine (HepB), 3-antigen (S, Pre-S1, Pre-S2), 10 mcg dosage, 3 dose schedule	3 PREVENTION SERVICES WITH EVIDENCE OF EFFECTIVENESS	CPT 90759 was placed on the Excluded File when reviewed as a new code in November, 2021 as it was not in the ACIP/CDC vaccine schedule. The OHA immunization sector staff have notified HERC staff that this vaccine (PreHevbrio) will be on the 2023 ACIP/CDC vaccine schedule as one option for hepatitis B vaccination in adults. This code will need to be opened by June 2022 as CDC plans to allow it for use at that time.	Add 90759 to line 3 Advise HSD to remove 90759 from the Excluded File
47562 47563	Laparoscopy, surgical; cholecystectomy Laparoscopy, surgical; cholecystectomy with cholangiography	641 GALLSTONES WITHOUT CHOLECYSTITIS	Two cholecystectomy codes are missing from line 641.	Add 47562 and 47563 to line 641

COVID-19 Related Codes
May 2022

Issues:

1) CDC and CMS released 3 new ICD-10 codes for COVID vaccination status effective April 1, 2022

2) New HCPCS codes were released for COVID vaccinations done by dentists. There are also 7 HCPCS codes that are already in effect for dentists to use. Staff recommends all of these be placed on line 3. See: https://www.ada.org/-/media/project/ada-organization/ada/ada-org/files/publications/cdt/covid-19_vaccinationprocedurecodeguidance_v2_2022mar.pdf?rev=b7ee2f99437246a8b6188d1f6e35789f&hash=2A13A6E543730634A59B6EA1B6A456DC

3) New CPT codes were released in early May for the Sanofi-GSK vaccine, which will be effective with FDA EUA/approval. Additionally, a new CPT code was released for the booster dose of the new Pfizer tri-sucrose formulation vaccine

4) It has come to HERC staff attention that multiple HCPCS codes have been released for the administration of Evusheld (tixagevimab/cilgavimab), a monoclonal antibody injection for patients who are unable to receive a COVID-19 vaccine for medical reasons or whose immune systems may not respond robustly to COVID-19 vaccination. This therapy should be on line 3 as a preventive measure.

5) There are also HCPCS codes for bebtelovimab and bamlinivimab injections, which are monoclonal antibody products for treatment of COVID. Similar therapies are on line 399 INFLUENZA, COVID-19 AND OTHER NOVEL RESPIRATORY VIRAL ILLNESS

HERC staff recommendations:

1) Advise HSD to place the new COVID-related ICD-10 codes as shown below

ICD-10 Code	Code Description	Recommended Placement
Z28.310	Unvaccinated for COVID-19	Informational File
Z28.311	Partially vaccinated for COVID-19	Informational File
Z28.39	Other under-immunization status [non-COVID vaccines]	Informational File

2) Add the following HCPCS codes to line 3 PREVENTION SERVICES WITH EVIDENCE OF EFFECTIVENESS or line 399 INFLUENZA, COVID-19 AND OTHER NOVEL RESPIRATORY VIRAL ILLNESS

HCPCS Code	Code Description	Recommended Placement
D1708	Pfizer-BioNTech Covid-19 vaccine administration – third dose	3
D1709	Pfizer-BioNTech Covid-19 vaccine administration – booster dose	3
D1710	Moderna Covid-19 vaccine administration – third dose	3
D1711	Moderna Covid-19 vaccine administration – booster dose	3
D1712	Janssen Covid-19 vaccine administration - booster dose	3

COVID-19 Related Codes
May 2022

HCPCS Code	Code Description	Recommended Placement
D1713	Pfizer-BioNTech Covid-19 vaccine administration tris-sucrose pediatric – first dose	3
D1714	Pfizer-BioNTech Covid-19 vaccine administration tris-sucrose pediatric – second dose	3
M0220	Injection, tixagevimab and cilgavimab, for the pre-exposure prophylaxis only, for certain adults and pediatric individuals (12 years of age and older weighing at least 40kg) with no known sars-cov-2 exposure, who either have moderate to severely compromised immune systems or for whom vaccination with any available covid-19 vaccine is not recommended due to a history of severe adverse reaction to a covid-19 vaccine(s) and/or covid-19 vaccine component(s), includes injection and post administration monitoring	3
M0221	Injection, tixagevimab and cilgavimab, for the pre-exposure prophylaxis only, for certain adults and pediatric individuals (12 years of age and older weighing at least 40kg) with no known sars-cov-2 exposure, who either have moderate to severely compromised immune systems or for whom vaccination with any available covid-19 vaccine is not recommended due to a history of severe adverse reaction to a covid-19 vaccine(s) and/or covid-19 vaccine component(s), includes injection 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	3
Q0220	Injection, tixagevimab and cilgavimab, for the pre-exposure prophylaxis only, for certain adults and pediatric individuals (12 years of age and older weighing at least 40kg) with no known sars-cov-2 exposure, who either have moderate to severely compromised immune systems or for whom vaccination with any available covid-19 vaccine is not recommended due to a history of severe adverse reaction to a covid-19 vaccine(s) and/or covid-19 vaccine component(s), 600 mg.	ANCILLARY PROCEDURES FILE
Q0221	Injection, tixagevimab and cilgavimab, for the pre-exposure prophylaxis only, for certain adults and pediatric individuals (12 years of age and older weighing at least 40kg) with no known sars-cov-2 exposure, who either have moderate to severely compromised immune systems or for whom vaccination with any available covid-19 vaccine is not recommended due to a history of severe adverse reaction to a covid-19 vaccine(s) and/or covid-19 vaccine component(s), 300 mg.	ANCILLARY PROCEDURES FILE
Q0222	Injection, bebtelovimab, 175 mg	ANCILLARY PROCEDURES FILE
M0222	Intravenous injection, bebtelovimab, includes injection and post administration monitoring	399

HCPCS Code	Code Description	Recommended Placement
M0223	Intravenous injection, bebtelovimab, includes injection 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
Q0239	Injection, bamlanivimab, 700 mg	ANCILLARY PROCEDURES FILE
M0239	Intravenous infusion, bamlanivimab-xxxx, includes infusion and post administration monitoring	399

3) Add the following CPT codes to line 3 PREVENTION SERVICES WITH EVIDENCE OF EFFECTIVENESS

CPT Code	Code Description	Recommended Placement
91310	Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) (coronavirus disease [COVID-19]) vaccine, monovalent, preservative free, 5 mcg/0.5 mL dosage, adjuvant AS03 emulsion, for intramuscular use	3 PREVENTION SERVICES WITH EVIDENCE OF EFFECTIVENESS *Pending FDA approval/EUA*
0104A	Immunization administration by intramuscular injection of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) (coronavirus disease [COVID-19]) vaccine, monovalent, preservative free, 5 mcg/0.5 mL dosage, adjuvant AS03 emulsion, booster dose	3 *Pending FDA approval/EUA*
0074A	Immunization administration by intramuscular injection of severe acute respiratory syndrome coronavirus 2 (SARS-CoV- 2) (coronavirus disease [COVID-19]) vaccine, mRNA-LNP, spike protein, preservative free, 10 mcg/0.2 mL dosage, diluent reconstituted, tris-sucrose formulation; booster dose	3 PREVENTION SERVICES WITH EVIDENCE OF EFFECTIVENESS

May 2022

Items Discussed with Leadership with No Changes Recommended

1) Yttrium-90 treatment for colorectal cancer metastatic to the liver
    a. In November 2018, this indication was reviewed and not found to have supporting evidence. An AHRQ review from 2012 that found it ineffective for this indication. Sirtex requested a re-review based on two new registry studies. HERC staff literature review found a recently-published RCT (Malcahy 2021) showing no survival benefit with Y-90 compared to conventional chemotherapy for this indication.
2) Breast tomosynthesis (3D Mammography)
    a. Dr. Nathalie Johnson requested a re-review of breast tomosynthesis, which is on line 662/GN173. USPSTF is currently doing an in-depth review of screening modalities for breast cancer, including breast tomosynthesis. HERC staff advised waiting until the USPSTF review is completed before addressing this topic.
3) Equine psychotherapy
    a. Psychotherapy is already covered and uses the same codes whether or not horses are used in the therapeutic setting. Staff review indicates insufficient evidence to support adding hippotherapy for any condition or modality.
4) Prescription therapeutic smart phone apps
    a. This is a new area of medicine with a rapidly developing research base. The MED project is going to undertake a systematic review of this technology in the next year. Freespira requested a review of their app for opioid use treatment. HERC staff advised waiting until the MED review is completed before addressing this topic.
5) Smoking cessation and elective surgery
    a. Dr. Amy Henninger requested that Guideline A4 be deleted because it disproportionately affects people of color and other groups with high smoking rates. This guideline was last reviewed in August 2021, and HERC considered deleting the guideline because of equity concerns and decided against deletion.

Section 5.0

New Discussion Items

Temporary Urethral Stents
May 2022

Plain Language Summary:
Background: Urethral stents are small tubes inserted into the urine duct (ureter) to treat or prevent a blockage that prevents the flow of urine from the kidney to the bladder. Last reviewed in 2015, temporary stents were not covered because there was not enough research to show they worked.

Should OHP cover this treatment? No, there is still not enough data to show benefit for temporary stent use.

Question: Should temporary urethral stents continue to be on line 662/GN173?

Question source: HERC staff

Issue: Temporary urethral stents were last reviewed in 2015 and found to be investigational. The CPT code for placement of such stents (CPT 53855) was placed on line 662/GN173. HERC staff recently identified a HCPCS code for this procedure that was overlooked in the 2015 review and continues to be Ancillary: HCPCS C9769 (Cystourethroscopy, with insertion of temporary prostatic implant/stent with fixation/anchor and incisional struts). Prior to adding this HCPCS code to the GN173 entry, staff re-reviewed the evidence on this topic as it has been more than 5 years since last review.

Temporary stents are designed primarily for short-term use in the treatment of symptomatic benign prostatic hyperplasia (BPH), for a duration of 6 months to 3 years. Temporary stents are made of non-absorbable material, which prevents epithelial ingrowth and therefore allows easy removal. However, this may lead to unintended migration. Some temporary stents are biodegradable, so that they break down into small fragments, which are excreted through the urethra over time. Temporary stents are also very commonly used after urologic procedures, such as stone removal. Alternatives to temporary urethral stents include permanent stents and long-term Foley catherization. Both of these alternatives are covered on the BPH line or as an Ancillary therapy.

CPT 52282 (Cystourethroscopy, with insertion of permanent urethral stent) is on lines 214 CANCER OF KIDNEY AND OTHER URINARY ORGANS, 271 CANCER OF BLADDER AND URETER, 327 FUNCTIONAL AND MECHANICAL DISORDERS OF THE GENITOURINARY SYSTEM INCLUDING BLADDER OUTLET OBSTRUCTION, and 511 BENIGN NEOPLASM OF KIDNEY AND OTHER URINARY ORGANS.

Evidence

1) **Sountoulides 2019**, review of treatment for BPH
    a. Overall, there is a diversity of stents design in terms of length, lumen diameter and material. In addition, the available studies are very small with short follow up, significant attrition rate and different definitions of efficacy. Therefore, there is a lack of robust data.
    b. The only temporary stent reviewed with the Spanner stent, which has two studies (N=30, 43). In the study of 43 men, 63% of the patients had an unsatisfactory outcome due to immediate or delayed retention or elective stent removal because of severe symptoms.

Temporary Urethral Stents
May 2022

Expert guidelines

1) **American Urological Association 2021**, Management of lower urinary tract symptoms attributed to benign prostatic hyperplasia
    a. Does not mention temporary urethral stents in the treatment recommendations

Other payer policies

1) Aetna and Wellmark BCBS consider temporary urethral stents (CPT 53855 and HCPCS C9769) to be investigational

HERC staff recommendations:

1) Add HCPCS C9769 (Cystourethroscopy, with insertion of temporary prostatic implant/stent with fixation/anchor and incisional struts) 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 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
53855 C9769	Temporary prostatic stents	Insufficient evidence of effectiveness	~~October, 2015~~ May 2022

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Current and emerging mechanical minimally invasive therapies for benign prostatic obstruction

Petros Sountoulides, Anastasios Karatzas and Stavros Gravas

Abstract: Transurethral resection of the prostate (TURP) is considered the 'gold standard' for the surgical management of lower urinary tract symptoms (LUTS) due to benign prostatic obstruction (BPO). However, during recent years TURP has been challenged by several minimally invasive therapies (MITs). The reasons for the development of these MITs are the need for anesthesia and the rather unchanged morbidity of TURP, including ejaculation disorders. Mechanical MITs may represent an attractive option for treating LUTS/BPO by using mechanical forces to maintain urethral patency without cutting, ablating, heating or removing prostatic tissue. The present paper provides an update on currently available mechanical devices for the treatment of LUTS/BPO including the prostatic urethral lift (PUL), the temporary implantable nitinol device, and new intraprostatic implants. It analyzes the evidence for their safety, tolerability, and efficacy in clinical practice and aims to define those subpopulations of patients who will benefit from these MITs. It is obvious that there is a wide variation in the degree of mature of the available mechanical MITs. Time and high-quality long-term studies will decide which of these therapies will be accepted by patients and urologists. At the moment, PUL is claiming its position in the armamentarium of BPO treatment.

Keywords: transurethral resection of the prostate, LUTS, benign prostatic obstruction, minimally invasive therapies

Received: 27 August 2018; revised manuscript accepted: 18 December 2018.

Introduction

A variety of minimally invasive therapies (MITs) have been developed to address the limitations and shortcomings of surgery and medical therapy for the management of lower urinary tract symptoms (LUTS) due to benign prostatic obstruction (BPO). Indeed, despite the variety of surgical procedures for BPO, there still exists a large population of men who are not convinced to pursue these options and desire a therapy with minimal surgical risks and fast recovery. The sexual side effects of surgical treatment of BPO, mostly ejaculatory disorders (EjDs), are certainly the more concerning and the ones that mostly discourage patients from opting for surgical treatment.[1] Moreover, living in the era of aging men, there is a substantial population of men bothered by LUTS not responsive to pharmacotherapy who are not medically fit for surgery. MITs aim to offer an alternative solution to these men by providing sustainable improvement in LUTS/BPO while minimizing the risks, complications and adverse events associated with surgery

The hallmarks of a successful MIT include (a) rapid and durable relief from symptoms, (b) fast recovery (c) minimal adverse events, (d) ambulatory setting procedure with minimal anesthesia requirements, which are important determinants for quality of life.[2]

Recently the concept of mechanical devices for the management of LUTS due to BPO has attracted renewed interest with innovative mechanical concepts for de-obstruction of the prostatic urethral lumen while preserving ejaculatory function being introduced with promising early clinical

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Approved by the AUA Board of Directors

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Authors' disclosure of potential conflicts of interest and author/staff contributions appear at the end of the article.

American Urological Association (AUA)

Management of Lower Urinary Tract Symptoms Attributed to Benign Prostatic Hyperplasia: AUA GUIDELINE

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EXECUTIVE SUMMARY

Purpose

Benign prostatic hyperplasia (BPH) is a histologic diagnosis that refers to the proliferation of smooth muscle and epithelial cells within the prostatic transition zone. The prevalence and the severity of lower urinary tract symptoms (LUTS) in the aging male can be progressive and is an important diagnosis in the healthcare of patients and the welfare of society. In the management of bothersome LUTS, it is important that healthcare providers recognize the complex dynamics of the bladder, bladder neck, prostate, and urethra. Further, symptoms may result from interactions of these organs as well as with the central nervous system or other systemic diseases (e.g., metabolic syndrome, congestive heart failure). Despite the more prevalent (and generally first line) use of medical therapy for men suffering from LUTS attributed to BPH (LUTS/BPH), there remain clinical scenarios where surgery is indicated as the initial intervention for LUTS/BPH and should be recommended, providing other medical comorbidities do not preclude this approach. It is the hope that this revised Guideline will provide a useful reference on the effective evidence-based management of male LUTS/BPH. Please see the accompanying algorithm for a summary of the procedures detailed in the Guideline.

Methodology

For the surgical management of BPH, the Minnesota Evidence Review Team searched Ovid MEDLINE, the Cochrane Library, and the Agency for Healthcare Research and Quality (AHRQ) database to identify studies indexed between January 2007 and September 2017. Following initial publication in 2018, this Guideline underwent an amendment in 2019 that included literature published through January 2019. An additional literature search was conducted through September 2019 and serves as the basis for a 2020 amendment. The Guideline underwent an additional amendment in 2021 to capture eligible literature published between September 2019 and September 2020.

For the medical management of BPH, the Minnesota Evidence Review Team searched Ovid MEDLINE, Embase, the Cochrane Library, and the AHRQ databases to identify eligible studies published and indexed between January 2008 and April 2019. An updated search was completed to capture studies published between April 2019 and December 2020. Search terms included Medical Subject Headings (MeSH) and keywords for pharmacological therapies, drug classes, and terms related to LUTS or BPH. Limits were used to restrict the search to English language publications. The review team also reviewed articles for inclusion identified by Guideline Panel Members.

When sufficient evidence existed, the body of evidence was assigned a strength rating of A (high), B (moderate), or C (low) for support of Strong, Moderate, or

Fecal Lactoferrin

Plain Language Summary:
Background: Fecal lactoferrin is a stool test to help diagnose the cause of bowel problems. The test can show if a person has Crohn's disease or ulcerative colitis or if the symptoms are from irritable bowel syndrome. It is a useful test when a person has certain symptoms like stomach pain and diarrhea without other problems such as unexplained weight loss or bleeding.

Should OHP cover fecal lactoferrin? Staff recommends OHP covering this test because it helps to rule out inflammatory bowel disease in patients who present with certain stomach and intestine symptoms; one type of this test is already covered.

Question: Should fecal lactoferrin be added as a diagnostic test?

Question source: Douglas Carr, CCO medical director

Issue: Fecal lactoferrin is a stool test that is used to help distinguish inflammatory bowel diseases (Crohn's disease and ulcerative colitis) from irritable bowel syndrome. It has also been proposed as a non-invasive test to monitor disease activity in patients already diagnosed with inflammatory bowel disease.

From the Wellmark coverage summary (2022):

> Fecal lactoferrin testing is very useful when a patient presents with nonspecific GI symptoms, such as abdominal pain and diarrhea, especially without evidence of alarm symptoms of weight loss or GI bleeding. These non-specific symptoms could be due to a functional etiology, such as IBS, or from IBD or GI infections. If the patient's fecal lactoferrin level is undetectable, low, or normal, the symptoms are not likely to be related to inflammation or infection and are more likely to be functional. On the other hand, a high fecal lactoferrin level should prompt an evaluation for either IBD (Crohn's disease or ulcerative colitis) or infectious etiologies through stool panel testing, colonoscopy, or both. With low fecal lactoferrin levels, the need for further workup can be reduced or avoided, and health care costs in the long run can potentially be lowered.

Currently, the qualitative test (CPT 83630) is on the Diagnostic Procedures File and the quantitative test (CPT 83631) is on line 662/GN173 with a date of last review of 2006. Dr. Carr has requested a review of CPT 83631 as it is being requested by providers in his CCO.

Current Prioritized List status:
83630 Lactoferrin, fecal; qualitative—Diagnostic Procedures File
83631 Lactoferrin, fecal; quantitative—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:

Fecal Lactoferrin

Procedure Code	Intervention Description	Rationale	Last Review
83631	Lactoferrin, fecal; quantitative	Insufficient evidence of effectiveness	January 2006

Fecal Lactoferrin

Evidence

1) **Wang 2015**, meta-analysis of diagnostic accuracy of fecal lactoferrin for inflammatory bowel disease
    a. N=7 studies (1816 patients)
        i. Compared fecal lactoferrin to colonoscopy findings as reference standard
    b. pooled FL sensitivity and pooled specificity were 0.82 (95% confidence interval [CI]: 0.72, 0.89) and 0.95 (95% CI: 0.88, 0.98), respectively.
    c. The positive and negative likelihood ratios were 16.63 and 0.18, respectively.
    d. The area under the summary receiver-operating characteristic curve (SROC) was 0.95 (95% CI: 0.93, 0.97), and the diagnostic odds ratio was 90.04 (95% CI: 37.01, 219.02).
    e. The pooled FL sensitivity and specificity for Crohn's disease (CD) diagnosis (sensitivity =75%, specificity =100%) was not as good as it was for ulcerative colitis (UC) diagnosis (sensitivity =82%, specificity =100%).
    f. Conclusion: our results indicate that FL is an inexpensive, simple, stable and useful screening marker with high specificity and modest sensitivity for differentiating between IBD and functional disorders, appearing to have greater ability to evaluate UC rather than CD
2) **Mosli 2015**, systematic review and meta-analysis of stool lactoferrin for detection of IBD disease activity
    a. N=19 studies (N=2499 patients)
        i. Various tests vs colonoscopy as the reference standard in patients with symptoms consistent with active IBD
    b. The pooled sensitivity and specificity estimates for SL [was] 0.82 (95% CI 0.73–0.88) and 0.79 (95% CI 0.62–0.89)
    c. CONCLUSIONS: Although CRP, FC, and SL are useful biomarkers, their value in managing individual patients must be considered in specific clinical contexts

Expert recommendations

1) **American College of Gastroenterology 2018**: guideline for management of Crohn's disease
    a. Monitoring disease activity
        i. Fecal calprotectin and fecal lactoferrin measurements may have an adjunctive role in monitoring disease activity.
2) **American College of Gastroenterology 2019**: guideline for management of ulcerative colitis
        i. Not included in recommendations

Other payer policies

1) Aetna 2022
    a. Aetna considers fecal lactoferrin medically necessary for distinguishing inflammatory bowel diseases (Crohn's disease, ulcerative colitis) from irritable bowel syndrome. Aetna considers fecal lactoferrin experimental and investigational for evaluation of infectious diarrhea, Clostridium difficile infection, and all other indications.

2) Cigna 2022
    a. Considered Experimental/Investigational/Unproven when used to report testing for serological and/or genetic markers for the diagnosis or management of inflammatory bowel disease:
        i. All other tests (include fecal lactoferrin)

3) Wellmark BCBS 2022

a. Fecal Lactoferrin Fecal measurement of lactoferrin may be considered medically necessary in one of the following:
    i. Establishing the diagnosis Crohn's disease; or
    ii. Establishing the diagnosis ulcerative colitis (UC); or
    iii. To assess the response to therapy and/or relapse in Crohn's disease; or
    iv. To assess the response to therapy and/or relapse in ulcerative colitis (UC)
b. Fecal measurement of lactoferrin is considered not medically necessary including but not limited to the following:
    i. When not used in decision making or diagnosis for Crohn's disease as indicated above
    ii. When not used in decision making or diagnosis for ulcerative colitis (UC) as indicated above
c. BCBS TEC summary of review as quoted in the Wellmark policy:
    i. In summary, numerous studies have evaluated the ability of fecal calprotectin and fecal lactoferrin testing to distinguish between patients with inflammatory bowel disease and non-inflammatory bowel disease, the FDA-approved indication for the fecal calprotectin and lactoferrin test. Generally, studies have shown that the fecal calprotectin and lactoferrin test is reasonably accurate for this purpose when used in an appropriate patient population; that is, patients with clinical suspicion of inflammatory bowel disease based on examination and history. Specifically, in the scenario where an endoscopy is planned and could possibly be avoided based on calprotectin testing results. The evidence is sufficient to determine that the technology results in an approvement in the net health outcomes

Utilization:
CPT 83630 (Lactoferrin, fecal; qualitative), which is currently diagnostic, had approximately 500 paid claims in 2020, paired with a variety of diagnoses such as diarrhea

The average reimbursement for CPT 83630 was approximately $14

Fecal Lactoferrin

HERC staff summary

Fecal lactoferrin appears to be a useful test to help rule out inflammatory bowel disease in patients who present with non-specific GI symptoms. It is less useful in the management of patients already diagnosed with inflammatory bowel disease. Most major insurers are covering this test. There are two types of these tests, and one is currently diagnostic and the other non-covered, which needs to be clarified. The qualitative code is being used quite extensively and no reason was identified by HERC staff to cover the qualitative but not the quantitative test.

HERC staff recommendations:

1) Remove 83631 Lactoferrin, fecal; quantitative from Line 662 CONDITIONS FOR WHICH CERTAIN INTERVENTIONS ARE UNPROVEN, HAVE NO CLINICALLY IMPORTANT BENEFIT OR HAVE HARMS THAT OUTWEIGH BENEFITS
    a. Advise HSD to place CPT 83631 on the Diagnostic Procedures File
2) Delete the GN173 entry for CPT 83631

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
~~83631~~	~~Lactoferrin, fecal; quantitative~~	~~Insufficient evidence of effectiveness~~	~~January 2006~~

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Original Article

Diagnostic accuracy of fecal lactoferrin for inflammatory bowel disease: a meta-analysis

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Abstract: Objective: To do a systematic review using meta-analysis to assess the diagnostic accuracy of fecal lactoferrin (FL) in patients with inflammatory bowel disease (IBD). Methods: We performed a literature review and systematically searched the Medline and EMBASE databases for eligible studies. The quality of the included studies was assessed using the QUADAS tool. The sensitivity, specificity, and other diagnostic indexes of FL were pooled using a random-effects model. Results: Seven studies, involving 1816 patients, met the inclusion criteria. In all studies, the pooled FL sensitivity and pooled specificity were 0.82 (95% confidence interval [CI]: 0.72, 0.89) and 0.95 (95% CI: 0.88, 0.98), respectively. The positive and negative likelihood ratios were 16.63 and 0.18, respectively. The area under the summary receiver-operating characteristic curve (SROC) was 0.95 (95% CI: 0.93, 0.97), and the diagnostic odds ratio was 90.04 (95% CI: 37.01, 219.02). The pooled FL sensitivity and specificity for Crohn's disease (CD) diagnosis (sensitivity =75%, specificity =100%) was not as good as it was for ulcerative colitis (UC) diagnosis (sensitivity =82%, specificity =100%). Conclusion: FL, as a noninvasive and screening marker, has a high specificity and a modest specificity during the diagnosis of suspected IBD.

Keywords: Fecal lactoferrin, inflammatory bowel disease, ulcerative colitis, Crohn's disease meta-analysis

Introduction

Inflammatory bowel disease (IBD), i.e., Crohn's disease (CD) and ulcerative colitis (UC), are chronic, nonspecific, and relapsing inflammatory conditions affecting varying layers of the gastrointestinal (GI) tract with a poor prognosis. In routine clinical practice, early and accurate diagnosis of IBD is essential for optimal treatment and the avoidance of surgery. The conventional diagnostic approaches to symptoms of IBD are based on a combination of clinical symptoms, colonoscopy, biopsy, radiologic techniques and serological markers. An endoscopy with biopsies remains the accepted gold standard for detecting and quantifying bowel inflammation [1, 2].

Although considered the current standard for evaluation of intestinal inflammation, these techniques create a heavy socioeconomic burden because they can be embarrassing, painful, invasive, costly and time-consuming for the patient [3, 4].

Therefore, in clinical practice, a simple, rapid, inexpensive, and noninvasive marker for screening and monitoring IBD is greatly needed.

With that in mind, several markers of the leukocyte proteins in feces, especially calprotectin (Cal) and lactoferrin (Lf), have been increasingly studied because of their non-invasive qualities [5].

Cal is a calcium and zinc binding protein and cytoplasmic antimicrobial component prominent in granulocytes, monocytes, and macrophages. Fetal calprotectin (FC) concentration reflects neutrophil migration in the intestines of IBD patients and helps to distinguish IBD from non-inflammatory bowel conditions, and, during remission, to predict an IBD patient's clinical relapse [6-10].

Lf is an iron-binding protein secreted by most mucosal membranes that is found in various secretions, such as saliva, breast milk, tears,

REVIEW

C-Reactive Protein, Fecal Calprotectin, and Stool Lactoferrin for Detection of Endoscopic Activity in Symptomatic Inflammatory Bowel Disease Patients: A Systematic Review and Meta-Analysis

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OBJECTIVES: **Persistent disease activity is associated with a poor prognosis in inflammatory bowel disease (IBD). Therefore, monitoring of patients with intent to suppress subclinical inflammation has emerged as a treatment concept. As endoscopic monitoring is invasive and resource intensive, identification of valid markers of disease activity is a priority. The objective was to evaluate the diagnostic accuracy of C-reactive protein (CRP), fecal calprotectin (FC), and stool lactoferrin (SL) for assessment of endoscopically defined disease activity in IBD.**

METHODS: **Databases were searched from inception to November 6, 2014 for relevant cohort and case-control studies that evaluated the diagnostic accuracy of CRP, FC, or SL and used endoscopy as a gold standard in patients with symptoms consistent with active IBD. Sensitivities and specificities were pooled to generate operating property estimates for each test using a bivariate diagnostic meta-analysis.**

RESULTS: **Nineteen studies (*n*=2499 patients) were eligible. The pooled sensitivity and specificity estimates for CRP, FC, and SL were 0.49 (95% confidence interval (CI) 0.34–0.64) and 0.92 (95% CI 0.72–0.96), 0.88 (95% CI 0.84–0.90) and 0.73 (95% CI 0.66–0.79), and 0.82 (95% CI 0.73–0.88) and 0.79 (95% CI 0.62–0.89), respectively. FC was more sensitive than CRP in both diseases and was more sensitive in ulcerative colitis than Crohn's disease.**

CONCLUSIONS: **Although CRP, FC, and SL are useful biomarkers, their value in managing individual patients must be considered in specific clinical contexts.**

SUPPLEMENTARY MATERIAL is linked to the online version of the paper at http://www.nature.com/ajg

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BACKGROUND

Inadequate control of inflammation in patients with inflammatory bowel disease (IBD) is associated with a poor prognosis (1,2). Accordingly, in recent years, a "treat to target" concept has emerged whereby therapy is intensified until a well-defined goal is achieved (3). Symptomatic remission has traditionally been used as the target; however, this approach is problematic as symptoms are often due to causes other than inflammation (4–9). Therefore, management based exclusively on symptoms can lead to inappropriate use of corticosteroids, immunosuppressives, or biologics with an attendant risk of serious adverse events (10).

Although endoscopy remains the gold standard for assessment of disease activity in IBD, it is not ideal for multiple reasons that

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CME

ACG Clinical Guideline: Management of Crohn's Disease in Adults

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Crohn's disease is an idiopathic inflammatory disorder of unknown etiology with genetic, immunologic, and environmental influences. The incidence of Crohn's disease has steadily increased over the past several decades. The diagnosis and treatment of patients with Crohn's disease has evolved since the last practice guideline was published. These guidelines represent the official practice recommendations of the American College of Gastroenterology and were developed under the auspices of the Practice Parameters Committee for the management of adult patients with Crohn's disease. These guidelines are established for clinical practice with the intent of suggesting preferable approaches to particular medical problems as established by interpretation and collation of scientifically valid research, derived from extensive review of published literature. When exercising clinical judgment, health-care providers should incorporate this guideline along with patient's needs, desires, and their values in order to fully and appropriately care for patients with Crohn's disease. This guideline is intended to be flexible, not necessarily indicating the only acceptable approach, and should be distinguished from standards of care that are inflexible and rarely violated. To evaluate the level of evidence and strength of recommendations, we used the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) system. The Committee reviews guidelines in depth, with participation from experienced clinicians and others in related fields. The final recommendations are based on the data available at the time of the production of the document and may be updated with pertinent scientific developments at a later time.

SUPPLEMENTARY MATERIAL is linked to the online version of the paper at http://www.nature.com/ajg

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INTRODUCTION

Crohn's disease has been increasing in incidence and prevalence worldwide. At the same time, the number of therapeutic options is rapidly increasing. The purpose of this guideline is to review Crohn's disease clinical features and natural history, diagnostics, and therapeutic interventions.

To prepare this guideline, literature searches on the different areas were conducted using Ovid MEDLINE from 1946 to 2018, EMBASE from 1988 to 2018, and SCOPUS from 1980 to 2018. The major terms that were searched were Crohn's disease, inflammatory bowel diseases (IBD), regional ileitis, and regional enteritis. These were translated into EMTREE controlled vocabulary as enteritis and Crohn's disease. The remainder of the search included key words related to the subject area that included clinical features, natural history, diagnosis, biomarkers, treatment, and therapy. For each of the therapeutic sections, key words included the individual drug names. The results used for analysis were limited to primary clinical trials, meta-analyses, systematic reviews, and prior guidelines. Where there were limited data, abstracts were used. In many areas reviewed, there were not available clinical trial data, and these areas are discussed as summary statements rather than GRADE statements.

To evaluate the level of evidence and strength of recommendations, we used the Grading of Recommendations Assessment,

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ACG Clinical Guideline: Ulcerative Colitis in Adults

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Ulcerative colitis (UC) is an idiopathic inflammatory disorder. These guidelines indicate the preferred approach to the management of adults with UC and represent the official practice recommendations of the American College of Gastroenterology. The scientific evidence for these guidelines was evaluated using the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) process. In instances where the evidence was not appropriate for GRADE, but there was consensus of significant clinical merit, "key concept" statements were developed using expert consensus. These guidelines are meant to be broadly applicable and should be viewed as the preferred, but not only, approach to clinical scenarios.

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INTRODUCTION

Ulcerative colitis (UC) is a chronic disease affecting the large intestine, with an increasing incidence worldwide. Nearly 1 million individuals each in the United States and Europe are affected by this condition and many more globally. Over the past decade, since the publication of the last guideline from the American College of Gastroenterology (ACG) on this topic, the management of disease has grown increasingly complex with availability of additional therapeutic classes. In addition, algorithms for initiating, optimizing, and monitoring response to existing therapies have undergone considerable evolution.

UC is a chronic immune-mediated inflammatory condition of the large intestine that is frequently associated with inflammation of the rectum but often extends proximally to involve additional areas of the colon. The absence of rectal involvement has been noted in fewer than 5% of adult patients with UC at diagnosis but may be seen in up to one-third of pediatric-onset colitis (1). The initial presentation of new UC is characterized by symptoms of an inflamed rectum, namely, bleeding, urgency, and tenesmus (a sense of pressure). The condition may present at any time and at all ages, but there is a predominant age distribution of onset that peaks between ages 15 and 30 years. The pattern of disease activity is most often described as relapsing and remitting, with symptoms of active disease alternating with periods of clinical quiescence, which is called remission. Some patients with UC have persistent disease activity despite diagnosis and medical therapy, and a small number of patients present with the rapid-onset progressive type of colitis known as fulminant disease (2,3).

UC causes significant morbidity and a described low incidence of mortality (4,5). Patients with active disease are more likely to have comorbid psychological conditions of anxiety and depression and are more likely to have impaired social interactions or career progression (6). Long-standing UC is also associated with a defined risk of dysplasia and colorectal cancer, which is believed to be related to long-standing unchecked inflammation (7–10).

Management of UC must involve a prompt and accurate diagnosis, assessment of the patient's risk of poor outcomes, and initiation of effective, safe, and tolerable medical therapies. The optimal goal of management is a sustained and durable period of steroid-free remission, accompanied by appropriate psychosocial support, normal health-related quality of life (QoL), prevention of morbidity including hospitalization and surgery, and prevention of cancer. An emerging goal in UC management is that of mucosal healing. To achieve these goals, understanding of the most effective diagnostic, treatment, and preventive strategies is necessary (11). As with any medical decision making, involvement of the patients' preferences forms an important component of care.

This clinical guideline addresses the diagnosis, treatment, and overall management of adult patients with UC, including an approach to the evaluation of the hospitalized patient and a separate section on colorectal cancer prevention. Additional recommendations regarding preventive care in inflammatory bowel disease (IBD) have been published by the ACG previously (12).

The guideline is structured in sections, each with recommendations, key concept statements, and summaries of the evidence. Each recommendation statement has an associated assessment of the quality of evidence and strength of recommendation based on the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) process. The GRADE system was used to evaluate the quality of supporting evidence (Table 1) (13). A "strong" recommendation is made when the benefits clearly outweigh the negatives and/or the result of no action. "Conditional" is used when some uncertainty remains about the balance of benefits and potential harms. The quality of the evidence is graded from high to low. "High"-quality evidence indicates that further research is unlikely to change the authors' confidence in the estimate of effect and that we are very confident that the true effect

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lies close to that of the estimate of the effect. "Moderate"-quality evidence is associated with moderate confidence in the effect estimate, although further research would be likely to have an impact on the confidence of the estimate, whereas "low"-quality evidence indicates that further study would likely have an important impact on the confidence in the estimate of the effect and would likely change the estimate. "Very low"–quality evidence indicates very little confidence in the effect estimate and that the true effect is likely to be substantially different than the estimate of effect.

Key concepts are statements that are not amenable to the GRADE process, either because of the structure of the statement or because of the available evidence. In some instances, key concepts are based on extrapolation of evidence and/or expert opinion.

Tables 2 and 3 summarize the GRADED recommendations and key concept statements in this guideline.

DIAGNOSIS, ASSESSMENT, AND PROGNOSIS OF ULCERATIVE COLITIS

Key concept statements

1. The diagnosis of UC should be suspected in patients with hematochezia and urgency.
2. Infectious etiologies should be excluded at the time of diagnosis.
3. Colonoscopy with intubation of the ileum and biopsies of affected and unaffected areas should be obtained to confirm the diagnosis of UC by a trained pathologist with expertise in gastrointestinal pathology when possible.
4. Categories of disease extent include (i) proctitis (within 18 cm of the anal verge, distal to the rectosigmoid junction), (ii) left-sided colitis (extending from the sigmoid to the splenic flexure), and (iii) extensive colitis (beyond the splenic flexure).
5. If the terminal ileum is normal, further evaluation of the stomach and small bowel by upper endoscopy and cross-sectional imaging is not needed unless there are other symptoms or findings to suggest proximal GI involvement or a diagnosis of Crohn's disease (CD) rather than UC.
6. Definitions of disease severity are needed to guide treatment decisions; definitions should be based on (i) patient-reported outcomes (PROs) (bleeding and normalization of bowel habits), (ii) inflammatory burden (endoscopic assessment including extent and severity and markers of inflammation), (iii) disease course (need for hospitalization, need for steroids, and failure to respond to medications), and (iv) disease impact (functionality and QoL).
7. Fecal calprotectin (FC) can be used in patients with UC as a noninvasive marker of disease activity and to assess response to therapy and relapse.

Recommendations

1. We recommend stool testing to rule out *Clostridioides difficile* (*C. diff*) in patients suspected of having UC (strong recommendation, very low quality of evidence).
2. We recommend against serologic antibody testing to establish or rule out a diagnosis of UC (strong recommendation, very low quality of evidence).
3. We recommend against serologic antibody testing to determine the prognosis of UC (strong recommendation, very low quality of evidence).

Summary of evidence Symptoms of bloody diarrhea, mucous, urgency, tenesmus, and abdominal cramping should trigger consideration of a UC diagnosis, particularly in the absence of an alternate cause. A full clinical history should include assessment

Table 1. Quality assessment criteria[a]

Study design	Quality of evidence	Lower if	Higher if
Randomized trial	High	Risk of bias	Large effect
		−1 serious	+1 large
		−2 very serious	+2 very large
	Moderate	Inconsistency	Dose-response
		−1 serious	+1 evidence of a gradient
		−2 very serious	
		Indirectness	All plausible confounding
		−1 serious	+1 would reduce a demonstrated effect or
		−2 very serious	+1 would suggest a spurious effect when results show no effect
Observational trial	Low	Imprecision	
		−1 serious	
		−2 very serious	
	Very low	Publication bias	
		−1 likely	
		−2 very likely	

[a]See Reference 13.

Gastric Neurostimulators

Plain Language Summary:
Background: Gastric neurostimulators are an implanted device used for diabetic stomach problems known as gastroparesis. Gastroparesis is a condition where the normal movement of food from the stomach to the small intestine is drastically slowed or has stopped. The devices have a limited form of FDA approval as a Humanitarian Use Device.

Should OHP cover gastric neurostimulators? Staff recommends OHP covering them. Though there are limited studies, evidence was found that for patients who were not able to take medication. Covering this would standardize the coordinated care organization review process for exceptions.

Question: Where should gastric neurostimulators be placed on the Prioritized List?

Question source: Holly Jo Hodges, CCO medical director

Issue: Gastric neurostimulators were removed from line 662/GN173 in October 2020 and placed in the Excluded File due to the fact that they did not have full FDA approval (humanitarian use approval only). Recently, a provider requested authorization to use a gastric neurostimulator and the relevant CCO requested HERC review of this technology.

Gastroparesis is a condition in which the normal movement of food from the stomach to the small intestine is drastically slowed or has stopped. This can lead to nausea and vomiting. Gastroparesis is frequently associated with diabetes. Gastric electrical stimulation (GES) is a treatment that sends weak electrical signals to the nerves and smooth muscles in the lower stomach. This treatment helps decrease nausea and vomiting caused by gastroparesis. A small battery-powered device is surgically placed in the skin in the lower belly area. Wires are then placed in the area to be stimulated.

Alternative treatments for gastroparesis include eating small meals, avoiding fizzy or high fiber foods, medications that stimulate stomach activity such as metoclopramide or domperidone, gastric or jejunostomy tube feeding, or parenteral nutrition.

Current FDA approval status: Humanitarian Device Exemption (HDE). This means that the FDA has found that the device "will not expose patients to an unreasonable or significant risk of illness or injury, and the probable benefit to health from using the device outweighs the risk of illness or injury." HUD devices are exempt from FDA effectiveness requirements and in many cases cannot be sold for profit.

Current Prioritized List status
The following codes are on the Excluded File:
CPT 43647 Laparoscopy, surgical; implantation or replacement of gastric neurostimulator electrodes, antrum
CPT 43648 Laparoscopy, surgical; revision or removal of gastric neurostimulator electrodes, antrum
CPT 43881 Implantation or replacement of gastric neurostimulator electrodes, antrum, open
CPT 43882 Revision or removal of gastric neurostimulator electrodes, antrum, open
HCPCS E0765 FDA approved nerve stimulator, with replaceable batteries, for treatment of nausea

ICD-10-CM K31.84 (Gastroparesis) is on line 529 DISORDERS OF FUNCTION OF STOMACH AND OTHER FUNCTIONAL DIGESTIVE DISORDERS

ICD-10-CM E11.43 (Type 2 diabetes mellitus with diabetic autonomic (poly)neuropathy) has the subdiagnosis of “Type 2 diabetes mellitus with diabetic gastroparesis” and is on line 27 TYPE 2 DIABETES MELLITUS

ICD-10-CM E10.43 (Type 1 diabetes mellitus with diabetic autonomic (poly)neuropathy) has the subdiagnosis of “Type 1 diabetes mellitus with diabetic gastroparesis” and is on line 8 TYPE 1 DIABETES MELLITUS

Evidence

1) **NICE 2014** Gastroelectrical stimulation for gastroparesis
    a. Current evidence on the efficacy and safety of gastric electrical stimulation for gastroparesis is adequate to support the use of this procedure
    b. Efficacy
        i. A meta-analysis of 4 studies including 169 patients with diabetic gastroparesis treated by gastroelectrical stimulation (part of a systematic review of 601 patients) reported improvement in total symptom severity score (weighted mean difference 8.96 [95% confidence interval {CI} 6.1 to 11.8]; p<0.00001) and a statistically significant improvement in gastric emptying at 4 hours (assessed using standardised radionucleotide scans of a solid meal: weighted mean difference 13.0 [95% CI 7.4 to 18.6]; p<0.00001). Subgroup analysis showed that the improvement was statistically significant in patients with diabetic or idiopathic gastroparesis but not in patients with post-surgical gastroparesis
        ii. A meta-analysis of 3 studies including 58 patients with idiopathic gastroparesis treated by gastroelectrical stimulation reported improvement in total symptom severity score (weighted mean difference 7.5 [95% CI 5.4 to 9.7]; p<0.00001).
        iii. In a systematic review of 364 patients, a meta-analysis of 4 studies including 75 patients with gastroparesis treated by gastroelectrical stimulation reported no statistically significant change in weight (weighted mean difference 3.7 [95% CI −0.2 to 7.6])
        iv. In the systematic review of 364 patients, a meta-analysis of 8 studies including 184 patients with gastroparesis treated by gastroelectrical stimulation reported a reduction in need for nutritional support from 44% (96/216) of patients at baseline to 11% (21/184) at follow-up (odds ratio 5.5 [95% CI 2.8 to 11.1]; p<0.00001)
    c. Safety
        i. Death (within 30 days) was reported in 3% (2/72) of patients treated by gastroelectrical stimulation, due to small bowel infarction and heart failure, and 3% (1/31) of patients treated by gastrectomy, due to myocardial infarction, in a comparative case series of 103 patients
        ii. Gastric perforation related to an episode of vomiting (2 months after the procedure) was reported in 1 patient in a case series of 17 patients. The device was removed and the perforation was repaired.
        iii. Device removal was reported in 11% (24/221) of patients in a case series of 221 patients (timing ranged from 1–43 months after the procedure). Reasons were infection at the pulse generator or electrode sites (13 patients), lack of symptom improvement (6 patients), lead dislodgements (2 patients), small bowel obstruction caused by wires (1 patient), penetration of electrode into the lumen of the stomach (1 patient) and 'associated with peptic ulcer disease' (1 patient)
2) **Ducrotte 2020**, randomized crossover study of gastric electrical stimulation for reducing refractory vomiting
    a. N=172 patients (133 with gastroparesis) with chronic vomiting related to diabetes or post-surgical
    b. All patients has GES inserted, half were randomized to have immediate activation and half randomized to a 4 month delay in activation
    c. Vomiting was measured on a 5 point scale from 0 (several vomiting episodes a day) to 4 (no vomiting)

d. vomiting scores were higher (improved) in the group with the device on (median score, 2) than the control group (median score, 1; P < .001), in diabetic and nondiabetic patients. Vomiting scores increased (improved) significantly when the device was ON in patients with delayed (P < .01) or normal gastric emptying (P = .05). Gastric emptying was not accelerated during the ON period compared with the OFF period. Having the GES turned on was not associated with increased quality of life
e. A total of 101 adverse events were reported in the study, with 45 therapy or device - related events: abdominal wall pain at the implantation site (n = 28), infections at the abdominal pouch level (n = 16), hematoma (n =1). In 3 cases, the device-related adverse events were serious enough to prompt device removal.

Expert guidelines

1) **American Gastroenterology Association 2022**, practice update on the management of medically refractory gastroparesis
    a. Clinicians can consider gastric electrical stimulation for gastroparesis patients with refractory/intractable nausea and vomiting who have failed standard therapy and are not on opioids and do not have abdominal pain as the predominant symptom
        i. GES does improve refractory nausea and vomiting in some patients with gastroparesis and may improve glycemic control, nutritional status, and quality of life, while reducing hospitalizations and medication use

Other payer policies

1) Premera BCBS 2021
    a. Gastric electrical stimulation may be considered medically necessary in the treatment of chronic, intractable nausea and vomiting secondary to gastroparesis of diabetic or idiopathic etiology when ALL of the following criteria are met:
        i. Significantly delayed gastric emptying as documented by standard scintigraphic imaging of solid food AND
        ii. Patient is refractory or intolerant of prokinetic medications and antiemetic medications AND
        iii. Patient's nutritional status is sufficiently low that total parenteral nutrition is likely to become medically necessary
    b. Gastric electrical stimulation is investigational for the treatment of obesity and all other indications

2) Cigna 2021
    a. Permanent gastric electrical stimulation (GES) or gastric pacing (e.g., Enterra™ Therapy) is considered medically necessary when provided in accordance with the Humanitarian Device Exemption (HDE) specifications of the U.S. Food and Drug Administration (FDA) for intractable nausea and vomiting secondary to gastroparesis with failure, contraindication, or intolerance of pharmaceutical therapy.
    b. Gastric electrical stimulation (GES) or gastric pacing for any other indication is considered experimental, investigational or unproven

Gastric Neurostimulators

HERC staff summary

Gastric electrical stimulation has a limited literature, and newer studies tend to find that GES reduces vomiting but does not improve quality of life. One highly trusted source (NICE) found the evidence sufficient for coverage. Most private insurance covers these devices for patients with diabetic or idiopathic (not post-surgical) gastroparesis who fail or are not able to tolerate medications.

Currently, idiopathic gastroparesis is on an uncovered line while diabetic gastroparesis is on the covered type 1 and type 2 diabetes lines. Addition of GES procedure codes and a new guideline would allow standardization of review in the exceptions process for CCOs for the uncovered diagnosis.

HERC staff recommendations:

1) Add the following codes to lines 8 TYPE 1 DIABETES MELLITUS, 27 TYPE 2 DIABETES MELLITUS and 529 DISORDERS OF FUNCTION OF STOMACH AND OTHER FUNCTIONAL DIGESTIVE DISORDERS
    a. CPT 43647 Laparoscopy, surgical; implantation or replacement of gastric neurostimulator electrodes, antrum
    b. CPT 43648 Laparoscopy, surgical; revision or removal of gastric neurostimulator electrodes, antrum
    c. CPT 43881 Implantation or replacement of gastric neurostimulator electrodes, antrum, open
    d. CPT 43882 Revision or removal of gastric neurostimulator electrodes, antrum, open
    e. HCPCS E0765 FDA approved nerve stimulator, with replaceable batteries, for treatment of nausea
2) Advise HSD to remove the above codes from the Excluded File
3) Adopt a new guideline for lines 8, 27, and 529 as shown below

GUIDELINE NOTE XXX GASTRIC ELECTRICAL STIMULATION

Line 8, 27,529

Gastric electrical stimulation (CPT 43657, 43648, 43881, 43882) is included on these lines only for pairing with diabetic gastroparesis (ICD-10-CM E10.43, E11.43) or idiopathic gastroparesis (ICD-10-CM K31.84) and only when ALL of the following criteria are met:

1) The patient has intractable nausea and vomiting secondary to gastroparesis of diabetic or idiopathic etiology; AND
2) The patient is refractory or intolerant of prokinetic medications and antiemetic medications; AND
3) The patient is not on opioid medications; AND
4) The patient does not have abdominal pain as the predominant symptom.

Gastroelectrical stimulation for gastroparesis

Interventional procedures guidance
Published: 28 May 2014
www.nice.org.uk/guidance/ipg489

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.

This guidance replaces IPG103.

1 Recommendations

This document replaces previous guidance on gastroelectrical stimulation (interventional procedure guidance 103).

1.1 Current evidence on the efficacy and safety of gastric electrical stimulation for gastroparesis is adequate to support the use of this procedure with normal arrangements for clinical governance, consent and audit.

1.2 During the consent process, clinicians should inform patients considering gastric electrical stimulation for gastroparesis that some patients do not get any benefit from it. They should also give patients detailed written information about the risk of complications, which can be serious, including the need to remove the device.

1.3 Patient selection and follow-up should be done in specialist gastroenterology units with expertise in gastrointestinal motility disorders, and the procedure should only be performed by surgeons working in these units.

1.4 Further publications providing data about the effects of the procedure on symptoms in the long term and on device durability would be useful.

2 Indications and current treatments

2.1 Gastroparesis is a chronic disorder in which the stomach empties more slowly than normal (delayed gastric emptying) in the absence of any type of mechanical obstruction. The most common symptoms are nausea and protracted vomiting. Other symptoms include abdominal bloating, and, in severe cases, malnutrition.

2.2 Gastroparesis most commonly occurs in people with type 1 diabetes. It can also occur in other situations such as after abdominal surgery or in association with anorexia nervosa and abdominal migraine. Some cases are idiopathic. Conservative treatment options include modification of dietary intake and medical therapy with antiemetics or prokinetics. Treatment options for chronic intractable (drug-refractory) symptoms include jejunostomy tube insertion for feeding, gastrostomy tube insertion for stomach decompression, and pyloroplasty.

2.3 Gastroelectrical stimulation is an option for treating chronic, intractable nausea and vomiting secondary to gastroparesis.

3 The procedure

3.1 Electrical stimulation is delivered via an implanted system that consists of a neurostimulator and 2 leads. Implantation is done with the patient under general anaesthesia by an open or laparoscopic approach. The stimulating electrode of each intramuscular lead is fixed to the muscle of the distal part of the stomach. The connector end of each lead is then attached to the neurostimulator, which is placed in a pocket in the abdominal wall. When the neurostimulator is turned on, electrical impulses are delivered. The rate and amplitude of stimulation can be adjusted wirelessly with a hand-held external programmer. Patients may need to return to hospital for adjustment or reprogramming of the device, to optimise the effect on gastric emptying.

4 Efficacy

This section describes efficacy outcomes from the published literature that the Committee considered as part of the evidence about this procedure. For more detailed information on the evidence, see the interventional procedure overview.

4.1 A meta-analysis of 4 studies including 169 patients with diabetic gastroparesis treated by gastroelectrical stimulation (part of a systematic review of 601 patients) reported improvement in total symptom severity score (weighted mean difference 8.96 [95% confidence interval {CI} 6.1 to 11.8]; $p<0.00001$; $I^2=68.6\%$). A meta-analysis of 3 studies including 58 patients with idiopathic gastroparesis treated by gastroelectrical stimulation reported improvement in total symptom severity score (weighted mean difference 7.5 [95% CI 5.4 to 9.7]; $p<0.00001$; $I^2=52.9\%$). A meta-analysis of 2 studies including 33 patients with post-surgical gastroparesis treated by gastroelectrical stimulation reported improvement in total symptom severity score (weighted mean difference 8.3 [95% CI 5.5 to 11.1]; $p<0.00001$; $I^2=0\%$). Length of follow-up was unclear in all the analyses.

4.2 A meta-analysis of 7 studies including 378 patients with diabetic, idiopathic or post-surgical gastroparesis treated by gastroelectrical stimulation (part of a

systematic review of 601 patients) reported a statistically significant improvement in gastric emptying at 4 hours (assessed using standardised radionucleotide scans of a solid meal: weighted mean difference 13.0 [95% CI 7.4 to 18.6]; p<0.00001; I^2=87.4%). Subgroup analysis showed that the improvement was statistically significant in patients with diabetic or idiopathic gastroparesis but not in patients with post-surgical gastroparesis. Length of follow-up was unclear in all the analyses.

4.3 In a systematic review of 364 patients, a meta-analysis of 4 studies including 75 patients with gastroparesis treated by gastroelectrical stimulation reported no statistically significant change in weight (weighted mean difference 3.7 [95% CI −0.2 to 7.6]; I^2=0%). Length of follow-up was not reported but 12-month outcomes were preferred.

4.4 In the systematic review of 364 patients, a meta-analysis of 8 studies including 184 patients with gastroparesis treated by gastroelectrical stimulation reported a reduction in need for nutritional support from 44% (96/216) of patients at baseline to 11% (21/184) at follow-up (odds ratio 5.5 [95% CI 2.8 to 11.1]; p<0.00001; I^2=27%). Length of follow-up was not reported but 12-month outcomes were preferred.

4.5 A randomised controlled trial (RCT) of 32 patients with gastroparesis of idiopathic origin reported that there was a significant reduction in weekly vomiting frequency from 61 to 87% (p<0.001) and improvements in gastroparesis symptoms, gastric emptying and days of hospitalisation (all p<0.05) at 1-year follow-up.

4.6 The systematic review of 364 patients reported a significant improvement in Short Form-36 physical component score (weighted mean difference 8.1 [95% CI 5.0 to 11.1]) and the mental component score (weighted mean difference 8.16 [95% CI 4.9 to 11.5]), based on meta-analyses of 4 studies with 78 patients. The difference was statistically significant (p<0.00001) for both outcomes with no heterogeneity. Length of follow-up was not reported but 12-month outcomes were preferred.

4.7 The specialist advisers listed key efficacy outcomes as reduced symptoms, reduced need for nutritional support, improved nutritional status and reduced frequency of hospital admissions.

5 Safety

This section describes safety outcomes from the published literature that the Committee considered as part of the evidence about this procedure. For more detailed information on the evidence, see the interventional procedure overview.

5.1 Death (within 30 days) was reported in 3% (2/72) of patients treated by gastroelectrical stimulation, due to small bowel infarction and heart failure, and 3% (1/31) of patients treated by gastrectomy, due to myocardial infarction, in a comparative case series of 103 patients.

5.2 Gastric perforation related to an episode of vomiting (2 months after the procedure) was reported in 1 patient in a case series of 17 patients. The device was removed and the perforation was repaired.

5.3 Device removal was reported in 11% (24/221) of patients in a case series of 221 patients (timing ranged from 1–43 months after the procedure). Reasons were infection at the pulse generator or electrode sites (13 patients), lack of symptom improvement (6 patients), lead dislodgements (2 patients), small bowel obstruction caused by wires (1 patient), penetration of electrode into the lumen of the stomach (1 patient) and 'associated with peptic ulcer disease' (1 patient). No further details were reported. Erosion through the skin (6 patients), device migration (1 patient) and pain at implantation site (4 patients) resulting in device removal or replacement (timing unclear) were reported in the systematic review of 364 patients.

5.4 Battery failure resulting in device replacement was reported in 2% (4/221) of patients in the case series of 221 patients (timing unclear).

5.5 Lead erosion (leading to a revision procedure) was reported in less than 1% (2/233) of patients in a case series of 266 patients.

5.6 Treatment failure was reported in 26% (19/72) of patients treated by gastroelectrical stimulation in a case series of 103 patients. Reasons included 'failure to respond' (14 patients), device malfunction (1 patient) and damage to the device (1 patient). The device was removed in 1 patient. Thirteen patients whose symptoms failed to respond were treated by gastrectomy.

5.7 The specialist advisers listed anecdotal events as pain at the site of insertion of the subcutaneous stimulation device, and 'pins and needles' sensation from the stimulation device.

6 Committee comments

6.1 The Committee concluded that the evidence of efficacy was adequate only after prolonged debate about the design of the available randomised trials. The trials included an initial phase before randomisation in which the device was left 'on'. There was concern that any beneficial effect of the device might therefore have been carried over into the control period, so reducing the symptoms in that phase of the trial. The Committee also noted the possibility of a placebo response.

6.2 The Committee recognised that gastroparesis can be a very debilitating condition with very few treatment options, and it noted patient commentaries describing substantial improvements in quality of life with gastroelectrical stimulation.

7 Further information

For related NICE guidance, see the NICE website.

Information for patients

NICE has produced information on this procedure for patients and carers (Information for the public). It explains the nature of the procedure and the guidance issued by NICE, and has been written with patient consent in mind.

About this guidance

NICE interventional procedures guidance makes recommendations on the safety and efficacy of the procedure. It does not cover whether or not the NHS should fund a procedure. Funding decisions are taken by local NHS bodies after considering the clinical effectiveness of the procedure and whether it represents value for money for the NHS.

This guidance was developed using the NICE interventional procedures guidance process.

It updates and replaces NICE interventional procedure guidance 103.

We have produced a summary of this guidance for patients and carers. Information about the evidence the guidance is based on is also available.

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Implementation of this guidance is the responsibility of local commissioners and/or providers. Commissioners and providers are reminded that it is their 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.

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CLINICAL AT

Gastric Electrical Stimulation Reduces Refractory Vomiting in a Randomized Crossover Trial

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See Covering the Cover synopsis on page 453; see editorial on page 461.

BACKGROUND & AIMS: There have been conflicting results from trials of gastric electrical stimulation (GES) for treatment of refractory vomiting, associated or not with gastroparesis. We performed a large, multicenter, randomized, double-blind trial with crossover to study the efficacy of GES in patients with refractory vomiting, with or without gastroparesis. **METHODS:** For 4 months, we assessed symptoms in 172 patients (66% women; mean age ± standard deviation, 45 ± 12 years; 133 with gastroparesis) with chronic (>12 months) of refractory vomiting (idiopathic, associated with a type 1 or 2 diabetes, or post-surgical). A GES device was implanted and left unactivated until patients were randomly assigned, in a double-blind manner, to groups that received 4 months of stimulation parameters (14 Hz, 5 mA, pulses of 330 μs) or no stimulation (control); 149 patients then crossed over to the other group for 4 months. Patients were examined at the end of each 4-month period (at 5 and 9 months after implantation). Primary endpoints were vomiting score, ranging from 0 (daily vomiting) to 4 (no vomiting), and the quality of life, assessed by the Gastrointestinal Quality of Life Index scoring system. Secondary endpoints were changes in other digestive symptoms, nutritional status, gastric emptying, and control of diabetes. **RESULTS:** During both phases of the crossover study, vomiting scores were higher in the group with the device on (median score, 2) than the control group (median score, 1; $P < .001$), in diabetic and nondiabetic patients. Vomiting scores increased significantly when the device was ON in patients with delayed ($P < .01$) or normal gastric emptying ($P = .05$). Gastric emptying was not accelerated during the ON period compared with the OFF period. Having the GES turned on was not associated with increased quality of life. **CONCLUSIONS:** In a randomized crossover study, we found that GES reduced the frequency of refractory vomiting in patients with and without diabetes, although it did not accelerate gastric emptying or increase of quality of life. Clinicaltrials.gov, Number: NCT00903799

Keywords: Nausea; Therapy; Treatment; Vomiting.

Chronic vomiting remains a clinical challenge when usual diet recommendations and pharmacologic options fail to improve patients' symptoms, and it may ultimately lead to impaired nutritional status.[1] Chronic vomiting episodes are often related to delayed gastric emptying, a condition in which vomiting is associated with dyspeptic symptoms and weight loss.[2] In some patients, vomiting is associated a normal gastric emptying.[3]

High-frequency gastric electrical stimulation (GES) (Enterra therapy, Medtronic, Minneapolis, MN) is currently considered a treatment option for patients with chronic refractory vomiting, whether associated or not with gastroparesis.[4–7] However, technique efficacy remains debatable.[8] The American Gastroenterological Association recommendations state that there is a moderate level of evidence for using GES in gastroparesis.[2] In fact, although several open trials have suggested that GES could be effective for the relief of refractory vomiting, whether associated or not with GE,[8] short randomized trials, conducted only in patients with gastroparesis, produced negative results. To date, only 1 double-blind study (Worldwide Anti-vomiting

Abbreviations used in this paper: **GES, gastric electrical stimulation; GIQLI, Gastrointestinal Quality of Life Index; ITT, intention to treat; QOL, quality of life.**

Most current article

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CLINICAL PRACTICE UPDATE

AGA Clinical Practice Update on Management of Medically Refractory Gastroparesis: Expert Review

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DESCRIPTION: **Delayed gastric emptying on objective testing defines gastroparesis, but symptoms overlap with functional dyspepsia and do not correlate well with gastric emptying delay. This review outlines a strategy for defining, diagnosing, and managing refractory gastroparesis.**

METHODS: **The Best Practice Advice statements presented here were developed from review of existing literature combined with expert opinion to provide practical advice. Because this was not a systematic review, formal rating of the quality of evidence or strength of recommendations was not performed.**

BEST PRACTICE ADVICE:

1. **Clinicians should review symptoms and evaluate physical examination findings to exclude disorders that can mimic medically refractory gastroparesis.**
2. **Clinicians should verify appropriate methodology of the gastric emptying study to ensure an accurate diagnosis of delayed gastric emptying.**
3. **Clinicians should classify patients with gastroparesis into mild, moderate, or severe based on symptoms and the results of a properly performed gastric emptying study.**
4. **Clinicians should identify the predominant symptom and initiate treatment based on that symptom.**
5. **Clinicians should be aware of the multiple treatment options to treat nausea and vomiting.**
6. **Clinicians should consider the use of neuromodulators to treat gastroparesis associated abdominal pain but should not use opioids.**
7. **Clinicians can consider gastric electrical stimulation for gastroparesis patients with refractory/intractable nausea and vomiting who have failed standard therapy and are not on opioids.**
8. **Clinicians can consider G-POEM for select refractory gastroparesis patients with severe delay in gastric emptying, using a thoughtful team approach involving motility specialists and advanced endoscopists at a center of excellence.**

Keywords: Gastroparesis; Nausea and Vomiting; Abdominal Pain.

Gastroparesis is a syndrome defined by symptomatic delay in gastric emptying in the absence of mechanical obstruction.[1] Typical gastroparesis symptoms of nausea, vomiting, early satiety, bloating, postprandial fullness, abdominal pain, and/or weight loss (Figure 1) overlap to a significant degree with functional dyspepsia (FD).[1–5] With an estimated prevalence per 100,000 persons of 37.8 for women and 9.6 for

Abbreviations used in this paper: FD, functional dyspepsia; FDA, Food and Drug Administration; FLIP, functional lumen imaging probe; GCSI, Gastroparesis Cardinal Symptom Index; GES, gastric electrical stimulation; G-POEM, gastric per-oral endoscopic myotomy; 5-HT_3, 5-hydroxytryptamine$_3$; NK-1, neurokinin-1; RCT, randomized controlled trial; SNRI, serotonin norepinephrine reuptake inhibitor; TCA, tricyclic antidepressant.

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MRI for Monitoring in Multiple Sclerosis

Plain Language Summary:
Background: Yearly MRI (a brain imaging test) for people with multiple sclerosis (MS) is currently not covered by OHP though many doctors now recommend it to help manage medications for the disease. Initial MRIs for diagnosis of MS are covered.

Should OHP cover yearly MRIs for MS? Staff recommends OHP cover this treatment because new evidence shows that regular MRIs can help doctors make better treatment decisions.

Question: Should coverage of MRI in multiple sclerosis (MS) be broadened to include annual or other regular monitoring?

Question source: Doug Carr, CCO medical director

Issue: Multiple sclerosis (MS) is a demyelinating disease of the central nervous system (CNS). MRIs are frequently used by neurologists to diagnose MS and to evaluate the effect of disease modifying therapy. Many neurologists recommend yearly MRIs of all MS patients to monitor therapy and to decide to modify therapy if new plaques or other changes are detected. Currently, MRI is covered for making the diagnosis of MS and in a few other limited circumstances, but not for routine monitoring of disease.

There has been considerable feedback to the Medical Directors and HERC staff from community neurologists expressing disagreement with this guideline. Specifically, neurologists generally consider regular (yearly or more frequent) MRI to be necessary to monitor medication effectiveness and identify new MS activity in the brain before clinical symptoms arise, in order to better modify medications. The HERC review of the evidence has not found significant evidence that yearly monitoring MRI improves clinical outcomes compared to MRI when there are clinical changes causing suspected drug failure.

New evidence and specialty guidelines have been published that argue that using regular MRI to monitor for increased plaques can inform drug changes and improve outcomes. The HERC has been asked to re-review our policy on routine MRI in MS.

HERC history

1) The use of MRI for monitoring asymptomatic MS patients was reviewed in August 2013. At that time, NICE and the European Federation of Neurological Societies Summary of Guidelines were reviewed, and did not recommend routine MRI for monitoring stable patients. Based on the lack of evidence that monitoring asymptomatic patients would change management or outcomes, the HERC adopted a new diagnostic guideline which limited MRI to diagnosis of MS, but prohibited use for routine monitoring of disease.
2) MRI for monitoring asymptomatic MS patients was again reviewed in March 2017 at the request of multiple neurologists. During that review, a 2016 MED report was reviewed that found no systematic reviews or meta-analyses that MRI monitoring for MS progression changed clinical management or outcomes. Based on expert input at this meeting, Diagnostic Guideline D10 was expanded from simply a statement that MRI is only covered for the diagnosis of MS, to also include use of MRI for suspected drug failure in cases of new neurologic symptoms, evaluation of patients with previously relapsing disease when conversion to secondary progressive MS is suspected, and for patients who require enhanced pharmacovigilance for medication side

effects. It was noted during this meeting that yearly MRI monitoring was standard of care and no randomized data on yearly MRI vs none would ever happen.

Current Prioritized List status:
ICD-10-CM G35 (Multiple sclerosis) is on line 251 MULTIPLE SCLEROSIS AND OTHER DEMYELINATING DISEASES OF CENTRAL NERVOUS SYSTEM and on the dysfunction lines.
MRI CPT codes are on the Diagnostic Procedures File

70551 MRI, brain without contrast
72141 MRI, cervical spine without contrast
72146 MRI, thoracic spine without contrast
72148 MRI, lumbar spine without contrast

DIAGNOSTIC GUIDELINE D10, MRI IN MULTIPLE SCLEROSIS
MRI is a diagnostic test for multiple sclerosis and should not be used for routine monitoring of disease.

MRI may be considered in the following circumstances:

A) Suspected drug failure in the setting of clinical relapse in patients with objective changes in neurological status or documented new clinical symptoms such as urinary urgency or cognitive changes
B) Evaluation of a clear objective progression in clinical symptoms in patients with previously relapsing disease to rule out ongoing inflammatory disease when conversion to secondary progressive MS is suspected
C) Patients who require enhanced pharmacovigilance, including
    1) Yearly monitoring for patients treated with natalizumab who are JCV seropositive
    2) One MRI for patients who switch from natalizumab to other therapeutics (including fingolimod, alemtuzumab and dimethyl fumarate) one year after the switch from natalizumab

Evidence
No new literature was identified using search terms for MRI and MS

Expert guidelines

1) **American Academy of Neurology 2018**, practice guideline recommendation summary for disease modifying therapies for adults with multiple sclerosis
    a. Clinicians may recommend serial imaging at least annually for the first 5 years and close follow-up rather than initiating disease modifying therapy (DMT) in people with clinically isolated symptom (CIS) or relapsing forms of MS who are not on DMT, have not had relapses in the preceding 2 years, and do not have active new MRI lesion activity on recent imaging (Level C).
    b. Multiple studies of DMTs in people with relapsing forms of MS who have had recent relapses or MRI activity or both have shown benefit of DMT in terms of reducing relapses and reducing MRI activity.
    c. Clinicians should monitor MRI disease activity from the clinical onset of disease to detect the accumulation of new lesions in order to inform treatment decisions in people with MS using DMTs. (Level B).

   d. Clinicians should discuss switching from one DMT to another in people with MS who have been using a DMT long enough for the treatment to take full effect and are adherent to their therapy when they experience 1 or more relapses, 2 or more unequivocally new MRI-detected lesions, or increased disability on examination, over a 1-year period of using a DMT (Level B).

2) **2021 Magnetic Resonance Imaging in Multiple Sclerosis study group, Consortium of Multiple Sclerosis Centres, and North American Imaging in Multiple Sclerosis Cooperative** consensus recommendation on the use of MRI in patients with multiple sclerosis
   a. Obtain a baseline brain MRI (with gadolinium if required by drug label) before starting or switching disease-modifying treatment.
   b. Obtain a new baseline brain MRI usually at 3–6 months after treatment onset to avoid misinterpretation of lesions that developed before therapeutic onset. Longer intervals are to be considered in patients who are treated with disease-modifying therapies that are slow acting.
   c. Obtain a new baseline MRI usually at 3–6 months after treatment initiation without gadolinium unless highly active disease at baseline or unexpected clinical activity.
   d. Consider gadolinium-enhanced MRI on first follow-up scan after treatment initiation in the absence of a new baseline scan.
   e. Obtain yearly brain MRI while the patient is on the disease-modifying treatment; consider longer intervals in clinically stable patients after the first few years of treatment, particularly if safety monitoring is not required.
   f. In patients who show MRI disease activity that is not associated with clinical activity on a follow-up scan, consider a new MRI scan without gadolinium 6 months later
3) **Multiple Sclerosis Therapy Consensus Group (MSTCG) 2021**: position statement on disease-modifying therapies for multiple sclerosis
   a. Activity is determined based on clinical relapses (severity of clinical symptoms/duration/tendency to regress) and MRI activity (contrast-enhancing lesions; new or enlarged T2 lesions).
   b. The choice of immunotherapy should be based on predictive parameters; primarily (1) MRI findings (number and localization of lesions) but also (2) extent of relapse regression, (3) multifocal presentation, and (4) CSF-specific OCB or chronic inflammatory CSF changes
   c. Initiation of DMT in RRMS is necessary to reach the treatment goal of reducing inflammatory activity in the form of disease flares and new lesions in MRI
   d. Patients with progressive MS benefit from disease modifying therapy (DMT), especially in the early stages of the disease, and must be treated when clinical and imaging activity is present.
   e. MRI examination of the brain and clinical parameters serve the evaluation of DMT response in MS patients.
   f. The goal of MS therapy is the best possible disease control and the best possible QoL for the patient. In practice, disease control must be measured by clinical parameters (especially relapses, disability) and MRI activity
   g. In DMT-treated patients, therapeutic success should be monitored by a clinical assessment every 3months and by comparison of a standardized cerebral MRI within 3–6months after treatment initiation (evaluated as so-called re-baselining) and with an MRI 12 months after treatment initiation and thereafter at annual intervals
   h. The switch from a DMT for a mild/moderate disease course to a DMT for a (highly) active course should be made if there is $\geq$1 relevant relapse, or $\geq$2–3 new or enlarged

MRI-lesions confirmed by experts, or an increase in disability ≥0.5–1 EDSS point (confirmed after 3–6months) within 1 year

Expert input

Dr. Jacqueline Bernard, Clinical Vice-Chair OHSU neurology

There are some additional things to consider: the concept of NEDA: No Evidence of Disease-Activity which incorporates at minimum definition annualized release rate (ARR), progression on exam and new MRI activity (NEDA-3). So if the goal of is achieving NEDA, and this by necessity incorporates MRI component, the MRI is essential by definition. Additionally, atrophy is increasingly something we can note on MRI, and also helps us in our decision-making. Finally, the data from a study that will tell us when it is safe to stop disease-modifying treatments in MS patients 55 and older (DISCO_MS), will be available soon and it too relies on presence or absence of new MRI lesions.

So we very much appreciate your thoughtful consideration of this very important biomarker which we use not only to diagnose but also for therapeutic decision making including stopping meds.

Equity considerations

Higher-resourced individuals with private insurance are receiving regular MRIs which are guiding their care. Lower-resourced individuals on Medicaid do not have access to this type of care currently. Additionally, some neurologists may choose not to see Medicaid patients if they can't practice what they believe to be standard of care, which would create an access issue.

MRI for Monitoring in Multiple Sclerosis

HERC staff summary

MRI lesion changes have become a standard diagnostic criteria for initiating or changing disease modifying therapy in multiple sclerosis. All major expert groups use MRI lesion activity as criteria in their guidelines for treatment of MS. All major expert groups recommend at least yearly MRI for monitoring, with more frequent MRIs during DMT changes. No new literature is expected to be produced looking at whether routine MRI affects clinical outcomes as routine MRI is now standard of care. HERC staff recommends deletion of the MRI in MS guideline.

HERC staff recommendation:

1) Delete Diagnostic Guideline D10

~~**DIAGNOSTIC GUIDELINE D10, MRI IN MULTIPLE SCLEROSIS**~~

~~MRI is a diagnostic test for multiple sclerosis and should not be used for routine monitoring of disease.~~

~~MRI may be considered in the following circumstances:~~

~~A) Suspected drug failure in the setting of clinical relapse in patients with objective changes in neurological status or documented new clinical symptoms such as urinary urgency or cognitive changes~~

~~B) Evaluation of a clear objective progression in clinical symptoms in patients with previously relapsing disease to rule out ongoing inflammatory disease when conversion to secondary progressive MS is suspected~~

~~C) Patients who require enhanced pharmacovigilance, including~~

~~1) Yearly monitoring for patients treated with natalizumab who are JCV seropositive~~

~~2) One MRI for patients who switch from natalizumab to other therapeutics (including fingolimod, alemtuzumab and dimethyl fumarate) one year after the switch from natalizumab~~

Practice guideline recommendations summary: Disease-modifying therapies for adults with multiple sclerosis

Report of the Guideline Development, Dissemination, and Implementation Subcommittee of the American Academy of Neurology

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Neurology® 2018;90:777-788. doi:10.1212/WNL.0000000000005347

Abstract

Objective

To develop recommendations for disease-modifying therapy (DMT) for multiple sclerosis (MS).

Methods

A multidisciplinary panel developed DMT recommendations, integrating findings from a systematic review; followed an Institute of Medicine–compliant process to ensure transparency and patient engagement; and developed modified Delphi consensus–based recommendations concerning starting, switching, and stopping DMTs pertinent to people with relapsing-remitting MS, secondary progressive MS, primary progressive MS, and clinically isolated syndromes of demyelination. Recommendations were supported by structured rationales, integrating evidence from one or more sources: systematic review, related evidence (evidence not from the systematic review), principles of care, and inference from evidence.

Results

Thirty recommendations were developed: 17 on starting DMTs, including recommendations on who should start them; 10 on switching DMTs if breakthrough disease develops; and 3 on stopping DMTs. Recommendations encompassed patient engagement strategies and individualization of treatment, including adherence monitoring and disease comorbidity assessment. The panel also discussed DMT risks, including counseling about progressive multifocal leukoencephalopathy risk in people with MS using natalizumab, fingolimod, rituximab, ocrelizumab, and dimethyl fumarate; and made suggestions for future research to evaluate relative merits of early treatment with higher potency DMTs vs standard stepped-care protocols, DMT comparative effectiveness, optimal switching strategies, long-term effects of DMT use, definitions of highly active MS, and effects of treatment on patient-specified priority outcomes. This guideline reflects the complexity of decision-making for starting, switching, or stopping MS DMTs. The field of MS treatment is rapidly changing; the Academy of Neurology development process includes planning for future updates.

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Comprehensive systematic review summary: Disease-modifying therapies for adults with multiple sclerosis: Report of the Guideline Development, Dissemination, and Implementation Subcommittee of the American Academy of Neurology
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Go to Neurology.org/N for full disclosures. Funding information and disclosures deemed relevant by the authors, if any, are provided at the end of the article.

Approved by the Guideline Development, Dissemination, and Implementation Subcommittee on October 9, 2017; by the Practice Committee on October 21, 2017; and by the AAN Institute Board of Directors on March 6, 2018.

2021 MAGNIMS–CMSC–NAIMS consensus recommendations on the use of MRI in patients with multiple sclerosis

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The 2015 Magnetic Resonance Imaging in Multiple Sclerosis and 2016 Consortium of Multiple Sclerosis Centres guidelines on the use of MRI in diagnosis and monitoring of multiple sclerosis made an important step towards appropriate use of MRI in routine clinical practice. Since their promulgation, there have been substantial relevant advances in knowledge, including the 2017 revisions of the McDonald diagnostic criteria, renewed safety concerns regarding intravenous gadolinium-based contrast agents, and the value of spinal cord MRI for diagnostic, prognostic, and monitoring purposes. These developments suggest a changing role of MRI for the management of patients with multiple sclerosis. This 2021 revision of the previous guidelines on MRI use for patients with multiple sclerosis merges recommendations from the Magnetic Resonance Imaging in Multiple Sclerosis study group, Consortium of Multiple Sclerosis Centres, and North American Imaging in Multiple Sclerosis Cooperative, and translates research findings into clinical practice to improve the use of MRI for diagnosis, prognosis, and monitoring of individuals with multiple sclerosis. We recommend changes in MRI acquisition protocols, such as emphasising the value of three dimensional-fluid-attenuated inversion recovery as the core brain pulse sequence to improve diagnostic accuracy and ability to identify new lesions to monitor treatment effectiveness, and we provide recommendations for the judicious use of gadolinium-based contrast agents for specific clinical purposes. Additionally, we extend the recommendations to the use of MRI in patients with multiple sclerosis in childhood, during pregnancy, and in the post-partum period. Finally, we discuss promising MRI approaches that might deserve introduction into clinical practice in the near future.

Introduction

The value of MRI in patients with multiple sclerosis for diagnostic, prognostic, and monitoring purposes is well established and its implementation has been specified in several consensus and guideline papers that vary slightly between North America, Europe, and the Middle East. Universal adoption of a standardised approach to MRI in clinical practice, including image acquisition protocols and timing of scans, is a major challenge because of differences in health-care systems and clinical practices between countries. The 2015 Magnetic Resonance Imaging in Multiple Sclerosis (MAGNIMS)[1,2] and 2016 Consortium of Multiple Sclerosis Centres (CMSC)[3] consensus guidelines on the use of MRI in patients for diagnosis, prognosis, and monitoring of multiple sclerosis guided neuroradiologists and neurologists to standardise their image acquisition protocols and the indications for when and how to use MRI, prompting international and national societies to establish similar recommendations.[4,5]

Since the publication of those guidelines, new developments and scientific data have led to considerable advances in knowledge. These include the 2017 revisions of the McDonald criteria,[6] evolving safety concerns about the repetitive administration of intravenous gadolinium-based contrast agents (GBCAs) due to the potential risk of gadolinium accumulation in the brain,[7,8] and emerging evidence regarding the role of spinal cord MRI for prognosis and monitoring of patients with multiple sclerosis. These and other new developments in the use of MRI in patients with multiple sclerosis prompted us to begin a critical review of the literature, revision of the 2015 MAGNIMS consensus guidelines, and harmonisation of these recommendations with a new revision of the 2016 CMSC guidelines and incorporation of the viewpoints of the North American Imaging in Multiple Sclerosis Cooperative (NAIMS).

These 2021 MAGNIMS–CMSC–NAIMS international consensus recommendations on MRI in patients with multiple sclerosis provide updated guidance on how and when to use MRI for diagnosis, prognosis, and treatment monitoring of multiple sclerosis, with special focus on the use of standardised MRI protocols, the judicious use of GBCAs, and standardised reporting. Additionally, we extend the recommendations to the use of MRI in special populations and situations, such as patients with multiple sclerosis during childhood, pregnancy, and the post-partum period. Finally, we discuss new and promising MRI techniques that might become clinically relevant in the near future.

Methods

A MAGNIMS panel of experts in the diagnosis and management of patients with multiple sclerosis convened in Graz, Austria, on April 12–13, 2019. The panel discussed and agreed on new or modified recommendations on the use of brain and spinal cord MRI in clinical practice. A second panel of experts convened independently in Newark, NJ, USA, on Oct 25, 2019, including members of the CMSC and the NAIMS. Following discussion among the chairs of the MAGNIMS, NAIMS, and CMSC Working

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Multiple Sclerosis Therapy Consensus Group (MSTCG): position statement on disease-modifying therapies for multiple sclerosis (white paper)

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***Abstract*:** Multiple sclerosis is a complex, autoimmune-mediated disease of the central nervous system characterized by inflammatory demyelination and axonal/neuronal damage. The approval of various disease-modifying therapies and our increased understanding of disease mechanisms and evolution in recent years have significantly changed the prognosis and course of the disease. This update of the Multiple Sclerosis Therapy Consensus Group treatment recommendation focuses on the most important recommendations for disease-modifying therapies of multiple sclerosis in 2021. Our recommendations are based on current scientific evidence and apply to those medications approved in wide parts of Europe, particularly German-speaking countries (Germany, Austria, and Switzerland).

Keywords: disease-modifying therapy, guideline, multiple sclerosis, treatment recommendation

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Essential facts at a glance

Multiple sclerosis (MS) is a complex, most likely autoimmune-mediated inflammatory neurodegenerative disease of the central nervous system (CNS), characterized by inflammatory demyelination and axonal/neuronal damage. In Germany, an estimated 250,000 people suffer from MS. In recent years, the approval of various therapies has significantly changed the course and prognosis of the disease. This position statement (white paper) by members of the KKNMS (Competence Network Multiple Sclerosis), members of the BDN (Association of German Neurologists), members of the DGN (German Society of Neurology), and members of the Austrian and Swiss neurological societies describes – based on available evidence – crucial issues and current status of disease-modifying pharmacological therapies for people with MS.

Currently, the distinction between relapsing MS (RMS), relapsing-remitting MS (RRMS), primary progressive MS (PPMS), and secondary progressive MS (SPMS) is still the pre-dominant description in regulatory documents. Whereas clinical classification of MS into (1) relapsing and (2) progressive forms, each of which can progress with and without activity [measured both

Coronary CT Angiography (CCTA)

Plain Language Summary:
Background: Coronary CT angiography (CCTA) is an imaging test that looks at the blood vessels called arteries that supply blood to the heart. The test looks for coronary artery disease (CAD) which can lead to heart attacks.

Should OHP cover coronary CT angiography? Staff recommends OHP cover this treatment because it is equally effective in detecting CAD as other tests.

Question: Should coverage be added for coronary CT angiography?

Question source: various CCO medical directors

Issue: Cardiac CT angiography (CCTA) is a test for evaluation of coronary artery disease (CAD). Noninvasive anatomic tests provide information on location and extent of blockage and include coronary CT angiography (CCTA) and cardiac magnetic resonance imaging (CMRI). Functional tests allow assessment of whether symptoms are correlated with narrowing leading to ischemic areas and generally include exercise (treadmill) electrocardiography (ECG), exercise/pharmacologic stress echocardiography, exercise/pharmacologic cardiac nuclear imaging with single-photon emission computed tomography (SPECT) or pharmacologic stress with positron emission tomography (PET).

Currently, CCTA is non-covered based on a 2013 coverage guidance. CCO medical directors have received requests for this procedure and would like an updated review and decision on coverage.

CMRI, treadmill stress test, pharmacologic stress echocardiography and SPECT are all currently covered as diagnostic tests for suspected CAD.

Summary of 2013 Coverage Guidance on CCTA

> Coronary computed tomographic angiography may be useful to "rule out" obstructive CAD in ED patients with acute chest pain and normal ECGs and initial cardiac enzymes, and in outpatients with stable chest pain in a population with low to intermediate probability of obstructive CAD. Cost-effectiveness analyses show either that CCTA is comparable or less costly than other diagnostic strategies, although for the most part, they did not consider the economic consequences of the harms of radiation or further evaluation of incidental findings. However, understanding how CCTA would be used in a clinical practice setting, and whether the cost-effectiveness assumptions are applicable as it would be used in clinical practice, is unclear. Use in other patient populations is not recommended due to unacceptable false positive or false negative results. Use in asymptomatic patients has not been evaluated
>
> "Blue box": Coronary Computed Tomography Angiography (CCTA) is not recommended for coverage.

HSD has also requested advice on the coverage of CPT 0501T-0504T (Noninvasive estimated coronary fractional flow reserve (FFR) derived from coronary computed tomography angiography data using computation fluid dynamics physiologic simulation software analysis of functional data to assess the severity of coronary artery disease). All private insurers cover these codes with CCTA.

Of note, coronary artery calcium scoring (CPT 75571) is a different procedure and is not included in this review.

Current Prioritized List status

CPT 75571 (Computed tomography, heart, without contrast material, with quantitative evaluation of coronary calcium) is on line 662 CONDITIONS FOR WHICH CERTAIN INTERVENTIONS ARE UNPROVEN, HAVE NO CLINICALLY IMPORTANT BENEFIT OR HAVE HARMS THAT OUTWEIGH BENEFITS:

CPT 75573 (Computed tomography, heart, with contrast material, for evaluation of cardiac structure and morphology in the setting of congenital heart disease (including 3D image postprocessing, assessment of left ventricular [LV] cardiac function, right ventricular [RV] structure and function and evaluation of vascular structures, if performed)) is on 20+ congenital heart disease lines

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
75572	Computed tomography, heart, with contrast material, for evaluation of cardiac structure and morphology	Insufficient evidence of effectiveness	December, 2009
75574	Computed tomography, heart	Insufficient evidence of benefit, unclear harms of radiation exposure	August, 2013 Coverage guidance

Evidence

1) **Washington HTA 2021**, Noninvasive Cardiac Imaging for Coronary Artery Disease – Re-review https://www.hca.wa.gov/assets/program/noninvasive-cardiac-imaging-final-report-2021019.pdf
    a. Effectiveness
        i. N=17 RCTs compared CCT with functional testing (stress nuclear or stress ECHO) for evaluation of suspected ACS in the emergency department or similar setting
            1. There is no clear difference in the frequency of later MI between CCTA and functional imaging tests (SOE Moderate).
            2. There was no association between CCTA and reduction in all-cause mortality compared with functional testing (SOE Moderate)
        ii. N=19 RCTs (22,335 patients) comparing CCTA to functional testing for referral for invasive cardiac testing (ICA):
            1. CCTA was associated with more frequent invasive coronary angiography (ICA) referral compared with functional testing (19 RCTs, 14.4 vs. 12 per 100 patients, pooled RR 1.25, 95% CI 1.09 to 1.47, I 2 =67%, RD 2.7, 95% CI 1 to 4 per 100, I 2 =59%) (SOE Moderate)
            2. Referral for any additional noninvasive testing was not different between CCTA and functional testing groups across populations (17 RCTs, 7.2 versus 7.6 per 100, pooled RR 0.82, 95% CI 0.53 to 1.28, I 2 =83%) (SOE Low) or when populations were considered individually
        iii. N=17 CTS (11,595 patients) comparing CCTA to functional testing for referral for any revascularization
            1. CCTA was associated with more frequent revascularization (9.5 per 100 patients) compared with functional testing (7.1 per 100 patients): 19 RCTs, pooled RR 1.52, 95% CI 1.26 to 1.90, I 2 =66%, RD 2.4, 95% CI 1.4 to 3.3 per 100) (SOE Moderate)
            2. CCTA was associate with higher frequency of PCI as a revascularization procedure compared with functional testing (12 RCTs, 8.2 vs. 6.0 per 100 patients, pooled RR 1.63, 95% CI 1.22 to 2.35, I 2 =74%, RD 2.4, 95% CI 1.3 to 3.6 per 100 patients) across populations (SOE Moderate).
        iv. For hospitalization in stable outpatients there was no difference in hospitalization between CCTA and functional testing across four RCTs (SOE Moderate)
        v. Subsequent ED visits: In patients with suspected ACS there was no difference in emergency department visits after index testing between CCTA and functional testing across studies, regardless of comparator, at 1 to 6.5 months (7 RCTs, pooled RR 0.84, 95% CI 0.66 to 1.06, I 2 =0%) or at ≥12 months (5 RCTs, pooled RR 1.06, 95% CI 0.93 to 1.56, I 2 =16%) (SOE High for both time frames)
        vi. Medication: CCTA was not consistently associated with initiation of, discontinuation of or changes in medications and results for many mediations were mixed. Evidence is insufficient to draw firm conclusions about the impact of testing on medication use (SOE Insufficient)
    b. Safety
        i. Major or serious test-related adverse events/harms are rare for all modalities
        ii. No major complications were observed across 3 RCTS at time of index test or within 24 hours. (SOE Low) The largest RCT in stable outpatients also reported no test-related hospitalization in the CCTA arm and 0.1% (5/4837) in the functional testing arm (SOE low).

iii. Contrast-related events related to CCTA occurred in ≤3% of patients at time of index testing as reported in six RCTs and one case series. Transient creatinine elevation not requiring dialysis were reported in two trials as 0.2% and 1% (SOE Low) and a third RCT18 reported that no contrast-induced nephropathy occurred (SOE Insufficient). Mild contrast reaction occurred in 0.5% to 2.1% of patients across six RCTs (SOE Low)

iv. Radiation from index tests: Across six RCTs comparing CCTA specifically with SPECT radiation exposure at index tended to be lower with CCTA (SOE Low). Five RCTs reported that CCTA was associated with a lower effective radiation dose for the index test; the sixth trial reported that CCTA was associated with slightly higher radiation (estimated difference 1.8 mSv). Rough estimates of difference between tests ranged from approximately 1.30 mSv to 11.9mSv. Stress echocardiography and ETT do not involve ionizing radiation (SOE Low).

c. Conclusions

i. There is no clear difference between CCTA and functional imaging tests (i.e., stress nuclear testing, stress echocardiography) regarding impact on improving clinical outcomes (MI, all-cause mortality) in stable outpatients with suspected CAD or in patients with suspected ACS presenting to the ED or similar settings.

ii. CCTA was associated with higher frequency of ICA referral and use of PCI for revascularization compared with functional imaging

iii. While radiation exposure at time of index testing tended to be lower in CCTA recipients compared with SPECT (stress echo does not involve ionizing radiation), the evidence suggests that cumulative radiation may be higher with CCTA as an initial test

iv. Incidental findings requiring follow-up in patients receiving CCTA are common and require additional resources.

v. Definitive conclusions regarding cost-effectiveness of any of the noninvasive imaging tests are not possible in large part due to substantial heterogeneity across economic studies regarding testing strategies and test sequencing

<u>Expert guidelines</u>

1) **AHA/ACC 2021** guideline for evaluation and diagnosis of chest pain
   a. Intermediate or high pretest likelihood of CAD in patients younger than 65 years of age OR less obstructive CAD suspected: CTTA is the favored test (vs stress testing)
   b. CCTA also recommended for use when prior functional study was inconclusive
   c. CCTA recommended when there are anomalous coronary arteries or when the patient requires evaluation of the aorta or pulmonary arteries
   d. CCTA is contraindicated when there is a contrast allergy, clinical instability, renal impairment, arrhythmia or contraindication to nitroglycerin

<u>Other payer policies</u>

1) Washington HTA 2021
   a. CCTA is a covered benefit with conditions for:
      i. Symptomatic adult patients (≥18 years of age) at intermediate or high risk of CAD, or
      ii. Adult patients with known CAD who have new or worsening symptoms.

2) Aetna 2022

a. Aetna considers cardiac computed tomography (CT) angiography of the coronary arteries using 64-slice or greater medically necessary for the following indications:
   i. Rule out obstructive coronary stenosis in symptomatic persons with a low or intermediate pre-test probability of coronary artery disease or atherosclerotic cardiovascular disease by Framingham risk scoring, Pooled Cohort Equations, or by American College of Cardiology (ACC) criteria,
   ii. Rule out obstructive coronary stenosis in persons with a low or intermediate pre-test probability of coronary artery disease or atherosclerotic cardiovascular disease by Framingham risk scoring, Pooled Cohort Equations, or by American College of Cardiology (ACC) criteria (see Appendix) with a positive (i.e., greater than or equal to 1 mm ST segment depression) stress test.
   iii. Evaluation of asymptomatic persons at an intermediate pre-test probability of coronary heart disease or atherosclerotic cardiovascular disease by Framingham risk scoring or Pooled Cohort Equations (see Appendix) who have an equivocal or uninterpretable exercise or pharmacological stress test or have resting electrocardiogram (ECG) changes (such as left bundle branch block (LBBB), pathologic q-waves, or right bundle branch block (RBBB) with left anterior fascicular block (LAFB) in which coronary artery disease (CAD) is a possible etiology. **Note**: Current guidelines from the American Heart Association recommend against routine stress testing for screening asymptomatic adults.
   iv. Pre-operative assessment of persons scheduled to undergo 'high-risk" non-cardiac surgery, where an imaging stress test or invasive coronary angiography is being deferred unless absolutely necessary. The ACC defines high-risk surgery as emergent operations, especially in the elderly, aortic and other major vascular surgeries, peripheral vascular surgeries, and anticipated prolonged surgical procedures with large fluid shifts and/or blood loss involving the abdomen and thorax.
   v. Pre-operative assessment for planned non-coronary cardiac surgeries including valvular heart disease, congenital heart disease, and pericardial disease, in lieu of cardiac catheterilzation as the initial imaging study, in persons with low or intermediate pretest risk of obstructive CAD.
   vi. Detection and delineation of suspected coronary anomalies in young persons (less than 30 years of age) with suggestive symptoms (e.g., angina, syncope, arrhythmia, and exertional dyspnea without other known etiology of these symptoms in children and adults; dyspnea, tachypnea, wheezing, periods of pallor, irritability (episodic crying), diaphoresis, poor feeding and failure to thrive in infants).
   vii. Calculation of fractional flow reserve (HeartFlow FFR_{CT}) for persons who have a coronary CTA that has shown coronary artery disease of uncertain functional significance, or is non-diagnostic.

3) Cigna 2011

a. CIGNA covers 64-slice or greater multidetector-row computed tomography angiography (CTA) as medically necessary as an adjunct to other testing for ANY of the following indications:
   i. evaluation of chest pain in an individual with a very low, low, or intermediate pre-test probability of coronary artery disease1 (CAD) when the individual cannot perform or has a contraindication to exercise and chemical stress testing

(i.e. exercise treadmill stress test, stress echo, and nuclear stress test [i.e., myocardial perfusion imaging])

ii. exclusion of CAD in an individual with a low or very low pre-test probability of CAD when recent stress test results (i.e., exercise treadmill, stress echo, or nuclear stress test [i.e., myocardial perfusion imaging]) are uninterpretable, equivocal, or there is a suspicion that the results are falsely positive

iii. exclusion of CAD in an individual with an intermediate pre-test probability of CAD when recent stress test results (i.e., exercise treadmill, stress echo, or nuclear stress test [i.e., myocardial perfusion imaging]) are uninterpretable or equivocal, AND CTA will be performed in lieu of an angiography.

iv. exclusion of CAD in a symptomatic individual (e.g., acute chest pain in an emergency department setting), and the individual has an intermediate pre-test probability of CAD, and there are no changes noted on the ECG and serial enzymes are negative

v. evaluation of suspected or known coronary artery anomalies associated with congenital conditions

vi. for morphologic evaluation of the coronary arteries in an individual with dilated cardiomyopathy or new onset heart failure, when ischemia is the suspected etiology and cardiac catheterization and/or nuclear stress test (i.e., myocardial perfusion imaging) have not been performed

vii. pre-operative assessment of coronary arteries in an individual undergoing repair of aortic dissection, aortic aneurysm repair or valvular surgery AND CTA will be performed in lieu of an angiography

viii. post-coronary artery bypass grafting (CABG) when BOTH of the following criteria are met:

1. repeat intervention is being considered
2. recent coronary angiography has been completed but additional information is needed before a treatment decision can be made

b. CIGNA does not cover multidetector-row computed tomography angiography (CTA) for any other indication, including but not limited to those listed below, because it is considered experimental, investigational or unproven:

i. evaluation of chest pain in an intermediate or high pre-test probability of CAD individual when recent stress test result (i.e., exercise treadmill, stress echo, or nuclear stress test [i.e., myocardial perfusion imaging]) are either clearly positive or unequivocally negative

ii. screening for CAD in an asymptomatic individual

iii. post-revascularization procedure (e.g., percutaneous coronary intervention, coronary artery bypass grafting surgery), including evaluation of bypass grafts, coronary anatomy or evaluation for in-stent restenosis except when an individual is post-coronary artery bypass grafting (CABG), repeat intervention is being considered but additional information is required following completion of recent coronary angiography

Expert input:

Dr. Abigail Khan, OHSU cardiology

I agree with your assessment that CCTA has a strong body of evidence supporting that it is not inferior to stress echo or SPECT and its diagnostic use is now supported by national guidelines. I do think we should cover CCTA given its use is quickly becoming standard of care in certain settings and there are situations in which it is the preferred test over stress testing. Importantly, it can also allow for more expedited assessment of symptomatic patients than stress testing, which is more labor intensive and has more scheduling complexities in real world practice.

…after consulting with a CT expert my feelings are that we do not need additional guidelines for CCTA if they are not in place for stress testing. There is actually a stronger body of literature supporting CCTA than stress testing at this point. CCTA is unlikely to be overutilized any more than stress testing (and is actually a cheaper test). The complexity is patients who have had prior stents in which the use of CCTA is not straightforward. That said I'm not sure if an OHP coverage guideline is the right way to go about addressing this issue. I suspect that providers will mostly send these patients for other testing (stress or cath) anyways, so we are not talking about a huge population of affected patients.

Dr. David Saenger, Cardiologist

Coronary CTA is becoming the standard first best test to evaluate patients for chest pain. This is both in the acute setting and in outpatient clinic. There are, of course, limitations and contraindications to CCTA. We have an algorithm that we wrote at OHVI that I can share. Bottom line is that relative contraindications are obesity (BMI > 35), tachycardia (especially a fib with RVR), prior PCI (except stents in large vessels like the left main are ok), and renal failure. There are contraindications to stress testing too, of course. So I don't think we need to have strict rules for ordering the test.

Coronary CT Angiography (CCTA)

HERC staff summary

CCTA is equally effective on improving clinical outcomes (MI and all-cause mortality) compared to stress ECHO or SPECT in patients suspected of having coronary artery disease (CAD). CCTA is associated with higher frequency of referral for invasive coronary artery catheterization and has a higher rate of incidental findings than other tests. The amount of radiation exposure from CCTA does not appear to be significant with newer protocols. The AHA/ACA guideline recommends CCTA as the test of choice for evaluation of patients under age 65 with intermediate or high suspicion of CAD or who have an indeterminate prior functional study. All private insurers surveyed cover this test, with different criteria. Experts consulted did not feel that there was a need for a guideline for this procedure.

HERC staff recommendations:

1) Remove CPT 75572 and 75574 (CT heart) from line 662 CONDITIONS FOR WHICH CERTAIN INTERVENTIONS ARE UNPROVEN, HAVE NO CLINICALLY IMPORTANT BENEFIT OR HAVE HARMS THAT OUTWEIGH BENEFITS
    a. Advise HSD to add CPT 75572 and 75574 to the Diagnostic Procedures File
    b. Remove the entries for CPT 75572 and 75574 from GN173
    c. Advise HSD to add CPT 0501T-0504T (Noninvasive estimated coronary fractional flow reserve (FFR) derived from coronary computed tomography angiography data using computation fluid dynamics physiologic simulation software analysis of functional data to assess the severity of coronary artery disease) to the Diagnostic Procedures File

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

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~~75574~~	~~Computed tomography, heart~~	~~Insufficient evidence of benefit, unclear harms of radiation exposure~~	~~August, 2013 Coverage guidance~~

Washington State Health Care Authority

Health Technology Clinical Committee
FINAL Findings and Decision

Topic: Noninvasive Cardiac Imaging
Meeting date: November 5, 2021
Final adoption: March 18, 2022

Number and coverage topic:

20211105A – Noninvasive Cardiac Imaging for Coronary Artery Disease

HTCC coverage determination:

Noninvasive cardiac imaging is a **covered benefit with conditions**.

HTCC reimbursement determination:

Limitations of coverage: The following noninvasive cardiac imaging technologies are **covered with conditions**:

- Stress echocardiography for:
  - Symptomatic adult patients (≥18 years of age) at intermediate or high risk of Coronary Artery Disease (CAD), or
  - Adult patients with known CAD who have new or worsening symptoms.
- Single Positron Emission Tomography (SPECT) for:
  - Patients under the same conditions as stress echocardiography when stress echocardiography is not technically feasible or clinically appropriate.
- Positron Emission Tomography (PET) for:
  - Patients under the same conditions as SPECT, when SPECT is not technically feasible or clinically appropriate.
- Coronary Computed Tomographic Angiography (CCTA) for:
  - Symptomatic adult patients (≥18 years of age) at intermediate or high risk of CAD, or
  - Adult patients with known CAD who have new or worsening symptoms.
- CCTA with Fractional Flow Reserve (FFR) for:
  - Patients under the same conditions as CCTA, when further investigation of functional significance of stenoses is clinically indicated.

Non-covered indicators:

N/A

Notes:

- Out of scope/data not reviewed for this decision:
  - Asymptomatic individuals, follow up of prior abnormal cardiac imaging studies, myocardial viability, preoperative evaluation
  - Patients presenting for evaluation of cardiac pathologies other than CAD
- This determination supersedes the following previous determinations:

- Coronary Computed Tomographic Angiography for detection of Coronary Artery Disease (20081114A)
- Cardiac Nuclear Imaging (20130920A)

Related documents:

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

Agency contact information:

Agency	Phone Number
Labor and Industries	1-800-547-8367
Public and School Employees Health Plan	1-800-200-1004
Washington State Medicaid	1-800-562-3022

HTCC coverage vote and formal action:

Committee decision

Based on the deliberations of key health outcomes, the committee decided that it had the most complete information: a comprehensive and current evidence report, public comments, and state agency utilization information. The committee decided that the current evidence on noninvasive cardiac imaging for coronary artery disease (CAD) was sufficient to make a determination. The committee discussed and voted on the evidence for the use of echocardiography, coronary computed tomography angiography (CCTA), single positron emission computed tomography (SPECT) and positron emission tomography (PET), and CCTA with fractional flow reserve (FFR). The committee considered the evidence, public comment and expert input, and gave greatest weight to the evidence it determined, based on objective factors, to be the most valid and reliable.

Based on these findings, the committee voted to cover with conditions noninvasive cardiac imaging technology review. The committee voted unanimously to cover with conditions.

	Not covered	Covered under certain conditions	Covered unconditionally
Noninvasive cardiac imaging for coronary artery disease	0	9	0

Discussion

The committee reviewed and discussed the available studies for use of noninvasive cardiac imaging for CAD. Conditions for coverage were discussed, drafted, and voted on. A majority of committee members supported the conditions of coverage for echocardiography, CCTA, SPECT, PET, and CCTA-FFR. Echocardiography, SPECT, CCTA, PET, and CCTA-FFR have conditional coverage. Details of study

design, inclusion criteria, outcomes, cost, cost-effectiveness, and other factors affecting study quality were discussed.

Limitations

Stress echocardiography is a covered benefit with conditions for:

- Symptomatic adult patients (≥18 years of age) at intermediate or high risk of CAD, or
- Adult patients with known coronary artery disease who have new or worsening symptoms.

SPECT is a covered benefit with conditions for:

- Patients under the same conditions as stress echocardiography when stress echocardiography is not technically feasible or clinically appropriate.

PET is a covered benefit with conditions for:

- Patients under the same conditions as SPECT, when SPECT is not technically feasible or clinically appropriate.

CCTA is a covered benefit with conditions for:

- Symptomatic adult patients (≥18 years of age) at intermediate or high risk of CAD, or
- Adult patients with known CAD who have new or worsening symptoms.

CCTA with FFR is a covered benefit with conditions for:

- Patients under the same conditions as CCTA, when further investigation of functional significance of stenoses is clinically indicated.

Action

The committee checked for availability of a Centers for Medicare and Medicaid Services (CMS) national coverage decision (NCD). There is a Medicare LCD for non-invasive fractional flow reserve for stable ischemic heart disease. There is no NCD for cardiac imaging for CAD as reviewed.

The committee discussed clinical guidelines identified from the following organizations:

- American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines, and the American College of Physicians, American Association for Thoracic Surgery, Preventive Cardiovascular Nurses Association, Society for Cardiovascular Angiography and Interventions, and Society of Thoracic Surgeons *Guideline for the Diagnosis and Management of Patients with Stable Ischemic Heart Disease* (2012)
- The Task Force for the diagnosis and management of chronic coronary syndromes of the European Society of Cardiology (ESC) *ESC Guidelines for the diagnosis and management of chronic coronary syndromes* (2019)
- National Institute for Health and Care Excellence (NICE) *Recent-onset chest pain of suspected cardiac origin: assessment and diagnosis* (2016)
- American College of Cardiology (ACC) and the American Heart Association (AHA) *Guideline for the Management of Patients With Non–ST-Elevation Acute Coronary Syndromes* (2014)

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

The committee vice chair directed HTA staff to prepare a findings and decision document on use of noninvasive cardiac imaging for coronary artery disease for public comment to be followed by consideration for final approval at the next committee meeting.

Health Technology Clinical Committee Authority:

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

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

JOURNAL OF THE AMERICAN COLLEGE OF CARDIOLOGY
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CLINICAL PRACTICE GUIDELINE: FULL TEXT

2021 AHA/ACC/ASE/CHEST/SAEM/SCCT/SCMR Guideline for the Evaluation and Diagnosis of Chest Pain

A Report of the American College of Cardiology/American Heart Association Joint Committee on Clinical Practice Guidelines

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*Writing committee members are required to recuse themselves from voting on sections to which their specific relationships with industry may apply; see Appendix 1 for detailed information.
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§Society of Cardiovascular Computed Tomography Representative.
‖Lay Patient Representative.
¶Society for Academic Emergency Medicine Representative.
#Former ACC/AHA Joint Committee member; current member during the writing effort.
**Society for Cardiovascular Magnetic Resonance Representative.
††American College of Chest Physicians Representative.
‡‡American Society of Echocardiography Representative.
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This document was approved by the American College of Cardiology Clinical Policy Approval Committee in May 2021, the American Heart Association Science Advisory and Coordinating Committee in May 2021, the Society of Cardiovascular Computed Tomography in July 2021, the Society for Academic Emergency Medicine in June 2021, the Society for Cardiovascular Magnetic Resonance in June 2021, the American College of Chest Physicians in June 2021, the American Society of Echocardiography in June 2021, the American Heart Association Executive Committee in July 2021, and the American College of Cardiology Science and Quality Committee in July 2021.

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Copies: This document is available on the websites of the American College of Cardiology (www.acc.org) and the American Heart Association (professional.heart.org). For copies of this document, please contact the Elsevier Inc. Reprint Department via fax (212-633-3820) or e-mail (reprints@elsevier.com).

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#Former ACC/AHA Joint Committee member; current member during the writing effort.

ABSTRACT

AIM This clinical practice guideline for the evaluation and diagnosis of chest pain provides recommendations and algorithms for clinicians to assess and diagnose chest pain in adult patients.

METHODS A comprehensive literature search was conducted from November 11, 2017, to May 1, 2020, encompassing randomized and nonrandomized trials, observational studies, registries, reviews, and other evidence conducted on human subjects that were published in English from PubMed, EMBASE, the Cochrane Collaboration, Agency for Healthcare Research and Quality reports, and other relevant databases. Additional relevant studies, published through April 2021, were also considered.

STRUCTURE Chest pain is a frequent cause for emergency department visits in the United States. The "2021 AHA/ACC/ASE/CHEST/SAEM/SCCT/SCMR Guideline for the Evaluation and Diagnosis of Chest Pain" provides recommendations based on contemporary evidence on the assessment and evaluation of chest pain. This guideline presents an evidence-based approach to risk stratification and the diagnostic workup for the evaluation of chest pain. Cost-value considerations in diagnostic testing have been incorporated, and shared decision-making with patients is recommended.

CONTENTS

Rhinophyma Treatment

Plain Language Summary:
Background: Rhinophyma shaving is removing thickened skin from the nose due to a skin condition. Rarely it can cause problems with function such as breathing or infections. Most cases are considered cosmetic, which would only improve a person's appearance, not function. If a case was severe, it would be coded as a sinus condition and covered.

Should OHP cover rhinophyma shaving? Staff recommends OHP not cover this treatment because most cases are considered cosmetic.

Question: Should the current placement of surgical planing for rhinophyma be changed?

Question source: HSD Medical Management Committee

Issue: Rhinophyma is soft tissue and sebaceous hyperplasia of the nose which is caused by severe rosacea. Rhinophyma responds to electrosurgery, laser excision, and surgical debulking. Because telangiectasias and rhinophyma do not cause functional limitations, their treatment is considered cosmetic by most insurance carriers.

Currently, surgical planing for rhinophyma is on the covered line for chronic sinusitis and on two uncovered lines for disorders of the nasal cavity. It is not on the rosacea line. MMC recently received a request for surgical planing for a patient which sinus issues and requested that the HERC review the current coverage of this procedure. If the rhinophyma was severe enough to cause nasal obstruction, the condition could be coded with ICD-10 J34.89 (Other specified disorders of nose and nasal sinuses) which is on line 506 NASAL POLYPS, OTHER DISORDERS OF NASAL CAVITY AND SINUSES

Current Prioritized List status
CPT 30120 (Excision or surgical planing of skin of nose for rhinophyma) is on lines
466 CHRONIC SINUSITIS
506 NASAL POLYPS, OTHER DISORDERS OF NASAL CAVITY AND SINUSES
525 BENIGN NEOPLASM OF NASAL CAVITIES, MIDDLE EAR AND ACCESSORY SINUSES

Rosacea is on line 522 ROSACEA; MILD/MODERATE ACNE

Other payer policies

1) Aetna 2021
    a. Aetna considers excision or shaving of rhinophyma medically necessary for the treatment of bleeding or infection refractory to medical therapy (i.e., the need for repeated cautery of bleeding telangiectasias or frequent courses of antibiotics for pustular eruptions)
2) Anthem BCBS 2021
    a. Excision or shaving of the rhinophyma is considered **medically necessary** when **both** of the following criteria are met:
        i. the medical record documentation includes evidence of bleeding or infection; **and**
        ii. the procedure can be reasonably expected to improve functional impairment as a result of bleeding or infection.

b. Excision or shaving of the rhinophyma is considered **cosmetic and not medically necessary** when the medically necessary criteria in this section are not met.

Rhinophyma Treatment

HERC staff recommendations

1) Remove CPT 30120 (Excision or surgical planing of skin of nose for rhinophyma) from the following lines
    a. 466 CHRONIC SINUSITIS
    b. 506 NASAL POLYPS, OTHER DISORDERS OF NASAL CAVITY AND SINUSES
    c. 525 BENIGN NEOPLASM OF NASAL CAVITIES, MIDDLE EAR AND ACCESSORY SINUSES
2) Add CPT 30120 to line 522 ROSACEA; MILD/MODERATE ACNE

Spinal Cord Stimulation for Diabetic Neuropathy

Plain Language Summary:
Background: Spinal cord stimulation is a treatment for lower body nerve issues for people with nerve problems. The studies showed that this device might help patients with nerve problems caused by diabetes, but there was a high rate of problems such as infections and equipment failure.

Should OHP cover this treatment? Staff recommends OHP not cover this treatment because there is limited evidence which shows harms outweigh benefits.

Question: Should spinal cord stimulation be added as a treatment for diabetic neuropathy?

Question source: Medtronic

Issue: On January 21, 2022, Medtronic received U.S. Food and Drug Administration approval of the Intellis™ rechargeable neurostimulator and Vanta™ recharge-free neurostimulator for the treatment of chronic pain associated with diabetic peripheral neuropathy (DPN) of the lower extremities. Medtronic requested review of neurostimulators for pairing with diabetic peripheral neuropathy.

Current Prioritized List Status
ICD-10-CM E10.4 family (Type 1 diabetes mellitus with diabetic neuropathy) is on line 8 TYPE 1 DIABETES MELLITUS
ICD-10-CM E11.4 family (Type 2 diabetes mellitus with diabetic neuropathy) is on line 2 TYPE 2 DIABETES MELLITUS

CPT 63650 (Percutaneous implantation of neurostimulator electrode array, epidural), 63655 (Laminectomy for implantation of neurostimulator electrodes, plate/paddle, epidural) and 63663-63688 (Revision or replacement of spinal neurostimulator equipment) are on lines 292 NEUROLOGICAL DYSFUNCTION IN POSTURE AND MOVEMENT CAUSED BY CHRONIC CONDITIONS, 346 CONDITIONS OF THE BACK AND SPINE WITH URGENT SURGICAL INDICATIONS and 530 CONDITIONS OF THE BACK AND SPINE WITHOUT URGENT SURGICAL INDICATIONS

Evidence

1) **Strand 2022,** systematic review of spinal cord stimulation for diabetic peripheral neuropathy
    a. Both authors with conflicts of interest
    b. Reported complications:
        i. Lead migration in 0-30%
        ii. Revision of leads in 0-30%
        iii. Infection in 0-20%
        iv. Explant in 0-17%
    c. RCTs of low frequency spinal cord stimulation
        i. De Vos et al
            1. N=60 patients (randomized 2:1 to best medical treatment or spinal cord stimulation)
                a. N=37 with spinal cord simulation
            2. Outcomes at six months for 36 participant receiving SCS and 18 control participant showed that pain scores decreased by 55% with LF-SCS, while there was no decrease in mean pain among control participant.

The responder rate was 69% (25 of 36) among participant treated with SCS, while 6% (1 of 18) of controls were responders after six months of treatment

ii. Slangen et al
    1. N=36 patients (N=22 randomized to spinal cord stimulation)
    2. Daytime mean pain NRS scores decreased by 3.1 points after six months of stimulation in the SCS group but did not change in the BMT group (P < .001), and corresponding nighttime pain scores declined 2.4 points in the SCS treatment arm and 0.9 points in the BMT arm (P < .003). The six-month daytime responder rate (≥50% pain relief) was 9 out of 16 (56%) in the per protocol (PP) population of the SCS arm and 0 out of 14 (0%) in the BMT arm (P < .001); while nighttime responder rates were 8 out of 16 (50%) in the SCS group and 1 out of 14 (7%) in the BMT group (P < .05). At the last follow-up, 12 of 16 participant (75%) treated with SCS and followed for six months reported a PGIC for pain score ≥6, demonstrating "much" or "very much" improvement, while none of the participant receiving BMT did (P < .001)

d. Conclusions: There is currently a substantial unmet need for safe and effective treatments for PDN. Many patients with PDN do not benefit from pharmacotherapies in current use and are candidates for treatment with neuromodulation. Conventional LF-SCS…are supported by high-quality evidence from RCTs and prospective studies

2) **Henson 2021**, systematic review of spinal cord stimulation for diabetic peripheral neuropathy
    a. N=14 prospective studies
    b. N=2 RCTs
        i. De Vos et al
        ii. Slangen et al
    c. N=11 prospective cohort studies
    d. Conclusion: Based on our analysis of the available evidence, there is moderate-quality evidence for the safety and efficacy of spinal cord stimulation for painful diabetic neuropathy. However, further high-quality research, including a large-scale randomized controlled trial is warranted
3) **Peterson 2021**: RCT of high frequency spinal cord stimulation for patients with painful diabetic neuropathy
    a. SENZA trial
    b. All authors reported conflicts of interest; study funded by industry
    c. N=216 patients with peripheral neuropathy refractory to at least 2 classes of medications and lower limb pain with an initial VAS score of 5 or higher
        i. N=103 assigned to conventional medical management (CMM)
            1. Data reported for 93 by 6 month follow up
        ii. N=113 assigned to CMM plus spinal cord stimulator (SCC plus CMM)
            1. Data reported for 87 by the 6 month follow up
    d. In the CMM group, 5 of 94 patients (5%) met the composite primary end point of 50% or more pain relief using the VAS without observed deterioration on neurological examination compared with 75 of 95 in the 10-kHz SCS plus CMM group (79%; difference, 73.6%; 95% CI, 64.2-83.0; P < .001).
    e. At 6-month follow-up, there was no change in mean pain VAS scores for the CMM group, with a baseline mean of 7.0 cm (95% CI, 6.7-7.3) and a 6-month mean of 6.9 cm

(95% CI, 6.5-7.3); however, lower limb pain VAS scores decreased by a mean of 76.3% (95% CI, 70.8-81.8) for the implanted group.

f. At 6 month follow up, there was no change for [health related quality of life score] in the CMM group but a mean 16-point (95% CI, 11.3-20.5) improvement for those in the 10-kHz SCS plus CMM group (P < .001)
g. Adverse events
    i. None in CMM group
    ii. there were 18 AEs reported among 14 patients in the 10-kHz SCS plus CMM group: 3 study-related AEs for infection, 2 for wound dehiscence, and 1 for impaired healing among 5 of 90 patients (6%). Of 90 total implanted patients, 2 (2%) required explant.
h. Conclusion: Patients with PDN refractory to best available treatments can be safely and effectively treated with high-frequency (10- kHz) SCS.

Other payer policies:

1) Aetna 2022 does not consider spinal cord stimulation medically necessary for diabetic peripheral neuropathy
2) Cigna 2020 did not list diabetic peripheral neuropathy as a covered indication for spinal cord stimulation

HERC staff summary

The evidence on spinal cord stimulation for diabetic peripheral neuropathy consists of 3 RCTs with a total of 146 patients in the SCS groups. These RCTs showed consistent improvement in pain relief for SCS vs medical management alone. However, there was a significant rate of adverse events, including infection and equipment breakage/failure. Diabetic neuropathy is a very common condition and RCTs with large populations are feasible.

HERC staff recommendation:

1) Make no change in non-pairing of spinal cord stimulators with diabetic peripheral neuropathy.

Symposium/Special Issue

Neuromodulation in the Treatment of Painful Diabetic Neuropathy: A Review of Evidence for Spinal Cord Stimulation

Journal of Diabetes Science and Technology
2022, Vol. 16(2) 332–340

DOI: 10.1177/19322968211060075
journals.sagepub.com/home/dst
SAGE

Natalie H. Strand, MD[1]
and Adam R. Burkey, MD, MSCE, FAAN[2,3]

Abstract

Background: Neuropathies, the most common complication of diabetes, manifest in various forms, including entrapments, mononeuropathies or, most frequently, a distal symmetric polyneuropathy. Painful diabetic neuropathy (PDN) in the classic "stocking" distribution is a disease of increasing prevalence worldwide and a condition for which standard medical treatment only provides modest relief. Neuromodulation offers a potential alternative to pharmacotherapies given its demonstrated efficacy in other refractory chronic neuropathic pain syndromes. High-quality evidence from randomized controlled trials (RCTs) is available in these other settings for two approaches to spinal cord stimulation (SCS): (1) conventional low-frequency SCS (LF-SCS), which modulates axonal activity in the dorsal column and is paresthesia-dependent, and (2) high-frequency SCS delivered at 10 kilohertz (10 kHz SCS), which targets neurons in the superficial dorsal horn and is paresthesia-independent.

Method: This review examines the evidence for SCS from published RCTs as well as prospective studies exploring the safety and effectiveness of treating PDN with neuromodulation.

Results: Two RCTs enrolling 60 and 36 participants with PDN showed treatment with LF-SCS reduced daytime pain by 45% to 55% for up to two years. An RCT testing 10 kHz SCS versus conventional medical management (CMM) in 216 participants with PDN revealed 76% mean pain relief after six months of stimulation. None of the studies revealed unexpected safety issues in the use of neuromodulation in this patient population.

Conclusion: These well-designed RCTs address the unmet need for improved PDN therapies and provide data on the safety, effectiveness, and durability of SCS therapy.

Keywords

10 kHz SCS, neuromodulation, neuropathic pain, diabetic peripheral neuropathy, painful diabetic neuropathy, spinal cord stimulation, diabetes

Introduction

Diabetes mellitus is an illness that may cause enormous detriment to a person's health-related quality of life and is rapidly increasing in prevalence worldwide.[1] In 2018, it was estimated that 34.1 million US adults (13%) had diabetes,[2] and diabetic peripheral neuropathy with both painful and non-painful symptoms as the most common complication.[3,4] Painful diabetic neuropathy (PDN) occurs in one-third to one-half of all persons with diabetes, and is a distal, symmetric polyneuropathy that commonly presents as tingling/shooting, burning pain in a stocking distribution that may or may not be accompanied by numbness.[5]

Pain due to PDN is challenging to manage, similar to other chronic neuropathic pain conditions.[6] Clinical treatment guidelines recommend anticonvulsant medications such as pregabalin and gabapentin, antidepressants including serotonin and norepinephrine reuptake inhibitors (SNRIs) and tricyclic antidepressants (TCAs), the atypical opioid

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REVIEW

Spinal Cord Stimulation for Painful Diabetic Peripheral Neuropathy: A Systematic Review

Josianna V. Henson · Narayana C. Varhabhatla · Zvonimir Bebic · Alan D. Kaye · R. Jason Yong · Richard D. Urman · Justin S. Merkow

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ABSTRACT

Painful diabetic neuropathy is a common disease that results in significant pain and disability. Treatment options have traditionally consisted of conservative measures including topical and oral medication management as well as transcutaneous electrical stimulation units. These treatments demonstrate various degrees of efficacy, and many times initial treatments are discontinued, indicating low levels of satisfaction or poor tolerability. Spinal cord stimulation has been proposed as an alternative therapy for treatment of painful diabetic neuropathy of the lower extremities. We performed a systematic literature review to evaluate the safety and effectiveness of this procedure. A literature search identified 14 prospective studies. Based on our analysis of the available evidence, there is moderate-quality evidence for the safety and efficacy of spinal cord stimulation for painful diabetic neuropathy. However, further high-quality research, including a large-scale randomized controlled trial is warranted.

Keywords: Diabetic peripheral neuropathy; Spinal cord stimulation; Peripheral neuropathy; Electric nerve stimulation; Neuromodulation; Diabetes; Neuropathic pain

Supplementary Information The online version contains supplementary material available at https://doi.org/10.1007/s40122-021-00282-9.

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JAMA Neurology | Original Investigation

Effect of High-frequency (10-kHz) Spinal Cord Stimulation in Patients With Painful Diabetic Neuropathy
A Randomized Clinical Trial

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IMPORTANCE Many patients with diabetic peripheral neuropathy experience chronic pain and inadequate relief despite best available medical treatments.

OBJECTIVE To determine whether 10-kHz spinal cord stimulation (SCS) improves outcomes for patients with refractory painful diabetic neuropathy (PDN).

DESIGN, SETTING, AND PARTICIPANTS The prospective, multicenter, open-label SENZA-PDN randomized clinical trial compared conventional medical management (CMM) with 10-kHz SCS plus CMM. Participants with PDN for 1 year or more refractory to gabapentinoids and at least 1 other analgesic class, lower limb pain intensity of 5 cm or more on a 10-cm visual analogue scale (VAS), body mass index (calculated as weight in kilograms divided by height in meters squared) of 45 or less, hemoglobin A_{1c} (HbA_{1c}) of 10% or less, daily morphine equivalents of 120 mg or less, and medically appropriate for the procedure were recruited from clinic patient populations and digital advertising. Participants were enrolled from multiple sites across the US, including academic centers and community pain clinics, between August 2017 and August 2019 with 6-month follow-up and optional crossover at 6 months. Screening 430 patients resulted in 214 who were excluded or declined participation and 216 who were randomized. At 6-month follow-up, 187 patients were evaluated.

INTERVENTIONS Implanted medical device delivering 10-kHz SCS.

MAIN OUTCOMES AND MEASURES The prespecified primary end point was percentage of participants with 50% pain relief or more on VAS without worsening of baseline neurological deficits at 3 months. Secondary end points were tested hierarchically, as prespecified in the analysis plan. Measures included pain VAS, neurological examination, health-related quality of life (EuroQol Five-Dimension questionnaire), and HbA_{1c} over 6 months.

RESULTS Of 216 randomized patients, 136 (63.0%) were male, and the mean (SD) age was 60.8 (10.7) years. Additionally, the median (interquartile range) duration of diabetes and peripheral neuropathy were 10.9 (6.3-16.4) years and 5.6 (3.0-10.1) years, respectively. The primary end point assessed in the intention-to-treat population was met by 5 of 94 patients in the CMM group (5%) and 75 of 95 patients in the 10-kHz SCS plus CMM group (79%; difference, 73.6%; 95% CI, 64.2-83.0; $P < .001$). Infections requiring device explant occurred in 2 patients in the 10-kHz SCS plus CMM group (2%). For the CMM group, the mean pain VAS score was 7.0 cm (95% CI, 6.7-7.3) at baseline and 6.9 cm (95% CI, 6.5-7.3) at 6 months. For the 10-kHz SCS plus CMM group, the mean pain VAS score was 7.6 cm (95% CI, 7.3-7.9) at baseline and 1.7 cm (95% CI, 1.3-2.1) at 6 months. Investigators observed neurological examination improvements for 3 of 92 patients in the CMM group (3%) and 52 of 84 in the 10-kHz SCS plus CMM group (62%) at 6 months (difference, 58.6%; 95% CI, 47.6-69.6; $P < .001$).

CONCLUSIONS AND RELEVANCE Substantial pain relief and improved health-related quality of life sustained over 6 months demonstrates 10-kHz SCS can safely and effectively treat patients with refractory PDN.

TRIAL REGISTRATION ClincalTrials.gov Identifier: NCT03228420

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Multimedia

Supplemental content

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Subacromial Spacers

Plain Language Summary:
Background: Where should shoulder surgery with balloon implants to treat conditions such as severely torn rotator cuffs be prioritized? This is a new treatment and is not well-studied. No other insurer appears to cover this treatment.

Should OHP cover this treatment? Staff recommends OHP not cover this treatment because there isn't good evidence to cover it.

Question: Where should arthroscopy with implantation of a subacromial spacer be prioritized?

Question source: HERC staff

Issue: CMS released a new HCPCS code effective 4/4/22 regarding placement of subacromial spacers. This HCPCS code was adopted "to describe the implantation of a saline-filled balloon for the shoulder to treat irreparably torn rotator cuff tendons." There is no similar HCPCS or CPT code currently available.

Code: HCPCS C9781 (Arthroscopy, shoulder, surgical; with implantation of subacromial spacer (e.g., balloon), includes debridement (e.g., limited or extensive), subacromial decompression, acromioplasty, and biceps tenodesis when performed)

Evidence:

1) **Johns 2020**, systematic review of implantable subacromial balloon spacers for patients with massive irreparable rotator cuff tears
    a. N=19 studies. 13 studies described as non-randomized clinical trials
        i. No comparator groups in any trial
        ii. N=337 patients
        iii. All studies included patients with persistent symptoms for a minimum of 3 to 6 months with failure of conservative treatment, including activity modification, treatment with non-steroidal anti-inflammatory medications, intra-articular corticosteroid injections, and/or physical therapy
    b. Patients treated with a subacromial balloon spacer demonstrated overall improvement in postoperative TCS compared with preoperative TCS based on the data from 11 studies (preoperative range: 22.5-41.8; postoperative range: 51.4-72.3). All of these studies reported statistically significant improvement in TCS from preoperative to postoperative measurements at all short-term and long-term follow-up timepoints
    c. There was significant improvement of shoulder abduction (preoperative range: 70-113 degrees; postoperative range: 110-165 degrees), shoulder flexion (preoperative range: 80-130 degrees; postoperative range: 106.5-161 degrees), and external rotation (preoperative range: 25-44.5 degrees; postoperative range: 35-63.7 degrees) from preoperative to postoperative ROM after placement of the subacromial balloon spacer
    d. Complications: 1 of 350 (0.29%) patients experienced a transient forearm dysesthesia in the lateral cutaneous nerve of the forearm after implantation of the subacromial balloon spacer. A total of 1 of 350 (0.29%) procedures was complicated by superficial wound infection at the surgical site, which resolved after a course of antibiotics per orem, and 1 of 350 (0.29%) procedures was complicated by a deep wound infection, which was culture-negative and treated with 1 week of intravenous antibiotics followed by 2 weeks of per orem antibiotics. One patient with an increasingly painful shoulder

was found to have remnants of a deflated InSpace Balloon with transformation to scar tissue in the subacromial space on MRI. In total, 11 of 350 (3.14%) of procedures required reoperation, including 5 (1.42%) for InSpace Balloon migration, 1 (0.29%) for synovitis, and 6 (1.71%) underwent reverse total shoulder arthroplasty due to absence of clinical improvement or worsening of symptoms at various postoperative follow-up durations ranging from 6 weeks to 16 months. A total of 4 patients were found to have synovitis on MRI at 3 years post-implantation, and there was 1 shoulder dislocation at 6 weeks postoperative secondary to an acute trauma

   e. Conclusions: Existing literature of subacromial balloon spacers has high risk of bias, lack of appropriate control, and low level of evidence. A qualitative synthesis indicates that subacromial balloon spacer implantation in patients with massive irreparable rotator cuff tears is cost-effective and leads to improved function (TCS and OSS) and ROM

2) **Stewart 2019**, systematic review of subacromial balloon spacer implantation for massive and irreparable rotator cuff tears
   a. N=12 studies (284 patients)
      i. 10 case series, 1 prospective cohort study, and 1 retrospective cohort study
   b. In 2 studies, strength was not statistically significant. In 1 study, statistical significance was not reported for any subscale value (pain, ADL, ROM, strength)
   c. 4 studies observed increases in active abduction; however, results from 1 of these studies were not statistically significant.
   d. Of the 3 studies that reported active anterior elevation, all observed increases; however, only the results from 1 study were statistically significant (P = .00000001)
   e. Complications occurred in 2.1% of patients. These complications included transient neurapraxia of the lateral antebrachial cutaneous nerve in 1 patient, superficial wound infection in 1 patient, deep wound infection in 1 patient, and balloon migration in 3 patients
   f. This systematic review of the existing literature suggests that subacromial balloon spacer placement is a minimally invasive, technically simple procedure with low rates of perioperative complications and favorable patient reported outcomes at limited short-term follow up
   g. Further prospective randomized or comparative studies are warranted to ascertain clinical outcomes of subacromial balloon spacer in the management of massive and irreparable RCTs

<u>Other payer policies</u>:
None found

Subacromial Spacers

HERC staff summary

Arthroplasty with subacromial balloon spacer placement is an emerging technology with very limited evidence of effectiveness. Of note, Metcalfe (2021) has published a protocol for an RCT of this technology (START:REACTS study).

HERC staff recommendation:

1) Place HCPCS C9781 Arthroscopy, shoulder, surgical; with implantation of subacromial spacer (e.g., balloon), includes debridement (e.g., limited or extensive), subacromial decompression, acromioplasty, and biceps tenodesis when performed) on line 662/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
C9781	Arthroscopy, shoulder, surgical; with implantation of subacromial spacer (e.g., balloon)	Insufficient evidence of effectiveness	May 2022

Systematic Review

Implantable Subacromial Balloon Spacers in Patients With Massive Irreparable Rotator Cuff Tears: A Systematic Review of Clinical, Biomechanical, and Financial Implications

William L. Johns, B.S., Nikhil Ailaney, B.S., Kevin Lacy, B.S., Gregory J. Golladay, M.D., Jennifer Vanderbeck, M.D., and Niraj V. Kalore, M.D.

Purpose: To determine the clinical, biomechanical, and financial impact of the use of subacromial balloon spacers in the surgical management of massive, irreparable rotator cuff tears (RCTs). **Methods:** All studies assessing the use of implantable subacromial balloon spacers for management of massive, irreparable RCTs were systematically searched. Risk of bias was assessed using Methodological Index for Non-Randomized Studies criteria. Data extraction and analysis was performed for pain and function scores, shoulder range of motion (ROM), glenohumeral contact pressure and vertical migration of humeral head, and cost. Subjective synthesis was performed with forest plots when outcomes were reported in 3 or more studies. **Results:** In total, 19 studies met inclusion criteria for analysis; 337 patients (mean age 68 years) had 343 subacromial balloon spacer implantations. Throughout a mean follow-up of 33 months, there was significant improvement in the Total Constant Score (preoperative: 22.5-41.8; postoperative: 51.4-72.3), Oxford Shoulder Score (preoperative: 21.3-26; postoperative: 34.39-48.2), American Shoulder and Elbow Surgeons score (preoperative: 24.5-59.1; postoperative: 72.5-85.7), and shoulder ROM parameters. Subacromial balloon spacer placement resisted superior humeral head migration (range of preoperative to postoperative difference: 2.8-6.2 mm) and decreased peak subacromial pressure during shoulder ROM. **Conclusions:** Existing literature of subacromial balloon spacers has a high risk of bias, lack of appropriate control, and low levels of evidence. A qualitative synthesis indicates that subacromial balloon spacer implantation in patients with massive irreparable RCTs is cost-effective and leads to improved function (Total Constant Score and Oxford Shoulder Score) and ROM. In cadaveric studies, subacromial balloon spacers resist superior humeral head migration and reduce subacromial pressure. The theoretical risk of biodegradation of the balloon spacer has not been substantiated in study of up to 5-years follow-up, and the risk of complications from this procedure appears to be minimal. **Level of Evidence:** IV; Systematic review of level III-IV studies.

Rotator cuff tears are found in nearly 50% of patients aged 70-90 years.[1,2] Among these rotator cuff tears, up to 40% of all tears are categorized as massive,[3,4] which is defined as the rupture of 2 or more rotator cuff tendons and/or retraction ≥5 cm away from the tendon insertion site.[5,6] A key issue for these massive rotator cuff tears is that many are irreparable, due to significant tendon retraction to the glenoid,[7,8] the tear being ≥3 cm in size,[7] extensive muscle atrophy,[7,8] or a combination of these factors.

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W.J. and N.A. contributed equally to this work.

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Outcomes of Subacromial Balloon Spacer Implantation for Massive and Irreparable Rotator Cuff Tears

A Systematic Review

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Investigation performed at the Department of Orthopaedic Surgery, Wake Forest University School of Medicine, Winston-Salem, North Carolina, USA

Background: Selection of optimal treatment for massive to irreparable rotator cuff tears (RCTs) entails a challenging decision-making process in which surgeons must consider several factors, including duration of symptoms, tear pattern, tear size, and muscle quality, as well as patient characteristics such as age, comorbidities, shoulder dominance, and activity level. Unfortunately, no clear consensus has been reached regarding optimal management.

Purpose: To systematically review the published literature assessing outcomes after subacromial balloon spacer implantation for treatment of massive and irreparable RCTs.

Study Design: Systematic review; Level of evidence, 4.

Methods: A comprehensive literature search was performed in September 2018 through use of MEDLINE and the Cochrane Library electronic databases. Studies were assessed for multiple outcomes of interest including Constant score, Oxford Shoulder Score (OSS), University of California Los Angeles (UCLA) Shoulder Score, complications, and patient satisfaction.

Results: After applying the selection criteria, 12 clinical studies were included for data extraction and analysis. In total, 291 shoulders (in 284 patients) treated with subacromial balloon spacer implantation were pooled for evaluation, with a mean follow-up of 22.9 ± 14.9 months (range, 6-60 months). Constant scores were used as an outcome metric for 267 shoulders (91.7%; 11 studies), with improvements in mean Constant score ranging from 18.5 to 49.6 points. Patient satisfaction was assessed in 105 patients (37.0%; 5 studies), with rates of patients indicating they were satisfied or very satisfied with their treatment outcome ranging from 45.8% to 100%. A total of 6 patients (2.1%) experienced complications related to balloon spacer implantation, including transient neurapraxia of the lateral antebrachial cutaneous nerve, superficial wound infection, deep wound infection, and balloon migration. Of these, 3 patients (2 balloon migration, 1 deep wound infection) required subsequent surgeries for balloon removal.

Conclusion: Placement of the subacromial balloon spacer is a minimally invasive, technically simple procedure with favorable patient-reported outcomes at limited short-term follow-up. However, inherent methodological limitations and patient heterogeneity between studies may impair our ability to fully characterize the longer term efficacy, particularly relative to other potential surgical options. Further prospective randomized or comparative studies are warranted to ascertain clinical outcomes of subacromial balloon spacer in the management of massive and irreparable RCTs.

Keywords: Shoulder; rotator cuff; subacromial balloon; shoulder biomechanics

Selection of optimal treatment for massive to irreparable rotator cuff tears (RCTs) requires a challenging decision-making process in which surgeons must consider several factors, including duration of symptoms, tear pattern, tear size, and muscle quality. Patient characteristics such as age, comorbidities, shoulder dominance, and activity level also must be considered. Cofield et al[12] classified massive tears as those greater than 5 cm in anteroposterior length. Gerber et al[24] defined massive tears as those involving 2 or more rotator cuff tendons. Surgical repair of RCTs with these characteristics is often technically challenging and is associated with higher rates of treatment failure or only

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BMJ Open

Protocol for a randomised controlled trial of Subacromial spacer for Tears Affecting Rotator cuff Tendons: a Randomised, Efficient, Adaptive Clinical Trial in Surgery (START:REACTS)

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ABSTRACT

Introduction Shoulder pain due to irreparable rotator cuff tears can cause substantial disability, but treatment options are limited. A balloon spacer is a relatively simple addition to a standard arthroscopic debridement procedure, but it is costly and there is no current randomised trial evidence to support its use. This trial will evaluate the clinical and cost-effectiveness of a subacromial balloon spacer for individuals undergoing arthroscopic debridement for irreparable rotator cuff tears. New surgical procedures can provide substantial benefit to patients. Good quality randomised controlled trials (RCTs) are needed, but trials in surgery are typically long and expensive, exposing patients to risk and the healthcare system to substantial costs. One way to improve the efficiency of trials is with an adaptive sample size. Such methods are well established in drug trials but have rarely, if ever, been used in surgical trials.

Methods and analysis Subacromial spacer for Tears Affecting Rotator cuff Tendons: a Randomised, Efficient, Adaptive Clinical Trial in Surgery (START:REACTS) is a participant and assessor blinded, adaptive, multicentre RCT comparing arthroscopic debridement with the InSpace balloon (Stryker, USA) to arthroscopic debridement alone for people with a symptomatic irreparable rotator cuff tear. It uses a group sequential adaptive design where interim analyses are performed using all of the 3, 6 and 12-month data that are available at each time point. A maximum of 221 participants will be randomised (1:1 ratio), this will provide 90% power (at the 5% level) for a 6 point difference in the primary outcome; the Oxford Shoulder Score at 12 months. A substudy will use deltoid-active MRI scans in 56 participants to assess the function of the balloon. Analysis will be on an intention-to-treat basis and reported according to principles established in the Consolidated Standards of Reporting Trials statement.

Ethics and dissemination NRES number 18/WM/0025. The results will be disseminated via peer-reviewed publications, presentations at conferences, lay summaries and social media.

Trial registration number ISRCTN17825590

Strengths and limitations of this study

- ► Multicentre randomised trial of a subacromial spacer balloon following debridement, compared with debridement alone, for irreparable rotator cuff tears of the shoulder.
- ► Participant-assessor blinding, including blinded operation notes with novel unblinding mechanism.
- ► Mechanistic MRI substudy of 56 participants with images at 8 weeks and 6 months after surgery.
- ► Statistical adaptive design, with hard stopping rules for futility or efficacy based on emerging outcomes.

INTRODUCTION

Subacromial spacer balloons

Shoulder pain is a common and disabling problem. The UK population prevalence of shoulder pain is approximately 16%.[1] Rotator cuff disease accounts for 70%–85% of this.[2–4] People with a symptomatic rotator cuff tear typically have pain, restricted movement, loss of strength and disability. The condition is associated with substantial expense to society through both costs of treatment and loss of work (both paid and unpaid).[5–8] Rotator cuff repair is a widely accepted treatment for symptomatic rotator cuff tears.[9 10] Some tears cannot be surgically repaired, these are called irreparable tears.

Section 6.0

Previously Discussed Items

Erythropoietin in Chronic Renal Disease

Plain Language Summary:
Background: Erythropoietin is a drug that is used to treat low blood count caused by kidney disease. Currently, it is covered only for the worst stage of chronic kidney failure with certain conditions.

Should OHP cover this drug for lower stages of chronic kidney disease? Staff recommends OHP expand coverage of this drug because the Oregon Health Authority's Pharmacy & Therapeutics Committee and the Food and Drug Administration (FDA) allow use of this drug to treat kidney disease of all stages. Other insurance companies also cover this drug for all stages of kidney disease when needed.

Question: Should several changes be made to the Prioritized List to add coverage for erythropoietin for non-end stage renal disease?

Question source: Jennifer Smith, PharmD, Pharmacy Manager, Providence Health Plan

Issue: Chronic renal failure with a hemoglobin level <10 was added as an indication for erythropoiesis-stimulating agents in Guideline Note 7 in 2012. The current GN 7 only applies to Line 59 END STAGE RENAL DISEASE. Line 59 only includes ICD-10-CM N18.5 (Chronic kidney disease, stage 5) and N18.6 (End stage renal disease). Earlier stages of chronic kidney disease (ICD-10-CM N18.1-N18.4 and N18.9) are on line 339 CHRONIC KIDNEY DISEASE, which is not referenced in the guideline.

The FDA has approved erythropoietin for all stages of chronic kidney disease with a low hemoglobin level. According to P&T, all ICD-10 codes above the funding line (i.e., all N18 series codes) are being funded for erythropoietin currently in their PA process. However, P&T staff report that as a physician-administered drug, there are very few PA requirements.

Additionally, Dr. Smith requested that ICD-10-CM D63.1 (Anemia in chronic kidney disease) be a code allowable to pair with erythropoietin. However, on further research, HERC staff has determined that D63.1 has only one sub-diagnosis and that is "Erythropoietin resistant anemia" and therefore would not be appropriate to use with erythropoietin.

FDA Epogen labeling 7/2018:
1 INDICATIONS AND USAGE

1.1 Anemia Due to Chronic Kidney Disease

Epogen is indicated for the treatment of anemia due to chronic kidney disease (CKD), including patients on dialysis and not on dialysis to decrease the need for red blood cell (RBC) transfusion.

For adult patients with CKD on dialysis:
• Initiate Epogen treatment when the hemoglobin level is less than 10 g/dL.
• If the hemoglobin level approaches or exceeds 11 g/dL, reduce or interrupt the dose of Epogen.
• The recommended starting dose for adult patients is 50 to 100 Units/kg 3 times weekly intravenously or subcutaneously. The intravenous route is recommended for patients on hemodialysis.

For adult patients with CKD not on dialysis:
• Consider initiating Epogen treatment only when the hemoglobin level is less than 10 g/dL and the following considerations apply:
    o The rate of hemoglobin decline indicates the likelihood of requiring a RBC transfusion and,

o Reducing the risk of alloimmunization and/or other RBC transfusion-related risks is a goal

• If the hemoglobin level exceeds 10 g/dL, reduce or interrupt the dose of Epogen, and use the lowest dose of Epogen sufficient to reduce the need for RBC transfusions.

• The recommended starting dose for adult patients is 50 to 100 Units/kg 3 times weekly intravenously or subcutaneously.

For pediatric patients with CKD:

• Initiate Epogen treatment only when the hemoglobin level is less than 10 g/dL.

• If the hemoglobin level approaches or exceeds 12 g/dL, reduce or interrupt the dose of Epogen.

• The recommended starting dose for pediatric patients (ages 1 month or older) is 50 Units/kg 3 times weekly intravenously or subcutaneously.

Evidence

1) **Stauffer 2014**, prevalence of anemia is CKD in the US
    a. NHANES survey of 12,077 adults
    b. Treatments for anemia include iron supplementation and erythropoietin stimulating agents
    c. The prevalence of anemia increased with stage of CKD
        i. 8.4% at stage 1
        ii. 12.2% at stage 2
        iii. 17.4% at stage 3
        iv. 50.3% at stage 4
        v. 53.4% at stage 5.
    d. A total of 22.8% of CKD patients with anemia reported being treated for anemia within the previous 3 months: 14.6% of patients at CKD stages 1–2 and 26.4% of patients at stages 3–4. 430.5 of stage 5 patients reported treatment

Other payer policies

1) Aetna 2022
    a. Allows all levels of chronic kidney disease (N18.1-N18.9) for use with epo administration

2) Cigna 2020
    a. Chronic Kidney Disease Anemia and EITHER of the following:
        i. Individual is on dialysis.
        ii. Individual is not on dialysis and EITHER of the following:
            1. Initial treatment and ONE of the following:
                a. The patient is ≥ 18 years of age with a hemoglobin < 10.0 g/dL OR
                b. The patient is < 18 years of age with a hemoglobin ≤ 11.0 g/dL
    b. Established treatment and ONE of the following:
        i. The patient is ≥ 18 years of age with a hemoglobin < 11.5 g/dL; OR
        ii. The patient is < 18 years of age with a hemoglobin ≤ 12.0 g/dL
    c. Note: no coding was included in their coverage document

Erythropoietin in Chronic Renal Disease

Current utilization

Per P&T staff, the following codes were used in the past 5 months for Epo administration

Patients	Claims	CodeFFSPHP	CodeDiagCondMedlDet	Diagnosis description
1108	4641	CCO	N18.6	End stage renal disease
86	298	CCO	N18.4	CKD stage 4
23	87	CCO	N18.5	CKD stage 5
25	77	CCO	N18.30	CKD stage 3 unspecified
29	76	CCO	N18.32	CKD stage 3b
15	36	CCO	N18.31	CKD stage 3a
9	20	CCO	N18.9	CKD unspecified
3	3	CCO	N18.2	CKD stage 2
84	260	FFS	N18.6	End stage renal disease
17	62	FFS	N18.4	CKD stage 4
5	13	FFS	N18.5	CKD stage 5
7	13	FFS	N18.32	CKD stage 3b
5	12	FFS	N18.31	CKD stage 3a
3	9	FFS	N18.9	CKD unspecified
1	4	FFS	N18.30	CKD stage 3 unspecified

Erythropoietin in Chronic Renal Disease

HERC staff summary

P&T criteria and FDA guidelines allow treatment with erythropoietin at all stages of CKD. Currently, only stage 5 (end stage) renal disease is paired with erythropoietin in GN7. Private payers are reimbursing for lower stages of CKD to be treated with erythropoietin if the patient meets anemia requirements. As P&T is allowing all N18 codes for erythropoietin use, HERC staff recommends that GN7 be added to line 339 CHRONIC KIDNEY DISEASE so that the anemia criteria in the guideline will apply to all the N18 codes, as these codes appear to be widely used for erythropoietin administration. This will also allow erythropoietin use in less severe stages of renal disease per FDA criteria.

HERC staff recommendations:

1) Add Guideline Note 7 to Line 339 CHRONIC KIDNEY DISEASE
    a. Will ensure that the N18 code series is included in and regulated by this guideline
2) Modify GN7 as shown below

GUIDELINE NOTE 7, ERYTHROPOIESIS-STIMULATING AGENT (ESA) GUIDELINE

Lines 12,59,92,94,111-115,125,133,135,157,158,161,163,179,191,199,200,208,210,214,215,217, 229,234,237,238,258-262,271,276,286-288,294,295,314-316,329,339,396,397,401,419,435,559,593

A) Indicated for anemia (Hgb < 10gm/dl or Hct < 30%) induced by cancer chemotherapy given within the previous 8 weeks or in the setting of myelodysplasia.
    1) Reassessment should be made after 8 weeks of treatment. If no response, treatment should be discontinued. If response is demonstrated, ESAs should be discontinued once the hemoglobin level reaches 10, unless a lower hemoglobin level is sufficient to avoid the need for red blood cell (RBC) transfusion.
B) Indicated for anemia (Hgb < 10gm/dl or HCT < 30%) associated with HIV/AIDS.
    1) An endogenous erythropoietin level < 500 IU/L is required for treatment, and patient may not be receiving zidovudine (AZT) > 4200 mg/week.
    2) Reassessment should be made after 8 weeks. If no response, treatment should be discontinued. If response is demonstrated, the lowest ESA dose sufficient to reduce the need for RBC transfusions should be used, and the Hgb should not exceed 11gm/dl.
C) Indicated for anemia (Hgb < 10 gm/dl or HCT <30%) associated with chronic renal disease ~~failure~~, with or without dialysis.
    1) Reassessment should be made after 12 weeks. If no response, treatment should be discontinued. If response is demonstrated, the lowest ESA dose sufficient to reduce the need for RBC transfusions should be used, and the Hgb should not exceed 11gm/dl. In those not on dialysis, the Hgb level should not exceed 10gm/dl.

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PLOS ONE

Prevalence of Anemia in Chronic Kidney Disease in the United States

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Abstract

Anemia is one of the many complications of chronic kidney disease (CKD). However, the current prevalence of anemia in CKD patients in the United States is not known. Data from the National Health and Nutrition Examination Survey (NHANES) in 2007–2008 and 2009–2010 were used to determine the prevalence of anemia in subjects with CKD. The analysis was limited to adults aged >18 who participated in both the interview and exam components of the survey. Three outcomes were assessed: the prevalence of CKD, the prevalence of anemia in subjects with CKD, and the self-reported treatment of anemia. CKD was classified into 5 stages based on the glomerular filtration rate and evidence of kidney damage, in accordance with the guidelines of the National Kidney Foundation. Anemia was defined as serum hemoglobin levels ≤12 g/dL in women and ≤13 g/dL in men. We found that an estimated 14.0% of the US adult population had CKD in 2007–2010. Anemia was twice as prevalent in people with CKD (15.4%) as in the general population (7.6%). The prevalence of anemia increased with stage of CKD, from 8.4% at stage 1 to 53.4% at stage 5. A total of 22.8% of CKD patients with anemia reported being treated for anemia within the previous 3 months–14.6% of patients at CKD stages 1–2 and 26.4% of patients at stages 3–4. These results update our knowledge of the prevalence and treatment of anemia in CKD in the United States.

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Introduction

The kidneys function as filters of the blood, removing waste products and controlling the balance of fluid and electrolytes. Filtration occurs via bundles of capillaries called glomeruli (singular, glomerulus). A reduction in the glomerular filtration rate (GFR) to <60 mL/min/1.73 m^2 indicates chronic kidney disease (CKD), as do structural or functional renal abnormalities, which may be present in people with normal GFR [1]. Cross-sectional estimates of the prevalence of CKD in the United States range from 1.5% to 15.6% [2].

One of the lesser known functions of the kidneys is the production of erythropoietin, a signaling molecule that stimulates red blood cell production, in response to decreased oxygen levels in the blood. Any disruption of this process, e.g., secondary to a functional abnormality due to CKD, has the potential to produce anemia, a condition in which the number of circulating red blood cells, and therefore the level of hemoglobin, is lower than normal [3].

Other possible causes of anemia in CKD include iron deficiency, inflammation, and the accumulation of uremic toxins [3,4]. Thus, the abnormal composition of blood or urine is an additional indicator of kidney damage.

Anemia in CKD is associated with cognitive impairment, sleep disturbances, CKD progression, cardiovascular comorbidities, and higher mortality [3,5–7]. Direct healthcare costs are higher in CKD patients with anemia than in those without [7], and quality of life issues (e.g., fatigue, reduced productivity) are common [3,5]. The prevalence of anemia (with or without CKD) increases with age [8,9], which means that, as the US population ages, the number of people affected by anemia in CKD will also increase.

Available population-based determinations of the prevalence of anemia in CKD are becoming dated, with many studies referring back to the National Health and Nutrition Examination Survey (NHANES) III, which ended in 1994 [8,10–12]. The most recent studies include NHANES data up to 2006 [8,13], but one was limited to adults over age 64 with advanced CKD [13] and the other used a GFR classification not directly comparable to that of most other studies [8]. This analysis assessed the prevalence of anemia in CKD in the adult (>18 years of age) US population during 2007–2010 using the GFR categories specified by the National Kidney Foundation.

Methods

Study Design and Data Source

This was an analysis of cross-sectional data from the NHANES in 2007–2008 and 2009–2010. The NHANES is a biennial national survey that assesses the physical health of the non-institutionalized civilian population in the United States (www.cdc.gov/nchs/nhanes.htm). It is carried out and overseen by the National Center for Health Statistics, whose institutional review board approves each survey cycle.

Erythropoiesis Stimulating Agents (ESAs)

Goal(s):

- Cover ESAs according to OHP guidelines and current medical literature.
- Cover preferred products when feasible.

Length of Authorization:

- 12 weeks initially, then up to 12 months
- Quantity limit of 30 day per dispense

Requires PA:

- All ESAs require PA for clinical appropriateness.

Covered Alternatives:

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

Approval Criteria		
1. What diagnosis is being treated?	Record ICD10 code	
2. Is this an OHP covered diagnosis?	**Yes:** Go to #3	**No:** Pass to RPh. Deny; not funded by the OHP
3. Is this continuation of therapy previously approved by the FFS program?	**Yes:** Go to #12	**No:** Go to #4
4. Is the requested product preferred?	**Yes:** Go to #6	**No:** Go to #5
5. Will the prescriber change to a preferred product? Message: • Preferred products do not require PA. • Preferred products are evidence-based reviewed for comparative effectiveness and safety by the Pharmacy and Therapeutics (P&T) Committee.	**Yes:** Inform prescriber of covered alternatives in class.	**No:** Go to #6
6. Is the diagnosis anemia due to chronic renal failure[1] or chemotherapy[2,3]?	**Yes:** Go to #7	**No:** Go to #8
7. Is Hgb <10 g/dL or Hct <30% **AND** Transferrin saturation >20% and/or ferritin >100 ng/mL?	**Yes:** Approve for 12 weeks with additional approval based upon adequate response.	**No:** Pass to RPh. Deny; medical appropriateness
8. Is the diagnosis anemia due to HIV[4]?	**Yes:** Go to #9	**No:** Go to #10

Approval Criteria		
9. Is the Hgb <10 g/dL or Hct <30% **AND** Transferrin saturation >20% **AND** Endogenous erythropoietin <500 IU/L **AND** If on zidovudine, is dose <4200 mg/week?	**Yes:** Approve for up to 12 months	**No:** Pass to RPh. Deny; medical appropriateness
10. Is the diagnosis anemia due to ribavirin treatment[5]?	**Yes:** Go to #11	**No:** Pass to RPh. Deny; medical appropriateness
11. Is the Hgb <10 g/dL or Hct <30% **AND** Is the transferrin saturation >20% and/or ferritin >100 ng/mL **AND** Has the dose of ribavirin been reduced by 200 mg/day and anemia persisted >2 weeks?	**Yes:** Approve up to the length of ribavirin treatment.	**No:** Pass to RPh. Deny; medical appropriateness
12. Has the patient responded to initial therapy?	**Yes:** Approve for up to 12 months	**No:** Pass to RPh. Deny; medical appropriateness

References:

1. National Kidney Foundation. NKF KDOQI Guidelines. *NKF KDOQI Guidelines* 2006. Available at: http://www.kidney.org/professionals/KDOQI/guidelines_anemia/index.htm . Accessed May 25, 2012.
2. Rizzo JD, Brouwers M, Hurley P, et al. American Society of Clinical Oncology/American Society of Hermatology Clinical Practice Guideline Update on the Use of Epoetin and Darbepoetin in Adult Patients With Cancer. *JCO* 2010:28(33):4996-5010. Available at: www.asco.org/institute-quality/asco-ash-clinical-practice-guideline-update-use-epoetin-and-darbepoetin-adult. Accessed May 1, 2012.
3. Rizzo JD, Brouwers M, Hurley P, et al. American Society of Hematology/American Society of Clinical Oncology clinical practice guideline update on the use of epoetin and darbepoetin in adult patients with cancer. *Blood*. 2010:116(20):4045-4059.
4. Volberding PA, Levine AM, Dieterich D, et al. Anemia in HIV infection: Clinical Impact and Evidence-Based Management Strategies. *Clin Infect Dis*. 2004:38(10):1454-1463. Available at: http://cid.oxfordjournals.org/content/38/10/1454. Accessed May 8, 2012.
5. Recombinant Erythropoietin Criteria for Use for Hepatitis C Treatment-Related Anemia. VHA Pharmacy Benefits Management Strategic Healthcare Group and Medical Advisory Panel. April 2007

P&T Review: *1/19 (JP); 7/16; 5/14; 11/12; 6/12; 2/12, 9/10*
Implementation: *10/13/16; 1/1/13; 9/24/12; 5/14/12*

Orthodontia Guideline Update

Issue: OHA Dental Director, Dr. Kaz Rafia, Dr. Rafia requested addition of a requirement to be clear of active dental decay and periodontal disease, as these conditions increase the medical risk of orthodontics. Dr. Rafia also requested the removal of #3-6 as they are redundant to #7 in the guideline.

HERC staff recommendation:

1) Modify Guideline Note 196 as shown below

GUIDELINE NOTE 169, ORTHODONTICS FOR CRANIOFACIAL ANOMALIES AND HANDICAPPING MALOCCLUSION

Line 256

Orthodontic treatment is included on this line for persons under the age of 21 with

1) Cleft lip and palate, cleft palate or cleft lip with alveolar process involvement, OR
2) Other craniofacial anomalies resulting in significant malocclusion expected to result in difficulty with mastication, speech, or other oral function, OR
3) ~~Deep impinging overbite when lower incisors are destroying the soft tissue of the palate, tissue laceration and/or clinical attachment must be present, OR~~
4) ~~Crossbite of individual anterior teeth when clinical attachment loss and recession of the gingival margin are present, OR~~
5) ~~Severe traumatic deviation, OR~~
6) ~~Overjet greater than 9mm with incompetent lips or mandibular protrusion (reverse overjet) greater than 3.5mm with masticatory and speech difficulties; OR~~
7) Severe malocclusions with a Handicapping Labiolingual Deviation Index California Modification score of 26 or higher; AND
8) Free and clear of active decay and periodontal disease, verified by a dental exam in past 6 months

Advanced dental imaging is included on this line only when required for surgical planning for repair of craniofacial anomalies.

HANDICAPPING LABIO-LINGUAL DEVIATION (HLD) INDEX CALIFORNIA MODIFICATION SCORE SHEET

(You will need this score sheet and a Boley Gauge or a disposable ruler)

Provider **Patient**

Name:_____ **Name:**_____

Number:_____

Date:_____

- Position the patient's teeth in centric occlusion.
- Record all measurements in the order given and round off to the nearest millimeter (mm).
- ENTER SCORE '0' IF THE CONDITION IS ABSENT

CONDITIONS #1 – #6A ARE AUTOMATIC QUALIFYING CONDITIONS **HLD Score**

1. Cleft palate deformity (See scoring instructions for types of acceptable documentation)
Indicate an 'X' if present and score no further ..... _____

2. Cranio-facial anomaly (Attach description of condition from a credentialed specialist)
Indicate an 'X' if present and score no further ..... _____

3. Deep impinging overbite **WHEN LOWER INCISORS ARE DESTROYING THE SOFT TISSUE OF THE PALATE. TISSUE LACERATION AND/OR CLINICAL ATTACHMENT LOSS MUST BE PRESENT.**
Indicate an 'X' if present and score no further ..... _____

4. Crossbite of individual anterior teeth **WHEN CLINICAL ATTACHMENT LOSS AND RECESSION OF THE GINGIVAL MARGIN ARE PRESENT**
Indicate an 'X' if present and score no further ..... _____

5. Severe traumatic deviation. (Attach description of condition. For example: loss of a premaxilla segment by burns or by accident, the result of osteomyelitis, or other gross pathology.)
Indicate an 'X' if present and score no further ..... _____

6A. Overjet greater than 9mm with incompetent lips or mandibular protrusion (reverse overjet) greater than 3.5mm with masticatory and speech difficulties. Indicate an 'X' if present and score no further ..... _____

THE REMAINING CONDITIONS MUST SCORE 26 OR MORE TO QUALIFY

6B. Overjet equal to or less than 9 mm ..... _____

7. Overbite in mm ..... _____

8. Mandibular protrusion (reverse overjet) equal to or less than 3.5 mm ..... _____ x 5 = _____

9. Open bite in mm ..... _____ x 4 = _____

IF BOTH ANTERIOR CROWDING AND ECTOPIC ERUPTION ARE PRESENT IN THE ANTERIOR PORTION OF THE SAME ARCH, SCORE ONLY THE MOST SEVERE CONDITION. DO NOT COUNT BOTH CONDITIONS.

10. Ectopic eruption (Identify by tooth number, and count each tooth, excluding third molars) _____ (tooth numbers) _____ (total) x 3 = _____

11. Anterior crowding (Score one for MAXILLA, and/or one for MANDIBLE) _____ (maxilla) _____ (mandible) _____ (total) x 5 = _____

12. Labio-Lingual spread in mm ..... _____

13. Posterior unilateral crossbite (must involve two or more adjacent teeth, one of which must be a molar. No score for bi-lateral posterior crossbite) ..... Score 4 _____

AUTHORIZATION OF SERVICES IS BASED ON MEDICAL NECESSITY. IF A PATIENT DOES NOT HAVE ONE OF THE SIX AUTOMATIC QUALIFYING CONDITIONS OR DOES NOT SCORE 26 OR ABOVE, THE PATIENT MAY STILL BE ELIGIBLE FOR THESE SERVICES BASED ON EARLY AND PERIODIC SCREENING, DIAGNOSTIC AND TREATMENT (EPSDT) CRITERIA NECESSARY TO CORRECT OR AMELIORATE THE PATIENT'S CONDITION. FOR A FURTHER EXPLANATION OF EPSDT CRITERIA, PLEASE SEE THE ORTHODONTICS SECTION OF THE CALIFORNIA MEDI-CAL DENTAL PROGRAM PROVIDER HANDBOOK.

HANDICAPPING LABIO-LINGUAL DEVIATION (HLD) INDEX CALIFORNIA MODIFICATION
SCORING INSTRUCTIONS

The intent of the HLD index is to measure the presence or absence, and the degree, of the handicap caused by the components of the Index, and not to diagnose 'malocclusion.' All measurements are made with a Boley Gauge (or a disposable ruler) scaled in millimeters. Absence of any conditions must be recorded by entering '0.' (Refer to the attached score sheet.)

The following information should help clarify the categories on the HLD Index:

1. **Cleft Palate Deformity:** Acceptable documentation must include at least one of the following: 1) diagnostic casts; 2) intraoral photograph of the palate; 3) written consultation report by a qualified specialist or Craniofacial Panel) Indicate an 'X' on the score sheet. Do not score any further if present. (This condition is automatically considered to qualify for orthodontic services.)

2. **Cranio-facial Anomaly:** (Attach description of condition from a credentialed specialist) Indicate an 'X' on the score sheet. Do not score any further if present. (This condition is automatically considered to qualify for orthodontic services.)

3. **Deep Impinging Overbite:** Indicate an 'X' on the score sheet when lower incisors are destroying the soft tissue of the palate and tissue laceration and/or clinical attachment loss are present. Do not score any further if present. (This condition is automatically considered to be a handicapping malocclusion without further scoring.)

4. **Crossbite of Individual Anterior Teeth:** Indicate an 'X' on the score sheet when clinical attachment loss and recession of the gingival margin are present. Do not score any further if present. (This condition is automatically considered to be a handicapping malocclusion without further scoring.)

5. **Severe Traumatic Deviation:** Traumatic deviations are, for example, loss of a premaxilla segment by burns or by accident; the result of osteomyelitis; or other gross pathology. Indicate an 'X' on the score sheet and attach documentation and description of condition. Do not score any further if present. (This condition is automatically considered to be a handicapping malocclusion without further scoring.)

6A **Overjet greater than 9mm with incompetent lips or mandibular protrusion (reverse overjet) greater than 3.5mm with masticatory and speech difficulties:** Overjet is recorded with the patient's teeth in centric occlusion and is measured from the labial of the lower incisors to the labial of the corresponding upper central incisors. This measurement should record the greatest distance between any one upper central incisor and it's corresponding lower central or lateral incisor. If the overjet is greater than 9mm with incompetent lips or mandibular protrusion (reverse overjet) is greater than 3.5mm with masticatory and speech difficulties, indicate an 'X' and score no further. (This condition is automatically considered to be a handicapping malocclusion without further scoring. Photographs shall be submitted for this automatic exception.)

6B **Overjet equal to or less than 9mm:** Overjet is recorded as in condition #6A above. The measurement is rounded off to the nearest millimeter and entered on the score sheet.

7. **Overbite in Millimeters:** A pencil mark on the tooth indicating the extent of overlap facilitates this measurement. It is measured by rounding off to the nearest millimeter and entered on the score sheet. ('Reverse' overbite may exist in certain conditions and should be measured and recorded.)

8. **Mandibular Protrusion (reverse overjet) equal to or less than 3.5mm:** Mandibular protrusion (reverse overjet) is recorded as in condition #6A above. The measurement is rounded off to the nearest millimeter. Enter on the score sheet and multiply by five (5).

9. **Open Bite in Millimeters:** This condition is defined as the absence of occlusal contact in the anterior region. It is measured from incisal edge of a maxillary central incisor to incisal edge of a corresponding mandibular incisor, in millimeters. The measurement is entered on the score sheet and multiplied by four (4). In cases of pronounced protrusion associated with open bite, measurement of the open bite is not always possible. In those cases, a close approximation can usually be estimated.

10. **Ectopic Eruption:** Count each tooth, excluding third molars. Each qualifying tooth must be more the 50% blocked out of the arch. Count only one tooth when there are mutually blocked out teeth. Enter the number of qualifying teeth on the score sheet and multiply by three (3). If anterior crowding (condition #11) also exists in the same arch, score the condition that scores the most points. **DO NOT COUNT BOTH CONDITIONS.** However, posterior ectopic teeth can still be counted separately from anterior crowding when they occur in the same arch.

11. **Anterior Crowding:** Arch length insufficiency must exceed 3.5mm. Mild rotations that may react favorably to stripping or mild expansion procedures are not to be scored as crowded. Score one (1) for a crowded maxillary arch and/or one (1) for a crowded mandibular arch. Enter total on the score sheet and multiply by five (5). If ectopic eruption (condition #10) exists in the anterior region of the same arch, count the condition that scores the most points. **DO NOT COUNT BOTH CONDITIONS.** However, posterior ectopic teeth can still be counted separately from anterior crowding when they occur in the same arch.

12. **Labio-Lingual Spread:** A Boley Gauge (or a disposable ruler) is used to determine the extent of deviation from a normal arch. Where there is only a protruded or lingually displaced anterior tooth, the measurement should be made from the incisal edge of that tooth to the normal arch line. Otherwise, the total distance between the most protruded anterior tooth and the most lingually displaced adjacent anterior tooth is measured. In the event that multiple anterior crowding of teeth is observed, all deviations from the normal arch should be measured for labio-lingual spread, but only the most severe individual measurement should be entered on the score sheet.

13. **Posterior Unilateral Crossbite**: This condition involves two or more adjacent teeth, one of which must be a molar. The crossbite must be one in which the maxillary posterior teeth involved may either be both palatal or both completely buccal in relation to the mandibular posterior teeth. The presence of posterior unilateral crossbite is indicated by a score of four (4) on the score sheet. **NO SCORE FOR BI-LATERIAL CROSSBITE.**

Section 7.0

Below the Line review

Below the Line Review 2022
Benign Carcinoid Gastrointestinal Tumors

Issue: Benign carcinoid tumors of the gut other than colon (ICD-10-CM D3A.0 family) are currently on line 638 BENIGN NEOPLASMS OF DIGESTIVE SYSTEM. Carcinoid tumors of the colon and appendix are on line 166 ANAL, RECTAL AND COLONIC POLYPS. Benign carcinoid tumors of other organs (lung, thymus) are on covered lines. Benign carcinoid tumors of the kidney (ICD-10CM D3A.093) are on line 511 ENIGN NEOPLASM OF KIDNEY AND OTHER URINARY ORGANS.

Malignant carcinoid tumors (ICD-10-CM C7A.0 family) are all on covered lines. Malignant GI carcinoid tumors are on line 157 CANCER OF COLON, RECTUM, SMALL INTESTINE AND ANUS.

Carcinoid tumor is a type of neuroendocrine tumor that grows from neuroendocrine cells and can occur in many parts of the body. Carcinoid tumors often grow very slowly. In children and young adults, carcinoid tumors are most often found in the appendix or in the lungs. In adults, carcinoid tumors are most often found in the digestive tract. Many patients have no symptoms from carcinoid tumors. Others have pain in the abdomen, nausea, diarrhea, or carcinoid syndrome (feeling flushed, nausea, diarrhea).

At the time of the creation of the Prioritized List, malignant and benign carcinoid tumors were thought to be distinct entities. Current understanding is that all carcinoid tumors are malignant and capable of metastasizing.

Per the NIH [https://www.cancer.gov/types/gi-carcinoid-tumors/patient/gi-carcinoid-treatment-pdq], carcinoid tumors are treated with surgery if resectable, radiation, chemotherapy, and/or hormone therapy.

HERC staff recommendations:

1) Add the ICD-10-CM D3A.0 family (benign GI carcinoid tumors) to line 157 CANCER OF COLON, RECTUM, SMALL INTESTINE AND ANUS and remove from line 638 BENIGN NEOPLASMS OF DIGESTIVE SYSTEM
2) Add ICD-10CM D3A.093 (Benign carcinoid tumor of the kidney) to line 214 CANCER OF KIDNEY AND OTHER URINARY ORGANS and remove from line 638 BENIGN NEOPLASMS OF DIGESTIVE SYSTEM

Section 8.0

Coverage Guidances

Coverage Guidance – PANDAS/PANS

Question: How should the Coverage Guidance *Pediatric Autoimmune Neuropsychiatric Disorders Associated with Streptococcal Infections (PANDAS) and Pediatric Acute-Onset Neuropsychiatric Syndrome (PANS)* be applied to the Prioritized List?

Question source: EbGS

Issue: EbGS approved a coverage guidance regarding PANDAS/PANS at their April 2022 meeting. The "blue box" wording is shown below:

HERC Coverage Guidance

Tonsillectomy, adenoidectomy, adenotonsillectomy, and prophylactic antibiotic therapy are not recommended for coverage to treat pediatric autoimmune neuropsychiatric disorders associated with streptococcal infections (PANDAS) and pediatric acute-onset neuropsychiatric syndrome (PANS) (*weak recommendation*).

Up to 3 monthly immunomodulatory courses of intravenous immunoglobulin (IVIG) therapy or therapeutic plasma exchange are recommended for coverage to treat PANDAS and PANS (*weak recommendation*) when both of the following are met:

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

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

Current Prioritized List status

CODES	DESCRIPTION	
ICD-10-CM Codes		
D89.89	Other specified disorders involving the immune mechanism, not elsewhere classified	313 DISORDERS INVOLVING THE IMMUNE SYSTEM
D89.9	Disorder involving the immune mechanism, unspecified	UNDEFINED CONDITIONS
G04.81	Other encephalitis and encephalomyelitis	536 VIRAL, SELF-LIMITING ENCEPHALITIS, MYELITIS AND ENCEPHALOMYELITIS and the dysfunction lines
CPT Codes		
Behavioral therapy		
90832	Psychotherapy, 30 minutes with patient	Multiple lines but not 313
90833	Psychotherapy, 30 minutes with patient when performed with an evaluation and management service (List separately in addition to the code for primary procedure)	See above
90834	Psychotherapy, 45 minutes with patient	See above
90836	Psychotherapy, 45 minutes with patient when performed with an evaluation and management service (List separately in addition to the code for primary procedure)	See above
90837	Psychotherapy, 60 minutes with patient	See above
90838	Psychotherapy, 60 minutes with patient when performed with an evaluation and management service (List separately in addition to the code for primary procedure)	See above
90839	Psychotherapy for crisis; first 60 minutes	See above
Intravenous immunoglobulin therapy		
90283	Immune globulin (IVIG), human, for intravenous use	Ancillary
96365	Intravenous infusion, for therapy, prophylaxis, or diagnosis (specify substance or drug); initial, up to 1 hour	Ancillary
96366	Intravenous infusion, for therapy, prophylaxis, or diagnosis (specify substance or drug); each additional hour (List separately in addition to code for primary procedure)	Ancillary
99601	Home infusion/specialty drug administration, per visit (up to 2 hours)	Ancillary
Plasma exchange		
36514	Therapeutic apheresis; for plasma pheresis	Multiple lines including 313

HERC staff recommendations:

1) Add ICD-10-CM D89.9 (Disorder involving the immune mechanism, unspecified) to line 313
2) Add a new guideline to line 313 DISORDERS INVOLVING THE IMMUNE SYSTEM as shown below
    a. There are no CPT codes on line 313 for tonsillectomy, adenoidectomy, or adenotonsillectomy; therefore no need to call out lack of coverage in the guideline
    b. CPT 36514 (Therapeutic apheresis) which is used for plasma pheresis is already on line 313.

GUIDELINE NOTE XXX PANDAS AND PANS

Line 313

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

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

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

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

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

Health Evidence Review Commission (HERC)

Coverage Guidance: Pediatric Autoimmune Neuropsychiatric Disorders Associated with Streptococcal Infections (PANDAS) and Pediatric Acute-Onset Neuropsychiatric Syndrome (PANS)

DRAFT for HERC meeting 5/19/2022

HERC Coverage Guidance

Tonsillectomy, adenoidectomy, adenotonsillectomy, and prophylactic antibiotic therapy are not recommended for coverage to treat pediatric autoimmune neuropsychiatric disorders associated with streptococcal infections (PANDAS) and pediatric acute-onset neuropsychiatric syndrome (PANS) (*weak recommendation*).

Up to 3 monthly immunomodulatory courses of intravenous immunoglobulin (IVIG) therapy or therapeutic plasma exchange are recommended for coverage to treat PANDAS and PANS (*weak recommendation*) when both of the following are met:

A) A clinically appropriate trial of two or more less-intensive treatments (for example, appropriate limited course of nonsteroidal anti-inflammatory drugs (NSAIDs), corticosteroids, selective serotonin reuptake inhibitors (SSRIs), behavioral therapy, short-course antibiotic therapy) was either not effective, not tolerated, or did not result in sustained improvement in symptoms (as measured by a lack of clinically meaningful improvement on a validated instrument directed at the patient's primary symptom complex). These trials may be done concurrently, AND

B) A consultation with and recommendation from a pediatric subspecialist (for example, pediatric neurologist, pediatric psychiatrist, neurodevelopmental pediatrician, pediatric rheumatologist, pediatric allergist/immunologist, pediatric infectious disease specialist) as well as the recommendation of the patient's primary care provider (for example, family physician, pediatrician, pediatric nurse practitioner, naturopath). The subspecialist consultation may be a teleconsultation. For adolescents, an adult subspecialist consult may replace a pediatric subspecialist consult.

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

Note: Other treatments (corticosteroids, SSRIs, NSAIDs, short-course antibiotics, and behavioral therapies) were included in an initial version of this report. These therapies were determined to be beyond the scope of a HERC coverage guidance, as these therapies are commonly used for many indications and are not typically subject to utilization control. Only treatments subject to coverage criteria were retained for the final version of this report.

Note. Definitions for strength of recommendation are in Appendix A, GRADE Table Element Descriptions. Rationales for each recommendation appear below in the GRADE tables.

Oregon Health Authority

Table of Contents

Rationale for development of coverage guidances and multisector intervention reports

Coverage guidances are developed to inform coverage recommendations for public and private health plans in Oregon as plan administrators seek to improve patients' experience of care, population health, and the cost-effectiveness of health care. In the era of public and private sector health system transformation, reaching these goals requires a focus on maximizing the benefits and minimizing the harms and costs of health interventions.

HERC uses the following principles in selecting topics for its reports to guide public and private payers:

- Represents a significant burden of disease or health problem
- Represents important uncertainty with regard to effectiveness or harms
- Represents important variation or controversy in implementation or practice
- Represents high costs or significant economic impact
- Topic is of high public interest

HERC bases its reports on a review of the best available research applicable to the intervention(s) in question. For coverage guidances, which focus on diagnostic and clinical interventions, evidence is evaluated using an adaptation of the Grading of Recommendations, Assessment, Development, and Evaluation (GRADE) methodology. For more information on coverage guidance methodology, see Appendix A.

Multisector interventions can be effective ways to prevent, treat, or manage disease at a population level. In some cases, HERC has reviewed evidence and identified effective interventions, but has not made formal coverage recommendations when these policies are implemented in settings other than traditional health care delivery systems because effectiveness could depend on the environment in which the intervention is implemented.

GRADE Tables

HERC develops recommendations by using the concepts of the GRADE system. GRADE is a transparent and structured process for developing and presenting evidence and for performing the steps involved in developing recommendations. The table below lists the elements that determine the strength of a recommendation. HERC reviews the evidence and assesses each element, which in turn is used to develop the recommendations presented in the coverage guidance box. Estimates of effect are derived from the evidence presented in this document. Assessments of confidence are from the published systematic reviews and meta-analyses, where available and judged to be reliable. The level of confidence in the estimate is determined by HERC based on the assessment of 2 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 Tables

Should prophylactic antibiotics be recommended for coverage for PANDAS/PANS?

Outcomes	Estimate of Effect for Outcome *Confidence in Estimate*	Resource Allocation	Values and Preferences	Other Considerations
Change in psychiatric symptom scores *(Critical outcome)*	In a single RCT (N = 37) comparing penicillin to placebo for 4 months, there was no significant difference in neuropsychiatric symptoms between children when they received penicillin or placebo. The cross-over design meant that each participant was in both the intervention and control group for the analysis. In a second RCT comparing prophylactic azithromycin (N = 17) to placebo (N = 14) for 4 weeks, the azithromycin group had a significantly greater reduction OCD severity, but no significant difference in number of obsessions and compulsions. Significantly more children were classified as responding at a clinically significant level in the azithromycin group (7/17) than in the placebo group (1/14). In a third RCT that tested prophylactic antibiotic therapy for 1 year, significantly more (5/11) children who received penicillin demonstrated significant reduction in symptoms compared to (1/12) children who received azithromycin. Compared to the year before baseline, children in both groups had fewer exacerbations during the trial year. ●○○○ *(very low confidence, based on 3 RCTs, n = 91)*	Antibiotics are inexpensive and readily available. Treatment of complications of long-term or frequent antibiotic use would add cost.	Some parents would want any treatment that might help their child's symptoms. However, other parents would have concerns about the risks and side effects of long-term or frequent antibiotic use.	Long-term or frequent antibiotic use is associated with a range of negative consequences, including but not limited to *C. difficile* infection, gut flora disruption, diarrhea, and increased antibiotic resistance leading to reduced ability to treat other infections with antibiotics. Most health plan cover short-term antibiotics without prior authorization criteria but may scrutinize or not cover long-term prescriptions.
Hospitalizations *(Critical outcome)*	No evidence identified.			

Should prophylactic antibiotics be recommended for coverage for PANDAS/PANS?

Outcomes	Estimate of Effect for Outcome *Confidence in Estimate*	Resource Allocation	Values and Preferences	Other Considerations
Harms *(Important outcome)*	The few harms that were reported included heart rate irregularity (9/12) for children who received azithromycin, and loose stool (no statistics reported). ●○○○ *(very low confidence, based on 1 RCTs, n = 23)*			
Function or quality of life for patient *(Important outcome)*	No evidence identified.			
Function or quality of life for patient *(Important outcome)*	No evidence identified.			

Balance of benefits and harms: We have very low confidence that prophylactic antibiotic use is helpful in PANDAS/PANS, given the small sample sizes in the included studies. There are concerning known harms of frequent or long-term antibiotic use.
Rationale: Prophylactic antibiotic therapy is not recommended for coverage for PANDAS/PANS because of insufficient comparative evidence that prophylactic antibiotic use leads to any measurable benefit for these conditions. The known risks of prophylactic or long-term antibiotic use outweigh potential benefits in these conditions. The recommendation is weak because of the very low quality of the evidence.
Recommendation: Prophylactic antibiotic therapy is not recommended for coverage for PANDAS/PANS (*weak recommendation*).

Note. GRADE table elements are described in Appendix A. A GRADE Evidence Profile is in Appendix B.
Abbreviations. OCD: obsessive-compulsive disorder; PANDAS: pediatric autoimmune neuropsychiatric disorders associated with streptococcal infections; PANS: pediatric acute-onset neuropsychiatric syndrome; RCT: randomized controlled trial.

Should tonsillectomy and/or adenoidectomy be recommended for coverage for PANDAS/PANS?

Outcomes	Estimate of Effect for Outcome/ *Confidence in Estimate*	Resource Allocation	Values and Preferences	Other Considerations
Change in psychiatric symptom scores *(Critical outcome)*	No difference in neuropsychiatric symptoms between surgery and non-surgery groups among children diagnosed with PANDAS. ●●○○ *(low confidence, based on 2 comparative cohort studies, n = 232)*	Tonsillectomy and adenoidectomy are invasive procedures requiring general anesthesia and specialty surgical care.	Parents would not value an invasive surgery with risks as well as the risks of general anesthesia for a procedure that has no evidence of benefits.	Tonsillectomy and/or adenoidectomy frequently have coverage limitations, such as multiple streptococcal infections in one year. This procedure has historically been overused.
Hospitalizations *(Critical outcome)*	No evidence identified.			
Harms *(Important outcome)*	No evidence identified.			
Function or quality of life for patient *(Important outcome)*	No evidence identified.			
Function or quality of life for patient *(Important outcome)*	No evidence identified.			

Balance of benefits and harms: We have low confidence that that there is no benefit from tonsillectomy and/or adenoidectomy for PANDAS/PANS, and this procedure has known harms.
Rationale: Tonsillectomy and/or adenoidectomy are not recommended for coverage for treatment of PANDAS/PANS because these procedures have known harms and because evidence shows that these procedures do not improve the outcomes in this condition. The recommendation is weak because of the low quality of the evidence.
Recommendation: Tonsillectomy and/or adenoidectomy are not recommended for coverage (*weak recommendation*) for treatment of PANDAS/PANS.

Note. GRADE table elements are described in Appendix A. A GRADE Evidence Profile is in Appendix B.

Abbreviations. PANDAS: pediatric autoimmune neuropsychiatric disorders associated with streptococcal infections; PANS: pediatric acute-onset neuropsychiatric syndrome.

Should IVIG be recommended for coverage for PANDAS/PANS?

Outcomes	Estimate of Effect for Outcome/ *Confidence in Estimate*	Resource Allocation	Values and Preferences	Other Considerations
Change in psychiatric symptom scores *(Critical outcome)*	<u>Compared to Saline Placebo</u> Among children meeting the criteria for PANDAS and OCD in an RCT, 7/18 had a significant decrease in symptoms 6 weeks after receiving 2 consecutive days of IVIG infusions, and 4/17 children in the placebo group had a significant decrease in symptoms. When comparing the IVIG group and placebo group, there were no statistically significant differences. During an open-label phase of this same trial, 17/24 children meeting the criteria for PANDAS and OCD had a significant decrease in symptoms 12 to 18 weeks after receiving 2 consecutive days of IVIG infusions on 1 or 2 occasions. Another RCT compared children who received IVIG (N = 9) to children who received saline placebo (N = 10) 1 month after treatment reported that the IVIG group improved significantly more on most measures compared to the placebo group. One year after treatment, the improvements in the IVIG group were maintained, but the placebo group was not followed to determine whether the IVIG group's symptoms remained significantly better than the placebo group's symptoms. <u>Compared to plasma exchange</u> No significant difference 1 month or 1 year after treatment between children receiving IVIG (N = 9) or plasma exchange (N = 10); both groups had	IVIG is expensive and requires the cost of an infusion center, nursing care, and possible hospitalization. Treatment for side effects of IVIG would add cost. IVIG is a scarce resource and shortages have been reported in the past.	Parents would value any treatment that would improve their child's symptoms. However, many parents would value avoiding a treatment with known side effects that has little evidence of effectiveness.	IVIG is a blood product with the inherent risks that accompany accepting any form of blood product. IVIG therapy has a significant rate of mild side effects including fever, body aches, nausea, rash, and fatigue. Severe side effects include thrombosis, renal dysfunction, and acute renal failure, and life-threatening allergic reaction. IVIG can interfere with vaccine effectiveness for vaccines given

Should IVIG be recommended for coverage for PANDAS/PANS?

Outcomes	Estimate of Effect for Outcome/ *Confidence in Estimate*	Resource Allocation	Values and Preferences	Other Considerations
	significant improvement in symptoms compared to baseline at both 1-month and 1-year follow-ups ●○○○ *(very low confidence, based on 2 RCTs, N = 54)*			within several months of IVIG. Several products on the market are FDA-approved for people under the age of 19.
Hospitalizations *(Critical outcome)*	No evidence identified.			
Harms *(Important outcome)*	1/33 children who received IVIG infusions had an allergic reaction to the IVIG infusion that resolved without complication. 31/33 children reported mild or moderate adverse events such as nausea, vomiting, headache, fever, joint pain, tiredness, stomach pain, or decreased appetite. ●○○○ *(very low confidence, based on 2 RCTs, N = 64)*			
Function or quality of life for patient *(Important outcome)*	No evidence identified.			
Function or quality of life for patient *(Important outcome)*	No evidence identified.			

Balance of benefits and harms: There were mixed results from 2 very small trials regarding the clinical effectiveness of IVIG. Outside of PANDAS, no evidence met inclusion criteria for PANS. IVIG has a significant rate of known harms.

Rationale: Expert opinion and lower-quality observational data indicate there may be benefit for some patients with these conditions, but recommended treatment protocols and criteria for treatment vary widely. Due to the severe impact of symptoms associated with PANDAS/PANS on child health, growth and development, and the lack of known effective treatments, coverage of IVIG is recommended when recommended by the patient's PCP and a pediatric subspecialist and after less-intensive therapies were not effective, were not tolerated or did not result in sustained improvement in symptoms. The recommendation is weak because of the very low quality of the evidence.

Should IVIG be recommended for coverage for PANDAS/PANS?

Outcomes	Estimate of Effect for Outcome/ *Confidence in Estimate*	Resource Allocation	Values and Preferences	Other Considerations
Recommendation: Up to 3 monthly immunomodulatory courses of intravenous immunoglobulin (IVIG) therapy are recommended for coverage to treat PANDAS and PANS (*weak recommendation*) when both of the following are met: a) A clinically appropriate trial of two or more less-intensive treatments (for example, appropriate limited course of nonsteroidal anti-inflammatory drugs (NSAIDs), corticosteroids, selective serotonin reuptake inhibitors (SSRIs), behavioral therapy, short-course antibiotic therapy) was either not effective, not tolerated, or did not result in sustained improvement in symptoms (as measured by a lack of clinically meaningful improvement on a validated instrument directed at the patient's primary symptom complex). These trials may be done concurrently, AND b) A consultation with and recommendation from a pediatric subspecialist (for example, pediatric neurologist, pediatric psychiatrist, neurodevelopmental pediatrician, pediatric rheumatologist, pediatric allergist/immunologist, pediatric infectious disease specialist) as well as the recommendation of the patient's primary care provider (for example, family physician, pediatrician, pediatric nurse practitioner, naturopath). The subspecialist consultation may be a teleconsultation. For adolescents, an adult subspecialist consult may replace a pediatric subspecialist consult. A reevaluation at 3 months by both the primary care provider and pediatric expert is required for continued therapy of IVIG. This evaluation must include clinical testing with a validated instrument, which must be performed pretreatment and posttreatment to demonstrate clinically meaningful improvement.				

Note. GRADE table elements are described in Appendix A. A GRADE Evidence Profile is in Appendix B.

Abbreviations. IVIG: intravenous immunoglobulin; OCD: obsessive-compulsive disorder; PANDAS: pediatric autoimmune neuropsychiatric disorders associated with streptococcal infections; PANS: pediatric acute-onset neuropsychiatric syndrome; RCT: randomized controlled trial.

Should therapeutic plasma exchange be recommended for coverage for PANDAS/PANS?

Outcomes	Estimate of Effect for Outcome/ *Confidence in Estimate*	Resource Allocation	Values and Preferences	Other Considerations
Change in psychiatric symptom scores *(Critical outcome)*	<u>Compared to saline placebo</u> In the same RCT that is described in the IVIG table, the plasma exchange group (N = 10) was compared to the same placebo group (N = 10) 1 month after treatment. The plasma exchange group improved significantly more on most measures compared to the placebo group. One year after treatment, the improvements in the plasma exchange were maintained, but the placebo group was not followed to determine whether the plasma exchange group's symptoms remained significantly better than the placebo group's symptoms. <u>Compared to intravenous immunoglobulin</u> No significant difference 1 month or 1 year after treatment between children receiving IVIG (N = 9) or plasma exchange (N = 10); both groups had significant improvement in symptoms compared to baseline at both 1-month and 1-year follow-ups ●○○○ *(very low confidence, based on 1 RCT, N = 29)*	Plasma exchange is an expensive therapy which requires a monitored infusion in a clinical setting. Children in the studies included in this review required multiple treatment sessions.	Parents would value any treatment that would improve their child's symptoms. However, many parents would value avoiding a treatment with known side effects that has little evidence of effectiveness.	High rates of patients undergoing plasma exchange report side effects, including fever, chills, and muscle cramps. Known complications of plasma exchange include circuit clotting, low or high blood pressure, nausea, vomiting, itchy skin, hives, low calcium levels in the blood, venous access malfunction, infections, thrombosis, and anaphylactic shock.
Hospitalizations *(Critical outcome)*	No evidence found.			
Harms *(Important outcome)*	All children who received plasma exchange (10/10) experienced mild side effects such as nausea, vomiting, anxiety, or fever. ●○○○ *(very low confidence, based on 1 RCT, N = 29)*			

Should therapeutic plasma exchange be recommended for coverage for PANDAS/PANS?

Outcomes	Estimate of Effect for Outcome/ *Confidence in Estimate*	Resource Allocation	Values and Preferences	Other Considerations
Function or quality of life for patient *(Important outcome)*	No evidence found.			
Function or quality of life for patient *(Important outcome)*	No evidence found.			

Balance of benefits and harms: The comparative evidence that plasma exchange is effective for treating PANDAS is very limited and shows no clear benefit. The harms of this treatment are generally mild but serious complications can occur.
Rationale: Expert opinion and lower-quality observational data indicate there may be benefit for some patients with these conditions, but recommended treatment protocols and criteria for treatment vary widely. Due to the severe impact of symptoms associated with PANDAS/PANS on child health, growth and development, and the lack of known effective treatments, coverage of plasma exchange is recommended when recommended by the patient's PCP and a pediatric subspecialist and after less-intensive therapies were not effective, were not tolerated or did not result in sustained improvement in symptoms.

Should therapeutic plasma exchange be recommended for coverage for PANDAS/PANS?

Outcomes	Estimate of Effect for Outcome/ *Confidence in Estimate*	Resource Allocation	Values and Preferences	Other Considerations
Recommendation: Up to 3 monthly immunomodulatory courses of therapeutic plasma exchange are recommended for coverage to treat PANDAS and PANS (*weak recommendation*) when both of the following are met: a) A clinically appropriate trial of two or more less-intensive treatments (for example, appropriate limited course of nonsteroidal anti-inflammatory drugs (NSAIDs), corticosteroids, selective serotonin reuptake inhibitors (SSRIs), behavioral therapy, short-course antibiotic therapy) was either not effective, not tolerated, or did not result in sustained improvement in symptoms (as measured by a lack of clinically meaningful improvement on a validated instrument directed at the patient's primary symptom complex). These trials may be done concurrently, AND b) A consultation with and recommendation from a pediatric subspecialist (for example, pediatric neurologist, pediatric psychiatrist, neurodevelopmental pediatrician, pediatric rheumatologist, pediatric allergist/immunologist, pediatric infectious disease specialist) as well as the recommendation of the patient's primary care provider (for example, family physician, pediatrician, pediatric nurse practitioner, naturopath). The subspecialist consultation may be a teleconsultation. For adolescents, an adult subspecialist consult may replace a pediatric subspecialist consult. A reevaluation at 3 months by both the primary care provider and pediatric expert is required for continued therapy of plasma exchange. This evaluation must include clinical testing with a validated instrument, which must be performed pretreatment and posttreatment to demonstrate clinically meaningful improvement.				

Note. GRADE table elements are described in Appendix A. A GRADE Evidence Profile is in Appendix B.
Abbreviations. IVIG: intravenous immunoglobulin; PANDAS: pediatric autoimmune neuropsychiatric disorders associated with streptococcal infections; PANS: pediatric acute-onset neuropsychiatric syndrome; RCT: randomized controlled trial.

Background

Pediatric autoimmune neuropsychiatric disorders associated with streptococcal infections (PANDAS) and pediatric acute-onset neuropsychiatric syndrome (PANS are conditions associated with a sudden onset of changes or regression in behaviors and experiences prior to puberty in multiple domains, such as motor, neurological, psychiatric, and biological systems.[1-3] Care providers and researchers from multiple disciplines (including microbiology, neurology, neuroimmunology, immunology, child psychiatry, infectious diseases, rheumatology, and pediatrics) have contributed to publications seeking to define these conditions.[3] These conditions have an abrupt onset of symptoms and may include exacerbations, sudden worsening of symptoms in short bursts, in a sawtooth-like pattern.[1-3]

In PANDAS, the triggering mechanism for these changes is hypothesized to be a beta-hemolytic streptococcal infection within 6 months of symptom onset, and is characterized by sudden onset of obsessive-compulsive disorder (OCD), along with verbal or motor tics.[2,4] This hypothesized disease pathway aligns with large epidemiological cohort studies of children in Europe[5] and Asia[6] that observed an 18% to 22% increased risk of any neuropsychiatric disorders in children who had streptococcal infections as compared with children without streptococcal infections, including a higher risk for obsessive-compulsive and tic disorders.[5,6] However, some researchers suggest that tying the diagnosis to streptococcus infection to the exclusion of other etiologies has limited the exploration of other disease pathways that could inform diagnosis and treatment of symptoms.[7,8]The prevalence of PANDAS is not known, but some studies suggest that males are more likely than females to be diagnosed with PANDAS.[9]

PANS is characterized by sudden onset of OCD, with or without severe eating restrictions, and 2 or more other symptoms in neurological, behavioral, or cognitive domains.[3] PANDAS can be considered a subset of PANS. These symptoms could result from multiple disease pathways or other disorders, including but not limited to streptococcus, varicella, or bacterial pneumonia infections.[3,10] The prevalence of PANS is not known.

Two other conditions with similar symptoms are pediatric infection-triggered autoimmune neuropsychiatric disorders (PITAND) and childhood acute neuropsychiatric syndromes (CANS).[10,11]

The natural histories of PANDAS and PANS are still being studied, but early signals suggest that 60% to 80% of pediatric patients have a significant reduction in symptoms over time, similar to childhood-onset OCD.[12] The American Academy of Child and Adolescent Psychiatry published a practice parameter for assessing and treating childhood-onset OCD; they noted some clinical experts believe a small subset of children that have been diagnosed with OCD or Tourette disorder might have clinical exacerbations linked to streptococcal infection.[13] The authors report that more males than females are diagnosed with pediatric OCD, typically diagnosed between the ages of 7 and 12 years; earlier onset is associated with comorbid psychiatric diagnoses (e.g., mood disorders, attention deficit disorder, anxiety disorders, phobias).[13]

There is some discussion about whether PANDAS and PANS is related to pediatric autoimmune encephalitis, which is also characterized by abrupt onset of similar abnormal behavioral symptoms and disruptions in multiple biological systems (e.g., gastrointestinal, nervous).[1,14-16] Autoimmune encephalitis in children is characterized by a sudden onset of symptoms including seizures, irritability, aggression, and abnormal movements, and could be associated with an acute infection or presence of a tumor.[1,14,17]

The prevalence of pediatric autoimmune encephalitis is not known, but a population study of adults and children suggested the incidence rate of autoimmune encephalitis was 0.8 per 100,000, and that males had more than twice the prevalence of females.[18] Autoimmune encephalitis is a life-threatening condition usually treated in a hospital setting.[1,15] Because of the differences in diagnostic criteria and disease process between autoimmune encephalitis and PANDAS/PANS, the scope of this report excludes autoimmune encephalitis.

Diagnostic Criteria and Tests

Table 1 presents diagnostic criteria and tests by condition and includes information from publications summarized in the Evidence Review and Clinical Practice Guidelines sections of this coverage guidance.[3,11,14-17,19-32]

Table 1. Proposed Diagnostic Criteria, Tests and Processes

Proposed Diagnostic Criteria	Proposed Diagnostic Tests and Processes
PANDAS[2]	
Presence of OCD, symptoms similar to attention deficit hyperactive disorder, or tics	In patients with OCD, complete blood count, erythrocyte sedimentation rate, C-reactive protein, metabolic panel, urine analysis, pharyngeal swab and anti-streptococcal antibodies. Positive results from the pharyngeal swab and anti-streptococcal antibodies indicate exposure to the streptococcal infection do not differentiate between the state of carrier and acute infection. For children with neurological and psychiatric symptoms, physical or neurological examination require the analysis of the cerebrospinal fluid and neuroimaging exams.
Onset of symptoms occurs between the ages of 3 and 12 (or prior to puberty)	
Symptoms had sudden onset, or existing symptoms worsened for a short period	
Confirmed culture or antibodies related to a streptococcal infection temporally associated with onset of symptoms	
Neurological anomalies such as hyperactivity, choreiform motor movements, bedwetting, anxiety, emotional lability, developmental regression or mood changes	
Rule out Sydenham's chorea, Tourette syndrome, OCD, central nervous system vasculitis, autoimmune encephalitis, and neuropsychiatric lupus	Differential diagnosis.
PANS[3,22]	
Sudden onset of OCD or eating restrictions, and at least 2 of the following:	Complete medical and psychiatric history, physical examination, laboratory testing of blood and possibly cerebrospinal fluid, and selected paraclinical evaluations, such as magnetic resonance imaging, electrocardiogram/ echocardiography, electroencephalography, and polysomnography.
• Anxiety (particularly separation anxiety)	
• Emotional lability or depression	
• Irritability, aggression, and/or severely oppositional behaviors	
• Deterioration in school performance (related to attention-deficit/hyperactivity disorder-like behaviors, memory deficits, and cognitive changes) • Sensory or motor abnormalities	

Proposed Diagnostic Criteria	Proposed Diagnostic Tests and Processes
• Somatic signs and symptoms, including sleep disturbances, enuresis, or urinary frequency	
Rule out Sydenham chorea, autoimmune encephalitis, neuropsychiatric lupus, central nervous system vasculitis, and other conditions that better account for the symptoms	Differential diagnosis.

Abbreviations. OCD: obsessive-compulsive disorder; PANDAS: pediatric autoimmune neuropsychiatric disorders associated with streptococcal infections; PANS: pediatric acute-onset neuropsychiatric syndrome.

We identified 4 publications that specifically presented or summarized evidence for diagnostic criteria and tests related to PANDAS or PANS.[4,9,33,34] Nielsen and colleagues performed a systematic review and meta-analysis of studies on the association between streptococcal infections and exacerbations of neuropsychiatric symptoms.[34] The authors concluded that although children diagnosed with PANDAS had more neuropsychiatric exacerbations than children with streptococcal infections without a follow-up diagnosis of PANDAS, these exacerbation were not significantly temporally associated with streptococcal infections.[34]

Baj and colleagues reviewed published literature in search of distinguishing features of patients diagnosed with PANDAS and concluded that despite more than 20 years of research into this condition, it remains challenging to differentiate PANDAS from OCD or tic disorders.[9] Their observations of characteristics that appear to be different for children diagnosed with PANDAS include[9]:

- some alterations of cortico-basal ganglia circuitry, due to the effect of antibodies produced in response to the condition on various neuronal proteins, including tubulin, lysoganglioside, and dopamine receptors;
- deposits of antibodies which are also accumulated in the striatal interneurons;
- significantly enlarged volumes of corpus striatum, caudate, putamen, globus pallidus, and basal ganglia; and
- significant alterations to the gut microbiota.

Gamucci and colleagues described the clinical, neuropsychological, and biological characterization of PANDAS and PANS, and recommended 4 categories of tools to add in the diagnostic process.[4] Proposed neuropsychological tests to assess motor and vocal tics, obsession and compulsion[4]:

- Children's Yale–Brown Obsessive Compulsive Scale for presence and severity of motor and vocal tics; and
- Yale Global Tic Severity Scale for presence and severity of child's obsession and compulsion.

Proposed neuropsychological tests to assess anxiety[4]:

- Multidimensional Anxiety Scale for Children (MASC) for the presence and types of child's anxiety symptoms for ages 8 to 19 years.

Proposed neuropsychological tests to assess short-term memory and attention[4]:

- Digit Span subtest Wechsler Intelligence Scale for Children for verbal short-term memory for ages 6 to 16 years;

- Coding subtest Wechsler Intelligence Scale for Children for visual-motor dexterity and nonverbal short-term memory for ages 6 to 16 years; and
- Symbol Search subtest Wechsler Intelligence Scale for Children for accuracy, attention and concentration for ages 6 to 16 years.

Proposed neuropsychological tests to assess processing speed[4]:

- Processing Speed Index Wechsler Intelligence Scale for Children (WISC III-IV) for speed of cognitive processes and response output on visual-motor tasks for ages 6 to 16 years

In addition to the scales proposed by Gamucci and colleagues above, Leibold and colleagues validated a Global Impairment Score scale to measure impairment in children and adolescents as part of the diagnostic process for PANS.[33] This scale was designed to be answered by a child's caregiver, and is scored on a scale of 0 to 100.[33]

For additional measures proposed in guidelines, please refer to the Clinical Practice Guidelines section of this coverage guidance.

Treatments

Table 2 presents treatments by condition and includes information about treatments from the publications summarized in the evidence review and clinical practice guidelines sections of this coverage guidance.[3,11,14-17,19-32] Not all treatments in Table 2 have been evaluated in studies with prospective comparative designs; the evidence review portion of this coverage guidance will synthesize findings from comparative studies related to treatments and outcomes.

Table 2. Treatments Proposed for PANDAS and PANS

Treatments	PANDAS	PANS
Antibiotics		
Amoxicillin	X	X
Aripiprazole		X
Azithromycin	X	
Penicillin	X	
Surgical Interventions		
Tonsillectomy	X	
Adenoidectomy	X	
Intravenous Immunoglobulin and Plasma Exchange		
Intravenous immunoglobulin	X	X
Plasma exchange	X	X
SSRIs		
Fluoxetine	X	
NSAIDs		
Naproxen sodium	X	
Antipsychotics		
Pimozide	X	
Risperidone		X
Corticosteroids		
Dexamethasone		X

Treatments	PANDAS	PANS
Prednisone	X	
Behavioral Interventions		
Cognitive behavioral therapy	X	

Abbreviations. NSAID: nonsteroidal anti-inflammatory drug; PANDAS: pediatric autoimmune neuropsychiatric disorders associated with streptococcal infections; PANS: pediatric acute-onset neuropsychiatric syndrome; SSRI: selective serotonin reuptake inhibitor.

Evidence Review

We identified 2 systematic reviews, 5 RCTs with 6 publications, and 2 comparative cohort studies that reported interventions for children diagnosed with PANDAS or PANS.[11,24-32] Table 3 summarizes key characteristics of each included study. Given the varied study designs, treatments, and outcomes collected, neither of the systematic reviews included a meta-analysis section.

Sigra and colleagues included in their systematic review any report of any treatments for children with PANDAS, PANS, CANS, or PITAND published in English that also reported outcomes; this expansive inclusion criteria resulted in 5 RCTs, 7 observational survey study, and 65 case reports.[24] We rated this systematic review itself as having a low risk of bias, although it is important to note that the review authors concluded that there is not enough rigorous research about treatments for children with PANDAS, PANS, CANS, or PITAND, and the existing studies themselves have a high risk of bias. Sigra and colleagues concluded there was insufficient evidence to clearly recommend specific treatments for children with these diagnoses, but that psychiatric behavioral interventions, immunomodulatory therapies, and antibiotics likely have roles in the treatment of these disorders and should be more systematically investigated.[24]

In addition to summarizing comparative evidence regarding antibiotics, tonsillectomy, IVIG, and therapeutic plasma exchange, Sigra and colleagues sumarized noncomparative evidence for behavioral therapy, corticosteroids, nonsteroidal anti-inflammatory drugs (NSAIDs), and selective serotonin reuptake inhibitors (SSRIs). The first draft of this coverage guidance included the latter interventions, although it was not possible to make a clear determination of effectiveness or harms of these interventions due to the lack of comparative evidence.

Farhood and colleagues included in their systematic review 13 studies testing treatments for PANDAS that also reported outcomes related to change in symptoms, and excluded case reports; 3 included studies were RCTs, and 10 had retrospective designs.[27] We rated this review as having a high risk of bias. This review included studies of adenotonsillectomy, antibiotic therapy, intravenous immunoglobulin (IVIG) therapy, and cognitive behavioral therapy.[27] The authors suggested that immunoglobulin therapy might be effective for certain populations, and that psychotherapy and antibiotic therapies were likely low-risk interventions.[27] However, the authors concluded that the study designs left results open to question due to inability to account for confounding factors, such as co-occurring treatments, and were unable to strongly recommend any specific course of treatment.[27] All of the studies included in Farhood and colleagues' systematic review were also included in Sigra and colleagues' systematic review. Given the later search and publication dates and the lower risk of bias for Sigra and colleagues' review, we restrict our summary of review findings to the Sigra review in the following sections.

The RCTs all had fewer than 40 participating children, so the number of children in each treatment and placebo group was also small during comparative stages of the trials. These RCTs compared antibiotics to placebo and had moderate to high risk of bias,[25,30,31] or compared IVIG to placebo or plasma exchange and had low to high risk of bias.[26,32] At the end of the trial phase, the investigators of 3 of the RCTs offered the active treatment under consideration to the children who had been in the group receiving a placebo, which makes the long-term follow-up of participants in these trials an open-label observation follow-up (range, 4 weeks to 57 months).[11,25,26,31]

The number of children included in the 2 comparative cohort studies was larger (more than 100), and both studies focused on surgical interventions for symptom relief for children diagnosed with PANDAS.[28,31] We rated both studies as having a high risk of bias, primarily due to an inability to account for confounding factors.

The following sections organize findings from these studies by type of intervention. First, we summarize relevant RCTs and comparative cohort studies, and then we compare those findings with conclusions from the systematic reviews that included results from noncomparative study designs such as case reports.

Table 3. Characteristics of Included Studies

First Author, Year Number Follow-up(s)	Inclusion Criteria	Exclusion Criteria	Intervention	Risk of Bias
Systematic Reviews				
Sigra et al., 2018[24] 5 RCTs, 7 observational survey studies, and 65 case reports Not applicable	Studies in which patients with PANDAS, PANS, CANS, or PITAND were given treatment, that presented outcome data, and were written in English	No exclusion criteria explicitly listed	Cognitive behavior therapy, antibiotics, tonsillectomy, corticosteroids, therapeutic plasma exchange, IVIG, rituximab, nonsteroidal anti-inflammatory drugs	Low
Farhood et al., 2016[27] 3 RCTs and 10 retrospective designs Not applicable	Studies testing treatments for PANDAS and reported outcomes, and were written in English or Spanish	Review articles, single case reports, and studies of natural history or diagnostic strategies	Tonsillectomy, adenoidectomy, antibiotics, IVIG, cognitive behavioral therapy, or SSRIs	High
RCTs				
Murphy et al., 2017[25] N = 31 2 and 4 weeks	Children with an acute onset or acute relapse within 6 months of evaluation (abrupt, dramatic overnight onset) of moderate or worse OCD symptoms and presence of a sudden and severe co-occurrence of at least 2 neuropsychiatric symptoms.	Children with a gradual onset or duration of OCD symptoms of more than 6 months; who were receiving extended-course antibiotics (i.e., not a typical treatment course of antibiotics for an infection, or prophylactic antibiotics) and/or other immune therapy for PANS; with a primary diagnosis of tics; who were receiving exposure-based cognitive behavioral therapy; who had a history of nonresponse to a prior antibiotic trial; or who had a diagnosis of moderate to severe autism spectrum disorder,	Azithromycin and probiotics versus placebo with probiotics for 4 weeks; after this all participants were offered azithromycin	Moderate

First Author, Year Number Follow-up(s)	Inclusion Criteria	Exclusion Criteria	Intervention	Risk of Bias
		intellectual disability, and/or chronic neurological disease.		
Williams et al., 2016[26] Leon et al., 2018[11] N = 35 3 and 6 months during the trial, and a 57-month observational follow-up	Children who were 4 to 13 years of age in first episode of PANDAS symptoms and documentation that symptoms first appeared within 6 to 8 weeks of streptococcal infection or exposure; who had a sudden onset or exacerbation of OCD (reaching peak severity and impairment within 24 to 48 hours); and had at least 3 neuropsychiatric symptoms (which meets criteria for PANS).	Children with a history of Sydenham chorea or acute rheumatic fever; who had symptoms consistent with autism spectrum disorder or schizophrenia; who had severe physical, behavioral, or psychiatric symptoms that would prevent study participation; or prior corticosteroid or immunomodulatory therapy for PANDAS	IVIG versus placebo for 6 weeks; participants in the placebo group were then given the opportunity to receive IVIG; 31 participants received at least 1 dose of IVIG over the course of the study	Low risk for original trial, and high risk for long-term follow-up
Snider et al., 2005[30] N = 23 12 months	Children with a tic disorder and/or OCD; who had a history of a sudden onset of symptoms or an episodic course with abrupt symptom exacerbations interspersed with periods of partial or complete remission; who had onset of neuropsychiatric symptoms prior to puberty; and who had documentation of a temporal association between a preceding streptococcal infection and the onset or exacerbation of neuropsychiatric symptoms.	No specific exclusion criteria listed.	Azithromycin versus penicillin for 12 months	High

First Author, Year Number Follow-up(s)	Inclusion Criteria	Exclusion Criteria	Intervention	Risk of Bias
Garvey et al., 1999[31] N = 37 4 months	Children between 4 and 15 years of age with a tic disorder and/or OCD; who had history of a sudden onset of symptoms or an episodic course with abrupt symptom exacerbations interspersed with periods of partial or complete remission (a sawtooth, rather than a waxing and waning course); who had an onset of symptoms prior to puberty; and evidence of a temporal association between a preceding streptococcal infection and the onset or exacerbation of neuropsychiatric symptoms.	Children who had tics or OCD of such a severity that hospitalization was considered; who required treatment for severe, active comorbid major psychiatric disorders; who had with autism, pervasive developmental delay, or "mental retardation"[a]; or who had neurologic diagnoses other than tics and Tourette syndrome, serious concurrent or chronic medical disorders, and a personal history of penicillin allergy.	Penicillin versus placebo for 4 months; cross-over design meant that all participants received penicillin during the 8 months of the study	High
Perlmutter et al., 1999[32] N = 29 1 month and 12 months	Children ages 5 to 14 years with a tic disorder and/or OCD; onset of neuropsychiatric signs and symptoms before puberty; a history of sudden onset of signs and symptoms, or an episodic course characterized by abrupt exacerbations and periods of partial or complete remission; evidence of, and association between, streptococcal infection and onset or exacerbation of signs and symptoms; and current exacerbation severe	Children with a history of Sydenham's chorea or rheumatic fever, autism, schizophrenia or other psychotic disorder, a neurological disorder other than a tic disorder, an autoimmune disorder, or other medical illness. Immunoglobulin concentrations were measured, and children were excluded from the study if they had IgA deficiency (a contraindication to IVIG administration).	Plasma exchange, IVIG, or placebo for 2 weeks	High

First Author, Year Number Follow-up(s)	Inclusion Criteria	Exclusion Criteria	Intervention	Risk of Bias
	enough to cause significant distress and interfere with the child's social functioning in at least 2 spheres (home, school, social relations).			
Comparative Cohort Studies				
Pavone et al., 2014[28] N = 120 Every 2 months for 2 years	Children with a tic disorder and/or OCD; who had infection-related symptom flare-ups, history of dramatic onset of either OCD or tics, new onset anxiety, sensory or motor abnormalities, behavioral regression, deterioration in school performance, emotional lability, or urinary symptoms (all these neuropsychiatric phenomena were in temporal association to streptococcal pharyngeal tonsillitis). The surgical group (n = 56) were referred to surgery based on a clinical history of recurrent inflammation in addition to the symptoms above.	No specific exclusion criteria listed	Surgery versus no surgery; surgery group had 25 tonsillectomies and 31 adenotonsillectomies	High
Murphy et al., 2013[29] N = 112 Not reported	Children with a tic disorder and/or OCD; and with infection-related symptom flare-ups, history of dramatic onset of either OCD or tics, new onset anxiety, sensory or motor	Children with a psychotic disorder, significant medical illness, or non-tic neurologic disorder	Surgery versus no surgery; surgery group had 4 tonsillectomies, 10 adenoidectomies, and 22 had both procedures	High

First Author, Year Number Follow-up(s)	Inclusion Criteria	Exclusion Criteria	Intervention	Risk of Bias
	abnormalities, behavioral regression, deterioration in school performance, emotional lability, or urinary symptoms. Participants on stable doses of psychotropic medication for their condition were not excluded. The surgical group comprised children who had a tonsillectomy and/or adenoidectomy procedure, and were matched to nonsurgery participants on age and sex.			

Note. This language was taken directly from the study; the coverage guidance authors recognize this language is no longer acceptable.
Abbreviations. CANS: childhood acute neuropsychiatric syndromes; IgA: immunoglobulin A; IVIG: intravenous immunoglobulin; OCD: obsessive-compulsive disorder; PANDAS: pediatric autoimmune neuropsychiatric disorders associated with streptococcal infections; PANS: pediatric acute-onset neuropsychiatric syndrome; PITAND: pediatric infection-triggered autoimmune neuropsychiatric disorders; RCT: randomized controlled trial; SSRI: selective serotonin reuptake inhibitor.

Antibiotics

We identified 3 RCTs that tested antibiotics as a primary intervention for children diagnosed with PANDAS or PANS.[25,30,31] As a reminder, children meeting the criteria for PANDAS also meet the criteria for PANS. Conclusions from both systematic reviews agreed with author conclusions of these 3 RCTs: there is some evidence that antibiotic prophylaxis might reduce exacerbations of neuropsychiatric symptoms for children diagnosed with PANDAS.[24,27]

Azithromycin

Murphy and colleagues conducted a double-blind RCT with 31 participants randomized to receive azithromycin prophylaxis (N = 17) for 4 weeks or to receive a placebo (N = 14) for 4 weeks; participants in the placebo group were then given the option to begin taking azithromycin, which launched the open-label observational portion of the study.[25] Both groups also received twice daily probiotics.[25] We rated the outcomes from the trial portion of this study as having a moderate risk of bias; no outcomes were reported for the open-label portion.

When comparing scores on the OCD Clinical Global Impressions Severity scale (which has a scale of 1 to 7), participants who received azithromycin reported statistically significantly greater reductions in symptom frequency 4 weeks after baseline (azithromycin group mean, 4.06; azithromycin group standard deviation [SD], 0.23; placebo group mean, 4.93; placebo group SD, 0.25; effect size, 0.11; $P = .003$).[25] The effect size for the difference in symptoms between the azithromycin and placebo groups suggests that there was only a very small difference between the 2 groups, and that the difference was not likely to be clinically significant. No significant difference was found between the group on the Children's Yale-Brown Obsessive-Compulsive Scale, and no difference between groups for the severity of symptoms.[25]

Investigators also assessed whether participants responded to their assigned therapy, using a 30% or greater reduction in symptoms to judge whether a participant responded. In the azithromycin group, 52.9% (9 of 17) were categorized as responders, and 21.4% (3 of 14) were categorized as responders in the placebo group.[25]

The authors reported that among participants with greater tic severity scores at baseline (measured as 1 standard deviation greater than average number of tics), participants in the azithromycin group were significantly more likely to have at least a 30% reduction in tic symptoms during the 4-week trial than control group participants (no statistics reported; $P < .05$).[25] If there is a treatment benefit to azithromycin, this suggests that it might have greater benefit for children with more severe tics.

Penicillin

Garvey and colleagues conducted a double-blind, balanced crossover study with 37 participants randomized to receive either penicillin prophylaxis or a placebo for 4 months.[31] After the first 4 months passed, the treatment assignment was reversed for 4 months; therefore, participants were followed for 8 months.[31] There was no wash out period between the reversal of treatment assignment.[31] We rated this study as having a high risk of bias. No statistically significant difference was reported between treatment groups for exacerbations of neuropsychiatric symptoms, with 38 exacerbations during the placebo phase and 35 exacerbations during the penicillin phase.[31] There were no clinically meaningful differences in depression or anxiety symptoms between the treatment phases.[31] Of the 27 parents who

provided global ratings of their child's behaviors, 22 reported an improvement of behavior during the penicillin phase; 18 of these parents correctly identified this as the active treatment phase when rating their child's behavior.[31] There were no statistically significant differences in neuropsychiatric symptoms between the penicillin and placebo phases, as measured by the Children's Yale-Brown Obsessive Compulsive Scale (P = .16) or the Yale Global Tic Severity Scale (P = .28).[31]

Azithromycin Versus Penicillin

Snider and colleagues conducted a double-blind RCT with 23 participants randomized to receive either azithromycin or penicillin prophylaxis for 12 months.[30] We rated this study as having a high risk of bias. The authors reported that both antibiotic therapies reduced the number of streptococcal infections during the study year compared to the year prior to the study (mean reduction of about 2 infections per year), with no significant difference between the 2 groups (mean for both groups, 0.1; SD for both groups, 0.3; P > .05).[30] Parent and child reports at baseline and the end of the study were reviewed and rated by the study authors to determine the presence and frequency of exacerbations of neuropsychiatric symptoms.[30] Both groups reported decreased neuropsychiatric exacerbations, but the participants who received penicillin reported significantly fewer exacerbations of neuropsychiatric symptoms (penicillin group mean, 0.5; penicillin group SD, 0.5; azithromycin group mean, 0.9; azithromycin group SD, 0.5; P < .01).[30]

Tonsillectomies and Adenoidectomies

We identified 2 comparative cohort studies that examined the association of tonsillectomies and adenoidectomies with change in symptoms for children diagnosed with PANDAS, and both compared children with PANDAS who had either or both of these surgeries (N = 88) to children with PANDAS who had received neither surgery (N = 140).[28,29] Both studies specifically named PANDAS as the diagnosis of focus.[28,29] We rated both of these studies as having a high risk of bias. Both systematic reviews agreed with the conclusions of the authors from these 2 studies that tonsillectomy and adenoidectomy do not appear to reduce neuropsychiatric symptom severity or exacerbations.[24,27] We did not identify any studies that tested the surgical interventions of tonsillectomies and adenoidectomies for the broader diagnosis of PANS.

In a prospective comparative cohort study including 120 participants, Pavone and colleagues reported that there was no significant difference in symptom remission rates between the surgery and nonsurgery groups (relative risk [RR], 1.39; 95% confidence interval [CI], 0.75 to 2.55; P = 0.29).[28] The authors also reported no significant difference in days to first symptom relapse (surgery group mean, 45.1; surgery group SD, 17.8; nonsurgery group mean, 39.3; nonsurgery group SD, 14.2; P = .09).[28]

Murphy and colleagues conducted a prospective comparative cohort study including 112 children who met the criteria for an OCD or tic diagnosis, and were divided into a group meeting the criteria for PANDAS and a group that did not meet criteria for PANDAS, according to a temporal relationship with a streptococcal infection.[29] The authors reported no significant difference in OCD or tic severity between the surgery and nonsurgery groups among children with or without a PANDAS diagnosis, as measured by the Children's Yale-Brown Obsessive Compulsive Scale (surgery group mean, 17.9; surgery group SD, 9.9; nonsurgery group mean, 18.7; nonsurgery group SD, 10.5; P = .71) or the Yale Global Tic Severity Scale (surgery group mean, 33.4; surgery group SD, 23.5; nonsurgery group mean, 33.6; nonsurgery group SD, 21.6; P = .97).[29] The authors also reported that there was no relationship between surgery status and

age of onset of OCD or tic symptoms (surgery group mean, 5.9 years; surgery group SD, 2.1 years; nonsurgery group mean, 6.5 years; nonsurgery group SD, 2.7 years; P = .32).[29] There was no statistically significant relationship between surgery status and duration of symptoms (surgery group mean, 2.5 years; surgery group SD, 2.1 years; nonsurgery group mean, 3.3 years; nonsurgery group SD, 2.5 years; *P* = .09).[29]

Both comparative cohort studies concluded that the surgical interventions had no effect on severity of symptoms or symptom progression.[28,29]

IVIG

We identified a single RCT that tested IVIG versus placebo,[11,26] and a single RCT that tested IVIG versus a placebo or plasma exchange.[32] Both RCTs enrolled children who met the diagnostic criteria for PANDAS and OCD.[26,32]

IVIG Versus Saline Placebo

Williams and colleagues randomized 35 children to receive IVIG or an intravenous saline placebo for 2 consecutive days at trial start.[26] All children were prescribed prophylactic antibiotics for the duration of the 6 months of this study, and penicillin was reported as the most commonly prescribed antibiotic (no number reported).[11] The investigators then offered the opportunity to children who had received the placebo to enter an open-label phase in which they received IVIG along with the children in the intervention group who were judged to be nonresponders to the treatment 6 weeks after the first infusion.[26] The investigators defined responding to treatment before the trial began as a 30% or greater decrease in symptoms as measured by the Children's Yale Brown Obsessive Compulsive Scale, or by a "much" or "very much" improved rating on the Clinical Global Impressions Improvement scale.[26] We rated the first phase of this trial as having a low risk of bias, and the 6- to 12-week open-label phase and the 24-week follow-up with any associated outcomes as having a high risk of bias.

At the conclusion of the 6-week blinded trial phase, there were no significant differences between the intervention and control groups for neuropsychiatric symptoms, as measured by changed in scores between baseline and 6-week follow-up on the Clinical Global Impressions Improvement scale and the Children's Yale Brown Obsessive Compulsive Scale.[26]

- Seven of the participants in the intervention group (38.9%; intervention group N = 18) were classified as responders to the treatment, meaning that they either demonstrated a 30% or greater decrease in symptoms as measured by the Children's Yale Brown Obsessive Compulsive Scale, or by a "much" or "very much" improved rating on the Clinical Global Impressions Improvement scale.[26] In the placebo group, 4 children were classified as having a significant decrease in symptoms (23.5%; placebo group N = 17).[26]
- There was not a significant difference in the number of children in each group who had a significant improvement in symptoms (*P* = .40).[26] The authors also reported that was no significant difference in the average change in symptoms between the intervention group and placebo group, as measured by the Clinical Global Impressions Improvement scale (*P* = .12) or the Children's Yale-Brown Obsessive Compulsive Scale (*P* = .44).[26]

During the nonblinded, open-label phase, 24 participants received IVIG.[26] This included 10 of 18 participants who were originally randomized to the intervention group and who were classified as

nonresponders at the end of the 6-week blinded phase; these participants therefore received doses of IVIG on 2 consecutive days twice: at baseline and 6 weeks after baseline.[26] Of the participants in the open-label phase, 17 (70.8%) were classified as responding to the treatment by 24 weeks.[26] However, there was no comparator group for this phase of the study and the authors did not report follow up at 24 weeks for the group of initial responders in the blinded phase of the RCT.

Leon and colleagues conducted additional follow-up interviews by telephone for all 35 original study participants for up to 5 years.[11] The authors reported that after the trial, 6 participants had tonsillectomy, 11 participants were diagnosed with new psychiatric conditions (i.e., attention-deficit/hyperactivity disorder, depression, anxiety, phobia, or chronic tic disorder), and 24 (68.6%) had experienced an exacerbation of symptoms.[11] Those exacerbations were treated with a variety of approaches, including additional IVIG, antibiotics, psychiatric medications, and cognitive behavioral therapy; treatments were often combined and used at the same time.[11]

IVIG Versus Plasma Exchange or Saline Placebo

Perlmutter and colleagues randomized 29 children who met the diagnostic criteria for PANDAS or OCD to receive IVIG, plasma exchange, or a saline placebo.[32] The authors compared symptoms at baseline to the same symptoms measured 1 month after treatment.[32] Participants in the plasma exchange group (N = 10) received 5 or 6 exchange transfusions, which required 85 to 121 minutes per transfusion.[32] Participants in the IVIG group (N = 9) received infusions during 2 days at the start of the trial; participants in the control group received a saline placebo (N = 10).[32] On average, participants in both the plasma exchange group and IVIG group reported significant reduction in symptoms from baseline to 1 month and between baseline and the 1-year follow-up, as measured by obsessive-compulsive symptoms, psychosocial functioning (i.e., anxiety, depression, and emotional lability), and global functioning.[32]

The authors reported comparisons of the change in symptoms for the 2 intervention groups to the change in symptoms for the saline placebo group between baseline and 1-month follow-up.[32] In comparison with the changes in scores in the saline placebo group (N = 10) 1 month after treatment, the IVIG group's (N = 9)[32]:

- scores for obsessions and compulsions decreased (45% vs. 3%; $P < .05$);
- scores for tics did not decrease significantly (19% vs. 12%; $P > .05$);
- sum of obsessions, compulsions, and tics decreased (45% vs. 6%; $P < .05$);
- scores for global impairment improved (26% vs. 1%; $P < .05$);
- scores for psychosocial functioning did not significantly improve (20% vs. 0%; $P > .05$); and
- scores for global severity improved significantly (26% vs. 1%; $P < .05$).

One year after treatment, all 9 participants who received IVIG were successfully followed and readministered the measures described above; 7 of 9 were judged to be "much" or "very much" improved in a global assessment of symptoms by their parents.[32] There were no comparisons made between the control group and the intravenous exchange group 1 year after baseline.[32]

The authors noted that there was not a statistically significant difference between the IVIG and plasma exchange groups for improvement in any symptoms at 1 month or 1 year after treatment.[32] They reported that scores for both active intervention groups remained significantly improved from baseline for obsessions and compulsions, psychosocial functioning, and global severity.[32] However, the

participants who received IVIG did not show a statistically significant improvement in tics at 1 year after baseline when compared to their own scores. [32]

Plasma Exchange

We identified a single RCT that tested plasma exchange versus placebo or IVIG for children who met the criteria for PANDAS and OCD; this study conducted by Perlmutter and colleagues is also described in the section that describes studies of IVIG.[32] We rated this study as having a high risk of bias. In comparison with the placebo group (N = 10) 1 month after treatment, the plasma exchange group's (N = 10)[32]:

- scores for obsessions and compulsions decreased (58% vs. 3%; *P* < .05);
- scores for tics decreased (49% vs. 12%; *P* <.05);
- sum of obsessions, compulsions, and tics decreased (54% vs. 6%; *P* < .05);
- scores for global impairment improved (36% vs. 1%; *P* < .05);
- scores for psychosocial functioning did not significantly improve (30% vs. 3%; *P* > .05); and
- scores for global severity improved (26% vs. 1%; *P* < .05).

One year after baseline, 8 of 10 participants who received plasma exchange were successfully followed and readministered the measures described above; 7 of 8 were judged to be "much" or "very much" improved in a global assessment of symptoms by their parents.[32] There were no comparisons made between the control group and the intravenous exchange group 1 year after treatment.[32]

The authors noted that there was not a statistically significant difference between the IVIG and plasma exchange groups for improvement in any symptoms at 1 month or 1 year after treatment.[32] They reported that scores for both active intervention groups remained significantly improved from baseline for obsessions and compulsions, psychosocial functioning, and global severity.[32] In addition to those measures, the participants who received plasama exchange also remained signifcantly improved on the measure of tics when compared to their scores at baseline.[32]

Harms

Sigra and colleagues' systematic review of any treatment for PANDAS, PANS, CANS or PITAND reported that adverse events reported in included studies were typically mild to moderate in nature, including nausea, vomiting, headache and stomachache.[24]

Antibiotics

Murphy and colleagues reported that some participants who received prophylactic azithromycin had loose stools (no number reported), and 9 out of 12 children who received azithromycin had heart rate irregularities.[25]

Other known adverse events associated with long-term antibiotic therapy include skin rashes, gastrointestinal disturbance, increased risk of childhood-onset chronic conditions (e.g., asthma, obesity, attention deficit hyperactivity disorder), and contribute to antibiotic resistance.[35,36] Use of azithromycin may also result in changes in the electrical activity of the heart that can lead to fatal irregular heart rhythm.[37]

Tonsillectomy and Adenoidectomy

Although the included studies did not report harms, adverse events associated with tonsillectomy and adenoidectomy may include hemorrhage, complications from anesthesia, and infection.[38,39]

IVIG

Williams and colleagues reported that a single participant appeared to have an allergic reaction to the IVIG infusion, but that the reaction resolved without complication. The authors also reported that several participants noted minor discomforts during treatment, such as joint pain, headache, stomach pain, tiredness, and anxiety.[26] Perlmutter and colleagues reported that 6 of 9 children receiving immunoglobulin infusions reported experiencing 1 or more of the following: nausea, vomiting, mild to moderately severe headache, and low grade fever.[32] All of these symptoms were resolved with hydration therapy, paracetamol, or diphenhydramine.[32] No long-term adverse events were reported, and none of the studies mentioned intending to collect information about long-term adverse events.[11,26,32]

The FDA categorized IVIG as a biologic agent, and 8 of the 12 products listed are approved for use in children under 18 years of age (ASCENIV, Flebogamma, Gammagard Liquid, Gammagard S/D, Gammaplex, Gamunex-C, PANZYGA, and Privigen).[40] None of the approved indications include PANDAS or PANS for these products, and the age range for approved use vary by product.[40] The package inserts for IVIG products include black box warnings for thrombosis, renal dysfunction, and acute renal failure.[40]

Plasma Exchange

Perlmutter and colleagues reported that 7 of 10 children who received plasma exchange reported pallor, dizziness, and nausea during the first exchange transfusions; 2 of these children also experienced vomiting.[32] Three additional children reported feeling anxious during the exchange transfusions.[32]

Known complications of plasma exchange include circuit clotting, low or high blood pressure, nausea, vomiting, itchy skin, hives, low calcium levels in the blood, venous access malfunction, infections, thrombosis, anaphylactic shock, and high fever.[41-44]

Ongoing Studies

We identified 3 ongoing studies that might provide upcoming information about diagnosis and treatment of PANDAS or PANS.[45-47]

A single double-blinded RCT plans to enroll 44 children diagnosed with PANDAS to test the effectiveness of taking naproxen sodium twice daily for 8 weeks on the severity of OCD symptoms, as measured by the second edition of the Children's Yale-Brown Obsessive-Compulsive Scale.[46] Enrolled participants will be between 6 and 15 years of age with first OCD symptom onset within 18 months prior to trial start date, and have symptoms that significantly interfere with daily life.[46] The estimated primary completion date is October 2022.[46]

A single RCT plans to enroll 92 children from 6 to 17 years of age with a confirmed diagnosis of PANS or PANDAS, and will randomize participants to receive intravenous immunoglobulin therapy or a placebo; the participant, care provider, investigator, and outcomes assessor will all be blinded.[47] The estimated study start date is August 30, 2021, and the estimated primary completion date is March 2023.[47] The

primary outcome measure will be the Children's Yale-Brown Obsessive Compulsive Scale at 9 weeks after treatment, which will be measured as a secondary outcome at week 18 along with Clinical Global Impression assessment, the Parent Obsessive-Compulsive Impact Scale, the Child Obsessive-Compulsive Impact Scale, the Swanson, Nolan, And Pelham Scale - Version IV (SNAP-IV; measures symptoms and behaviors that could impact child's behaviors at school), and the Parent Tic Questionnaire.[47]

This study will exclude children whose symptoms had first onset more than 6 months before the trial start date, children with current relapse of symptoms whose first onset was more than 12 months before the trial start date; who have a contraindication for intravenous immunoglobulin; who have severely restricted food intake, whose body mass index is 40 or greater; who have symptoms of autism or schizophrenia, bipolar disorder, or other psychotic disorder; who have serious or unstable mental illness; who have been treated with corticosteroids or began cognitive behavioral therapy within the 8 weeks prior to randomization; who have a history of rheumatic fever; who have had prior immunomodulatory treatment; who had taken antibiotics or antivirals for an acute infection within 1 week of randomization; who have severe liver disease; who have known hepatitis B, hepatitis C, or HIV infection; pregnant or lactating women or women unwilling to comply with contraception protocol; or who participated in another interventional trial within 3 months of randomization or during the course of this study.[47]

A single observational matched cohort study plans to enroll 500 children diagnosed with PANS who have not yet received any treatment, whose symptoms began within 1 month of enrollment date, and who are 18 years of age or younger.[45] The investigators plan to match these children with healthy children without a PANS diagnosis to examine immunologic, neurologic, genomic, and behavioral differences between the two cohorts.[45] This study began in 2013 and has an estimated primary completion date of March 2028.[45] Outcome measures include the following, measured ever every 2 to 4 weeks for up to 12 years: Global Impairment Score, Children's Yale-Brown Obsessive Compulsive Scale, Columbia Impairment Score, Caregiver Burden Inventory, and neurological findings (e.g., irregular movements).[45]

Evidence Summary

The origins and progression of symptoms associated with PANDAS and PANS are still being studied and documented; there are few published studies that tested whether antibiotic therapy, surgical interventions, IVIG, or plasma exchange might improve symptoms in children diagnosed with these conditions. It is also difficult to know how long any improvements in symptoms last after children receive the treatments we reviewed in this coverage guidance, because they often receive multiple treatments (simultaneously or 1 after another). Additionally, it is hard to distinguish whether patterns of exacerbation and resolution of symptoms can be directly attributed to infections and treatments, or if there is an underlying pattern of increase of symptoms followed by a decrease of symptoms that would occur without these treatments. It is not clear how long any treatment benefit might be sustained before another exacerbation, or whether any treatment alone or in combination with other treatments can prevent or shorten the length of exacerbations.

- We have very low confidence that prophylactic antibiotic therapy reduces exacerbations of neuropsychiatric symptoms. Risks for long-term antibiotic use include skin rashes, gastrointestinal disturbance, increased risk of childhood-onset chronic conditions (e.g., asthma, obesity, attention deficit hyperactivity disorder), and contribute to antibiotic resistance.[35,36]

- We did not identify any evidence testing antibiotics in response to current psychiatric exacerbation.
- We have low confidence that surgical interventions such as tonsillectomy and adenoidectomy do not reduce neuropsychiatric symptom exacerbations. Harms of tonsillectomy and adenoidectomy may include hemorrhage, complications from anesthesia, and infection.[38,39]
- We have very low confidence that IVIG decreases neuropsychiatric symptoms. It is not clear how long any treatment benefit might be sustained. There is an ongoing trial of IVIG for children with PANS or PANDAS that might have published results in 2023 or 2024. The package inserts for IVIG products include serious warnings for thrombosis, renal dysfunction, and acute renal failure.[48]
- We have very low confidence that plasma exchange decreases neuropsychiatric symptoms. It is not clear how long any treatment benefit might be sustained. Known complications of plasma exchange transfusions include high fever, blood clots, infection, minor or severe allergic reactions, and high or low blood pressure.[41-44]

The very low and low confidence we have in the findings above means that findings from new comparative studies that test treatments for PANDAS or PANS could change the recommendations that we make for which treatments should be covered for children diagnosed with PANDAS or PANS.

Clinical Practice Guidelines

We identified 6 publications that included recent guidelines for the diagnosis and treatment of individuals with PANDAS or PANS.[3,19-23] We rated all the guidelines as having poor methodological quality.

PANS/PANDAS Clinical Research Consortium

The most recent clinical guidelines written and published in the US for treating PANS was written by members of the PANS/PANDAS Research Consortium at workgroup meetings partially sponsored by the National Institutes of Health.[3] The workgroups reviewed literature, reviewed more than 1,000 cases of children diagnosed with PANDAS/PANS, and then prepared summaries to be reviewed by review panels of clinical experts who either worked with children suspected of having PANDAS/PANS or were experts in child psychiatry, pediatrics, infectious diseases, microbiology, neurology, neuroimmunology, immunology, and rheumatology.[3] Not all experts agreed on all treatments proposed in the guidelines, so the guideline committee opted to describe multiple treatment options beyond the treatments that had the highest consensus.[3] The authors of the committee summary stated that they expect the guidelines to be altered over time in response to the initiation and completion of new controlled clinical trials testing the efficacy of treatments.[3]

As an overview, the guidelines recommend a 3-pronged approach to treating PANS[3,19,20,22]:

- "treating the symptoms with psychoactive medications, psychotherapies (particularly cognitive behavioral therapy), and supportive interventions;
- removing the source of the inflammation with antimicrobial interventions; and
- treating disturbances of the immune system with immunomodulatory and/or anti-inflammatory therapies" (pp. 562; Swedo et al., 2017).

The guidelines presented the following 6 principles for the identification and treatment of PANS:

1. Establish that PANS is the correct ‘‘diagnosis of exclusion’’ by completing a comprehensive diagnostic evaluation.[23]
2. Provide symptomatic relief with psychiatric medications and behavioral interventions, prioritizing treatment of symptoms causing the greatest distress and interference.[22]
3. Treat underlying infections and consider use of therapeutic or prophylactic antibiotics.[20]
4. Treat symptoms resulting from neuroinflammation or postinfectious autoimmunity with anti-inflammatory or immunomodulatory therapies, chosen on the basis of symptom severity and disease trajectory.[19]
5. Evaluate effectiveness of the treatment regimen at frequent intervals, making modifications as warranted by improvement or worsening of symptoms.[3]
6. Treatment can be tapered downward or stopped when symptoms resolve. However, treatment may be necessary again at some point in the future, given the relapsing–remitting nature of PANS symptoms.[3]

Clinical Guidance About PANS from Nordic Countries

The Nordic Pediatric Immunopsychiatry group published guidance for diagnosis and management of suspected PANS in 2021, and included pediatric neurologists, child psychologists, and child psychiatrists from Denmark, Norway, Sweden and Great Britain.[21] The authors intended this guidance to propose a standard set of diagnostic criteria for PANDAS and PANS, and to propose a standard process for diagnostic evaluation.[21]

The authors agreed to adopt the clinical criteria proposed by Chang and colleagues for PANS that was published in 2015[21,23]:

1. Abrupt, dramatic onset (culmination within 72 hours) of OCD or severely restricted food intake.
2. Concurrent presence of additional neuropsychiatric symptoms, with similarly severe and acute onset, from at least two of the following seven categories (see reference for full description):
    - Anxiety,
    - Emotional liability and/or depression,
    - Irritability, aggression and/or severely oppositional behaviors,
    - Behavioral (developmental) regression,
    - Deterioration in school performance,
    - Sensory or motor abnormalities and
    - Somatic signs and symptoms, including sleep disturbances, enuresis or increased urinary frequency.
3. Symptoms are not better explained by a known medical disorder, such as Sydenham's chorea, systemic lupus erythematosus, Tourette disorder or others.

The authors agreed to adopt Swedo and colleagues’ diagnostic criteria for PANDAS that were published in 1998[21,49]:

1. Presence of Obsessive Compulsive Disorder and/or a tic disorder: The patient must meet lifetime diagnostic criteria (DSM- III- R or DSM- IV) for Obsessive Compulsive Disorder or a tic disorder.
2. Pediatric onset: Symptoms of the disorder first become evident between 3 years of age and the beginning of puberty.

3. Episodic course of symptom severity: Clinical course is characterized by the abrupt onset of symptoms or by dramatic symptom exacerbations. Symptoms usually decrease significantly between episodes and occasionally resolve completely between exacerbations.
4. Association with group A Beta- hemolytic streptococcus infection: Symptom exacerbations must be temporally related to group A Beta- hemolytic streptococcus infection, that is associated with positive throat culture and/or significantly elevated anti- group A Beta- hemolytic streptococcus antibody titers.
5. Association with neurological abnormalities: During symptom exacerbations, patients will have abnormal results on neurological examination. Motoric hyperactivity and adventitious movements (including choreiform movements or tics) are particularly common.

In addition to the criteria listed above, the authors further proposed a definition of severe symptoms and required that the child meet at least 1 major criteria and 1 minor criteria.[21] The major criteria included: total Children's Yale- Brown Obsessive Compulsive Scale (CY- BOCS) score ≥24; reduced intake of food or fluid, leading to less urine production (less than three urinations daily) or weight loss (more than 10%); and severe tics (Yale Global Tic Severity Scale (YGTSS) total tic severity score ≥40 but <50).[21] Minor criteria included being absent from school at least 50% of class days during 1 month, and inability to participate in leisure activities or loss of social contact.[21]

The authors then proposed a standard clinical work-up, which is described in Table 4.

Table 4. Nordic Pediatric Immunopsychiatry Group's Proposed Clinical Work-Up for PANS

Examination	Instrument or Analysis	Description
Psychiatric		
General	Achenbach System of Empirically Based Assessment (ASEBA),19 Mini international neuropsychiatric interview (M.I.N.I.- KID) or equivalent	General assessment of psychiatric conditions
	Child and Adolescent Trauma Screen (CATS)	Trauma screening
	Children's Global Assessment Scale (C- GAS)	Assessment of general functioning
	Clinical Global Impression- Severity Scale (CGI- S)	Clinician- rated severity of the patient's illness at time of assessment
	Pediatric Quality of Life Inventory (PedsQL)	Assessment of quality of life
	Optional: Work and Social Adjustment Scale (WSAS) 2	Measure of impaired functioning
	Optional: KIDSCREEN	Assessment of subjective health and well- being
Symptom-specific	Children's Yale- Brown Obsessive Compulsive Scale (CY- BOCS)	OCD inventory
	The Screen for Child Anxiety Related Disorders (SCARED)	Screening for child anxiety related disorders
	Yale Global Tic Severity Scale (YGTSS)	Tics inventory

Examination	Instrument or Analysis	Description
	Kiddie Schedule for Affective Disorders and Schizophrenia (Kiddie- SADS)	Interview screening for psychiatric diagnoses
	ADHD rating scale (ADHD- RS)	Questionnaire related to inattention, hyperactivity and impulsivity
	Behavior Rating Inventory of Executive Function (BRIEF)	Behavior Rating Inventory of Executive Function
Infectious		
General	Throat: bacterial culture	No description
	Blood: complete blood cell count with differential count, antistreptolysin- O and anti-deoxyribonuclease B antibodies	No description
Symptom-specific	Throat: Mycoplasma Polymerase Chain Reaction (PCR)	No description
	Nasopharynx: Aspirate PCR panel	Common viral airway infections such as influenza virus and enterovirus
	Urine analysis and culture	No description
Extended workup	Cerebrospinal fluid cell count, protein, glucose, lactate; Epstein- Barr-virus/cytomegalovirus/varicella zoster virus/ herpes simplex virus/Mycoplasma/ enterovirus/influenza virus immunoglobulin G and immunoglobulin M +Polymerase Chain Reaction (PCR); Borrelia burgdorferi immunoglobulin G and immunoglobulin M (paired with serum)	No description
Immunological		
General	Blood: erythrocyte sedimentation rate (ESR), antiphospholipid antibodies (anticardiolipin and beta2 glycoprotein 1 antibodies), antinuclear antibodies (antidsDNA, ANA IIF, anti- ENA screen: Anti- SSA, anti- SSA, anti- SSB, anti- Sm, anti-Scl–70, anti- Jo1, anti- Centromer B (- CENP- B) and anti- U1- RNP), immunoglobulins subclasses, tissue- transglutaminase IgA and deamined gliadinpeptide IgG (Celiac disease), neuronal antibodies, Myelin oligodendrocyte glycoprotein (MOG) antibodies, antithyroperoxidase (TPO), thyroid stimulating hormone (TSH) receptor antibodies, TSH, T3 and free T4, complement C3 and C4, angiotensin- converting enzyme (ACE), Vitamin- D, Vitamin B12, ferritin, cupper, ceruloplasmin, cytokines	No description

Examination	Instrument or Analysis	Description
Extended work-up	Cerebrospinal fluid Lumbar opening pressure, neuronal antibodies (standard panel), immunoglobulin G, index and electrophoresis for oligoclonal bands (paired with serum), and cytokines	No description
Toxicological		
Symptom-specific	Drug screening	No description
Metabolic		
Symptom-specific	Urine metabolic screening	No description
Radiological		
Extended work-up	Cerebral MRI including contrast: structural, diffusion and FLAIR sequences	No description
Neuropsychological		
Extended work-up	Standard or sleep electroencephalogram	No description

Note. This table is reproduced from Tables 3 and 4 on pages 4 and 5 of the Nordic Pediatric Immunopsychiatry group's published guidance for diagnosis and management of suspected PANS.[18,21] *Abbreviations. FLAIR: fluid attenuated inversion recovery; MRI: magnetic resonance imaging; OCD: obsessive-compulsive disorder; PANS: pediatric acute-onset neuropsychiatric syndrome.*

The authors recommended that verified or strongly suspected bacterial infections should be treated at the discretion of the provider for a maximum of 14 days; however, they do not recommend prophylactic antibiotic therapy.[21] They further recommended that any other treatment occur within ongoing clinical research or under the guidance of centers that specialize in the care of children with suspected PANS.[21] Such treatments for children with severe symptoms might begin with oral non-steroidal anti-inflammatory drugs, proceed to steroids if ineffective, and finally proceed to intravenous immunoglobulin.[21] The authors state that plasma exchange, and cytostatic and immunomodulatory drugs are only clinically indicated when a child has been diagnosed with autoimmune encephalitis.[21]

Policy Landscape

Payer Coverage Policies

We did not identify coverage policies for Washington State's Medicaid program or national or local coverage determinations for Medicare related to PANDAS or PANS.

We identified coverage policies related to PANDAS and PANS from 2 private payers (Aetna and Cigna), but we did not identify coverage policies related to PANDAS or PANS for BlueCross BlueShield or for Moda.

Private Payers

Aetna considers parenteral immunoglobulins, rituximab, and plasmapheresis to be investigational or experimental for PANDAS and autoimmune encephalitis.[50-52]

Cigna considers plasmapheresis, immune globulin, and rituximab to be investigational or experimental for PANDAS and PANS in policies last updated in 2021.[53-55] These coverage policies consider plasmapheresis to be medically necessary as a primary therapy for autoimmune encephalitis characterized by the presence of the n-methyl D-aspartate receptor antibody.[55]

Recommendations from Others

We did not identify policy statements or recommendations for PANDAS or PANS from the American Neurology Association, the American Academy of Pediatrics, the American Association of Immunologists, the Infectious Diseases Society of America, or the American Psychiatric Association.

PANDAS Physician Network

The PANDAS Physician Network maintains a website with tools such as flowcharts for diagnosing and treating PANS and PANDAS, and for classifying symptoms into mild, moderate, or severe cases.[56] The authors recommend that children with moderate or severe symptoms be treated by an experienced team of multidisciplinary providers or a PANS/PANDAS specialist.[56] To summarize the proposed elements of the treatment guidelines (please note that this list is simplified)[56]:

1. Start with 14 days of antibiotic therapy, and consider the appropriateness of prophylactic antibiotic therapy; lengthen therapy if infection is not resolved or symptoms persist.
2. Consider 5 to 7 days of non-steroidal anti-inflammatory drugs.
3. Ensure family access to cognitive behavioral therapy, and parenting management techniques.
4. Consider steroid course if no improvement from first 3 steps.
5. Escalate to intravenous immunoglobulin therapy if first 4 steps have not resolved symptoms.
6. If symptoms do not resolve, consider a second course of intravenous immunoglobulin or evaluate the need for plasma exchange, and prescribe prophylactic antibiotic therapy.

References

1. Garg D, Mohammad SS, Sharma S. Autoimmune encephalitis in children: an update. *Indian Pediatr.* 2020;57(7):662-670.
2. Dop D, Marcu IR, Padureanu R, Niculescu CE, Padureanu V. Pediatric autoimmune neuropsychiatric disorders associated with streptococcal infections (Review). *Experimental Ther.* 2021;21(1):94. doi: https://dx.doi.org/10.3892/etm.2020.9526.
3. Swedo SE, Frankovich J, Murphy TK. Overview of treatment of pediatric acute-onset neuropsychiatric syndrome. *J Child Adolesc Psychopharmacol.* 2017;27(7):562-565. doi: 10.1089/cap.2017.0042.
4. Gamucci A, Uccella S, Sciarretta L, et al. PANDAS and PANS: clinical, neuropsychological, and biological characterization of a monocentric series of patients and proposal for a diagnostic protocol. *J Child Adolesc Psychopharmacol.* 2019;29(4):305-312. doi: 10.1089/cap.2018.0087.
5. Orlovska S, Vestergaard CH, Bech BH, Nordentoft M, Vestergaard M, Benros ME. Association of Streptococcal Throat Infection With Mental Disorders: Testing Key Aspects of the PANDAS Hypothesis in a Nationwide Study. *JAMA psychiatry.* 2017;74(7):740-746. doi: https://dx.doi.org/10.1001/jamapsychiatry.2017.0995.
6. Wang HC, Lau CI, Lin CC, Chang A, Kao CH. Group A Streptococcal Infections Are Associated With Increased Risk of Pediatric Neuropsychiatric Disorders: A Taiwanese Population-Based Cohort Study. *J Clin Psychiatry.* 2016;77(7):e848-854. doi: 10.4088/JCP.14m09728.
7. Hyman SE. PANDAS: too narrow a view of the neuroimmune landscape. *Am J Psychiatry.* 2021;178(1):5-7. doi: https://dx.doi.org/10.1176/appi.ajp.2020.20111598.
8. Wald ER. A pediatric infectious disease perspective on pediatric autoimmune neuropsychiatric disorder associated with streptococcal infection and pediatric acute-onset neuropsychiatric syndrome. *Pediatr Infect Dis J.* 2019;38(7):706-709. doi: 10.1097/INF.0000000000002295.
9. Baj J, Sitarz E, Forma A, Wroblewska K, Karakula-Juchnowicz H. Alterations in the nervous system and gut microbiota after beta-hemolytic streptococcus group a infection-characteristics and diagnostic criteria of pandas recognition. *International Journal of Molecular Sciences.* 2020;21(4):21. doi: https://dx.doi.org/10.3390/ijms21041476.
10. Zibordi F, Zorzi G, Carecchio M, Nardocci N. CANS: childhood acute neuropsychiatric syndromes. *Europ J Paediatr Neurol.* 2018;22(2):316-320. doi: https://dx.doi.org/10.1016/j.ejpn.2018.01.011.
11. Leon J, Hommer R, Grant P, et al. Longitudinal outcomes of children with pediatric autoimmune neuropsychiatric disorder associated with streptococcal infections (PANDAS). *Eur Child Adolesc Psychiatry.* 2018;27(5):637-643. doi: 10.1007/s00787-017-1077-9.
12. Wilbur C, Bitnun A, Kronenberg S, et al. PANDAS/PANS in childhood: controversies and evidence. *Paediatr child health.* 2019;24(2):85-91. doi: https://dx.doi.org/10.1093/pch/pxy145.
13. Geller D, March JS, Walter J, et al. Practice parameter for the assessment and treatment of children and adolescents with obsessive-compulsive disorder. *J Am Acad Child Adolesc Psychiatry.* 2012;51(1):98-113. doi: 10.1016/j.jaac.2011.09.019.
14. Abboud H, Probasco JC, Irani S, et al. Autoimmune encephalitis: proposed best practice recommendations for diagnosis and acute management. *J Neurol Neurosurg Psychiatry.* 2021;92(7):757-768. doi: https://dx.doi.org/10.1136/jnnp-2020-325300.
15. Cellucci T, Van Mater H, Graus F, et al. Clinical approach to the diagnosis of autoimmune encephalitis in the pediatric patient. *Neurol Neuroimmunol Neuroinflamm.* 2020;7(2). doi: 10.1212/NXI.0000000000000663.

16. Mooneyham GC, Ferrafiat V, Stolte E, Fuchs DC, Cohen D. Developing consensus in the assessment and treatment pathways for autoimmune encephalitis in child and adolescent psychiatry. *Front Psychiatry.* 2021;12:638901. doi: 10.3389/fpsyt.2021.638901.
17. Graus F, Titulaer MJ, Balu R, et al. A clinical approach to diagnosis of autoimmune encephalitis. *Lancet neurol.* 2016;15(4):391-404. doi: https://dx.doi.org/10.1016/S1474-4422(15)00401-9.
18. Dubey D, Pittock S, Kelly C, et al. The incidence and prevalence of autoimmune encephalitis and a comparison to infectious encephalitis: a population-based study. *Neurology.* 2018;90.
19. Frankovich J, Swedo S, Murphy T, et al. Clinical management of pediatric acute-onset neuropsychiatric syndrome: part ii—use of immunomodulatory therapies. *J Child Adolesc Psychopharmacol.* 2017;27(7):574-593. doi: 10.1089/cap.2016.0148.
20. Cooperstock MS, Swedo SE, Pasternack MS, Murphy TK, for the PPC. Clinical management of pediatric acute-onset neuropsychiatric syndrome: part iii—treatment and prevention of infections. *J Child Adolesc Psychopharmacol.* 2017;27(7):594-606. doi: 10.1089/cap.2016.0151.
21. Pfeiffer HCV, Wickstrom R, Skov L, et al. Clinical guidance for diagnosis and management of suspected Pediatric Acute-onset Neuropsychiatric Syndrome in the Nordic countries. *Acta Paediatr.* 2021;13:13. doi: 10.1111/apa.15875.
22. Thienemann M, Murphy T, Leckman J, et al. Clinical management of pediatric acute-onset neuropsychiatric syndrome: part i-psychiatric and behavioral interventions. *J Child Adolesc Psychopharmacol.* 2017;27(7):566-573. doi: 10.1089/cap.2016.0145.
23. Chang K, Frankovich J, Cooperstock M, et al. Clinical evaluation of youth with pediatric acute-onset neuropsychiatric syndrome (PANS): recommendations from the 2013 PANS Consensus Conference. *J Child Adolesc Psychopharmacol.* 2015;25(1):3-13. doi: 10.1089/cap.2014.0084.
24. Sigra S, Hesselmark E, Bejerot S. Treatment of PANDAS and PANS: a systematic review. *Neurosci Biobehav Rev.* 2018;86:51-65. doi: 10.1016/j.neubiorev.2018.01.001.
25. Murphy TK, Brennan EM, Johnco C, et al. A double-blind randomized placebo-controlled pilot study of azithromycin in youth with acute-onset obsessive-compulsive disorder. *J Child Adolesc Psychopharmacol.* 2017;27(7):640-651. doi: 10.1089/cap.2016.0190.
26. Williams KA, Swedo SE, Farmer CA, et al. Randomized, controlled trial of intravenous immunoglobulin for pediatric autoimmune neuropsychiatric disorders associated with streptococcal infections. *J Am Acad Child Adolesc Psychiatry.* 2016;55(10):860-867 e862. doi: 10.1016/j.jaac.2016.06.017.
27. Farhood Z, Ong AA, Discolo CM. PANDAS: a systematic review of treatment options. *Int J Pediatr Otorhinolaryngol.* 2016;89:149-153. doi: 10.1016/j.ijporl.2016.08.008.
28. Pavone P, Rapisarda V, Serra A, et al. Pediatric autoimmune neuropsychiatric disorder associated with group a streptococcal infection: the role of surgical treatment. *Int J Immunopathol Pharmacol.* 2014;27(3):371-378. doi: 10.1177/039463201402700307.
29. Murphy TK, Lewin AB, Parker-Athill EC, Storch EA, Mutch PJ. Tonsillectomies and adenoidectomies do not prevent the onset of pediatric autoimmune neuropsychiatric disorder associated with group A streptococcus. *Pediatr Infect Dis J.* 2013;32(8):834-838. doi: 10.1097/INF.0b013e31829062e2.
30. Snider LA, Lougee L, Slattery M, Grant P, Swedo SE. Antibiotic prophylaxis with azithromycin or penicillin for childhood-onset neuropsychiatric disorders. *Biol Psychiatry.* 2005;57(7):788-792. doi: 10.1016/j.biopsych.2004.12.035.
31. Garvey MA, Perlmutter SJ, Allen AJ, et al. A pilot study of penicillin prophylaxis for neuropsychiatric exacerbations triggered by streptococcal infections. *Biol Psychiatry.* 1999;45(12):1564-1571. doi: 10.1016/s0006-3223(99)00020-7.

32. Perlmutter SJ, Leitman SF, Garvey MA, et al. Therapeutic plasma exchange and intravenous immunoglobulin for obsessive-compulsive disorder and tic disorders in childhood. *Lancet.* 1999;354(9185):1153-1158. doi: 10.1016/S0140-6736(98)12297-3.
33. Leibold C, Thienemann M, Farhadian B, Willett T, Frankovich J. Psychometric properties of the pediatric acute-onset neuropsychiatric syndrome global impairment score in children and adolescents with pediatric acute-onset neuropsychiatric syndrome. *Journal of Child & Adolescent Psychopharmacology.* 2019;29(1):41-49. doi: https://dx.doi.org/10.1089/cap.2018.0029.
34. Nielsen MO, Kohler-Forsberg O, Hjorthoj C, Benros ME, Nordentoft M, Orlovska-Waast S. Streptococcal infections and exacerbations in PANDAS: a systematic review and meta-analysis. *Pediatr Infect Dis J.* 2019;38(2):189-194. doi: https://dx.doi.org/10.1097/INF.0000000000002218.
35. Ahmed H, Davies F, Francis N, Farewell D, Butler C, Paranjothy S. Long-term antibiotics for prevention of recurrent urinary tract infection in older adults: systematic review and meta-analysis of randomised trials. *BMJ Open.* 2017;7(5):e015233. doi: 10.1136/bmjopen-2016-015233.
36. Aversa Z, Atkinson EJ, Schafer MJ, et al. Association of infant antibiotic exposure with childhood health outcomes. *Mayo Clin Proc.* 2021;96(1):66-77. doi: 10.1016/j.mayocp.2020.07.019.
37. Ray WA, Murray KT, Hall K, Arbogast PG, Stein CM. Azithromycin and the risk of cardiovascular death. *N Engl J Med.* 2012;366(20):1881-1890. doi: 10.1056/NEJMoa1003833.
38. Erwin DZ, Heichel PD, Wright LB, et al. Post-tonsillectomy hemorrhage control with nebulized tranexamic acid: A retrospective cohort study. *Int J Pediatr Otorhinolaryngol.* 2021;147:110802. doi: 10.1016/j.ijporl.2021.110802.
39. Dhaduk N, Rodgers A, Govindan A, Kalyoussef E. Post-tonsillectomy bleeding: A national perspective. *Ann Otol Rhinol Laryngol.* 2021;130(8):941-947. doi: 10.1177/0003489420987438.
40. US Food and Drug Administration. Immune globulins. 2020; https://www.fda.gov/vaccines-blood-biologics/approved-blood-products/immune-globulins. Accessed August 16, 2021.
41. Sik G, Demirbuga A, Annayev A, Akcay A, Citak A, Ozturk G. Therapeutic plasma exchange in pediatric intensive care: Indications, results and complications. *Ther Apher Dial.* 2020;24(2):221-229. doi: 10.1111/1744-9987.13474.
42. Veerachit OLT, Siritho S, Prayoonwiwat N. Retrospective study of the adverse events of the treatment for an acute attack of neuromyelitis optica spectrum disorder. *Ther Apher Dial.* 2020;24(4):453-460. doi: 10.1111/1744-9987.13456.
43. Abe Y, Kusaoi M, Tada K, Yamaji K, Tamura N. Successful treatment of anti-MDA5 antibody-positive refractory interstitial lung disease with plasma exchange therapy. *Rheumatology (Oxford).* 2020;59(4):767-771. doi: 10.1093/rheumatology/kez357.
44. Lu J, Zhang L, Xia C, Tao Y. Complications of therapeutic plasma exchange: A retrospective study of 1201 procedures in 435 children. *Medicine (Baltimore).* 2019;98(50):e18308. doi: 10.1097/MD.0000000000018308.
45. Clinical Trials Registry. Neurobiologic, immunologic, and rheumatologic markers in youth with PANS. 2016; https://clinicaltrials.gov/ct2/show/NCT02889016. Accessed August 4, 2021.
46. Clinical Trials Registry. Trial of naproxen sodium for the treatment of OCD in children with PANDAS. 2020; https://www.clinicaltrials.gov/ct2/show/NCT04015596.
47. Clinical Trials Registry. Study to compare the effect of panzyga versus placebo in patients with pediatric acute-onset neuropsychiatric syndrome. 2021; https://clinicaltrials.gov/ct2/show/NCT04508530. Accessed August 16, 2021.
48. Octapharma. PANZYGA package insert. 2021; https://www.fda.gov/media/115397/download. Accessed August 16, 2021.

49. Swedo SE, Leonard HL, Garvey M, et al. Pediatric autoimmune neuropsychiatric disorders associated with streptococcal infections: clinical description of the first 50 cases. *Am J Psychiatry.* 1998;155(2):264-271.
50. Aetna. Medical clinical policy bulletins: parenteral immunoglobulins. 2021; https://www.aetna.com/cpb/medical/data/200_299/0206.html. Accessed July 21, 2021.
51. Aetna. Medical clinical policy bulletins: Rituximab. 2021; https://www.aetna.com/cpb/medical/data/300_399/0314.html. Accessed July 21, 2021.
52. Aetna. Medical clinical policy bulletins: plasmapheresis plasma exchange therapeutic apheresis. 2021; https://www.aetna.com/cpb/medical/data/200_299/0285.html. Accessed July 21, 2021.
53. Cigna. Drug and biologic coverage policy: immune globulin. 2021; https://static.cigna.com/assets/chcp/pdf/coveragePolicies/pharmacy/ph_5026_coveragepositioncriteria_Immune_Globulin_Intravenous_IGIV.pdf. Accessed July 21, 2021.
54. Cigna. Drug and biologic coverage policy: rituximab for non-oncology indications. 2021; https://static.cigna.com/assets/chcp/pdf/coveragePolicies/pharmacy/ph_5108_coveragepositioncriteria_rituximab_rituxan.pdf. Accessed July 21, 2021.
55. Cigna. Medical coverage policy: plasmapheresis. 2021; https://static.cigna.com/assets/chcp/pdf/coveragePolicies/medical/mm_0153_coveragepositioncriteria_plasmapheresis.pdf. Accessed July 21, 2021.
56. PANDAS Physician Network. Clinician resources for PANS/PANDAS. 2021; https://www.pandasppn.org/. Accessed August 16, 2021.

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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) for Antibiotics							
No. of Studies	**Study Design(s)**	**Risk of Bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other Factors**	**Level of Confidence**
Change in Psychiatric Symptoms							
3	RCTs	Moderate to High	Not serious	Not serious	Serious	Small sample sizes, short follow-up	Very Low ●○○○
Hospitalizations							
Harms							
1	RCT	High	Unable to rate	Not serious	Serious	Small sample sizes, short follow-up	Very Low ●○○○
Function or Quality of Life for Patient							
0							
Function or Quality of Life for Parent							
0							

Abbreviation. RCT: randomized controlled trial.

Quality Assessment (Confidence in Estimate of Effect) for Tonsillectomy or Adenoidectomy							
No. of Studies	**Study Design(s)**	**Risk of Bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other Factors**	**Level of Confidence**
Change in Psychiatric Symptoms							
2	Comparative cohort	High	Not serious	Serious	Not serious	None	Low ●●○○
Hospitalizations							
0							
Harms							
0							
Function or Quality of Life for Patient							
0							
Function or Quality of Life for Parent							
0							

Quality Assessment (Confidence in Estimate of Effect) for IVIG							
No. of Studies	**Study Design(s)**	**Risk of Bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other Factors**	**Level of Confidence**
Change in Psychiatric Symptoms							
2	RCTs	High	Not serious	Not serious	Not Serious	Very small samples, incomplete reporting	Very low ●○○○
Hospitalizations							
Harms							
2	RCTs	High	Not serious	Not Serious	Not Serious	Very small samples, incomplete reporting	Very low ●○○○
Function or Quality of Life for Patient							
Function or Quality of Life for Parent							

Abbreviation. RCT: randomized controlled trial.

Quality Assessment (Confidence in Estimate of Effect) for Plasma Exchange							
No. of Studies	**Study Design(s)**	**Risk of Bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other Factors**	**Level of Confidence**
Change in Psychiatric Symptoms							
1	RCT	High	Not serious	Not serious	Not Serious	Very small sample, incomplete reporting	Very low ●○○○
Hospitalizations							
Harms							
1	RCT	High	Not serious	Not Serious	Not Serious	Very small sample, incomplete reporting	Very low ●○○○
Function or Quality of Life for Patient							
Function or Quality of Life for Parent							

Abbreviation. RCT: randomized controlled trial.

Appendix C. Methods

Scope Statement

Populations

Children diagnosed with:

- Pediatric Autoimmune Neuropsychiatric Disorders Associated with Streptococcal Infections (PANDAS),
- Pediatric Acute-Onset Neuropsychiatric Syndrome (PANS)

Population scoping notes: Patients without either of the above conditions are excluded

Interventions

Therapeutic plasma exchange; intravenous immunoglobulin (IVIG); antibiotics; tonsillectomy and/or adenoidectomy

Intervention exclusions: Behavioral interventions, selective serotonin reuptake inhibitors, nonsteroidal inflammatory drugs

Comparators

Usual care or other interventions

Outcomes

Critical: Change in psychiatric symptom scores (e.g., Children's Yale-Brown Obsessive Compulsive Scale, Clinical Global Impressions-Improvement, Yale Global Tic Severity scale); Hospitalizations, including institutionalization or emergency visits

Important: Harms; standardized measures of function or quality of life for patients and caregivers

Considered but not selected for the GRADE table: None

Key Questions

KQ1: What is the effectiveness of treatments for PANDAS/PANS as compared to the named comparators?

KQ2: Does the comparative effectiveness of treatments for PANDAS/PANS differ by:

a. Patient characteristics
b. Condition characteristics
c. Intervention
d. Provider characteristics (e.g., Center of Excellence)

KQ3: What are the harms of interventions for PANDAS/PANS in children?

Contextual Questions

CQ1: What are the evidence-based criteria available for the diagnosis of PANDAS/PANS, and what are the diagnostic accuracy of available criteria or tests?

Search Strategy

A full search of the core sources was conducted to identify systematic reviews, meta-analyses, and technology assessments that meet the criteria for the scope described above. Searches of core sources were limited to citations published after 2015.

The following core sources were searched:

Agency for Healthcare Research and Quality (AHRQ)
Canadian Agency for Drugs and Technologies in Health (CADTH)
Cochrane Library (Wiley Online Library)
Institute for Clinical and Economic Review (ICER)
Medicaid Evidence-based Decisions Project (MED)
National Institute for Health and Care Excellence (NICE)
Tufts Cost-effectiveness Analysis Registry
Veterans Administration Evidence-based Synthesis Program (ESP)
Washington State Health Technology Assessment Program

An Ovid MEDLINE® search was also conducted to identify systematic reviews, meta-analyses, and technology assessments, using the search terms *paediatric autoimmune neuropsychiatric disorder associated with streptococcal infection, pediatric autoimmune neuropsychiatric disorder associated with streptococcal infection, pediatric acute-onset neuropsychiatric syndrome, pediatric infection triggered autoimmune neuropsychiatric disorder, childhood acute onset neuropsychiatric syndrome, paediatric acute-onset neuropsychiatric syndrome, autoimmune encephalitis*. The search was limited to publications in English published since 2012. In addition, a MEDLINE® search was conducted for randomized controlled trials and comparative cohort studies.

Searches for clinical practice guidelines were limited to those published since 2015. A search for relevant clinical practice guidelines was also conducted using MEDLINE® and the following sources:

Australian Government National Health and Medical Research Council (NHMRC)
Canadian Agency for Drugs and Technologies in Health (CADTH)
Centers for Disease Control and Prevention (CDC), Community Preventive Services
National Institute for Health and Care Excellence (NICE)
Scottish Intercollegiate Guidelines Network (SIGN)
United States Preventive Services Task Force (USPSTF)
Veterans Administration/Department of Defense (VA/DoD) Clinical Practice Guidelines

Inclusion/Exclusion Criteria

Studies were excluded if they were not published in English, did not address the scope statement, or were study designs other than systematic reviews, meta-analyses, technology assessments, randomized controlled trials, comparative cohort studies, or clinical practice guidelines.

Appendix D. Applicable Codes

Coding note: PANS does not have ICD-10-CM index entries; PANDAS is indexed to D89.89.

CODES	DESCRIPTION
ICD-10-CM Codes	
D89.89	Other specified disorders involving the immune mechanism, not elsewhere classified
D89.9	Disorder involving the immune mechanism, unspecified
G04.81	Other encephalitis and encephalomyelitis
CPT Codes	
Behavioral therapy	
90832	Psychotherapy, 30 minutes with patient
90833	Psychotherapy, 30 minutes with patient when performed with an evaluation and management service (List separately in addition to the code for primary procedure)
90834	Psychotherapy, 45 minutes with patient
90836	Psychotherapy, 45 minutes with patient when performed with an evaluation and management service (List separately in addition to the code for primary procedure)
90837	Psychotherapy, 60 minutes with patient
90838	Psychotherapy, 60 minutes with patient when performed with an evaluation and management service (List separately in addition to the code for primary procedure)
90839	Psychotherapy for crisis; first 60 minutes
Intravenous immunoglobulin therapy	
90283	Immune globulin (IVIG), human, for intravenous use
96365	Intravenous infusion, for therapy, prophylaxis, or diagnosis (specify substance or drug); initial, up to 1 hour
96366	Intravenous infusion, for therapy, prophylaxis, or diagnosis (specify substance or drug); each additional hour (List separately in addition to code for primary procedure)
99601	Home infusion/specialty drug administration, per visit (up to 2 hours)
Plasma exchange	
36514	Therapeutic apheresis; for plasma pheresis
Tonsillectomy and adenoidectomy	
42820	Tonsillectomy and adenoidectomy; younger than age 12
42821	Tonsillectomy and adenoidectomy; age 12 or over
42825	Tonsillectomy, primary or secondary, younger than age 12
42826	Tonsillectomy, primary or secondary, age 12 or over
42830	Adenoidectomy, primary; younger than age 12
42831	Adenoidectomy, primary; age 12 or over
42835	Adenoidectomy, secondary; younger than age 12
42836	Adenoidectomy, secondary; age 12 or over
HCPCS Level II Codes	
Intravenous immunoglobulin therapy	
J1459	Injection, immune globulin (privigen), intravenous, non-lyophilized (e.g., liquid), 500 mg
J1555	Injection, immune globulin (cuvitru), 100 mg
J1556	Injection, immune globulin (bivigam), 500 mg
J1557	Injection, immune globulin, (gammaplex), intravenous, non-lyophilized (e.g., liquid), 500 mg
J1558	Injection, immune globulin (xembify), 100 mg
J1559	Injection, immune globulin (hizentra), 100 mg
J1561	Injection, immune globulin, (gamunex-c/gammaked), non-lyophilized (e.g., liquid), 500 mg
J1562	Injection, immune globulin (vivaglobin), 100 mg
J1566	Injection, immune globulin, intravenous, lyophilized (e.g., powder), not otherwise specified, 500 mg

J1568	Injection, immune globulin, (octagam), intravenous, non-lyophilized (e.g., liquid), 500 mg
J1569	Injection, immune globulin, (gammagard liquid), non-lyophilized, (e.g., liquid), 500 mg
J1572	Injection, immune globulin, (flebogamma/flebogamma dif), intravenous, non-lyophilized (e.g., liquid), 500 mg
J1599	Injection, immune globulin, intravenous, non-lyophilized (e.g., liquid), not otherwise specified, 500 mg
S9338	Home infusion therapy, immunotherapy, administrative services, professional pharmacy services, care coordination, and all necessary supplies and equipment (drugs and nursing visits coded separately), per diem
SSRIs, NSAIDs, and corticosteroids	
J1094	Injection, dexamethasone acetate, 1 mg
J1100	Injection, dexamethasone sodium phosphate, 1 mg
J0702	Injection, betamethasone acetate 3 mg and betamethasone sodium phosphate 3 mg
J1700	Injection, hydrocortisone acetate, up to 25 mg
J1710	Injection, hydrocortisone sodium phosphate, up to 50 mg
J1720	Injection, hydrocortisone sodium succinate, up to 100 mg
J2650	Injection, prednisolone acetate, up to 1 ml
J7510	Prednisolone oral, per 5 mg
J7512	Prednisone, immediate release or delayed release, oral, 1 mg
J8540	Dexamethasone, oral, 0.25 mg
J7624	Betamethasone, inhalation solution, compounded product, administered through DME, unit dose form, per mg
J1130	Injection, diclofenac sodium, 0.5 mg

Note. Inclusion on this list does not guarantee coverage.

HERC Coverage Guidance: Pediatric Autoimmune Neuropsychiatric Disorders Associated with Streptococcal Infections (PANDAS) and Pediatric Acute-Onset Neuropsychiatric Syndrome (PANS) Disposition of Public Comments

Table of Contents

Discussion Table

IDs/#s	Summary of Issue	Draft Subcommittee Response
A1, C1, D1, G3, I1, J1, K1, L1, M1, N1, O1, Q1, R1, S1, U1	The proposed requirement to have two pediatric subspecialists evaluate a patient and recommend IVIG and/or plasmapheresis would be difficult to implement due to access issues and may prevent timely access to care. A patient's primary care provider should be considered as one of the two clinicians who determines eligibility for IVIG and/or plasmapheresis. A primary care provider in Oregon can include naturopaths.	***For EbGS discussion:*** *Due to the complex nature of these conditions and the need to rule out serious alternative diagnoses, at least 1 pediatric subspecialist should be involved in the patient's care. Such subspecialist involvement will ensure the best possible diagnostic and treatment plan for these severely affected children. Adolescents may also be adequately evaluated by an adult subspecialist who feels comfortable caring for their age group.* *However, to address concerns raised regarding access, EbGS can consider modifying the 2-subspecialist consultation requirement to 1 subspecialist in addition to the recommendation of the primary care provider, who could be a physician, naturopath, nurse practitioner, etc. If the requirement is reduced to 1 subspecialist, then the consultation should be in-person or via teleconsultation (not provider-to-provider or e-consult). The relevant clause would be modified as follows:* Option 1: A consultation with and recommendation by 2 pediatric subspecialists (for example, pediatric neurologist, pediatric psychiatrist, neurodevelopmental pediatrician, pediatric rheumatologist). One of these

IDs/#s	Summary of Issue	Draft Subcommittee Response
		consultations may consist of a provider-to-provider consultation or e-consultation. Option 2: b) A consultation with and recommendation from a pediatric subspecialist (for example, pediatric neurologist, pediatric psychiatrist, neurodevelopmental pediatrician, pediatric rheumatologist) as well as the recommendation of the patient's primary care provider (for example, family physician, pediatric nurse practitioner, naturopath). The subspecialist consultation may be a teleconsultation. For adolescents, an adult subspecialist consult may replace a pediatric subspecialist consult. *Similarly, the reevaluation clause could be modified to include a reevaluation by the primary care provider and 1 subspecialist:* Option 1: A reevaluation at 3 months by both pediatric experts is required for continued therapy of IVIG or plasma exchange. Option 2: A reevaluation at 3 months by both the primary care provider and subspecialist is required for continued therapy of IVIG or plasma exchange.
A3	The proposed criteria do not account for a level of severity of illness which would allow for immediate access to IVIG or plasmapheresis.	*In instances in which a patient faces incapacitating or life-threatening illness, the patient is best treated in the hospital environment. Hospital-level care is beyond the scope of this coverage guidance.*
A4	More clarification is needed regarding the requirement that a patient try and fail two therapies prior to being considered for IVIG and/or plasmapheresis, including 1) the duration of a trial of therapy and 2) how to determine if the less intensive therapy is not effective.	*The duration of a trial of therapy will differ by type of therapy. For example, an appropriate course of antibiotics may be a 14-day course while an appropriate trial of an SSRI might be 6 weeks. Additionally, these therapies may be tried concurrently. However, as these therapies have few serious side effects and may be effective, the subcommittee feels that a trial of such less intensive therapy prior to therapy escalation is important to the care of children with PANDAS/PANS.*

IDs/#s	Summary of Issue	Draft Subcommittee Response
		The trial of less intensive therapy would be considered to have not been effective when no significant clinical improvement was found on whatever objective clinical instrument is used for the most concerning clinical presenting symptom(s), for example a scale for rating OCD symptoms or for rating depression symptoms. *Staff have also noted in discussion with experts that a clinical improvement that is nonsustained, such as with a course of steroids, is also an indication for IVIG or plasmapheresis.* ***For EbGS discussion:*** *Consider modifying the current requirement wording to clarify what is considered a "trial" of an alternative therapy.* Option 1: At least 2 less-intensive therapies (for example, appropriate limited course of nonsteroidal antiinflammatory drugs [NSAIDs], corticosteroids, selective serotonin reuptake inhibitors [SSRIs], behavioral therapy, short-course antibiotic therapy) have been tried and were not effective. Option 2: A clinically appropriate trial of at least 2 less-intensive treatments (for example, appropriate limited course of nonsteroidal antiinflammatory drugs [NSAIDs], corticosteroids, selective serotonin reuptake inhibitors [SSRIs], behavioral therapy, short-course antibiotic therapy) was either not effective, not tolerated, or did not result in sustained improvement in symptoms (as measured by a lack of significant improvement on a validated objective instrument directed at the patient's primary symptom complex). These trials may be performed concurrently.

IDs/#s	Summary of Issue	Draft Subcommittee Response
		For EbGS discussion: *Similarly, the reevaluation at 3 months should be done with a validated objective instrument.* Option 1: This evaluation must include objective clinical testing, which must be performed pretreatment and posttreatment to demonstrate significant clinical improvement. Option 2: This evaluation must include objective clinical testing with a validated instrument, which must be performed pretreatment and posttreatment to demonstrate significant clinical improvement.
A1, A5, C1, H1, I1, L1, M1, N1, O1, Q1, R1, S1	There is concern about workforce training, education, and willingness to see patients with PANDAS/PANS symptoms, as well as lengthy wait times to access appointments with subspecialists.	*Training and education of providers is beyond the scope of the HERC. It is also beyond the scope of the HERC to require providers to see certain patients or prescribe certain treatments. Likewise, workforce issues regarding the number of specialists and access to specialists is beyond the scope of the HERC, though it is important context for HERC decisions.* *Previously suggested modifications (see above) would allow for use of telemedicine to accomplish visits and consultations, and would improve access to specialists for patients in rural or underserved areas. Other modifications would allow adolescents to be evaluated by adult subspecialists which should also help to address the access to care issue.*
D1, E1, F1, G1, H1, I1, J1, K1, M1, N1, O1, Q1, S1	Description of personal stories of affected children and caregiver experience.	*We thank you for taking the time to share your and your loved ones' experiences and stories. Such real-life stories add needed context to the subcommittee's deliberations.* *While individual stories provide context for the subcommittee's decisions, the subcommittee makes coverage decisions on a population-level basis and*

IDs/#s	Summary of Issue	Draft Subcommittee Response
		must base these decisions on evidence and other factors with respect to the population in general.
G2	There is concern about the credentials of the appointed experts for this topic.	*For this topic, OHA selected 2 Oregon experts knowledgeable of local practice patterns and standards of care regarding PANDAS/PANS. One out-of-state expert was nominated by the PANS Consortium as a subject matter expert. The subcommittee places a preference on local expertise to shape care guidelines that will affect Oregon patients, payers and providers.*
A2, B7	The coverage exclusion of other interventions (for example, tonsillectomy) does not align with PANS Consortium (advocacy organization) treatment guidelines, and is supported by unpublished studies.	*Our review found published evidence from 2 comparative observational studies and 2 systematic reviews indicating that tonsillectomies are not effective for reducing neuropsychiatric symptom severity or exacerbations in children with a PANDAS diagnosis. Unpublished literature is not eligible for inclusion in the coverage guidance evidence review.*

Commenters

Identification	Stakeholder
A	Sarah Lemley, Executive Director, Northwest PANDAS/PANS Network *[Submitted December 7, 2021]*
B	Dritan Agalliu, PhD; Associate Professor; Departments of Neurology, Pathology and Cell Biology; Columbia University Medical Center *[Submitted December 8, 2021]*
C	Donna Kirchoff, MD, Integrative Developmental & Behavioral Pediatrics *[Submitted December 9, 2021]*
D	Deborah Miller, parent/caregiver of a child with PANDAS *[Submitted December 9, 2021]*
E	Heather Winkeljohn, parent/caregiver of a child with PANDAS/PANS *[Submitted December 9, 2021]*
F	Jennifer Rowan, parent/caregiver of a child with PANDAS/PANS *[Submitted December 10, 2021]*
G	Cathy Daraee, RN, grandparent of a child with PANDAS/PANS *[Submitted December 13, 2021]*
H	Meggan Bennett, parent/caregiver of a child with PANDAS/PANS *[Submitted December 15, 2021]*
I	Carrie Ann McGowan, parent/caregiver of a child with PANDAS/PANS *[Submitted December 17, 2021]*
J	Andrea Jones, RN, and parent/caregiver of a child with PANDAS/PANS *[Submitted December 17, 2021]*

K	Kamiar Daraee, grandparent of a child with PANDAS/PANS *[Submitted December 20, 2021]*
L	Lara Winn, MSW student clinician, Collective Care Clinic *[Submitted December 23, 2021]*
M	Christina and Ivan Vejar, parents/caregivers of a child with PANDAS/PANS *[Submitted January 3, 2022]*
N	Jeremy Johnson, relative of a child with PANDAS/PANS *[Submitted January 5, 2022]*
O	Jessica Johnson, relative of a child with PANDAS/PANS *[Submitted January 5, 2022]*
P	Ivan Vejar, Board Member, Northwest PANDAS/PANS Network *[Submitted January 5, 2022]*
Q	Carly Absher, parent/caregiver of a child with PANDAS/PANS *[Submitted January 6, 2022]*
R	Kym McCornack, NWPPN Oregon Outreach Coordinator *[Submitted January 6, 2022]*
S	Sara E. Zeman, JD, LLM, and parent/caregiver of a child with PANDAS/PANS *[Submitted January 6, 2022]*
T	Paul Terdal, management consultant, Terdal Consulting LLC *[Submitted January 6, 2022]*
U	Paul Ryan, President, PACE Foundation *[Submitted January 6, 2022]*

Public Comments

ID/#	Comment	Disposition
A1	Option #1 Guidance Concerns: The revised HERC guidance unnecessarily perpetuates barriers to care by requiring 2 physician specialists attest to the need for IVIG and/or Plasma Exchange when the list of specialists specified by the Evidence Based SubCommittee are NOT those who are well versed in treating this population and in fact, 2 of the 4 specialties identified REFUSE TO SEE THESE PATIENTS. These requirements would further perpetuate health inequity in our state, especially those who live in rural areas or who don't have the resources needed to access 2 specialists (location, transportation, trauma, time off work, etc). Oregon already faces a critical shortage of PANDAS/PANS-competent providers, especially within the restricted list of specialties identified in the revised HERC report. These requirements would inappropriately exclude many disciplines and providers with PANDAS/PANS expertise who are currently caring for this population and are well versed in the diagnostic and treatment guidelines for care.	*Thank you for your comments. We have written specific responses to individual sections of your public comment in the rows that follow.* *Due to the complex nature of these conditions and the need to rule out serious alternative diagnoses, at least 1 pediatric subspecialist should be involved in the patient's care. Such subspecialist involvement will ensure the best possible diagnostic and treatment plan for these severely affected children. Additionally, adolescents may be adequately evaluated by an adult subspecialist who feels comfortable caring for their age group.*

ID/#	Comment	Disposition
	Imposing cumbersome requirements in order to access medically necessary care only compounds the health disparities that already exist for these disorders. We would ask the HERC EbGS Committee to remove the 2-physician consultation and recommendation requirement for accessing IVIG or Plasma Exchange. The removal of this requirement will ensure inclusivity of medical providers with PANDAS/PANS expertise who are currently being excluded by the drafted HERC requirement language and allow for more timely access to care and treatment interventions. Alternatively, drop the requirement to one physician specialist which will alleviate some of the barrier and still ensure you have some oversight. Please note, accessing consultation with Pediatric Neurologists and Pediatric Psychiatrists, especially those who take Oregon Health Plan, can be 6 months to a year out for a new patient.	
A2	In addition, the exclusion of tonsillectomy coverage overlooks PANDAS Physician Network's guidance on this issue: "Many PANS/PANDAS patients have damaged or cryptic tonsils, but the potential benefit of tonsillectomy is not limited to patients with those tonsil characteristics. In an unpublished research study done at Georgetown Medical Center, PANDAS patients had their tonsils removed, analyzed, and the children subsequently tracked for over six months. The tonsils relative to non-PANDAS patients had many pathogens, most prominent being staphylococcus (staph). Streptococcus pyogenes was not found in PANDAS patients but was present in non-PANDAS controls. Other notable pathogens included MRSA, E. coli, Pseudomonas and Serratia marcens. The absence of Streptococcus in the PANDAS cohort suggests that once the patient has been "sensitized" other pathogens can induce neurologic symptoms in susceptible patients. In addition, the tonsils belonging to PANDAS patients contained elevated levels of TH17, indicating a consistent immune response to the pathogens lodged within the tonsils. TH17 has been found in animal PANDAS research to be a potential agent for opening the blood brain barrier, allowing inflammation in targeted regions of the brain.	*Our review found published evidence from 2 comparative observational studies and 2 systematic reviews indicating that tonsillectomies are not effective for reducing neuropsychiatric symptom severity or exacerbations in children with a PANDAS diagnosis. Unpublished literature, such as the referenced Georgetown study, is not eligible for inclusion in the coverage guidance evidence review.*

ID/#	Comment	Disposition
	The Georgetown study and physician experience indicates that removal of the tonsils can provide remission of PANS & PANDAS symptoms for some patients. There is no marker to determine which patient a tonsillectomy will result in remission of PANS/PANDAS symptoms. A clear benefit of tonsillectomy that was found in the Georgetown study and further observed by practitioners who see many PANS/PANDAS patients, is that those PANS/PANDAS cases that have undergone tonsillectomy, have a significantly lower chance of recurrence post-immunotherapy such as IVIG. Since immunotherapy suppresses the potential cause of basal ganglia encephalitis and in some cases like IVIG "reboots" the immune response, then removing a consistent infectious trigger housed within the tonsil or removing a repository for new pathogen agitators would most likely be beneficial." We would also ask for the committee to take more time to understand the importance of tonsillectomy in these disorders by utilizing a subject expert who has been on faculty at Georgetown for more than 25 years (Dr. Earl Harley) and has put forth written comments and will be available during the hearing. He can also be reached at *[email redacted*].	
A3	Lastly, these requirements dismiss the PANS Consortium treatment guidelines which indicate the necessity to progress to these lines of treatment (IVIG and Plasma Exchange) for those patients whose severity is "incapacitating, life threatening, or occupy 71%-100% of waking hours". Delaying needed medical care for a child suffering from a severe presentation of PANDAS/PANS because of these imposed requirements would be inappropriate in a life-threatening situation. We would ask the HERC EbGS Committee to remove the requirement of two failed therapies before proceeding to IVIG or PE as treatment guidelines published by the PANS Consortium and PANDAS Physician Network recommend treatment based on severity. To force a child with life-threatening presentation of these disorders to	*In instances in which a patient faces incapacitating or life-threatening illness, the patient is best treated in the hospital environment. Hospital-level care is beyond the scope of this coverage guidance.* *We reviewed both the PANS/PANDAS Clinical Research Consortium treatment guidelines and the Nordic Pediatric Immunopsychiatry guidelines and included a discussion in the coverage guidance (pg. 32-36). Both guidelines were rated as having a high risk of methodological bias. Authors of the PANS/PANDAS Consortium guidelines recognized that there was*

ID/#	Comment	Disposition
	fail less-intensive therapies first can result in irreversible health outcomes because of delayed medical care.	*disagreement regarding proposed treatments among contributing clinicians and that the recommended treatment pathway is subject to amendment pending further evidence.*
A4	We would also request clarification on: The duration required of the less-intensive therapies (NSAIDS, corticosteroids, SSRIS, therapy and/or antibiotics)? How would effectiveness or failed effectiveness of these therapies be measured and by whom? The reevaluation post 3 months of IVIG or PE, what specific 'objective clinical testing' would be utilized and how would providers be trained to ensure they are using it consistently?	*The duration of a trial of therapy will differ by type of therapy. For example, an appropriate trial of antibiotics may be a 14-day course, while an appropriate trial of an SSRI might be 6 weeks. Additionally, these therapies may be tried concurrently.* *As these therapies have few serious side effects and may be effective, the subcommittee feels that a trial of such less intensive therapy prior to therapy escalation is important to the care of children with PANDAS/PANS.* *The trial of less intensive therapy would be considered to have not been effective when no significant clinical improvement was found on whichever validated instrument is used for the most concerning clinical presenting symptom(s), for example, a scale for rating OCD symptoms or for rating depression symptoms.*

HERC Coverage Guidance: Pediatric Autoimmune Neuropsychiatric Disorders Associated with Streptococcal Infections (PANDAS) and Pediatric Acute-Onset Neuropsychiatric Syndrome (PANS)
Disposition of Public Comments

ID/#	Comment	Disposition
A5	Why the Committee would not trust current clinicians to prescribe medically necessary care and instead, require referral to specialists that lack expertise, experience and acceptance of these disorders with access issues that would only delay needed medical care? How the Committee would provide training and education to the identified specialists and ensure their willingness to treat this population given the historical reports of almost all Oregon families having to seek medical care outside of these specialties and even outside of our state as there is a lack of expertise locally?	*Training and education of providers is beyond the scope of the HERC. It is also beyond the scope of the HERC to require providers to see certain patients or prescribe certain treatments. Likewise, workforce issues regarding the number of specialists and access to specialists is beyond the scope of the HERC.*
B1	My laboratory has a long-standing interest in understanding the role of the adaptive immune system (Th17/Th1 lymphocytes) in autoimmune central nervous system (CNS) sequelae following recurring S. pyogenes (Group A Streptococcus; GAS) infections, specifically how CD4+ T cell subtypes induce neurovascular damage, neuroinflammation and neuronal circuit dysfunction in animal models for PANDAS/PANS. We have shown that S. pyogenes-specific Th17 cells from the nose enter the olfactory bulb and brain via olfactory sensory axons, where they damage the structural and functional integrity of the blood-brain barrier (BBB) and allow autoantibodies to enter the brain. Recently, we have demonstrated that while the loss of excitatory synapses in the olfactory bulb is transient after multiple infections, there is a persistent functional deficit in odor processing and neuronal function. Moreover, using mice that lack Th17 lymphocytes, we have shown that they are critical for selective CNS entry of autoantibodies across the blood-brain barrier, microglial activation and neural circuit impairment during post-infectious basal ganglia encephalitis. We are currently working to further understand the origin of inflammatory chemokines and cytokines present in the blood of children with PANDAS/PANS and elucidate how they affect the pathology in the brain. Furthermore, my laboratory has significant expertise regarding the	*Thank you for your comments. We have written specific responses to individual sections of your letter in the rows that follow.*

ID/#	Comment	Disposition
	neuroimmunological mechanisms that promote blood-brain barrier breakdown and immune cell infiltration into the CNS in Experimental Autoimmune Encephalomyelitis, a mouse model for multiple sclerosis. As a basic scientist, I have the required expertise to evaluate the literature in the field of PANDAS/PANS and to provide an independent assessment whether the "literature-based evidence" presented to the HERC Evidence-Based Guideline Subcommittee via the HERC Review of the Literature and Coverage Guidance for PANDAS/PANS/Pediatric AE on September 9, 2021 (Pages 70 - 117) is accurate. After reviewing the HERC document in detail, I regret to inform the committee that: a) the literature presented in the document is INCOMPLETE and b) the papers presented as evidence against treatment do not accurately reflect the conclusions of the study. I have attached a rebuttal outlining the missing literature and I have attached the PDFs for some of the recent studies that the committee needs to take into consideration. Pediatric Acute-onset Neuropsychiatric Syndrome (PANS) is characterized by the abrupt and dramatic onset of obsessive-compulsive symptoms, restricted intake of food or fluids (sometimes to the point of starvation or dehydration), anxiety, depression and suicidality, emotional lability, personality changes, sensory hypersensitivity, cognitive deficits and physical symptoms, such as arthralgias, urinary dysfunction, and severe insomnia. As its name implies, PANS affect children, primarily those aged 4 - 9 years. When Group A streptococcal infections (such as strep throat) triggers symptoms, the disorder is known as Pediatric Autoimmune Neuropsychiatric Disorders Associated with Streptococcal Infections (PANDAS). Recently, a number of studies have demonstrated that PANS/PANDAS is a form of autoimmune encephalopathy—or inflammation of the brain. Below, I outline several critical old and recent basic and clinical studies that demonstrate a	

ID/#	Comment	Disposition
	very strong association of GAS with PANDAS and treatment strategies for PANDAS and PANS.	
B2	Basic studies in animal models of PANDAS/PANS have demonstrated that both cellular (Th17 lymphocytes) and humoral (antibodies) adaptive immunity, generated in response to multiple GAS infections, target the brain and trigger neuroinflammation, blood-brain barrier damage, neuroinflammation and neuronal dysfunction (Brimberg et al., 2012; Dileepan et al., 2016; Hoffman et al., 2004; Platt et al., 2020; Yaddanapudi et al., 2010). These animal models have been focused on demonstrating the ability of GAS to prime development of an autoimmune reaction by stimulating adaptive cellular and humoral immune responses. In the mouse, intranasal (i.n.) infections with live bacteria polarize T cells located in the nasal-associated lymphoid tissue (NALT, the mouse structural analog of human tonsils and adenoids) toward a Th17 phenotype, a T cell subtype that is both essential for mucosal immune protection against bacteria but also strongly implicated in many autoimmune diseases. Multiple i.n. S. pyogenes infections strengthen this Th17 immune response, largely due to induction of IL-6 and TGF-β1, which are two pro-inflammatory cytokines essential for Th17 differentiation. This model has been used to demonstrate that repeated i.n. infections with S. pyogenes induce migration of GAS-specific Th17 cells and other T cell subtypes from the nasal epithelium to the olfactory bulb (OB), where sensory axons make connections with projection interneurons to form the neural circuitry essential for odor discrimination, as well as to other CNS regions (Dileepan et al., 2016). The presence of Streptococcus-specific Th17 cells in the CNS after repeated i.n. infections increases the permeability of capillaries in several CNS regions thereby enabling deposition of serum IgGs and potential anti-CNS autoantibodies. This is largely due to disruption in the organization of tight junction (TJ)-associated proteins, which	*We reviewed the references provided in this public comment. Animal model studies are not eligible for inclusion in HERC guidance documents as they provide indirect evidence and are outside of the scope of the coverage guidance evidence review.* *Your work to address the evidence gaps is helpful and may motivate others to perform more rigorous human subjects research on these conditions. However, the subcommittee uses only peer-reviewed studies regarding important clinical outcomes performed on human subjects and generally requires between-group comparison for evidence of treatment effectiveness.*

ID/#	Comment	Disposition
	control an essential aspect of blood-brain barrier function. The intranasal model produces profound changes in olfactory neural circuitry by reducing excitatory input at the presynaptic terminals of olfactory sensory axons and perturbing the excitatory/inhibitory balance within the primary olfactory circuit. This model of post-S. pyogenes autoimmunity demonstrates a central role for the cellular adaptive immune response (for example, bacterial-specific Th17 cells in the CNS) in disrupting blood-brain barrier function, thus promoting entry of antibodies into the CNS and inducing changes in synaptic signaling. Although such a cellular adaptive immune response has not been identified to date in the nervous systems of children suffering from BGE, S. pyogenes-specific Th17 cells can be found in the tonsils of human patients (Dileepan et al., 2016), making Th17 lymphocytes a potential causative agent in either initiation or persistence of disease pathogenesis. Moreover, mice that lack Th17 lymphocytes, have reduced blood-brain barrier damage and antibody entry into the CNS, reduced microglial activation and preservation of neural circuit function in the mouse model for PANDAS (Platt et al., 2020). Since Th17 lymphocytes are critical for pathogenesis in multiple autoimmune diseases such as Multiple Sclerosis, Lupus, and Psoriasis and they are also necessary for disease pathogenesis in rodent models for PANDAS (Platt et al., 2020), these findings suggest a critical requirement for the adaptive cellular immune response in PANDAS pathogenesis in addition to the role of the humoral immune response. A second group of rodent models for BGE employs subcutaneous immunization with an antigenic target (bacterial homogenate) plus complete Freund's adjuvant to activate the immune system, in conjunction with agents (i.e., B. pertussis toxin) that open the BBB to provide access to brain targets. In this model, mice and rats develop a strong humoral immune response toward S. pyogenes and show	

ID/#	Comment	Disposition
	behavioral abnormalities. Specifically, GAS-immunized rodents display increased rearing and decreased locomotion, as well as increased repetitive and perseverative behaviors, impaired pre-pulse inhibition, and reduced concentrations of serotonin in the prefrontal cortex as compared to controls (Brimberg et al., 2012; Hoffman et al., 2004; Yaddanapudi et al., 2010). Moreover, adoptive transfer of serum IgGs from S. pyogenes-immunized mice to naive recipient mice, or direct infusion of sera into rat brains, recapitulates some of the behavioral deficits in recipient rodents, whereas no effects were observed after adoptive transfer of IgG-depleted serum. Histological examination of brain tissue revealed antibody deposition in the deep cerebellar nuclei and hippocampus in mice and the striatum, cortex, and thalamus in rats (Brimberg et al., 2012; Hoffman et al., 2004; Yaddanapudi et al., 2010). Serum IgG isolated from immunized rodents recognizes both cerebellar targets and human D1/ D2 dopamine receptors by either western blotting or ELISA. Thus, the subcutaneous animal models for BGE have provided useful information regarding the humoral immune response after bacterial infection (i.e., the presence of antibodies directed against GAS and CNS) and demonstrate a clear link between S. pyogenes exposure and behavioral abnormalities. A comprehensive review of animal models for PANDAS/PANS is discussed in a recent review that we published in Frontiers in Immunology (Platt et al., 2017). Overall, the summary outlined above from studies in animal models of PANDAS/PANS provides a very strong evidence that there is an immune-based component (cellular and humoral) underlying the pathogenesis of disease that should be taken into serious consideration for recommendation to treat children suffering from PANDAS/PANS. I want to remind the committee that the mouse model for multiple sclerosis, Experimental Autoimmune Encephalomyelitis, which	

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	has some similarities to the human MS, has been proven very valuable to understand a) the mechanisms of human MS and b) develop treatments for the disease. Therefore, the committee should take into consideration the animal studies for PANDAS/PANS for their decision.	
B3	Studies in sera of patients suffering from Sydenham's chorea, PANDAS and PANS have identified anti-neuronal autoantibodies targeting the basal ganglia, including the D1 and D2 dopamine receptors and recently cholinergic interneurons (Cox et al., 2013; Dale et al., 2012; Kirvan et al., 2003; Kirvan et al., 2006; Sinmaz et al., 2015; Xu et al., 2020). These antibodies induce neuronal dysfunction in vitro (Kirvan et al., 2003; Xu et al., 2020) and elicit behavioral abnormalities in rodents after adoptive transfer [reviewed in (Platt et al., 2017)], suggesting a critical role for the humoral immune response in the pathogenesis of these diseases. Moreover, the titer of these pathological antibodies is reduced in the sera of Sydenham's chorea, PANDAS or PANS patients during the convalescence period that corresponds with improved symptomatology (neurological and psychiatric manifestations) (Chain et al., 2020; Xu et al., 2020). Finally, a recent clinical study has shown that in 41 pediatric subjects, followed for over a 24-month period, 65% of new GAS [Group A streptococcal] infections caused no symptoms, yet these subjects developed antibodies against GAS suggesting that the majority of GAS infections are not detected in clinic (Hysmith et al., 2017). This could result in missed opportunities for primary prevention of rheumatic fever and rheumatic heart disease, Sydenham's chorea or PANDAS with appropriate antimicrobial therapy. In addition to the presence of D2R antibodies, a recent study (Pilli et al, 2020) characterized the presence of proinflammatory D2R-specific T cells in movement and psychiatric disorders in 24 cases and 16 controls. D2R-specific T cells were	*We reviewed the references you provided and determined these studies are ineligible for inclusion in the coverage guidance report, given that these are basic science research papers, animal model studies, and/or do not report clinical outcomes that are relevant to the evidence review. We recognize the important role of basic science research, but coverage decisions regarding interventions require evidence of clinically important benefits in humans.*

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	identified by flow cytometric quantification of CD4+CD25+CD134+ T cells. Cytokine secretion was analyzed using a cytometric bead array and ELISA. HLA genotypes were examined in D2R-specific T-cell-positive patients. D2R antibody seropositivity was determined using a flow cytometry live cell-based assay. The study identified three immunodominant regions of D2R that specifically activated CD4+ T cells in 8/24 patients. Peptides corresponding to these regions were predicted to bind with high affinity to the HLA of the eight positive patients and had also elicited the secretion of pro-inflammatory cytokines IL-2, IFN-g, TNF, IL-6, IL-17A and IL-17F. Therefore, autoreactive D2R-specific T cells and a proinflammatory Th1 and Th17 cytokine profile characterize a subset of pediatric patients with movement and psychiatric disorders, further underpinning the theory of immune dysregulation in these disorders.	
B4	Recently, two large epidemiological cohort studies of children in Europe (N=1,068,000) (Orlovska et al., 2017) and Asia (N=28,600) (Wang et al., 2016) reported that children hospitalized with GAS infections had a 96% higher risk of neuropsychiatric disorders (Taiwan) (Wang et al., 2016), 51% higher risk for obsessive-compulsive disorder (OCD) and a 35% higher risk for tic disorders (Denmark) (Orlovska et al., 2017). These recent epidemiological studies together with previous findings that more than 25% of pediatric cases presenting with obsessive-compulsive disorders (OCD) and tic disorders (for example, Tourette syndrome) originate as PANDAS (Swedo et al., 1998) strongly argue for a critical role of recurrent GAS infections in the etiology of PANDAS or PANS and that these diseases are rare similar in incidence to Lupus.	*Thank you for providing this background. We reviewed these references and determined that, while they are out of scope for inclusion in the evidence review since they do not evaluate the effectiveness of potential treatments for PANDAS/PANS, they do provide helpful epidemiologic context. Therefore, the Orlovska et al., 2017 and Wang et al., 2016 references have been added to the coverage guidance background section after the submission of this comment.*
B5	PANDAS and PANS cases are increasingly being classified as a form of Autoimmune Encephalitis. The Mayo Clinic conducted a study in 2018 warning that more than 90,000 Autoimmune Encephalitis cases are being missed on an annual basis	*After reviewing the literature on autoimmune encephalitis, the subcommittee determined that autoimmune encephalitis is a life-threatening condition*

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	worldwide (Dubey et al., 2018). We contend that many PANDAS and PANS cases fall within that category as recently discussed in detail in studies published in the American Academy of Neurology (Cellucci et al., 2020) and Lancet Psychiatry (Pollak et al., 2020). Furthermore, PANDAS and PANS are now considered as a form of basal ganglia encephalitis demanding attention and urgent care, as argued in recent editorial by esteemed physicians in Immunology, Neurology & Psychiatry of PANDAS/PANS. (Dale et al., 2017).	*that could be associated with an acute infection or presence of a tumor and is, therefore, acutely treated in a hospital setting. The specific diagnostic criteria currently in broad clinical use for autoimmune encephalitis is unique and has biological markers. Because of the differences in diagnostic criteria and disease processes between autoimmune encephalitis and PANDAS/PANS, the subcommittee voted to exclude autoimmune encephalitis from the scope of this report in its September 9, 2021 meeting.*
B6	A recent Italian study (Murgia et al., 2021) used a metabolomics approach to identify a specific metabolic pattern in patients affected by PANS compared to healthy subjects. Thirty-four outpatients referred for PANS and 25 neurotypical subjects matched for age and gender, were subjected to metabolite analysis. The study found a unique plasma metabolic profile in PANS patients, significantly differing from that of healthy children, that suggests the involvement of specific patterns of neurotransmission (tryptophan, glycine, histamine/histidine) as well as a state of neuroinflammation and oxidative stress in the disorder. This metabolomics study offers new insights into biological mechanisms underpinning the disorder and supports research to identify potential biomarkers implicated in PANS.	*We reviewed this reference and determined that it is out of scope for inclusion in the coverage guidance as it does not evaluate any of the prespecified interventions or clinical outcomes for the evidence review. See also response to B3.*
B7	The NIMH PANS consortium formed by a large number of experts from the disciplines of pediatrics, infectious disease, neurology, immunology and psychiatry have published the guidelines for treatment of PANDAS/PANS which rely on antibiotic therapy, steroids, IVIG, and psychiatric treatments (Thienemann et al., 2017; Frankovich et al., 2017: Cooperstock et al., 2017). The PANS Research	*Thank you for your comment. The coverage guidance currently contains a summary of the PANDAS/PANS Clinical Research Consortium guidelines based on the same sources cited in this section.*

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	Consortium has based its diagnosis and treatment guidelines on their experience of managing more than 1,000 patients in the U.S. The majority of the children are under age 13 and those who are left untreated can suffer dire consequences into young adulthood, including suicide. Treatment of PANS/PANDAS involves a three-pronged approach that utilizes psychiatric medications to provide symptomatic relief, antibiotics to eliminate the source of neuroinflammation and immune-modulating therapies to treat disturbances of the immune system. When these therapies are instituted promptly, many children recover completely and return to full functioning. Delays in obtaining treatment not only prolong the child's suffering needlessly but also increase the risk that the PANS/PANDAS symptoms will become entrenched, leading to long- term psychiatric, neurologic, and cognitive dysfunction.	
B8	A Stage 3 Clinical Trial of IVIG will be conducted in January 2021, "A Superiority Study to Compare Panzyga Versus Placebo in Patients with PANS," Clinical Trials.gov, NCT04508530 in both Europe and USA in approximately 200 children to examine the effectiveness of IVIG in PANDAS and PANS children in a larger cohort.	*Thank you for your comment. We are currently monitoring the status of this trial for future consideration.*
C1	I would like to provide written testimony regarding Medicaid coverage of specific treatments for PANDAS/PANS for children who have Medicad *[sic]* insurance. My understanding is that one coverage option under consideration is that in order to qualify for PE or IVIG, a Medicaid patient would require both documentation of failed treatment (which I think is very reasonable) AND would REQUIRE 2 MD Subspecialists (Pediatric Neurology, Rheumatology, Psychiatry or Neurodevelopmental) to consult and recommend treatment (which I do not think is reasonable). Unfortunately, the requirement to have 2 specific subspecialists recommend treatment creates an unnecessary and cumbersome barrier to appropriate care, as	*Thank you for your comment. Please see the response to A5.* *Additionally, while it is outside of the scope of this coverage guidance review process to specify or include a pool of eligible providers who treat a specific condition in its report, we have listed examples of the types of providers, such as naturopaths, that can provide consultations for PANDAS/PANS in our draft Coverage Guidance recommendation.*

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	our state not only lacks access to physicians in these specialties (a 12+ month wait to see both clinicians would be very common), but there are also only a very small number of physicians within those specialties that are willing to evaluate or treat a child for PANS/PANDAS. The language also excludes currently treating clinicians (Pediatricians, Naturopaths and Nurse Practitioners) who may have the required expertise to diagnose and treat PANS/PANDAS. Unlike AZ and CA, OR does not have CPAE/PANS clinic to serve this need. PANS/PANDAS is an extremely challenging disorder to diagnose and treat, and when it is severe enough that IVIG and/or PE is indicated, is devastating for not only the children who are impacted but for their entire families, due to the extreme impact it has on mood and behavior. Please consider changing the coverage language to allow a wider range of clinicians to verify this diagnosis and recommend IVIG/PE treatment, as the current language will essentially make IVIG/PE impossible for Medicaid patients to get in a timely manner.	
D1	I am the mother of a 12 year old son with PANDAS. I am opposed to requiring 2 physicians to approve IVIG for children with PANDAS/PANS. My son, *[name redacted]*, is not able to get the treatment that he needs despite the fact that there is a National Standard of Care for children suffering from PANDAS and PANS. Despite the fact that there are multiple multi disciplinary institutions across the country with clinics dedicated to treating children with PANDAS/PANS using this national standard of care with success. Making it a requirement for two physicians to approve IVIG will only make it harder for my son and other children suffering from PANDAS/PANS to get the treatment that they require to heal. It is unethical to withhold treatment for these children and leave them to suffer when there is, once again, a National Standard of Care.	*Thank you for taking the time to share your and your loved ones' experiences and stories. Such real-life stories add needed context to the subcommittee's deliberations.*

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	My son is a victim of a broken health care system in the state of Oregon that has left him a shell of the child he should be because he does not have access to the lifesaving treatment that he requires. I say lifesaving because my son has spoken multiple times about wanting to kill himself. He would rather be dead then deal with the effects of PANDAS. Tics, uncontrollable rage, hallucinations, black out episodes, OCD, extreme anxiety, baby talking and loss of friendships to name a few. *[Name redacted]*'s story does not have to end this way. His story can end happily if he is given access to the treatment that he requires to save him from irreversible brain damage. *[Name redacted]* needs IVIG ever 4 weeks for a recommended 5-6 months at a cost of over $5500 a round. It is sickening that the state of Oregon add another road block with a 2 physician requirement for IVIG. It is sickening that the state of Oregon would leave my son to suffer rather than giving access to treatment. My 12 year old son has been suffering with PANDAS for 10 long years. Enough is enough. He deserves to know what a healthy childhood looks like. We should be removing roadblock to treatment not adding them. I plead with you to make treatment for children suffering from PANDAS/PANS accessible so that other children like *[name redacted]* won't be left to suffer and can live a happy healthy life.	
E1	Your decision and failure to recognize PANDAS/PANS as a legitimate condition is not only damaging but it is dire and detrimental to the health and wellness of children. Six years ago, here in New Mexico, I heard those words that any PANDAS/PANS parents hates to hear from a provider, "PANDAS/PANS is controversial." Luckily, I did not accept that and pursued proper treatment from a well versed Internal Medicine Physician and also from the PANDAS clinic in Tucson,	*Our review found published evidence from 2 comparative observational studies and 2 systematic reviews indicating that tonsillectomies are not effective for reducing neuropsychiatric symptom severity or exacerbations in children with a PANDAS diagnosis. Unpublished literature is not eligible for inclusion in the*

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	Arizona. Thankfully, my child has improved but not without lasting effects. Her pediatrician was knowledgeable about the disease, but the Neurologist was not. We were luckily in a position to pay for our child's treatments, one of which involved tonsillectomy. Many families are not so lucky. EARLY treatment and recognition is key. You must stop this draconian, shameful and archaic belief. Look at the research out of some of the leading Universities in America. Put your egos aside and look at the SCIENCE!	*coverage guidance evidence review. We hope that future research provides effective treatments available to children experiencing these symptoms.* *Thank you for taking the time to share your and your loved ones' experiences and stories. Such real-life stories add needed context to the subcommittee's deliberations.*
F1	I am writing to express my deep distress that a Center for Neurodevelopmental Pediatrics in Oregon is refusing to treat children with PANS/PANDAS. I implore you to please work to remove barriers to care for our children. My son developed PANS at the age of 4. My well-adjusted, happy boy became a completely different child overnight, losing language and social awareness, developing extreme OCD and anorexia, and attempting suicide twice, among other terrifying symptoms. Getting appropriate treatment was a frightening, exhausting ordeal. A psychologist and colleague first identified his symptoms as consistent with PANS, and encouraged me to seek medical treatment. His initial diagnosis by our local doctor was 'autism with psychosis', which makes zero sense for a child who was neurotypical a week ago. After a night at OHSU which included a spinal tap, MRI and various other tests, no diagnosis was offered, except that I was an anxious mom who was causing his symptoms. At the third hospital we visited, Randall's, we finally met with reason. The doctor we saw said, "In the absence of another diagnosis I am willing to treat this as PANS." We went through all of that simply to get my son antibiotics, and we are so lucky that antibiotics and other over the counter treatments were all he needed to heal. Two days after his first dose his symptoms improved dramatically, and now at age eight years he is happy, healthy	*Thank you for taking the time to share your and your loved ones' experiences and stories. Such real-life stories add needed context to the subcommittee's deliberations.*

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	and doing well in all respects. He has had setbacks however, and I live with the fear that I will lose him again and be unable to afford or access the care he will need to regain his personality and lead a normal life. It is a cloud that haunts us always. For those families whose children need treatment now, my heart is utterly broken. An estimated 1:200 children are affected by PANS/PANDAS. Will your child, or grandchild, niece or nephew be one of them? I wish that upon no one, but I also wish you could walk in our shoes for just a day so you would know how critical it is for our children to be assured access to care. Mitigate the personal and societal costs of lifelong psychiatric treatment, special education, and unemployment. Make the sensible choice and do everything possible to remove barriers to care. Insist that our hospitals recognize PANS/PANDAS as the very real disorder it is, and demand that they provide the treatment our children need. Thank you.	
G1	I am an Oregonian, having lived here for over 40 years. I am also a retired Registered Nurse having been in practice for 40 + years. I understand the importance of evidence-based medicine. We must acknowledge science evolves. Learning should never stop and we should always seek to understand without doing harm. Just because the medical community in Oregon is behind the curve on the scientific evidence behind PANDAS/PANS and the efficacy of treatment, does not signify its non existence.	*Thank you for your comments. We agree that science evolves, and the subcommittee supports making coverage decisions based on the best currently-available evidence, and updating policy when new evidence becomes available. We have written specific responses to individual sections of your letter in the rows that follow.*
G2	The lack of true expertise in our state is evidenced by the 2 out of the 3 subjects experts chosen to advice this subcommittee on PANDAS/PANS. Medical ethics should require that an "expert" is well vetted when contributing to the decision making process specific to access of medically needed care. This is especially pertinent when those 2 subject experts have something to gain by being labeled an "expert" in a region that lacks treating providers.	*Thank you for your comment.* *For this topic, OHA selected two Oregon experts that were knowledgeable of local practice patterns and standards of care regarding PANDAS/PANS. One out-of-state expert was nominated by the PANS Consortium as a subject matter expert. The subcommittee places a preference on local expertise to*

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	This is not only misleading, but appears unethical to accept someone as a expert who lacks the true experience needed to contribute to such important conversations. The NW, specifically Oregon, is negligently behind the science when it comes to providing care to children and youth with post - infectious storms of encephalitis. One only has to look at the fact that 8 other states have mandated coverage for their children to understand the dire need parents face in lobbying for access to critically necessary care. I am the Grandmother to an Oregon child with PANS. The HERC's role is the review of clinical evidence in order to guide the OHA in making benefit-related decisions for its health plans. You have the evidence. Your local non-profit has brought in far superior PANDAS/PANS expertise then any "self-proclaimed expert" on your panel (other then Dr. Daines). Dr. Agaillu wrote wrote a very detailed rebuttal of the evidence presented during the first hearing while identifying the lack of evidence included and considered pertinent to this decision.	*shape care guidelines that will affect Oregon patients, payers and providers.* *We have responded to Dr. Agalliu's comments during this public comment period; see responses to B1-B8.*
G3	The HERC's role is NOT to impose additional barriers to care by requiring 2 subspecialists in order to access IVIG. You do RECOGNIZE THAT A LACK OF SUPPORTIVE AND ACCESSIBLE subspecialists exist in the disciplines you identified. There are NO Rheumatologists willing to treat this population. The Neuro developmental center at OHSU REFUSES TO TREAT THIS POPULATION. While access issues are not in your scope, do NOT IMPOSE IMPOSSIBLE HURDLES TO CARE for children who are suffering from brain inflammation and families who are suffering levels of trauma equal to that of caring for an Alzheimer's patient.	*Thank you for your comment.* *See response to A5 regarding provider willingness to treat patients with PANDAS/PANS symptoms.* *See response to A1 regarding the 2-subspecialist requirement.* *See response to C1 regarding provider eligibility for treatment consultation.*

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	Please listen to your community members affected by this disorder. You have the evidence that IVIG can result in symptom reduction or alleviation for moderate to severe children with PANDAS/PANS. PLEASE CHANGE THE GUIDANCE TO ONLY REQUIRE 1 PHYSICIAN SUBSPECIALIST and for this to include pediatric or adult subspecialists since access in many parts of Oregon struggle with the presence of any of the sub specialties. Also, in reference to those in rural areas and a lack of subspecialists, please allow for a physician to physician consult or file review to ensure a timely turnaround on a critical medical treatment Lastly, please consider the inclusion of a Naturopathic Physician in the list of subspecialists. The LEADING, TREATING MEDICAL PROVIDER IN OUR STATE, who head of Children Psychiatry at OHSU and the Medical Director at Unity Psych Hospital refer patients to a NATUROPATHIC PHYSICIAN in our state who has more expertise in treating these cases the 2 of the 3 "experts" on your committee.	
H1	I am writing you in hopes that you will limit the road blocks for children with PANDAS/PANS to receive IVIG. My son has seen plenty of specialty providers to include a neurologist and psychiatrist. Neither of these providers acknowledged my son's illness as being legitimate. My son was put on psychiatric medication which almost killed him as it caused serotonin syndrome. The only providers that have offered us any help is our Pediatrician who ordered IVIG when I had private insurance (it was denied coverage) and our ND. I currently pay out of pocket for Ozone infusions, supplements, and hyperberic *[sic]* chamber treatments. Requiring "specialists" or potentially harmful medications for a child causes a delay in life saving treatment and is an unnecessary roadblock. In our State there are no experts when it comes to PANDAS/PANS. I implore you to listen to us as parents	*Thank you for taking the time to share your and your loved ones' experiences and stories. Such real-life stories add needed context to the subcommittee's deliberations.* *Ozone infusions, hyperbaric oxygen therapy and supplements are outside the scope of this coverage guidance.* *See response to A1 regarding the 2-subspecialist requirement.*

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	when we say we our children deserve the right to treatment to save them, to solve the underlying problem, what they do not need is a band-aid to mask the symptoms or potentially make them worse. A pediatrician or ND is perfectly capable of making the decision on the health care needs of our children. I appreciate your time.	*See response to A5 regarding provider willingness to treat patients with PANDAS/PANS symptoms.* *See response to C1 regarding provider eligibility for treatment consultation.*
I1	I am writing with concerns about your guidelines for the treatment of PANS/PANDAS (referred to as PANS most of the time from this point). First, as a parent of a child with PANDAS, I have had a very hard time finding treatment options in Oregon. It is my understanding that you have made it a requirement for children who have not responded adequately to the first level treatments of PANS to have the acquiescence of two specialists from delineated specialties to access the more advanced immunotherapies. Two of these specialties have no specialists who are willing to even consider seeing a PANS patient (developmental pediatricians and rheumatologists). The other two have few specialists that are willing or competent enough to see PANS patients and as a result, they are hard to get into. It has taken us 2.5 years to assemble a team to treat our daughter--in the meantime, she has lost IQ points, dropped from above average to the 25th percentile in working memory, dropped from average to the 2nd percentile for processing speed, developed dyspraxia, a tremor, and various other movement abnormalities, and spent years stewing in anger, rage, OCD, and misery. My 7-year-old daughter is losing her childhood while we try to get her the treatment she needs. Steroids are not a permanent solution. Your guidelines are simply a barrier to treatment and will lead to suffering and permanent damage to the children and families dealing with this condition. In addition to affecting the children on OHP, it will trickle out to affect how private insurance treats PANS patients. We currently	*Thank you for taking the time to share your and your loved ones' experiences. Such real-life stories add needed context to the subcommittee's deliberations.* *See response to A1 regarding the 2-subspecialist requirement.* *See response to A5 regarding provider willingness to treat patients with PANDAS/PANS symptoms.* *See response to C1 regarding provider eligibility for treatment consultation.* *See response to G2 regarding the selection of appointed experts for this coverage guidance report.*

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	have the full endorsement for IVIG from 3 different specialists (neurologist, rheumatologist-we had to leave the state to find one, psychiatrist, and then also our PANS specialist) on your list and we still cannot gain pre-approval. There are implications beyond just what happens with OHP. Insurance companies will look at this as tacit approval to deny treatment to desperately sick children. I believe that you likely have made this a requirement because you have been misled by people who have labeled themselves "experts" when they have no qualifications to do so. These people flout the research done by those actually researching and treating PANS, to offer their own unfounded opinions about what PANS is, the way it is treated, and the state of PANS treatment in Oregon. You should be looking for actual renowned experts, not people who call themselves experts but do not treat PANS patients regularly and are out of step with the research and conduct none themselves. Talk to Dr. Latimer in DC or Dr. Kovacevic in Chicago. Talk to Dr. Swedo. I cannot stress this enough, your experts are...not experts. I speak from personal experience. I will be frank...our family is struggling. I mean, really, really struggling, due to the lack of understanding of these sorts of conditions. I cannot even begin to count how many times I have felt hopeless, despondent, and emotionally destroyed by this disorder and the lack of affordable treatment options. My daughter is the center of my universe and I'm losing her. I'm losing her due to the failures of our medical system to understand, study, and treat this condition. The future she has now is bleak without further treatment. Please do not leave children and their families in this position. Give them options. Include PANS practitioners on your list of specialists. Lower your requirements for treatment--1 specialist should be enough. This is such an awful illness made even worse by the barriers to care and the seeming indifference of those in power to the suffering of children. I would be	

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	happy to send you audio recordings of my daughter during some of her more mild flares. The more intense episodes require too much to have the time or thought to record her. I don't think you realize what this condition is like. If you did, I firmly believe that you would be moved to help these children. Please reconsider.	
J1	I am a former pediatric nurse of over 15 years and have worked at Randall Children's Hospital for that duration with some of the best doctors in the United States. I am well educated, and resourceful, however nothing could prepare me for my daughters diagnosis with PANDAS 3 years ago. I am adept at advocating for patients and know the lingo with physicians, and yet it was nearly impossible to find a physician who would look into possible treatment for my daughter. We have amazing insurance, but because of the rulings previously made about pans/pandas, only 5% of her treatments are actually covered by insurance. We have had to refinance our home 3 times just to cover the tens of thousands of dollars in medical bills we accrue each year for her illness. Why am I sharing this with you? Because this committee is ruling to have 2 subspecialists to approve for the treatment of IVIG. IVIG is LIFE CHANGING for pandas and is currently the gold standard nationwide. My question for you is, are two subspecialists required to sign off for IVIG in the case of Kawasaki's? (Another rare childhood illness that causes the body to attack itself). If not, than this added measure will create yet another impossible barrier for parents to jump over. I implore you- follow the research. Finding qualified providers who understand PANDAS and are willing to touch it is hard enough- don't make it even harder for parents who are already exhausted, poor and in desperate need.	*Thank you for taking the time to share your and your loved ones' experiences. Such real-life stories add needed context to the subcommittee's deliberations.* *See response to A1 regarding the 2-subspecialist requirement.*

HERC Coverage Guidance: Pediatric Autoimmune Neuropsychiatric Disorders Associated with Streptococcal Infections (PANDAS) and Pediatric Acute-Onset Neuropsychiatric Syndrome (PANS)
Disposition of Public Comments

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K1	I understand your committee is imposing requirements for children on Medicaid that would make accessing care near impossible. These cumbersome requirements are unnecessary. Oregon lacks true experience within the medical communities when it comes to diagnosing and treating PANDAS/PANS. This is why it was necessary for my Granddaughter to travel to Southern California to be evaluated and treated by a PANDAS/PANS expert. To impose restrictions that require TWO subspecialists to recommend treatment is impossible in this state. If the committee desires oversight, ADJUST THE SUBSPECIALIST RECOMMENDATION TO ONE REQUIRED INSTEAD OF TWO. These families are traumatized. They are barely getting by day by day. Many on Medicaid may lack the resources that other families navigate support and care for their severely psychiatric child. Requiring that a traumatized parent, who has probably struggled to find a treating provider has to obtain TWO additional recommendations for care, and timely treatment is VITAL when addressing a child with brain inflammation is not realistic. This type of requirement, imposed on those who are less resourced, is inequitable and the committee should take this into consideration. TO IMPOSE REQUIREMENTS WITHOUT RECOGNIZING THEIR ILL EFFECT IS NEGLIGENT. I ask that the committee change the requirement to ONE subspecialist and include naturopathic physician to those who can be consulted with. The subspecialist you list are unsupportive and not willing to treat this population.	*Thank you for taking the time to share your and your loved ones' experiences. Such real-life stories add needed context to the subcommittee's deliberations.* *See response to A1 regarding the 2-subspecialist requirement.* *See response to C1 regarding provider eligibility for treatment consultation.*
L1	As someone who works with patients with PANS/PANDAS, I have significant concerns that the requirements imposed by the committee will increase barriers to care.	*Thank you for your comment.* *See response to A1 regarding the 2-subspecialist requirement.*

HERC Coverage Guidance: Pediatric Autoimmune Neuropsychiatric Disorders Associated with Streptococcal Infections (PANDAS) and Pediatric Acute-Onset Neuropsychiatric Syndrome (PANS)
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	Requiring that 2 MD subspecialists recommend IVIG and/or plasma exchange means that virtually no families will qualify because Oregon has a critical shortage of PANS/PANDAS competent providers. These requirements would also exclude providers from other disciplines who do have PANS/PANDAS experience. I urge you to reconsider these requirements because they increase the substantial barriers to care that families suffering with PANS/PANDAS already face.	*See response to A5 regarding provider willingness to treat patients with PANDAS/PANS symptoms.*
M1	We have suffered for 6 years (diagnosis at age 6), to help my child live a live free from neuropsychiatric symptoms that have prevented her from going to school, sleeping, eating, and performing the activities of daily life - while trying to get help from specialists in the state of Oregon. There are NO medical sub-specialists in the state of Oregon who are experts in diagnosing and treating PANDAS/PANS - no rheumatologists, neurologists, psychiatrists, who work in tandem to support the "guardrails" that these HERC guidelines are imposing on us. We live in HELL with our child on a daily basis, trying whatever we can to help and support her while trying to find insurance coverage for IVIG. We have waiting LONG ENOUGH! We are unable to own a home; we live on a single income because my child has been unable to consistently attend school due to her illness (adding on the anxiety of living for 2+ years in a pandemic, being completely isolated from the world, due to worries that contracting COVID would exacerbate her autoimmune disorder); and trying to manage our own anxiety and PTSD of living with a child who could effectively be treated with IVIG, but being prevented from doing so by the impossible standards of insurance companies. Children with pediatric cancer or juvenile rheumatoid arthritis are NOT denied treatment (including IVIG), while our children are ignored.	*Thank you for taking the time to share your and your loved ones' experiences. Such real-life stories add needed context to the subcommittee's deliberations.* *See response to A1 regarding the 2-subspecialist requirement.* *See response to A5 regarding provider willingness to treat patients with PANDAS/PANS symptoms.*

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	Please consider changing these guidelines. The system is NOT being abused. There are not lines of children waiting outside clinics for IVIG. It should be for children like mine, who suffer daily FOR YEARS, and run the risk of permanent brain and bodily damage, due to the constant flaring of her untreated autoimmune disorder.	
N1	I understand your committee is imposing requirements for PANDAS/PANS children on Medicaid that would make accessing medical care near impossible. These cumbersome requirements are unnecessary. Oregon already lacks true expertise within the medical communities when it comes to diagnosing and treating PANDAS/PANS. This is why many of these families who have the financial resources to do so, travel outside of the state to be evaluated by a competent and supportive PANDAS/PANS expert. Your guidance report, as it stands now with the requirement to somehow find 2 specialists supportive enough to see PANDAS/PANS patients, is impossible in this state. Many of these families, depending on where they live in Oregon, cannot find one medical provider in their area knowledgeable enough or willing to see these cases. If the committee desires oversight, adjust the subspecialist recommendation to one required instead of two. Our family was traumatized by this disorder. Previously normal lives were turned upside down by the devastating onset of psychiatric symptoms in a previously healthy child. The grief and trauma sustained by these disorders should not be further burdened by state imposed restrictions that do nothing but create additional barriers to medical care. Many on Medicaid may lack the resources that other families have to navigate support and care for their severely psychiatric child. Requiring that a traumatized parent, who has already probably struggled to find a treating provider, have to	*Thank you for taking the time to share your and your loved ones' experiences. Such real-life stories add needed context to the subcommittee's deliberations.* *See response to A1 regarding the 2-subspecialist requirement.* *See response to A5 regarding provider willingness to treat patients with PANDAS/PANS symptoms.* *See response to C1 regarding provider eligibility for treatment consultation.*

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	obtain TWO additional recommendations for care when timely treatment is vital, is not realistic. This type of requirement, imposed on those who are less resourced, is inequitable and the committee should take that into consideration. To impose requirements without recognizing their ill effect is negligent. I ask that the committee change the requirement to ONE subspecialist requirement and include naturopathic physicians, nurse practitioners and physician assistants in those who can be consulted with. The subspecialists you list are unsupportive and not willing to treat this population.	
O1	I understand your committee is imposing requirements for PANDAS/PANS children on Medicaid that would make accessing medical care near impossible. These cumbersome requirements are unnecessary. Oregon already lacks true expertise within the medical communities when it comes to diagnosing and treating PANDAS/PANS. This is why many of these families who have the financial resources to do so, travel outside of the state to be evaluated by a competent and supportive PANDAS/PANS expert. Your guidance report, as it stands now with the requirement to somehow find 2 specialists supportive enough to see PANDAS/PANS patients, is impossible in this state. Many of these families, depending on where they live in Oregon, cannot find one medical provider in their area knowledgeable enough or willing to see these cases. If the committee desires oversight, adjust the subspecialist recommendation to one required instead of two. Our family was traumatized by this disorder. Previously normal lives were turned upside down by the devastating onset of psychiatric symptoms in a previously healthy child. The grief and trauma sustained by these disorders should not be	*Thank you for taking the time to share your and your loved ones' experiences. Such real-life stories add needed context to the subcommittee's deliberations.* *See response to A1 regarding the 2-subspecialist requirement.* *See response to A5 regarding provider willingness to treat patients with PANDAS/PANS symptoms.* *See response to C1 regarding provider eligibility for treatment consultation.*

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	further burdened by state imposed restrictions that do nothing but create additional barriers to medical care. Many on Medicaid may lack the resources that other families have to navigate support and care for their severely psychiatric child. Requiring that a traumatized parent, who has already probably struggled to find a treating provider, have to obtain TWO additional recommendations for care when timely treatment is vital, is not realistic. This type of requirement, imposed on those who are less resourced, is inequitable and the committee should take that into consideration. To impose requirements without recognizing their ill effect is negligent. I ask that the committee change the requirement to ONE subspecialist requirement and include naturopathic physicians, nurse practitioners and physician assistants in those who can be consulted with. The subspecialists you list are unsupportive and not willing to treat this population.	
P1	In regards to the current draft guidance on PANDAS/PANS, Oregon's only PANDAS/PANS non-profit, Northwest PANDAS/PANS Network, along with the PACE Foundation and a number of leading PANS/CPAE clinics and centers from around the country, including University of Arizona, Stanford, Harvard/Massachusetts General, Dartmouth and University of Arkansas strongly recommend the below revised verbiage for item 2b of the current HERC guidance. These clinics and centers are leaders in this management of these disorders and are the most well versed clinicians when it comes to best practices. Their recommendation to change the HERC's verbiage should be weighed heavily and given the strongest consideration for effective implementation and oversight of the treatments being considered.	*Thank you for your comment.* *The proposed amendment submitted to modify item 2b is neither feasible nor enforceable, as OHA does not have the authority to compel providers of any scope or specialty to respond to consultation requests.*

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	Proposed Draft 2b) A consultation with and recommendation by 1 pediatric subspecialist (for example, neurologist, psychiatrist, neurodevelopmental specialist, immunologist, infectious disease, rheumatologist). Consultation can be provider-to-provider in-person, or via an e-consultation (including a file review). If no response is received within 96 hours from consulting subspecialist, once information received, then item 2b of this HERC requirement is deemed to be waived. We hope that Oregon will benefit from the guidance that is being provided by these leading PANS/CPAE clinics and centers, especially given that our region lacks any such expertise. Their efforts, experience and dedication to treating this population should absolutely be recognized in the absence of any equivalent. Thank you for your consideration on this extremely important matter and recognizing the utter importance of modifying the language in line 2b.	
Q1	I am writing as the mother of two daughters diagnosed with post-infectious encephalopathies (NMDAR and PANS/PANDAS) in Washington. These disorders have the same type of acute onset, extremely similar symptoms…just different antibodies responsible for the suffering they inflict. IVIG and Super high dose steroids are bottom tier treatment options for NMDAR encaphalitis…and it is covered by insurance. Because of a complete lack of awareness, or perhaps willful and criminal ignorance of the latest research concerning PANS/PANDAS by NW Higher Education institutions, a total lack of providers who treat these horrifying disorders, and because suffering families already experience extreme duress & medical discrimination while trying to access healing and relief for their children… the HERC Committee's requirement of 2-sub-specialists to verify a child's need for IVIG or	*Thank you for taking the time to share your and your loved ones' experiences. Such real-life stories add needed context to the subcommittee's deliberations.* *See response to A1 regarding the 2-subspecialist requirement.* *See response to A5 regarding provider willingness to treat patients with PANDAS/PANS symptoms.*

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	plasmapheresis is simply adding to the caseloads of the VERY few doctors who do successfully treat it... and this requirement will continue to send families traveling outside the Pacific NW to access treatment for their children. And worst of all, families like mine will have to pay exhorbitant fees to heal their children. All providers who are genuinely knowledgable of PANS/PANDAS go through a tiered treatment process of NSAIDS, steroids, antibiotics and anti-virals, and many other immune suppressing medications before ever considering IVIG for their patients. Once all else has failed, only then does a knowledgable PANS/PANDAS physicians AND naturopaths prescribe the use of IVIG. Only about 10-20% of PANDAS patients require this treatment. 1 in 200 kids have PANDAS/PANS. There are roughly over 4,000 PANS/PANDAS patients (mostly undiagnosed) in Oregon…that means this committee could change the lives of approximately 400 Oregon children and their families. My NDMAR daughter was misdiagnosed for 4 years. Because doctors did not understand the signs and symptoms of her disease. Same is true for my PANS/PANDAS daughter who suffered misdiagnosis for 6 years: she was prescribed unnecessary and ineffective psychiatric medications, endured 4 inpatient psychiatric stays, 1 long term residential treatment stay out of state, unsuccessful wrap-around services...and a host of other horrifying problems that I cannot begin to describe in an email, before we traveled to Chicago to visit a PANDAS specialist who saw her dire need for proper medical intervention. He immediately ordered steroids and high dose IVIG for my daughter. After losing over 6 years of her childhood, she finally began healing with relief of symptoms. Today, she does not take a single psychiatric medication. We paid for her IVIG completely out of pocket.	

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	Her current state of health is saving my insurance company huge sums of money every year. She will graduate from high school this year and attend Portland State University. This is no less than a miracle for our family - we never imagined a future was possible for her and it wasn't possible...until IVIG. Do not make the mistake of causing more harm to families who desperately need help to heal their children by adding more obstacles to their children's paths to healing. What PANDAS/PANS families endure is unimaginable to clinicians and to the rest of the world. Please do the right thing: help our children who suffer the most with no relief, who have no hope of a future. How much is a life worth?	
R1	I'm writing about PANDAS/PANS treatment. I very much appreciate the work you have done to date and understand you want to provide medically necessary care to this population. Allowing patient to access IVIG as part of treatment for PANDAS/PANS is a huge step to ensure the best outcome for children who need that level of care. It also aligns more closely with the National Standard of Care for the treatment of PANDAS/PANS. Working at Northwest PANDAS/PANS Network the last 3+ years has allowed me to become very familiar with the treating landscape in Oregon. There are very few providers treating this population across all disciplines. Because of this, the requirement of 2 subspecialist to access IVIG will act as a roadblock. I urge you to revise the guidance to allow access with 1 subspecialist. Also, removing pediatric as to include adult subspecialists would be helpful for rural areas that may not have a pediatric subspecialist.	*Thank you for your comments in support of the recommendation for coverage.* *See response to A1 regarding the 2-subspecialist requirement. Additionally, adolescents may be adequately evaluated by an adult subspecialist who feels comfortable caring for their age group.* *See response to A5 regarding provider willingness to treat patients with PANDAS/PANS symptoms.*
S1	I am a retired health care attorney who's spent the last year singularly focused on helping my PANS/PANDAS-diagnosed child. I am writing to urge you NOT to require two specialists' opinions for Medicaid coverage of IVIG treatment. I further urge you not to impose any specialist requirement but allow coverage where generalists	*Thank you for taking the time to share your and your loved ones' experiences. Such real-life stories add needed context to the subcommittee's deliberations.*

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	prescribe this treatment. I will describe what my family has endured to demonstrate what barriers to care already exist and why your proposal creates additional, virtually impassible barriers. The amount of trauma this illness has inflicted upon my child and family cannot be overstated. Our daughter went from being a bright, empathic, highly functional, socially-engaged child—a gifted/talented student, award-winning artist, former symphony member, "the life of the party," etc., to a child who's so emotionally labile and psychologically distraught that she runs out of the house barefoot at night, intent on throwing herself into traffic. She's so adversely mentally affected at times that she has not recognized her own parents. She's been unable to even attend school for the past year. She barely ever leaves her dark bedroom and cannot tolerate lights, sounds, smells. She spends her days trapped in unending cycles of elaborate OCD rituals that are a hallmark of PANS. As parents feeling helpless to break our child free from this suffering—we've experienced nothing worse. Indeed, my whole family suffers immense, ongoing trauma living with the psychiatric chaos this disease has wrought. There has been no stability, no predictability, no security, living with this illness. Further, my child is aware of her suffering and of its impact on our family; she begs us almost daily to 'let her die.' We've been living through hell, and we've had no hope that our beloved child would ever return, or that any of us could live a normal life again. Not, that is, until about four months ago, when we found the Doctor of Naturopath who is now actually treating our daughter. With this doctor, we have finally felt hope, because, at last, an experienced, well-regarded clinician understands what's happening to our child, is confident in her ability to treat her, and is committed to seeing her through to recovery. Indeed, my daughter's severe psychiatric illness has been refractory to all standard treatments, save the protocols for PANS/PANDAS that	*See response to A1 regarding the 2-subspecialist requirement.* *See response to A5 regarding provider willingness to treat patients with PANDAS/PANS symptoms.* *See response to C1 regarding provider eligibility for treatment consultation.*

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	this doctor has been leading us through. We anticipate and discuss that my child likely will undergo IVIG therapy soon. Because Medicaid coverage decisions tend to influence private insurers' and medical practices' policies, your proposed restriction on IVIG therapy has the potential to directly impede my child's treatment and recovery and to seriously harm my family's finances, health, and welfare. 1. Pediatric mental health care is in extremely short supply in Oregon, which delays crucial PANS/PANDAS treatment. Advocates of the proposed rule assert it is easy to access specialists. However, that was not my experience. Like most families with a child with PANS/PANDAS, we began our search for care with our pediatrician and standard psychiatric care and therapy. This was prior to the pandemic, but, even then, psychiatric appointments were near impossible to obtain, with practices closed or having months-long wait lists. As it became clear that our child's needs exceeded the scope of typical outpatient services, we quickly learned of the inadequacy of mental health services for Oregon children. As our child's crisis grew more urgent, her doctors failed to respond appropriately; her treating psychologist even terminated her services, saying our child needed a higher level of care (of course, none was readily available). Despite our best efforts, we found practice after practice closed to new patients; program wait lists months-long or even closed. OHSU said it would take a year to get a Neurocognitive evaluation. We learned adolescent psychiatric beds are virtually nonexistent—only 20 beds for all of Oregon's adolescents. Our daughter spent one week essentially warehoused in an ER, waiting for inpatient psychiatric care that never materialized. She was kept in virtual solitary confinement and provided with no psychiatric care despite being in crisis. Referrals to specialty mental health care dissolved as program directors and intake	

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	coordinators advised our child was not within their purview. None of the mental health providers we saw recognized our child's severe PANS/PANDAS crisis; this went on for months. 2. Medical specialists in Oregon are not experienced with PANS/PANDAS treatment. Unfortunately, my husband (a university professor) and I have found that medical and psychological specialists in Oregon likewise are not experienced in recognizing, diagnosing, or treating PANS/PANDAS. Despite discussing our child's refractory-to-treatment OCD in clinic visits with pediatric specialists in Psychiatry, Neurology, Neurosurgery, Psychology, Neurocognitive Psychology, Pediatric Emergency Medicine, Otolaryngology, and Gastroenterology, none recognized her PANS/PANDAS crisis. None offered any diagnostic work-up, treatment, or referral for PANS/PANDAS. One specialist even canceled scheduled treatment due to our child's deteriorating mental status, despite that being a standard sign of PANS/PANDAS. Our exhaustive search for help belies that Oregon lacks a supply of specialists ready, willing, and able to treat PANS/PANDAS. Our Naturopath is the only provider we've found competent and available to treat our child's PANS/PANDAS. 3. Physicians in Oregon will decline to offer treatments that invite scrutiny. Eventually, relevant Oregon clinicians will adopt national PANS/PANDAS diagnostic and treatment protocols. Imposing extraordinary practice oversight, of the kind routine for medical education or licensing discipline, will disincentivize clinicians willing to fill this crucial role. Doctors already contend with insurers' medical necessity and pre-authorization burdens. There's no reason these customary safeguards cannot serve this committee's well-intentioned goals. The proposed rule of two specialists for IVIG treatment coverage adds unnecessary impediments	

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	to delivery of care. In violation of the physician's oath, this will directly harm critically ill children by preventing them from timely accessing healing therapies. Your committee reviewed that it is not in the business of creating a center for care. Neither should it be in the business of creating roadblocks to care.	
T1	I am writing to express concern about the proposed treatment limitations on coverage of PANDAS and PANS that: (1) Limit coverage to "Up to 3 monthly...courses of...(IVIG) therapy" (2) Require "fail first" protocols ("Two or more less-intensive therapies...have been tried and were not effective") (3) Require "A consultation with and recommendation by 2 pediatric subspecialists...." PANDAS and PANS are neuropsychiatric disorders that fall within the scope of the Paul Wellstone and Pete Domenici Mental Health Parity and Addiction Equity Act of 2008 (MHPAEA). The Oregon Department of Justice has affirmed, in a publicly released legal opinion[1], that MHPAEA applies to Coordinated Care Organizations. The Center for Medicare and Medicaid Services (CMS) has released a "Parity Compliance Toolkit" with detailed technical information and guidance to help states assess compliance with the final Medicaid/CHIP parity rule. As specified in the final parity rule, and the CMS toolkit, Medicaid programs must not impose either quantitative or non-quantitative treatment limitations (NQTLs) on mental health benefits that are not comparable to, or applied more stringently that, those used with respect to the medical / surgical benefits in the same classification. The limit on coverage of "Up to 3 monthly ... courses of ... (IVIG) therapy" is a quantitative limitation for the purposes of MHPAEA • CMS guidance on MHPAEA specifically identifies "fail first" protocols, such as requiring "Two or more less-intensive therapies," as NQTLs	*Thank you for your comment.* *The Commission recognizes the importance of complying with these and other laws, and develops coverage criteria that can be implemented in a compliant fashion.* *Our understanding is that PANDAS and PANS are not mental health conditions as defined by state and federal law because they do not appear under any of the diagnostic categories listed in the mental disorders section of the current edition of the International Classification of Disease, and do not appear in the Diagnostic and Statistical Manual of Mental Disorders.*

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	• CMS guidance also identifies preauthorization requirements, such as the requirement for "A consultation with and recommendation by 2 pediatric subspecialists," as NQTLs The proposed PANDAS / PANS benefits are classified as "outpatient" benefits under the final parity rule. This means that the Oregon Health Plan cannot impose these kinds of quantitative and non-quantitative treatment limitations on treatment for PANDAS / PANS unless it imposes comparable limits on substantially all medical / surgical outpatient benefits. A review of the prioritized list indicates that these proposed limitations for PANDAS / PANS are unique: • The predominant medical / surgical outpatient benefits on the list are NOT limited to "3 monthly courses ... of ... therapy" • The predominant medical / surgical outpatient benefits on the list do NOT have stringent fail-first requirements • The predominant medical / surgical outpatient benefits on the list do NOT require consultation and referrals from multiple specialists Therefore, the proposed limitations on PANDAS / PANS are unlawful. A CCO that attempted to implement those limitations could be subject to legal action under MHPAEA. I urge you instead to provide coverage of the proposed treatment for PANDAS / PANS without these onerous and unlawful limitations. Note also that the Early and Periodic Screening, Diagnostic and Treatment (EPSDT) requires states "to provide any additional health care services" (for children under age 21) "that are coverable under the Federal Medicaid program and found to be medically necessary to treat, correct or reduce illnesses and conditions discovered regardless of whether the service is covered in a state's Medicaid plan."	

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	Health services for PANDAS / PANS must be covered for children under age 21 as an EPSDT benefit.	
U1	The PACE Foundation, established in 2016, is dedicated to improving the diagnosis, treatment and quality of life for persons with Pediatric Autoimmune Neurological Disorders through advocacy, treatment and research. In the past few years, with the assistance from the NIMH, PACE has established or partnered with a number of leading medical institutions, to create a national standard of care for pediatric Postinfectious Autoimmune Encephalopathy disorders like PANS and PANDAS (see attached clinical map). PACE representatives have attended and presented both written and verbal testimony at each of the prior HERC hearings on PANS/PANDAS Following the in-depth discussion at the 9/9 HERC session, regarding item 2b of the current HERC PANS/PANDAS guidance, PACE would recommend that the committee change item 2b as follows: 1. Require a consultation and recommendation by only 1 pediatric sub-specialist 2. Supply a specific list of sub-specialists (for example, neurologist, neurodevelopmental specialist, immunologist, infectious disease, rheumatologist, etc.) 3. Provide a specified timeframe for sub-specialists to respond to a request for consultation before item 2b is waived PACE is aware that the Oregon organization named NWPPN, has drafted a substitute amendment for the current item 2b. PACE fully supports the NWPPN proposed amendment. Our organization strongly believes that if the HERC Committee does not adopt the changes to item 2b noted above, Oregon may become the most restrictive	*Thank you for your comments.* *See response to P1 regarding the proposed amendment to item 2b.* *See response to A1 regarding the 2-subspecialist requirement.* *Finally, it is outside of the scope of this coverage guidance review process to specify or include a pool of eligible providers who treat a specific condition in its report. We have listed examples of the types of providers that can provide consultations for PANDAS/PANS in our draft Coverage Guidance recommendation.*

HERC Coverage Guidance: Pediatric Autoimmune Neuropsychiatric Disorders Associated with Streptococcal Infections (PANDAS) and Pediatric Acute-Onset Neuropsychiatric Syndrome (PANS)
Disposition of Public Comments

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	PANS/PANDAS treatment state in the country. Conversely, if the HERC Committee does adopt the suggested changes to item 2b, it will mirror the requirement for the majority of states in the US.	

References Provided by Commenters

ID	References
A	Georgetown study (unpublished)
B	**Newly included in the Background section of the coverage guidance** • Orlovska S, Vestergaard CH, Bech BH, Nordentoft M, Vestergaard M, Benros ME. Association of streptococcal throat infection with mental disorders: testing key aspects of the PANDAS hypothesis in a nationwide study. *JAMA Psychiatry*. 2017;74(7):740-746. doi: 10.1001/jamapsychiatry.2017.0995. • Wang HC, Lau CI, Lin CC, Chang A, Kao CH. Group A streptococcal infections are associated with increased risk of pediatric neuropsychiatric disorders: a Taiwanese population-based cohort study. *J Clin Psychiatry*. 2016;77(7):e848-854. doi: 10.4088/JCP.14m09728. **Already included in the coverage guidance** • Cellucci T, Van Mater H, Graus F, et al. Clinical approach to the diagnosis of autoimmune encephalitis in the pediatric patient. *Neurol Neuroimmunol Neuroinflamm*. 2020;7(2) e663. doi: 10.1212/NXI.0000000000000663. • Cooperstock MS, Swedo SE, Pasternack MS, Murphy TK, Consortium PP. Clinical management of pediatric acute-onset neuropsychiatric syndrome: part III- treatment and prevention of infections. *J Child Adolesc Psychophamacol.* 2017; 27:594-606. • Frankovich J, Swedo S, Murphy T, et al. Clinical management of pediatric acute-onset neuropsychiatric syndrome: part II- use of immunomodulatory therapies. *J Child Adolesc Psychophamacol.* 2017; 27:574-593. • Swedo SE, Leonard HL, Garvey M, et al. Pediatric autoimmune neuropsychiatric disorders associated with streptococcal infections: clinical description of the first 50 cases. *Am J Psychiatry.* 1998;155(2):264-271. doi: 10.1176/ajp.155.2.264. • Thienemann M, Murphy T, Leckman J, et al. Clinical management of pediatric acute-onset neuropsychiatric syndrome: part 1- psychiatric and behavioral interventions. *J Child Adolesc Psychophamacol.* 2017;27:566-73. doi: 10.1089/cap.2016.0145. **Excluded from the coverage guidance** • Brimberg L, Benhar I, Mascaro-Blanco A, et al. Behavioral, pharmacological, and immunological abnormalities after streptococcal exposure: a novel rat model of Sydenham chorea and related neuropsychiatric disorders. *Neuropsychopharmacology.* 2012;37(9):2076-2087. • Chain JL, Alvarez K, Mascaro-Blanco A, et al. Autoantibody biomarkers for basal ganglia encephalitis in Sydenham chorea and pediatric autoimmune neuropsychiatric disorder associated with streptococcal infections. *Front Psychiatry.* 2020;11:564.

ID	References
	• Cox CJ, Sharma M, Leckman JF, et al. Brain human monoclonal autoantibody from Sydenham chorea targets dopaminergic neurons in transgenic mice and signals dopamine d2 receptor: implications in human disease. *J Immunol*. 2013;191(11):5524-5541. • Dale RC, Gorman MP, Lim M. Autoimmune encephalitis in children: clinical phenomenology, therapeutics, and emerging challenges. *Curr Opin Neurol*. 2017;30(3):334-344. • Dale RC, Merheb V, Pillai S, et al. Antibodies to surface dopamine-2 receptor in autoimmune movement and psychiatric disorders. *Brain*. 2012;135(pt 11):3453-3468. • Dileepan T, Smith ED, Knowland D, et al. Group A streptococcus intranasal infection promotes CNS infiltration by streptococcal-specific T cells. *J Clin Invest*. 2016;126(1):303-317. • Dubey D, Pittock SJ, Kelly CR, et al. Autoimmune encephalitis epidemiology and a comparison to infectious encephalitis. *Ann Neurol.* 2018;83(1):166-177. • Hoffman KL, Hornig M, Yaddanapudi K, Jabado O, Lipkin WI. A murine model for neuropsychiatric disorders associated with group A beta-hemolytic streptococcal infection. *J Neurosci*. 2004;24(7):1780-1791. • Hysmith ND, Kaplan EL, Cleary PP, Johnson DR, Penfound TA, Dale JB. Prospective longitudinal analysis of immune responses in pediatric subjects after pharyngeal acquisition of group A streptococci. *J Pediatric Infect Dis Soc.* 2017;6(2):187-196. • Kirvan CA, Swedo SE, Heuser JS, Cunningham MW. Mimicry and autoantibody- mediated neuronal cell signaling in Sydenham chorea. *Nat Med.* 2003;9(7):914-920. • Kirvan CA, Swedo SE, Snider LA, Cunningham MW. Antibody-mediated neuronal cell signaling in behavior and movement disorders. *J Neuroimmunol*. 2006;179(1-2):173-179. • Murgia F, Gagliano A, Tanca MG, et al. Metabolomic characterization of pediatric acute-onset neuropsychiatric syndrome (PANS). *Front Neurosci*. 2021;15:645267. doi: 10.3389/fnins.2021.645267. • Platt MP, Agalliu D, Cutforth T. Hello from the other side: how autoantibodies circumvent the blood-brain barrier in autoimmune encephalitis. *Front Immunol.* 2017;8:442. • Platt MP, Bolding KA, Wayne CR, et al. Th17 lymphocytes drive vascular and neuronal deficits in a mouse model of postinfectious autoimmune encephalitis. *Proc Natl Acad Sci U S A.* 2020;117(12):6708-6717. doi/10.1073/pnas.1911097117. • Pilli D, Zou A, Dawes R, et al. Pro-inflammatory dopamine-2 receptor-specific T cells in pediatric movement and psychiatric disorders. *Clin Transl Immunology*. 2020;9(12):e1229. doi: 10.1002/cti2.1229.

ID	References
	• Pollak TA, Lennox BR, Muller S, et al. Autoimmune psychosis: an international consensus on an approach to the diagnosis and management of psychosis of suspected autoimmune origin. *Lancet Psychiatry*. 2020;7(1):93-108. • Sinmaz N, Amatoury M, Merheb V, Ramanathan S, Dale RC, Brilot F. Autoantibodies in movement and psychiatric disorders: updated concepts in detection methods, pathogenicity, and CNS entry. *Ann N Y Acad Sci.* 2015;1351:22-38. • Xu J, Liu RJ, Fahey S, et al. Antibodies from children with PANDAS bind specifically to striatal cholinergic interneurons and alter their activity. *Am J Psychiatry.* 2020;178(1):48-64. doi: 10.1176/appi.ajp.2020.19070698. Yaddanapudi K, Hornig M., Serge R, et al. Passive transfer of streptococcus-induced antibodies reproduces behavioral disturbances in a mouse model of pediatric autoimmune neuropsychiatric disorders associated with streptococcal infection. *Mol Psychiatry.* 2010;15(7):712-726.
C–U	None provided

Pediatric Autoimmune Neuropsychiatric Disorders Associated with Streptococcal Infections (PANDAS) and Pediatric Acute-Onset Neuropsychiatric Syndrome (PANS)

Draft Coverage Guidance for HERC Consideration

May 19, 2022

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. Each slide will contain the accompanying page number(s) from the draft coverage guidance (CG)
- The full draft CG can be found elsewhere in the meeting materials.
- Citation of studies corresponds with the reference number assigned in the CG (e.g., Sigra et al., 2018 = CG ref #24)

Appointed Ad Hoc Experts

- **Alison Christy, MD, PhD**
  - Specialty: pediatric neuroimmunology, neuroimmunological disorders, pediatric neurology, and movement disorders
  - Conflicts to disclose: None
- **Michael Daines, MD**
  - Specialty: pediatric allergy and immunology, rheumatology
  - Conflicts to disclose: Lead investigator of Phase 3 clinical trial of IVIG for PANS; industry funding for design of clinical trial (Octapharma); travel reimbursements from PACE Foundation, a PANDAS/PANS advocacy group
- **Paria Zarrinnegar, MD**
  - Specialty: psychiatry, biopsychosocial assessment of children and adolescents
  - Conflicts to disclose: None

Scope Adjustments

- HERC approved a scope statement for the following interventions:
  - IVIG, plasma exchange, tonsillectomy, adenoidectomy, corticosteroids, SSRIs, short-course antibiotics, prophylactic antibiotic therapy, behavioral therapies, NSAIDs
- However, EbGS excluded interventions not subject to utilization controls, such as corticosteroids, NSAIDs, SSRIs, behavioral therapies, prophylactic antibiotics
- Pediatric autoimmune encephalitis was removed as a Condition from the scope due to different diagnostic criteria and higher acuity of the condition

Background

- Sudden onset of changes or regressions in behaviors in multiple domains, typically including symptoms of OCD and verbal or motor tics
- Symptom severity can range from mild to severe and can significantly interfere with daily activities (e.g., school)
- PANDAS and PANS are diagnoses of exclusion and include ruling out:
  - Primary psychiatric diagnoses, such as OCD
  - Sydenham chorea, pediatric autoimmune encephalitis, neuropsychiatric lupus, central nervous system vasculitis
  - Other conditions that better account for the symptoms

Background

- Prevalence of PANDAS and PANS is unknown
- Natural histories of PANDAS and PANS still being studied
  - Emerging research suggests that 60% to 80% of pediatric patients have significant reduction in symptoms over time
  - American Academy of Child and Adolescent Psychiatry practice parameter suggests small subset of children diagnosed with OCD or Tourette disorder may experience exacerbations related to streptococcal infection

Scope Statement

Populations	• Children diagnosed with PANDAS or PANS
Interventions	• Therapeutic plasma exchange; IVIG; antibiotics; tonsillectomy and/or adenoidectomy
Comparators	• Usual care or other interventions

Scope Statement

Critical Outcomes

- Change in psychiatric symptom scores
- Hospitalizations, including institutionalization or emergency visits

Important Outcomes

- Harms
- Standardized measures of function or quality of life for patients and caregivers

Scope Statement

Key Questions

1. Effectiveness of treatments
2. Comparative effectiveness for populations based on:
    a. Patient characteristics
    b. Condition characteristics
    c. Intervention
    d. Provider characteristics (e.g., Center of Excellence)
3. Harms of treatments

Evidence Review

Oregon Health Authority

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Evidence Sources

- Most recent systematic review: Sigra et al., 2018 (CG ref #24)
- 5 RCTs (CG refs #25, 26, 30-32)
- 2 comparative cohort studies (CG ref #28-29)

Populations	Interventions
• PANDAS • PANS • CANS • PITAND • Abrupt-onset OCD	• Antibiotics • Tonsillectomy • Therapeutic plasma exchange • IVIG • Tonsillectomy • Adenoidectomy • Adenotonsillectomies

Evidence Section Overview

- Overall, small sample sizes and short follow-ups in comparative studies
- Reported outcomes
  - No evidence identified for hospitalizations and function or quality of life for patient or caregivers
  - Very little data on comparative effectiveness by subpopulations
  - Change in psychiatric symptoms and harms summarized by intervention type on following slides

GRADE Table: Prophylactic Antibiotics

Outcomes	Estimate of Effect for Outcome *Confidence in Estimate*
Change in psychiatric symptom scores *(Critical outcome)*	Mixed results for antibiotics (i.e., penicillin, azithromycin) administered for 4 weeks to 1 year, compared to placebo or other antibiotic. ●○○○ *(very low confidence, based on 3 RCTs, n = 91)*
Hospitalizations *(Critical outcome)*	No evidence identified.
Harms *(Important outcome)*	The few harms that were reported included heart rate irregularity (9/12) for children who received azithromycin, and loose stool (no statistics reported). ●○○○ *(very low confidence, based on 1 RCTs, n = 23)*
Function or quality of life for patient *(Important outcome)*	No evidence identified.
Function or quality of life for patient *(Important outcome)*	No evidence identified.

GRADE Table: Tonsillectomy and Adenoidectomy

Outcomes	Estimate of Effect for Outcome *Confidence in Estimate*
Change in psychiatric symptom scores *(Critical outcome)*	No difference in neuropsychiatric symptoms between surgery and non-surgery groups among children diagnosed with PANDAS. ●●○○ *(low confidence, based on 2 comparative cohort studies, n = 232)*
Hospitalizations *(Critical outcome)*	No evidence identified.
Harms *(Important outcome)*	No evidence identified.
Function or quality of life for patient *(Important outcome)*	No evidence identified.
Function or quality of life for patient *(Important outcome)*	No evidence identified.

GRADE Table: IVIG

Outcomes	Estimate of Effect for Outcome/ *Confidence in Estimate*
Change in psychiatric symptom scores *(Critical outcome)*	Compared to saline placebo, some children had decreased symptoms. Compared to plasma exchange, no significant difference. ●○○○ *(very low confidence, based on 2 RCTs, n = 54)*
Hospitalizations *(Critical outcome)*	No evidence identified.
Harms *(Important outcome)*	1/33 had an allergic reaction to the IVIG infusion that resolved without complication. 31/33 children reported mild or moderate adverse events (e.g., nausea, vomiting, headache, fever, joint pain). ●○○○ *(very low confidence, based on 2 RCTs, n = 64)*
Function or quality of life for patient *(Important outcome)*	No evidence identified.
Function or quality of life for patient *(Important outcome)*	No evidence identified.

GRADE Table: Plasma Exchange

Outcomes	Estimate of Effect for Outcome *Confidence in Estimate*
Change in psychiatric symptom scores *(Critical outcome)*	Compared to saline placebo, improvements on most measures. Compared to IVIG, no significant difference. ●○○○ *(very low confidence, based on 1 RCT, n = 29)*
Hospitalizations *(Critical outcome)*	No evidence found.
Harms *(Important outcome)*	All children who received plasma exchange (10/10) experienced mild side effects such as nausea, vomiting, anxiety, or fever. ●○○○ *(very low confidence, based on 1 RCT, n = 29)*
Function or quality of life for patient *(Important outcome)*	No evidence found.
Function or quality of life for patient *(Important outcome)*	No evidence found.

Ongoing Studies

- Double-blind RCT (N = 44) to test naproxen sodium for 8 weeks in children with PANDAS
  - Estimated completion: October 2022
- Quadruple-blind RCT (N = 92) to test IVIG in children with PANDAS or PANS
  - Estimated completion: March 2023
- Observational matched cohort study (N = 500) to examine immunologic, neurologic, genomic, and behavioral differences between children with PANS and healthy children for up to 15 years
  - Estimated completion: March 2028

Evidence Summary

- The natural histories of PANDAS and PANS are still being studied
- The very low and low confidence we have in the findings means that findings from new comparative studies that test treatments for PANDAS or PANS could easily change the evidence underpinning decisions about which treatments should be covered for children with PANDAS or PANS

Clinical Practice Guidelines

Oregon Health Authority

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PANS/PANDAS Clinical Research Consortium

- Proposed a 3-pronged approach to treatment (CG ref #3, 19, 20, 22):
  - Treat psychiatric symptoms with psychoactive medications and psychotherapy;
  - Remove source of inflammation with antimicrobial interventions; and
  - Treat immune system disturbances with immunomodulatory and/or anti-inflammatory therapies
- Not all involved experts agreed on treatments proposed in publication (CG ref #3)

Nordic Countries Guideline

- Treatment should be overseen at specialized centers
- Verified or strongly suspected infections should be treated with antibiotics for no longer than 14 days
  - Do not recommend prophylactic antibiotic therapy
- Severe symptoms may be treated first with NSAIDs, then possibly escalate to IVIG
- Authors state plasma exchange and immunomodulatory drugs are only clinically indicated for children diagnosed with autoimmune encephalitis (CG ref #21)

Policy Landscape

Oregon Health Authority

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Payer Policies

- No policies identified for Washington State Medicaid, Medicare, Moda, or BlueCross BlueShield

Aetna

- The following are considered investigational or experimental for PANDAS:
  - Parenteral immunoglobulins
  - Plasma exchange
  - Rituximab

Cigna

- The following are considered investigational or experimental for PANDAS and PANS:
  - IVIG
  - Plasma exchange
  - Rituximab

Other Recommendations

- PANDAS Physician Network (CG ref #56)
  - Recommends that children with moderate to severe symptoms be treated by experienced multidisciplinary team or PANDAS/PANS specialist
  - Summary of proposed treatment sequence (see website for details):
    1. Start with 14 days of antibiotic therapy, lengthen therapy if infection is not resolved or symptoms persist. Consider prophylactic antibiotic therapy
    2. Consider 5 to 7 day course of NSAIDs
    3. Ensure access to CBT and parenting management techniques
    4. Consider steroid course
    5. Escalate to IVIG
    6. Administer second course of IVIG or plasma exchange plus prophylactic antibiotics

Discussion

Discussion: General

Resource Allocation

Some of the proposed treatments (antibiotics, NSAIDs, SSRIs) are inexpensive and widely available. Other proposed treatments are more expensive and may have limited access (IVIG, therapeutic plasmapheresis, behavioral therapy).

Untreated PANDAS/PANS has high costs with frequent medical visits, hospitalizations, school disruption, parental inability to work, and other factors.

Values and Preferences

Some parents would value any treatment that might help their child's symptoms.

Other parents would have concerns about the risks and side effects of the therapies being considered, and/or the unproven efficacy of the intervention.

Discussion: Prophylactic Antibiotic Therapy

Other Considerations

Long-term or frequent antibiotic use is associated with a range of negative consequences, including but not limited to C. difficile infection, diarrhea, and increased antibiotic resistance leading to reduced ability to treat other infections with antibiotics. Most health plans cover short-term antibiotics without prior authorization criteria but may scrutinize or not cover long-term prescriptions.

Balance of Benefits and Harms

We have very low confidence that prophylactic antibiotic use is helpful in PANDAS/PANS, given the small sample sizes in the included studies. There are concerning known harms of frequent or long-term antibiotic use.

Rationale

Prophylactic antibiotic therapy is not recommended for coverage for PANDAS/PANS because of insufficient comparative evidence that prophylactic antibiotic use leads to any measurable benefit for these conditions. The known risks of prophylactic or long-term antibiotic use outweigh potential benefits in these conditions.

Discussion: Tonsillectomy and Adenoidectomy

Other Considerations

Tonsillectomy and/or adenoidectomy have known harms such as bleeding, anesthesia reactions, and death. Tonsillectomy and/or adenoidectomy frequently have coverage limitations, such as multiple streptococcal infections in one year. Historically, this procedure has been overused.

Balance of Benefits and Harms

We have low confidence that that there is no benefit from tonsillectomy and/or adenoidectomy for PANDAS, and this procedure has known harms. This treatment has not been proposed for PANS.

Rationale

Tonsillectomy and/or adenoidectomy are not recommended for coverage for treatment of PANDAS/PANS because these procedures have known harms and because evidence shows that these procedures do not improve the outcomes in this condition.

Discussion: IVIG

Other Considerations

IVIG is a blood product with the inherent risks that accompany accepting any form of blood product. IVIG has a significant rate of mild side effects including fever, body aches, nausea, rash, and fatigue. Severe side effects include thrombosis, renal dysfunction, and acute renal failure, and life-threatening allergic reaction. IVIG can interfere with vaccine effectiveness for vaccines given within several months of IVIG. Several products on the market are FDA-approved for people under the age of 19.

Balance of Benefits and Harms

There were mixed results from 2 very small trials regarding the clinical effectiveness of IVIG. Outside of PANDAS, no evidence met inclusion criteria for PANS. IVIG has a significant rate of known harms.

Rationale

Expert opinion and lower-quality observational data indicate there may be benefit for some patients with these conditions, but recommended treatment protocols and criteria for treatment vary widely. Due to the severe impact of symptoms associated with PANDAS/PANS on child health, growth and development, and the lack of known effective treatments, coverage of IVIG is recommended when recommended by the patient's PCP and a pediatric subspecialist and after less-intensive therapies were not effective, were not tolerated or did not result in sustained improvement in symptoms.

Discussion: Plasma Exchange

Other Considerations

High rates of patients undergoing plasma exchange report side effects, including fever, chills, and muscle cramps. Known complications of plasma exchange include circuit clotting, low or high blood pressure, nausea, vomiting, itchy skin, hives, low calcium levels in the blood, venous access malfunction, infections, thrombosis, and anaphylactic shock.

Balance of Benefits and Harms

The comparative evidence that plasma exchange is effective at treating PANDAS is very limited and shows no clear benefit. The harms of this treatment are generally mild but serious complications can occur.

Rationale

Expert opinion and lower-quality observational data indicate there may be benefit for some patients with these conditions, but recommended treatment protocols and criteria for treatment vary widely. Due to the severe impact of symptoms associated with PANDAS/PANS on child health, growth and development, and the lack of known effective treatments, coverage of plasma exchange is recommended when recommended by the patient's PCP and a pediatric subspecialist and after less-intensive therapies were not effective, were not tolerated or did not result in sustained improvement in symptoms.

Recommendation

Tonsillectomy, adenoidectomy, adenotonsillectomy, and prophylactic antibiotic therapy are not recommended for coverage to treat pediatric autoimmune neuropsychiatric disorders associated with streptococcal infections (PANDAS) and pediatric acute-onset neuropsychiatric syndrome (PANS) (*weak recommendation*).

Up to 3 monthly immunomodulatory courses of intravenous immunoglobulin (IVIG) therapy or therapeutic plasma exchange are recommended for coverage to treat PANDAS and PANS (*weak recommendation*) when both of the following are met:

A) A clinically appropriate trial of two or more less-intensive treatments (for example, appropriate limited course of nonsteroidal anti-inflammatory drugs (NSAIDs), corticosteroids, selective serotonin reuptake inhibitors (SSRIs), behavioral therapy, short-course antibiotic therapy) was either not effective, not tolerated, or did not result in sustained improvement in symptoms (as measured by a lack of clinically meaningful improvement on a validated instrument directed at the patient's primary symptom complex). These trials may be done concurrently, AND

B) A consultation with and recommendation from a pediatric subspecialist (for example, pediatric neurologist, pediatric psychiatrist, neurodevelopmental pediatrician, pediatric rheumatologist, pediatric allergist/immunologist, pediatric infectious disease specialist) as well as the recommendation of the patient's primary care provider (for example, family physician, pediatrician, pediatric nurse practitioner, naturopath). The subspecialist consultation may be a teleconsultation. For adolescents, an adult subspecialist consult may replace a pediatric subspecialist consult.

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

Supplemental Materials

Oregon Health Authority

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Abbreviations

- **Conditions**
  - CANS: childhood acute neuropsychiatric syndromes
  - OCD: obsessive-compulsive disorder
  - PANDAS: pediatric autoimmune neuropsychiatric disorders associated with streptococcal infections
  - PANS: pediatric acute-onset neuropsychiatric syndrome
  - PITAND: pediatric infection-triggered autoimmune neuropsychiatric disorders
- **Treatment**
  - IVIG: intravenous immunoglobulin
- **Other abbreviations**
  - RCT: randomized controlled trial