Health Evidence Review Commission's Value-based Benefits Subcommittee

November 17, 2022

8:00 AM - 1:00 PM

Online Meeting

Join online meeting here

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Section 1.0

Call to Order

AGENDA
VALUE-BASED BENEFITS SUBCOMMITTEE
11/17/2022
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. Previous Discussion Items **8:05 AM**

A. Corneal collagen cross linkage for keratoconus (*Treatment for condition of the outer layer of the eye (cornea))*

III. Straightforward/Consent agenda **8:30 AM**

A. Consent table *(Routine changes that may be approved without discussion)*
B. Straightforward guideline note changes
C. COVID codes
D. 24-hour sleep wake disorder
E. Additional diagnosis codes for handicapping malocclusion *(Braces for severely misaligned teeth that affect speech or eating)*

IV. Items discussed with leadership with no changes recommended **8:40 AM**

A. Kyphoplasty *(A procedure in the bones of the spine to treat painful fractures)*
B. Neurofeedback/Biofeedback *(Techniques that help you learn to control bodily functions such as heart rate or breathing)*
C. Pneumatic compression devices for lymphedema *(A pump with varying pressure which fills an inflatable garment with compressed air used to treat swelling of the arms or legs (lymphedema))*

V. Staff report **9:00 AM**

A. Errata
B. New "what we are working on" webpage
C. Below the line review update
D. EPSDT update

VI. Advisory panel reports **9:15 AM**

A. OHAP
A. 2023 CDT code review *(New dental services)*
B. Dental implant removal *(Removal of the metal post that replaces the root portion of a missing tooth)*

C. Labial frenectomy *(A lip-tie procedure for infants who have breastfeeding problems)*

B. BHAP

A. Behavioral health related CPT codes *(New behavioral health code placements)*
   1. Multiple-family group behavior management/modification training for parent(s)/guardian(s)/caregiver(s) of patients with a mental or physical health diagnosis *(Parent/care giver training)*
   2. Remote therapeutic monitoring of a device for cognitive behavioral therapy *(Digital health products review)*
   3. BHAP related HCPCS code placement

B. Perpetrator services *(Treatment for someone who has harmed another person, or who might do harm)*

C. Intentional self harm *(Diagnosis codes that describe ways people harm themselves)*

C. GAP

A. NCCN version updates in guidelines

B. 2023 genetics related CPT codes *(Placement of new genetic codes on the List)*
   1. GAP genetic code issues
   2. TPMT gene and enzyme testing *(A genetic test that helps predict whether a patient will have a bad reaction to a certain class of drugs)*
   3. Gene panels of tumor tissue *(New code placements for tests that look at mutations in certain cancers)*

C. Decipher Prostate *(A test for prostate cancer patients who are considering radiation therapy)*

BREAK **10:00 AM**

VII. 2023 CPT and HCPCS Code review **10:10 AM**

1) Straightforward codes *(Routine changes that may be approved without much discussion)*

2) Codes requiring review
   a. Absorbable mesh/prosthesis for delayed wound closure *(Mesh implant for wound care)*
   b. Second level lumbar artificial disc replacement *(A treatment for low back pain caused by damaged discs in two or more locations)*
   c. Radiofrequency repair of nasal valve collapse *(Non-surgical treatment in the nose to help breathing problems)*
   d. Gastric balloons *(A durable balloon placed in the stomach to help you lose weight)*
   e. Hepatitis B surface antigen quantitative test

f. Respiratory syncytial virus vaccine
g. Orthoptic training
h. Quantitative pupillometry

3) 2023 HCPCS code review
   a. Immunization counseling
   b. Home COVID tests
   c. Doula services

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

A. Hydrocele repair in adults *(Consideration for coverage for adults for swelling or fluid collection in the scrotum)*

IX. New discussion items **11:15 AM**

A. Human growth hormone guideline *(Use of growth hormone for adults)*
B. Eosinophilic esophagitis *(A chronic inflammatory disorder that can make swallowing difficult and painful)*
C. Botulinum toxin for strabismus
D. 2022 Acupuncture review *(A procedure that inserts thin needles into the skin)*
E. IUD for treatment of endometrial cancer *(An alternative treatment for cancer of the lining of the uterus)*
F. Cochlear implant guideline review *(A device that provides a sense of sound for people who are deaf or severely hard of hearing)*
G. Obstructive sleep apnea/sleep study related topics
   A. CPAP titration *(An overnight sleep study used to properly set continuous positive airway pressure (CPAP) therapy)*
   B. Definition of apneic events on sleep studies *(Episodes of lack of oxygen during sleep)*
H. PET rescan 2022 *(An imaging test used to look at cancer)*

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

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

Value-based Benefits Subcommittee Recommendations Summary
For Presentation to:
Health Evidence Review Commission on October 6, 2022

For specific coding recommendations and guideline wording, please see the text of the 10/6/2022 VbBS minutes.

RECOMMENDED CODE MOVEMENT (changes to the 1/1/2023 Prioritized List unless otherwise noted)

- Add residential therapy treatment codes to the funded generalized anxiety line
- Delete several behavioral health-related diagnoses codes that appear on funded lines from an unfunded line
- Add the diagnosis code for an ear anomaly that impairs hearing (small ear) to a funded line
- Delete several diagnosis codes related to deformities of hands and feet that appear on funded lines from an unfunded line
- Make several other various straightforward coding changes

ITEMS CONSIDERED BUT NO RECOMMENDATIONS FOR CHANGES MADE

- No changes were made to the diagnosis codes on an unfunded line for deformities of the knee

RECOMMENDED GUIDELINE CHANGES (changes to the 1/1/2023 Prioritized List unless otherwise noted)

- Change the acupuncture guideline to specify that a substance use disorder treatment plan does not have to part of a formal treatment program
- Clarify the requirements for inflammatory skin disease medications.
- Adopt a new guideline showing when to cover microtia (small ear) treatment
- Adopt a new statement of intent regarding public health emergencies
- Make several other straightforward guideline note changes

VALUE-BASED BENEFITS SUBCOMMITTEE
Online meeting
October 6, 2022
9:00 AM – 1:00 PM

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

Members Absent: Kevin Olson, MD; Brian Duty, MD.

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

Also Attending: Shauna Durbin & Val King (OHSU); Ambyr Leigh; Dana Hargunani, MD (OHA); Ellie Solares-Solis; Emily Rigler-Wright; Jamie Schlarbaum, MD; Jana Peterson-Besse (OHSU); Jennifer Olson; Julie Dhossche, MD (OHSU); Justin Hageman; Kristen Darmody (OHA); Lavinia Goto; Lisa Ashton; Lorren Sandt (Caring Ambassadors Program); MacKenzie; Meghan Moyer (Disability Rights Oregon); Mina Colon (OHA); Nick Budnick (Lund Report); Paul Terdal; Rafat Fields; Renee Taylor; Sara van Geertruyden; Tholanda Newborne; The Honorable Tony Coelho; Tracy Carver (Comagine Health); Tracy Funk, MD; Yvonne Hubbard.

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

The meeting was called to order at 9:00 am and roll was called. A quorum of members was present at the meeting. Minutes from the August 11, 2022 VbBS meeting were reviewed and approved (Irwin abstained due to not attending August meeting).

Gingerich announced the new CMS-approved waiver for the Oregon Health Plan (OHP). The new waiver includes several changes that affect how HERC's work will be implemented. The state's EPSDT waiver will expire on January 1, 2023. A new webpage (https://www.oregon.gov/oha/HSD/OHP/Pages/EPSDT.aspx) contains implementation information about the expiration. Additional waiver authority related to the Prioritized List will expire January 1, 2027.

Dana Hargunani, Chief Medical Officer of OHA, presented on changes to Oregon's 1115 waiver for the Medicaid program. She said that the Prioritized List remains in effect to define the benefit package for the Oregon Health Plan. In addition, Oregon will be the first state approved to use federal Medicaid funds to pay for items such as housing, food and nutritional support, and items like air conditioners. The waiver also expands coverage for children. All children under 6 years of age will have continuous coverage under OHP, and the spacing of review for client eligibility will be expanded to two years. She acknowledged and thanked the volunteer members for all their service and said that Oregon will continue to rely on the HERC to guide its decisions on efficacy and medical necessity criteria through its transparent public process. After nearly 30 years, Oregon's transparent public process to determine benefits is no longer experimental and will be moved out of the 1115 demonstration waiver and into the Medicaid State Plan. To ensure an appropriate transition to a State Plan Amendment by 2027, the state will complete a detailed regulatory and operational review with the potential for needed changes in law, rules and processes. In line with OHA's goal of eliminating health inequities in Oregon, she said staff will continue efforts to ensure the HERC processes are broadly accessible to the public, and work products

reflect available evidence as well as extensive input from patients, community organizations, caregivers, providers, health plans and others interested in benefit policy in Oregon.

Gingerich announced an upcoming HERC vacancy as Holly Jo Hodges is terming off at the end of the year. This position will be open for applications soon and all interested persons were invited to apply.

At its March 2021 meeting, HERC requested that staff conduct a claims utilization query for CPT 87913 (genotype analysis to identify COVID variants) after 6 months; there have been no claims to date.

Gingerich also announced that public comment that is submitted will be posted on HERC's public webpage going forward.

Gingerich stated that the new WPATH Standards of Care 8 guidelines are published for gender dysphoria care and staff are reviewing this guideline for discussion at a future meeting.

- **Topic: Straightforward/Consent Agenda**

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

  Recommended Actions:

  1) Add Z69.021, Z69.12 and Z69.82 (Encounter for mental health services for perpetrator of non-parental child/spousal or partner/other abuse) to line 120 ABUSE AND NEGLECT
  2) Add CPT 15771 and 15772 (Grafting of autologous fat harvested by liposuction technique to trunk, breasts, scalp, arms, and/or legs) to line 312 GENDER DYSPHORIA/TRANSEXUALISM
  3) Modify GN 127 as shown in Appendix A
  4) Modify GN 154 as shown in Appendix A
  5) Modify GN 24 as shown in Appendix A
  6) Add ICD-10-CM T81.9XXA (Unspecified complication of procedure, initial encounter) to line 573 REDUNDANT PREPUCE
  7) Modify GN73 as shown in Appendix A
  8) Add the following CPT codes to line 3 PREVENTION SERVICES WITH EVIDENCE OF EFFECTIVENESS
     a. 91313 Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) (coronavirus disease [COVID-19]) vaccine, mRNA-LNP, spike protein, bivalent, preservative free, 50 mcg/0.5 mL dosage, for intramuscular use
     b. 0134A administration of the vaccine represented by 91313
     c. 91314 Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) (coronavirus disease [COVID-19]) vaccine, mRNA-LNP, spike protein, bivalent, preservative free, 25 mcg/0.25 mL dosage, for intramuscular use
     d. 0144A administration of the vaccine represented by 91314
     e. 91312 Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) (coronavirus disease [COVID-19]) vaccine, mRNA-LNP, bivalent spike protein, preservative free, 30 mcg/0.3 mL dosage, tris-sucrose formulation, for intramuscular use
     f. 0124A administration of the vaccine represented by 91312
     g. 91315 Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) (coronavirus disease [COVID-19]) vaccine, mRNA-LNP, bivalent spike protein, preservative free, 10

mcg/0.2 mL dosage, diluent reconstituted, tris-sucrose formulation, for intramuscular use

h. 0154A administration of the vaccine represented by 91315

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

- **Topic: Behavioral Health Advisory Panel report**

Discussion: There was no substantive discussion about residential treatment for anxiety or the somatization and related disorders topics.

For the guideline revision related to acupuncture for substance use disorder, Pinzon asked who was responsible for documenting the treatment program, and whether this type of documentation would further limit access to these programs. Hodges noted that acupuncture would be part of an individual treatment plan. Documentation could be provided by the PCP, an SUD treatment provider, a therapist, etc.

Recommended Actions:

1) Add HCPCS H0017 (Behavioral health; residential (hospital residential treatment program), without room and board, per diem) and H0018 (Behavioral health; short-term residential (non-hospital residential treatment program), without room and board, per diem) to line 414 OVERANXIOUS DISORDER; GENERALIZED ANXIETY DISORDER; ANXIETY DISORDER, UNSPECIFIED
2) Modify GN92 as shown in Appendix A
3) Remove the following ICD-10-CM diagnoses from line 552 SOMATIC SYMPTOMS AND RELATED DISORDERS as they already appear on other funded lines
    i. F44.0 Dissociative amnesia
    ii. F44.1 Dissociative fugue
    iii. F44.2 Dissociative stupor
    iv. F44.81 Dissociative identity disorder
    v. F44.89 Other dissociative and conversion disorders
    vi. F45.22 Body dysmorphic disorder
    vii. F45.42 Pain disorder with related psychological factors
4) Remove ICD-10-CM F52.5 (Unspecified sexual dysfunction not due to a substance or known physiological condition) from line 552 SOMATIC SYMPTOMS AND RELATED DISORDERS and add to line 523 SEXUAL DYSFUNCTION

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

- **Topic: Quality-adjusted life year (QALY) review**

Discussion: Cantor reviewed the summary document.

Public testimony:

1) **Lorren Sandt, Executive Director, Caring Ambassadors**: Sandt testified against the use of QALYs by HERC, stating they are illegal and are not aligned with the agency's health equity goals. She said Options 2 and 3 hide transparency. She said Option 4 would be ideal but is concerned that would leave a lack of evidence to consider and lead to noncoverage of services. She advocated

for considering Option 1 with some merits and some concerns. However, she advocated for a novel measure that HERC would use to evaluate services. She requested that more than 5 minutes be considered for public testimony, especially for sensitive topics. She said QALYs are discriminatory because most evidence is based on clinical trials, which has inclusion criteria that excludes certain groups of people. The results of these trials feed into QALY calculations.

2) **Meghan Moyer, Public Policy Director, Basic Rights Oregon**: Moyer stated that Oregon has used QALYs prior to 2017 and relied on QALYs to create the Prioritized List. She noted that most of the condition-treatment pairs have not been reprioritized since then. She said QALY calculations reduce the importance of treatments that don't bring a person back to perfect health, which discriminates against a person with a disability. Quality of life is multi-factorial and the methodology of assessing the quality of life is fundamentally flawed. She stated QALYs also have validity and reliability concerns. There are alternatives to the use of QALYs, such as value frameworks that use patient preferences. She said it would be difficult, if not impossible, to use QALYs in a non-discriminatory manner.
3) **Tony Coehlo, Chairman, Partnership to Improve Patient Care**: Coehlo said he authored the Americans with Disabilities Act in Congress. He recommended against Options 2 or 3, as these options only hide the use of QALYs. He preferred Option 4, and stated that use of discriminatory measures like QALYs in decision-making creates winners and losers. This discriminates against populations with disabilities and people of color. He advocated against the use of evidence that feeds bias in health care. He shared his personal health story and stated the ADA was enacted to counter bias based on disability.

Pinzon asked for clarification about Figure 1.9, previously a part of HERC's ranking methodology. Gingerich said the flowchart in the materials was initially part of the methodology but was never applied during line ranking determinations. Gingerich then presented the HERC's current ranking criteria that is applied to the Prioritized List. Clinical effectiveness, cost effectiveness, population effects, and impact on healthy life are criteria, among others. He noted that, prior to the Affordable Care Act, that last criterion was Impact on Health Life Years, but has since been modified. He said HERC staff conducted a comprehensive review of the unfunded region of the Prioritized List and have moved multiple items to the funded region based on this review.

Pinzon asked Sandt about non-discriminatory measures to replace QALYs. Sandt noted that many of these are included in the staff summary.

Gingerich said that HERC staff do not calculate QALYs, and that articles used to inform HERC decisions often include QALYs along with many other kinds of information that may be important to HERC decisions.

- **Topic: Inflammatory skin disease guideline**

Discussion: Smits reviewed the summary document.

Julie Dhossche, a pediatric dermatologist at OHSU, provided invited testimony. Atopic dermatitis is common but generally mild. Significant eczema that may affect the ability to attend school or results in secondary infection needs to be treated with effective medications. Many of the newer treatments address specific immune dysregulation underlying severe eczema. Many of the medications in the current guideline are broad immunosuppressants, require lab monitoring, and

carry significant risks. Targeted immunomodulators (TIM) are safer and don't require close monitoring. Phototherapy can be time- and cost-prohibitive for patients and can actually worsen eczema. She noted that other state Medicaid programs have TIM on their formularies as first-line treatments. Dhossche stated that JAK inhibitors, an oral immunomodulatory therapy, have emerged as an important and superior treatment to atopic dermatitis, and these are an FDA approved treatment for this condition.

There was minimal discussion. The guideline modifications were approved as presented.

Recommended Actions:
1) Modify GN21 as shown in Appendix A

MOTION: To recommend the guideline note changes as presented in option 2 from the meeting material. CARRIES 8-0.

- **Topic: Corneal collagen cross linkage for keratoconus**

Discussion: Smits reviewed the summary document. There were questions from subcommittee members regarding why the evidence is poor to support this treatment, whether it was due to lack of studies, or whether there was newer evidence. The members requested that staff reach out to experts to have them attend the November VBBS meeting to answer member questions.

Recommended Actions:
1) Staff will work with experts to refine this topic and come to answer member questions at the next VBBS meeting. Tabled until a future meeting

- **Topic: Statement of intent for public health emergencies**

Discussion: There was minimal discussion on this topic.

Recommended Actions:
1) Adopt a new statement of intent as shown in Appendix B

MOTION: To add the statement of intent as presented. CARRIES 8-0.

- **Topic: Solid organ transplant lines review**

Discussion: Smits reviewed the summary document.

There was consensus that the general criteria (for example, smoking cessation and control of other illnesses) were helpful. There were concerns about the requirements for specific transplants, such as heart transplants. Saenger noted that refractory ventricular arrythmias was an indication for cardiac transplant. Members recommended that staff contact the transplant centers at Providence, Legacy and OHSU to have any guideline/criteria/coding changes reviewed by transplant experts.

Recommended Actions:

1) Staff will review the criteria with transplant program staff and bring back a revised guideline. Tabled until a future meeting

- **Topic: Hydrocele repair in adults**

Discussion: Smits reviewed the issue summary.

There was discussion about whether there is evidence of benefit for treatment of hydroceles in adults. Hodges suggested adding language to the guideline requiring the hydrocele to interfere with function or other requirements from the hernia guideline. The group felt that this topic should be tabled until Brian Duty can attend the meeting so that he is able to address member questions.

Recommended Actions:

1) Tabled until a future meeting

- **Topic: Below the line review**

Discussion: There was minimal discussion about these agenda items.

Recommended Actions:

1) Remove the ICD-10-CM codes shown below from line 528 DEFORMITIES OF UPPER BODY AND ALL LIMBS

ICD-10-CM code	Code description
M20.02 family	Boutonniere deformity of finger
M20.03 family	Swan-neck deformity of finger
M20.09 family	Other deformity of finger
M21.0 family	Valgus deformity of elbow, hip, knee, ankle
M21.12-M21.16 families	Varus deformity of elbow, hip, knee
M21.2 family	Flexion deformity, shoulder, elbow, wrist, fingers, hip, knees, toes
M21.37 family	Foot drop
M21.52 family	Acquired clubhand
M21.7 family	Unequal limb length (acquired), arm and leg bones
M21.8 family	Other specified acquired deformities of arm or leg
M21.90-M21.05 families	Unspecified acquired deformity of arm or leg
M24.03-M24.05 families	Loose body in wrist, finger, hip
M24.15 family	Other articular cartilage disorders in hip
M25.15 family	Fistula, hip
Q67.6	Pectus excavatum
Q72.70	Split foot, unspecified lower limb

2) Add ICD-10-CM Q17.2 (Microtia) to line 406 BILATERAL ANOMALIES OF EXTERNAL EAR WITH IMPAIRMENT OF HEARING

3) Rename line 406 ~~BILATERAL~~ ANOMALIES OF EXTERNAL EAR WITH IMPAIRMENT OF HEARING
4) Add CPT 21086 (Impression and custom preparation; auricular prosthesis) to line 406
5) Adopt a new guideline for line 406 as shown in Appendix B
6) Remove ICD-10-CM N91.4 (Secondary oligomenorrhea) and N91.5 (Oligomenorrhea, unspecified) from line 658 GENITOURINARY CONDITIONS WITH NO OR MINIMALLY EFFECTIVE TREATMENTS OR NO TREATMENT NECESSARY
    - Advise HSD to add to the DIAGNOSTIC WORKUP FILE (DWF)
7) Add ICD-10-CM N93.9 (Abnormal uterine and vaginal bleeding, unspecified) to line 423 MENSTRUAL BLEEDING DISORDERS and remove from line 658 GENITOURINARY CONDITIONS WITH NO OR MINIMALLY EFFECTIVE TREATMENTS OR NO TREATMENT NECESSARY

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

- **Topic: CPAP titration**

  Tabled to the November HERC meeting

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

  Discussion: There was minimal discussion of this topic.

  Recommended Actions:
  1) Add ICD-10-CM Q66.9x (Congenital deformity of feet, unspecified) to line 543 DEFORMITIES OF FOOT and delete from line 359 DEFORMITY/CLOSED DISLOCATION OF JOINT AND RECURRENT JOINT DISLOCATIONS

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

- **Topic: Human growth hormone guideline review**

  Tabled to the November HERC meeting

- **Topic: Chronic disease self-management programs**

  Discussion: Smits reviewed the summary document for chronic disease self-management programs (CDSMP). Pinzon noted that the evidence review supported that these programs have a significant effect on self-efficacy, which is important for engaging patients in their care.

Public testimony
1) Lavinia Goto, operations manager for Oregon Wellness Network (OWN): Goto testified in support of OHA coverage for CDSMP. OWN represents groups on aging. Programs in OWN have been providing these CDSMP for over a decade in Oregon. She noted that 13 community

organizations submitted written testimony in support of this benefit. She personally provides these programs and trains program leaders. CDSMPs support patients to manage their illness and improves self-efficacy. It helps patients feel in control and be confident to effect change. CDSMP does not compete with traditional medicine but complements it. These programs activate the patient so that they engage in their care.

2) Tholanda Newborne, Multnomah County REACH Program contractor: Newborne testified that she is a contracted facilitator to help community members manage their diabetes. The REACH program provides a culturally specific program. She supports CDSMP implementation.

Pinzon stated that these programs address social determinants of health and that this coverage request is coming from the community. These programs have impacts beyond the impact on the individual; these programs develop cultural liaisons and community advocates. She expressed concern that if coverage of these programs are left up to the discretion of the CCOs, they won't be offered uniformly across the state.

Hodges noted that many of these programs are already being funded currently in many ways. She supports EBGS review to allow standardization of what interventions are offered throughout the state.

Gingerich noted that many of these programs cannot bill with traditional billing codes and require clinician supervision, posing implementation challenges to making these a funded benefit. There was also mention that evidence for a specific indication (such as asthma or hypertension) is problematic.

Saenger asked about whether these programs have quality certification or accreditation. Smits noted that these programs are recognized by the CDC. Goto informed members that CDSMP providers use a curriculum originally developed by Stanford that is standardized and updated yearly. The Self-Management Resource Center (SMRC) certifies trainers and requires annual reviews. The curriculum addressed topics such as how to talk to a provider, how to manage medications, and so forth. A master trainer does not need any specific degree or license.

Irwin agreed that these programs have utility in empowering patients. She expressed concern about the heterogeneity of disease conditions that these could be used to treat. Such heterogeneity makes it difficult to map to specific lines. She supported EBGS doing a systematic review to inform next steps.

Schabel asked about the price/cost of these programs. Goto answered that these programs involve 2.5 hour weekly sessions for 6 weeks. The cost ranges based on administrative costs (room rent, etc.) as well as paying for the leaders. Cost is nominal per participant, such as $1000 for the whole group for a session (up to 16 clients). There is also a virtual model which is lower cost.

The group voted to recommend to HERC to direct EBGS to create a multisector intervention review of chronic disease self-management programs.

Recommended Actions:

1) Recommend to HERC to direct EBGS to undertake a multisector intervention review of chronic disease self-management programs.

MOTION: To make the recommendation as presented. CARRIES 8-0.

- **Public Comment:**

  No additional public comment was received.

- **Issues for next meeting:**
  - CPAP titration
  - Human growth hormone guideline
  - Transplant coverage
  - Corneal collagen cross-linkage
  - Hydrocele coverage in adults

- **Next meeting:**

  November 17, 2022, virtual meeting

- **Adjournment:**

  The meeting adjourned at 12:55 PM.

Appendix A

Revised Guideline Notes

GUIDELINE NOTE 21, SEVERE INFLAMMATORY SKIN DISEASE

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

Inflammatory skin conditions included in this guideline are:

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

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

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

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

For severe psoriasis, treatments included on this line are topical agents, phototherapy, targeted immune modulator medications and other systemic medications. ~~first line agents include topical agents, phototherapy and methotrexate. Second line agents include other systemic agents and oral retinoids and should be limited to those who fail, or have contraindications to, or do not have access to first line agents. Biologics are included on this line only for the indication of severe plaque psoriasis; after documented failure of first line agents and failure of (or contraindications to) a second line agent.~~

For severe atopic dermatitis/eczema, ~~first line agents include~~ treatments included on this line are topical moderate- to high- potency corticosteroids, topical calcineurin inhibitors (~~e.g.~~ for example, pimecrolimus, tacrolimus), narrowband UVB~~. Second line agents include topical calcineurin inhibitors (e.g. pimecrolimus, tacrolimus),~~ topical phosphodiesterase (PDE)-4 inhibitors ~~(e.g. crisaborole)~~, and oral immunomodulatory therapy (e.g. cyclosporine, methotrexate, ~~azathioprine, mycophenolate mofetil,~~ or oral corticosteroids). ~~Use of the topical second line agents (e.g. calcineurin inhibitors and phosphodiesterase (PDE)-4 inhibitors) should be limited to those who fail or have contraindications to first line agents. Biologic agents~~ Targeted immune modulators (for example, dupilumab) are included on this line ~~for atopic dermatitis only after failure of or contraindications to at least one agent from each of the following three classes: 1) moderate to high potency topical corticosteroids, 2) topical calcineurin inhibitors or topical phosphodiesterase (PDE)-4 inhibitors, and 3) oral immunomodulator therapy.~~ when

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

b. 12 weeks of phototherapy.

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

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

GUIDELINE NOTE 24, COMPLICATED HERNIAS

Lines 168,524

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

A) Causes symptoms of intestinal obstruction and/or strangulation; OR
B) Is incarcerated (defined as non-reducible by physical manipulation); OR
C) Causes pain and functional limitations as assessed and documented by a medical professional; OR
D) Affects the patient's ability to obtain or maintain gainful employment.

Otherwise, inguinal and femoral hernias in men are included on line 524.

Repair of inguinal and femoral hernias in women and in children age 18 or younger are included on Line 168 due to the different natural history of disease in these populations.

Ventral hernias are included on Line 524. Incarcerated ventral hernias (including incarcerated abdominal incisional and umbilical hernias) are included on Line 524, because the chronic incarceration of large ventral hernias does not place the patient at risk for impending strangulation. Ventral hernias are defined as anterior abdominal wall hernias and include primary ventral hernias (epigastric, umbilical, Spigelian), paratomal hernias and most incisional hernias (ventral incisional hernias). ICD-10-CM K42.0, K43.0, K43.3, K43.6 and K46.0 are included on Line 524 when used to designate incarcerated abdominal incisional and umbilical hernias without intestinal obstruction or gangrene.

GUIDELINE NOTE 73, PENILE ANOMALIES

Lines 424,~~433~~ 434,~~571~~,573, 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

Appendix A

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~~ 573 or Line 658.

GUIDELINE NOTE 92, ACUPUNCTURE

Lines 1,4,5,64,65,92,111,112,114,125,129,133,135,157,158,191,199-201,208,210,214,215,229,234, 237,238,258,259,262,271,276,286,287,294,314-316,329,342,361,396,397,402,410,419,435,464,541, 559

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

Line 1 PREGNANCY

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

Hyperemesis gravidarum

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

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

Breech presentation

ICD-10-CM: O32.1

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

Back and pelvic pain of pregnancy

ICD-10-CM: O99.89

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

Line 4 SUBSTANCE USE DISORDER,Line 62 SUBSTANCE-INDUCED MOOD, ANXIETY, DELUSIONAL AND OBSESSIVE-COMPULSIVE DISORDERS,Line 65 SUBSTANCE-INDUCED DELIRIUM; SUBSTANCE INTOXICATION AND WITHDRAWAL

Acupuncture is included on these lines only when used as part of a ~~program~~ documented broader treatment plan that offers patients a variety of evidence-based interventions including behavioral interventions, social support, and Medication Assisted Treatment (MAT), as appropriate.

Line 5 TOBACCO DEPENDENCE

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

Appendix A

Lines 92, 111, 112, 114, 125, 129, 133, 135, 157, 158, 191, 199, 200, 208, 210, 214, 215, 229, 234, 237, 238, 258, 259, 261, 262, 271, 276, 286, 287, 294, 314, 315, 316, 329, 342, 372, 396, 397, 419, 435 and 559

Acupuncture is paired only with the ICD-10 code G89.3 (Neoplasm related pain (acute) (chronic)) when there is active cancer and limited to 12 total sessions per year; patients may have additional visits authorized beyond these limits if medically appropriate.

Line 201 CHRONIC ORGANIC MENTAL DISORDERS INCLUDING DEMENTIAS

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

Line 361 SCOLIOSIS

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

Line 402 CONDITIONS OF THE BACK AND SPINE

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

Line 410 MIGRAINE HEADACHES

Acupuncture pairs on Line 410 for migraine (ICD-10-CM G43.0, G43.1, G43.5, G43.7, G43.8, G43.9), for up to 12 sessions per year.

Line 464 OSTEOARTHRITIS AND ALLIED DISORDERS

Acupuncture pairs on Line 464 for osteoarthritis of the knee only (ICD-10-CM M17), for up to 12 sessions per year.

*Line 541 TENSION HEADACHES

Acupuncture is included on Line 541 for treatment of tension headaches (ICD-10-CM G44.2), for up to 12 sessions per year.

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

*Below the current funding line.

GUIDELINE NOTE 127, GENDER DYSPHORIA

Line 312

Hormone treatment with GnRH analogues for delaying the onset of puberty and/or continued pubertal development is included on this line for gender questioning children and adolescents. This therapy should be initiated at the first physical changes of puberty, confirmed by pubertal levels of estradiol or testosterone, but no earlier than Tanner stages 2-3. Prior to initiation of puberty suppression therapy, adolescents must fulfill eligibility and readiness criteria and must have a comprehensive mental health evaluation. Ongoing psychological care is strongly encouraged for continued puberty suppression therapy.

Cross-sex hormone therapy is included on this line for treatment of adolescents and adults with gender dysphoria who meet appropriate eligibility and readiness criteria. To qualify for cross-sex hormone therapy, the patient must:

A) have persistent, well-documented gender dysphoria
B) have the capacity to make a fully informed decision and to give consent for treatment
C) have any significant medical or mental health concerns reasonably well controlled

D) have a comprehensive mental health evaluation provided in accordance with Version 7 of the World Professional Association for Transgender Health (WPATH) Standards of Care (www.wpath.org).

Sex reassignment surgery is included for patients who are sufficiently physically fit and meet eligibility criteria. To qualify for surgery, the patient must:

A) have persistent, well documented gender dysphoria
B) for genital surgeries, have completed twelve months of continuous hormone therapy as appropriate to the member's gender goals unless hormones are not clinically indicated for the individual
C) have completed twelve months of living in a gender role that is congruent with their gender identity unless a medical and a mental health professional both determine that this requirement is not safe for the patient
D) have the capacity to make a fully informed decision and to give consent for treatment
E) have any significant medical or mental health concerns reasonably well controlled
F) for breast/chest surgeries, have one referral from a mental health professional provided in accordance with version 7 of the WPATH Standards of Care.
G) For genital surgeries, have two referrals from mental health professionals provided in accordance with version 7 of the WPATH Standards of Care.

Electrolysis (CPT 17380) and laser hair removal (CPT 17110,17111) are only included on this line as part of pre-surgical preparation for chest or genital surgical procedures also included on this line. These procedures are not included on this line for facial or other cosmetic procedures or as pre-surgical preparation for a procedure not included on this line.

Mammoplasty (CPT 15771, 15772, 19316, ~~19324~~-19325, 19340, 19342, 19350) is only included on this line when 12 continuous months of hormonal (estrogen) therapy has failed to result in breast tissue growth of Tanner Stage 5 on the puberty scale OR there is any contraindication to, intolerance of or patient refusal of hormonal therapy.

Revisions to surgeries for the treatment of gender dysphoria are only covered in cases where the revision is required to address complications of the surgery (wound dehiscence, fistula, chronic pain directly related to the surgery, etc.). Revisions are not covered solely for cosmetic issues.

Pelvic physical therapy (CPT 97110,97140,97161-97164, and 97530) is included on this line only for pre- and post-operative therapy related to genital surgeries also included on this line and as limited in Guideline Note 6 REHABILITATIVE AND HABILITATIVE THERAPIES.

GUIDELINE NOTE 154, EAR DRUM REPAIR

Lines 311,446,476

Repair of open wounds or perforations of the ear drum (~~codes included on these lines from~~ ICD-10-CM H72~~,~~ and S09.2) are only included on Lines 311 and 446 when there is documented conductive hearing loss greater than or equal to 25dB persistent for more than three months. Otherwise, such repairs are included on Line 476 CHRONIC OTITIS MEDIA; OPEN WOUND OF EAR DRUM.

Appendix B

New Guideline Notes

STATEMENT OF INTENT XX, PUBLIC HEALTH EMERGENCIES

It is the intent of the Commission that If the state Public Health Director determines that there exists a disease outbreak, epidemic or other condition of public health importance in a geographic area of this state or statewide, under ORS 743A.264, then all necessary antitoxins, serums, vaccines, immunizing agents, antibiotics, antidotes and other pharmaceutical agents, medical supplies or other prophylactic measures approved or with emergency use authorization by the United States Food and Drug Administration that the director deems necessary to prevent the spread of the disease, epidemic or other condition of public health importance should be covered.

GUIDELINE NOTE XXX MICROTIA

Line 406, 602

ICD-10-CM Q17.2 (microtia) is included on line 406 for external ear reconstruction when ANY of the following criteria are met:

1) Hearing is expected to improve; OR
2) Reconstruction is necessary to allow for use of a conventional air conduction hearing aid; OR
3) The external ear deformity is preventing the functional ability to use eyewear for the correction of visual loss; OR
4) The patient is under 21 years of age and reconstruction is determined to be medically appropriate and necessary after individual case review.

Otherwise, this diagnosis is included on line 602.

Section 2.0

Previously Discussed Items

Corneal Collagen Cross-Linkage

Plain Language Summary:
Background: Should a treatment for a condition which results in vision problems from thinning of the outer layer of the eye (cornea) be covered on the Oregon Health Plan?

Should OHP cover this treatment? Staff recommends covering this treatment because evidence shows the treatment works for certain conditions and it is recommended by experts.

Question: Should corneal collagen cross-linkage be added as a treatment of keratoconus?

Question source: Holly Jo Hodges, CCO medical director

Issue: Keratoconus is a corneal thinning disorder occurring when the normally round dome-shaped cornea, the clear tissue covering the front of the eye, progressively changes shape to a conical bulge. This causes refractive error, which is usually a myopic shift and is often associated with astigmatism, leading to visual impairment. It commonly affects children and young adults and may be progressive.

In mild to moderate keratoconus, clinical management to correct visual acuity is by glasses or contact lenses. With disease progression, rigid gas permeable contact lenses may be fitted, or corneal ring segment inserts used. However, if the corneal shape deteriorates further, some form of corneal surgery may be required, including deep lamellar keratoplasty or penetrating keratoplasty for severe progressive keratoconus. Corneal collagen cross-linkage (CXL) using riboflavin and ultraviolet A (UV A) radiation was piloted on patients in 2003. It increases corneal biomechanical stiffness thereby strengthening and stabilizing the cornea. This is achieved by increasing the number of 'anchors' that bond collagen fibers together. The aim is to stop disease progression and need for corneal transplant.

This topic was discussed at the October 2022 VBBS meeting. The subcommittee members requested that further evidence review be conducted to better understand the effectiveness of the procedure. The members also requested that an ophthalmologist be invited to come to the November meeting to answer questions.

Current Prioritized List status
Never Reviewed:
CPT 0402T Collagen cross-linking of cornea (including removal or the corneal epithelium and intraoperative pachymetry when performed)

ICD-10-CM H18.6 family (keratoconus) is on line 310 CORNEAL OPACITY AND OTHER DISORDERS OF CORNEA with various surgical treatments paired

Evidence:

1) **Craig 2014,** systematic review and meta-analysis of corneal collagen cross-linkage for keratoconus
    a. N=71 papers on efficacy, 26 papers on adverse events
        i. 8 RCTs (4 unique trials), 29 prospective case series, 7 retrospective case series, 5 case series
    b. In all cases the estimated change at 12 months follow-up was significant, with max and mean K values reducing by about 1 D and min K by 0.75 D.
    c. Epithelium-off CXL was associated with statistically significant improvement in corrected and uncorrected visual acuity over all time periods
    d. Meta-analyses of studies comparing epithelium-off CXL eyes and control eyes at 12 months follow-up reported significant improvement in corrected visual acuity (-0.19 LogMAR) but reported no improvement in uncorrected visual acuity (-0.45 LogMAR)
    e. Meta-analysis results for the differences between preoperative and postoperative data showed statistically significant improvements in astigmatism at 6, 12, and 24 months (-0.4 D at 6 months, -0.7 D at 12 months, and -0.5 D at 24 months), with absolute benefit increasing to 12 months and stabilizing.
    f. Meta-analysis results for differences between epithelium-off CXL and control groups from 2 RCTs showed no significant differences at 12 months (-1.42 D [-3.85; 1.00])
    g. Forty serious complications in 39 patients undergoing epithelium-off CXL were reported in the 49 efficacy and 26 safety papers. Common side effects were pain, corneal edema, and corneal haze. These and other minor complications resolved usually within a few days after the procedure
2) **NICE 2013** systematic review on photochemical corneal collagen cross-linkage
    a. N=49 papers on efficacy and N=26 papers on safety
        i. Generally given a grade of low or very low quality
    b. Improvements in measures of topography were found for Max K, mean K and Min K, respectively at 6, 12 months and 24 months. Benefit increased to 12 months and then stabilized. This evidence came from a comparison of baselines before and after procedure; no randomized control data were available.
    c. For measures of visual acuity, meta-analysis of change between treated and control groups at 12 months found no significant differences for uncorrected visual acuity but a significant difference of around -0.20 (LogMAR) for corrected visual acuity. One RCT reporting at 18 months only, however, found non-significant differences between the treatment and control groups in corrected visual acuity. The results for differences between post-treatment and baseline values for treated patients showed significant improvements for corrected and uncorrected visual acuity at 6, 12 and 24 months. Improvement was also indicated by the results from all papers reporting this outcome.
    d. No significant differences were found between the treatment and control groups for measures of astigmatism. Differences between post-treatment and baseline values for treated patients showed statistically significant improvements in astigmatism at 6, 12 and 24 months, and for spherical equivalence measures, significant differences at 12 months.
    e. A meta-analysis of 6 papers found a statistically significant reduction in central corneal thickness values between post-treatment and baseline values for treated patients at 12 months. Evidence from 25 papers was supportive of a reduction.
    f. Evidence on intraocular pressure is poor but suggestive of a tendency to higher intraocular pressure after procedure.

g. The procedure is generally reported as safe but serious complications were reported, including the need for 4 patients to have corneal transplant, and a similar number suffering long-term loss in visual acuity. Cause of the events was seldom disclosed. For example, some infections may be due to the patient failing to comply with advice on after care, while other events may be due to operator error. Most events resolved over time with no major consequences for the patient.

Other payer policies:

1) **NICE 2013**
   a. Current evidence on the safety and efficacy of epithelium-off CXL for keratoconus and keratectasia is adequate in quality and quantity. Therefore, this procedure can be used provided that normal arrangements are in place for clinical governance, consent and audit
   b. Current evidence on the safety and efficacy of epithelium-on (transepithelial) CXL, and the combination (CXL-plus) procedures for keratoconus and keratectasia is inadequate in quantity and quality. Therefore, these procedures should only be used with special arrangements for clinical governance, consent and audit or research
2) **Aetna 2022**
   a. Aetna considers epithelium-off photochemical collagen cross-linkage using riboflavin (Photrexa) and ultraviolet A medically necessary for keratoconus and keratectasia.
   b. Aetna considers photochemical collagen cross-linkage experimental and investigational for all other indications because its effectiveness for other indications has not been established.
   c. Aetna considers epithelium-on (transepithelial) collagen cross-linkage experimental and investigational for keratoconus, keratectasia, and all other indications.
   d. Aetna considers performance of photochemical collagen cross-linkage in combination with other procedures (CXL-plus) (e.g., intrastromal corneal ring segments, PRK or phakic intra-ocular lens implantation) experimental and investigational.
3) **Cigna 2021**
   a. Conventional, epithelium-off, corneal collagen crosslinking (C-CXL) using a U.S. Food and Drug Administration (FDA) approved drug/device system (e.g., Photrexa® Viscous or Photrexa® with the KXL® System) (CPT Code® 0402T; HCPCS Code J2787) is considered medically necessary for the treatment of EITHER of the following:
      i. progressive keratoconus
      ii. corneal ectasia following refractive surgery
      iii. when ALL of the following criteria are met:
         1. age 14–65 years
         2. progressive deterioration in vision
         3. absence of visual disturbance from a significant central corneal opacity or other eye disease (e.g., herpetic keratitis, neurotrophic keratopathy)
   b. C-CXL is considered experimental, investigational or unproven for any other indication including when combined with a second refractive procedure. All other corneal collagen crosslinking procedures (e.g., epithelium-on/trans-epithelial) are considered experimental, investigational or unproven.
4) **Blue Cross/Blue Shield**
   a. Corneal collagen cross-linking using riboflavin and ultraviolet A may be considered medically necessary as a treatment of:

   i. progressive keratoconus OR
   ii. corneal ectasia after refractive surgery in patients who have failed conservative treatment (e.g., spectacle correction, rigid contact lens).

b. Progressive keratoconus or corneal ectasia is defined as one or more of the following:
   i. An increase of 1 diopter (D) in the steepest keratometry value;
   ii. An increase of 1 D in regular astigmatism evaluated by subjective manifest refraction;
   iii. A myopic shift (decrease in the spherical equivalent) of 0.50 D on subjective manifest refraction;
   iv. A decrease ≥0.1 mm in the back optical zone radius in rigid contact lens wearers where other information was not available.

Expert input

Dr. Travis Redd, OHSU ophthalmology

I strongly support OHP providing CXL coverage. It would make a huge positive impact for our patients.

Dr. Winston Chamberlain, OHSU ophthalmology

This is very important topic to us because many of our patients are not getting access to vision saving care because of OHP's current lack of coverage policy for crosslinking. The problem is bad enough that many OHP patients have lost vision or required more expensive and more risky procedures…The procedure is not inexpensive because of J codes required to Cover the medication under the current approval status of the procedure in the United States and the equipment and facility costs. But it is a fraction of the cost of the alternative procedure that OHP has historically forced us to consider which is a corneal transplant with lifelong risks to patients and maintenance.

Corneal Collagen Cross-Linkage

HERC staff summary

Corneal collagen cross linking has evidence of significant improvement in corrected and uncorrected visual acuity as a treatment for keratoconus. This procedure is covered by all major insurers surveyed for progressive keratoconus or corneal ectasia following refractive surgery when there is a progressive deterioration in vision. Experts recommend coverage as vision saving cost-effective care.

HERC staff recommendations:

1) Add CPT 0402T (Collagen cross-linking of cornea (including removal or the corneal epithelium and intraoperative pachymetry when performed)) to line 310 CORNEAL OPACITY AND OTHER DISORDERS OF CORNEA
2) Adopt a new guideline for line 310 as shown below

GUIDELINE NOTE XXX CORNEAL COLLAGEN CROSS LINKING

Line 310

CPT 0402T is included on this line only when used for conventional epithelium-off corneal collagen cross linking and only for treatment of:

1) progressive keratoconus, OR
2) corneal ectasia following refractive surgery; and

only when there is objective progressive deterioration in vision.

Epithelium-Off Photochemical Corneal Collagen Cross-Linkage Using Riboflavin and Ultraviolet A for Keratoconus and Keratectasia: A Systematic Review and Meta-Analysis

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ABSTRACT This report presents the results of a systematic review and meta-analyses of studies on epithelium-off photochemical corneal collagen cross-linkage for the management of keratoconus and secondary ectasia. The literature search identified 3,400 records of which 49 were considered for inclusion in the meta-analyses. Eight papers reported 4 unique randomized controlled trials, 29 studies were prospective, and 12 were retrospective studies. The majority of the studies (39/49) were graded as very low quality evidence. Twenty-six studies described adverse events and were included in the safety analysis. Meta-analyses are presented for changes in four outcomes: visual acuity, topography, refraction and astigmatism, and central corneal thickness. Statistically significant improvements were found in all efficacy outcomes at 12 months after the operation. Common side effects were pain, corneal edema, and corneal haze, which resolved usually within a few days after the procedure. The remaining uncertainty is duration of benefit to establish the procedure's potential benefit in avoiding or delaying disease progression and possibly reducing the need for corneal transplantation.

KEY WORDS epithelium-off collagen cross-linkage, keratoconus, keratectasia, meta-analysis, systematic review

I. INTRODUCTION

Keratoconus, a form of corneal ectasia, is a pathological degeneration of the structure of the cornea to form a cone-shaped protrusion. The changed shape causes reduced visual acuity, astigmatism, and sensitivity to light and glare, limiting daily activities, including driving and reading. Keratoconus is a progressive disease of unknown etiology that generally affects both eyes, with a prevalence of about 0.05% (1 in 2,000) in the population. Onset is early, typically presenting in adolescence and progressing in a variable manner.[1]

Secondary (or iatrogenic) corneal ectasia can also result from an infrequent but serious complication of laser-assisted in situ keratomileusis (**LASIK**) surgery and is called *keratectasia*. Disease presentation and pathways are similar to those of keratoconus. In both cases, management of keratoconus ectasia depends on disease severity. The Amsler-Krumeich scale grades keratoconus severity from grade I (mild) to grade IV (severe). With mild-to-moderate keratoconus, visual acuity can be corrected with spectacles, contact lenses, and intracorneal ring segment (**ICRS**) implantation. With increasingly irregular

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YHEC
York Health Economics Consortium

The Newcastle upon Tyne Hospitals NHS
NHS Foundation Trust

Providing consultancy and research in health economics for the NHS, pharmaceutical and health care industries since 1986

INTERVENTIONAL PROCEDURE ADVISORY COMMITTEE

Photochemical Corneal Collagen Cross-Linkage Using Riboflavin and Ultraviolet A for Keratoconus: A Systematic Review

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MAY 2013

THE UNIVERSITY of York

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Executive Summary

1. BACKGROUND

The systematic review is of two groups of patients, namely those with a diagnosis of keratoconus or keratectasia.

Keratoconus is a corneal thinning disorder occurring when the normally round dome-shaped cornea, the clear tissue covering the front of the eye, progressively changes shape to a conical bulge. Thinning occurs primarily in the stroma layers and one potential explanation for this a defect in the collagen process.

Keratoconus has a prevalence of under 0.05% (1 in 2,000) of the population, with an earlier onset than most chronic eye diseases with a patient median age of 25 years. Those with the disease suffer a loss in visual acuity, making tasks such as driving, reading and screen work difficult.

Keratoconus can also be secondary, resulting from an infrequent but serious complication of laser-assisted *in situ* keratomileusis (LASIK) surgery, and is then called keratectasia. If the cornea's structure is weakened during LASIK surgery, it can bulge forward in an irregular fashion, causing increasing astigmatism and distorted vision. This cannot be corrected with spectacles, contact lenses, or a LASIK enhancement procedure. Patients with thin corneas prior to LASIK have a higher risk of developing keratectasia. The treatment pathway is similar to that for keratoconus.

Diagnosis of keratoconus is often not straightforward and typically requires a review of family history, looking for clinical signs, and use of various instruments to measure corneal topography and central corneal thickness. The management of keratoconus depends on the stage of the disease. The stage can be identified using the Amsler-Krumeich classification which has 4 stages from mild (grade I) to severe (grade IV).

In mild to moderate keratoconus, clinical management to correct visual acuity is by spectacles or contact lenses. With disease progression, rigid gas permeable contact lenses may be fitted or corneal ring segment inserts used. However, if the corneal shape deteriorates further some form of corneal surgery may be required, including deep lamellar keratoplasty or penetrating keratoplasty for severe progressive keratoconus.

Prior to introduction of corneal collagen cross-linkage (CXL), no interventions were available to arrest or slow disease progression, with corneal transplantation required in up to 21% of keratoconic eyes. Visual acuity may not be fully restored after transplant and the disease may recur, requiring subsequent interventions.

CXL using riboflavin and ultraviolet A (UV A) radiation was piloted on patients in 2003. It increases corneal biomechanical stiffness thereby strengthening and stabilising the cornea. This is achieved by increasing the number of 'anchors' that bond collagen fibres together. The aim is to stop disease progression.

With 'epithelium-off cross-linkage', the epithelium is removed with a blunt spatula or laser. Riboflavin eye drops are applied to the corneal surface 5 minutes before the procedure to enable penetration into the corneal tissue and then every 3 to 5 minutes during the procedure. The corneal surface is exposed to the UV A radiation, usually for up to 30 minutes. Postoperatively, topical antibiotics and anti-inflammatory drops will normally be prescribed with topical steroids if necessary. In some cases, a bandage contact lens may

also be used for a few days. The outpatient procedure takes 60 to 90 minutes in most cases.

With transepithelial corneal cross-linkage (epithelium-on) the corneal epithelial surface is left intact, which requires a longer riboflavin loading time but may reduce the risk of infection.

CXL can be used in conjunction with various techniques designed to improve visual acuity. Adjunct procedures include:

- A range of corneal implants, also known as intracorneal ring segments (ICRS);
- Topography-guided and other forms of photorefractive keratectomy (PRK), a form of laser ablation;
- Phakic intraocular lens (PIOL).

The most common complications reported after the procedure are stromal haze, which usually resolves, and pain. More serious events include infection, corneal melting, perforation and ulceration, and stromal scarring.

2. OBJECTIVE

The objective of this systematic review is to examine evidence for the efficacy and safety of CXL using riboflavin and ultraviolet A for keratoconus and keratectasia, alone or in combination with interventions designed to improve visual acuity. These combination interventions are referred to as 'CXL-Plus'.

The evidence will allow the Interventional Procedures Advisory Committee to reassess guidance on the procedure. This was originally issued in November 2009 by the National Institute for Health and Clinical Excellence (NICE). This recommended that, given inadequate evidence, the procedure should only be used with special arrangements for clinical governance, consent and audit or research. Subsequently, new evidence has been published.

3. LITERATURE SEARCH AND SYNTHESIS OF PAPERS

The systematic review adopted a search strategy designed to identify all relevant published, unpublished and grey literature. A date limit of 2000 to 31 October 2012 was applied. The search returned 1,747 abstracts, after removal of duplicates. Inclusion criteria were:

- English-language reports and human studies;
- Patients with keratoconus or keratectasia;
- Reports with interventions using photochemical corneal collagen cross-linkage using riboflavin and ultraviolet alone, or in combination or sequence with other treatments;
- Original reports with defined study methodology;
- Reports including standardised measurements on outcome events such as technical access, safety, efficacy, durability, vision, quality of life or patient satisfaction;
- Systematic reviews, meta-analyses, randomised controlled trials, observational studies, retrospective analyses, case series, case studies, letters, comments and conference abstracts.

These eligibility criteria were applied to abstracts and titles to inform provisional study selection. Two researchers reviewed the retrieved abstracts and titles, for those with no abstract, and made their selections independently. Differences were reconciled by mutual

agreement. Two hundred and fifteen papers were selected by agreement, 17 were in a foreign language and not retrieved, and a further 8 papers could not be obtained. The remaining 190 papers were retrieved.

The inclusion and exclusion criteria were applied to the full papers to judge which should be included in this study. Seventy-one papers on efficacy and 26 on adverse events were selected for full data extraction, with 93 papers excluded. Of these, 19 were efficacy studies with fewer than 10 patients or less than 6 months follow-up; these were partially extracted and reported as an appendix, but not considered in the analysis. Full data extraction was undertaken on the 71 efficacy papers and a more limited extraction on the 26 papers on safety events.

Formal meta-analyses were undertaken on publications reporting results using the epithelium-off procedure. Extracted data showing effect sizes, study end points and time periods were reviewed and any inconsistencies or unexpected results checked by going back to original papers. The relevant end points agreed with NICE were:

- Change in visual acuity;
- Change in topography;
- Change in refraction and astigmatism;
- Change in intraocular pressure;
- Change in central corneal thickness.

Where sufficient data were available across common time periods they were synthesised using meta-analysis based on both random effects and fixed effects models. Heterogeneity was identified by using the I^2 statistic. Meta-analysis results were reported using forest plots.

For CXL-Plus interventions and the transepithelial corneal cross-linkage (epithelium-on) procedure, a narrative synthesis of the same end points was undertaken.

4. RESULTS

4.1 Evidence on epithelium-off CXL

Identified evidence comprised 49 papers on the efficacy of epithelium-off CXL and 26 on the safety of epithelium-off CXL. Of the 49 efficacy papers, 8 were randomised controlled trials (RCTs), reporting 4 unique studies with the main comparator being fellow-eyes; the exception was an Australian RCT which did randomise eyes matched for disease status. Only preliminary results have been reported from that study.

The remaining papers reported changes before and after the procedure, which limits the ability to draw conclusions on the causal nature of the effect presented. However, given the disease is progressive, evidence of halting progression or indeed reversing it is supportive of a beneficial effect.

Of the non-RCT papers, the majority (25) were prospective case series, usually with well-defined inclusion criteria and trial design. However, few papers reported drop-out rates or reasons for them, thereby limiting the strength of the evidence.

Seven of the remaining papers were retrospective reviews, often using patient records as the data source. Using such data has strengths including that of reflecting actual outcomes in settings which may be similar to those of the NHS and are, thus, representative of clinical practice. However, there was concern about potential for bias in patient selection.

Almost 60% of papers were set in European tertiary centres, with a further 15% set in the USA; all sites undertook very similar CXL procedures. These settings are anticipated to be comparable to NHS settings. Two papers explicitly excluded patients with Amsler-Krumeich scale grade IV; otherwise the main inclusion criterion was progressive keratoconus. Thuse, there were no major concerns about the external validity of the results to a UK setting.

Overall, 39 papers were graded as very low evidence, six as low and four moderate. Those graded moderate reported on 4 RCTs but, as noted, these do not provide comparative evidence in eyes with progressive keratoconus.

Summary of findings from epithelium-off CXL papers

As noted, meta-analyses were conducted when sufficient data were reported for consistent end-points and time periods. To enable results for papers which could not be formally synthesised to be captured, a simple arithmetic mean across time periods was calculated. The results were grouped into consistent end points and by time period: 6, 12 and 24 months. Papers reporting at 9 months were included under the 12-month period and those reporting at 18 months under the 24-month period to avoid removing evidence. Papers reporting end points where the units measured were unclear or used measures which could not be aggregated with others were not included. The remaining results were used to calculate the mean value of the change reported for each end point/time period combination.

These assumptions and methodology were adopted for all parameters. The estimates are not offered as a precise estimate of the change in measures as a result of CXL, rather they give an indication of the size effect and its direction. They are intended to display the trend in evidence for each group of similar parameters but do no more than that.

Many meta-analyses displayed moderate to high heterogeneity across papers, giving wide confidence intervals, which suggests the studies were not consistent in their conduct.

Topography

Due to a lack of data, no meta-analyses of change between treated and control groups could be undertaken for measures of topography. Meta-analysis results for differences between post-treatment and baseline values for treated patients reported significant improvements for Max K (maximum keratometry) at 6, 12 and 24 months; these improvements were -0.8 dioptres (D) at 6 months and around -1.0 D at 12 and 24 months. For Min (minimum) K and mean K, meta-analysis was only undertaken at 6 and 12 months. Meta-analysis results were only significant at 12 months; average changes of around -1.0 D and -0.7 D were found for mean K and Min K, respectively.

The number of papers synthesized was for:

- Max K: 10, 18 and 6 papers at 6, 12 and 24 months, respectively;
- Min K: 4 and 8 papers at 6 and 12 months, respectively;
- Mean K: 7 and 12 papers at 6 and 12 months, respectively.

In total, 38 papers reported 104 comparable measures of topography over the three time periods, with 41 (38%) reporting statistically significant improvements in K values. The improvement increased over time with 4 papers reporting statistically significant differences at 12 months but not at 6 months. Of the 8 papers reporting data at 12 and 24 months, the 24-month values showed an improvement or no change on the 12-month values in all cases but one. One paper reporting a longer follow-up showed the improvement continued into year 3 and was then maintained to year 6. However, the number of patients lost to follow-up was large, thereby limiting the weight attributed to these results.

No precise estimate of the benefit across all papers is possible. However, a simple arithmetic mean calculated from the 104 measures gave an improvement of 1.5 D for Max K, 1.4 D for mean K and 1.1 D for Min K at 12 months, which were slightly higher than the meta-analyses results.

Visual acuity

Due to a lack of data, a meta-analysis of change between treated and control groups was only undertaken for visual acuity at 12 months. Only 3 studies contributed to the meta-analysis of corrected visual acuity and only two to the meta-analysis of uncorrected visual acuity. No significant difference was found between treatment and control groups for uncorrected visual acuity, whereas a significant difference of around -0.20 (LogMAR) was found for corrected visual acuity.

Differences between treatment and control groups over time were not significant for uncorrected visual acuity. For corrected visual acuity, there seemed to be an improvement over time, as the difference between treatment and control groups was not significant at 3 months but was so at both 6 and 12 months (-0.12 and -0.19 LogMAR, respectively). However, non-significant differences were reported at 18 months between treatment and control groups.

Based on results for differences between post-treatment and baseline values for treated patients, significant improvements were reported for corrected and uncorrected visual acuity at 6, 12 and 24 months. These were calculated using data from 12, 18 and 6 papers for uncorrected visual acuity and 15, 22 and 7 papers for corrected visual acuity, at 6, 12, and 24 months, respectively. Improvements on the LogMAR scale were in the order of -0.15 for uncorrected visual acuity and -0.10 for corrected visual acuity across the various time points.

In total, 38 papers reported 104 usable results on visual acuity of which 52 (50%) reported significant improvements in visual acuity. Arithmetic means of the differences calculated from this larger data set were similar to those from the meta-analyses. For uncorrected and corrected visual acuity the estimated benefit at 12 months was 0.19 and 0.10, respectively, on the LogMAR scale.

Astigmatism and cylinder measures

Due to a lack of data, meta-analysis was only undertaken for grouped astigmatism measured at 12 months. Only 2 studies contributed and no significant differences between treatment and control groups were found from the random effects model.

Meta-analysis results for differences between post-treatment and baseline values for treated patients showed statistically significant improvements in astigmatism at 6, 12 and 24 months, in the order of -0.4 D at 6 months, -0.7 D at 12 months and -0.5 D at 24 months. For spherical equivalence, meta-analysis was only undertaken at 6 and 12 months. The meta-analysis results, which were only significant at 12 months, showed a reduction of between 0.3 and 0.5 D.

These analyses included 7, 13 and 5 papers on astigmatism at 6, 12 and 24 months, respectively, and 8 and 10 papers on spherical equivalence at 6 and 12 months, respectively.

In total, 31 papers provided 88 usable results of astigmatism and refraction measures, of which 21 (23%) were statistically significant. Eleven values reported in 8 papers were negative (increase in a negative value), showing deterioration in the measure, but none were statistically significant. Analysing the usable results from all papers provided estimates of the reduction at 12 months of:

- 0.9 D for astigmatism, somewhat higher than the value from meta-analysis;
- 1.0 D in spherical equivalence.

Central corneal thickness

Due to a lack of data, no meta-analyses of change between treated and control groups could be undertaken for central corneal thickness. Two meta-analyses of data from 6 papers estimated differences in central corneal thickness values between post-treatment and baseline values for treated patients at 6 and 12 months. A significant decrease of 14 µm in central corneal thickness was found at 12 months. No significant difference was found in the meta-analysis of 6-month results.

In total, 25 papers reported on central corneal thickness measurements, of which three noted no statistical differences at any time period and two reported statistically significant reductions at 12 months. The arithmetic means of the changes across 23 papers at 6 and 12 months were -12 µm and -8 µm respectively, which support the results of the meta-analyses.

One paper reported changes in central corneal thickness for patients with keratoconus and keratectasia. Patients with keratectasia regained the pre procedure level of central corneal thickness at 12 months, whilst patients with keratoconus had a reduced central corneal thickness of about 6 µm.

Intraocular pressure

No meta-analyses of change between treated and control groups could be undertaken for intraocular pressure. Following clinical advice, only 2 studies were included in an analysis of differences between post-treatment and baseline values for treated patients, and this was undertaken at 6 months only. No significant differences were found.

Four papers stated that intraocular pressure was unchanged over all time periods, and one reported a statistically significant increase in intraocular pressure at 12 months of 2.9 mmHg. This was the only statistically significant value reported. Overall, 3 negative values with a mean value of -0.3 mmHg were reported, compared with 11 positive values with a mean value of 0.8 mmHg.

Adverse events and complications

Table 1 summarises adverse events reported in the 49 efficacy studies and 26 safety papers. In total, 40 serious complications were reported in 39 patients. To address events which did not resolve, 4 patients had corneal transplants and one an unspecified procedure. Four patients suffered reduced visual acuity and 6 had unresolved corneal oedema. In the other patients there were no major long-term complications. Some adverse events may be due to poor after care compliance by the patient and others may be site specific. For example, the 4 transplants were reported in one paper which was set in multiple centres in France.

Several studies reported pain, corneal oedema and corneal haze as common side effects. Sterile keratitis was reported in 20 patients. Other minor complications included striae, Descemet, blepharitis, endothelial irregularities and mild photophobia. These resolved over time.

Section 3.0

Consent Agenda-

Straightforward Items

Consent Agenda Issues—November 2022

Code	Code Description	Line(s) Involved	Issue	Recommendation(s)
Q67.6	Pectus excavatum	401 BENIGN CONDITIONS OF BONE AND JOINTS AT HIGH RISK FOR COMPLICATIONS 528 DEFORMITIES OF UPPER BODY AND ALL LIMBS	ICD-10-CM Q67.6 was mistakenly removed from line 528 at the October 2022 VBBS/HERC meeting. It belongs on both line 528 and on line 401, governed by guideline 94 PECTUS EXCAVATUM.	Do not remove Q67.6 from line 528 as previously decided

Straightforward Guideline Note Changes
November 2022

Gastric neurostimulator guideline

1) The new gastric neurostimulator guideline does not include the HCPCS code for the actual neurostimulator: E0765 (Fda approved nerve stimulator, with replaceable batteries, for treatment of nausea and vomiting).
    a. HERC staff recommendation:
        i. Modify GN227 as shown below

GUIDELINE NOTE 227, GASTRIC ELECTRICAL STIMULATION

Line 8,27,529

Gastric electrical stimulation (CPT 43657, 43648, 43881, 43882; HCPCS E0765) 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:

A) The patient has intractable nausea and vomiting secondary to gastroparesis of diabetic or idiopathic etiology; AND

B) The patient is refractory or intolerant of prokinetic medications and antiemetic medications; AND

C) The patient is not on opioid medications; AND

D) The patient does not have abdominal pain as the predominant symptom.

Botulinum toxin for bladder chemodenervation

2) The Oregon Surgicenter requested clarification of the guideline regarding botulinum toxin for bladder chemodenervation. Currently, GN219 requires that "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)." Oregon Surgicenter desired clarification as to whether beta-3 agonists such as Myrbetriq or Gemtesa would qualify. OHA P&T staff recently reviewed medications for overactive bladder and found no difference in efficacy between antimuscarinics or beta-3 agonists. P&T staff recommend modifying GN219 to allow beta-3 agonists to be one of the two medications required to be tried prior to chemodenervation.

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 or beta-3 adrenergic therapies (e.g. fesoterodine, oxybutynin, solifenacin, darifenacin, tolterodine, trospium, mirabegron, vibegron). 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.

COVID-19 Related Codes
November 2022

Issues:

1) New COVID vaccine codes were released for the booster of the Novavax vaccine

HERC staff recommendations:

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

CPT Code	Code Description
0044A	Immunization administration by intramuscular injection of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) (coronavirus disease [COVID-19]) vaccine, recombinant spike protein nanoparticle, saponinbased adjuvant, preservative free, 5 mcg/0.5 mL dosage; booster dose

November 2022 Consent Items

Issue: A dental care organization (DCO) requested consideration of additional diagnosis codes for line 256 DEFORMITIES OF HEAD AND HANDICAPPING MALOCCLUSION for use with the new handicapping malocclusion benefit. These conditions could also be used for people who might need orthodontia that meets the criteria specified in Guideline Note 169.

In addition, clarifications are needed to communicate that orthodontia services not included on line 256 appear on line 618 DENTAL CONDITIONS (E.G. MALOCCLUSION) / ORTHODONTIA (I.E. FIXED AND REMOVABLE APPLIANCES AND ASSOCIATED SURGICAL PROCEDURES) and line 645 DENTAL CONDITIONS WHERE TREATMENT IS CHOSEN PRIMARILY FOR AESTHETIC CONSIDERATIONS, where they are in 2022 to account for other services such as cosmetic orthodontia or cosmetic dentistry.

Staff have consulted with Dr. Stacy Geisler who recommends adding the following ICD-10-CM codes to line 256.

Planned coverage:
Diagnoses to be added to line 256 on 1/1/2023 (previously approved), with guideline note:

ICD-10 Code	Code description	Current placement (10/1/2022 List)
K00.1	Supernumerary teeth	645 DENTAL CONDITIONS WHERE TREATMENT IS CHOSEN PRIMARILY FOR AETHETIC CONSIDERATIONS
K00.2	Abnormalities of size and form of teeth	645
K00.5	Hereditary disturbances in tooth structure, not elsewhere classified	645
K00.6	Disturbances in tooth eruption	645
K00.9	Disorder of tooth development, unspecified	645
M26.211	Malocclusion, Angle's class I	618 DENTAL CONDITIONS (E.G., MALOCCLUSION)
M26.212	Malocclusion, Angle's class II	618
M26.213	Malocclusion, Angle's class II	618
M26.219	Malocclusion, Angle's class, unspecified	618
M26.220	Open anterior occlusal relationship	618
M26.221	Open posterior occlusal relationship	618
M26.23	Excessive horizontal overlap	618
M26.24	Reverse articulation	618
M26.25	Anomalies of interarch distance	618
M26.29	Other anomalies of dental arch relationship	618
M26.31	Crowding of fully erupted teeth	618
M26.33	Horizontal displacement of fully erupted tooth or teeth	618
M26.34	Vertical displacement of fully erupted tooth or teeth	618
M26.35	Rotation of fully erupted tooth or teeth	618
M26.36	Insufficient interocclusal distance of fully erupted teeth (ridge)	618

M26.37	Excessive interocclusal distance of fully erupted teeth	618
M26.4	Malocclusion, unspecified	618
M26.70	Unspecified alveolar anomaly	618
Z46.4	Encounter for fitting and adjustment of orthodontic device	618

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) Severe malocclusions with a Handicapping Labiolingual Deviation Index California Modification score of 26 or higher; AND
4) 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

Staff recommendation:

1. Add the ICD-10-CM codes listed below to the previously approved 1/1/2023 line 256 DEFORMITIES OF HEAD AND HANDICAPPING MALOCCLUSION TREATMENT: CRANIOTOMY/CRANIECTOMY; ORTHODONTIA

ICD-10 Code	**Code Description**	**Current Placement**
M26.01	Maxillary hyperplasia	617 ANOMALIES OF RELATIONSHIP OF JAW TO CRANIAL BASE, MAJOR ANOMALIES OF JAW SIZE, OTHER SPECIFIED AND UNSPECIFIED DENTOFACIAL ANOMALIES
M26.02	Maxillary hypoplasia	617
M26.03	Mandibular hyperplasia	617
M26.04	Mandibular hypoplasia	617
M26.05	Macrogenia	617
M26.06	Microgenia	617
M26.11	Maxillary asymmetry	617
M26.12	Other jaw asymmetry	617
M26.19	Other specified anomalies of jaw-cranial base relationship	617
M26.89	Other dentofacial anomalies	617
M26.9	Dentofacial anomaly, unspecified	617

2. Restore diagnoses previously moved to line 256 to also appear on line 267, 618 or 645 (where they are on the 10/2022 list), so they are present for cosmetic orthodontia. They will be added on line 256 effective January 1, 2023.

ICD-10 Code	Code description	Recommended Placement
K00.1	Supernumerary teeth	256, 645 DENTAL CONDITIONS WHERE TREATMENT IS CHOSEN PRIMARILY FOR AESTHETIC CONSIDERATIONS
K00.2	Abnormalities of size and form of teeth	256, 645
K00.5	Hereditary disturbances in tooth structure, not elsewhere classified	256, 645
K00.6	Disturbances in tooth eruption	256, 267 DENTAL CONDITIONS (TIME SENSITIVE EVENTS)
K00.9	Disorder of tooth development, unspecified	256, 645
M26.211	Malocclusion, Angle's class I	256, 618
M26.212	Malocclusion, Angle's class II	256, 618
M26.213	Malocclusion, Angle's class II	256, 618
M26.219	Malocclusion, Angle's class, unspecified	256, 618
M26.220	Open anterior occlusal relationship	256, 618
M26.221	Open posterior occlusal relationship	256, 618
M26.23	Excessive horizontal overlap	256, 618
M26.24	Reverse articulation	256, 618
M26.25	Anomalies of interarch distance	256, 618
M26.29	Other anomalies of dental arch relationship	256, 618
M26.31	Crowding of fully erupted teeth	256, 618
M26.33	Horizontal displacement of fully erupted tooth or teeth	256, 618
M26.34	Vertical displacement of fully erupted tooth or teeth	256, 618
M26.35	Rotation of fully erupted tooth or teeth	256, 618
M26.36	Insufficient interocclusal distance of fully erupted teeth (ridge)	256, 618
M26.37	Excessive interocclusal distance of fully erupted teeth	256, 618
M26.4	Malocclusion, unspecified	256, 618
M26.70	Unspecified alveolar anomaly	256, 618
Z46.4	Encounter for fitting and adjustment of orthodontic device	256, 618

3. Edit guideline note 169 as follows:

GUIDELINE NOTE 169, ORTHODONTICS FOR CRANIOFACIAL ANOMALIES AND HANDICAPPING MALOCCLUSION

Lines 256,618

Orthodontic treatment is included on ~~this~~ line 256 DEFORMITIES OF HEAD AND HANDICAPPING MALOCCLUSION TREATMENT: CRANIOTOMY/CRANIECTOMY; ORTHODONTIA 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) Severe malocclusions with a Handicapping Labiolingual Deviation Index California Modification score of 26 or higher; AND
4) 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

All other orthodontic services appear on line 618 DENTAL CONDITIONS (E.G., MALOCCLUSION).

Section 4.0

Items discussed with leadership

Items Discussed with Leadership with No Changes Recommended
Kyphoplasty

Plain Language Summary:
Background: A procedure in the neck (to vertebra) to treat painful fractures. A device manufacturer said the policy of not covering this treatment should be looked at again.

Should OHP cover this treatment? The Washington Health Technology Assessment report did not find good evidence to cover this procedure. The submitted literature was based expert panel opinion. The staff recommend no change in the current non-coverage of kyphoplasty.

Question: Should kyphoplasty be added as a treatment for vertebral fracture?

Question source: Medtronic

Issue: Kyphoplasty (also known as balloon-assisted vertebroplasty) is a minimally-invasive orthopedic procedure, which has been developed to restore bone height lost due to painful osteoporotic compression fractures. It involves the insertion of 1 or 2 balloon devices into the fractured vertebral body. Once inserted, the surgeon inflates the balloon(s) to create a cavity and to compact the deteriorated bone with the intent to restore vertebral height. The balloon(s) are then removed and the newly created cavity is filled with the surgeon's choice of bone filler material, creating an internal cast for the fractured area.

Kyphoplasty was last reviewed in 2016, when the 2013 coverage guidance VERTEBROPLASTY, KYPHOPLASTY, SACROPLASTY was affirmed. The 2013 review recommended that kyphoplasty only be covered for patients hospitalized with uncontrolled pain related to their vertebral fracture.

Current Prioritized List status
On line 478 CLOSED DISLOCATIONS/FRACTURES OF NON-CERVICAL VERTEBRAL COLUMN WITHOUT NEUROLOGIC INJURY OR STRUCTURAL INSTABILITY
CPT 22510-22512 (Percutaneous vertebroplasty)
CPT 22513-22515 (Percutaneous vertebral augmentation, including cavity creation (fracture reduction and bone biopsy included when performed) using mechanical device (eg, kyphoplasty), 1 vertebral body, unilateral or bilateral cannulation, inclusive of all imaging guidance)

GUIDELINE NOTE 109, VERTEBROPLASTY, KYPHOPLASTY, AND SACROPLASTY
Line 478
Vertebroplasty and kyphoplasty are not included on this line (or any other line) for the treatment of routine osteoporotic compression fractures.

Vertebroplasty and kyphoplasty are only included on this line for the treatment of vertebral osteoporotic compression fractures when they are considered non-routine and meet all of the following conditions:

A) The patient is hospitalized under inpatient status due to pain that is primarily related to a well-documented acute fracture, and

B) The severity of the pain prevents unassisted ambulation, and
C) The pain is not adequately controlled with oral or transcutaneous medication, and
D) The patient must have failed an appropriate 4-to-6 week trial of conservative management.

Sacroplasty is not included on these or any lines of the Prioritized List for coverage consideration.

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

From Medtronic:

> It recently came to our attention that a patient in Oregon who is covered by Medicaid was denied prior authorization for BKP. Our understanding is that prior authorization was denied because the patient is not hospitalized under inpatient status due to back pain. Given that BKP is usually done in a physician office, we reviewed the current coverage guidance which was approved in 2013 and affirmed in 2016. The guidance references outdated Current Procedural Terminology (CPT)® coding for both BKP and a related therapy called vertebroplasty (codes 22520, 22521, 22522 for vertebroplasty and 22523, 22524, and 22525 for BKP). Current coding was adopted in 2015 and utilizes 22510, 22511, 22512 for vertebroplasty and 22513, 22514, and 22515 for BKP. For additional detail, you can access Medtronic's current Reimbursement Coding and Payment Guides for both therapies.
>
> In addition to these coding updates, I wanted to make sure HERC is aware that the RAND™/UCLA Appropriateness Method (RAM), used by a multispecialty expert panel, helped establish a clinical care pathway for patients with vertebral compression fractures (VCF) in 2018. This pathway includes key signs and symptoms of suspected VCF, diagnostic evaluation of patients with suspected VCF, appropriateness criteria for vertebral augmentation or non-surgical management, contraindications, and follow up after treatment recommendations. After reviewing the publication, Medicare and other local commercial plans understood the clinical importance of having vertebral fracture patients treated early. In fact, each of the Medicare Administrative Contractors (MACs) and some commercial payers have used this clinical publication to update their requirements and now require acute treatment of vertebral fractures.

Evidence

1) **Washington HTA 2020**, Vertebroplasty, Kyphoplasty, Sacroplasty: Assessing Signals for Update - https://www.hca.wa.gov/assets/program/signal-search-vertebroplasty-kyphoplasty-sacroplasty-20200708.pdf
    a. HTA 2010 review did not find sufficient evidence to cover kyphoplasty
        i. "the evidence for the procedure remains low and the efficacy, safety and economic impact are not well understood."
        ii. "In addition to typical complications from invasive procedures, cementoplasty techniques include risk of possible increase of subsequent compression fractures near a cemented vertebra due to increased rigidity of the treated vertebrae and risk of cement leakage"

b. This report is an update of a 2016 signal review
c. A total of three unblinded RCTs (2 new) comparing kyphoplasty (KP) with conservative medical care (usual care) in patients with osteoporotic fractures have been identified.
    i. The three RCTs together suggest that KP may be associated with improved pain and function versus CMT but clinical importance is unclear; the two new poor quality trials are not considered pivotal and do not change the conclusions from the previous report (criteria A-1 or A3), nor provide major changes in the evidence (criteria B1-B4).
    ii. Safety: Data on safety were poorly reported in studies comparing KP with CMT specifically; they do not change the conclusions from the previous report for this comparison (criteria Criterion A2).
    iii. Cost-effectiveness: Findings of economic studies do not change the conclusions from the previous report (criteria A-1 or A-3), nor provide major changes in the evidence (criteria B-1).

Medline search for kyphoplasty and RCT from 2020-2022 did not find any trials comparing kyphoplasty to conservative treatment.

Submitted literature

1) **Hirsch 2018**, Management of vertebral fragility fractures: a clinical care pathway developed by a multispecialty panel using the RAND/UCLA Appropriateness Method
    a. Funded by Medtronic, all authors reported funding by Medtronic
    b. 12 member expert panel consensus report
    c. Unclear what literature was reviewed
    d. Vertebral augmentation was considered appropriate in patients with positive findings on advanced imaging and in whom symptoms had worsened and in patients with 2 to 4 unfavorable conditions (eg, progression of height loss and severe impact on functioning), dependent on their relative weight. Time since fracture was considered less relevant for treatment choice.
    e. In conclusion, using the RUAM a multispecialty expert panel established a CCP that may guide clinicians to make informed and reasoned decisions on the detection, diagnostic evaluation, treatment choice, and follow-up of patients with or suspected of having a VFF. The pathway may be helpful to reduce undesirable practice variations and improve quality of care. However, validity of the recommendations and usefulness in daily practice needs further research.

HERC staff summary

A recent Washington HTA evidence search did not find studies that showed that kyphoplasty results in clinically meaningful improvement in pain or function. Submitted literature consists of an expert panel opinion report. Staff recommends maintaining the current prioritization and guideline note.

HERC staff recommendation:

1) Make no change in the current prioritization of kyphoplasty

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Technical Report

Management of vertebral fragility fractures: a clinical care pathway developed by a multispecialty panel using the RAND/UCLA Appropriateness Method

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Abstract

BACKGROUND CONTEXT: Vertebral fragility fractures (VFFs), mostly due to osteoporosis, are very common and are associated with significant morbidity and mortality. There is a lack of consensus on the appropriate management of patients with or suspected of having a VFF.
PURPOSE: This work aimed at developing a comprehensive clinical care pathway (CCP) for VFF.
STUDY DESIGN/SETTING: The RAND/UCLA Appropriateness Method was used to develop patient-specific recommendations for the various components of the CCP. The study included two individual rating rounds and two plenary discussion sessions.

FDA device/drug status: Not applicable.

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Neurofeedback and Biofeedback for Trauma

Plain Language Summary:
Background: Techniques and equipment that help you learn to control bodily functions such as heart rate or breathing. A subcommittee member asked if these techniques should be covered for children with a history of trauma.

Should OHP cover this treatment? Staff recommends to not cover this treatment because no new evidence exists to show that biofeedback and/or neurofeedback for PTSD of childhood trauma works.

Question: Should neurofeedback and/or biofeedback be paired with trauma, PTSD, or additional indications?

Question source: Lisa Kouzes, DC

Issue: Dr. Kouzes has requested consideration of neurofeedback and/or biofeedback for children with a history of trauma. Biofeedback is a non-invasive psychophysiological treatment technique with a bio-monitoring system and sensors to measure, amplify, and feedback information that enables an individual to learn how to change physiological activity (such as respiration, heart rate variability, blood flow and blood pressure) and thus improve health and performance. Neurofeedback is a specific type of biofeedback. Biofeedback has been used for the treatment of migraine headaches, urinary incontinence, pelvic floor dysfunction, and cancer pain. Neurofeedback focusses on the central nervous system and the brain to improve neuro regulation and stabilization.

From Dr. Kouzes:

> I came across a person who works in Oregon's foster care system as an administrator. She notes that a lot of families are turning to neurofeedback for their foster kids with significant histories of trauma. She reports good results anecdotally and notes that it is not covered by OHP and families are spending a lot out-of-pocket for it. She has found that once families become proficient at the neurofeedback in-office, they are purchasing a unit for home use...
> I looked at the literature and found this RCT: Rogel, A., et al. (2020).
>
> I also did a lot more searching and found there is gaining momentum for neurofeedback, biofeedback, and computer games/apps as adjunct or supplemental interventions (often for home use) for kids. Given the behavioral health system is strained in OR, I was wondering if the HERC would consider evaluating neurofeedback as a covered services for kids suffering from psychological trauma, and/or look into what in-office and/or at-home electronic devices/apps might benefit OHP members for mental health conditions

Previous HSC/HERC review history
Review of old minutes finds that 90901 was on all the cancer lines at one point. In May 2004, the HSC removed 90901 from all lines and placed on the Never Covered File.

In January 2021, biofeedback was formally reviewed. That review included a CADTH 2017 systematic review of neurofeedback and biofeedback for mood and anxiety disorders and a 2019 evidence review of biofeedback for medical conditions from the VA Evidence Synthesis Program. This topic was reviewed by the Behavioral Health Advisory Panel who advised that biofeedback should not be added to any behavioral health or SUD lines. The HERC staff summary from the 2021 review read in part: “There is no evidence supporting the use of biofeedback for the treatment of mental health conditions, and no

private payer is covering biofeedback for this indication. BHAP does not recommend its use for behavioral health conditions."

Current Prioritized List status

CPT 90875 and 90876 (Individual psychophysiological therapy incorporating biofeedback training by any modality (face-to-face with the patient), with psychotherapy (eg, insight oriented, behavior modifying or supportive psychotherapy); 30/45 minutes) are on lines 410 MIGRAINE HEADACHES, 541 TENSION HEADACHES

CPT 90901 (Biofeedback training by any modality) is on lines 410, 541

Evidence:

1) **Rogel 2020**, RCT on impact of neurofeedback on children with developmental trauma
    a. N=37
        i. N=20 neurofeedback, 17 usual treatment
        ii. Follow up 4 months
    b. This pilot study demonstrated that 24 sessions of NFT significantly decreased PTSD symptoms, internalizing, externalizing, other behavioral and emotional symptoms, and significantly improved the executive functioning of children aged 6 –13 years with severe histories of abuse and neglect who had not significantly benefited from any previous therapy.
    c. Conclusions: NFT offers the possibility to improve learning, enhance self-efficacy, and develop better social relationships in this hitherto largely treatment-resistant population

No additional RCTs or systematic reviews identified

HERC staff summary: No significant new evidence has emerged regarding efficacy of biofeedback and/or neurofeedback for PTSD or childhood trauma.

HERC staff recommendation:

1) Make no change in lack of pairing of biofeedback or neurofeedback with PTSD or related conditions

AMERICAN PSYCHOLOGICAL ASSOCIATION
DIVISION 56 TRAUMA PSYCHOLOGY AMERICAN PSYCHOLOGICAL ASSOCIATION

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The Impact of Neurofeedback Training on Children With Developmental Trauma: A Randomized Controlled Study

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Objective: Developmental trauma or chronic early childhood exposure to abuse and neglect by caregivers has been shown to have a long-lasting pervasive impact on mental and neural development, including problems with attention, impulse control, self-regulation, and executive functioning. Its long-term effects are arguably the costliest public health challenge in the United States. Children with developmental trauma rarely have a satisfactory response to currently available evidence-based psychotherapeutic and pharmacological treatments. Neurofeedback training (NFT) is a clinical application of brain computer interface technology, aiming to alter electrical brain activity associated with various mental dysfunctions. NFT has shown promise to improve posttraumatic stress disorder (PTSD) symptoms. ***Method:*** This randomized controlled study examined the effects of NFT on 37 children, aged 6–13 years with developmental trauma. Participants were randomly divided into active NFT ($n = 20$) or treatment-as-usual control ($n = 17$). Both groups underwent 4 assessments during equivalent timelines. The active group received 24 NFT sessions twice a week. ***Results:*** This pilot study demonstrated that 24 sessions of NFT significantly decreased PTSD symptoms, internalizing, externalizing, other behavioral and emotional symptoms, and significantly improved the executive functioning of children aged 6–13 years with severe histories of abuse and neglect who had not significantly benefited from any previous therapy. ***Conclusions:*** NFT offers the possibility to improve learning, enhance self-efficacy, and develop better social relationships in this hitherto largely treatment-resistant population.

Clinical Impact Statement

Abuse and neglect of children by caregivers often have long-lasting and pervasive effects on mental and neural development, including problems with attention, impulse control, self-regulation, and executive functioning. Impairment of affect regulation is thought to be the largest obstacle to effective intervention. In this pilot study of neurofeedback for polysymptomatic children with such histories, we found a significant improvement on affect regulation and executive functioning after 24 sessions of neurofeedback treatment. This offers the possibility of being able to improve learning, enhance self-efficacy, and develop better social relationships in this hitherto largely treatment resistant population.

Keywords: neurofeedback, children, developmental trauma, posttraumatic stress disorder (PTSD)

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Items Discussed with Leadership with No Changes Recommended
Pneumatic Compression Devices for Lymphedema Therapy

Plain Language Summary:
Background: A pump with varying pressure which fills an inflatable garment with compressed air used to treat abnormal swelling of the arms or legs. A device manufacturer requested a re-review.

Should OHP cover this treatment? Staff recommends no change in the status of non-coverage of this device because there is no evidence that this treatment adds any additional benefit to standard lymphedema therapy.

Question: Should pneumatic compression devices be included as a treatment for lymphedema?

Question source: BioTAB Healthcare

Issue:
Pneumatic compression devices are used to treatment lymphedema, which is a swelling of the upper or lower extremity. Lymphedema can be idiopathic or caused by surgery, particularly lymph node removal. BioTAB Healthcare is requesting a review of the non-coverage of this technology.

The last review of pneumatic compression devices for lymphedema was conducted in 2019. That review included a 2010 AHRQ and a 2017 CADTH technology review. The conclusion of the 2019 review was "The evidence for the use of pneumatic compression devices for treatment of lymphedema is of low quality. The limited evidence base suggests that intermittent pneumatic compression (IPC) may not provide additional benefits when used in combination with the routine management of lymphedema." The HCPCS codes for these devices were placed on line 662/GN173 as a result of that review.

BioTAB Healthcare is requesting a re-review based on a study of 128 patients that showed reduced hospitalization, a study of 69 patients showing reduced symptoms and hospitalization, and an economic study showing a reduction in medical costs. Biotab's presentation includes an indication of chronic venous insufficiency, but no evidence to support this indication is mentioned.

Items Discussed with Leadership with No Changes Recommended
Pneumatic Compression Devices for Lymphedema Therapy

Current Prioritized List status:

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

Line 662

The following Interventions are prioritized on Line 662 CONDITIONS FOR WHICH CERTAIN INTERVENTIONS ARE UNPROVEN, HAVE NO CLINICALLY IMPORTANT BENEFIT OR HAVE HARMS THAT OUTWEIGH BENEFITS:

Procedure Code	Intervention Description	Rationale	Last Review
E0650-E0673, E0676	Pneumatic compressors and associated appliances, including intermittent devices	Insufficient evidence of effectiveness	May, 2019

ICD-10-CM I87.2 Venous insufficiency (chronic) (peripheral) is on line 639 VARICOSE VEINS OF LOWER EXTREMITIES WITHOUT ULCER OR OTHER MAJOR COMPLICATION

ICD-10-CM I89.0 Lymphedema, not elsewhere classified is on line 422 LYMPHEDEMA

Items Discussed with Leadership with No Changes Recommended
Pneumatic Compression Devices for Lymphedema Therapy

Evidence
Limited review for studies published in 2019 or later

1) **Desai 2019**
    a. Prospective cohort study
        i. N=128 patients (232 extremities)
        ii. Patients were not described as participating in routine decongestive treatment
        iii. Funded by Bio Compression Systems, Inc
    b. Pneumatic compression therapy was utilized for all patients and led to a 28% decrease in absolute limb volume ($P < 0.001$), decrease in body mass index (BMI) ($P < 0.001$), significant improvement in SF-36 quality of life in 7 out of 8 domains ($P < 0.001$), and a significant improvement in LLCS ($P < 0.001$) at 1 year. A subsequent decrease in hospitalization for lymphedema-associated complications saved over $3,200 per patient per year.
2) **Tastaban 2020**
    a. RCT of decongestive treatment with or without intermittent pneumatic compression
        i. N=76 patients
            1. N=38 standard treatment (complex decongestive therapy)
            2. N=38 complex decongestive therapy + intermittent pneumatic compression
    b. Lymphoedema was similar at baseline, but treatments significantly reduced the excess volume (from 373mL to 203mL in Group 1 (complex decongestive treatment) and 379.5 mL to 189.5mL in Group 2 (complex decongestive treatment + pneumatic compression). Percentage excess volumes (PEVs) decreased in both groups. The percentage reduction of excess volume was better in Group 2 than Group 1, but the intergroup difference was not significant. The clinical scores reflected improvements, but the heaviness and tightness read significantly lower in Group 2 than Group 1.
    c. Conclusion: Intermittent pneumatic compression seems to add no benefit when combined with complex decongestive treatment of lymphoedema, but, may be functional in reducing the sensations of heaviness and tightness for the patients with pitting edema (a clinical sign of fluid overload).
3) **Modanado 2021**
    a. Prospective cohort study
        i. N=74 patients
        ii. Generally older men with phlebolymphdema
        iii. Study participants were withdrawn if they did not use the device at least 3 times a week by the 4^{th} week of enrollment
        iv. Patients did not appear to be in routine decongestive therapy
        v. 81% of patients wore static compression garments during study (not report percent wearing prior to study)
        vi. Study supported by Tactile Medical
    b. No significant difference was seen in QOL at 12 weeks. However, at 52 weeks, the Lymphedema Quality of Life scores had significantly improved from baseline

(6.3 vs 7.4; P < .0001) and the short form-36 had demonstrated significant improvement from baseline in the physical component (38.6 vs 40.8; P = .035), with an effect toward overall improvement in the mental component (49.9 vs 51.3; P = .549).

c. APCD treatment was associated with a significant reduction in cellulitis episodes (24.3% vs 8.1%; P ¼ .005), lymphedema-related clinic visits (2.2 vs 0.7; P ¼ .02), urgent care visits (1.2 vs 0.3; P ¼ .004), and hospital admissions (0.5 vs 0.1; P ¼ .047) per patient.

Other Payer policies

Anthem BCBS 2022

Single or multi-chamber or segment *non-programmable* compression devices for the treatment of upper or lower limb lymphedema are considered **medically necessary** when:

A. The individual's lymphedema is not improving; **and**
B. The individual has been compliant with conservative therapy (that is, elevation of the affected limb, exercise, massage, use of an appropriate compression bandage system or compression garment).

Single or multi-chamber or segment *programmable* (for example, calibrated gradient pressure) compression devices for the treatment of upper or lower limb lymphedema are considered **medically necessary** when criteria above for a non-programmable compression device are met and *either* criteria A or criteria B below have been met:

Criteria A:

1. A single or multi-chamber or segment *non-programmable* compression device has been tried for a minimum of 3 months; **and**
2. There is documentation of compliance with treatment with the *non-programmable* pneumatic compression device; **and**
3. The records provide objective documentation that lymphedema has progressed;

or

Criteria B:

1. There is clear documentation of a condition that prevents the satisfactory treatment of lymphedema with a *non-programmable* device. Such conditions may include, but are not limited to the following:
    a. Contracture; **or**
    b. Sensitive skin; **or**
    c. Significant scarring.

Items Discussed with Leadership with No Changes Recommended
Pneumatic Compression Devices for Lymphedema Therapy

HERC staff summary

The evidence for the use of pneumatic compression devices for treatment of lymphedema continues to be of low quality. The limited evidence base suggests that intermittent pneumatic compression (IPC) may not provide additional benefits when used in combination with the routine management of lymphedema.

Studies published since the last review in 2019 either showed no benefit of intermittent pneumatic compression in addition to standard decompressive therapy, or were cohort studies with no comparison to this standard of care.

For patients who are unable to access standard decompressive therapy, pneumatic compression devices might be considered as an alternative treatment option; however, this would not be standard of care.

HERC staff recommendation

1) Make no change in the current non-coverage of pneumatic compression devices for lymphedema therapy
    a. Update the date of last review in GN173

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

Line 660

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
E0650-E0673, E0676	Pneumatic compressor Segmental pneumatic appliance for use with pneumatic compressor	Insufficient evidence of effectiveness	~~May, 2019~~ November, 2022

Superior Clinical, Quality of Life, Functional, and Health Economic Outcomes with Pneumatic Compression Therapy for Lymphedema

Sapan S. Desai,[1] and Michael Shao,[2] on behalf of the Vascular Outcomes Collaborative, Chicago, Illinois

Background: Pneumatic compression therapy is one of several options for the management of lymphedema. The lack of clarity around clinical outcomes, quality of life, cost of care, and its proper application, as a function of lymphedema complexity, limit its use in clinical practice. This is compounded by difficulties associated with insurance approval and uncertainty about the role of this modality in the treatment algorithm. The purpose of this study is to elucidate the healthcare economics and value of pneumatic compression therapy for lymphedema.

Methods: All patients who underwent treatment for lymphedema at a single institution were followed prospectively over a 2-year period. Patient demographics, comorbidities, treatment modality, and treatment efficacy were determined. Direct costs over the 2-year period, inclusive of hospitalization and device costs, SF-36 quality of life, and leg lymphedema complexity score (LLCS), were measured.

Results: A total of 128 patients were enrolled over a period of 3 years for a total of 232 extremities treated for secondary lymphedema. Pneumatic compression therapy was utilized for all patients and led to a 28% decrease in absolute limb volume ($P < 0.001$), decrease in body mass index (BMI) ($P < 0.001$), significant improvement in SF-36 quality of life in 7 out of 8 domains ($P < 0.001$), and a significant improvement in LLCS ($P < 0.001$) at 1 year. A subsequent decrease in hospitalization for lymphedema-associated complications saved over $3,200 per patient per year.

Conclusions: Pneumatic compression therapy leads to improved clinical outcomes, quality of life, and functional status for clinically significant lymphedema. Significant per capita direct cost savings, a beneficial impact on pay for performance measures, and a reduction in lymphedema-related complications suggest that earlier adoption of this treatment modality may offer a superior value proposition to patients, physicians, hospitals, and the healthcare system.

Funding: This research was supported by an unrestricted educational grant provided by Bio Compression Systems, Inc.

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INTRODUCTION

Lymphedema is a vexing problem both in terms of clinical diagnosis and treatment. Treatment modalities include manual lymphatic drainage (MLD), medically prescribed compression garments, and pneumatic compression therapy. Although a number of surgical procedures have also been described for the management of recalcitrant lymphedema, these procedures are uncommon due to their significant morbidity.[1]

The effectiveness of MLD alone as a singular treatment modality is controversial. Prospectively

Original Article

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Role of intermittent pneumatic compression in the treatment of breast cancer–related lymphoedema: a randomized controlled trial

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Abstract

Objective: To evaluate the role of intermittent pneumatic compression in the treatment of breast cancer–related lymphoedema.

Design: Randomized controlled trial.

Setting: Physical medicine and rehabilitation clinic at a university hospital.

Subjects: Seventy-six patients with lymphoedema.

Interventions: Patients were allocated into Group 1 (complex decongestive treatment, $n = 38$) and Group 2 (complex decongestive treatment + intermittent pneumatic compression, $n = 38$). The complex decongestive treatment involved skin care, manual lymphatic drainage, compression bandaging, and exercise for 20 sessions. Group 2 additionally received intermittent pneumatic compression.

Main measures: Quantitative outcomes consisted of volumetric measures prior to and after the treatment. Clinical assessments included severity of pain, heaviness and tightness, disability, grip strength, and depression.

Results: Lymphoedema was similar at baseline, but treatments significantly reduced the excess volume (from 373 mL to 203 mL in Group 1 and 379.5 mL to 189.5 mL in Group 2). Percentage excess volumes (PEVs) decreased in both groups. The percentage reduction of excess volume was better in Group 2 than Group 1, but the intergroup difference was not significant. The clinical scores reflected improvements, but the heaviness and tightness read significantly lower in Group 2 than Group 1.

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Conclusion: Intermittent pneumatic compression seems to add no benefit when combined with complex decongestive treatment of lymphoedema, but, may be functional in reducing the sensations of heaviness and tightness for the patients with pitting oedema.

Keywords
Breast cancer–related lymphoedema, complex decongestive therapy, intermittent pneumatic compression

Date received: 26 April 2019; accepted: 22 October 2019

Introduction

Despite the progress made in early diagnosis and treatment, breast cancer–related lymphoedema still remains a major complication and hinders the patient management.[1] Its incidence ranges from 14% to 40% due to the preferences in treatment approaches.[2] The clinical signs of breast cancer–related lymphoedema such as swelling, pain, tightness, heaviness, impaired limb function, and psychosocial disturbances generally depend on the duration and severity of the disease.[3] The treatment of breast cancer–related lymphoedema mainly focuses on volume reduction and maintenance while controlling the symptoms and preventing the complications.[4,5]

Complex decongestive treatment of breast cancer–related lymphoedema is an accepted strategy and considered as an international standard for treatment.[6] A previous review concluded that complex decongestive therapy has a positive impact on the volume of arm and quality of life in different stages of lymphoedema.[7] However, other auxiliary options are also currently explored. Intermittent pneumatic compression is one of those and implemented to address oedema formation in the arm.[8] In principle, the applied compression acts as a muscle pump and facilitates lymphatic flow by creating gradual pressure gradients on lymphatic vessels.

According to a systematic review and meta-analysis, intermittent pneumatic compression reported to be beneficial in reducing oedema volume in the acute phase of treatment.[9] When instituted properly, it is possible to achieve an extremity volume reduction from 3% to 66% depending on the therapeutic regimen.[10] However, the role of intermittent pneumatic compression combined with complex decongestive therapy is still debated, as the 2016 Consensus Document of the International Society of Lymphology states that the act of combining intermittent pneumatic compression with manual lymph drainage is yet to be evaluated sufficiently.[11]

The aim of this study is to establish the value of intermittent pneumatic compression by investigating its effectiveness and contribution to complex decongestive therapy in recovery from breast cancer–related lymphoedema under a clinical trial setting.

Methods

The study was registered at ClinicalTrials.gov (NCT03992508) and designed as a randomized controlled trial as shown by the flow diagram in Figure 1. The study protocol was approved by Adnan Menderes University Medical Faculty Ethics Committee with the decision no. 2012/99. Participants were recruited from Adnan Menderes University Physical Medicine and Rehabilitation in-patient clinic between November 2012 and December 2018. Power analysis performed with alfa = 0.05 and statistical power = 0.80 yielded 26 as minimum sample size, but our enrollment exceeded this number substantially ($n = 38$) for producing meaningful data.

Patients who diagnosed with unilateral arm lymphoedema related to breast cancer were enrolled in the study after signing an informed consent form. Inclusion criteria were having surgical intervention due to unilateral breast cancer, completed chemotherapy and radiotherapy, and more than 2 cm difference at the circumference measurements or >10%

Assessment of quality of life changes in patients with lower extremity lymphedema using an advanced pneumatic compression device at home

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ABSTRACT

Objective: Lymphedema is associated with significant morbidity and healthcare resource usage. Conventional therapy efficacy has been limited, with poor surgical salvage options. Preliminary studies have demonstrated that the use of advanced pneumatic compression devices (APCDs) improves clinical outcomes. However, limited evidence regarding their role in healthcare cost mitigation or health-related quality of life (QOL) is available.

Methods: The present postmarket, multicenter, single-arm, observational clinical trial conducted in the Veterans Affairs Healthcare System evaluated patients with a diagnosis of primary or secondary edema of unilateral or bilateral lower extremities treated with the Flexitouch APCD (Tactile Medical, Minneapolis, Minn) from February 2016 to March 2019. The patients were assessed at baseline and 12, 24, and 52 weeks from enrollment by limb circumference, QOL assessments (short form-36 and Lymphedema Quality of Life), device compliance, cellulitis episodes, and lymphedema-related healthcare use since the previous visit. The primary endpoints of interest were the QOL at baseline compared with at 12 weeks, unscheduled lymphedema-related clinic visits, and hospital admissions at 52 weeks. The secondary endpoints included the change in limb girth and QOL at 52 weeks compared with baseline.

Results: A total of 178 patients with lower extremity lymphedema were prospectively enrolled. The present study reports the interim data for the first 74 subjects to complete 52 weeks of APCD treatment. The cohort was predominately male (94.6%), elderly (mean age, 67 years), obese (median body mass index, 32 kg/m^2), and most commonly enrolled for the treatment of phlebolymphedema (71.6%) with largely bilateral lower extremity involvement (91.9%). No significant difference was seen in QOL at 12 weeks. However, at 52 weeks, the Lymphedema Quality of Life scores had significantly improved from baseline (6.3 vs 7.4; $P < .0001$) and the short form-36 had demonstrated significant improvement from baseline in the physical component (38.6 vs 40.8; $P = .035$), with an effect toward overall improvement in the mental component (49.9 vs 51.3; $P = .549$). The limb circumference had decreased significantly at 12 weeks compared with baseline (28.5 cm vs 27.7 cm; $P = .0005$) in the most affected lower extremity, and this reduction had remained stable for the study duration. APCD treatment was associated with a significant reduction in cellulitis episodes (24.3% vs 8.1%; $P = .005$), lymphedema-related clinic visits (2.2 vs 0.7; $P = .02$), urgent care visits (1.2 vs 0.3; $P = .004$), and hospital admissions (0.5 vs 0.1; $P = .047$) per patient.

Conclusions: The Flexitouch APCD resulted in initial significant limb girth reduction as early as 12 weeks and a steady and sustained improvement in health-related QOL for ≤1 year. The latter was likely reflective of a decrease in cellulitis episodes and fewer associated lymphedema-related clinic and urgent care visits and hospital admissions. (J Vasc Surg Venous Lymphat Disord 2021;9:745-52.)

Keywords: Cellulitis; Chronic venous insufficiency; FLX; Lymphedema; Phlebolymphedema; Pneumatic compression; Quality of life

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Section 5.0

Staff Report

Errata
November 2022

On November 7, the following correction was made:

1. Line 465 COLLAPSED LUNG was erroneously attached to Guideline Note 118 SEPTOPLASTY. This was corrected to Line 466 CHRONIC SINUSITIS.

On October 20, 2022, the following two corrections were made:

1. The line numbers for Guideline Note 227 GASTRIC ELECTRICAL STIMULATION were corrected:

GUIDELINE NOTE 227, GASTRIC ELECTRICAL STIMULATION
Lines 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:

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

2. The sentence structure for Guideline Note 144 PROTON PUMP INHIBITOR THERAPY FOR GASTROESOPHAGEAL REFLUX DISEASE (GERD) was clarified:

GUIDELINE NOTE 144, PROTON PUMP INHIBITOR THERAPY FOR GASTROESOPHAGEAL REFLUX DISEASE (GERD)
Lines 314, 380, 513

Short term treatment (up to 8 weeks) of GERD without Barrett's (ICD-10-CM K20.8, K20.9, K21.0, K21.9) with proton pump inhibitor therapy is included on Line 380. Long term treatment is included on Line 513.

Long term proton pump inhibitor therapy is included on Line 380 for Barrett's esophagus (ICD-10-CM K22.70) and on Line 314 for Barrett's esophagus with dysplasia (ICD-10-CM K22.71).

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)
Staff review	Broader Orthopedic review	11/17/2022		Resolved with other issues (deformities of foot, knee)
BHAP request	Personality disorders	11/17/2022		Reviewed with BHAP, no changes recommended
Dr. Hoffman	Congenital ear anomalies without hearing impairment	10/6/2022	1/1/2023	Added coverage of microtia with a new guideline.
Staff review	Somatic symptoms line (Extreme feelings and anxiety about physical symptoms)	10/6/2022	1/1/2023	Housekeeping changes only.
Staff review	Deformities of upper body and all limbs	10/6/2022	1/1/2023	Housekeeping changes only.
Staff review	Genitourinary with minimal or no treatment required (genital and urinary organs)	10/6/2022	1/1/2023	Minor changes made.
Staff review	Deformities of foot	10/6/2022		Housekeeping changes only.
Dr. Hoffman	Conduct disorder/impulse disorders (A type of behavior disorder)	8/11/2022	1/1/2022	BHAP recommended adding to funded region
Staff review	Behavioral health coding	8/11/2022	1/1/2022	Based on review of social emotional learning codes.
Staff review	Sleep disorders other than sleep apnea (including insomnia)	8/11/2022	1/1/2023	Consider adding insomnia above the funding line for cognitive behavioral therapy for insomnia (CBTi). Consider role of medication.
HSD nurse reviewer	Median and radial nerve lesions	8/11/2022	1/1/2022	Proposal to add to covered nerve lesion line with ulnar nerve lesions

Request source	Topic Description	Meeting Date	Planned Imp. Date	Summary of change (or recommended change, decision not to change)
Staff review	Benign neoplasm of the digestive system (Surgery for an abnormal growth found in the stomach or intestines)	5/19/2022		Added benign carcinoid tumors to funded region
HSD	Bilateral bone anchored hearing aids (BAHA) (A specific type of hearing aid for children)	5/19/2022	10/1/2022	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	10/1/2022	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	10/1/2022	Propose to rename line "Minor" as diagnoses are minor
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
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
CCO	Dorsal rhizotomy	3/10/2022	10/1/2022	Added to funded region
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)
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
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
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
Staff review	Congenital anomalies of knee (Knee problems since birth)	10/6/2022	n/a	No change made.
Staff (Val King)	Temporomandibular Joint Syndrome (TMJ) (Pain and dysfunction in the jaw joint and muscles controlling jaw movement)	8/11/2022		Review evidence; no change recommended at this time

Request source	Topic Description	Meeting Date	Planned Imp. Date	Summary of change (or recommended change, decision not to change)
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
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

Request source	Topic Description	Meeting Date	Planned Imp. Date	Summary of change (or recommended change, decision not to change)
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	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
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

Request source	Topic Description	Meeting Date	Planned Imp. Date	Summary of change (or recommended change, decision not to change)
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.

Section 6.0

OHAP report

CDT CODE	NOMENCLATURE	Comments	Recommended Placement
D0372	intraoral tomosynthesis – comprehensive series of radiographic	Replaces traditional dental xrays. DCO group felt that these systems are too new to have comparative data and recommended non-coverage. Not widely available.	EXCLUDED FILE
D0373	intraoral tomosynthesis - bitewing – radiographic image	See D0372	EXCLUDED FILE
D0374	intraoral tomosynthesis - periapical radiographic image	See D0372	EXCLUDED FILE
D0387	intraoral tomosynthesis – comprehensive series of radiographic images – capture only	See D0372	EXCLUDED FILE
D0388	intraoral tomosynthesis bitewing – radiographic image - capture only	Used for techician time	EXCLUDED FILE
D0389	intraoral tomosynthesis - periapical radiographic image – capture only	Used for techician time	EXCLUDED FILE
D0801	3D dental surface scan – direct	Used for orthodontia (e.g. handicapping maloclusion); the guideline for handicapping maloclusion already limits advanced imaging on line 256: "Advanced dental imaging is included on this line only when required for surgical planning for repair of craniofacial anomalies." Replaces D0351 (3d photographic image) which is currently on the Excluded File	256 DEFORMITIES OF HEAD Modify GN169 regarding advanced imaging: "Advanced dental imaging is included on this line only when required for surgical planning for repair of craniofacial anomalies and handicapping malocclusion."
D0802	3D dental surface scan – indirect	See D0802	256 DEFORMITIES OF HEAD
D0803	3D facial surface scan – direct	Replaces D0351 (3d photographic image) which is Excluded. The facial scan is used mainly for aesthetic purposes. Facial CT is already covered for evaluation of craniofacial anomalies	EXCLUDED FILE
D0804	3D facial surface scan – indirect	See D0804	EXCLUDED FILE

CDT CODE	NOMENCLATURE	Comments	Recommended Placement
D1781	vaccine administration – human papillomavirus		3 PREVENTION SERVICES WITH EVIDENCE OF EFFECTIVENESS
D1782	vaccine administration – human papillomavirus		3 PREVENTION SERVICES WITH EVIDENCE OF EFFECTIVENESS
D1783	vaccine administration – human papillomavirus		3 PREVENTION SERVICES WITH EVIDENCE OF EFFECTIVENESS
D4286	removal of non-resorbable barrier	OHAP recommended placement on line 492 DENTAL CONDITIONS (E.G., PERIODONTAL DISEASE) Treatment: ADVANCED PERIODONTICS (E.G., SURGICAL PROCEDURES AND SPLINTING). The rationale was that other periodontal codes are on line 492 and could be approved by exception for coverage if there was severe infection or other complication	492 DENTAL CONDITIONS (E.G., PERIODONTAL DISEASE)
D6105	removal of implant body not requiring bone removal nor flap elevation	see separate issue	344 DENTAL CONDITIONS (E.G., SEVERE CARIES, INFECTION) 619 DENTAL CONDITIONS (E.G., MISSING TEETH)
D6106	guided tissue regeneration – resorbable barrier, per implant	Dental implant related procedure. Similar codes are on line 619	619 DENTAL CONDITIONS (E.G., MISSING TEETH)
D6107	guided tissue regeneration – non-resorbable barrier, per implant	see D6107	619 DENTAL CONDITIONS (E.G., MISSING TEETH)
D6197	replacement of restorative material used to close an access opening of a screw-retained implant supported prosthesis, per implant	see D6107	619 DENTAL CONDITIONS (E.G., MISSING TEETH)

CDT CODE	NOMENCLATURE	Comments	Recommended Placement
D7509	marsupialization of odontogenic cyst	Removal of odontogenic cyst (D7450-D7451) are on lines 344 and 627 treatment of cyst-cover. Line 627 is a medical line only	344 DENTAL CONDITIONS (E.G., SEVERE CARIES, INFECTION) *additional coding change: remove D7450 and D7451 from line 627 BENIGN NEOPLASMS OF SKIN AND OTHER SOFT TISSUES
D7956	Guided tissue regeneration, edentulous area – resorbable barrier, per site	Similar codes are on line 646	646 DENTAL CONDITIONS WHERE TREATMENT RESULTS IN MARGINAL IMPROVEMENT
D7957	guided tissue regeneration, edentulous area – non-resorbable barrier, per site	Similar codes are on line 646	646 DENTAL CONDITIONS WHERE TREATMENT RESULTS IN MARGINAL IMPROVEMENT
D9953	reline custom sleep apnea appliance (indirect)	Fabrication, adjustment and repair of sleep apnea appliances (D9947-D9949) are on line 202	202 SLEEP APNEA, NARCOLEPSY AND REM BEHAVIORAL DISORDER

Dental Implant Removal

Plain Language Summary:
Background: The metal post that replaces the root portion of a missing tooth removal. The Oregon Health Authority Ombuds Office recommends "pain" to be a reason for removal.

Should OHP cover this treatment? Oral Health Advisory Panel members said "pain" is subjective and decided not to recommend including that in its recommendations. Based on this, staff does not recommend adding coverage for implant removal for patients experiencing implant-related pain. However, a new code needs to be added to the existing line and guideline to continue coverage based on the current rules.

Question: Should the dental implant removal guideline be broadened to include more indications?

Question source: OHA Ombuds office

Issue: The current dental implant removal guideline allows coverage only for "advanced peri-implantitis with bone loss and mobility, abscess or implant fracture." The Ombuds office recently had a case where there was severe pain and inability to chew, and the claim was denied as not meeting the guideline note criteria. The Ombuds office also notes that the advanced dental imaging needed to determine need for dental implant removal is not specifically called out in the guideline as covered. The Ombuds office requested that a possible expansion of indications for dental implant removal be considered by HERC, as well as possible coverage of advanced dental imaging in cases with possible dental implant complications.

The advanced imaging needed to evaluate a failed dental implant are only on line 256 DEFORMITIES OF HEAD governed by GUIDELINE NOTE 169, ORTHODONTICS AND CRANIOFACIAL SURGERY FOR CRANIOFACIAL ANOMALIES which specifies that "Advanced dental imaging is included on this line only when required for surgical planning for repair of craniofacial anomalies."

In addition to the above issue, a new 2023 CDT code also requires placement: CDT D6105 (removal of implant body not requiring bone removal nor flap elevation).

Current Prioritized List status:
GUIDELINE NOTE 123, DENTAL IMPLANT REMOVAL
Lines 344,619
Removal of dental implants (D6100) is included on Line 344 only when there is advanced peri-implantitis with bone loss and mobility, abscess or implant fracture. Otherwise, this procedure is included on Line 619.

CDT code	Code Description	Current Line(s)
D6100	Surgical removal of implant body	344 DENTAL CONDITIONS (E.G., SEVERE CARIES, INFECTION) 619 DENTAL CONDITIONS (E.G., MISSING TEETH)
D0364	Cone beam ct capture and interpretation with limited field of view - less than one whole jaw	256 DEFORMITIES OF HEAD

D0365	Cone beam ct capture and interpretation with field of view of one full dental arch - mandible	256
D0366	Cone beam ct capture and interpretation with field of view of one full dental arch - maxilla, with or without cranium	256
D0367	Cone beam ct capture and interpretation with field of view of both jaws, with or without cranium	256

OHAP discussion:
HERC staff brought forward a possible modification to GN123 for OHAP discussion:

GUIDELINE NOTE 123, DENTAL IMPLANT REMOVAL
Lines 344,619
Removal of dental implants (D6100, D6105) is included on Line 344 only when there is
1) advanced peri-implantitis with bone loss and mobility, abscess or implant fracture; OR
2) pain, inability to masticate or inhibition of oral function related to the dental implant.
Otherwise, this procedure is included on Line 619.

Advanced dental imaging is included on line 344 only when needed to evaluate pain or dysfunction associated with a dental implant site.

OHAP members unanimously felt like the proposed guideline changes were overly broad. Allen had reviewed private plans and found that most have no benefit at all for dental implants, including removal. Patients with private dental insurance had to pay out of pocket for dental implant removal for any reason. OHP already has broader coverage that most private dental plans by allowing coverage of removal with peri-implantitis, abscess or implant fracture.

OHAP members were very concerned about inclusion of pain as a criterion. Pain is very subjective. It is also difficult to determine the source of the pain in many cases. OHAP members did not see any indication for advanced dental imaging for implant removal. The group unanimously agreed that the addition of pain was very problematic and recommended no change to the guideline other than the addition of the new CDT code.

HERC staff recommendations:
1) Add CDT D6105 (removal of implant body not requiring bone removal nor flap elevation) to lines 344 DENTAL CONDITIONS (E.G., SEVERE CARIES, INFECTION) and 619 DENTAL CONDITIONS (E.G., MISSING TEETH)
2) Modify GN123 as shown below

GUIDELINE NOTE 123, DENTAL IMPLANT REMOVAL
Lines 344,619
Removal of dental implants (D6100, D6105) is included on Line 344 only when there is advanced peri-implantitis with bone loss and mobility, abscess or implant fracture. Otherwise, this procedure is included on Line 619.

Labial Frenulectomy

Plain Language Summary:
Background: This condition is a lip-tie procedure for infants who have breastfeeding problems. An advisory panel member asked for this non-covered condition to be looked at again.

Should OHP cover this treatment? Staff recommends to not cover this treatment because there is very little evidence that it improves breastfeeding.

Question: Should the breastfeeding difficulties in infants be added as a covered condition for labial frenulectomy?

Question source: Gary Allen, DMD

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

Dr. Allen has requested reconsideration of the guideline for frenulectomy, which currently limits this procedure to persons over age 12. Specifically, he is requesting consideration of coverage of maxillary labial frenulectomy in infants with difficulties with breastfeeding due to lip tie.

This topic was previously reviewed in June, 2017 and no evidence was found to support adding coverage. The evidence review at that time included a systematic review from 2015 and a 2015 AHRQ review.

Of note, HERC staff identified a problem with the placement of the 2021 CDT codes related to frenectomy. Two new CDT codes (D7961 and D7962) replaced the previous CDT code (D7960) in 2021. The CDT code D7961 was mistakenly not updated in the frenectomy guideline nor placed on the uncovered line specified in that guideline.

Current Prioritized List status

Code	Code Description	Current Line(s)
ICD-10-CM		
Q18.9	Congenital malformation of face and neck, unspecified [used for lip tie]	**661** MISCELLANEOUS CONDITIONS WITH NO OR MINIMALLY EFFECTIVE TREATMENTS OR NO TREATMENT NECESSARY
Q38.1	Ankyloglossia	**18** FEEDING PROBLEMS IN NEWBORNS, ANOMALIES OF TONGUE
CPT		
40806	Incision of labial frenum (frenotomy))	**661**
41010	Incision of lingual frenum (frenotomy))	**18** **164** CARCINOMA IN SITU OF UPPER AIRWAY, INCLUDING ORAL CAVITY **597**
CDT		
D7961	Buccal / labial frenectomy (frenulectomy)	**344**
D7962	Lingual frenectomy (frenulectomy)	**18, 344**

GUIDELINE NOTE 48, FRENULECTOMY/FRENULOTOMY

Line 344

Frenulectomy/frenulotomy (D7960) is included on this line for the following situations:

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

GUIDELINE NOTE 139, FRENOTOMY FOR TONGUE TIE IN NEWBORNS

Lines 18,597

Ankyloglossia (ICD-10-CM Q38.1 is included on Line 18 for pairing with frenotomy (CPT 41010, CDT D7962) only when it interferes with breastfeeding. Otherwise, Q38.1 and CPT 41010 are included on Line 597.

Evidence

1) **Nakhash 2019,** systematic review of upper lip tie and breastfeeding
    a. N=15 articles
        i. One systematic review, 6 reviews of surgical techniques, 4 cohort prospective studies of the incident of upper lip tie, 2 case reports and 2 retrospective cohort studies
    b. The four cohort studies that assessed the effect of tie release on clinical outcomes were that of Pransky et al.,Siegel, Ghaheri et al., and Benoiton et al. Neither of these studies was randomized and had control group, which did not undergo release procedures for comparison
    c. We found that the definition of upper lip tie is unclear
    d. In terms of treatment, we found that contrary to the literature on tongue-tie, there was no one single RCT that compared the efficacy of an ULT release procedure on breastfeeding difficulties. In the absence of such studies, it is impossible to determine with certainty whether short-term and/or long-term outcomes of breastfeeding are improved by the release
    e. We strongly believe from the available evidence that there is no justification for routine upper lip tie release in infants with breastfeeding difficulties

Expert guideline

1) **Messner 2020**, AAOLG-HNS Clinical consensus statement on ankyloglossia in children
    a. Presence of an upper lip frenulum is normal in an infant.
    b. Upper lip tie is an inconsistently defined condition.
    c. Upper lip tie has an unclear relationship to breastfeeding difficulties.
    d. In some communities upper lip tie is being overdiagnosed
    e. Regarding feeding issues, while several studies purport to establish the effectiveness of the MLF release for infant feeding difficulties, the studies are hampered by unclear definitions of lip tie, the absence of control groups, small patient cohorts, the presence of confounding variables, and short surgical follow-up.

Labial Frenulectomy

Other payer policies:

1) **Aetna 2022**
    a. Aetna considers lingual or labial frenectomy, frenotomy, or frenuloplasty medically necessary for ankyloglossia when newborn feeding difficulties or childhood articulation problems exist.
2) Other private insurers appear to cover with dental policies

HERC staff summary:

There is very limited evidence for the effectiveness of maxillary labial frenulectomy for breastfeeding difficulties. ENT guidelines do not endorse frenulectomy due to difficulties with diagnosis and lack of evidence that frenulectomy is associated with better breastfeeding outcomes.

Housekeeping changes need to be made with CDT D7961 and D7962 and their respective guideline notes.

HERC staff recommendations:

1) Add CDT D7961 to line 661 MISCELLANEOUS CONDITIONS WITH NO OR MINIMALLY EFFECTIVE TREATMENTS OR NO TREATMENT NECESSARY.
    a. Modify GN 48 as shown below
2) Add D7962 (Lingual frenectomy (frenulectomy)) to line 597 TONGUE TIE AND OTHER ANOMALIES OF TONGUE
    a. Modify GN 139 as shown below

GUIDELINE NOTE 48, FRENULECTOMY/FRENULOTOMY

Line 344,661

Frenulectomy/frenulotomy (~~D7960~~ CDT D7961) is included on this line for the following situations:

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

Otherwise D7961 is included on line 661.

GUIDELINE NOTE 139, FRENOTOMY FOR TONGUE TIE IN NEWBORNS

Lines 18,597

Ankyloglossia (ICD-10-CM Q38.1) is included on Line 18 for pairing with frenotomy (CPT 41010, CDT D7962) only when it interferes with breastfeeding. Otherwise, Q38.1 and CPT 41010 and CDT D7962 are included on Line 597.

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Review

Upper Lip Tie and Breastfeeding: A Systematic Review

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Abstract

Background: Upper lip tie (ULT) articles have been recorded in Medline since 1998, while ''labial frenum'' articles have been recorded since 1946.
Objective: to study the existing medical literature on ULT (or labial frenum or fraenum) as they relate to breastfeeding.
Materials and Methods: Medline search engine was used to determine and subsequently retrieve all articles published on ULT from 1946 to 2018. Key-words of upper lip tie OR labial frenum were used for the search. We also used Google Scholar and Embase to widen our search, and used the PRISMA criteria for systematic reviews (SRs). Articles were classified as case reports (or series), reviews, editorials (or opinions), cohort studies, clinical trials (nonrandomized), randomized controlled trials (RCT), and SRs according to Medline's own classification. We systematically summarized all articles published to date.
Results and Conclusion: No RCT were found, and the evidence for routine ULT release in infants with breastfeeding difficulties is poor. The classification system proposed by Kotlow has not been found reliable both in terms of inter and intraobserver agreement and in terms of predicting the severity of the breastfeeding difficulties.

Keywords: lip tie, breastfeeding, labial frenum, upper lip tie

Introduction

Upper lip tie (ULT) is believed to be linked to breastfeeding difficulties, and it has been suggested by Kotlow that lip tie release improves breastfeeding.[1] The ULT is the anatomic entity that tethers the upper lip to the upper gum. Most infants have some degree of ULT, but it has been postulated by Kotlow and others that when the ULT becomes large and tight enough, it may prevent the upper lip from flaring out or curling up during breastfeeding, and subsequently prevents the creation of an adequate seal with the breast.[1,2] It has also been claimed that if the ULT is tight enough, an infant may have trouble feeding even from a bottle.[2]

Many practitioners involved with the surgical treatment of tongue-tie also perform ULT release during the same surgical session, with the claim that breastfeeding difficulties may be ameliorated by this double procedure.[2] A classification system of the severity of the condition has even been proposed by Kotlow[3] and used in several articles by this author.

In a recent systematic review (SR),[4] we described a dramatic increase in the number of articles published every year in relationship to tongue-tie, frenotomy, and breastfeeding. However, despite this increasingly abundant literature, we found that there were many unanswered questions, and that the amount of medical evidence in favor or against routine frenotomy in infants with breastfeeding difficulties and tongue-tie was very sparse.[4] Furthermore, since it is known that in many cases, the issue of tongue-tie improves over time, it has been suggested that the rapid rise in frenotomy rates might be a ''fad'' driven by practitioners for financial gain.[5] In neonates, ULT release is usually performed by practitioners who also perform tongue-tie release.

We thus conducted the following SR to evaluate the existing literature on ULT. We aimed to provide an updated review of the literature. Based on evidence, we attempted to define whether or not ULT may impair breast feeding and whether or not ULT release may improve breastfeeding in infants with breastfeeding difficulties.

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AMERICAN ACADEMY OF OTOLARYNGOLOGY–HEAD AND NECK SURGERY FOUNDATION

Invited Article

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SAGE

Clinical Consensus Statement: Ankyloglossia in Children

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Abstract

Objective. To identify and seek consensus on issues and controversies related to ankyloglossia and upper lip tie in children by using established methodology for American Academy of Otolaryngology–Head and Neck Surgery clinical consensus statements.

Methods. An expert panel of pediatric otolaryngologists was assembled with nominated representatives of otolaryngology organizations. The target population was children aged 0 to 18 years, including breastfeeding infants. A modified Delphi method was used to distill expert opinion into clinical statements that met a standardized definition of consensus, per established methodology published by the American Academy of Otolaryngology–Head and Neck Surgery.

Results. After 3 iterative Delphi method surveys of 89 total statements, 41 met the predefined criteria for consensus, 17 were near consensus, and 28 did not reach consensus. The clinical statements were grouped into several categories for the purposes of presentation and discussion: ankyloglossia (general), buccal tie, ankyloglossia and sleep apnea, ankyloglossia and breastfeeding, frenotomy indications and informed consent, frenotomy procedure, ankyloglossia in older children, and maxillary labial frenulum.

Conclusion. This expert panel reached consensus on several statements that clarify the diagnosis, management, and treatment of ankyloglossia in children 0 to 18 years of age. Lack of consensus on other statements likely reflects knowledge gaps and lack of evidence regarding the diagnosis, management, and treatment of ankyloglossia. Expert panel consensus may provide helpful information for otolaryngologists treating patients with ankyloglossia.

Keywords

ankyloglossia, tongue-tie, lip tie, frenotomy, frenuloplasty, lingual frenulum, frenectomy, frenulotomy, frenuloplasty, maxillary labial frenulum, maxillary frenotomy, breastfeeding

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Introduction

Medical practitioners have long been concerned that a restrictive lingual frenulum could adversely affect a child's health by interfering with the ability to breastfeed, speak, or perform mechanical/social skills, such as licking the lips or keeping the teeth clean. In 1679, a surgical textbook was published with woodcuts showing an infant's frenulum being cut with scissors.[1] Midwives in the 18th century reportedly kept 1 fingernail long so that they could lyse the frenulum following birth to facilitate breastfeeding.[2]

Over the past decade, there has been an exponential increase in the number of children diagnosed and treated with ankyloglossia in more affluent countries. A 2017 study by Walsh et al of pediatric inpatients in the United States

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Section 7.0

BHAP report

2023 CPT Code Review
BHAP Issues

1) Code: **96202-96203**
    a. Code descriptions:
        i. **96202** Multiple-family group behavior management/modification training for parent(s)/guardian(s)/caregiver(s) of patients with a mental or physical health diagnosis, administered by physician or other qualified health care professional (without the patient present), face-to-face with multiple sets of parent(s)/guardian(s)/caregiver(s); initial 60 minutes
        ii. **96203** each additional 15 minutes
    b. Information: Training of parents or caregivers to help learn behavior management skills to help the child/affected person learn new desirable behaviors/coping skills and help to reduce and eliminate undesirable behaviors (for example, self-injury)
    c. Similar codes:
        i. 90849 (Multiple-family group psychotherapy) is on all behavioral health lines
        ii. 97157 (Multiple-family group adaptive behavior treatment guidance, administered by physician or other qualified health care professional (without the patient present), face-to-face with multiple sets of guardians/caregivers, each 15 minutes) is on lines 193 AUTISM SPECTRUM DISORDERS and 438 STEREOTYPED MOVEMENT DISORDER WITH SELF-INJURIOUS BEHAVIOR DUE TO NEURODEVELOPMENTAL DISORDER
    d. Evidence
        i. **Deb 2020**, systematic review and meta-analysis of parent training for children with autism spectrum disorder
            1. N=15 studies (17 papers)
            2. Fifteen papers showed a positive treatment effect when compared with the control group, although not always significant. Meta-analysis based on pooled data from only two studies in each respective intervention, showed small to moderate treatment effects for three interventions, DIR/Floortime, Pivotal Response and Parent focused training respectively.
            3. Conclusions: As in previous systematic reviews there was a mild to moderate treatment effects of three specific types of interventions respectively. However, it was difficult to draw any definitive conclusion about the effectiveness and generalizability of any intervention because of the wide variation in the interventions, control groups, outcome measures, small sample size, small number of studies in meta-analysis, overlap between the intervention and control procedures used in the included studies
        ii. **Woolfenden 2010**, Cochrane review of family therapy for conduct disorder
            1. N=8 trials (749 children and their families)
            2. At follow up, family and parenting interventions significantly reduced the time spent by juvenile delinquents in institutions (WMD 51.34 days, 95%CI 72.52 to 30.16). There was also a significant reduction in the risk of a juvenile delinquent being re-arrested (RR 0.66, 95%CI 0.44 to 0.98) and in their rate of subsequent arrests at 1-3 years (SMD -0.56, 95% CI -1.100 to - 0.03).

3. At present there is insufficient evidence that family and parenting interventions reduce the risk of being incarcerated (RR=0.50, 95% CI 0.20 to 1.21). No significant difference was found for psychosocial outcomes such as family functioning, and child/adolescent behavior.
4. Conclusion: The evidence suggests that family and parenting interventions for juvenile delinquents and their families have beneficial effects on reducing time spent in institutions

iii. **Lee 2012**, meta-analysis of behavioral parent training (BPT) for children with ADHD
1. N=40 studies
2. When compared with the waiting list control or other treatment, 28 studies found small to large positive effects (r range: .90 to .06) supporting the effects of BPT at post-treatment, whereas 12 studies found small negative effects of BPT (r range: -.01 to -.33). On average, a moderate effect (r = .34, k = 40) was found that supported BPT as an effective intervention in enhancing child and parent behavior as well as parental perception about parenting. In 17 studies, follow-up outcomes of BPT were measured at 3 months to 3 years after the intervention and found a small positive effect (r = .17, k = 17, range: .66 to -.40). BPT effects remained meaningful but declined at follow-up
3. Conclusion: Behavioral parent training is an effective intervention for children with attention deficit hyperactivity disorder

e. Expert recommendations
i. **CDC**: parent training for behavior management for ADHD
1. https://www.cdc.gov/ncbddd/adhd/behavior-therapy.html
a. Accessed September 30, 2022
2. Behavior therapy is an effective treatment for attention-deficit/hyperactivity disorder (ADHD) that can improve a child's behavior, self-control, and self-esteem. It is most effective in young children when it is delivered by parents… When parents become trained in behavior therapy, they learn skills and strategies to help their child with ADHD succeed at school, at home, and in relationships.

ii. **Pilling 2013**, summary of NICE guidance on management of conduct disorders in children
1. Offer a group parent training programme to the parents of those aged 3-11 years who have or are at high risk of oppositional defiant disorder or conduct disorder or are in contact with the criminal justice system because of antisocial behaviour. [Based on moderate to high quality evidence from randomised controlled trials]
2. Offer a group foster carer/guardian training programme to foster carers and guardians of those aged 3-11 years who have or are at high risk of oppositional defiant disorder or conduct disorder or are in contact with the criminal justice system because of antisocial behaviour. [Based on limited high quality evidence from randomised controlled trials and on the experience and opinion of the GDG]

f. BHAP discussion: The group generally supported pairing these codes with diagnoses that had evidence to support use, such as autism spectrum disorder, ADHD, and conduct disorder. Lindsay expressed concern about whether these groups are support groups or training groups. She felt that there needs to be clarity on the type of service, the license or training of the group leader, and the quality of the program before these should be covered. Lindsey noted that there is good evidence that any program that affects the family system can help children. Savicki recommended looking at asthma, eating disorders, and other conditions that are impacted by the family system.

   Yvonne Hubbard suggested looking at adjustment disorders for possible evidence review. Her program (Oregon Community Programs) works with families in the foster care system. Many of these children have gone through trauma and are having behaviors on the extreme end. Ms. Hubbard suggested including coverage for caregivers (biologic or foster parents) of children in the foster system with more extreme behaviors. These trainings are given by qualified mental health professional and are referred to as PMTO and PCIT training. Lindsey noted that young children in many cases cannot be given a specific diagnosis, which might complicate pairing for foster care issues related issues.

   Note: HERC staff conducted a literature review of caregiver training for eating disorders and found scanty evidence, but the protocol for an RCT was published in 2021. It appears that this is an active area of investigation. No literature was found on caregiver training for adjustment disorder. There was good evidence for use of these trainings for resource parents (previously called foster parents). However, this training is required by and provided by DHS as part of the resource parent certification. After consultation with the agency responsible for resource parent training, HERC staff have concluded that such training is not in the purview of OHP.

g. <u>HERC staff summary</u>: Parent/caregiver training appears to have limited evidence of effectiveness for children with autism spectrum disorders, ADHD and conduct disorder. The new CPT codes could be used for a broad range of diagnoses. Current multi-family group therapy CPT codes are only on the autism related lines. Group psychotherapy codes (with patient present) are on all behavioral health lines. Staff review of the literature did not find sufficient evidence to support use for eating disorders or adjustment disorders. Use with resource patents (formerly foster parents) is paid for out of non-OHP funding sources.

h. <u>BHAP/HERC staff recommendations</u>:
   i. Place CPT **96202-96203** on the following lines
      1. 121 ATTENTION DEFICIT/HYPERACTIVITY DISORDERS
      2. 193 AUTISM SPECTRUM DISORDERS
      3. 420 OPPOSITIONAL DEFIANT DISORDER; CONDUCT DISORDER AGE 18 OR UNDER
      4. 438 STEREOTYPED MOVEMENT DISORDER WITH SELF-INJURIOUS BEHAVIOR DUE TO NEURODEVELOPMENTAL DISORDER

2) Code: **98978**
    a. Code description: Remote therapeutic monitoring (eg, therapy adherence, therapy response); device(s) supply with scheduled (eg, daily) recording(s) and/or programmed alert(s) transmission to monitor cognitive behavioral therapy, each 30 days
    b. Information:
        a. Previously coded with CPT 0702T (Remote therapeutic monitoring of a standardized online digital cognitive behavioral therapy program ordered by a physician or other qualified health care professional; supply and technical support, per 30 days) and 0703T (Management services by physician or other qualified health care professional, per calendar month).
        b. Digital health products are technologies, platforms, and systems that engage consumers for lifestyle, wellness, and health-related purposes. Digital therapeutic products differ from digital health products in that they are practitioner-prescribed software that delivers evidence-based therapeutic interventions to prevent, manage, or treat a medical disorder or disease. Digital therapeutic products have been proposed to supplement or replace individual or group therapy and/or to deliver cognitive-behavioral therapy for the treatment of substance use disorders.
    c. Similar codes:
        a. 98975-98981 (Remote therapeutic monitoring) are EXCLUDED
    d. BHAP discussion: HERC staff noted that these codes are limited to FDA approved devices. CMS is still working on determining what would be an approved device. BHAP agreed that these codes should be EXCLUDED until further input is received from MED and CMS.
    e. <u>HERC staff summary</u>: The Medicaid Evidence Based Decision program (MED) is performing a review of digital health products, which will include behavioral health and substance use treatment products. This review is expected to be complete within the next year. Current remote therapeutic monitoring CPT codes are EXCLUDED. Staff recommend putting the new CBT remote monitoring code on EXCLUDED until the MED review is completed.
    f. <u>BHAP/HERC staff recommendation</u>:
        a. Place CPT **98978** on the EXCLUDED file
            i. Similar to current remote therapeutic monitoring codes
            ii. Await the final MED report and readdress placement at that time

Deb et al. BMC Psychiatry (2020) 20:583
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BMC Psychiatry

RESEARCH ARTICLE Open Access

The effectiveness of parent training for children with autism spectrum disorder: a systematic review and meta-analyses

Shoumitro (Shoumi) Deb[1*], Ameeta Retzer[2], Meera Roy[3], Rupali Acharya[1], Bharati Limbu[1] and Ashok Roy[4]

Abstract

Background: Various parent training interventions have been shown to have some effect on the symptoms of children with autism. We carried out a systematic review and meta-analyses to assess effectiveness of parental training for children with autism on their symptoms and parental stress.

Methods: Four electronic databases, CINAHL, EMBASE, MEDLINE and PsycINFO were searched until March 2020 for relevant literature. Two reviewers independently screened bibliographies using an eligibility checklist and extracted data using a structured proforma. We have also carried out meta-analyses when data were available for pooling.

Results: Seventeen papers from 15 studies were included for data analysis. Fifteen papers showed a positive treatment effect when compared with the control group, although not always significant. Meta-analysis based on pooled data from only two studies in each respective intervention, showed small to moderate treatment effects for three interventions, DIR/Floortime, Pivotal Response and Parent focused training respectively.

Conclusions: As in previous systematic reviews there was a mild to moderate treatment effects of three specific types of interventions respectively. However, it was difficult to draw any definitive conclusion about the effectiveness and generalisability of any intervention because of the wide variation in the interventions, control groups, outcome measures, small sample size, small number of studies in meta-analysis, overlap between the intervention and control procedures used in the included studies. There is an urgent need for experts in various international centres to jointly standardise a parent training intervention for children with autism and carry out a large scale RCT to assess its clinical and economic effectiveness.
Research Registry Unique Identifying Number: reviewregistry915.

Keywords: Parent training, Autism, Children, Systematic review, Meta-analysis

Background

Autism is a neurodevelopmental disorder, with an estimated prevalence of 0·4% for the core disorder and about 1% for the broad autism spectrum disorder (ASD) [1]. The triad of impairments of social interaction, communication and restricted behaviour patterns have a profound effect on the child's social development into adulthood and importance of early psychosocial intervention has been advocated in the UK National Autism Plan for Children [2]. The National Institute for Health and Care Excellence, in the UK (Clinical Guideline no. 170) [3] found from meta-analyses that there was small to moderate effects on social interactions, measured by the Autism Diagnostic Observation Schedule (ADOS) [4], joint attention between parent and child, and engagement when caregivers or preschool teachers carried out social communication interventions. Meta-analysis

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Cochrane Library

Cochrane Database of Systematic Reviews

Family and parenting interventions in children and adolescents with conduct disorder and delinquency aged 10-17 (Review)

Woolfenden S, Williams KJ, Peat J

Woolfenden S, Williams KJ, Peat J.
Family and parenting interventions in children and adolescents with conduct disorder and delinquency aged 10-17.
Cochrane Database of Systematic Reviews 2001, Issue 2. Art. No.: CD003015.
DOI: 10.1002/14651858.CD003015.

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WILEY

[Intervention Review]

Family and parenting interventions in children and adolescents with conduct disorder and delinquency aged 10-17

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ABSTRACT

Background

Conduct disorder and delinquency are significant problems for children and adolescents and their families, with the potential to consume much of the resources of the health, social care and juvenile justice systems. A number of family and parenting interventions have been recommended and are used for these conditions. The aim of this review was to determine if these interventions are effective in the management of conduct disorder and delinquency in children and adolescents, aged 10-17.

Objectives

To determine if family and parenting interventions improve the child/adolescent's behaviour; parenting and parental mental health; family functioning and relations; and have an effect on the long term psychosocial outcomes for the child/adolescent.

Search methods

Randomised controlled trials were identified in September 1999 through searching the Cochrane Controlled Trial Register (CCTR), databases (MEDLINE, EMBASE, PsycINFO, CINAHL, Sociofile, ERIC, Healthstar), reference lists of articles and contact with authors.

Selection criteria

Randomised controlled trials with a major focus on parenting and/or family functioning were eligible for inclusion in the review. Trials needed to include at least one objective outcome measure (e.g. arrest rates) or have used a measure that had been published in peer review publications and validated for the relevant purpose. Studies were required to have a control group, which could be a no intervention group, a wait list group or a usual intervention group (e.g. probation).

Trials in children and adolescents aged 10 to 17 years with conduct disorder and/or delinquency and their families were considered. Conduct disorder was defined by a standardised psychological assessment (for example, using a child behaviour checklist), or a psychiatric diagnosis. Delinquency was defined by a referral from a juvenile justice or another legal system for a child/adolescent who has committed a serious crime e.g assault and/or offended on at least two occasions.

Data collection and analysis

Two reviewers independently reviewed all eligible studies for inclusion, assessed study quality (allocation concealment, blinding, follow up, clinically important outcomes) and extracted data. Heterogeneity was assessed using the Chi squared test of heterogeneity along with visual inspection of the data. A significance level less than 0.1 was interpreted as evidence of statistically significant heterogeneity. For data where heterogeneity was found the reviewers looked for an explanation. If studies with heterogeneous results were thought to be

comparable the statistical synthesis of the results was done using a random effects model. This model takes into account within-study sampling error and between-studies variation in the assessment of uncertainty and will give wider confidence intervals to the effect size and hence a more conservative result.

Sensitivity analysis was performed to explore the effects of the varying quality of the studies included on the results.

Main results

Of the nine hundred and seventy titles initially identified through the search strategy, eight trials met the inclusion criteria. A total of 749 children and their families were randomised to receive a family and parenting intervention or to be in a control group. In seven of these studies the participants were juvenile delinquents and their families and in only one the participants were children/adolescents with conduct disorder who had not yet had contact with the juvenile justice system.

At follow up, family and parenting interventions significantly reduced the time spent by juvenile delinquents in institutions (WMD 51.34 days, 95%CI 72.52 to 30.16). There was also a significant reduction in the risk of a juvenile delinquent being re arrested (RR 0.66, 95%CI 0.44 to 0.98) and in their rate of subsequent arrests at 1-3 years (SMD -0.56, 95% CI -1.100 to - 0.03). For both of these outcomes there was substantial heterogeneity in the results suggesting a need for caution in interpretation. At present there is insufficient evidence that family and parenting interventions reduce the risk of being incarcerated (RR=0.50, 95% CI 0.20 to 1.21). No significant difference was found for psychosocial outcomes such as family functioning, and child/adolescent behaviour.

Authors' conclusions

The evidence suggests that family and parenting interventions for juvenile delinquents and their families have beneficial effects on reducing time spent in institutions. This has an obvious benefit to the participant and their family and may result in a cost saving for society. These interventions may also reduce rates of subsequent arrest but at present these results need to be interpreted with caution due to the heterogeneity of the results.

PLAIN LANGUAGE SUMMARY

Family and parenting interventions in children and adolescents with conduct disorder and delinquency aged 10-17

Conduct disorder and delinquency are significant problems for children and adolescents and their families, with the potential to consume much of the resources of the health, social care and juvenile justice systems. A number of family and parenting interventions have been recommended and are used for these conditions. The aim of this review was to determine if these interventions are effective in the management of conduct disorder and delinquency in children and adolescents, aged 10-17. Current evidence suggests that family and parenting interventions for juvenile delinquents and their families have beneficial effects on reducing time spent in institutions. This has an obvious benefit to the participant and their family and may result in a cost saving for society. These interventions may also reduce rates of later arrest, but at present these results need to be interpreted with caution, because of diversity in the results of studies.

Research in Developmental Disabilities 33 (2012) 2040–2049

Contents lists available at SciVerse ScienceDirect

Research in Developmental Disabilities

A meta-analysis of behavioral parent training for children with attention deficit hyperactivity disorder

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ABSTRACT

This meta-analysis examined the effect of behavioral parent training on child and parental outcomes for children with attention deficit hyperactivity disorder. Meta-analytic procedures were used to estimate the effect of behavioral parent training on children with attention deficit hyperactivity disorder. Variables moderating the intervention effect were examined. Forty studies were included and generated an overall moderate effect size at post-treatment and a small effect size at follow-up. The majority of outcome categories were associated with a moderate effect size at post-treatment that decreased to a small effect size at follow-up. Parenting competence was the only outcome that had a large effect, which decreased to moderate at follow-up. The strength of the effect differed between questionnaire and observation measures. Behavioral parent training is an effective intervention for children with attention deficit hyperactivity disorder. Sustainability of the effects over time is a problem that awaits further scrutiny. Recommendations for further research and clinical practices are provided.

1. Introduction

Attention deficit hyperactivity disorder (ADHD) is a developmental disorder that may seriously affect a child's home, school, and social functions (American Psychiatric Association, 2000). Observational studies of children with ADHD and their parents found conflicted parent–child interaction patterns and less positive parenting practice (Deault, 2010). Participation in daily activities, such as going to bed or completing homework, might be challenging for children with ADHD and their parents and adversely affect their parent–child relationships (Segal, 2000; Segal & Hinojosa, 2006). Several studies have found that ADHD is associated with significantly increased parenting stress (Deault, 2010).

Behavioral therapy is an empirically supported intervention for children with ADHD, but is often labor intensive (Hinshaw, 2009). Therefore, parent involvement in implementation of behavioral therapy is suggested and may promote

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PRACTICE

GUIDELINES

Recognition, intervention, and management of antisocial behaviour and conduct disorders in children and young people: summary of NICE-SCIE guidance

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This is one of a series of *BMJ* summaries of new guidelines based on the best available evidence; they highlight important recommendations for clinical practice, especially where uncertainty or controversy exists.

Antisocial behaviour and conduct disorders (including oppositional defiant disorder and conduct disorder) are the most common mental and behavioural problems in children and young people globally, with the frequency increasing in Western countries.[1] In the United Kingdom 5% of mental and behavioural problems in children and young people (≤ 18 years) meet criteria for a conduct disorder, as do almost 40% of looked-after children, children who have been abused, and those on child protection or safeguarding registers.[2] Conduct disorders are strongly associated with poor performance at school, social isolation, substance misuse, and involvement with the criminal justice system.[3] A large proportion of children and young people with a conduct disorder will go on to be antisocial adults with impoverished and destructive lifestyles,[3] especially if the conduct problems develop early,[4] and a large minority will be diagnosed with antisocial personality disorder.[5] Antisocial behaviour and conduct disorders often coexist with other mental health problems, place a heavy personal and economic burden on individuals and society,[6] and involve a wide range of health, social care, educational, and criminal justice services.

This article summarises the most recent recommendations from the National Institute for Health and Clinical Excellence (NICE) on recognising and managing antisocial behaviour and conduct disorders in children and young people.[7] The guideline was developed jointly with the Social Care Institute for Excellence (SCIE).

Recommendations

NICE recommendations are based on systematic reviews of the best available evidence and explicit consideration of cost effectiveness. When minimal evidence is available, recommendations are based on the Guideline Development Group's experience and opinion of what constitutes good practice. Evidence levels for the recommendations are given in italic in square brackets.

Working safely and effectively

Health and social care professionals working with children and young people who present with behaviour suggestive of a conduct disorder, or who have a conduct disorder, should be trained and competent to work with children and young people of all levels of learning ability, cognitive capacity, emotional maturity, and development. [*Based on the experience and opinion of the Guideline Development Group (GDG)*]

Selective prevention

Offer classroom based emotional learning and problem solving programmes for children typically aged 3-7 years in schools where classes have a high proportion of children identified to

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2023 Behavioral Health HCPCS Code Review

Issue: One new HCPCS code was identified related to Behavioral Health. This code was reviewed by BHAP via email discussion after the October BHAP meeting and the placement below approved.

BHAP/HERC staff recommendation:

HCPCS Code	Code Description	Similar Code(s)/Comment	Recommended Placement
H2038	Skills training and development, per diem	H2014 (Skills training and development, per 15 minutes) is on all behavioral health lines	All behavioral health lines

Perpetrator Services

This issue summary contains material and discussion about child abuse, partner abuse and other forms of abuse.
If you or someone you know needs help, call 800.799.SAFE (7233) to be connected with a trained staff member in your area.
The National Domestic Violence Hotline is a safe, confidential service. When you call the hotline, only the first six numbers of the phone number are used to route the call, and your complete phone number is never stored in our system. Most states do have laws that require local staff to contact authorities in certain situations, like if there is a child or vulnerable adult who is in danger.

Plain Language Summary:
Background: In October, HERC approved coverage for mental health services for some perpetrators of abuse. Based on additional review and feedback, adding these codes could allow for coverage of ineffective or harmful treatments. More work is required to determine optimal coverage for these kinds of services.

Should OHP cover services for this condition? Staff recommends reversing the decision because some of the services that could be provided under it may be harmful. Staff also plans continued work to improve coverage of services which may prevent abuse.

Question: Should the October 2022 decision to cover diagnoses for perpetrators of abuse be reversed (at least temporarily)?

Question source: BHAP, CCO medical directors

Issue: At the October 2022 meeting, VBBS/HERC added three ICD-10-CM codes for perpetrators of abuse to the covered line for abuse and neglect (line 120 ABUSE AND NEGLECT) as a consent agenda item. These codes were previously on the INFORMATIONAL file. This change was made at the request of the Oregon Youth Authority to allow continued treatment of youth once they leave custody. Specifically, OYA is interested in coverage of perpetrators of sex related abuse (molestation, assault, etc.).

CCO medical directors at the QHOC and BHAP members at their October meeting both expressed concerns about this coverage change. BHAP noted that the evidence is poor that treatment was effective for these patients. QHOC members expressed concern that this treatment is frequently court-ordered and therefore outside the scope of what a CCO can reimburse. BHAP members and QHOC members requested that HERC reverse the decision to cover these codes until HERC staff conduct an evidence review and address who is responsible for payment for such services and under what circumstances. In at least some circumstances, Oregon statute does not allow Medicaid to pay for sex abuse treatment, but Medicaid could pay for treatments for other conditions these individuals may have if they are medically necessary and appropriate.

From the BHAP minutes:

> HERC staff will conduct an evidence review of the effectiveness of treatment on perpetrators of abuse. Staff will work with other sections of OHA to address who (corrections, legal, Medicaid) is responsible for payment for such services. This evidence review, as well as BHAP concerns regarding opening these diagnosis codes will be brought to the November VBBS/HERC meetings for further discussion and determine if the October HERC decision should be readdressed.

Further discussion with providers of counseling for perpetrators of abuse as well as OYA found that in some circumstances, perpetrators or their guardians reach out for treatment outside of the legal system. This type of counseling may be medically necessary, in which case it may be covered by OHP. "Sex offender treatment" specifically cannot be reimbursed by OHP under ORS, no can OHP cover treatment that is court ordered. However, frequently these patients have other conditions such as PTSD or ADHD that OHP does cover for counseling. The providers requested that ICD-10-CM Z69.021 (Encounter for mental health services for perpetrator of non-parental child abuse) be covered in some limited manner. This group of providers was exclusively involved with juveniles; however, they acknowledged that this code could also be used by providers treating adults or people who have committed physical abuse. The ICD-10-CM definition of Z69.021 could include non-parental child neglect as well as physical, emotional or sexual child abuse.

ICD-10-CM Codes
Z69.011 Encounter for mental health services for perpetrator of parental child abuse
Z69.021: Encounter for mental health services for perpetrator of non-parental child abuse
Z69.12: Encounter for mental health services for perpetrator of spousal or partner abuse
Z69.82: Encounter for mental health services for perpetrator of other abuse

Past VBBS/HERC review history:
The "Z" codes were reviewed as a consent item in October 2016. Among the changes suggested in that review was adding ICD-10-CM Z69.011 (Encounter for mental health services for perpetrator of parental child abuse) to what is now line 120 ABUSE AND NEGLECT and removing this code from the Informational File. There was no evidence review or discussion of this change, or indication regarding why this change was recommended.

Z69.021, Z69.12 and Z69.82 were included in the October 2016 review and kept on the Informational File.

Evidence on treatment for intimate partner violence

1) **Rand 2022**, Intimate Partner Abuse Solution Programs
    a. Approaches include the Duluth Model of power and control, cognitive behavioral therapy, Circles of Peace Program
    b. Research on effectiveness of programs
        i. Studies conducted to date often have limitations in their methodologies or the generalizability of findings, precluding any broad conclusions about whether IPAS programs work
        ii. Several meta-analyses since 2019 examining the efficacy of IPAS programs overall concluded that, although IPAS programs appear to have a significant positive effect on IPV recidivism when measured by official reports of rearrest, they have no effect when recidivism is reported by the survivor
        iii. The overarching observation made in research reviews is that the more rigorous the methods of evaluation studies, the less encouraging their findings

iv. Efforts to assess and compare IPAS efficacy are complicated not only by the exigencies of a real-world setting but also by variation in program length and components (even among interventions that carry the same label), differences in implementation quality, and measurement issues. Limited funding and relatively short timelines for research pose additional challenges.

2) **Smedslund 2011**, Cochrane review of CBT for men who physical abuse their female partner
   a. N=6 trials (2343 participants)
   b. A meta-analysis of four trials comparing CBT with a no-intervention control (1771 participants) reported that the relative risk of violence was 0.86 (favoring the intervention group) with a 95% confidence interval (CI) of 0.54 to 1.38. This is a small effect size, and the width of the CI suggests no clear evidence for an effect
   c. Conclusion: There are still too few randomized controlled trials to draw conclusions about the effectiveness of cognitive behaviour therapy for male perpetrators of domestic violence
3) **Arce 2020**, meta-analytical review of interventions for batterers
   a. N=25 studies (20,860 participants)
   b. The results of a global meta-analysis showed a positive, significant, and of a medium magnitude effect size for batterer interventions, but not generalizable. Nevertheless, the results exhibited a significantly higher rate of recidivism measured in couple reports (CRs) than in official records (ORs)
   c. The meta-analysis on the studies measuring intervention efficacy on the recidivism rate in CRs, with a sample of 1,351 batterers and 16 effect sizes, revealed that interventions had no effect on recidivism, with a null (δ = 0.005) mean true effect size (U1 = 0.007, i.e., the independence of the distributions of treated and non-treated batterers was only 0.7%), and could be negative by up to -0.10 or, in other words, the intervention could have a negative effect increasing recidivism rate by up to 4.99% (r = -.0499).
   d. The meta-analysis on studies estimating intervention efficacy on recidivism in ORs, with a sample of 19,509 batterers and 46 effect sizes, showed a positive, significant (confidence interval for *d* does not include zero), small-medium (δ = 0.45) and non-generalizable (credibility interval for δ includes zero) mean true effect size in the intervention, with possible negative effects of up to 4.99% (80% LCV converted to r = -.0499)
   e. As for the intervention model, positive and significant effects were observed under the Duluth Model and cognitive-behavioral treatment programs (CBTPs), but a higher effect size was obtained with CBTPs in comparison to the Duluth Model (under this model, interventions may have negative effects, i.e., an increase in recidivism rate).
   f. In conclusion, there is a corpus of literature on the efficacy of interventions, showing significant effects in reducing recidivism in official records. In other words, intervened batterers were less likely to be accused/sentenced again in (ORs) for the same offence. Notwithstanding, not all of the interventions were effective in ORs. Thus, short interventions were completely ineffective and could have negative effects of up to 40%, and certain interventions based on the Duluth Model may have negative effects of up to 10%. In contrast, long interventions based on CBTPs or OTIs (the results may not be generalized to other techniques than those revised) were on average effective and without negative effects on recidivism in ORs

Evidence on treatment of perpetrators of child abuse

1) **CDC 2020**, technical package for policies and programmatic activities for preventing child abuse and neglect
    a. Behavioral parent training programs such as Parent-Child Interaction Therapy (PCIT), The Incredible Years, and SafeCare demonstrate success in preventing recidivism for abuse in families with substantiated cases of child abuse and neglect, and in reducing child abuse and neglect risk factors in high-risk families (e.g., those who use harsh/ punitive parenting practices). A study conducted with parents reported to CPS found fewer re-reports of physical abuse and/or neglect at a 36-month follow-up for parents who completed SafeCare (15% recidivism) than families who completed services as usual (46% recidivism). Physically abusive parents in the child welfare system who participated in PCIT had significantly fewer re-reports of physical abuse than parents who participated in services as usual (19% vs 49%). In a study of families with chronic and severe neglect and/or physical abuse histories, PCIT plus a motivational enhancement was effective in reducing future child welfare reports, with a stronger effect observed when children were returned to the home sooner rather than later. The Incredible Years is effective in reducing harsh parenting and conduct problems and increasing positive discipline and nurturing parenting. In a study of primarily neglectful biological and foster parents, positive parenting skills increased for parents who participated in The Incredible Years program (when compared to controls), and the improvements were greatest when parents attended six or more sessions.

Evidence and background on treatment techniques for~~of~~ youth with problem sexual behavior

1) **California Evidence-Based Clearinghouse for Child Welfare**
    a. **https://www.cebc4cw.org/program/multisystemic-therapy-for-youth-with-problem-sexual-behaviors/**
    b. Gives multisystemic therapy for youth with problem sexual behaviors (MST-PSB) a "1" rating for well supported by research for treatment sexual behaviors and abusive behaviors in youth between 10 and 17.5 years of age
    c. Multisystemic Therapy for Youth with Problem Sexual Behaviors (MST-PSB) is a clinical adaptation of Multisystemic Therapy (MST) that has been specifically designed and developed to treat youth (and their families) for problematic sexual behavior. Building upon the research and dissemination foundation of standard MST, the MST-PSB model represents a practice uniquely developed to address the multiple determinants underlying problematic juvenile sexual behavior. MST-PSB is delivered in the community, occurs with a high level of intensity and frequency, incorporates treatment interventions from *MST*, and places a high premium on approaching each client and family as unique entities. Treatment incorporates intensive family therapy, parent training, cognitive-behavioral therapy, skills building, school and other community system interventions, and clarification work. Ensuring client, victim, and community safety is a paramount mission of the model.
2) **Borduin 2021**, long term effects of multisystemic therapy for problem sexual behaviors: a 24.9 year follow up to an RCT
    a. N=48 individuals
        i. randomized to MST-PSB or to usual community services (UCS)

        ii. Inclusion in the original study required that youths (a) had been arrested for a serious sexual offense (i.e., rape/sexual assault or molestation of younger children) with a subsequent court order for outpatient sexual offender counseling, (b) were currently living with at least one parent figure, and (c) showed no evidence of psychosis or serious intellectual disability
    b. Arrest, incarceration, and civil suit data were obtained in middle adulthood when participants averaged 39.4 years of age.
    c. Intent-to-treat analyses showed that MST-PSB participants had 85% fewer sexual offenses and 70% fewer nonsexual offenses than did UCS participants. In addition, MST-PSB participants were sentenced to 46% fewer days of incarceration and had 62% fewer family-related civil suits
    d. Conclusion: The current study is the longest and most comprehensive follow-up to date of an MST-PSB clinical trial. Over a period extending 24.9 years after the end of treatment, the results demonstrated that MST-PSB participants were less likely to be arrested for any felony offense than were UCS participants (37.5% vs. 79.2%).
3) **Langstrom 2013**, systematic review of medical and psychological interventions for preventing child sexual abuse
    a. Limited evidence (one randomized controlled trial with moderate study quality) suggested that multisystemic therapy could be effective in preventing sexual reoffending among moderate risk adolescent sex offenders (relative risk 0.18, 95% confidence interval 0.04 to 0.73)
        i. Borduin above (multiple publications)
    b. The scientific evidence was insufficient (one observational study with moderate quality34) to determine if cognitive behavioral therapy is effective at preventing sexual reoffending among moderate risk adolescent sex offenders
    c. No evidence was available to determine the effect of cognitive behavioural therapy on sexual reoffending among adolescent sex offenders with low or high risk of reoffending
    d. evidence was lacking to determine the effectiveness of methods aimed at preventing sexual offending in adolescents who have not sexually abused a child but are at risk of doing so.

Evidence on treatment of adults with problem sexual behavior

1) **Dennis 2012**, Cochrane review of psychological interventions for adults who have sexually offended or who are at risk
    a. N=10 studies (944 adult men)
        i. Anderson-Varney 1991; Brown 1996; Hopkins 1991; Marques 1994; McAnaney 1981; McConaghy 1985; McConaghy 1988; Romero 1983; Rooth 1974; Ryan 1997;
    b. Five trials involved primarily cognitive behavioral interventions (CBT) (n = 664). Of these, four compared CBT with no treatment or wait list control, and one compared CBT with standard care. Long-term outcome data are reported for groups in which the mean years 'at risk' in the community are similar (8.3 years for treatment (n = 259) compared to 8.4 in the control group (n = 225)). There was no difference between these groups in terms of the risk of reoffending as measured by reconviction for sexual offences (risk ratio (RR) 1.10; 95% CI 0.78 to 1.56).

   c. One study compared psychodynamic intervention with probation. Results for this study (n = 231) indicate a slight trend in favour of the control group (probation) over the intervention (group therapy) in terms of sexual offending as measured by rearrest (RR 1.87; 95% CI 0.78 to 4.47) at 10-year follow-up
   d. Authors' conclusions: The inescapable conclusion of this review is the need for further randomized controlled trials. While we recognize that randomization is considered by some to be unethical or politically unacceptable (both of which are based on the faulty premise that the experimental treatment is superior to the control - this being the point of the trial to begin with), without such evidence, the area will fail to progress. Not only could this result in the continued use of ineffective (and potentially harmful) interventions, but it also means that society is lured into a false sense of security in the belief that once the individual has been treated, their risk of reoffending is reduced. Current available evidence does not support this belief.

2) **Langstrom 2013**, systematic review of medical and psychological interventions for preventing child sexual abuse
   a. N=8 studies with low to moderate risk of bias
   b. For adults, evidence from five trials was insufficient regarding both benefits and risks with psychological treatment and pharmacotherapy
   c. For adolescents, limited evidence from one trial suggested that multisystemic therapy prevented reoffence (relative risk 0.18, 95% confidence interval 0.04 to 0.73)
   d. Finally, we found no eligible research on preventive methods for adults and adolescents who had not sexually abused children but were at higher risk of doing so (such as those with pedophilic sexual preference)
   e. Conclusion There are major weaknesses in the scientific evidence, particularly regarding adult men

Perpetrator Services

HERC staff summary: Existing literature on the effectiveness of programs to treat the perpetrators of intimate partner abuse find that such programs are generally ineffective and possibly harmful. These programs appear to reduce re-arrests, but actually increase violence against the victim(s).

The CDC recommends several evidence based behavioral parent training programs for treatment of families to reduce child physical abuse and neglect and reduce recidivism. Currently, the diagnosis code for mental health services for perpetrators of parental child abuse is on a covered line. This code contains the sub-diagnosis "encounter for mental health services for perpetrator of parental child sexual abuse" as well as psychological abuse and neglect.

Based on 1 RCT (N=48 adolescents), there is limited evidence that treatment of youth with problem sexual behaviors with multisystemic therapy is effective at reducing unwanted behaviors and recidivism. Such treatment is recommended by providers and by OYA. There evidence does not show effectiveness for the psychological treatment of adults with problem sexual behaviors. BHAP recommended against coverage of treatment of unwanted sexual behaviors due to lack of evidence that these programs are effective.

HERC staff recommendations:

1) Reverse the October 2022 decision to add the following ICD-10-CM codes to line 120 ABUSE AND NEGLECT and continue their placement on the INFORMATIONAL file
    a. Z69.12: Encounter for mental health services for perpetrator of spousal or partner abuse
    b. Z69.82: Encounter for mental health services for perpetrator of other abuse
2) Reverse the October 2022 decision to add ICD-10-CM Z69.021 (Encounter for mental health services for perpetrator of non-parental child abuse) to line 120 ABUSE AND NEGLECT
    a. Add Z69.021 to the DIAGNOSTIC WORKUP File
    b. Will allow initial evaluation for other, covered diagnoses such as PTSD or ADHD
    c. Temporarily addresses OYA and provider concerns until further clarification and research can be done as below
3) Keep ICD-10-CM Z69.011 (Encounter for mental health services for perpetrator of parental child abuse) on line 120 ABUSE AND NEGLECT for CDC recommended treatment programs
4) HERC staff will work with other state agencies, other parts of OHA, and outside stakeholders to determine the best prioritization of these diagnoses, and clarify billing rules/statutes and responsibilities
5) HERC staff will bring this topic back to BHAP at an upcoming meeting in 2023 for further input and discussion

PRIORITY
Criminal Justice
NEEDS INITIATIVE
A project of the RAND Corporation, the Police Executive Research Forum, RTI International, and the University of Denver

Intimate Partner Abuse Solution Programs

Identifying High-Priority Needs Within the Criminal Justice System for Programs Focused on Intimate Partner Violence Prevention

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EXECUTIVE SUMMARY

Intimate partner abuse solution (IPAS) programs were first developed in the 1970s as diversion programs to prevent jail overcrowding and have historically been referred to as *batterer intervention programs*. Although these programs are now known by different labels and apply different approaches and philosophies, collectively they are designed as alternatives to incarceration that prevent intimate partner violence (IPV) by holding perpetrators accountable for their behavior and prioritizing safety and justice for victims.

Despite widespread adoption and use of IPAS programs by court systems around the United States, there remains inconsistent and limited information on their effectiveness broadly and on which models offer the most promise. For example, a 2020 meta-analysis found that studies of IPAS programs to date have shown overall positive and significant results for reducing the incidence of IPV, yet the effects are not significant when studies are based on couples' reports of recidivism rather than official reports of recidivism, such as rearrest records (Arce et al., 2020). This suggests that using official records to measure success may provide a false picture of the extent to which the programs have worked. Similarly, findings suggest that varying program lengths may affect the effectiveness of these programs (Arce et al., 2020; Arias, Arce, and Vilariño, 2013; Babcock, Green, and Robie, 2004). There is also mixed evidence as to whether the Duluth Model, one of the most commonly used IPAS programs; cognitive behavioral therapy models; or newer models that incorporate such elements as a restorative justice framework are more or less effective and for whom (Cheng et al., 2021; Dutton and Corvo, 2007; Eckhardt et al., 2013; Gondolf, 2002; Herman et al., 2014; National Institute of Justice [NIJ], 2013b). Practitioners and researchers alike note that there is a need to enhance the evidence base around IPAS programs by focusing on more-rigorous evaluations; developing more-robust measures of outcomes or indicators of success (i.e., looking beyond simply reducing recidivism), particularly among different populations of people who commit IPV; and examining how these programs fit within a larger community violence prevention context.

SELECTED PRIORITY NEEDS

RESULTS

Program content

- Systems that incorporate evidence from trauma-informed and evidence-informed approaches that help individuals understand accountability for their actions should be developed and appropriately funded.
- Innovative approaches to engage and actively partner with multiple sectors across the community should be developed and implemented.

Program implementation

- Rigorous research should be conducted that includes outcomes that are not just recidivism, are informed by survivor voices, and are most relevant to survivors.
- Approaches that help participants address logistical or access challenges (e.g., warm handoff) should be developed and implemented.

Connection with criminal justice and community entities

- Potential bias and disparities should be assessed in decisions to mandate IPAS programs, as well as the economic impacts on participants and likelihood of completion.
- Opportunities for more referrals from first responders, community health systems, etc. should be provided in lieu of an overreliance on criminal justice system referrals.

Challenges related to rigorous research

- Funded research should be required to follow a plan that is developed for research translation and dissemination that is practitioner- and publicly accessible.
- Collaboration between researchers, practitioners, and other stakeholders should be promoted to identify and implement approaches to measure success that go beyond recidivism and program completion.

Cochrane Library

Cochrane Database of Systematic Reviews

Cognitive behavioural therapy for men who physically abuse their female partner (Review)

Smedslund G, Dalsbø TK, Steiro A, Winsvold A, Clench-Aas J

Smedslund G, Dalsbø TK, Steiro A, Winsvold A, Clench-Aas J.
Cognitive behavioural therapy for men who physically abuse their female partner.
Cochrane Database of Systematic Reviews 2011, Issue 2. Art. No.: CD006048.
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[Intervention Review]

Cognitive behavioural therapy for men who physically abuse their female partner

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ABSTRACT

Background

In national surveys, between 10% and 34% of women have reported being physically assaulted by an intimate male partner. Cognitive behavioural therapy (CBT) or programmes including elements of CBT are frequently used treatments for physically abusive men. Participants either enrol voluntarily or are obliged to participate by means of a court order. CBT not only seeks to change behaviour using established behavioural strategies, but also targets thinking patterns and beliefs.

Objectives

To measure effectiveness of CBT and programmes including elements of CBT on men's physical abuse of their female partners.

Search methods

We searched CENTRAL (The Cochrane Library Issue 4, 2009), C2-SPECTR (2006), MEDLINE (1950 to 1 January 2010), EMBASE (1980 to 2009 week 53), CINAHL (1982 to December 2009), PsycINFO (1806 to week 4, December 2009), ERIC (1966 to December 2009), Social Care Online, previously CareData (13 January 2010), Sociological Abstracts (1963 to December 2009), Criminal Justice Abstracts (2003), Bibliography of Nordic Criminology (13 January 2010), and SIGLE (2003). We also contacted field experts and the authors of included studies.

Selection criteria

Randomised controlled trials that evaluated the effectiveness of cognitive behavioural therapy for men who have physically abused their female partner and included a measure of the impact on violence.

Data collection and analysis

Two reviewers independently assessed references for possible inclusion, extracted data using an online data extraction form and assessed the risk of bias in each included study. Where necessary, we contacted study authors for additional information.

Main results

Six trials, all from the USA, involving 2343 participants, were included. A meta-analysis of four trials comparing CBT with a no-intervention control (1771 participants) reported that the relative risk of violence was 0.86 (favouring the intervention group) with a 95% confidence interval (CI) of 0.54 to 1.38. This is a small effect size, and the width of the CI suggests no clear evidence for an effect. One study (Wisconsin Study) compared CBT with process-psychodynamic group treatment and reported a relative risk of new violence of 1.07 (95% CI 0.68 to 1.68). Even though the process-psychodynamic treatment did marginally better than CBT, this result is equivocal. Finally, one small study (N = 64) compared a combined CBT treatment for substance abuse and domestic violence (SADV) with a Twelve-Step Facilitation (TSF)

group. An analysis involving 58 participants investigated the effect on reduction in frequency of physical violence episodes. The effect size was 0.30 (favouring TSF) with 95% CI from -0.22 to 0.81.

Authors' conclusions

There are still too few randomised controlled trials to draw conclusions about the effectiveness of cognitive behaviour therapy for male perpetrators of domestic violence.

PLAIN LANGUAGE SUMMARY

Cognitive behavioural therapy for men who physically abuse their female partner

Violence by men against an intimate female partner is a serious and common problem, with between 10% and 34% of women reporting in national surveys that they have been assaulted by a male partner. Cognitive behavioural therapy (CBT) is used to reduce male violence by bringing about changes in how men think about violence and how they manage their behaviour. Some men volunteer to attend CBT treatment, while others are court mandated to participate. We included trials that involved both types of participants. The review found all randomised controlled evaluations of the effects of CBT on men's physical violence to their female partners worldwide, but there were only six small trials with a total of 2343 participants that met the inclusion criteria. The results of four of these trials, which compared men who received CBT with men getting no treatment, were combined. This was not able to show us whether or not CBT was better than no treatment. Similarly, the individual results of the other two trials, which compared CBT with another treatment, were inconclusive. Overall, the evidence from the included studies is insufficient to draw any conclusions.

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Are Interventions with Batterers Effective? A Meta-analytical Review

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A B S T R A C T

The inconsistency in the results both internally and between of previous meta-analyses on batterer intervention program efficacy, and the publication of new batterer interventions underscored the need for an up-to-date meta-analytical review. A total of 25 primary studies were found from literature search, obtaining 62 effect sizes, and a total sample of 20,860 intervened batterers. The results of a global meta-analysis showed a positive, significant, and of a medium magnitude effect size for batterer interventions, but not generalizable. Nevertheless, the results exhibited a significantly higher rate of recidivism measured in couple reports (CRs) than in official records (ORs). As a consequence, intervention efficacy measuring in CRs was null, whilst in ORs was positive and significant. As for the intervention model, positive and significant effects were observed under the Duluth Model and cognitive-behavioural treatment programs (CBTPs), but a higher effect size was obtained with CBTPs in comparison to the Duluth Model (under this model, interventions may have negative effects, i.e., an increase in recidivism rate). In relation to intervention length, short interventions failed to reduce recidivism in ORs and may have negative effects, while long interventions were effective in reducing recidivism rate in ORs without negative effects. Efficacy evaluations in short follow-ups were invalid as artificially boosted recidivism reduction rate. Limitations of ORs and short follow-ups as measures of the intervention efficacy and implications of results for batterer intervention are discussed.

¿Son efectivas las intervenciones con los maltratadores? Una revisión metaanalítica

Palabras clave:
Maltratador
Evaluación de la intervención
Modelo Duluth
Programas de tratamiento cognitivo-conductuales
Registros oficiales
Informes de las parejas

R E S U M E N

La inconsistencia interna y entre las revisiones metaanalíticas en los resultados sobre la eficacia de los programas de intervención con maltratadores, así como la publicación de nuevos estudios, pone de manifiesto la necesidad de llevar a cabo una revisión metaanalítica actualizada. Se encontró un total de 25 estudios primarios, de los que se obtuvieron 62 tamaños del efecto para una muestra total de 20,860 maltratadores intervenidos. Los resultados del metaanálisis global mostraron un tamaño del efecto promedio positivo, significativo y de una magnitud moderada para la intervención con maltratadores, pero no generalizable. Sin embargo, los resultados revelaron una tasa de reincidencia mayor medida en los informes de las parejas (IPs) que en los registros oficiales (ROs). Como consecuencia, la eficacia de la intervención medida en los IPs resultó nula, mientras que en los ROs fue positiva y significativa. En relación al modelo de intervención, se encontraron tamaños del efecto positivos y significativos con el Modelo Duluth y los programas de tratamiento cognitivo-conductuales (PTC-Cs), pero el tamaño del efecto obtenido con los PTC-Cs era significativamente mayor que con el Modelo Duluth (con este modelo las intervenciones pueden tener efectos negativos, es decir, un incremento en la tasa de reincidencia). En relación a la longitud de la intervención, las intervenciones breves fallaron en la reducción de la reincidencia en los ROs y pueden tener efectos negativos, en tanto que las intervenciones largas fueron eficaces en la reducción de la tasa de reincidencia en los ROs y no dan lugar a efectos negativos. Las evaluaciones de la eficacia de la intervención en períodos cortos de seguimiento resultaron no válidas al incrementar artificialmente la tasa de reducción de la reincidencia. Se discuten las limitaciones de la medida de la eficacia de la intervención en los ROs y en períodos cortos de seguimiento, así como las implicaciones para la intervención con maltratadores.

Intervention programs for batterers have been the subject of controversy ever since their conception. These interventions have been open to criticism from both a restorative perspective and a feminist perspective demanding resources should be allocated to victims, not to batterers. Such criticism, however, comes into direct conflict with the legal and judicial mandate of prison institutions that are obliged

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Long-Term Effects of Multisystemic Therapy for Problem Sexual Behaviors: A 24.9-Year Follow-Up to a Randomized Clinical Trial

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Objective: Although there is evidence that the positive impact of multisystemic therapy for problem sexual behaviors (MST-PSB) reaches as far as young adulthood, the longer-term effects of MST-PSB into midlife are unknown. The present study examined criminal and civil court outcomes for sexually offending youths who participated on average 24.9 years earlier in a clinical trial of MST-PSB (Borduin et al., *Journal of Consulting and Clinical Psychology*, 2009, *77*, p. 26). ***Method:*** Participants were 48 individuals who were originally randomized to MST-PSB or usual community services (UCS) and were at high risk of continued criminality. Arrest, incarceration, and civil suit data were obtained in middle adulthood when participants averaged 39.4 years of age. ***Results:*** Intent-to-treat analyses showed that MST-PSB participants had 85% fewer sexual offenses and 70% fewer nonsexual offenses than did UCS participants. In addition, MST-PSB participants were sentenced to 46% fewer days of incarceration and had 62% fewer family-related civil suits. Moreover, the favorable effects of MST-PSB on participants' crimes and civil suits were mediated by improved peer and family relations during treatment. ***Conclusion:*** The current study represents the longest and most comprehensive follow-up to date of an MST-PSB clinical trial and demonstrates that the positive effects of an evidence-based youth treatment for sexual crimes can last well into adulthood. Implications of the findings for policymakers, service providers, and researchers are discussed.

What is the public health significance of this article?
This study demonstrates that a comprehensive, family-based treatment for youth sexual offending can have a lasting impact on participants' lives. The findings are useful for policymakers and service providers to consider in their selection of mental health interventions for youths who engage in sexual offenses.

Keywords: sexual offense, multisystemic therapy for problem sexual behaviors, MST-PSB, evidence-based treatment, cognitive-behavioral therapy, randomized clinical trial

Sexual offenses engender considerable pain and suffering for victims as well as substantial economic costs for the health care, social services, and criminal justice systems (Hailes et al., 2019; Freyd et al., 2005; Letourneau et al., 2014). Notably, youths under the age of 18 years account for almost one-fifth of all arrests for rape and other sexual assaults (U.S. Department of Justice, 2018) and for more than one-third of all sexual offenses against minors (Finkelhor et al., 2009). Moreover, youths whose sexual offenses are adjudicated through the juvenile justice system are at increased risk for continued criminality, including both sexual and nonsexual offenses, into adulthood (Hagan et al., 2001; Lussier, 2017; Vandiver, 2006). Thus, there is a critical need to develop treatments that can prevent or attenuate persistent criminal activity among youths who engage in sexual offenses.

Historically, juvenile justice and mental health services have had little success in ameliorating sexually offending behaviors in youths (see Brown & Kolko, 1998; Davis & Leitenberg, 1987; Reitzel & Carbonell, 2006, for earlier reviews). Indeed, in the United States, juvenile justice services for youths convicted of sexual offenses have prioritized public safety, resulting in disproportionately punitive and restrictive legal responses such as community notification, sex offender registration, and residential treatment (Chaffin, 2008; Letourneau et al., 2014). Furthermore, mental health services for this population have primarily used cognitive-behavioral therapy (CBT) models that focus on individual-level risk factors

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(e.g., atypical sexual interests, cognitive distortions, problem-solving skills deficits; Hanson, 2014; McGrath et al., 2010). These legal and clinical approaches represent downward extensions of services for adults who offend sexually, despite concerns that such services are largely ineffective (and possibly harmful) with sexually offending youths (Dopp, Borduin, Rothman, & Letourneau, 2017). Although our understanding of service effects has been complicated by the fact that most youths who engage in illegal sexual behaviors have low rates of recidivism for sexual crimes in adulthood (e.g., 5%–7% in meta-analyses by Caldwell, 2010, 2016), it is well-documented that these youths have a similar risk for nonsexual recidivism as do youths who commit nonsexual offenses only (nearly 50%; Caldwell, 2010, 2016) and that a subset of sexually offending youths shows sexual recidivism rates as high as 30%–60% into adulthood (Langstrom, 2002; Lussier et al., 2012). In sum, it seems imperative to move beyond the status quo in our societal responses to youths who commit harmful sexual behaviors.

Recently, there has been increased recognition that the most successful treatments for youths who engage in problem sexual behaviors are comprehensive (i.e., address multiple risk factors for antisocial behavior), include high levels of caregiver involvement, and are individualized to match each youth's strengths and needs (Association for the Treatment of Sexual Abusers, 2012; Dopp, Borduin, Rothman, & Letourneau, 2017; Przybylski, 2015; Seto & Lalumiere, 2010). Examples include a family-oriented CBT treatment (Carpentier et al., 2006) designed as a preventive intervention for sexual behavior problems in younger children, ages 5 to 12 years; and multisystemic therapy for problem sexual behaviors (MST-PSB; Borduin & Munschy, 2014), a more intensive treatment for youths (ages 11 to 17 years) at high risk for continued sexual offending. Among these treatments, MST-PSB has the highest level of empirical support (Dopp, Borduin, Rothman, & Letourneau, 2017), with favorable outcomes in several randomized clinical trials. For example, in a community-based effectiveness trial, Letourneau et al. (2009) showed that MST-PSB was more effective than treatment as usual (i.e., outpatient group CBT) in reducing youth problem sexual behaviors, self-reported delinquency, and out-of-home placements; these positive results were sustained at a 2-year follow-up (Letourneau et al., 2013). Similarly, in an efficacy-effectiveness hybrid trial (i.e., conducted in a university setting but with minimal exclusion criteria) that included an 8.9-year follow-up, Borduin et al. (2009) found that MST-PSB participants had lower recidivism rates than did participants in usual community services (UCS; i.e., outpatient group and individual CBT) for sexual (8% vs. 46%, respectively) and nonsexual (29% vs. 58%, respectively) crimes. This latter study was important in demonstrating the ability of MST-PSB to curtail criminal activity in sexually offending youths through early adulthood.

Although extant research indicates that the positive effects of MST-PSB on serious crime reach as far as young adulthood, the longer-term impact of MST-PSB on criminal activity has not been examined. However, in light of evidence that sexual offending during adolescence can continue into midlife (Lussier et al., 2012), especially for youths who have also committed nonsexual offenses (Beaudry-Cyr et al., 2017; Ronis & Borduin, 2013), it seems important to determine whether MST-PSB is effective in preventing longer-term criminal activity. Information about the lasting benefits of evidence-based treatments such as MST-PSB could assist program administrators in identifying and implementing mental health interventions for youths who engage in sexual offenses. On the other hand, if treatment effects comparable to those observed at shorter follow-ups did not continue for a longer period of time, this could indicate a need for refinements in interventions or for support services throughout adulthood.

In the present study, we examined both sexual and nonsexual offenses among former MST-PSB participants in middle adulthood. In addition, we obtained information about punitive sentencing (i.e., days sentenced to incarceration or probation) for each offense as an index of crime severity. We also examined a noncriminal outcome among the former participants in adulthood. Indeed, to date, we know little about the impact of MST-PSB on areas of functioning outside of involvement in criminal activity. However, there is substantial evidence that youths who engage in serious antisocial activities experience wide-ranging problems that interfere with their ability to accomplish important life tasks (e.g., establish committed romantic relationships; raise children; Farrington et al., 2009; Laub & Sampson, 2003). In this study, we used civil suits as indices of adult functioning in the domain of family relationships to provide a broader picture of the developmental impact of MST-PSB on participants' lives.

Finally, we examined theoretically plausible mediators as well as potential moderators of significant treatment effects on criminal and noncriminal outcomes in midlife. Because the MST-PSB theory of change (Borduin et al., 2016) emphasizes that improved social bonds are key mechanisms in reducing the problem behaviors of sexually offending youths, we assessed both family (i.e., cohesion and adaptability) and peer relations (i.e., attachment to prosocial peers) as potential mediating variables. In addition, based on findings that youths with histories of both sexual and nonsexual offenses frequently associate with peers who also engage in antisocial behaviors (Ronis & Borduin, 2007), we evaluated whether changes in youth involvement with deviant peers mediated changes in outcomes during adulthood. In regard to possible moderators, prior research (Letourneau et al., 2009) had indicated that the effects of MST-PSB were not moderated by perpetrator-victim age differential or level of aggression in the sexual offense. Given those results, as well as a pressing need to evaluate the efficacy of psychosocial treatments for youths and families from different backgrounds (see Pina et al., 2019), we chose to focus on more general demographic and criminal history characteristics as potential moderators, including age, socioeconomic status (SES), race, family composition, and the number of pretreatment arrests.

In summary, the current study from the Missouri Delinquency Project examined criminal and civil court outcomes for youths who participated on average 24.9 years earlier in a randomized clinical trial of MST-PSB (Borduin et al., 2009). Specifically, we evaluated the long-term impact of MST-PSB on the likelihood and number of (a) arrests for sexual and nonsexual offenses, (b) days sentenced to incarceration or probation in criminal court, and (c) civil suits related to family instability. In addition, we examined potential mediators and moderators of treatment effects on criminal offenses, punitive sentencing, and civil suits. As such, this study provides the most comprehensive and longest follow-up of an MST-PSB clinical trial.

Method

Design

In this study, we tracked the long-term criminal and civil court outcomes of 48 youths who received either MST-PSB or UCS in an earlier clinical trial (Borduin et al., 2009). The original trial used a pretest–posttest control group design, with random assignment to treatment conditions (MST-PSB vs. UCS). Because this sample has been described extensively elsewhere, a shorter description of the participants is provided here.

Participants

Participants were the full sample of 48 individuals from the original clinical trial (Borduin et al., 2009). These individuals had been referred to the Missouri Delinquency Project by juvenile court personnel from July 1990 through November 1993. Inclusion in the original study required that youths (a) had been arrested for a serious sexual offense (i.e., rape/sexual assault or molestation of younger children) with a subsequent court order for outpatient sexual offender counseling, (b) were currently living with at least one parent figure, and (c) showed no evidence of psychosis or serious intellectual disability. As depicted in Figure 1, 51 eligible youths and their families were referred to and recruited for the study, and 48 of these youths/families consented to participate and were randomly assigned (using a random number table) to the MST-PSB ($n = 24$) or UCS ($n = 24$) conditions. Pre- and posttreatment assessment batteries were completed by all (100%) of the families in the MST-PSB condition and 22 (91.7%) of the families in the UCS condition. The posttreatment assessment was conducted within 1 week of the end of treatment for each family. Research participation at posttreatment in the UCS condition was attenuated by the out-of-home placement of two youths in Department of Youth Services residential facilities; these youths were classified as dropouts but were included in analyses of rearrests, days sentenced, and civil suits (i.e., intent-to-treat analysis).

The pretreatment arrest histories of the participants attested to their serious criminal involvement: The youths averaged 4.33 arrests ($SD = 4.81$) for sexual ($M = 1.62$) and nonsexual ($M = 2.71$) felonies (83.3% had both types of felonies), and all youths had been detained at least 4 weeks; the MST-PSB and UCS youths did not differ on their arrest histories. The youths' mean age at pretreatment assessment was 14.0 years ($SD = 1.9$); 95.8% were boys and 4.2% were girls; 72.9% were White and 27.1% were Black, and among all youths 2.1% indicated Hispanic ethnicity; and 68.7% lived with two caregivers. The primary caretaker included biological mothers (91.7%), biological fathers (6.3%), or stepmothers (2.1%). The majority (54.2%) of families were of lower SES (Class IV or V; Hollingshead, 1975). As shown in Table 1, MST-PSB and UCS youths did not differ on their demographic characteristics.

Treatment Conditions

The mean length of treatment was 30.8 weeks ($SD = 12.3$) for MST-PSB and 30.1 weeks ($SD = 18.0$) for UCS; these means were not significantly different, $F(1,47) = 0.02$, $p = 0.89$. Variability in the duration of each treatment condition reflected the individualized nature of the interventions as well as varying degrees of success in

Figure 1
Flow Diagram of Participants From Referral to Follow-up

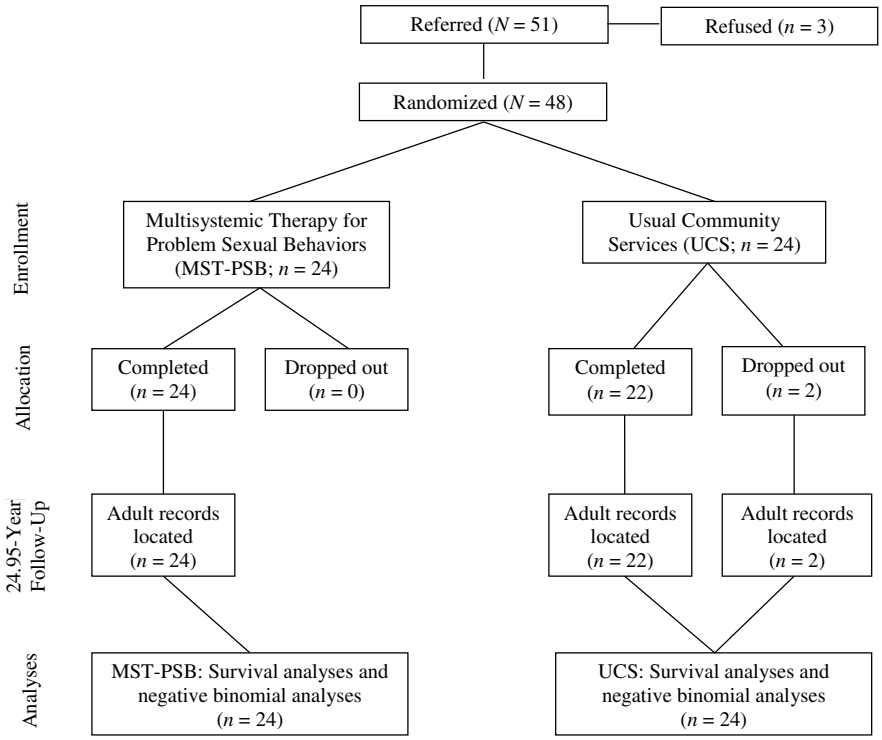


Table 1
Demographic Characteristics of Participants at Pretreatment Assessment

Variable	Group		Analyses	
	MST-PSB	UCS	*T*	χ^2
Age (years)	—	—	0.67	—
M	14.2	13.8	—	—
SD	1.8	2.1	—	—
Male gender (%)	95.8	95.8	—	0.00
Race (%)	—	—	—	0.95
White	79.2	66.7	—	—
Black	20.8	33.3	—	—
Two-caregiver household (%)	70.8	66.7	—	0.10
Social class[a] (%)	—	—	—	0.79
Class V	25.0	16.7	—	—
Class IV	33.3	33.3	—	—
Class III	37.5	41.7	—	—
Class II	4.2	8.3	—	—
Class I	0.0	0.0	—	—

Note. Sample sizes for therapy conditions are as follows: Multisystemic therapy for problem sexual behaviors (MST-PSB; $n = 24$); usual community services (UCS; $n = 24$). For age, $df = 46$; for male gender, race, and one-caregiver household dfs $= 1$; for social class, $df = 4$. For all T and χ^2 values, $ps > .05$.
[a] Based on Hollingshead (1975) Four-Factor Index of Social Status.

achieving treatment goals. Details about the therapists, supervision practices, and treatment fidelity in each condition are provided in Borduin et al. (2009).

Multisystemic Therapy For Problem Sexual Behaviors

Standard MST interventions are described in a clinical volume (Henggeler & Borduin, 1990) and treatment manual (Henggeler, Schoenwald, et al., 2009). These interventions fit closely with findings from research on the correlates of serious antisocial behavior, including juvenile sexual offending (e.g., McCuish et al., 2015; Ronis & Borduin, 2007; Seto & Lalumiere, 2010), and target a comprehensive set of risk factors (e.g., across individual, family, peer, and school domains) using an individualized approach. The MST model uses a broad-based ecological framework to integrate evidence-based clinical techniques from behavioral and cognitive-behavioral therapies and structural/strategic family therapy.

MST-PSB is an adaptation of standard MST for youths with problem sexual behaviors (Borduin & Munschy, 2014). The MST-PSB model is based on the same principles and relies on many of the same evidence-based techniques as in standard MST but focuses on aspects of the youth's social environment that are functionally related to the problem sexual behavior. Family-level interventions in MST-PSB often focus on (a) reducing caregiver and youth denial about the problem sexual behaviors and their sequelae; (b) implementing effective parenting practices (i.e., rules, privileges, and consequences) that are appropriate to the youth's developmental stage; (c) supporting caregivers in the development and ongoing adaptation of plans for risk reduction, relapse prevention, and victim safety; and (d) promoting cohesion and communication between family members. Peer-level interventions are conducted by the youth's caregivers, with the guidance of the therapist, and often include active encouragement of relationship skills and friendships with nonproblem (i.e., prosocial) peers, as well as substantive discouragement of associations with deviant peers (e.g., applying compelling sanctions). Similarly, at the school level, the therapist helps caregivers to promote the youth's academic progress (e.g., facilitate communication between caregivers and teachers, restructure after-school hours to enhance academic efforts). Finally, individual interventions are sometimes used with a youth or caregiver to alter perspective-taking skills, beliefs, or attitudes that contribute to problem sexual behavior.

As in standard MST, MST-PSB was provided in the family's natural ecology (home, school, and/or neighborhood) and at convenient times for the family's schedule. Interventions were delivered by graduate students in clinical psychology, each of whom had approximately 1.5 years of clinical experience with children or adolescents. Youths and their families received about 3 hr of intervention per week (i.e., across family, school, peer, and individual systems). Given the complexity of many cases involving youths with problem sexual behaviors (including intense community safety concerns), the MST-PSB condition had a higher average length of treatment (i.e., 7 months) and smaller therapist caseloads (i.e., 4–5 families) compared to standard MST; these parameters are consistent with quality assurance standards for MST-PSB (see Borduin et al., 2016).

Usual Community Services

The youths in this condition received cognitive-behavioral group and individual therapy through the treatment services branch of the local juvenile court. This condition represented the usual community (i.e., outpatient) treatment for youths with illegal sexual behaviors in our judicial district and in the vast majority of other judicial districts as well (see McGrath et al., 2010). Each of the therapists was licensed; had a master's degree in counseling psychology, clinical psychology, or social work; and had been certified through a university-based training program for the treatment of youths with illegal sexual behaviors. The youths attended group therapy for 90 min twice a week and individual therapy for 60–90 min once a week. Group therapy (4–6 youths who were participants in the clinical trial) focused on having each youth (a) take responsibility for his or her sexual offense(s), (b) eliminate deviant sexual cognitions, (c) learn new social skills (including anger management), (d) develop awareness and empathy for victims, and (e) engage in behaviors and thoughts that prevent relapse. Individual treatment for each youth was provided by a therapist other than the youth's group leader and was designed to reinforce progress in meeting group therapy goals.

Research Procedures

The Institutional Review Board of the University of Missouri approved all procedures. Those procedures and measures relevant to the present study are described below.

Original Outcome Study

Families referred to the project were contacted by telephone or home visit and asked to participate in a 2-hr research assessment prior to the start of treatment and again after treatment had ended. Families were informed that participation in the research was

voluntary and that refusing to participate or discontinuing participation would not jeopardize the receipt of treatment services or result in sanctions from the court. Families were also informed that juvenile arrest records would be collected through the youths' 17th birthdays and that adult arrest records and other public records would be obtained for the youths thereafter. Family members provided written consent (caregivers) or assent (youths) for the pretreatment/posttreatment research assessments and follow-ups. After completion of the pretreatment assessment, a sealed envelope was opened, and the family was informed of the treatment condition to which they had been randomized. The posttreatment assessment included the same measures as the pretreatment assessment. A teacher of the youth also completed a paper-and-pencil measure before and after treatment; the teacher was randomly selected and told that the youth was a participant in a study of adolescent socialization. Original study procedures are described more fully in Borduin et al. (2009).

Present Study

Public information for criminal (i.e., arrests and sentencing) and noncriminal (i.e., civil suits) court records was obtained within the state of Missouri. We confirmed Missouri residency to determine whether each participant had lived in the state since the time of an earlier follow-up completed in October 2001 (Borduin et al., 2009) and, thus, whether they were available to have a court record (i.e., arrests, sentencing, and civil suits) in the state through October 2017, when the present follow-up was completed. Accordingly, several steps were followed to confirm residency. First, we searched state court records and noted all records that were registered after the end of treatment for a given individual. Second, for individuals whose names did not appear in state court records, we conducted a search of state driver's license records; an individual was considered a Missouri resident if they held a Missouri driver's license. Third, we searched property ownership and marital records for individuals for whom there were no court records or driver's license records. Finally, we used addresses of parents to confirm residence in the state of several remaining individuals who could not be located through earlier steps. Each individual's follow-up period was anchored by the date of release from juvenile probation (i.e., within 2 weeks of treatment termination for completers and an average of 7 months from the time of referral for dropouts) and ran through the latest date for which the individual youth could be confirmed to live in the state. Overall, we located 100% of the sample ($N = 48$) and determined that all participants had lived in the state since the time of the prior follow-up period (during which the entire sample had also lived in the state).

Outcome Measures

We used both juvenile and adult criminal records as well as adult civil court records in the current study. Borduin et al. (2009) obtained juvenile criminal records in the original trial through yearly juvenile office records searches by research assistants who were uninformed as to each participant's treatment condition. For the present study, we obtained adult criminal and civil court records, which are available to the public in the state of Missouri, using an Internet database searched separately by two research assistants (also uninformed as to treatment condition). The research assistants searched the records following a standardized protocol that used participants' names, known aliases, alternative first names (e.g., Bob for Robert), and alternative last names for women who may have changed their names due to marriage or remarriage (based on state-level court records and county-level marriage records).

We took several steps to reduce the possibility of false positives for those participants whose names appeared in court records. First, we matched participants to records by date of birth, middle name or middle initial, and suffixes (e.g., Jr.). Second, when those indicators were absent, we matched the participant to records based on similarity to cases that met the first search criterion, including previously known addresses, court locations, and names of other persons listed on the docket (e.g., spouses). We were able to match all of the participants' records using these steps.

For both juvenile and adult criminal records, we focused on arrests for felony offenses because these offenses generally pose the greatest threat to public safety. We included only substantiated arrests (i.e., convictions) in the data set and did not record charges that were dismissed or that were not yet disposed at the time of data collection. We coded each offense by date of arrest and classified each offense as either a sexual (e.g., rape, child molestation) or a nonsexual crime (e.g., breaking and entering, physical assault, distribution of cocaine). We measured sentencing for juveniles as the number of days that a youth was assigned to a Department of Youth Services residential facility. We measured sentencing for adults as the number of days that an individual was assigned to incarceration and/or probation; when an incarceration sentence had been suspended in favor of probation, we recorded only the days sentenced to probation. We combined juvenile and adult criminal records in our analyses to provide a complete record of all offenses (i.e., number and type) and sentencing. The average length of the follow-up period was 24.95 years ($SD = 1.02$; range = 23.23–26.56 years).

From civil court files, we recorded suits reflective of family instability (i.e., domestic or adult abuse, child protection or endangerment, and paternity) in which the participant in our study was the respondent (i.e., person against whom the suit was filed). We assumed that the respondents in such suits would generally display coercive behaviors (e.g., manipulation and intimidation) in their family relationships and that such behaviors are relatively common in families with high rates of antisocial behavior (Patterson, 2016). There were no instances in which a participant in our study was the petitioner (i.e., initiator) in a family instability suit. Again, we recorded only those cases that had been disposed at the time of data collection.

We provided approximately 20 hr of training to the research assistants prior to their coding of court records, and we assessed their interrater reliability on 30% of the participants. There were no discrepancies between the results obtained by the research assistants ($k = 1.0$). The intraclass correlation between the five outcome variables (i.e., sexual crimes, nonsexual crimes, incarceration days, probation days, and family instability suits) was .091 (95% confidence interval = −.004–.224, $p = .031$), indicating a small level of overlap among the variables.

Measures of Potential Mediators of Treatment Effects

We examined two sets of hypothesized mediators of treatment effects on youths' long-term outcomes. The putative mediators

included youth peer relations (two measures) and family relations (two measures). The participants completed the measures of these domains during the aforementioned 2-hr pretreatment and posttreatment assessment sessions in the clinical trial. All of the measures had demonstrated favorable outcomes (i.e., significantly more positive changes) for MST-PSB participants relative to UCS participants in the trial.

Peer Relations

We assessed both youth attachment (i.e., emotional bonding) to prosocial peers and youth association with deviant peers. We measured *attachment to prosocial peers* using caregiver and teacher reports on the five-item Emotional Bonding subscale from the Missouri Peer Relations Inventory (MPRI-EB; Borduin et al., 1989). Item scores range from 1 (*rarely*) to 5 (*often*). Coefficient alphas for caregiver and teacher reports, respectively, were .79 and .74; we averaged these reports to create a composite score. The *M*s (and *SD*s) for the MPRI-EB composite score at pretreatment and posttreatment, respectively, were 12.28 (3.99) and 15.19 (3.02) for MST-PSB participants, and 12.79 (2.91) and 10.95 (3.02) for UCS participants. We measured a*ssociation with deviant peers* through caregiver reports on the 17-item Socialized Aggression subscale from the Revised Behavior Problem Checklist (RBPC-SA; Quay & Peterson, 1987). Item scores range from 0 (*no problem*) to 2 (*severe problem*). The coefficient alpha was .81 in the current study. The *M*s (and *SD*s) on the RBPC-SA at pretreatment and posttreatment, respectively, were 9.10 (4.80) and 3.35 (2.81) for MST-PSB participants, and 7.91 (4.06) and 11.77 (6.59) for UCS participants.

Family Relations

We measured caregiver and youth perceptions of family relations with the 30-item Family Adaptability and Cohesion Evaluations Scales-II (FACES-II; Olson et al., 1982). The FACES-II assesses the dimensions of *adaptability*, which refers to the capacity of the family system to change its power structure, role relations, and relationship rules in response to situational and developmental stress; and *cohesion*, defined as the emotional bonding and individual autonomy of family members. Respondents rate the Likert-type items on a scale from 1 (*almost never*) to 5 (*almost always*). Coefficient alphas for the adaptability and cohesion subscales, respectively, were .83 and .88 for caregivers' reports, and .79 and .90 for youths' reports. We created composite ratings of adaptability and cohesion by averaging caregiver and youth scores on each scale. For the adaptability composite, the *M*s (and *SD*s) at pretreatment and posttreatment, respectively, were 33.11 (13.83) and 41.47 (12.36) for MST-PSB participants, and 40.10 (12.96) and 35.91 (13.45) for UCS participants. For cohesion, the *M*s (and *SD*s) at pretreatment and posttreatment, respectively, were 45.74 (12.62) and 53.58 (10.63) for MST-PSB participants, and 50.91 (12.67) and 47.42 (14.88) for UCS participants.

Measures of Potential Moderators of Treatment Effects

We also evaluated demographic and criminal history variables as possible moderators of treatment effects on participants' outcomes in adulthood. These variables included youth age (in years) at pretreatment assessment, SES (five categories based on Hollingshead, 1975), race (all families were Black or White), number of caregivers in the home (one vs. two), and number of pretreatment arrests.

Results

We used three sets of analyses to examine differences between the MST-PSB and UCS groups on criminal and civil court outcomes. First, we used descriptive statistics to evaluate the percentages and relative odds of dichotomous outcomes (e.g., rearrested vs. not rearrested) for each group. Second, we used survival analyses to examine between-group differences in length of time to the first instance of a given outcome (i.e., rearrest and civil suit). Third, we used negative binomial regression analyses to estimate differences between groups on continuous outcomes (i.e., number of rearrests, days sentenced to incarceration or probation, and civil suits). In addition, we used causal mediation analyses to evaluate the effects of potential mediators of treatment outcomes, and we used negative binomial regression analyses to evaluate the effects of potential moderators of treatment outcomes.

Relative Odds of Rearrests and Civil Suits

We computed the percentages and relative odds of felony rearrests and civil suits in the UCS group versus the MST-PSB group. Odds ratios greater than 1.0 denoted higher odds for UCS participants relative to MST-PSB participants; results for which the associated confidence interval did not include 1.0 were unlikely to occur by chance (Cohen, 1994). As described in Table 2, 79.2% of UCS participants versus 37.5% of MST-PSB participants had been rearrested at least once by the end of the 24.95-year follow-up period; the odds of recidivism for any felony offense during follow-up were 6.33 times higher for the UCS group than for the MST-PSB group ($p = .003$). Similarly, when crime subtypes were examined, youths in the UCS group were 8.27 times more likely to have an arrest for a sexual offense ($p = .002$) and 3.40 times more likely to have an arrest for a nonsexual offense ($p = .042$). Regarding civil court outcomes, the odds of involvement in suits related to family

Table 2
Percentages and Odds of Arrests and Civil Suits During Follow-Up by Therapy Condition

Variable	%	*OR*	95% CI
Criminal arrests			
Any offense	—	6.33	[1.75, 22.91]
UCS	79.2	—	—
MST-PSB	37.5	—	—
Any sexual offense	—	8.27	[1.94, 35.34]
UCS	54.2	—	—
MST-PSB	12.5	—	—
Any nonsexual offense	—	3.40	[1.03, 11.26]
UCS	62.5	—	—
MST-PSB	29.2	—	—
Family civil suits	—	3.80	[1.11, 14.58]
UCS	50.0	—	—
MST-PSB	20.8	—	—

Note. Sample sizes for therapy conditions are as follows: Usual community services (UCS; $n = 24$); multisystemic therapy for problem sexual behaviors (MST-PSB; $n = 24$). *OR* = odds ratio; CI = confidence interval.

instability were 3.80 times greater for UCS participants than for MST-PSB participants ($p = .039$).

Survival Functions for Rearrests and Civil Suits

We used survival analyses (Cox proportional hazards regressions; SPSS for Windows, Version 26.0) to obtain cumulative survival functions for rearrest outcomes among participants who received either MST-PSB or UCS, whose average follow-up periods were 24.92 and 24.98 years, respectively. Survival analyses are useful because they model data that are censored (i.e., when some participants do not experience an event, such as arrest; Keiley & Martin, 2005). The cumulative survival function represents the proportion of participants who survived any type of felony arrest (i.e., were not arrested) in each group by the length of time (in years) from release from treatment. As depicted in Figure 2, a log-rank test (with the Kaplan–Meier estimator; Kaplan & Meier, 1958) revealed that the survival functions for the two groups on any offense were significantly different, $\chi^2(1, N = 48) = 7.98$, $p = .005$, with MST-PSB participants at lower risk of rearrest (i.e., more likely to survive) during follow-up than were UCS participants. The hazard ratio for the treatment group was 1.01, suggesting a large effect size for MST-PSB.

We also used survival analyses to examine between-group differences on time to first arrest for different types of felony crimes. The results demonstrated that MST-PSB participants were at significantly lower risk of arrest for both sexual offenses, $\chi^2(1, N = 48) = 11.65$, $p = .001$; and nonsexual offenses, $\chi^2(1, N = 48) = 3.75$, $p = .05$. The hazard ratio tests of these survival functions again suggested large effect sizes for MST-PSB versus UCS (sexual offenses, ß = 1.22; nonsexual offenses, ß = 1.12).

Finally, we used a survival analysis to compare MST-PSB and UCS participants on time to a first civil suit related to family instability. As shown in Figure 3, MST-PSB participants were at lower risk of involvement in family instability suits than were UCS participants, $\chi^2(1, N = 48) = 4.44$, $p = .035$; the hazard ratio (ß = 0.98) indicated a large effect size for MST-PSB.

Number of Arrests, Days Sentenced, and Civil Suits

We conducted additional analyses to examine the number of criminal and civil suit outcomes among participants in the MST-PSB and UCS groups. The outcome variables in this study can be considered censored-dependent variables (see Greene, 1993) because they are continuous, nonnormal, and nonnegative (i.e., no negative values). Furthermore, the majority of the variables were overdispersed (i.e., variance exceeded mean). Accordingly, we used negative binomial regression analyses (see Osborn & Tseloni, 1998) to evaluate between-group differences in the number of (a) felony arrests, (b) days sentenced to incarceration or probation, and (c) civil suits during the follow-up period. These differences were expressed as the rate of a given outcome among UCS participants relative to MST-PSB participants. We used the "MASS" package (Venables & Ripley, 2002) in R (version 3.6.1; R Core Team, 2019) to compute all negative binomial regressions, in which we dummy-coded treatment condition (with UCS = 1 and MST-PSB = 0). We present descriptive statistics and regression coefficients in Table 3.

Figure 2

Survival Functions for Multisystemic Therapy for Problem Sexual Behaviors (MST-PSB) and Usual Community Services (UCS) Groups on Time to First Arrest for Any Offense Following Treatment

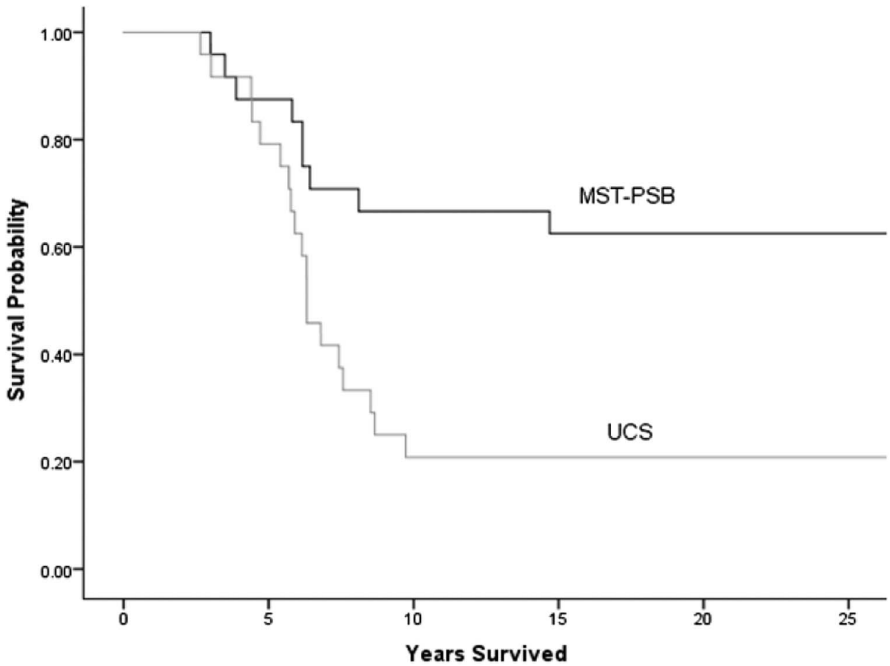
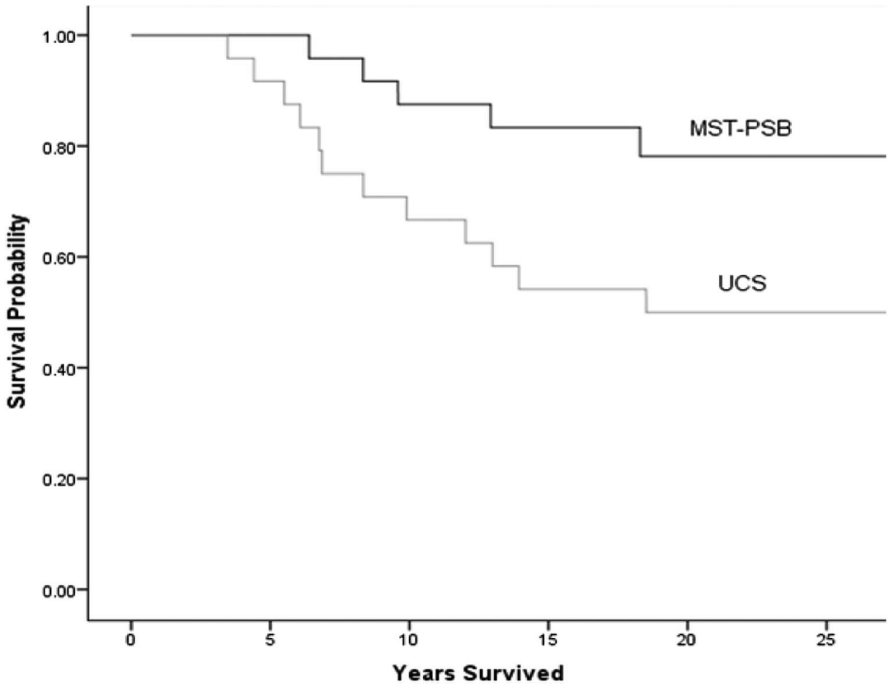


Figure 3
Survival Functions for Multisystemic Therapy for Problem Sexual Behaviors (MST-PSB) and Usual Community Services (UCS) Groups on Time to First Civil Suit Related to Family Instability Following Treatment



For criminal outcomes, the results showed that the estimated rate of any felony offense for UCS participants was 4.67 times higher than for MST-PSB participants. In addition, the estimated rates of sexual offenses and nonsexual offenses, respectively, were 13.13 and 3.79 times higher for participants in the UCS group than for their MST-PSB counterparts. Moreover, results demonstrated that the estimated rates of days sentenced to incarceration and probation, respectively, were 5.25 and 2.67 times greater for UCS participants than for MST-PSB participants. For civil suit outcomes, a nonsignificant trend ($p = .065$) revealed that the estimated rate of involvement in family instability suits was 1.13 times greater for participants in the UCS group relative to participants in the MST-PSB group.

Potential Mediators of Arrests, Days Sentenced, and Civil Suits

We used causal mediation analyses to evaluate whether the positive effects of MST-PSB on participants' outcomes during follow-up were mediated by pre- to posttreatment (a) increases in youth attachment to prosocial peers, (b) decreases in youth association with deviant peers, and (c) improvements in family relations.

Table 3
Descriptive Statistics and Negative Binomial Regression Results for Criminal and Civil Suit Outcomes

Variable	MST-PSB		UCS		Regression coefficient
	M	*SD*	*M*	*SD*	
Criminal arrests (no.)					
Any offense	1.26	2.07	4.67	7.35	4.67**
Sexual offense	0.13	0.34	0.88	1.08	13.13**
Nonsexual offense	1.13	1.85	3.79	6.97	3.79*
Punitive sentencing (days)					
Incarceration	1,040.96	2,198.81	1,939.48	3,261.68	5.25***
Probation	836.42	1,110.36	978.87	1,366.04	2.67***
Family civil suits (no.)	0.42	0.93	1.12	1.70	1.13+

Note. Sample sizes for therapy conditions are as follows: Multisystemic therapy for problem sexual behaviors (MST-PSB; $n = 24$); usual community services (UCS; $n = 24$).
+ $p = .065$. * $p < .05$. ** $p < .01$. *** $p < .001$.

Results for which the associated confidence interval did not include zero were unlikely to occur by chance. Imai et al. (2010) developed a causal mediation framework for linear models with continuous and count variables, which made it an ideal technique for testing mediation with our outcome data. We used the "Mediation" package (Tingley et al., 2014) in R (version 3.6.1; R Core Team, 2019) to compute all causal mediation analyses.

Most (94.4%) of the data for the potential mediating variables were available from the original clinical trial; the MST-PSB and UCS participants did not differ significantly in their amounts of missing data, $F(1,47) = 0.64$, $p = .43$. Aside from the two treatment dropouts in the UCS condition, there were no observable patterns in the missing data, suggesting that the data were missing at random and able to be replaced through multiple imputation (Little & Rubin, 2014), as recommended by Enders and Baraldi (2018). Although the original trial used random assignment to MST-PSB or UCS, we calculated residualized change scores for each group on the potential mediating variables to control for possible between-group differences on these variables at pretreatment. We used the residuals derived from this procedure as the indices of change.

As shown in Table 4, the results demonstrated that improvements in youths' peer and family relations during treatment had significant causal mediating effects on long-term outcomes in MST-PSB. Below, we describe the nature of the significant mediating effects on these outcomes (i.e., criminal arrests, punitive sentencing, and civil suits).

Criminal Arrests

An increase in youths' attachment to prosocial peers (as reported by caregivers and teachers on the MPRI) mediated the lower rates of sexual offenses for MST-PSB participants. In addition, a reduction in youths' association with deviant peers (as reported by caregivers on the RBPC) mediated the lower rates of nonsexual offenses for MST-PSB participants, although the mediating effect was only marginally significant ($p = .09$).

Punitive Sentencing

A reduction in youths' involvement with deviant peers (RBPC) also mediated the lower number of days that MST-PSB participants were sentenced to incarceration. Furthermore, reduced involvement with deviant peers mediated the effect of MST-PSB on the days that participants were sentenced to probation.

Civil Suits

An increase in caregivers' and youths' perceived adaptability (composite measure) on the FACES-II mediated the effect of MST-PSB on participants' lower involvement in family instability suits. Similarly, an increase in family members' perceived cohesion (FACES-II) also mediated the effect of MST-PSB on involvement in family instability suits.

Potential Moderators of Arrests, Days Sentenced, and Civil Suits

We also used negative binomial regression analyses to evaluate whether the positive effects of MST-PSB on participants' long-term outcomes (i.e., numbers of arrests, days sentenced to incarceration or probation, and civil suits) were moderated by demographic (i.e., age, SES, race, and two-caregiver household) and criminal history variables (i.e., pretreatment arrests). For each regression, we simultaneously entered a dummy variable (for the treatment group), the moderating variable, and the cross-product term of the treatment group and the moderating variable. We centered continuous moderator variables around their means in each cross-product term. A significant regression coefficient for the cross-product term denoted whether MST-PSB was differentially effective with youths from dissimilar backgrounds. The analyses revealed no significant moderator for any outcome variable.

Discussion

The current study is the longest and most comprehensive follow-up to date of an MST-PSB clinical trial. Over a period extending 24.9 years after the end of treatment, the results demonstrated that MST-PSB participants were less likely to be arrested for any felony offense than were UCS participants (37.5% vs. 79.2%). More specifically, MST-PSB participants had 85% fewer arrests for sexual offenses and 70% fewer arrests for nonsexual offenses during follow-up than did UCS participants. In addition, MST-PSB

Table 4
Causal Mediation Analyses Evaluating Peer and Family Relations Measures as Mediators of MST-PSB Outcomes

	Peer relations				Family relations			
	Prosocial peers (MPRI-EB)		Deviant peers (RBPC-SA)		Adaptability (FACES-II)		Cohesion (FACES-II)	
Outcome Variable	ß	95% CI	ß	95% CI	ß	95% CI	ß	95% CI
Criminal arrests								
Sexual offense	−0.14*	[−0.27, −0.02]	0.01	[−0.16, 0.19]	0.04	[−0.09, 0.16]	0.04	[−0.08, 0.16]
Nonsexual offense	−1.54	[−4.70, 1.46]	4.63+	[−1.16, 10.84]	1.31	[−1.91, 4.74]	1.22	[−1.85, 4.30]
Punitive sentencing								
Incarceration	3.09	[−19.79, 13.83]	35.59*	[4.98, 67.08]	4.79	[−12.31, 22.21]	5.06	[11.89, 22.34]
Probation	−0.30	[−2.23, 1.76]	2.67*	[.07, 4.75]	0.71	[−1.42, 2.83]	0.98	[−1.08, 2.87]
Family civil suits	0.10	[−0.17, 0.40]	0.09	[−0.34, 0.53]	−0.33**	[−0.65, −0.06]	−0.36**	[−0.69, −0.11]

Note. Sample sizes for therapy conditions are as follows: Multisystemic therapy for problem sexual behaviors (MST-PSB; $n = 24$); usual community services ($n = 24$). MPRI-EB = Missouri Peer Relations Inventory, Emotional Bonding subscale; RBPC-SA = Revised Behavior Problem Checklist, Socialized Aggression subscale; FACES-II = Family Adaptability and Cohesion Evaluation Scales-II; CI = Confidence Interval.
+ $p = .09$. * $p < .05$. ** $p < .01$.

participants were sentenced to 46% fewer days of incarceration than were UCS participants. Moreover, the odds of being involved in civil suits related to family instability were 3.80 times lower for MST-PSB participants than for UCS participants. Notably, the positive effects of MST-PSB on participants' long-term criminality and civil suits were mediated by improved relations with peers and family members. Furthermore, consistent with the conclusions of reviewers about the cross-cultural effectiveness of standard MST (e.g., Pina et al., 2019), analyses of potential moderators (e.g., race, SES) suggested that MST-PSB was not differentially effective with participants from different backgrounds.

The results show that MST-PSB had enduring effects in reducing serious criminal offenses (i.e., felonies) and incarceration among former participants. These results extend those of an earlier follow-up with the current sample in which MST-PSB participants were less likely to be rearrested and imprisoned 8.9 years after treatment (Borduin et al., 2009). The lasting impact of MST-PSB on criminal activity and its consequences for almost a quarter-century is especially important given the urgent need for interventions that can prevent or attenuate serious antisocial behavior in youths, including sexual violence and abuse. Although the childhood behavioral histories of the individuals in the present sample are not known, their arrest records prior to treatment ($M = 4.33$ felonies across treatment conditions) and high rates of recidivism at follow-up (79% in the UCS condition) suggest that these individuals are largely representative of those slow-to-desist (i.e., life-course-persistent) offenders who are of greatest concern to researchers, policymakers, and the broader community (see Lussier, 2017; Moffitt, 2018).

The favorable effects of MST-PSB on criminal outcomes in adulthood are likely due, at least in part, to the capacity of MST-PSB interventions to address empirically identified risk and protective factors for youth antisocial behavior. Regarding risk factors, results of the causal mediation analyses indicated that the positive impact of MST-PSB on rates of nonsexual offending and punitive sentencing (i.e., incarceration and probation) during follow-up were mediated by reductions in youth involvement with deviant peers. These results, in conjunction with those from a previous study of MST-PSB mediators of short-term (i.e., 1-year follow-up) improvements in self-reported antisocial behavior (Henggeler, Letourneau, et al., 2009), suggest that empowering caregivers to discourage their youths' associations with deviant peers is essential to the amelioration of youth criminality in MST-PSB. At the same time, it would appear that caregiver support of youth involvement with prosocial peers is also critical to the success of MST-PSB. Indeed, our results showed that the positive effect of MST-PSB on rates of sexual offending was mediated by increases in youth attachment to prosocial peers. When one considers that youths who engage in sexual offenses often have difficulty maintaining close interpersonal relations and are isolated from prosocial peers (Blaske et al., 1989; Ronis & Borduin, 2007), the explicit focus of MST-PSB on helping caregivers to promote healthier (i.e., positive, age-appropriate, and strength focused) peer relations and activities (e.g., sports, church youth groups, clubs) for their youths would seem to be particularly important in the treatment of sexual offending.

Civil court records revealed that MST-PSB participants had 62% fewer suits related to family instability than did their UCS counterparts. In addition, the positive effect of MST-PSB on participants' civil suits was mediated by increases in both family adaptability and cohesion. These results are consistent with the emphasis that MST-PSB places on the development of effective parenting strategies as well as on the promotion of warmth and affection between family members (Borduin & Munschy, 2014). Nevertheless, the long-term influence of family interventions in MST-PSB has not been demonstrated previously and is noteworthy because such interventions appear to play a durable role in preventing difficulties in family relations during adulthood (i.e., as indexed by suits related to family instability). Of course, it would be more conclusive to directly measure family relations (and other domains of functioning) among former MST-PSB participants and their children, and we plan to do so in future research. Indeed, considering the present findings as well as a host of investigations documenting the intergenerational transmission of psychosocial risk (see Besemer et al., 2016; Serbin & Karp, 2004; Thornberry, 2005), it seems reasonable to propose that the benefits of MST-PSB may carry over from former participants to their offspring.

Viewed together, the results of this study also have important clinical and policy implications. At a clinical level, there is increasing recognition that serious antisocial behaviors in youths, including both sexual and nonsexual offenses, share a number of common risk factors across multiple levels of the youth's social ecology (McCuish et al., 2015; Seto & Lalumiere, 2010) and that the most effective treatments for youth antisocial behaviors are designed to address those risk factors (Dopp, Borduin, White, & Kuppens, 2017; McCart & Sheidow, 2016). Because MST-PSB was adapted from a well-established treatment approach for nonsexual offending in youths (i.e., standard MST), the present findings augur well for adapting other effective approaches for youth nonsexual offending [e.g., Treatment Foster Care Oregon (Chamberlain, 2003); Functional Family Therapy (Alexander et al., 2000)] to the treatment of youth sexual offending, given the considerable overlap in clinical emphases (i.e., comprehensive interventions across key social systems, ecologically valid service delivery). At a policy level, the reductions in criminality in the MST-PSB condition speak to the fiscal viability of this treatment. In fact, a cost-benefit study (Dopp, Borduin, Willroth, & Sorg, 2017) based on the 8.9-year follow-up in our original clinical trial indicated that reductions in arrests associated with MST-PSB led to economic benefits for both taxpayers and crime victims, with cumulative benefits ranging from $343,445 to $450,366 per participant; stated differently, every dollar spent on MST-PSB recovered $48.81 to $61.98 in savings to taxpayers and crime victims over the follow-up. The continuing effectiveness of MST-PSB in reducing criminal activity, as demonstrated in the present study, should result in even greater economic savings and create a compelling argument for increased funding of comprehensive family-based treatments for youths with sexual offenses.

It should be noted that the present study has several methodological limitations. First, the felony arrest records that we used to measure criminal offenses during follow-up are likely an underestimate of actual criminal activities because (a) felony offenses are sometimes pleaded down to less serious (i.e., misdemeanor) offenses and (b) many offenses (both felonies and misdemeanors) are not reported and adjudicated (see Loeber & Farrington, 1998). However, felony arrest records are a key index of involvement in crime and likely provided an accurate estimate of the relative effectiveness of the two treatment conditions in our study. Second, while we determined that all of the participants were residing in

Missouri at the time of the present follow-up, we could not confirm that participants had (a) maintained continuous residency in the state for the entire follow-up period or (b) not committed crimes in other states. Nevertheless, it is unlikely that residency length or a number of crimes committed outside of Missouri would vary systematically by treatment condition. Third, the original trial did not assess potential mediating variables at times other than pretest and posttest; thus, it is possible that we missed some important mediational pathways during the course of treatment or follow-up. Finally, given the relatively modest sample size in this study, a few of our findings reached only marginal levels of statistical significance. Even so, in an area of research in which randomized trials are rare, the present study can provide useful information on the enduring benefits of an evidence-based treatment for problem sexual behavior (for a discussion of the statistical justification of knowledge, see Rosnow & Rosenthal, 1989).

In conclusion, the results of this study provide additional support for the effectiveness of MST-PSB with sexually offending youths, whose behaviors pose a high risk of harm yet are often treated with interventions that lack an evidence base. Over a follow-up period that extended into middle adulthood, MST-PSB produced lasting reductions in a broad range of serious criminal offenses and in civil suits related to family instability. In addition, the positive effects of MST-PSB on participants' outcomes during follow-up were mediated by improvements in peer and family relations during treatment. As evidence-based treatments are disseminated more broadly, our findings should be considered by policymakers and service providers in the adoption of interventions for youths with problem sexual behaviors. Moreover, our hope is that the favorable results of this study correspond to more satisfying lives for youths and their families, increases in cost savings for taxpayers, and lower risks of victimization for members of the community.

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RESEARCH

Preventing sexual abusers of children from reoffending: systematic review of medical and psychological interventions


OPEN ACCESS

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Abstract

Objective To evaluate the effectiveness of current medical and psychological interventions for individuals at risk of sexually abusing children, both in known abusers and those at risk of abusing.

Design Systematic review of interventions designed to prevent reoffending among known abusers and prevention for individuals at risk of sexually abusing children. Randomised controlled trials and prospective observational studies were eligible. Primary outcomes were arrests, convictions, breaches of conditions, and self reported sexual abuse of children after one year or more.

Results After review of 1447 abstracts, we retrieved 167 full text studies, and finally included eight studies with low to moderate risk of bias. We found weak evidence for interventions aimed at reducing reoffending in identified sexual abusers of children. For adults, evidence from five trials was insufficient regarding both benefits and risks with psychological treatment and pharmacotherapy. For adolescents, limited evidence from one trial suggested that multisystemic therapy prevented reoffence (relative risk 0.18, 95% confidence interval 0.04 to 0.73); lack of adequate research prevented conclusions about effects of other treatments. Evidence was also inadequate regarding effectiveness of treatment for children with sexual behavioural problems in the one trial identified. Finally, we found no eligible research on preventive methods for adults and adolescents who had not sexually abused children but were at higher risk of doing so (such as those with paedophilic sexual preference).

Conclusion There are major weaknesses in the scientific evidence, particularly regarding adult men, the main category of sexual abusers of children. Better coordinated and funded high quality studies including several countries are urgently needed. Until conclusive evidence is available, realistic clinical strategies might involve reduction of specific risk factors for sex crimes, such as sexual preoccupation, in abusers at risk of reoffending.

Introduction

Sexual abuse of children is a global problem, and systematic reviews suggest that 18-20% of women and 7-8% of men in the general population report being abused before the age of 18.[1 2] Rates have not differed substantially in recent decades but might vary across regions.[2]

Although most research designs are suboptimal for robust conclusions regarding causal effects, sexual violence is undoubtedly associated with a lasting impact on the health of children who have been abused.[3-6] Putative consequences include risky sexual behaviour, chronic pain syndromes, anxiety, and depressive disorders including post-traumatic stress disorder,[7-9] substance misuse,[7-10] suicide attempts,[8] and sexually aggressive behaviour.[11-13] Identified associations are generally small to moderate in size and are influenced by sample origin and size.

The high prevalence and adverse consequences of sexual abuse of children warrant increased investment in development of preventive and therapeutic strategies.[14-16] Such efforts should directly deal with children, their caregivers, and their environments to prevent potential abuse and effectively manage

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Extra material supplied by the author (see http://www.bmj.com/content/347/bmj.f4630?tab=related#webextra)

Appendix 1: Search strategies, assessment of risk of bias, and the GRADE system
Appendix 2: Supplementary tables (GRADE evidence)
Appendix 3: Study evaluation protocols

Psychological interventions for adults who have sexually offended or are at risk of offending (Review)

Dennis JA, Khan O, Ferriter M, Huband N, Powney MJ, Duggan C

This is a reprint of a Cochrane review, prepared and maintained by The Cochrane Collaboration and published in *The Cochrane Library* 2012, Issue 12

http://www.thecochranelibrary.com

[Intervention Review]

Psychological interventions for adults who have sexually offended or are at risk of offending

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ABSTRACT

Background

Sexual offending is a legal construct that overlaps, but is not entirely congruent with, clinical constructs of disorders of sexual preference. Sexual offending is both a social and a public health issue. Victim surveys illustrate high incidence and prevalence levels, and it is commonly accepted that there is considerable hidden sexual victimisation. There are significant levels of psychiatric morbidity in survivors of sexual offences.

Psychological interventions are generally based on behavioural or psychodynamic theories.

Behavioural interventions fall into two main groups: those based on traditional classical conditioning and/or operant learning theory and those based on cognitive behavioural approaches. Approaches may overlap. Interventions associated with traditional classical and operant learning theory are referred to as behaviour modification or behaviour therapy, and focus explicitly on changing behaviour by administering a stimulus and measuring its effect on overt behaviour. Within sex offender treatment, examples include aversion therapy, covert sensitisation or olfactory conditioning. Cognitive behavioural therapies are intended to change internal processes - thoughts, beliefs, emotions, physiological arousal - alongside changing overt behaviour, such as social skills or coping behaviours. They may involve establishing links between offenders' thoughts, feelings and actions about offending behaviour; correction of offenders' misperceptions, irrational beliefs and reasoning biases associated with their offending; teaching offenders to monitor their own thoughts, feelings and behaviours associated with offending; and promoting alternative ways of coping with deviant sexual thoughts and desires.

Psychodynamic interventions share a common root in psychoanalytic theory. This posits that sexual offending arises through an imbalance of the three components of mind: the id, the ego and the superego, with sexual offenders having temperamental imbalance of a powerful id (increased sexual impulses and libido) and a weak superego (a low level of moral probation), which are also impacted by early environment.

This updates a previous Cochrane review but is based on a new protocol.

Objectives

To assess the effects of psychological interventions on those who have sexually offended or are at risk of offending.

Search methods

In September 2010 we searched: CENTRAL, MEDLINE, Allied and Complementary Medicine (AMED), Applied Social Sciences Index and Abstracts (ASSIA), Biosis Previews, CINAHL, COPAC, Dissertation Abstracts, EMBASE, International Bibliography of the Social Sciences (IBSS), ISI Proceedings, Science Citation Index Expanded (SCI), Social Sciences Citation Index (SSCI), National Criminal Justice Reference Service Abstracts Database, PsycINFO, OpenSIGLE, Social Care Online, Sociological Abstracts, UK Clinical Research Network Portfolio Database and ZETOC. We contacted numerous experts in the field.

Selection criteria

Randomised trials comparing psychological intervention with standard care or another psychological therapy given to adults treated in institutional or community settings for sexual behaviours that have resulted in conviction or caution for sexual offences, or who are seeking treatment voluntarily for behaviours classified as illegal.

Data collection and analysis

At least two authors, working independently, selected studies, extracted data and assessed the studies' risk of bias. We contacted study authors for additional information including details of methods and outcome data.

Main results

We included ten studies involving data from 944 adults, all male.

Five trials involved primarily cognitive behavioural interventions (CBT) (n = 664). Of these, four compared CBT with no treatment or wait list control, and one compared CBT with standard care. Only one study collected data on the primary outcome. The largest study (n = 484) involved the most complex intervention versus no treatment. Long-term outcome data are reported for groups in which the mean years 'at risk' in the community are similar (8.3 years for treatment (n = 259) compared to 8.4 in the control group (n = 225)). There was no difference between these groups in terms of the risk of reoffending as measured by reconviction for sexual offences (risk ratio (RR) 1.10; 95% CI 0.78 to 1.56).

Four trials (n = 70) compared one behavioural programme with an alternative behavioural programme or with wait list control. No meta-analysis was possible for this comparison. For two studies (both cross-over, n = 29) no disaggregated data were available. The remaining two behavioural studies compared imaginal desensitisation with either covert sensitisation or as part of adjunctive drug therapy (n = 20 and 21, respectively). In these two studies, results for the primary outcome (being 'charged with anomalous behaviour') were encouraging, with only one new charge for the treated groups over one year in the former study, and in the latter study, only one new charge (in the drug-only group) over two years.

One study compared psychodynamic intervention with probation. Results for this study (n = 231) indicate a slight trend in favour of the control group (probation) over the intervention (group therapy) in terms of sexual offending as measured by rearrest (RR 1.87; 95% CI 0.78 to 4.47) at 10-year follow-up.

Data for adverse events, 'sexually anomalous urges' and for secondary outcomes thought to be 'dynamic' risk factors for reoffending, including anger and cognitive distortions, were limited.

Authors' conclusions

The inescapable conclusion of this review is the need for further randomised controlled trials. While we recognise that randomisation is considered by some to be unethical or politically unacceptable (both of which are based on the faulty premise that the experimental treatment is superior to the control - this being the point of the trial to begin with), without such evidence, the area will fail to progress. Not only could this result in the continued use of ineffective (and potentially harmful) interventions, but it also means that society is lured into a false sense of security in the belief that once the individual has been treated, their risk of reoffending is reduced. Current available evidence does not support this belief. Future trials should concentrate on minimising risk of bias, maximising quality of reporting and including follow-up for a minimum of five years 'at risk' in the community.

PLAIN LANGUAGE SUMMARY

Psychological interventions for sex offenders or those who have sexually offended or are at risk of offending

Sexual offending is both a social and a public health issue. Victim surveys show that sexual abuse is common and that much of it is never brought to the attention of criminal justice systems.

Psychological interventions are generally based on behavioural or psychodynamic theories. Interventions might be designed to change an offender's thoughts, feelings or views on relationships, with the ultimate aim of changing their behaviour.

A Cochrane review published 10 years ago considered the evidence for psychological treatments for sexual offenders and found insufficient data to reach any conclusions (Kenworthy 2003). Our current review is based on a new protocol and a literature search conducted in September 2010.

We examined the evidence for the effectiveness of psychological interventions for sexual offenders or those considered likely to offend. We excluded interventions for sex offenders with learning disability as this is the subject of a separate Cochrane review (Ashman 2008).

We identified 10 relevant studies involving data from 944 adults, all male. Few of these studies provided information about the primary outcome of this review, which was reoffending. This was usually because studies did not collect data for a sufficiently long period outside prison or the treatment setting. Many studies relied on other outcome measures (for example, anger or social skills) chosen by investigators in the hope that they were linked in some way with future offending, although it cannot be stated with certainty that such connections reliably predict reoffending.

Five of the trials we found involved 664 men and used primarily cognitive behavioural interventions (CBT). In the largest study, which had the most complex and intense 'package' of treatment both within and outside of prison, there was no difference between the group who had received CBT and those who had not in terms of the risk of reoffending as measured by reconviction for sexual offences.

One study, involving 231 men, compared psychodynamic intervention with standard care, which was probation, and suggested that probation was mildly superior in terms of reducing reoffending.

Behavioural programmes were looked at in four trials involving 70 men. For two studies, not enough data were reported to assess the effectiveness of treatment. For the remaining two, encouraging results with regards to reconvictions and self-reported urges have to be treated with caution as the studies are relatively old, meaning that many participants would not now seek or be offered treatment, as some of the targeted behaviours have been decriminalised.

Data for adverse events, 'sexually anomalous urges' and for secondary outcomes thought to be 'dynamic' risk factors for reoffending, including anger and cognitive distortions, were limited.

We concluded that further randomised controlled trials are urgently needed in this area, so that society is not lured into a false sense of security in the belief that once the individual has been treated, then their risk of reoffending is reduced. Currently, the evidence does not support this belief.

BACKGROUND

Description of the condition

Sexual offending is a legal construct that overlaps, but is not entirely congruent with, the clinical constructs of disorders of sexual preference as described in the *ICD-10 Classification of Mental and Behavioural Disorders* (WHO 1992) or paraphilias as described in the *Diagnostic and Statistical Manual of Mental Disorders* (DSM-IV) (APA 1994). Most sexual offences do not arise as a result of disorders of sexual preference or paraphilias. Furthermore, not all disorders of sexual preference or paraphilias are sexual offences. Clinically-defined diagnoses such as paedophilia, voyeurism, frotteurism, exhibitionism, zoophilia and necrophilia (if acted upon) also meet the rubric for sexual offences but, for instance, fetishism and transvestic fetishism do not. With regard to offences against children, evidence is mixed, with some data suggesting that 50% to 60% of offenders with child victims could be identified as paedophiles (Seto 2008a). Crimes such as rape and incest with adult victims are not, of themselves, classified as disorders of sexual preference or paraphilias, although it may be that a similar proportion of offenders with adult victims show a deviant sexual preference (Lalumière 2005).

An important distinction for this review is thus between sexual offending - that is, behaviour that refers to specific, legally-defined

Intentional Self-Harm

If you or someone you know is struggling or in crisis, help is available.
Call or text 988 or go to 988lifeline.org
The 988 Suicide & Crisis Lifeline (formerly known as the National Suicide Prevention Lifeline) offers 24/7 call text and chat access to trained crisis counselors who can help people experiencing suicidal substance use and/or mental health crisis or any other kind of emotional distress. People can also dial 988 if they are worried about a loved one who may need crisis support.

Plain Language Summary:
Background: These are codes that describe ways people harm themselves. Are these codes better served on behavior health or poisoning lines?

Should OHP cover this treatment? Based on input from the Behavioral Health Advisory panel, staff recommends no change in the covered status of these codes.

Question: Should the ICD-10 codes related to "intentional self-harm" be moved from the Diagnostic List or poisoning lines and placed on a behavioral health line?

Question source: OHA metrics group, HERC staff

Issue: There are a variety of diagnosis codes that include the phrase "intentional self-harm." Most of these codes appear on line 102 POISONING BY INGESTION, INJECTION, MEDICINAL AND NON-MEDICINAL AGENTS. These codes start with "poisoning" or "toxic effect" and are the "T" family of ICD-10-CM codes (for example, T36.0X2A Poisoning by penicillins, intentional self-harm, initial encounter and T51.0X2A Toxic effect of ethanol, intentional self-harm, initial encounter). There are other "intentional self harm" codes in the "X" family of ICD-10-CM codes that are on the 7 MAJOR DEPRESSION, RECURRENT; MAJOR DEPRESSION, SINGLE EPISODE, SEVERE? (for example, X81.0XXA Intentional self-harm by jumping or lying in front of motor vehicle, initial encounter).

Additionally, the ICD-10-CM code T14.91 (Suicide attempt) appears on the Diagnostic Workup File.

The OHA Behavioral Health team added these "T" and "X" intentional self-harm codes to the Social Emotional Reach Metric list, based on their expert perspective as potential ways young children could present for behavioral health services or supports. The "T" codes will be covered based on their placement on line 102, but not for behavioral health interventions. However, the underlying condition such as major depression would pair with behavioral health interventions on other lines. "X" codes are external causes of morbidity, so shouldn't be the condition being treated (the resulting injury or illness should be the billing diagnosis) and therefore are informational in HERC system.

BHAP input
BHAP felt that the current placement of the "intentional self-harm" T and X diagnosis codes as well as ICD-10-CM T14.91 were appropriate and did not require any changes. There was concern about coverage of low level self harm that did not reach the level of needing urgent/emergent behavioral health care. OHA metrics group had specifically asked about use of these codes in young children who could not be given another diagnosis. BHAP and HERC staff noted that young children do not have

"intent" and therefore these codes are inappropriate in this group. Young children would be given the "accidental" or "intentionally harmed by another" version of these codes.

BHAP/HERC staff recommendation:

1) Make no change in the placement of ICD-10-CM T14.91 (Suicide attempt) and the T/X codes for "intentional self harm"
    a. ICD-10-CM T14.91: DIAGNOSTIC WORKUP FILE
    b. "Intentional self harm" codes: line 102 POISONING BY INGESTION, INJECTION, MEDICINAL AND NON-MEDICINAL AGENTS

Section 8.0

GAP report

GAP Consent Guideline Changes

1) Issue: the NCCN guideline references need to be updated in Diagnostic Guideline D25 and Guideline Note 3. GAP approved these changes without discussion at their October 2022 meeting.

HERC staff recommendations:

1) Update Diagnostic Guideline D25 as shown below
2) Update Guideline Note 3 as shown below

DIAGNOSTIC GUIDELINE D25, HEREDITARY CANCER GENETIC TESTING

Related to genetic testing for patients with breast/ovarian and colon/endometrial cancer or other related cancers suspected to be hereditary, or patients at increased risk to due to family history, services are provided according to the Comprehensive Cancer Network Guidelines.

A) Lynch syndrome (hereditary colorectal, endometrial and other cancers associated with Lynch syndrome) services (CPT 81288, 81292-81300, 81317-81319, 81435, 81436) and familial adenomatous polyposis (FAP) services (CPT 81201-81203) should be provided as defined by the NCCN Clinical Practice Guidelines in Oncology (Genetic/Familial High-Risk Assessment: Colorectal V1.2022 (6/8/22) ~~V1.2021 (5/11/21)~~ www.nccn.org).

B) Breast and ovarian cancer syndrome genetic testing services (CPT 81162-81167, 81212, 81215-81217) for patients without a personal history of breast, ovarian and other associated cancers should be provided to high-risk patients as defined by the US Preventive Services Task Force or according to the NCCN Clinical Practice Guidelines in Oncology (Genetic/Familial High-Risk Assessment: Breast, Ovarian and Pancreatic V1.2023 (9/7/22) ~~V1.2022 (8/11/21)~~ www.nccn.org).

C) Breast and ovarian cancer syndrome genetic testing services (CPT 81162-81167, 81212, 81215-81217)) for women with a personal history of breast, ovarian, or other associated cancers and for men with breast or other associated cancers should be provided according to the NCCN Clinical Practice Guidelines in Oncology (Genetic/Familial High-Risk Assessment: Breast, Ovarian and Pancreatic V1.2023 (9/7/22) ~~V1.2022 (8/11/21)~~ www.nccn.org).

D) PTEN (Cowden syndrome) services (CPT 81321-81323) should be provided as defined by the NCCN Clinical Practice Guidelines in Oncology (Genetic/Familial High-Risk Assessment: Ovarian and Pancreatic. V1.2023 (9/7/22) ~~V1.2022 (8/11/21)~~ or Genetic/Familial High-Risk Assessment: Colorectal V1.2022 (6/8/22) www.nccn.org).

Genetic counseling should precede genetic testing for hereditary cancer whenever possible.

A) Pre and post-test genetic counseling should be covered when provided by a suitable trained health professional with expertise and experience in cancer genetics. Genetic counseling is recommended for cancer survivors when test results would affect cancer screening.
    1) "Suitably trained" is defined as board certified or active candidate status from the American Board of Medical Genetics, American Board of Genetic Counseling, or Genetic Nursing Credentialing Commission.

B) If timely pre-test genetic counseling is not possible for time-sensitive cases, appropriate genetic testing accompanied by pre- and post- test informed consent and post-test disclosure performed by a board-certified physician with experience in cancer genetics should be covered.
    1) Post-test genetic counseling should be performed as soon as is practical.

If the mutation in the family is known, only the test for that mutation is covered. For example, if a mutation for BRCA 1 has been identified in a family, a single site mutation analysis for that mutation is covered (CPT 81215), while a full sequence BRCA 1 and 2 (CPT 81163) analyses is not. There is one

exception, for individuals of Ashkenazi Jewish ancestry with a known mutation in the family, the panel for Ashkenazi Jewish BRCA mutations is covered (CPT 81212).

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

Hereditary breast cancer-related disorders genomic sequence analysis panels (CPT 81432, 81433, 81479) are only included for patients meeting the criteria for hereditary cancer syndrome testing per NCCN guidelines.

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

Line 191

Bilateral prophylactic breast removal and/or salpingo-oophorectomy are included on Line 191 for women without a personal history of invasive breast cancer who meet the criteria in the NCCN Clinical Practice Guidelines in Oncology (Genetic/Familial High-Risk Assessment: Breast, Ovarian and Pancreatic V1.2023 (9/7/22) ~~V1.2022 (8/11/21)~~ www.nccn.org). Prior to surgery, women without a personal history of breast cancer must have a genetics consultation as defined in section B of the DIAGNOSTIC GUIDELINE D1, NON-PRENATAL GENETIC TESTING GUIDELINE.

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

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

Code	Code Description	Similar code	Recommended placement
81404	Molecular pathology procedure, Level 5 (eg, analysis of 2-5 exons by DNA sequence analysis, mutation scanning or duplication/deletion variants of 6-10 exons, or characterization of a dynamic mutation disorder/triplet repeat by Southern blot analysis) ACADS (acyl-CoA dehydrogenase, C-2 to C-3 short chain) (eg, short chain acyl-CoA dehydrogenase deficiency), targeted sequence analysis (eg, exons 5 and 6) AQP2 (aquaporin 2 [collecting duct]) (eg, nephrogenic diabetes insipidus), full gene sequence ARX (aristaless related homeobox) (eg, X-linked lissencephaly with ambiguous genitalia, X-linked mental retardation), full gene sequence AVPR2 (arginine vasopressin receptor 2) (eg, nephrogenic diabetes insipidus), full gene sequence BBS10 (Bardet-Biedl syndrome 10) (eg, Bardet-Biedl syndrome), full gene sequence BTD (biotinidase) (eg, biotinidase deficiency), full gene sequence C10orf2 (chromosome 10 open reading frame 2) (eg, mitochondrial DNA depletion syndrome), full gene sequence CAV3 (caveolin 3) (eg, CAV3-related distal myopathy, limb-girdle muscular dystrophy type 1C), full gene sequence CD40LG (CD40 ligand) (eg, X-linked hyper IgM syndrome), full gene sequence CDKN2A (cyclin-dependent kinase inhibitor 2A) (eg, CDKN2A-related cutaneous malignant melanoma, familial atypical mole-malignant melanoma syndrome), full gene sequence CLRN1 (clarin 1) (eg, Usher syndrome, type 3), full gene sequence COX6B1 (cytochrome c oxidase subunit VIb polypeptide 1) (eg, mitochondrial respiratory chain complex IV deficiency), full gene sequence CPT2 (carnitine palmitoyltransferase 2) (eg, carnitine palmitoyltransferase II deficiency), full gene sequence CRX (cone-rod homeobox) (eg, cone-rod dystrophy 2, Leber congenital amaurosis), full gene sequence CYP1B1 (cytochrome P450, family 1, subfamily B, polypeptide 1) (eg, primary congenital glaucoma), full gene sequence EGR2 (early growth response 2) (eg, Charcot-Marie-Tooth), full gene sequence EMD (emerin) (eg, Emery-Dreifuss muscular dystrophy), duplication/deletion analysis EPM2A (epilepsy, progressive myoclonus type 2A, Lafora disease [laforin]) (eg, progressive myoclonus epilepsy), full gene sequence FGF23 (fibroblast growth factor 23) (eg, hypophosphatemic rickets), full gene sequence FGFR2 (fibroblast growth factor receptor 2) (eg, craniosynostosis, Apert syndrome, Crouzon syndrome), targeted sequence analysis (eg, exons 8, 10) FGFR3 (fibroblast growth factor receptor 3) (eg, achondroplasia, hypochondroplasia), targeted sequence analysis (eg, exons 8, 11, 12, 13) FHL1 (four and a half LIM domains 1) (eg, Emery-Dreifuss muscular dystrophy), full gene sequence FKRP (fukutin	Other molecular pathology procedure codes (e.g. 81407, 81403) are DIAGNOSTIC PROCEDURES	DIAGNOSTIC PROCEDURES

Code	Code Description	Similar code	Recommended placement
81405	Molecular pathology procedure, Level 6 (eg, analysis of 6-10 exons by DNA sequence analysis, mutation scanning or duplication/deletion variants of 11-25 exons, regionally targeted cytogenomic array analysis) ABCD1 (ATP-binding cassette, sub-family D [ALD], member 1) (eg, adrenoleukodystrophy), full gene sequence ACADS (acyl-CoA dehydrogenase, C-2 to C-3 short chain) (eg, short chain acyl-CoA dehydrogenase deficiency), full gene sequence ACTA2 (actin, alpha 2, smooth muscle, aorta) (eg, thoracic aortic aneurysms and aortic dissections), full gene sequence ACTC1 (actin, alpha, cardiac muscle 1) (eg, familial hypertrophic cardiomyopathy), full gene sequence ANKRD1 (ankyrin repeat domain 1) (eg, dilated cardiomyopathy), full gene sequence APTX (aprataxin) (eg, ataxia with oculomotor apraxia 1), full gene sequence ARSA (arylsulfatase A) (eg, arylsulfatase A deficiency), full gene sequence BCKDHA (branched chain keto acid dehydrogenase E1, alpha polypeptide) (eg, maple syrup urine disease, type 1A), full gene sequence BCS1L (BCS1-like [S. cerevisiae]) (eg, Leigh syndrome, mitochondrial complex III deficiency, GRACILE syndrome), full gene sequence BMPR2 (bone morphogenetic protein receptor, type II [serine/threonine kinase]) (eg, heritable pulmonary arterial hypertension), duplication/deletion analysis CASQ2 (calsequestrin 2 [cardiac muscle]) (eg, catecholaminergic polymorphic ventricular tachycardia), full gene sequence CASR (calcium-sensing receptor) (eg, hypocalcemia), full gene sequence CDKL5 (cyclin-dependent kinase-like 5) (eg, early infantile epileptic encephalopathy), duplication/deletion analysis CHRNA4 (cholinergic receptor, nicotinic, alpha 4) (eg, nocturnal frontal lobe epilepsy), full gene sequence CHRNB2 (cholinergic receptor, nicotinic, beta 2 [neuronal]) (eg, nocturnal frontal lobe epilepsy), full gene sequence COX10 (COX10 homolog, cytochrome c oxidase assembly protein) (eg, mitochondrial respiratory chain complex IV deficiency), full gene sequence COX15 (COX15 homolog, cytochrome c oxidase assembly protein) (eg, mitochondrial respiratory chain complex IV deficiency), full gene sequence CPOX (coproporphyrinogen oxidase) (eg, hereditary coproporphyria), full gene sequence CTRC (chymotrypsin C) (eg, hereditary pancreatitis), full gene sequence CYP11B1 (cytochrome P450, family 11, subfamily B, polypeptide 1) (eg, congenital adrenal hyperplasia), full gene sequence CYP17A1 (cytochrome P450, family 17, subfamily A, polypeptide 1) (eg, congenital adrenal hyperplasia), full gene sequence CYP21A2 (cytochrome P450, family 21, subfamily A, polypeptide2) (eg,	Other molecular pathology procedure codes (e.g. 81407, 81403) are DIAGNOSTIC PROCEDURES	DIAGNOSTIC PROCEDURES

Code	Code Description	Similar code	Recommended placement
81406	Molecular pathology procedure, Level 7 (eg, analysis of 11-25 exons by DNA sequence analysis, mutation scanning or duplication/deletion variants of 26-50 exons) ACADVL (acyl-CoA dehydrogenase, very long chain) (eg, very long chain acyl-coenzyme A dehydrogenase deficiency), full gene sequence ACTN4 (actinin, alpha 4) (eg, focal segmental glomerulosclerosis), full gene sequence AFG3L2 (AFG3 ATPase family gene 3-like 2 [S. cerevisiae]) (eg, spinocerebellar ataxia), full gene sequence AIRE (autoimmune regulator) (eg, autoimmune polyendocrinopathy syndrome type 1), full gene sequence ALDH7A1 (aldehyde dehydrogenase 7 family, member A1) (eg, pyridoxine-dependent epilepsy), full gene sequence ANO5 (anoctamin 5) (eg, limb-girdle muscular dystrophy), full gene sequence ANOS1 (anosmin-1) (eg, Kallmann syndrome 1), full gene sequence APP (amyloid beta [A4] precursor protein) (eg, Alzheimer disease), full gene sequence ASS1 (argininosuccinate synthase 1) (eg, citrullinemia type I), full gene sequence ATL1 (atlastin GTPase 1) (eg, spastic paraplegia), full gene sequence ATP1A2 (ATPase, Na+/K+ transporting, alpha 2 polypeptide) (eg, familial hemiplegic migraine), full gene sequence ATP7B (ATPase, Cu++ transporting, beta polypeptide) (eg, Wilson disease), full gene sequence BBS1 (Bardet-Biedl syndrome 1) (eg, Bardet-Biedl syndrome), full gene sequence BBS2 (Bardet-Biedl syndrome 2) (eg, Bardet-Biedl syndrome), full gene sequence BCKDHB (branched-chain keto acid dehydrogenase E1, beta polypeptide) (eg, maple syrup urine disease, type 1B), full gene sequence BEST1 (bestrophin 1) (eg, vitelliform macular dystrophy), full gene sequence BMPR2 (bone morphogenetic protein receptor, type II [serine/threonine kinase]) (eg, heritable pulmonary arterial hypertension), full gene sequence BRAF (B-Raf proto-oncogene, serine/threonine kinase) (eg, Noonan syndrome), full gene sequence BSCL2 (Berardinelli-Seip congenital lipodystrophy 2 [seipin]) (eg, Berardinelli-Seip congenital lipodystrophy), full gene sequence BTK (Bruton agammaglobulinemia tyrosine kinase) (eg, X-linked agammaglobulinemia), full gene sequence CACNB2 (calcium channel, voltage-dependent, beta 2 subunit) (eg, Brugada syndrome), full gene sequence CAPN3 (calpain 3) (eg, limb-girdle muscular dystrophy [LGMD] type 2A, calpainopathy), full gene sequence CBS (cystathionine-beta-synthase) (eg, homocystinuria, cystathionine beta-synthase deficiency), full gene sequence CDH1 (cadherin 1, type 1, E-cadherin [epithelial]) (eg, hereditary diffuse gastric cancer), full gene sequence CDKL5 (cyclin-dependent kinase-like 5) (eg, early infantile epileptic encephalopathy), full gene	Other molecular pathology procedure codes (e.g. 81407, 81403) are DIAGNOSTIC PROCEDURES	DIAGNOSTIC PROCEDURES
81418	Drug metabolism (eg, pharmacogenomics) genomic sequence analysis panel, must include testing of at least 6 genes, including CYP2C19, CYP2D6, and CYP2D6 duplication/deletion analysis	See issues document	DIAGNOSTIC PROCEDURES

Code	Code Description	Similar code	Recommended placement
81441	Inherited bone marrow failure syndromes (IBMFS) (eg, Fanconi anemia, dyskeratosis congenita, Diamond-Blackfan anemia, Shwachman-Diamond syndrome, GATA2 deficiency syndrome, congenital amegakaryocytic thrombocytopenia) sequence analysis panel, must include sequencing of at least 30 genes, including BRCA2, BRIP1, DKC1, FANCA, FANCB, FANCC, FANCD2, FANCE, FANCF, FANCG, FANCI, FANCL, GATA1, GATA2, MPL, NHP2, NOP10, PALB2, RAD51C, RPL11, RPL35A, RPL5, RPS10, RPS19, RPS24, RPS26, RPS7, SBDS, TERT, and TINF2	See issues document	DIAGNOSTIC PROCEDURES
81449	Targeted genomic sequence analysis panel, solid organ neoplasm, 5-50 genes (eg, ALK, BRAF, CDKN2A, EGFR, ERBB2, KIT, KRAS, MET, NRAS, PDGFRA, PDGFRB, PGR, PIK3CA, PTEN, RET), interrogation for sequence variants and copy number variants or rearrangements, if performed; RNA analysis	See issues document	DIAGNOSTIC PROCEDURES
81451	Targeted genomic sequence analysis panel, hematolymphoid neoplasm or disorder, 5-50 genes (eg, BRAF, CEBPA, DNMT3A, EZH2, FLT3, IDH1, IDH2, JAK2, KIT, KRAS, MLL, NOTCH1, NPM1, NRAS), interrogation for sequence variants, and copy number variants or rearrangements, or isoform expression or mRNA expression levels, if performed; RNA analysis	See issues document	DIAGNOSTIC PROCEDURES
81456	Targeted genomic sequence analysis panel, solid organ or hematolymphoid neoplasm or disorder, 51 or greater genes (eg, ALK, BRAF, CDKN2A, CEBPA, DNMT3A, EGFR, ERBB2, EZH2, FLT3, IDH1, IDH2, JAK2, KIT, KRAS, MET, MLL, NOTCH1, NPM1, NRAS, PDGFRA, PDGFRB, PGR, PIK3CA, PTEN, RET), interrogation for sequence variants and copy number variants or rearrangements, or isoform expression or mRNA expression levels, if performed; RNA analysis	See issues document	DIAGNOSTIC PROCEDURES
84433	Thiopurine S-methyltransferase (TPMT)	See individual issue	DIAGNOSTIC PROCEDURES

2023 CPT Codes
Genetic Testing Related Codes

1) Code **81418**
    a. Code description: Drug metabolism (eg, pharmacogenomics) genomic sequence analysis panel, must include testing of at least 6 genes, including CYP2C19, CYP2D6, and CYP2D6 duplication/deletion analysis
    b. Information: Cytochrome P450 2D6 (*CYP2D6*) is a critical pharmacogene involved in the metabolism of ~20% of commonly used drugs across a broad spectrum of medical disciplines including psychiatry, pain management, oncology and cardiology. Nevertheless, *CYP2D6* is highly polymorphic with single-nucleotide polymorphisms, small insertions/deletions and larger structural variants including multiplications, deletions, tandem arrangements, and hybridizations with non-functional *CYP2D7* pseudogenes. The frequency of these variants differs across populations, and they significantly influence the drug-metabolizing enzymatic function of CYP2D6. Importantly, altered CYP2D6 function has been associated with both adverse drug reactions and reduced drug efficacy
    c. Similar codes:
        i. The following drug metabolism codes are on the DIAGNOSTIC PROCEDURES file:
            1. 81225 CYP2C19 (cytochrome P450, family 2, subfamily C, polypeptide 19) (eg, drug metabolism), gene analysis, common variants (eg, *2, *3, *4, *8, *17)
            2. 81226 CYP2D6 (cytochrome P450, family 2, subfamily D, polypeptide 6) (eg, drug metabolism), gene analysis, common variants (eg, *2, *3, *4, *5, *6, *9, *10, *17, *19, *29, *35, *41, *1XN, *2XN, *4XN)
            3. 81227 CYP2C9 (cytochrome P450, family 2, subfamily C, polypeptide 9) (eg, drug metabolism), gene analysis, common variants (eg, *2, *3, *5, *6)
        ii. The current non-prenatal genetic testing guideline lists the following criteria for the above tests:
            1. CPT 81225-81227, 81230-81231 (cytochrome P450). Covered only for determining eligibility for medication therapy if required or recommended in the FDA labelling for that medication. These tests have unproven clinical utility for decisions regarding medications when not required in the FDA labeling (e.g. psychiatric, anticoagulant, opioids).
            2. See entire guideline note in Appendix A
    d. GAP discussion: GAP members felt that the staff recommendation was appropriate. Public testimony was heard from Devki Nagar, from Myriad Genetics. Myriad requested consideration of CPIC guidelines in addition to FDA guidelines. Nagar noted that Medicare is allowing FDA or CPIC guidelines to be followed for determination of coverage for this test. Staff was directed to look into CPIC guidelines further.

       CPIC guidelines are available at: https://cpicpgx.org/guidelines/. CPIC guidelines include recommendations for genetic testing of P450 enzyme mutations prior to use of various proton pump inhibitors, clopidogrel, voriconazole, phenytoin, warfarin, atomoxetine,

ondansetron, tropisetron, tamoxifen, SSRIs, tricyclic antidepressants, opioids, and tacrolimus. In general, the reviews appeared to be current (within the past 5 yrs), evidence based, and funded by impartial bodies (for example, the NIH). Some authors had conflicts of interest. Staff conclusion was that these reviews are evidence based, but the recommendations went far beyond current standard of care. Staff recommendation is to continue to use FDA guidelines and monitor CPIC and other evidence-based sources going forward.

e. **GAP/HERC staff recommendations**:
   i. Place **81418** on the DIAGNOSTIC PROCEDURES file
   ii. Modify the entry in DIAGNOSTIC GUIDELINE D1, NON-PRENATAL GENETIC TESTING GUIDELINE to read as below [see Appendix A for entire guideline with edit]:

CPT 81225-81227, 81230-81231**,** 81418 (cytochrome P450). Covered only for determining eligibility for medication therapy if required or recommended in the FDA labelling for that medication. These tests have unproven clinical utility for decisions regarding medications when not required in the FDA labeling (e.g. psychiatric, anticoagulant, opioids).

2) Code **81441**
   a. Code description: Inherited bone marrow failure syndromes (IBMFS) (eg, Fanconi anemia, dyskeratosis congenita, Diamond-Blackfan anemia, Shwachman-Diamond syndrome, GATA2 deficiency syndrome, congenital amegakaryocytic thrombocytopenia) sequence analysis panel, must include sequencing of at least 30 genes, including BRCA2, BRIP1, DKC1, FANCA, FANCB, FANCC, FANCD2, FANCE, FANCF, FANCG, FANCI, FANCL, GATA1, GATA2, MPL, NHP2, NOP10, PALB2, RAD51C, RPL11, RPL35A, RPL5, RPS10, RPS19, RPS24, RPS26, RPS7, SBDS, TERT, and TINF2
   b. Information:
      i. Patients with inherited bone marrow failure syndrome (IBMFS) can develop peripheral blood cytopenia, which can ultimately progress to myelodysplastic syndrome (MDS) or acute myeloid leukemia (AML).
      ii. Maintaining a high suspicion for rare IBMFSs is critical when evaluating patients of all ages with unusual cytopenia, especially in patients ≤40 years of age. Thorough physical examination and family history are important. An accurate diagnosis of IBMFS including laboratory workup, a surveillance schedule for malignancy, and potential therapeutic options according to disease severity, is critical for proper management. Additionally, cascade testing of at-risk relatives is required.
   c. Similar codes: Previously coded with 81443 (Genetic testing for severe inherited conditions (eg, cystic fibrosis, Ashkenazi Jewish-associated disorders [eg, Bloom syndrome, Canavan disease, Fanconi anemia type C, mucolipidosis type VI, Gaucher disease, Tay-Sachs disease], beta hemoglobinopathies, phenylketonuria, galactosemia), genomic sequence analysis panel, must include sequencing of at least 15 genes (eg, ACADM, ARSA, ASPA, ATP7B, BCKDHA, BCKDHB, BLM, CFTR, DHCR7, FANCC, G6PC, GAA,

GALT, GBA, GBE1, HBB, HEXA, IKBKAP, MCOLN1, PAH)) which is on the DIAGNOSTIC PROCEDURES file

d. GAP discussion: GAP members agreed with staff recommendation.
e. **HERC staff recommendation**:
    i. Place **81441** on the DIAGNOSTIC PROCEDURES file

2023 CPT Codes
Genetic Testing Related Codes

Appendix A

DIAGNOSTIC GUIDELINE D1, NON-PRENATAL GENETIC TESTING GUIDELINE

A) Genetic tests are covered as diagnostic, unless they are listed below in section E1 as excluded or have other restrictions listed in this guideline. To be covered, initial screening (e.g. physical exam, medical history, family history, laboratory studies, imaging studies) must indicate that the chance of genetic abnormality is > 10% and results would do at least one of the following:
   1) Change treatment,
   2) Change health monitoring,
   3) Provide prognosis, or
   4) Provide information needed for genetic counseling for patient; or patient's parents, siblings, or children

B) Pretest and posttest genetic counseling is required for presymptomatic and predisposition genetic testing. Pretest and posttest genetic evaluation (which includes genetic counseling) is covered when provided by a suitable trained health professional with expertise and experience in genetics.
   1) "Suitably trained" is defined as board certified or active candidate status from the American Board of Medical Genetics, American Board of Genetic Counseling, or Genetic Nursing Credentialing Commission.

C) A more expensive genetic test (generally one with a wider scope or more detailed testing) is not covered if a cheaper (smaller scope) test is available and has, in this clinical context, a substantially similar sensitivity. For example, do not cover CFTR gene sequencing as the first test in a person of Northern European Caucasian ancestry because the gene panels are less expensive and provide substantially similar sensitivity in that context.

D) Related to diagnostic evaluation of individuals with intellectual disability (defined as a full scale or verbal IQ < 70 in an individual > age 5), developmental delay (defined as a cognitive index <70 on a standardized test appropriate for children < 5 years of age), Autism Spectrum Disorder, or multiple congenital anomalies:
   1) CPT 81228, 81229 and 81349, Cytogenomic constitutional microarray analysis: Cover for diagnostic evaluation of individuals with intellectual disability/developmental delay; multiple congenital anomalies; or, Autism Spectrum Disorder accompanied by at least one of the following: dysmorphic features including macro or microcephaly, congenital anomalies, or intellectual disability/developmental delay in addition to those required to diagnose Autism Spectrum Disorder.
   2) CPT 81243, 81244, 81171,81172 Fragile X genetic testing is covered for individuals with intellectual disability/developmental delay. Although the yield of Fragile X is 3.5-10%, this is included because of additional reproductive implications.
   3) A visit with the appropriate specialist (often genetics, developmental pediatrics, or child neurology), including physical exam, medical history, and family history is covered. Physical exam, medical history, and family history by the appropriate specialist, prior to any genetic testing is often the most cost-effective strategy and is encouraged.

E) Related to preconception testing/carrier screening:
   1) The following tests are covered for a pregnant patient or patient contemplating pregnancy as well as the male reproductive partner:
      a) Screening for genetic carrier status with the minimum testing recommended by the American College of Obstetrics and Gynecology:

i) Screening for cystic fibrosis carrier status (CPT 81220-81224)
ii) Screening for fragile X status (CPT 81243, 81244, 81171, 81172)
iii) Screening for spinal muscular atrophy (CPT 81329)
iv) Screening for Canavan disease (CPT 81200), familial dysautonomia (CPT 81260), and Tay-Sachs carrier status (CPT 81255). Ashkenazi Jewish carrier panel testing (CPT 81412) is covered if the panel would replace and would be of similar or lower cost than individual gene testing including CF carrier testing.
v) Screening for hemoglobinopathies (CPT 83020, 83021)

b) Expanded carrier screening (CPT 81443): A genetic counseling/geneticist consultation must be offered prior to ordering test and after test results are reported. Expanded carrier testing is ONLY covered when all of the following are met:
i) the panel includes only genes with a carrier frequency of ≥ 1 in 200 or greater per ACMG Guideline (2021), AND
ii) the included genes have well-defined phenotype, AND
iii) the included genes result in conditions have a detrimental effect on quality of life OR cause cognitive or physical impairment OR require surgical or medical intervention, AND
iv) the included genes result in conditions have an onset early in life, AND
v) the included genes result in conditions that must be diagnosable prenatally to inform antenatal interventions and/or changes in delivery management and/or education of parents about special needs after birth.

F) Related to other tests with specific CPT codes:
1) Certain genetic tests have not been found to have proven clinical benefit. These tests are listed in Guideline Note 173 INTERVENTIONS THAT ARE UNPROVEN, HAVE NO CLINICALLY IMPORTANT BENEFIT OR HAVE HARMS THAT OUTWEIGH BENEFITS FOR CERTAIN CONDITIONS.
2) The following tests are covered only if they meet the criteria in section A above AND the specified situations:
a) CPT 81205, BCKDHB (branched-chain keto acid dehydrogenase E1, beta polypeptide) (eg, Maple syrup urine disease) gene analysis, common variants (eg, R183P, G278S, E422X): Cover only when the newborn screening test is abnormal and serum amino acids are normal
b) Diagnostic testing for cystic fibrosis (CF)
i) CFTR, cystic fibrosis transmembrane conductance regulator tests. CPT 81220, 81221, 81222, 81223: For infants with a positive newborn screen for cystic fibrosis or who are symptomatic for cystic fibrosis, or for clients that have previously been diagnosed with cystic fibrosis but have not had genetic testing, CFTR gene analysis of a panel containing at least the mutations recommended by the American College of Medical Genetics* (CPT 81220) is covered. If two mutations are not identified, CFTR full gene sequencing (CPT 81223) is covered. If two mutations are still not identified, duplication/deletion testing (CPT 81222) is covered. These tests may be ordered as reflex testing on the same specimen.

c) CPT 81224, CFTR (cystic fibrosis transmembrane conductance regulator) (eg. cystic fibrosis) gene analysis; introm 8 poly-T analysis (eg. male infertility): Covered only after genetic counseling.

d) CPT 81225-81227, 81230-81231, 81418 (cytochrome P450). Covered only for determining eligibility for medication therapy if required or recommended in the FDA labelling for that medication. These tests have unproven clinical utility for decisions regarding medications when not required in the FDA labeling (e.g. psychiatric, anticoagulant, opioids).

e) CPT 81240, F2 (prothrombin, coagulation factor II) (eg, hereditary hypercoagulability) gene analysis, 20210G>A variant: Factor 2 20210G>A testing should not be covered for adults with idiopathic venous thromoboembolism; for asymptomatic family members of patients with venous thromboembolism and a Factor V Leiden or Prothrombin 20210G>A mutation; or for determining the etiology of recurrent fetal loss or placental abruption.

f) CPT 81241, F5 (coagulation Factor V) (eg, hereditary hypercoagulability) gene analysis, Leiden variant: Factor V Leiden testing should not be covered for: adults with idiopathic venous thromoboembolism; for asymptomatic family members of patients with venous thromboembolism and a Factor V Leiden or Prothrombin 20210G>A mutation; or for determining the etiology of recurrent fetal loss or placental abruption.

g) CPT 81247, G6PD (glucose-6-phosphate dehydrogenase) (eg, hemolytic anemia, jaundice), gene analysis; common variant(s) (eg, A, A-) should only be covered
   i) After G6PD enzyme activity testing is done and found to be normal; AND either
      (a) There is an urgent clinical reason to know if a deficiency is present, e.g. in a case of acute hemolysis; OR
      (b) In situations where the enzyme activity could be unreliable, e.g. female carrier with extreme Lyonization.

h) CPT 81248, G6PD (glucose-6-phosphate dehydrogenase) (eg, hemolytic anemia, jaundice), gene analysis; known familial variant(s) is only covered when the information is required for genetic counseling.

i) CPT 81249, G6PD (glucose-6-phosphate dehydrogenase) (eg, hemolytic anemia, jaundice), gene analysis; full gene sequence is only covered
   i) after G6PD enzyme activity has been tested, and
   ii) the requirements under CPT 81247 above have been met, and
   iii) common variants (CPT 81247) have been tested for and not found.

j) CPT 81256, HFE (hemochromatosis) (eg, hereditary hemochromatosis) gene analysis, common variants (eg, C282Y, H63D): Covered for diagnostic testing of patients with elevated transferrin saturation or ferritin levels. Covered for predictive testing ONLY when a first degree family member has treatable iron overload from HFE.

k) alpha-1-antitrypsin deficiency), gene analysis, common variants (eg, *S and *Z): The alpha-1-antitrypsin protein level should be the first line test for a suspected diagnosis of AAT deficiency in symptomatic individuals with unexplained liver disease or obstructive lung disease that is not asthma or in a middle age individual with unexplained dyspnea. Genetic testing of the anpha-1 phenotype test is appropriate if the protein test is abnormal or borderline. The genetic test is appropriate for siblings of people with AAT deficiency regardless of the AAT protein test results.

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

m) CPT 81430-81431, Hearing loss (eg, nonsyndromic hearing loss, Usher syndrome, Pendred syndrome); genomic sequence analysis panel: Testing for mutations in GJB2 and GJB6 need to be done first and be negative in non-syndromic patients prior to panel testing.
n) CPT 81440, 81460, 81465, mitochondrial genome testing: A genetic counseling/geneticist or metabolic consultation is required prior to ordering test.
o) CPT 81425-81427, whole genome sequencing: testing is only covered when
    i) The testing is for a critically ill infant up to one year of age admitted to an inpatient intensive care unit (NICU/PICU) with a complex illness of unknown etiology; AND
    ii) Whole genome sequencing is recommended by a medical geneticist or other physician sub-specialist, including but not limited to a neonatologist or pediatric intensivist with expertise in the conditions and/or genetic disorder for which testing is being considered.

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

TPMT Gene and Enzyme Testing
GAP 2023 CPT Code Review

Plain Language Summary:
Background: This is a genetic test that helps predict whether a patient will have a bad reaction to a certain class of drugs (azathioprine and 6-MP).

Should OHP cover this test? Staff recommends adding coverage for these tests as they can help prevent serious drug reactions.

1) Code: **84433**
    a. Code description: Thiopurine S-methyltransferase (TPMT)
        i. Used for phenotype testing
    b. Information: Thiopurine drugs such as 6-mercaptopurine are used as chemotherapeutic agents and immunosuppressive drugs. Genetic polymorphisms that affect this enzymatic activity are correlated with variations in sensitivity and toxicity to such drugs within individuals. About 1/300 individual is deficient for the enzyme. Measurement of TPMT activity is encouraged prior to commencing the treatment of patients with thiopurine drugs such as azathioprine, 6-mercaptopurine and 6-thioguanine. Patients with low activity (10% prevalence) or especially absent activity (prevalence 0.3%) are at a heightened risk of drug-induced bone marrow toxicity due to accumulation of the unmetabolized drug
        i. TPMT can be tested in two ways:
            1. TPMT activity test (phenotype)—this method tests the activity level of the enzyme thiopurine S-methyltransferase (TPMT) in a person's red blood cells. Depending on the enzyme activity level, a person may be prescribed a standard dose of the thiopurine drug, a reduced dose of the thiopurine drug, or a different drug other than a thiopurine
            2. TPMT genetic test (genotype)—an alternative test to TPMT enzyme activity level is a genetic test that can identify genetic variations in the TPMT gene. Approximately 10 per cent of people have one wild-type gene and one gene variation associated with decreased TPMT (heterozygous) and intermediate enzyme activity. Approximately one in 300 individuals have two copies of TPMT with variations resulting in little or no enzyme activity (homozygous). While numerous variations can occur in TPMT, there are five variations in particular that have been proven to be associated with TPMT deficiencies. Most genetic tests look for these five variations, although depending on the method used, more variations can be detected. This genetic test provides information about a person's likely response to thiopurines, but it will not quantify how much TPMT enzyme is actually being made by the body. There can be significant person-to-person and ethnic variability in TPMT production, even in people with the same gene variations
    c. Previously, TPMT phenotype testing was coded with CPT 82657 (Enzyme activity in blood cells, cultured cells, or tissue, not elsewhere specified; nonradioactive substrate, each specimen) which is DIAGNOSTIC

d. Similar code 81335 (TPMT (thiopurine S-methyltransferase) (eg, drug metabolism), gene analysis) is on line 662/GN173

e. Prior GAP review:
   i. 81335 was reviewed as a new code in November 2017. At that time, one article was reviewed (Coenen 2015) that found "Screening for variants in TPMT did not reduce the proportions of patients with hematologic ADRs during thiopurine treatment for IBD." There was no GAP discussion and unanimous agreement to place this code on line 662/GN173
   ii. Last review was 5 years ago; therefore, review needs to be updated

f. Updated evidence review—genetic testing for TPMT
   i. **Abaji 2017**, review of influence of genetic testing on treatment response
      1. Acute lymphoblastic leukemia
         a. 7 trials, prospective or retrospective cohort studies
         b. Affecting dosing, reduced dosing in heterozygous patients reduced risk of secondary malignancy
         c. "all these trials demonstrate the importance of preemptive TPMT genetic screening and subsequent dose adjustment in mitigating the toxicity associated with thiopurine treatment while maintaining, if not enhancing, treatment efficacy and favorable long-term outcome."
      2. Inflammatory bowel disease
         a. A systematic review followed by a meta-analysis that eventually combined the results of 47 studies that investigated the risk of myelosuppression with respect to intermediate TPMT activity demonstrated a 4.19-fold increase in oddratio of leukopenia (95% CI: 3.20–5.48) in IBD patients with reduced TPMT activity compared with wild-type
         b. Two independent meta-analysis of cohort and case-control studies further investigated the impact of pharmacogenetics on treatment response by exclusively combining studies (14 and 9 studies, respectively) that investigated the association between TPMT polymorphisms and adverse drug reactions (ADRs) in IBD patients…They involved 2206 and 1309 patients respectively, and both concluded that TPMT polymorphisms were significantly associated with thiopurine-induced overall ADRs and bone marrow toxicity (around 3- and 6-fold increase in the odd-ratios, respectively) but not with hepatotoxicity, pancreatitis, flu-like symptoms, GI or skin reaction
         c. TARGET RCT (N=333 patients)
            i. No differences were found between the conventional and pharmacogenetics arms with respect to the frequency of treatment interruption due to ADRs (frequency: 27.7% vs 28.8%; odds ratio [OR]: 1.1; 95% CI: 0.66–1.8; P=0.74)
            ii. the study did not find any difference in the rate of remission between the intervention and control groups

indicating that the adjustment did not affect treatment efficacy

d. TOPIC RCT (N=783 patients)
    i. Showed no significant overall impact of TPMT genotype-guided dosing of thiopurines on treatment efficacy or on the risk of hematologic ADRs (i.e., leukopenia and thrombocytopenia) between the genotyped and nongenotyped arms (frequency: 7.4% vs 7.9%; relative risk: 0.93; 95% CI: 0.57–1.52). The efficacy results of this study further advocate that a reduced thiopurine dose does not result in under-treatment

3. In conclusion, although it is currently well established that TPMT polymorphisms can explain a certain portion of thiopurine-induced ADRs, particularly hematotoxicity, it is surely not capable of predicting all of them. Indeed, many studies have found that certain ADRs were not associated with a reduced TPMT activity such as pancreatitis and hepatotoxicity. This holds true in the context of ALL, IBD and the different types of autoimmune disorders. Consequently, regular clinical testing and hematologic assessment remain the mainstay in the monitoring of thiopurine treatment while genetic testing adds the advantage of refining the initial dosing and patient stratification processes, as well as suggesting customized monitoring for certain patient groups.

g. Expert guidelines—TPMT genetic testing

i. **NCCN 2022** Guideline for treatment of acute lymphoblastic leukemia (ALL)
    1. For patients receiving 6-MP, consider testing for TPMT gene polymorphisms, particularly in patients who develop severe neutropenia after starting 6-MP. Testing for both TPMT and NUDT15 variant status should be considered, especially for patients of East Asian origin
        a. NUDT15 testing is coded with CPT 81479 (Unlisted molecular pathology procedure) which is DIAGNOSTIC

ii. **ACG 2019** clinical guideline for treatment of ulcerative colitis in adults
    1. No mention of TPMT gene testing

iii. **ACG 2017** clinical guideline management of Crohn's disease in adults
    1. Thiopurine methyltransferase (TPMT) testing should be considered before initial use of azathioprine or 6-mercaptopurine to treat patients with Crohn's disease (strong recommendation, low level of evidence)
        a. Unclear if this refers to gene testing or enzyme activity testing

h. Evidence review—enzyme activity testing

i. **Lennard 2013** review of TPMT gene and enzyme testing
    1. The overall concordance between genotype and phenotype in healthy volunteers is 98.4%, but in the 'intermediate' range of TPMT activities this falls to 86%

i. Expert guidelines—TPMT enzyme activity testing

i. **ACG 2017** clinical guideline management of Crohn's disease in adults

1. Thiopurine methyltransferase (TPMT) testing should be considered before initial use of azathioprine or 6-mercaptopurine to treat patients with Crohn's disease (strong recommendation, low level of evidence)
    a. Unclear if this refers to gene testing or enzyme activity testing

j. Regulatory information
    i. FDA labeling of azathioprine
        1. TPMT genotyping or phenotyping can help identify patients who are at an increased risk for developing IMURAN toxicity
    ii. FDA labeling of 6-mercaptopurine
        1. Consider testing in patients with severe myelosuppression or repeated episodes of myelosuppression for thiopurine S-methyltransferase (TPMT) or nucleotide diphosphatase (NUDT15) deficiency. Patients with homozygous or homozygous TPMT or NUDT15 deficiency may require a dose reduction

k. Utilization: CareOregon reported paying for the TPMT genetic test 6 times in 2021 (cost $88-283). All payers found 6 claims with all CCOs for 2021. Other CCOs report paying for only one test (phenotype or genotype)

l. GAP discussion: members supported moving both gene and phenotype testing to the Diagnostic Procedures file.

m. **HERC staff summary**: Gene and phenotype testing for TPMT is recommended by expert groups and mentioned in the FDA labeling of azathioprine and 6-MP. There is evidence that such testing can result in changes to prescribing; however, the evidence is less robust that such testing results in reductions in adverse outcomes. At a minimum, testing appears to be indicated in people treated with azathioprine and 6-MP who have myelosuppression or possibly those being treated for ALL. Testing could be added for genotype testing, phenotype testing, or both.

n. GAP/HERC staff recommendation
    i. Add CPT **84433** [Thiopurine S-methyltransferase (TPMT)] enzyme activity testing to the DIAGNOSTIC PROCEDURES file
    ii. Add CPT **81335** [TPMT (thiopurine S-methyltransferase) (eg, drug metabolism), gene analysis] to the DIAGNOSTIC PROCEDURES file
        1. Remove from line 662 and the entry from GN173

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

Line 662

The following Interventions are prioritized on Line 662 CONDITIONS FOR WHICH CERTAIN INTERVENTIONS ARE UNPROVEN, HAVE NO CLINICALLY IMPORTANT BENEFIT OR HAVE HARMS THAT OUTWEIGH BENEFITS:

Procedure Code	Intervention Description	Rationale	Last Review
~~81335~~	~~TPMT (thiopurine S-methyltransferase) (eg, drug metabolism), gene analysis~~	~~Insufficient evidence of effectiveness~~	~~November, 2017~~

Pharmacogenomics and Personalized Medicine

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REVIEW

Thiopurine S-methyltransferase polymorphisms in acute lymphoblastic leukemia, inflammatory bowel disease and autoimmune disorders: influence on treatment response

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Abstract: The *thiopurine S-methyltransferase* (*TPMT*) gene encodes for the TPMT enzyme that plays a crucial role in the metabolism of thiopurine drugs. Genetic polymorphisms in this gene can affect the activity of the TPMT enzyme and have been correlated with variability in response to treatment with thiopurines. Advances in the pharmacogenetics of *TPMT* allowed the development of dosing recommendations and treatment strategies to optimize and individualize prescribing thiopurine in an attempt to enhance treatment efficacy while minimizing toxicity. The influence of genetic polymorphisms in the *TPMT* gene on clinical outcome has been well-documented and replicated in many studies. In this review, we provide an overview of the evolution, results, conclusions and recommendations of selected studies that investigated the influence of *TPMT* pharmacogenetics on thiopurine treatment in acute lymphoblastic leukemia, inflammatory bowel disease and autoimmune disorders. We focus mainly on prospective studies that explored the impact of individualized TPMT-based dosing of thiopurines on clinical response. Together, these studies demonstrate the importance of preemptive *TPMT* genetic screening and subsequent dose adjustment in mitigating the toxicity associated with thiopurine treatment while maintaining treatment efficacy and favorable long-term outcomes. In addition, we briefly address the cost-effectiveness of this pharmacogenetics approach and its impact on clinical practice as well as the importance of recent breakthrough advances in sequencing and genotyping techniques in refining the *TPMT* genetic screening process.

Keywords: TPMT, pharmacogenetics, thiopurine, 6-mercaptopurine, azathioprine, ADRs.

Introduction

Thiopurine S-methyltransferase (TPMT) is an important cytoplasmic enzyme that catalyses the rate-limiting step in the metabolism of thiopurine drugs. It is coded by the *TPMT* gene and exerts its effect via S-adenosyl-L-methionine as the S-methyl donor and S-adenosyl-L-homocysteine as a by-product.[1–3] Thiopurine drugs, mainly 6-mercaptopurine (6-MP), and its prodrug azathioprine (AZA), are implicated as antimetabolite cytotoxic and immunosuppressive agents in the treatment of malignancies such as acute lymphoblastic leukemia (ALL), inflammatory disorders like inflammatory bowel disease (IBD) and many autoimmune disorders, including rheumatoid arthritis (RA), systemic lupus erythematosus (SLE), autoimmune hepatitis (AIH) and generalized eczematous disorders.[3–5] However, gastrointestinal disturbances (like nausea and vomiting), rashes, as well as more serious adverse drug reactions (ADRs) like bone marrow toxicity, hepatotoxicity and pancreatitis can lead to discontinuation of therapy in up to one-third of patients;[6] these factors limit the use of these drugs.[2]

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

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Abstract

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.

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

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Implementation of TPMT testing

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azathioprine, childhood leukaemia, mercaptopurine, thioguanine nucleotides, thiopurine methyltransferase, TPMT

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The activity of the enzyme thiopurine methyltransferase (TPMT) is regulated by a common genetic polymorphism. One in 300 individuals lack enzyme activity and 11% are heterozygous for a variant low activity allele and have an intermediate activity. The thiopurine drugs azathioprine, mercaptopurine and thioguanine are substrates for TPMT; these drugs exhibit well documented myelosuppressive effects on haematopoietic cells and have a track record of idiosyncratic drug reactions. The development of severe bone marrow toxicity, in patients taking standard doses of thiopurine drugs, is associated with TPMT deficiency whilst the TPMT heterozygote is at an increased risk of developing myelosuppression. Factors influencing TPMT enzyme activity, as measured in the surrogate red blood cell, are discussed in this review to enable an appreciation of why concordance between TPMT genotype and phenotype is not 100%. This is particularly important for lower/intermediate TPMT activities to avoid misclassification of TPMT status. TPMT testing is now widely available in routine service laboratories. The British National Formulary suggests TPMT testing before starting thiopurine drugs. Dermatologists were quick to adopt routine TPMT testing whilst gastroenterologists do not specifically recommend TPMT screening. TPMT testing is mandatory prior to the use of mercaptopurine in childhood leukaemia. Thiopurine drug dose and other treatment related influences on cell counts explain some of the differing recommendations between clinical specialities. TPMT testing is cost-effective and the major role is in the identification of the TPMT deficient individual prior to the start of thiopurine drugs.

Introduction

Individual variations in human red blood cell (RBC) thiopurine methyltransferase (TPMT, E.C.2.1.1.67) activity were first described by Weinshilboum *et al.* [1] in the late 1970s. Subsequent Caucasian population studies demonstrated that the level of TPMT activity was inherited in an autosomal codominant fashion. The frequency distribution of TPMT activities conformed to Hardy–Weinberg predictions for the inheritance of two alleles one for high (*TPMT*^{H}) and one for low (*TPMT*^{L}) enzyme activity. Approximately 89% of a randomly selected population were homozygous for an allele for high RBC TPMT activity, about 11% heterozygous with an intermediate activity and one in every 300 subjects homozygous for an allele for low RBC TPMT activity, the latter lacking detectable TPMT activity [2]. It was soon established that the genetic polymorphism controlling RBC TPMT activity also controlled the level of enzyme activity in all other cells and tissues [3–5] but it was over a decade later before the *TPMT* gene was isolated, sequenced and the variant alleles described at a genetic level [6–8]. Controversy remains over various aspects of TPMT genotype/phenotype concordance and whether genotype or phenotype is the most accurate predictor of TPMT status.

The TPMT genetic polymorphism represents a well validated example of the clinical importance of pharmacogenetics [9]. Very low, or deficient, TPMT activity is associated with grossly abnormal thiopurine drug metabolism, excess production of cytotoxic metabolites and profound life-threatening myelotoxicity, in patients taking thiopurine drugs. Although this association was reported in the late 1980s [10], there was, initially, a minimal use of TPMT testing prior to the start of thiopurine

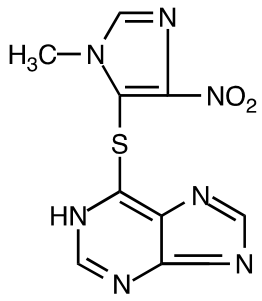
PRODUCT INFORMATION

IMURAN® (azathioprine)
50-mg Scored Tablets
Rx only

WARNING - MALIGNANCY
Chronic immunosuppression with IMURAN, a purine antimetabolite increases *risk of malignancy* in humans. Reports of malignancy include post-transplant lymphoma and hepatosplenic T-cell lymphoma (HSTCL) in patients with inflammatory bowel disease. Physicians using this drug should be very familiar with this risk as well as with the mutagenic potential to both men and women and with possible hematologic toxicities. Physicians should inform patients of the risk of malignancy with IMURAN. See WARNINGS.

DESCRIPTION:
IMURAN (azathioprine), an immunosuppressive antimetabolite, is available in tablet form for oral administration. Each scored tablet contains 50 mg azathioprine and the inactive ingredients lactose, magnesium stearate, potato starch, povidone, and stearic acid.

Azathioprine is chemically 6-[(1-methyl-4-nitro-1*H*-imidazol-5-yl)thio]-1*H*-purine. The structural formula of azathioprine is:



It is an imidazolyl derivative of 6-mercaptopurine and many of its biological effects are similar to those of the parent compound.

Azathioprine is insoluble in water, but may be dissolved with addition of one molar equivalent of alkali. Azathioprine is stable in solution at neutral or acid pH but hydrolysis to mercaptopurine occurs in excess sodium hydroxide (0.1N), especially on warming. Conversion to mercaptopurine also occurs in the presence of sulfhydryl compounds such as cysteine, glutathione, and hydrogen sulfide.

CLINICAL PHARMACOLOGY:
Azathioprine is well absorbed following oral administration. Maximum serum radioactivity occurs at 1 to 2 hours after oral ^{35}S-azathioprine and decays with a half-life of 5 hours. This is not an estimate of the half-life of azathioprine itself, but is the decay rate for all ^{35}S-containing metabolites of the drug. Because of extensive metabolism, only a fraction of the radioactivity is present as azathioprine. Usual doses produce blood levels of azathioprine, and of mercaptopurine derived from it, which are low (<1 mcg/mL). Blood levels are of little predictive value for therapy since the magnitude and duration of clinical effects correlate with thiopurine nucleotide levels in tissues rather than with plasma drug levels. Azathioprine and mercaptopurine are moderately bound to serum proteins (30%) and are partially dialyzable. See OVERDOSAGE.

Azathioprine is metabolized to 6-mercaptopurine (6-MP). Both compounds are rapidly eliminated from blood and are oxidized or methylated in erythrocytes and liver; no azathioprine or mercaptopurine is detectable in urine after 8 hours. Activation of 6-mercaptopurine occurs via hypoxanthine-guanine phosphoribosyltransferase (HGPRT) and a series of multi-enzymatic processes involving kinases to form 6-thioguanine nucleotides (6-TGNs) as major

metabolites (See Metabolism Scheme in Figure 1). The cytotoxicity of azathioprine is due, in part, to the incorporation of 6-TGN into DNA.

6-MP undergoes two major inactivation routes (Figure 1). One is thiol methylation, which is catalyzed by the enzyme thiopurine S-methyltransferase (TPMT), to form the inactive metabolite methyl-6-MP (6-MeMP). TPMT activity is controlled by a genetic polymorphism.[1, 2, 3] For Caucasians and African Americans, approximately 10% of the population inherit one non-functional TPMT allele (heterozygous) conferring intermediate TPMT activity, and 0.3% inherit two TPMT non-functional alleles (homozygous) for low or absent TPMT activity. Non-functional alleles are less common in Asians. TPMT activity correlates inversely with 6-TGN levels in erythrocytes and presumably other hematopoietic tissues, since these cells have negligible xanthine oxidase (involved in the other inactivation pathway) activities, leaving TPMT methylation as the only inactivation pathway. Patients with intermediate TPMT activity may be at increased risk of myelotoxicity if receiving conventional doses of IMURAN. Patients with low or absent TPMT activity are at an increased risk of developing severe, life-threatening myelotoxicity if receiving conventional doses of IMURAN.[4-9] TPMT genotyping or phenotyping (red blood cell TPMT activity) can help identify patients who are at an increased risk for developing IMURAN toxicity.[2, 3, 7, 8, 9] Accurate phenotyping (red blood cell TPMT activity) results are not possible in patients who have received recent blood transfusions. See WARNINGS, PRECAUTIONS: Drug Interactions, PRECAUTIONS: Laboratory Tests and ADVERSE REACTIONS sections.

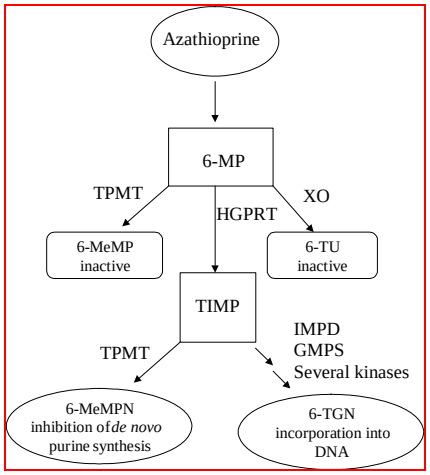


Figure 1. Metabolism pathway of azathioprine: competing pathways result in inactivation by TPMT or XO, or incorporation of cytotoxic nucleotides into DNA.
GMPS: Guanosine monophosphate synthetase; HGPRT: Hypoxanthine-guanine-phosphoribosyl-transferase; IMPD: Inosine monophosphate dehydrogenase; MeMP: Methylmercaptopurine; MeMPN: Methylmercaptopurine nucleotide; TGN: Thioguanine nucleotides; TIMP: Thioinosine monophosphate; TPMT: Thiopurine S-methyltransferase; TU Thiouric acid; XO: Xanthine oxidase (Adapted from *Pharmacogenomics* 2002; 3:89-98; and *Cancer Res* 2001; 61:5810-5816.)

Another inactivation pathway is oxidation, which is catalyzed by xanthine oxidase (XO) to form 6-thiouric acid. The inhibition of xanthine oxidase in patients receiving allopurinol (ZYLOPRIM®) is the basis for the azathioprine dosage reduction required in these patients (see PRECAUTIONS: Drug Interactions). Proportions of metabolites are different in individual patients, and this presumably accounts for variable magnitude and duration of drug effects. Renal clearance is probably not important in predicting biological effectiveness or toxicities, although dose reduction is practiced in patients with poor renal function.

Homograft Survival: The use of azathioprine for inhibition of renal homograft rejection is well established, the mechanism(s) for this action are somewhat obscure. The drug suppresses hypersensitivities of the cell-mediated type and causes variable alterations in antibody production. Suppression of T-cell effects, including ablation of T-cell

suppression, is dependent on the temporal relationship to antigenic stimulus or engraftment. This agent has little effect on established graft rejections or secondary responses.

Alterations in specific immune responses or immunologic functions in transplant recipients are difficult to relate specifically to immunosuppression by azathioprine. These patients have subnormal responses to vaccines, low numbers of T-cells, and abnormal phagocytosis by peripheral blood cells, but their mitogenic responses, serum immunoglobulins, and secondary antibody responses are usually normal.

Immunoinflammatory Response: Azathioprine suppresses disease manifestations as well as underlying pathology in animal models of autoimmune disease. For example, the severity of adjuvant arthritis is reduced by azathioprine.

The mechanisms whereby azathioprine affects autoimmune diseases are not known. Azathioprine is immunosuppressive, delayed hypersensitivity and cellular cytotoxicity tests being suppressed to a greater degree than are antibody responses. In the rat model of adjuvant arthritis, azathioprine has been shown to inhibit the lymph node hyperplasia, which precedes the onset of the signs of the disease. Both the immunosuppressive and therapeutic effects in animal models are dose-related. Azathioprine is considered a slow-acting drug and effects may persist after the drug has been discontinued.

INDICATIONS AND USAGE:

IMURAN is indicated as an adjunct for the prevention of rejection in renal homotransplantation. It is also indicated for the management of active rheumatoid arthritis to reduce signs and symptoms.

Renal Homotransplantation: IMURAN is indicated as an adjunct for the prevention of rejection in renal homotransplantation. Experience with over 16,000 transplants shows a 5-year patient survival of 35% to 55%, but this is dependent on donor, match for HLA antigens, anti-donor or anti-B-cell alloantigen antibody, and other variables. The effect of IMURAN on these variables has not been tested in controlled trials.

Rheumatoid Arthritis: IMURAN is indicated for the treatment of active rheumatoid arthritis (RA) to reduce signs and symptoms. Aspirin, non-steroidal anti-inflammatory drugs and/or low dose glucocorticoids may be continued during treatment with IMURAN. The combined use of IMURAN with disease modifying anti-rheumatic drugs (DMARDs) has not been studied for either added benefit or unexpected adverse effects. The use of IMURAN with these agents cannot be recommended.

CONTRAINDICATIONS:

IMURAN should not be given to patients who have shown hypersensitivity to the drug. IMURAN should not be used for treating rheumatoid arthritis in pregnant women. Patients with rheumatoid arthritis previously treated with alkylating agents (cyclophosphamide, chlorambucil, melphalan, or others) may have a prohibitive risk of malignancy if treated with IMURAN.

WARNINGS:

Malignancy

Patients receiving immunosuppressants, including IMURAN, are at increased risk of developing lymphoma and other malignancies, particularly of the skin. Physicians should inform patients of the risk of malignancy with IMURAN. As usual for patients with increased risk for skin cancer, exposure to sunlight and ultraviolet light should be limited by wearing protective clothing and using a sunscreen with a high protection factor.

Post-transplant

Renal transplant patients are known to have an increased risk of malignancy, predominantly skin cancer and reticulum cell or lymphomatous tumors. The risk of post-transplant lymphomas may be increased in patients who receive aggressive treatment with immunosuppressive drugs, including IMURAN. Therefore, immunosuppressive drug therapy should be maintained at the lowest effective levels.

Rheumatoid Arthritis

Information is available on the risk of malignancy with the use of IMURAN in rheumatoid arthritis (see ADVERSE REACTIONS). It has not been possible to define the precise risk of malignancy due to IMURAN. The data suggest the risk may be elevated in patients with rheumatoid arthritis, though lower than for renal transplant patients. However, acute myelogenous leukemia as well as solid tumors have been reported in patients with rheumatoid arthritis who have received IMURAN.

Inflammatory Bowel Disease

Postmarketing cases of hepatosplenic T-cell lymphoma (HSTCL), a rare type of T-cell lymphoma, have been reported in patients treated with IMURAN. These cases have had a very aggressive disease course and have been fatal. The majority of reported cases have occurred in patients with Crohn's disease or ulcerative colitis and the majority were in adolescent and young adult males. Some of the patients were treated with IMURAN as monotherapy and some had received concomitant treatment with a TNFα blocker at or prior to diagnosis. The safety and efficacy of IMURAN for the treatment of Crohn's disease and ulcerative colitis have not been established.

Cytopenias

Severe leukopenia, thrombocytopenia, anemias including macrocytic anemia, and/or pancytopenia may occur in patients being treated with IMURAN. Severe bone marrow suppression may also occur. Patients with intermediate thiopurine S-methyl transferase (TPMT) activity may be at an increased risk of myelotoxicity if receiving conventional doses of IMURAN. Patients with low or absent TPMT activity are at an increased risk of developing severe, life-threatening myelotoxicity if receiving conventional doses of IMURAN. TPMT genotyping or phenotyping can help identify patients who are at an increased risk for developing IMURAN toxicity.[2-9] (See PRECAUTIONS: Laboratory Tests). Hematologic toxicities are dose-related and may be more severe in renal transplant patients whose homograft is undergoing rejection. It is suggested that patients on IMURAN have complete blood counts, including platelet counts, weekly during the first month, twice monthly for the second and third months of treatment, then monthly or more frequently if dosage alterations or other therapy changes are necessary. Delayed hematologic suppression may occur. Prompt reduction in dosage or temporary withdrawal of the drug may be necessary if there is a rapid fall in or persistently low leukocyte count, or other evidence of bone marrow depression. Leukopenia does not correlate with therapeutic effect; therefore the dose should not be increased intentionally to lower the white blood cell count.

Serious infections

Serious infections are a constant hazard for patients receiving chronic immunosuppression, especially for homograft recipients. Fungal, viral, bacterial, and protozoal infections may be fatal and should be treated vigorously. Reduction of azathioprine dosage and/or use of other drugs should be considered.

Effect on Sperm in Animals

IMURAN has been reported to cause temporary depression in spermatogenesis and reduction in sperm viability and sperm count in mice at doses 10 times the human therapeutic dose;[10] a reduced percentage of fertile matings occurred when animals received 5 mg/kg.[11]

Pregnancy: Pregnancy Category D. IMURAN can cause fetal harm when administered to a pregnant woman. IMURAN should not be given during pregnancy without careful weighing of risk versus benefit. Whenever possible, use of IMURAN in pregnant patients should be avoided. This drug should not be used for treating rheumatoid arthritis in pregnant women.[12]

IMURAN is teratogenic in rabbits and mice when given in doses equivalent to the human dose (5 mg/kg daily). Abnormalities included skeletal malformations and visceral anomalies.[11]

Limited immunologic and other abnormalities have occurred in a few infants born of renal allograft recipients on IMURAN. In a detailed case report, [13] documented lymphopenia, diminished IgG and IgM levels, CMV infection, and a decreased thymic shadow were noted in an infant born to a mother receiving 150 mg azathioprine and 30 mg prednisone daily throughout pregnancy. At 10 weeks most features were normalized. DeWitte et al reported pancytopenia and severe immune deficiency in a preterm infant whose mother received 125 mg azathioprine and 12.5 mg prednisone daily. [14] There have been two published reports of abnormal physical findings. Williamson and Karp described an infant born with preaxial polydactyly whose mother received azathioprine 200 mg daily and prednisone 20 mg every other day during pregnancy. [15] Tallent et al described an infant with a large myelomeningocele in the upper lumbar region, bilateral dislocated hips, and bilateral talipes equinovarus. The father was on long-term azathioprine therapy. [16]

Benefit versus risk must be weighed carefully before use of IMURAN in patients of reproductive potential. There are no adequate and well-controlled studies in pregnant women. If this drug is used during pregnancy or if the patient becomes pregnant while taking this drug, the patient should be apprised of the potential hazard to the fetus. Women of childbearing age should be advised to avoid becoming pregnant.

PRECAUTIONS:

General: A gastrointestinal hypersensitivity reaction characterized by severe nausea and vomiting has been reported. These symptoms may also be accompanied by diarrhea, rash, fever, malaise, myalgias, elevations in liver enzymes, and occasionally, hypotension. Symptoms of gastrointestinal toxicity most often develop within the first several weeks of therapy with IMURAN and are reversible upon discontinuation of the drug. The reaction can recur within hours after re-challenge with a single dose of IMURAN.

Information for Patients: Patients being started on IMURAN should be informed of the necessity of periodic blood counts while they are receiving the drug and should be encouraged to report any unusual bleeding or bruising to their physician. They should be informed of the danger of infection while receiving IMURAN and asked to report signs and symptoms of infection to their physician. Careful dosage instructions should be given to the patient, especially when IMURAN is being administered in the presence of impaired renal function or concomitantly with allopurinol (see Drug Interactions subsection and DOSAGE AND ADMINISTRATION). Patients should be advised of the potential risks of the use of IMURAN during pregnancy and during the nursing period. The increased risk of malignancy following therapy with IMURAN should be explained to the patient.

Laboratory Tests: ***Complete Blood Count (CBC) Monitoring:*** Patients on IMURAN should have complete blood counts, including platelet counts, weekly during the first month, twice monthly for the second and third months of treatment, then monthly or more frequently if dosage alterations or other therapy changes are necessary.

TPMT Testing: It is recommended that consideration be given to either genotype or phenotype patients for TPMT. Phenotyping and genotyping methods are commercially available. The most common non-functional alleles associated with reduced levels of TPMT activity are *TPMT*2, TPMT*3A and TPMT*3C*. Patients with two non-functional alleles (homozygous) have low or absent TPMT activity and those with one non-functional allele (heterozygous) have intermediate activity. Accurate phenotyping (red blood cell TPMT activity) results are not possible in patients who have received recent blood transfusions. TPMT testing may also be considered in patients with abnormal CBC results that do not respond to dose reduction. Early drug discontinuation in these patients is advisable. **TPMT TESTING CANNOT SUBSTITUTE FOR COMPLETE BLOOD COUNT (CBC) MONITORING IN PATIENTS RECEIVING IMURAN.** See CLINICAL PHARMACOLOGY, WARNINGS, ADVERSE REACTIONS and DOSAGE AND ADMINISTRATION sections.

Drug Interactions: ***Use with Allopurinol:*** One of the pathways for inactivation of azathioprine is inhibited by allopurinol. Patients receiving IMURAN and allopurinol concomitantly should have a dose reduction of IMURAN, to approximately 1/3 to 1/4 the usual dose. It is recommended that a further dose reduction or alternative therapies be considered for patients with low or absent TPMT activity receiving IMURAN and allopurinol because both TPMT and XO inactivation pathways are affected. See CLINICAL PHARMACOLOGY, WARNINGS, PRECAUTIONS:Laboratory Tests and ADVERSE REACTIONS sections.

Use with Aminosalicylates: There is in vitro evidence that aminosalicylate derivatives (e.g., sulphasalazine, mesalazine, or olsalazine) inhibit the TPMT enzyme. Concomitant use of these agents with IMURAN should be done with caution.

Use with Other Agents Affecting Myelopoesis: Drugs which may affect leukocyte production, including co-trimoxazole, may lead to exaggerated leukopenia, especially in renal transplant recipients.

Use with Angiotensin-Converting Enzyme Inhibitors: The use of angiotensin-converting enzyme inhibitors to control hypertension in patients on azathioprine has been reported to induce anemia and severe leukopenia.

Use with Warfarin: IMURAN may inhibit the anticoagulant effect of warfarin.

Use with ribavirin: The use of ribavirin for hepatitis C in patients receiving azathioprine has been reported to induce severe pancytopenia and may increase the risk of azathioprine-related myelotoxicity. Inosine monophosphate dehydrogenase (IMDH) is required for one of the metabolic pathways of azathioprine. Ribavirin is known to inhibit IMDH, thereby leading to accumulation of an azathioprine metabolite, 6-methylthioionosine monophosphate (6-MTITP), which is associated with myelotoxicity (neutropenia, thrombocytopenia, and anemia). Patients receiving azathioprine with ribavirin should have complete blood counts, including platelet counts, monitored weekly for the first month, twice monthly for the second and third months of treatment, then monthly or more frequently if dosage or other therapy changes are necessary.

Carcinogenesis, Mutagenesis, Impairment of Fertility: See WARNINGS section.

Pregnancy: ***Teratogenic Effects:*** Pregnancy Category D. See WARNINGS section.

Nursing Mothers: The use of IMURAN in nursing mothers is not recommended. Azathioprine or its metabolites are transferred at low levels, both transplacentally and in breast milk. [17, 18, 19] Because of the potential for tumorigenicity shown for azathioprine, a decision should be made whether to discontinue nursing or discontinue the drug, taking into account the importance of the drug to the mother.

Pediatric Use: Safety and efficacy of azathioprine in pediatric patients have not been established.

ADVERSE REACTIONS:

The principal and potentially serious toxic effects of IMURAN are hematologic and gastrointestinal. The risks of secondary infection and malignancy are also significant (see WARNINGS). The frequency and severity of adverse reactions depend on the dose and duration of IMURAN as well as on the patient's underlying disease or concomitant therapies. The incidence of hematologic toxicities and neoplasia encountered in groups of renal homograft recipients is significantly higher than that in studies employing IMURAN for rheumatoid arthritis. The relative incidences in clinical studies are summarized below:

Toxicity	Renal Homograft	Rheumatoid Arthritis
Leukopenia (any degree)	>50%	28%
<2500 cells/mm^3	16%	5.3%
Infections	20%	<1%
Neoplasia		*
Lymphoma	0.5%	
Others	2.8%	

* Data on the rate and risk of neoplasia among persons with rheumatoid arthritis treated with azathioprine are limited. The incidence of lymphoproliferative disease in patients with RA appears to be significantly higher than that in the general population. In one completed study, the rate of lymphoproliferative disease in RA patients receiving higher than recommended doses of azathioprine (5 mg/kg per day) was 1.8 cases per 1000 patient-years of follow-up, compared with 0.8 cases per 1000 patient-years of follow-up in those not receiving azathioprine. However, the proportion of the increased risk attributable to the azathioprine dosage or to other therapies (i.e., alkylating agents) received by patients treated with azathioprine cannot be determined.

Hematologic: Leukopenia and/or thrombocytopenia are dose-dependent and may occur late in the course of therapy with IMURAN. Dose reduction or temporary withdrawal may result in reversal of these toxicities. Infection may

occur as a secondary manifestation of bone marrow suppression or leukopenia, but the incidence of infection in renal homotransplantation is 30 to 60 times that in rheumatoid arthritis. Anemias, including macrocytic anemia, and/or bleeding have been reported.

TPMT genotyping or phenotyping can help identify patients with low or absent TPMT activity (homozygous for non-functional alleles) who are at increased risk for severe, life-threatening myelosuppression from IMURAN. See CLINICAL PHARMACOLOGY, WARNINGS and PRECAUTIONS:Laboratory Tests. Death associated with pancytopenia has been reported in patients with absent TPMT activity receiving azathioprine. [6, 20]

Gastrointestinal: Nausea and vomiting may occur within the first few months of therapy with IMURAN, and occurred in approximately 12% of 676 rheumatoid arthritis patients. The frequency of gastric disturbance often can be reduced by administration of the drug in divided doses and/or after meals. However, in some patients, nausea and vomiting may be severe and may be accompanied by symptoms such as diarrhea, fever, malaise, and myalgias (see PRECAUTIONS). Vomiting with abdominal pain may occur rarely with a hypersensitivity pancreatitis.

Hepatotoxicity manifest by elevation of serum alkaline phosphatase, bilirubin, and/or serum transaminases is known to occur following azathioprine use, primarily in allograft recipients. Hepatotoxicity has been uncommon (less than 1%) in rheumatoid arthritis patients. Hepatotoxicity following transplantation most often occurs within 6 months of transplantation and is generally reversible after interruption of IMURAN. A rare, but life-threatening hepatic veno-occlusive disease associated with chronic administration of azathioprine has been described in transplant patients and in one patient receiving IMURAN for panuveitis.[21, 22, 23] Periodic measurement of serum transaminases, alkaline phosphatase, and bilirubin is indicated for early detection of hepatotoxicity. If hepatic veno-occlusive disease is clinically suspected, IMURAN should be permanently withdrawn.

Others: Additional side effects of low frequency have been reported. These include skin rashes, alopecia, fever, arthralgias, diarrhea, steatorrhea, negative nitrogen balance, reversible interstitial pneumonitis, hepatosplenic T-cell lymphoma (see Warnings – Malignancy), and Sweet's Syndrome (acute febrile neutrophilic dermatosis).

OVERDOSAGE:

The oral LD_{50}s for single doses of IMURAN in mice and rats are 2500 mg/kg and 400 mg/kg, respectively. Very large doses of this antimetabolite may lead to marrow hypoplasia, bleeding, infection, and death. About 30% of IMURAN is bound to serum proteins, but approximately 45% is removed during an 8-hour hemodialysis.[24] A single case has been reported of a renal transplant patient who ingested a single dose of 7500 mg IMURAN. The immediate toxic reactions were nausea, vomiting, and diarrhea, followed by mild leukopenia and mild abnormalities in liver function. The white blood cell count, SGOT, and bilirubin returned to normal 6 days after the overdose.

DOSAGE AND ADMINISTRATION:

TPMT TESTING CANNOT SUBSTITUTE FOR COMPLETE BLOOD COUNT (CBC) MONITORING IN PATIENTS RECEIVING IMURAN. TPMT genotyping or phenotyping can be used to identify patients with absent or reduced TPMT activity. Patients with low or absent TPMT activity are at an increased risk of developing severe, life-threatening myelotoxicity from IMURAN if conventional doses are given. Physicians may consider alternative therapies for patients who have low or absent TPMT activity (homozygous for non-functional alleles). IMURAN should be administered with caution to patients having one non-functional allele (heterozygous) who are at risk for reduced TPMT activity that may lead to toxicity if conventional doses are given. Dosage reduction is recommended in patients with reduced TPMT activity. Early drug discontinuation may be considered in patients with abnormal CBC results that do not respond to dose reduction.

Renal Homotransplantation: The dose of IMURAN required to prevent rejection and minimize toxicity will vary with individual patients; this necessitates careful management. The initial dose is usually 3 to 5 mg/kg daily, beginning at the time of transplant. IMURAN is usually given as a single daily dose on the day of, and in a minority of cases 1 to 3 days before, transplantation. Dose reduction to maintenance levels of 1 to 3 mg/kg daily is usually possible. The dose of IMURAN should not be increased to toxic levels because of threatened rejection.

Discontinuation may be necessary for severe hematologic or other toxicity, even if rejection of the homograft may be a consequence of drug withdrawal.

Rheumatoid Arthritis: IMURAN is usually given on a daily basis. The initial dose should be approximately 1.0 mg/kg (50 to 100 mg) given as a single dose or on a twice-daily schedule. The dose may be increased, beginning at 6 to 8 weeks and thereafter by steps at 4-week intervals, if there are no serious toxicities and if initial response is unsatisfactory. Dose increments should be 0.5 mg/kg daily, up to a maximum dose of 2.5 mg/kg per day. Therapeutic response occurs after several weeks of treatment, usually 6 to 8; an adequate trial should be a minimum of 12 weeks. Patients not improved after 12 weeks can be considered refractory. IMURAN may be continued long-term in patients with clinical response, but patients should be monitored carefully, and gradual dosage reduction should be attempted to reduce risk of toxicities.

Maintenance therapy should be at the lowest effective dose, and the dose given can be lowered decrementally with changes of 0.5 mg/kg or approximately 25 mg daily every 4 weeks while other therapy is kept constant. The optimum duration of maintenance IMURAN has not been determined. IMURAN can be discontinued abruptly, but delayed effects are possible.

Use in Renal Dysfunction: Relatively oliguric patients, especially those with tubular necrosis in the immediate postcadaveric transplant period, may have delayed clearance of IMURAN or its metabolites, may be particularly sensitive to this drug, and are usually given lower doses.

Procedures for proper handling and disposal of this immunosuppressive antimetabolite drug should be considered. Several guidelines on this subject have been published.[25-31] There is no general agreement that all of the procedures recommended in the guidelines are necessary or appropriate.

HOW SUPPLIED: 50 mg overlapping circle-shaped, yellow to off-white, scored tablets imprinted with "IMURAN" and "50" on each tablet; bottle of 100 (NDC 65483-590-10).

Store at 15° to 25°C (59° to 77°F) in a dry place and protect from light.

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PROMETHEUS LABORATORIES INC.
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Hunt Valley, MD 21031
for Prometheus Laboratories Inc.
San Diego, CA 92121

May 2011 IM005I

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use PURINETHOL safely and effectively. See full prescribing information for PURINETHOL.

PURINETHOL® (mercaptopurine) tablets, for oral use
Initial U.S. Approval: 1953

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

Warnings and Precautions, Treatment Related Malignancies (5.4) 4/2020
Warnings and Precautions, Macrophage Activation Syndrome (5.5) 4/2020

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

PURINETHOL is a nucleoside metabolic inhibitor indicated for treatment of adult and pediatric patients with acute lymphoblastic leukemia (ALL) as part of a combination chemotherapy maintenance regimen. (1.1)

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

- The recommended starting dose of PURINETHOL is 1.5 mg/kg to 2.5 mg/kg orally once daily as part of a combination chemotherapy maintenance regimen. Adjust dose to maintain desirable absolute neutrophil count and for excessive myelosuppression. (2.1)
- Renal Impairment: Use the lowest recommended starting dose or increase the dosing interval. (2.3, 8.6)
- Hepatic Impairment: Use the lowest recommended starting dose. (2.3, 8.7)

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

Tablets: 50 mg (3)

----------CONTRAINDICATIONS----------

None.

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

- Myelosuppression: Monitor complete blood count (CBC) and adjust the dose of PURINETHOL for excessive myelosuppression. Consider testing in patients with severe myelosuppression or repeated episodes of myelosuppression for thiopurine S-methyltransferase (TPMT) or nucleotide diphosphatase (NUDT15) deficiency. Patients with homozygous or homozygous TPMT or NUDT15 deficiency may require a dose reduction. (2.2, 5.1)
- Hepatotoxicity: Monitor transaminases, alkaline phosphatase and bilirubin. Withhold PURINETHOL at onset of hepatotoxicity. (5.2)
- Immunosuppression: Response to all vaccines may be diminished and there is a risk of infection with live virus vaccines. Consult immunization guidelines for immunocompromised patients. (5.3)
- Treatment Related Malignancies: Aggressive and fatal cases of hepatosplenic T-cell lymphoma have occurred. (5.4)
- Macrophage Activation Syndrome: Monitor for and treat promptly; discontinue PURINETHOL. (5.5)
- Embryo-Fetal Toxicity: Can cause fetal harm. Advise patients of reproductive potential of the potential risk to a fetus and to use effective contraception. (5.6, 8.1, 8.3)

----------ADVERSE REACTIONS----------

The most common adverse reaction (>20%) is myelosuppression, including anemia, leukopenia and thrombocytopenia. Adverse reactions occurring in 5% to 20% of patients include anorexia, nausea, vomiting, diarrhea, malaise and rash. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Stason Pharmaceuticals at (888) 598-7707 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

----------DRUG INTERACTIONS----------

- Allopurinol: Reduce the dose of PURINETHOL when co-administered with allopurinol. (2.4, 7.1)
- Warfarin: PURINETHOL may decrease the anticoagulant effect. (7.2)

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

- Lactation: Advise not to breastfeed. (8.2)
- Infertility: Can impair fertility. (8.3)

See 17 for PATIENT COUNSELING INFORMATION

Revised: 12/2020

FULL PRESCRIBING INFORMATION: CONTENTS*

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

FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

1.1 Acute Lymphoblastic Leukemia

PURINETHOL is indicated for treatment of adult and pediatric patients with acute lymphoblastic leukemia (ALL) as part of a combination chemotherapy maintenance regimen.

2 DOSAGE AND ADMINISTRATION

2.1 Recommended Dosage

The recommended starting dosage of PURINETHOL is 1.5 mg/kg to 2.5 mg/kg orally once daily as part of combination chemotherapy maintenance regimen. A recommended dosage for patients less than 17 kg is not achievable, because the only available strength is 50 mg. Take PURINETHOL either consistently with or without food.

After initiating PURINETHOL, monitor complete blood count (CBC) and adjust the dose to maintain absolute neutrophil count (ANC) at a desirable level and for excessive myelosuppression. Evaluate the bone marrow in patients with prolonged myelosuppression or repeated episodes of myelosuppression to assess leukemia status and marrow cellularity.

Evaluate thiopurine S-methyltransferase (TPMT) and nucleotide diphosphatase (NUDT15) status in patients with severe myelosuppression or repeated episodes or myelosuppression *[see Dosage and Administration (2.2)]*.

Do not administer to patients who are unable to swallow tablets.

If a patient misses a dose, instruct the patient to continue with the next scheduled dose.

PURINETHOL is a cytotoxic drug. Follow special handling and disposal procedures.

2.2 Dosage Modifications in Patients with TPMT and NUDT15 Deficiency

Consider testing for TPMT and NUDT15 deficiency in patients who experience severe myelosuppression or repeated episodes of myelosuppression *[see Warnings and Precautions (5.1), Clinical Pharmacology (12.5)]*.

Homozygous Deficiency in either TPMT or NUDT15

Patients with homozygous deficiency of either enzyme typically require 10% or less of the recommended dosage. Reduce the recommended starting dosage of PURINETHOL in patients who are known to have homozygous TPMT or NUDT15 deficiency.

Heterozygous Deficiency in TPMT and/or NUDT15

Reduce the PURINETHOL dose based on tolerability. Most patients with heterozygous TPMT or NUDT15 deficiency tolerate the recommended dosage, but some require a dose reduction based on adverse reactions. Patients who are heterozygous for both TPMT and NUDT15 may require more substantial dose reductions.

2.3 Dosage Modifications in Renal and Hepatic Impairment

Renal Impairment

Use the lowest recommended starting dosage for PURINETHOL in patients with renal impairment (CLcr less than 50 mL/min). Adjust the dosage to maintain absolute neutrophil count (ANC) at a desirable level and for adverse reactions *[see Uses in Specific Populations (8.6)]*.

Hepatic Impairment

Use the lowest recommended starting dosage for PURINETHOL in patients with hepatic impairment. Adjust the dosage to maintain absolute neutrophil count (ANC) at a desirable level and for adverse reactions *[see Uses in Specific Populations (8.7)]*.

2.4 Dosage Modification with Concomitant Use of Allopurinol

Reduce the dose of PURINETHOL to one-third to one-quarter of the current dosage when coadministered with allopurinol *[see Drug Interactions (7.1)]*.

3 DOSAGE FORMS AND STRENGTHS

Tablets: 50 mg, biconvex, round, pale yellow to buff, scored tablets imprinted with “9|3”

4 CONTRAINDICATIONS

None.

5 WARNINGS AND PRECAUTIONS

5.1 Myelosuppression

The most consistent, dose-related adverse reaction is myelosuppression, manifested by anemia, leukopenia, thrombocytopenia, or any combination of these. Monitor CBC and adjust the dosage of PURINETHOL for excessive myelosuppression *[see Dosage and Administration (2.1)]*.

Consider testing for TPMT or NUDT15 deficiency in patients with severe myelosuppression or repeated episodes of myelosuppression. TPMT genotyping or phenotyping (red blood cell TPMT activity) and NUDT15 genotyping can identify patients who have reduced activity of these enzymes. Patients with heterozygous or homozygous TPMT or NUDT15 deficiency may require a dose reduction *[see Dosage and Administration (2.2), Clinical Pharmacology (12.5)]*.

Myelosuppression can be exacerbated by coadministration with allopurinol, aminosalicylates or other products that cause myelosuppression *[see Drug Interactions (7.1, 7.3, 7.4)]*. Reduce the dose of PURINETHOL when coadministered with allopurinol *[see Dosage and Administration (2.4)]*.

5.2 Hepatotoxicity

Mercaptopurine is hepatotoxic. There are reports of deaths attributed to hepatic necrosis associated with the administration of mercaptopurine. Hepatic injury can occur with any dosage but seems to occur with greater frequency when the recommended dosage is exceeded. In some patients, jaundice has cleared following withdrawal of mercaptopurine and reappeared with rechallenge.

Usually, clinically detectable jaundice appears early in the course of treatment (1 to 2 months); however, jaundice has been reported as early as 1 week and as late as 8 years after the starting mercaptopurine. The hepatotoxicity has been associated in some cases with anorexia, diarrhea, jaundice and ascites. Hepatic encephalopathy has occurred.

Monitor serum transaminase levels, alkaline phosphatase, and bilirubin levels at weekly intervals when first beginning therapy and at monthly intervals thereafter. Monitor liver tests more frequently in patients who are receiving PURINETHOL with other hepatotoxic products *[see Drug Interactions (7.5)]* or with known pre-existing liver disease. Withhold PURINETHOL at onset of hepatotoxicity.

5.3 Immunosuppression

Mercaptopurine is immunosuppressive and may impair the immune response to infectious agents or vaccines. Due to the immunosuppression associated with maintenance chemotherapy for ALL, response to all vaccines may be diminished and there is a risk of infection with live virus vaccines. Consult immunization guidelines for immunocompromised patients.

5.4 Treatment Related Malignancies

Hepatosplenic T-cell lymphoma has been reported in patients treated with mercaptopurine for inflammatory bowel disease (IBD), an unapproved use. Mercaptopurine is mutagenic in animals and humans, carcinogenic in animals, and may increase the risk of secondary malignancies.

Patients receiving immunosuppressive therapy, including mercaptopurine, are at an increased risk of developing lymphoproliferative disorders and other malignancies, notably skin cancers (melanoma and non-melanoma), sarcomas (Kaposi's and non-Kaposi's) and uterine cervical cancer in situ. The increased risk appears to be related to the degree and duration of immunosuppression. It has been reported that discontinuation of immunosuppression may provide partial regression of the lymphoproliferative disorder.

A treatment regimen containing multiple immunosuppressants (including thiopurines) should therefore be used with caution as this could lead to lymphoproliferative disorders, some with reported fatalities. A combination of multiple

immunosuppressants, given concomitantly increases the risk of Epstein-Barr virus (EBV)-associated lymphoproliferative disorders.

5.5 Macrophage Activation Syndrome

Macrophage activation syndrome (MAS) (hemophagocytic lymphohistiocytosis) is a known, life-threatening disorder that may develop in patients with autoimmune conditions, in particular with inflammatory bowel disease (IBD), and there could potentially be an increased susceptibility for developing the condition with the use of mercaptopurine (an unapproved use). If MAS occurs, or is suspected, discontinue PURINETHOL. Monitor for and promptly treat infections such as EBV and cytomegalovirus (CMV), as these are known triggers for MAS.

5.6 Embryo-Fetal Toxicity

PURINETHOL can cause fetal harm when administered to a pregnant woman. An increased incidence of miscarriage has been reported in women who received mercaptopurine in the first trimester of pregnancy. Adverse embryo-fetal findings, including miscarriage and stillbirth, have been reported in women who received mercaptopurine after the first trimester of pregnancy. Advise pregnant women of the potential risk to a fetus. Advise females of reproductive potential to use effective contraception during treatment with PURINETHOL and for 6 months after the last dose. Advise males with female partners of reproductive potential to use effective contraception during treatment with PURINETHOL and for 3 months after the last dose *[see Use in Specific Populations (8.1, 8.3)]*.

6 ADVERSE REACTIONS

The following clinically significant adverse reactions are described elsewhere in the labeling:

- Myelosuppression *[see Warnings and Precautions (5.1)]*
- Hepatotoxicity *[see Warnings and Precautions (5.2)]*
- Immunosuppression *[see Warnings and Precautions (5.3)]*
- Treatment related malignancies *[see Warnings and Precautions (5.4)]*
- Macrophage activation syndrome *[see Warnings and Precautions (5.5)]*

6.1 Clinical Trials Experience

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

Based on multicenter cooperative group ALL trials, the most common adverse reaction occurring in > 20% of patients was myelosuppression, including anemia, neutropenia, lymphopenia and thrombocytopenia. Adverse reactions occurring in 5% to 20% of patients included anorexia, nausea, vomiting, diarrhea, malaise and rash. Adverse reactions occurring in < 5 % of patients included urticaria, hyperuricemia, oral lesions, increased transaminases, hyperbilirubinemia, hyperpigmentation, infections, and pancreatitis. Oral lesions resemble thrush rather than antifolic ulcerations. Delayed or late adverse reactions include hepatic fibrosis, hyperbilirubinemia, alopecia, pulmonary fibrosis, oligospermia and secondary malignancies *[see Warnings and Precautions (5.1, 5.2)]*.

Drug fever has been reported with mercaptopurine.

Additional adverse reactions that have been reported in patients who have received mercaptopurine include photosensitivity, hypoglycemia, and portal hypertension.

7 DRUG INTERACTIONS

7.1 Allopurinol

Allopurinol can inhibit the first-pass oxidative metabolism of mercaptopurine by xanthine oxidase, which can lead to an increased risk of mercaptopurine adverse reactions (i.e., myelosuppression, nausea, and vomiting) *[see Warnings and Precautions (5.1), Adverse Reactions (6.1)]*. Reduce the dose of PURINETHOL when coadministered with allopurinol *[see Dosage and Administration (2.4)]*.

7.2 Warfarin

The concomitant administration of PURINETHOL and warfarin may decrease the anticoagulant effectiveness of warfarin. Monitor the international normalized ratio (INR) in patients receiving warfarin and adjust the warfarin dosage as appropriate.

7.3 Myelosuppressive Products

PURINETHOL can cause myelosuppression. Myelosuppression may be increased when PURINETHOL is coadministered with other products that cause myelosuppression. Enhanced myelosuppression has been noted in some patients also receiving trimethoprim-sulfamethoxazole. Monitor the CBC and adjust the dose of PURINETHOL for excessive myelosuppression *[see Dosage and Administration (2.1), Warnings and Precautions (5.1)]*.

7.4 Aminosalicylates

Aminosalicylates (e.g., mesalamine, olsalazine or sulfasalazine) may inhibit the TPMT enzyme, which may increase the risk of myelosuppression when coadministered with PURINETHOL. When aminosalicylates and PURINETHOL are coadministered, use the lowest possible doses for each drug and monitor more frequently for myelosuppression *[see Warnings and Precautions (5.1)]*.

7.5 Hepatotoxic Products

PURINETHOL can cause hepatotoxicity. Hepatotoxicity may be increased when PURINETHOL is coadministered with other products that cause hepatotoxicity. Monitor liver tests more frequently in patients who are receiving PURINETHOL with other hepatotoxic products *[see Warnings and Precautions (5.2)]*.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

PURINETHOL can cause fetal harm when administered to a pregnant woman *[see Clinical Pharmacology (12.1)]*. Pregnant women who receive mercaptopurine have an increased incidence of miscarriage and stillbirth *(see Data)*. Advise pregnant women of the potential risk to a fetus.

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

Data

Human Data

Women receiving mercaptopurine in the first trimester of pregnancy have an increased incidence of miscarriage; the risk of malformation in offspring surviving first trimester exposure is not known. In a series of 28 women receiving mercaptopurine after the first trimester of pregnancy, 3 mothers died prior to delivery, 1 delivered a stillborn child, and 1 aborted; there were no cases of macroscopically abnormal fetuses.

Animal Data

Mercaptopurine was embryo-lethal and teratogenic in several animal species (rat, mouse, rabbit, and hamster) at doses less than the recommended human dose.

8.2 Lactation

Risk Summary

There are no data on the presence of mercaptopurine or its metabolites in human milk, the effects on the breastfed child, or the effects on milk production. Because of the potential for serious adverse reactions in the breastfed child, advise women not to breastfeed during treatment with PURINETHOL and for 1 week after the last dose.

8.3 Females and Males of Reproductive Potential

PURINETHOL can cause fetal harm when administered to pregnant women *[see Use in Specific Populations (8.1)]*.

Pregnancy Testing

Verify the pregnancy status in females of reproductive potential prior to initiating PURINETHOL *[see Use in Specific Populations (8.1)]*.

Contraception

Females

Advise females of reproductive potential to use effective contraception during treatment with PURINETHOL and for 6 months after the last dose.

Males

Based on genotoxicity findings, advise males with female partners of reproductive potential to use effective contraception during treatment with PURINETHOL and for 3 months after the last dose *[see Nonclinical Toxicology (13.1)]*.

Infertility

Females and Males

Based on findings from animal studies, PURINETHOL can impair female and male fertility *[see Nonclinical Toxicology (13.1)]*. The long-term effects of mercaptopurine on female and male fertility, including the reversibility have not been studied.

8.4 Pediatric Use

Safety and effectiveness of PURINETHOL has been established in pediatric patients. Use of PURINETHOL in pediatrics is supported by evidence from the published literature and clinical experience. Symptomatic hypoglycemia has been reported in pediatric patients with ALL receiving mercaptopurine. Reported cases were in pediatrics less than 6 years of age or with a low body mass index.

8.5 Geriatric Use

Clinical studies of mercaptopurine did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects. Other reported clinical experience has not identified differences in responses between the elderly and younger patients. In general, dose selection for an elderly patient should be cautious, usually starting at the low end of the dosing range, reflecting the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or another drug therapy.

8.6 Renal Impairment

Use the lowest recommended starting dosage for PURINETHOL or increase the dosing interval to every 36-48 hours in patients with renal impairment (CLcr less than 50 mL/min). Adjust the dose to maintain absolute neutrophil count (ANC) at a desirable level and for adverse reactions *[see Dosage and Administration (2.3)]*.

8.7 Hepatic Impairment

Use the lowest recommended starting dosage for PURINETHOL in patients with hepatic impairment. Adjust the dose to maintain absolute neutrophil count (ANC) at a desirable level and for adverse reactions *[see Dosage and Administration (2.3)]*.

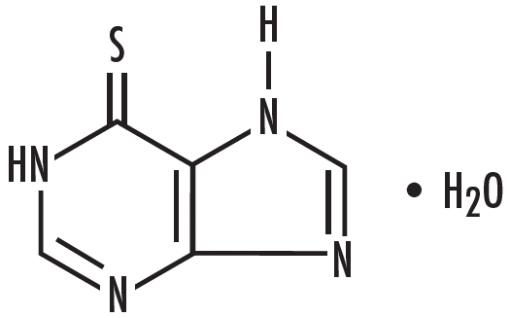
10 OVERDOSAGE

Signs and symptoms of mercaptopurine overdosage may be immediate (anorexia, nausea, vomiting, and diarrhea); or delayed (myelosuppression, liver dysfunction, and gastroenteritis). Dialysis cannot be expected to clear mercaptopurine. Hemodialysis is thought to be of marginal use due to the rapid intracellular incorporation of mercaptopurine into active metabolites with long persistence.

Withhold PURINETHOL immediately for severe or life-threatening adverse reactions occur during treatment. If a patient is seen immediately following an accidental overdosage, it may be useful to induce emesis.

11 DESCRIPTION

Mercaptopurine is a nucleoside metabolic inhibitor, the chemical name is 6*H*-purine-6-thione, 1,7-dihydro-, monohydrate. The molecular formula is $C_5H_4N_4S \cdot H_2O$ and the molecular weight is 170.20. Its structural formula is:



Mercaptopurine is a yellow, crystalline powder. Mercaptopurine is practically insoluble in water and in ether. It has a pKa of 7.8, an average tapped density of 1.0 g/mL and average bulk density of 0.85 g/mL. It dissolves in solutions of alkali hydroxides.

PURINETHOL is available for oral use. Each scored tablet contains 50 mg mercaptopurine and the following inactive ingredients: corn starch, pregelatinized, potato starch, lactose, magnesium stearate and stearic acid.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Mercaptopurine is a purine analog that undergoes intracellular transport and activation to form metabolites including thioguanine nucleotides (TGNs). Incorporation of TGNs into DNA or RNA results in cell-cycle arrest and cell death. TGNs and other mercaptopurine metabolites are also inhibitors of de novo purine synthesis and purine nucleotide interconversions. Mercaptopurine was cytotoxic to proliferating cancer cells in vitro and had antitumor activity in mouse tumor models. It is not known which of the biochemical effects of mercaptopurine and its metabolites are directly or predominantly responsible for cell death.

12.2 Pharmacodynamics

Exposure-Response Relationships

Mercaptopurine exposure-response relationships and the time course of pharmacodynamics response are unknown.

12.3 Pharmacokinetics

Following a single oral dose of mercaptopurine 50 mg under fasted conditions to adult healthy subjects, the mean $AUC_{0\text{-}INF}$ was 129 h·ng/mL and C_{max} was 69 ng/mL.

Absorption

Food Effect

Food has been shown to decrease the exposure of mercaptopurine.

Distribution

The volume of distribution usually exceeded that of the total body water. There is negligible entry of mercaptopurine into cerebrospinal fluid.

Plasma protein binding averages 19% over the concentration range 10 to 50 mcg/mL (a concentration only achieved by intravenous administration of mercaptopurine at doses exceeding 5 to 10 mg/kg).

Elimination

The elimination half-life is less than 2 hours following a single oral dose.

Metabolism

Mercaptopurine is inactivated via two major pathways. One is thiol methylation, which is catalyzed by the polymorphic enzyme thiopurine S-methyltransferase (TPMT), to form the inactive metabolite methyl-mercaptopurine. The second inactivation pathway is oxidation, which is catalyzed by xanthine oxidase. The product of oxidation is the inactive metabolite 6-thiouric acid.

Excretion

Following the oral administration of radiolabeled mercaptopurine, 46% of the dose was recovered in the urine (as parent drug and metabolites) in the first 24 hours.

12.5 Pharmacogenomics

Several published studies indicate that patients with reduced TPMT or NUDT15 activity receiving usual doses of mercaptopurine, accumulate excessive cellular concentrations of active 6-TGNs, and are at higher risk for severe myelosuppression. In a study of 1028 children with ALL, the approximate tolerated mercaptopurine dosage for patients with TPMT and/or NUDT15 deficiency on mercaptopurine maintenance therapy (as a percentage of the planned dosage) was as follows: heterozygous for either TPMT or NUDT15, 50-90%; heterozygous for both TPMT and NUDT15, 30-50%; homozygous for either TPMT or NUDT15, 5-10%.

Approximately 0.3% (1:300) of patients of European or African ancestry have two loss-of-function alleles of the TPMT gene and have little or no TPMT activity (homozygous deficient or poor metabolizers), and approximately 10% of patients have one loss-of-function TPMT allele leading to intermediate TPMT activity (heterozygous deficient or intermediate metabolizers). The TPMT*2, TPMT*3A, and TPMT*3C alleles account for about 95% of individuals with reduced levels of TPMT activity.

NUDT15 deficiency is detected in <1% of patients of European or African ancestry. Among patients of East Asian ancestry (i.e., Chinese, Japanese, Vietnamese), 2% have two loss-of-function alleles of the NUDT15 gene, and approximately 21% have one loss-of-function allele. The p.R139C variant of NUDT15 (present on the *2 and *3 alleles) is the most commonly observed, but other less common loss-of-function NUDT15 alleles have been observed.

Consider all clinical information when interpreting results from phenotypic testing used to determine the level of thiopurine nucleotides or TPMT activity in erythrocytes, since some coadministered drugs can influence measurement of TPMT activity in blood and blood from recent transfusions will misrepresent a patient's actual TPMT activity *[see Dosage and Administration (2.2), Warnings and Precautions (5.1)]*.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Mercaptopurine is carcinogenic in animals.

Mercaptopurine causes chromosomal aberrations in cells derived from animals and humans and induces dominant-lethal mutations in the germ cells of male mice.

Mercaptopurine can impair fertility. In mice, surviving female offspring of mothers who received chronic low doses of mercaptopurine during pregnancy were found sterile, or if they became pregnant, had smaller litters and more dead fetuses as compared to control animals

15 REFERENCES

1. OSHA Hazardous Drugs. OSHA. http://www.osha.gov/SLTC/hazardousdrugs/index.html

16 HOW SUPPLIED/STORAGE AND HANDLING

PURINETHOL is supplied as biconvex, round, pale yellow to buff, scored tablets containing 50 mg mercaptopurine, imprinted with "9|3" available in:

- bottles of 25 NDC 62033-601-12

Store at 20°C to 25°C (68°F to 77°F); excursions permitted to 15°C to 30°C (59°F to 86°F) [see USP Controlled Room Temperature]. Store in a dry place. Dispense in tight container as defined in the USP.

PURINETHOL is a cytotoxic drug. Follow special handling and disposal procedures[1].

17 PATIENT COUNSELING INFORMATION

Major Adverse Reactions

Advise patients and caregivers that PURINETHOL can cause myelosuppression, hepatotoxicity, and gastrointestinal toxicity. Advise patients to contact their healthcare provider if they experience fever, sore throat, jaundice, nausea, vomiting, signs of local infection, bleeding from any site, or symptoms suggestive of anemia *[see Warnings and Precautions (5.1, 5.2, 5.3)]*.

Embryo-Fetal Toxicity

- Advise pregnant women of the potential risk to a fetus. Advise females of reproductive potential to inform their healthcare provider of a known or suspected pregnancy *[see Warnings and Precautions (5.6), Use in Specific Populations (8.1)]*.
- Advise females of reproductive potential to use effective contraception during treatment with PURINETHOL and for 6 months after the last dose *[see Use in Specific Populations (8.3)]*.
- Advise males with female partners of reproductive potential to use effective contraception during treatment with PURINETHOL and for 3 months after the last dose *[see Use in Specific Populations (8.3), Nonclinical Toxicology (13.1)]*.

Lactation

Advise women not to breastfeed during treatment with PURINETHOL and for 1 week after the last dose *[see Use in Specific Populations (8.2)]*.

Infertility

Advise males and females of reproductive potential that PURINETHOL can impair fertility *[see Use in Specific Populations (8.3)]*.

Other Adverse Reactions

Instruct patients to minimize sun exposure due to risk of photosensitivity *[see Adverse Reactions (6.1)]*.

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Next Generation Multi-Gene Sequencing/Targeted Genomic Sequencing Panels

Plain Language Summary:
Background: There are new genetic tests to guide treatment for certain cancers that include testing for multiple changes in the cancer DNA at one time.

Should OHP cover this test? Staff recommends coverage of these tests, and having a workgroup meet to provide advice on any guidelines for such testing.

Question: Should next generation multi-gene sequencing be covered for certain cancers?

Question source: New 2023 CPT codes, HERC staff, FoundationOne

Issue: Some types of cancers routinely have biomarker genetic testing done on tumor tissue to determine if there is an actionable mutation, to target drug therapy, or to determine prognosis. Initially, much of this testing was for single gene targets. Recent technical advances, in particular "next generation" or "massively parallel" sequencing (NGS), have enabled the simultaneous assessment of multiple genetic markers in a single assay run.

For some cancers, specific genetic tests are standard-of-care determinants for FDA-approved targeted therapies and are incorporated into professional practice guidelines from the National Comprehensive Cancer Network (NCCN). For other cancers, genetic tests are used to exclude the use of a targeted therapy and shift the focus of treatment instead towards other modalities. In still other cancers, genetic tests are used to indicate suitability for treatment with an investigational agent, as an alternative to an ineffective traditional therapy that is expected to have marginal, if any, benefit. Finally, genetic testing of cancer samples can be used to establish a definitive diagnosis or for stratification into risk-based treatment groups.

For patients, physicians, and laboratories, the advantages of the NGS panel tests are (1) more efficient use of limited samples, (2) more rapid time to a completed set of results, (3) more efficient resource utilization compared to performing multiple individual tests, (4) better ability to rapidly incorporate new genes into a panel in order to support clinical decision making since evidence in the field is rapidly evolving, and (5) identification of unexpected clinically actionable mutations that are not customarily associated with the tissue type of the tumor. A growing body of evidence supports the use of expanded panel testing in selected tumor types. The evidence shows that for selected tumors, expanded panel testing reveals “driver mutations”, (mutations that activate signaling pathways which cause uncontrolled tumor cell growth) for which there are known and/or investigational drugs that will improve outcomes in patients with these tumors in comparison to conventional cytotoxic therapy. HOWEVER, such testing many not be useful in some cancer types or in cancers in which such testing will not drive treatment decisions.

Targeted genomic sequencing can be focused on tumor DNA, tumor RNA, or both. Targeted RNA-sequencing (RNA-Seq) is a highly accurate method for selecting and sequencing specific transcripts of interest. It offers both quantitative and qualitative information.

Next Generation Multi-Gene Sequencing/Targeted Genomic Sequencing Panels

Previous HERC review
Targeted genetic sequencing of tumor DNA and tumor DNA and RNA together were added to the DIAGNOSTIC PROCEDURES file in 2014 as new 2015 CPT codes with minimal review. The entire HERC review on these codes was to indicate that as the component genes were covered; therefore the panel should be covered.

There are three new 2023 CPT codes related to targeted genetic sequencing of tumor RNA alone.

Current Prioritized List status:

The following codes are on the DIAGNOSTIC PROCEDURES file with no entry in the non-prenatal genetic testing guideline:

1) 81445 Targeted genomic sequence analysis panel, solid organ neoplasm, 5-50 genes (eg, ALK, BRAF, CDKN2A, EGFR, ERBB2, KIT, KRAS, MET, NRAS, PDGFRA, PDGFRB, PGR, PIK3CA, PTEN, RET), interrogation for sequence variants and copy number variants or rearrangements, if performed; DNA analysis or combined DNA and RNA analysis
2) 81450 Targeted genomic sequence analysis panel, hematolymphoid neoplasm or disorder, 5-50 genes (eg, BRAF, CEBPA, DNMT3A, EZH2, FLT3, IDH1, IDH2, JAK2, KIT, KRAS, MLL, NOTCH1, NPM1, NRAS), interrogation for sequence variants, and copy number variants or rearrangements, or isoform expression or mRNA expression levels, if performed; DNA analysis or combined DNA and RNA analysis
3) 81455 Targeted genomic sequence analysis panel, solid organ or hematolymphoid neoplasm or disorder, 51 or greater genes (eg, ALK, BRAF, CDKN2A, CEBPA, DNMT3A, EGFR, ERBB2, EZH2, FLT3, IDH1, IDH2, JAK2, KIT, KRAS, MET, MLL, NOTCH1, NPM1, NRAS, PDGFRA, PDGFRB, PGR, PIK3CA, PTEN, RET), interrogation for sequence variants and copy number variants or rearrangements, or isoform expression or mRNA expression levels, if performed; DNA analysis or combined DNA and RNA analysis

New 2023 CPT code descriptions

1) 81449 Targeted genomic sequence analysis panel, solid organ neoplasm, 5-50 genes (eg, ALK, BRAF, CDKN2A, EGFR, ERBB2, KIT, KRAS, MET, NRAS, PDGFRA, PDGFRB, PGR, PIK3CA, PTEN, RET), interrogation for sequence variants and copy number variants or rearrangements, if performed; RNA analysis
2) 81451 Targeted genomic sequence analysis panel, hematolymphoid neoplasm or disorder, 5-50 genes (eg, BRAF, CEBPA, DNMT3A, EZH2, FLT3, IDH1, IDH2, JAK2, KIT, KRAS, MLL, NOTCH1, NPM1, NRAS), interrogation for sequence variants, and copy number variants or rearrangements, or isoform expression or mRNA expression levels, if performed; RNA analysis
3) 81456 Targeted genomic sequence analysis panel, solid organ or hematolymphoid neoplasm or disorder, 51 or greater genes (eg, ALK, BRAF, CDKN2A, CEBPA, DNMT3A, EGFR, ERBB2, EZH2, FLT3, IDH1, IDH2, JAK2, KIT, KRAS, MET, MLL, NOTCH1, NPM1, NRAS, PDGFRA, PDGFRB, PGR, PIK3CA, PTEN, RET), interrogation for sequence variants and copy number variants or rearrangements, or isoform expression or mRNA expression levels, if performed; RNA analysis

In addition to the above CPT codes, there are a large number of CPT codes that refer to a specific proprietary test (usually designated with 0XXXU).

There are also specific CPT codes for single gene tests or for gene panel testing for a specific type of cancer, which are included in Guideline note 148.

GUIDELINE NOTE 148, BIOMARKER TESTS OF CANCER TISSUE

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

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

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

- Oncotype DX Breast Recurrence Score (CPT 81519) for breast tumors that are estrogen receptor positive, HER2 negative, and either lymph node negative, or lymph node positive with 1-3 involved nodes.
- EndoPredict (CPT 81522) and Prosigna (CPT 81520 or PLA 0008M) for breast tumors that are estrogen receptor positive, HER2 negative, and lymph node negative.
- MammaPrint (using CPT 81521, 81523 or HCPCS S3854) for breast tumors that are estrogen receptor or progesterone receptor positive, HER2 negative, lymph node negative, and only in those cases categorized as high clinical risk.

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

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

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

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

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

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

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

For prostate cancer, Oncotype DX Genomic Prostate Score, Prolaris Score Assay (CPT 81541), and Decipher Prostate RP (CPT 81542) are included on Line 662 CONDITIONS FOR WHICH CERTAIN INTERVENTIONS ARE UNPROVEN, HAVE NO CLINICALLY IMPORTANT BENEFIT OR HAVE HARMS THAT OUTWEIGH BENEFITS.

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

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

Selected expert guidelines

ASCO 2020: Somatic genomic testing is patients with metastatic or advanced cancer

1) Genomic testing should be performed for patients with metastatic or advanced solid tumors with adequate performance status in the following two clinical scenarios:
   - **a.** When there are genomic biomarker–linked therapies approved by regulatory agencies for their cancer.
   - **b.** When considering a treatment for which there are specific genomic biomarker–based contraindications or exclusions (strength of recommendation: strong)

NCCN Breast Cancer Version 4.2022

1) Neurotrophic tropomyosin receptor kinase (NTRK) gene fusions are seen in of a few rare types of cancer, such as secretory carcinoma of the breast or salivary gland and infantile fibrosarcoma and also infrequently in some common cancers, such as melanoma, glioma and carcinomas of the thyroid, lung and colon. NTRK fusions are identified by fluorescence in situ hybridization (FISH), Next Generation Sequencing (NGS) or polymerase chain reaction (PCR). Larotrectinib and entrectinib are two NTRK-inhibitors that are U.S FDA approved for the treatment of solid tumors that have an NTRK gene fusion without a known acquired resistance mutation and have no satisfactory alternative treatments or that have progressed following treatment. If patient with recurrent/stage IV breast presents with a tumor with an NTRK fusion, treatment with a NTRK-inhibitor is an option if no satisfactory alternative treatments exists or that have progressed following treatment

NCCN Melanoma 3.2022

1) Other uncommon mutations detected by NGS panel
   - a. Fusions in NTRK1, NTRK2, and NTRK3 occur uncommonly (<1%) across subtypes of melanoma
     - i. Fusions in these genes correspond with a high response rate to the TRK inhibitors larotrectinib or entrectinib
   - b. Fusions in ALK and ROS1, more common in lung cancer, occur uncommonly (<1%) across subtypes of melanoma
     - i. Fusions in these genes may predispose to clinical activity from inhibitors of these genes (eg, crizotinib, entrectinib)

2) NGS, also known as high-throughput sequencing, describes a number of different sequencing technologies that allow sequencing of DNA and RNA much more quickly and cheaply than the previously used Sanger sequencing. Single-gene or small multigene panels are also used in some cases to test either one gene (BRAF) or a limited number of genes.
    a. Molecular testing on tumor tissue is preferred, but may be performed on peripheral blood (liquid biopsy) if tumor tissue is not available
    b. The panel does not recommend BRAF or NGS testing for resected stage I–II cutaneous melanoma unless it will inform clinical trial participation
3) Principles of molecular testing
    a. For initial presentation with stage IV disease or clinical recurrence, obtain tissue to ascertain alterations in BRAF, and in the appropriate clinical setting, KIT from either biopsy of the metastasis (preferred) or archival material if the patient is being considered for targeted therapy. Broader genomic profiling (eg, larger NGS panels, BRAF non-V600 mutations) is recommended if feasible, especially if the test results might guide future treatment decisions or eligibility for participation in a clinical trial.
    b. If BRAF single-gene testing was the initial test performed, and is negative, clinicians should strongly consider larger NGS panels to identify other potential genetic targets (eg, KIT, BRAF non-V600).

NCCN 1.2022 Colon Cancer

1) Work up for metastatic disease
    a. Determination of tumor gene status for RAS and BRAF mutations and HER2 amplifications (individually or as part of tissue- or blood-based next-generation sequencing [NGS] panel)
    b. determination of tumor gene status for KRAS/NRAS and BRAF mutations, as well as HER2 amplifications and MSI/MMR status (if not previously done), are recommended for patients with mCRC. Testing may be carried out for individual genes or as part of an NGS panel, although no specific methodology is recommended. NGS panels have the advantage of being able to pick up rare and actionable genetic alterations, such as neurotrophic tyrosine receptor kinase (NTRK) fusions
2) Principle of pathologic and molecular review
    a. All patients with metastatic colorectal cancer should have tumor genotyped for RAS (KRAS and NRAS) and BRAF mutations individually or as part of an NGS panel. Patients with any known KRAS mutation (exon 2, 3, 4) or NRAS mutation (exon 2, 3, 4) should not be treated with either cetuximab or panitumumab.53-55 BRAF V600E mutation makes response to panitumumab or cetuximab highly unlikely unless given with a BRAF inhibitor
    b. Testing for MSI may be accomplished by polymerase chain reaction (PCR) or a validated NGS panel, the latter especially in patients with metastatic disease who require genotyping of RAS and BRAF

NCCN 5.2022 Ovarian cancer

1) With the availability of next-generation sequencing technology, the panel discussed whether comprehensive tumor molecular analysis should be recommended for all patients. Some panel members stated that comprehensive tumor testing may not be necessary for certain patients in the upfront setting, specifically those with a germline mutation in

BRCA1/2 or other homologous recombination/DNA repair pathway genes. However, some patients (such as those who lack a BRCA1/2 mutation or experience disease recurrence) may benefit from a more thorough tumor molecular analysis to inform additional targeted therapy options. The panel agreed that tumor testing may be beneficial at multiple points throughout the evolution of the disease. Therefore, the current guidelines recommend tumor molecular analysis both in the upfront setting and upon recurrence (OV-B 1 of 3). The goal of tumor testing in the upfront setting is to optimize identification of molecular alterations that can inform the use of interventions with demonstrated benefit in this setting, such as PARP inhibitors. Molecular alterations that should be probed for in this setting include BRCA1/2 status, loss of heterozygosity, or homologous recombination status, in the absence of a germline BRCA mutation. Other tumor tissue molecular markers may inform selection of treatment for persistent or recurrent disease but testing for these is not needed until the disease has proven to be refractory or at time of relapse. The panel recommends that tumor molecular analysis in the recurrence setting should include, at a minimum, tests to identify potential benefit from targeted therapeutics that have tumor-specific or tumor-agnostic benefit. These include (but are not limited to): BRCA1/2, HR status, microsatellite instability (MSI), mismatch repair (MMR), tumor mutational burden (TMB), BRAF, and NTRK, if prior testing did not include these markers. The panel emphasizes that more comprehensive tumor analysis may be particularly important for less common histologies with limited approved treatment options. Prior to selection of systemic therapy for refractory or recurrent disease, validated tumor molecular testing should be performed in a Clinical Laboratory Improvement Amendments (CLIA)-approved facility using the most recent available tumor tissue.

Selected payer policies

1) **Evicore 2021**: Somatic mutation testing-solid tumors
    a. The member has a tumor type that will benefit from information provided by the requested tumor marker test based on at least one of the following:
        i. All criteria are met from a test-specific guideline if one is available, or
        ii. An oncology therapy FDA label requires results from the tumor marker test to effectively or safely use the therapy for the member's cancer type (See Common cancer types and associated tumor markers table below for examples of currently recognized companion diagnostics), or
        iii. NCCN guidelines include the tumor marker test in the management algorithm for that particular cancer type and all other requirements are met (specific pathology findings, staging, etc.); however, the tumor marker must be explicitly included in the guidelines and not simply included in a footnote as an intervention that may be considered (See Common cancer types and associated tumor markers table below for examples of currently recommended gene tests)
    b. Note If five or more individually billed tumor marker tests are under review together (a "panel") and the member either has non-small cell lung cancer, metastatic colorectal cancer, or stage IV cutaneous melanoma OR meets criteria for 5 or more individual tumor markers, the panel will be approved. However, the laboratory will be redirected to use a panel CPT code for billing purposes (e.g. 81445 or 81455)
    c. When a multi-gene panel is being requested and will be billed with a single panel CPT code (e.g. 81445 or 81455), the panel will be considered medically necessary when the following criteria are met:
        i. The requested testing is a companion diagnostic per the FDA label for the member's cancer type and specific treatments being considered (e.g. FoundationOne CDx testing in an individual with ovarian cancer for treatment with olaparib), OR
        ii. The member has a diagnosis of one of the following cancers:
            1. Metastatic colorectal cancer
            2. Stage IV cutaneous melanoma
            3. Non-small cell lung cancer, OR
        iii. The member has a diagnosis of one of the following cancers, when the panel includes at least five of the genes associated with that cancer type listed in the below table Common cancer types and associated tumor markers:
            1. Gastrointestinal Stromal Tumor (GIST)
            2. Infiltrative glioma
            3. Locally advanced, metastatic, or recurrent pancreatic cancer
            4. Malignant peripheral nerve sheath tumor
            5. Regional or metastatic prostate cancer
            6. Metastatic urothelial bladder cancer that has progressed following at least one line of prior platinum-containing chemotherapy
            7. Metastatic or unresectable uveal melanoma that has progressed following all available treatments, OR
        iv. The member does not have one of the cancers listed in the section above, but at least 5 tumor markers included in the panel individually meet criteria for the member's tumor type based on one of the following:
            1. All criteria are met from a test-specific guideline if one is available, or

2. An oncology therapy FDA label requires results from the tumor marker test to effectively or safely use the therapy for the member's cancer type (See Common cancer types and associated tumor markers table below for examples of currently recognized companion diagnostics for available therapies.), or
3. NCCN guidelines include the tumor marker test in the management algorithm for that particular cancer type and all other requirements are met (specific pathology findings, staging, etc.); however, the tumor marker must be explicitly included in the guidelines and not simply included in a footnote as an intervention that may be considered.

2) **Wellmark BCBS 2021** Circulating tumor DNA and circulating tumor cells for cancer management (liquid biopsies)
    a. Has an extensive table with type of cancer and when the test is covered (diagnostic, stage of cancer, recurrent cancer, metastatic cancer, for monitoring, etc.)

GAP discussion: Members noted that there are a high volume of requests for this testing. HERC staff had drafted a guideline to help determine when these tests should be covered. However, GAP members felt that these tests are standard of care. Furthermore, the review required by the proposed guideline would be very time consuming if the reviewer had to constantly refer to the NCCN guidelines. GAP members recommended coverage of all 6 codes as diagnostic without a guideline.

HERC staff summary

The field of cancer biomarker testing is expanding at an extremely rapid pace. Single gene testing is rapidly being replaced in many instances by large gene panel testing. The ability to monitor and research each test and each indication is daunting. Such biomarker testing is required prior to treatment with certain agents by the FDA, and may be part of cancer treatment algorithms, such as the NCCN algorithms.

The Evidence-based Guidelines Subcommittee is planning on conducting a re-review of their cancer biomarkers coverage guidance. To inform this review, or possibly to better facilitate HERC changes, HERC staff are convening a work group of cancer genetic counselors, oncologists, and cancer pathologists. This work group will start meeting this winter.

In the interim, HERC staff recommends placing the new RNA panel testing on the DIAGNOSTIC PROCEDURES file to match the placement of the DNA and DNA+RNA panel tests. The placement of all 6 codes can be readdressed after the EbGS review. GAP members agreed with this recommendation.

GAP/HERC staff recommendation:

1) Place the new CPT codes 81449, 81451, and 81456 on the DIAGNOSTIC PROCEDURES file
    a. 81449 Targeted genomic sequence analysis panel, solid organ neoplasm, 5-50 genes (eg, ALK, BRAF, CDKN2A, EGFR, ERBB2, KIT, KRAS, MET, NRAS, PDGFRA, PDGFRB, PGR, PIK3CA, PTEN, RET), interrogation for sequence variants and copy number variants or rearrangements, if performed; RNA analysis
    b. 81451 Targeted genomic sequence analysis panel, hematolymphoid neoplasm or disorder, 5-50 genes (eg, BRAF, CEBPA, DNMT3A, EZH2, FLT3, IDH1, IDH2, JAK2, KIT, KRAS, MLL, NOTCH1, NPM1, NRAS), interrogation for sequence variants, and copy number variants or rearrangements, or isoform expression or mRNA expression levels, if performed; RNA analysis
    c. 81456 Targeted genomic sequence analysis panel, solid organ or hematolymphoid neoplasm or disorder, 51 or greater genes (eg, ALK, BRAF, CDKN2A, CEBPA, DNMT3A, EGFR, ERBB2, EZH2, FLT3, IDH1, IDH2, JAK2, KIT, KRAS, MET, MLL, NOTCH1, NPM1, NRAS, PDGFRA, PDGFRB, PGR, PIK3CA, PTEN, RET), interrogation for sequence variants and copy number variants or rearrangements, or isoform expression or mRNA expression levels, if performed; RNA analysis

ASCO special articles

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

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abstract

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

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

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

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

J Clin Oncol 40:1231-1258.

INTRODUCTION

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

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

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

ASSOCIATED CONTENT

Appendix

Data Supplement

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

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THE BOTTOM LINE

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

Research Question

What are appropriate recommendations for genomic testing in metastatic or advanced cancer?

Target Population

Patients with metastatic or advanced solid tumors. Note that the neoadjuvant and adjuvant treatment settings are specifically excluded from this Provisional Clinical Opinion (PCO), as were nonsolid tumor cancers (eg, lymphoma).

Target Audience

Oncologists, pathologists, and other clinicians involved in deciding appropriate care for patients with metastatic or advanced cancer, as well as patients and caregivers.

Methods

Informal consensus is based on the review of existing approved testing and therapy combinations, available marker prevalence data, and expert opinion. As no formal systematic review of the clinical trial evidence was conducted for this PCO, and all the recommendations are based on the informal consensus of the Expert Panel, no recommendation-by-recommendation statement of evidence quality is provided. The strength of the recommendation is defined in the Appendices (Table A2, online only).

Provisional Clinical Opinion

Section 1: Framework for decision making on multigene panel–based genomic sequencing with disease-specific approved markers.

For what clinical scenarios are there biomarker-linked regulatory approvals for the treatment of specific genomic alterations?

PCO 1.1. Genomic testing should be performed for patients with metastatic or advanced solid tumors with adequate performance status in the following two clinical scenarios:

- When there are genomic biomarker–linked therapies approved by regulatory agencies for their cancer.
- When considering a treatment for which there are specific genomic biomarker–based contraindications or exclusions (strength of recommendation: strong).

When should multigene panel–based genomic testing be performed when there is only a single genomic biomarker or small numbers of genomic biomarkers linked to regulatory approvals of anticancer drugs?

PCO 1.2.1. For patients with metastatic or advanced solid tumors, genomic testing using multigene genomic sequencing is preferred whenever patients are eligible for a genomic biomarker–linked therapy that a regulatory agency has approved (strength of recommendation: moderate).

PCO 1.2.2. Multigene panel–based genomic testing should be used whenever more than one genomic biomarker is linked to a regulatory agency–approved therapy (strength of recommendation: strong).

What are other important considerations when ordering and interpreting genomic testing?

PCO 1.3. If the genomic sequencing results are used to inform clinical care, such testing must be performed in an appropriately certified laboratory (strength of recommendation: strong).

PCO 1.4. Clinical decision making should incorporate (1) the known or predicted impact of a specific genomic alteration on protein expression or function and (2) clinical data on the efficacy of targeting that genomic alteration with a particular agent (strength of recommendation: strong)

PCO 1.5. Germline testing for genetic alterations linked to approved therapies should be performed in patients with metastatic or advanced solid tumors considered for such treatment. It should not be limited by family history–based or clinical criteria used for familial risk assessment. Patients with pathogenic or likely pathogenic (P/LP) variants should be referred for genetic counseling for education about secondary cancer risks, possible inheritance of germline mutations among blood relatives, and the differences between germline and somatic mutations, if they did not receive pretest counseling (strength of recommendation: strong).

Qualifying statement

Germline testing and genetic counseling may still be needed in patients with personal or family histories suggestive of an inherited predisposition, even when no germline alterations are identified during tumor genomic sequencing using various sequencing panels.

(continued on following page)

Decipher Prostate

Plain Language Summary:
Background: This is a test for prostate cancer patients who are considering radiation therapy. It is currently a non-covered test based on a 2017 evidence report.

Should OHP cover this test? Staff recommends covering this test now as the National Comprehensive Cancer Network (NCCN) gives Decipher a "1" rating for evidence supporting its use for helping make treatment decisions.

Question: Should Decipher Prostate genetic testing be covered?

Question source: Carl Stevens, MD CCO medical director; GAP

Issue: Decipher Prostate (CPT 81542) was reviewed in the 2017 HTAS Coverage Guidance on Gene Expression Profiling for Prostate Cancer and found to have little evidence to support its use. This test was included in GN148 BIOMARKER TESTS OF CANCER TISSUE as non-covered and listed in GN173 as non-covered. Dr. Stevens noted at the 2022 GAP meeting that Decipher Prostate is now recommended by NCCN for use in prostate cancer patients for consideration of radiation therapy.

HERC/subcommittee review history
The 2017 Biomarker for Prostate Cancer coverage guidance evidence review included only one cohort study (Gore et al 2017). NCCN relied on the results of two large prospective cohort studies (Marascio et al 2020 and Vince et al 2020) to inform their recommendations on Decipher.

Biomarkers for prostate cancer was reviewed in March, 2021 by VBBS. At that time, an AHRQ 2020 review was found that reported "We found no evidence that met our predefined inclusion criteria for the newer prognostic (proprietary) biomarkers such as Decipher, Oncotype Dx and Prolaris as it relates to comparative effectiveness modification." A 2018 review by Washington HTA included 8 studies at high risk for bias. This review concluded: "There is a mix of low-quality, very low-quality, and no evidence to support the other included tests for prostate cancer, colon cancer, and multiple myeloma. Multiple ongoing clinical trials on most of the tests will be reporting results in the next few years and will hopefully improve the evidence base for decision making regarding the clinical usefulness and economic effects of these tests." In the 2021 VBBS review, NCCN was noted to have only footnotes regarding biomarker assays in their prostate cancer treatment guideline.

Current Prioritized List status

GUIDELINE NOTE 148, BIOMARKER TESTS OF CANCER TISSUE
Lines 157,184,191,229,262,271,329
The use of tissue of origin testing (e.g. CPT 81504) is included on Line 662 CONDITIONS FOR WHICH CERTAIN INTERVENTIONS ARE UNPROVEN, HAVE NO CLINICALLY IMPORTANT BENEFIT OR HAVE HARMS THAT OUTWEIGH BENEFITS.

For early stage breast cancer, the following breast cancer genome profile tests are included on Line 191 when the listed criteria are met. One test per primary breast cancer is covered when the patient is

willing to use the test results in a shared decision-making process regarding adjuvant chemotherapy. Lymph nodes with micrometastases less than 2 mm in size are considered node negative.

- Oncotype DX Breast Recurrence Score (CPT 81519) for breast tumors that are estrogen receptor positive, HER2 negative, and either lymph node negative, or lymph node positive with 1-3 involved nodes.
- EndoPredict (CPT 81522) and Prosigna (CPT 81520 or PLA 0008M) for breast tumors that are estrogen receptor positive, HER2 negative, and lymph node negative.
- MammaPrint (using CPT 81521, 81523 or HCPCS S3854) for breast tumors that are estrogen receptor or progesterone receptor positive, HER2 negative, lymph node negative, and only in those cases categorized as high clinical risk.

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

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

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

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

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

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

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

For prostate cancer, Oncotype DX Genomic Prostate Score, Prolaris Score Assay (CPT 81541), and Decipher Prostate RP (CPT 81542) are included on Line 662 CONDITIONS FOR WHICH CERTAIN INTERVENTIONS ARE UNPROVEN, HAVE NO CLINICALLY IMPORTANT BENEFIT OR HAVE HARMS THAT OUTWEIGH BENEFITS.

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

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

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

Line 662

The following Interventions are prioritized on Line 662 CONDITIONS FOR WHICH CERTAIN INTERVENTIONS ARE UNPROVEN, HAVE NO CLINICALLY IMPORTANT BENEFIT OR HAVE HARMS THAT OUTWEIGH BENEFITS:

Procedure Code	Intervention Description	Rationale	Last Review
Prostate Cancer Gene Expression tests billed with nonspecific codes (e.g. 81479, 81599, 84999)	• Oncotype DX Genomic Prostate Score • Decipher RP for prostate cancer	Unproven Intervention	March, 2021 Coverage guidance
81541	Oncology (prostate), mRNA gene expression profiling by real-time RT-PCR of 46 genes (31 content and 15 housekeeping)	Insufficient evidence of effectiveness	March, 2021
81542	Oncology (prostate), mRNA, microarray gene expression profiling of 22 content genes, utilizing formalin-fixed paraffin-embedded tissue, algorithm reported as metastasis risk score	Insufficient evidence of effectiveness	March, 2021

Expert guidelines

1) **NCCN 1.2023** treatment guideline for prostate cancer
    a. Several tissue-based molecular assays have been developed in an effort to improve decision-making in newly diagnosed patients considering active surveillance and in treated patients considering adjuvant therapy or treatment for recurrence. Uncertainty about the risk of disease progression can be reduced if such molecular assays can provide accurate and reproducible prognostic or predictive information beyond NCCN risk group assignment and currently available life expectancy tables and nomograms. Retrospective case cohort studies have shown that these assays provide prognostic information independent of NCCN or CAPRA risk groups, which include likelihood of death with conservative management, likelihood of biochemical recurrence after radical prostatectomy or EBRT, likelihood of adverse pathologic features after radical prostatectomy, and likelihood of developing metastasis after operation, definitive EBRT, or post-recurrence EBRT
    b. Decipher: Given a level of evidence of 1 for prognostic testing
    c. Patients with NCCN low, favorable intermediate, unfavorable intermediate, or high-risk disease and life expectancy ≥10 y may consider the use of the following tumor-based molecular assays: Decipher, Oncotype DX Prostate, and Prolaris.
        i. Note: Oncotype Dx and Prolaris testing are also non-covered
        ii. Note: NCCN gives Oncotype Dx and Prolaris a level of evidence of 3 for prognostic testing
    d. For patients with PSA persistence/recurrence and a life expectancy > 5 yrs, NCCN recommends risk stratification with a PSADT
        i. Foot note: “PSADT can be calculated to inform nomogram use and counseling and/or Decipher molecular assay (category 2B) can be considered to inform counseling.”
    e. Post-Prostatectomy Radiation Therapy
        i. The panel recommends use of nomograms and consideration of age and comorbidities, clinical and pathologic information, PSA levels, PSADT, and Decipher molecular assay to individualize treatment discussion. Patients with high Decipher genomic classifier scores (GC >0.6) should be strongly considered for EBRT and addition of ADT when the opportunity for early EBRT has been missed.
            1. EBRT with 2 years of 150 mg/day of bicalutamide demonstrated improved overall and metastasis-free survival on a prospective randomized trial (RTOG 9601) versus radiation alone in the salvage setting. A secondary analysis of RTOG 9601 found that patients with PSA ≤0.6 ng/mL had no overall survival improvement with the addition of the antiandrogen to EBRT. In addition, results of a retrospective analysis of RP specimens from patients in RTOG 9601 suggest that those with low PSA and a low Decipher score derived less benefit (development of distant metastases, overall survival) from bicalutamide than those with a high Decipher score.
            2. EBRT with 6 months of ADT (luteinizing hormone-releasing hormone [LHRH] agonist) improved biochemical or clinical progression at 5 years on a prospective randomized trial (GETUG-16) versus radiation alone in patients with rising PSA levels between 0.2 and 2.0 ng/mL after RP.

f. The Decipher molecular assay is recommended to inform adjuvant treatment if adverse features are found post-radical prostatectomy, and can be considered as part of counseling for risk stratification in patients with PSA resistance/recurrence after radical prostatectomy (category 2B).
g. Decisions about when to initiate post-radical prostatectomy radiation and whether to include ADT are complex. The Panel recommends use of nomograms and consideration of age and comorbidities, clinical and pathologic information, PSA levels, PSADT, and Decipher molecular assay to individualize treatment discussion.
h. the panel believes that patients with low or favorable intermediate disease and life expectancy greater than or equal to 10 years may consider the use of Decipher, Oncotype DX Prostate, or Prolaris during initial risk stratification.

Decipher Prostate

HERC staff summary

The area of biomarkers for prostate cancer is rapidly changing. Since the last review 18 months ago, NCCN has come out with significantly updated recommendations regarding biomarker testing, based on two large prospective cohort studies on Decipher. NCCN gives Decipher a "1" rating for evidence supporting its use for prognosis, while the panel gives OncotypeDx Prostate and Prolaris "3" evidence ratings. NCCN notes that Decipher can be useful in decision making regarding adjuvant radiation or other treatment.

HERC staff recommendations:

1) Add CPT 81542 (Oncology (prostate), mRNA, microarray gene expression profiling of 22 content genes, utilizing formalin-fixed paraffin-embedded tissue, algorithm reported as metastasis risk score) to the DIAGNOSTIC PROCEDURES file and remove from line 662 CONDITIONS FOR WHICH CERTAIN INTERVENTIONS ARE UNPROVEN, HAVE NO CLINICALLY IMPORTANT BENEFIT OR HAVE HARMS THAT OUTWEIGH BENEFITS
    a. Do not change non-coverage of OncotypeDx Prostate and Prolaris given the low evidence rating in NCCN
2) Modify GN148 as shown below
3) Modify GN173 as shown below
4) Add a note to the coverage guidance "Gene Expression Profiling for Prostate Cancer" indicating this review supersedes the portion of the coverage guidance addressing Decipher.

GUIDELINE NOTE 148, BIOMARKER TESTS OF CANCER TISSUE

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

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

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

- Oncotype DX Breast Recurrence Score (CPT 81519) for breast tumors that are estrogen receptor positive, HER2 negative, and either lymph node negative, or lymph node positive with 1-3 involved nodes.
- EndoPredict (CPT 81522) and Prosigna (CPT 81520 or PLA 0008M) for breast tumors that are estrogen receptor positive, HER2 negative, and lymph node negative.
- MammaPrint (using CPT 81521, 81523 or HCPCS S3854) for breast tumors that are estrogen receptor or progesterone receptor positive, HER2 negative, lymph node negative, and only in those cases categorized as high clinical risk.

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

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

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

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

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

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

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

For prostate cancer, Oncotype DX Genomic Prostate Score~~,~~ and Prolaris Score Assay (CPT 81541)~~, and Decipher Prostate RP (CPT 81542)~~ are included on Line 662 CONDITIONS FOR WHICH CERTAIN INTERVENTIONS ARE UNPROVEN, HAVE NO CLINICALLY IMPORTANT BENEFIT OR HAVE HARMS THAT OUTWEIGH BENEFITS.

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

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

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

Line 662

The following Interventions are prioritized on Line 662 CONDITIONS FOR WHICH CERTAIN INTERVENTIONS ARE UNPROVEN, HAVE NO CLINICALLY IMPORTANT BENEFIT OR HAVE HARMS THAT OUTWEIGH BENEFITS:

Decipher Prostate

Procedure Code	Intervention Description	Rationale	Last Review
Prostate Cancer Gene Expression tests billed with nonspecific codes (e.g. 81479, 81599, 84999)	• Oncotype DX Genomic Prostate Score • ~~Decipher RP for prostate cancer~~	Unproven Intervention	~~**March, 2021**~~ November 2022 Coverage guidance
81541	Oncology (prostate), mRNA gene expression profiling by real-time RT-PCR of 46 genes (31 content and 15 housekeeping)	Insufficient evidence of effectiveness	~~**March, 2021**~~ November 2022
~~81542~~	~~Oncology (prostate), mRNA, microarray gene expression profiling of 22 content genes, utilizing formalin-fixed paraffin-embedded tissue, algorithm reported as metastasis risk score~~	~~Insufficient evidence of effectiveness~~	~~**March, 2021**~~

Section 9.0

New Codes

Code	Code Description	Similar code	Recommended placement
15853	Removal of sutures or staples not requiring anesthesia (List separately in addition to E/M code)	Similar codes 15850 and 15851 (Removal of sutures under anesthesia (other than local), same/other surgeon) are Ancillary	ANCILLARY PROCEDURES
15854	Removal of sutures and staples not requiring anesthesia (List separately in addition to E/M code)	See 15853	ANCILLARY PROCEDURES
33900	Percutaneous pulmonary artery revascularization by stent placement, initial; normal native connections, unilateral	Stenting is a standard treatment for pulmonary artery stenosis (PAS) from congenital or acquired causes. Congenital conditions with PAS are on line 104 and aquired conditions are on line 357.	104 TETRALOGY OF FALLOT (TOF); CONGENITAL VENOUS ABNORMALITIES 357 CONDITIONS OF PULMONARY ARTERY
33901	Percutaneous pulmonary artery revascularization by stent placement, initial; normal native connections, bilateral	See 33900	104 TETRALOGY OF FALLOT (TOF); CONGENITAL VENOUS ABNORMALITIES 357 CONDITIONS OF PULMONARY ARTERY
33902	Percutaneous pulmonary artery revascularization by stent placement, initial; abnormal connections, unilateral	See 33900	104 TETRALOGY OF FALLOT (TOF); CONGENITAL VENOUS ABNORMALITIES 357 CONDITIONS OF PULMONARY ARTERY
33903	Percutaneous pulmonary artery revascularization by stent placement, initial; abnormal connections, bilateral	See 33900	104 TETRALOGY OF FALLOT (TOF); CONGENITAL VENOUS ABNORMALITIES 357 CONDITIONS OF PULMONARY ARTERY
33904	Percutaneous pulmonary artery revascularization by stent placement, each additional vessel or separate lesion, normal or abnormal connections (List separately in addition to code for primary procedure)	See 33900	104 TETRALOGY OF FALLOT (TOF); CONGENITAL VENOUS ABNORMALITIES 357 CONDITIONS OF PULMONARY ARTERY

Code	Code Description	Similar code	Recommended placement
36836	Percutaneous arteriovenous fistula creation, upper extremity, single access of both the peripheral artery and peripheral vein, including fistula maturation procedures (eg, transluminal balloon angioplasty, coil embolization) when performed, including all vascular access, imaging guidance and radiologic supervision and interpretation	Done for creation of dialysis access Similar codes (e.g. 36825 Creation of arteriovenous fistula by other than direct arteriovenous anastomosis (separate procedure); autogenous graft) are on line 339	339 CHRONIC KIDNEY DISEASE
36837	Percutaneous arteriovenous fistula creation, upper extremity, separate access sites of the peripheral artery and peripheral vein, including fistula maturation procedures (eg, transluminal balloon angioplasty, coil embolization) when performed, including all vascular access, imaging guidance and radiologic supervision and interpretation	See 36836	339 CHRONIC KIDNEY DISEASE
43291	Esophagogastroduodenoscopy, flexible, transoral; with removal of intragastric bariatric balloon(s)	Removal may be necessary due to a complication, infection, perforation, etc.	424 COMPLICATIONS OF A PROCEDURE USUALLY REQUIRING TREATMENT
49591	Repair of anterior abdominal hernia(s) (ie, epigastric, incisional, ventral, umbilical, spigelian), any approach (ie, open, laparoscopic, robotic), initial, including implantation of mesh or other prosthesis when performed, total length of defect(s); less than 3 cm, reducible	Replaces CPT 49652 (Laparoscopy, surgical, repair, ventral, umbilical, spigelian or epigastric hernia (includes mesh insertion, when performed); reducible) as well as the individual open repair codes which were on lines 168, 524. There is a guideline regarding hernia repair	168 COMPLICATED HERNIAS; PERSISTENT HYDROCELE 524 UNCOMPLICATED HERNIA AND VENTRAL HERNIA (OTHER THAN DIAPHRAGMATIC HERNIA)

Code	Code Description	Similar code	Recommended placement
49592	Repair of anterior abdominal hernia(s) (ie, epigastric, incisional, ventral, umbilical, spigelian), any approach (ie, open, laparoscopic, robotic), initial, including implantation of mesh or other prosthesis when performed, total length of defect(s); less than 3 cm, incarcerated or strangulated	Replaces CPT 49653 (Laparoscopy, surgical, repair, ventral, umbilical, spigelian or epigastric hernia (includes mesh insertion, when performed); incarcerated or strangulated) as well as the individual open repair codes which were on lines 168, 524. There is a guideline regarding hernia repair	168 COMPLICATED HERNIAS; PERSISTENT HYDROCELE 524 UNCOMPLICATED HERNIA AND VENTRAL HERNIA (OTHER THAN DIAPHRAGMATIC HERNIA)
49593	Repair of anterior abdominal hernia(s) (ie, epigastric, incisional, ventral, umbilical, spigelian), any approach (ie, open, laparoscopic, robotic), initial, including implantation of mesh or other prosthesis when performed, total length of defect(s); 3 cm to 10 cm, reducible	See 49591	168 COMPLICATED HERNIAS; PERSISTENT HYDROCELE 524 UNCOMPLICATED HERNIA AND VENTRAL HERNIA (OTHER THAN DIAPHRAGMATIC HERNIA)
49594	Repair of anterior abdominal hernia(s) (ie, epigastric, incisional, ventral, umbilical, spigelian), any approach (ie, open, laparoscopic, robotic), initial, including implantation of mesh or other prosthesis when performed, total length of defect(s); 3 cm to 10 cm, incarcerated or strangulated	See 49592	168 COMPLICATED HERNIAS; PERSISTENT HYDROCELE 524 UNCOMPLICATED HERNIA AND VENTRAL HERNIA (OTHER THAN DIAPHRAGMATIC HERNIA)
49595	Repair of anterior abdominal hernia(s) (ie, epigastric, incisional, ventral, umbilical, spigelian), any approach (ie, open, laparoscopic, robotic), initial, including implantation of mesh or other prosthesis when performed, total length of defect(s); greater than 10 cm, reducible	See 49591	168 COMPLICATED HERNIAS; PERSISTENT HYDROCELE 524 UNCOMPLICATED HERNIA AND VENTRAL HERNIA (OTHER THAN DIAPHRAGMATIC HERNIA)

Code	Code Description	Similar code	Recommended placement
49596	Repair of anterior abdominal hernia(s) (ie, epigastric, incisional, ventral, umbilical, spigelian), any approach (ie, open, laparoscopic, robotic), initial, including implantation of mesh or other prosthesis when performed, total length of defect(s); greater than 10 cm, incarcerated or strangulated	See 49592	168 COMPLICATED HERNIAS; PERSISTENT HYDROCELE 524 UNCOMPLICATED HERNIA AND VENTRAL HERNIA (OTHER THAN DIAPHRAGMATIC HERNIA)
49613	Repair of anterior abdominal hernia(s) (ie, epigastric, incisional, ventral, umbilical, spigelian), any approach (ie, open, laparoscopic, robotic), recurrent, including implantation of mesh or other prosthesis when performed, total length of defect(s); less than 3 cm, reducible	See 49591	168 COMPLICATED HERNIAS; PERSISTENT HYDROCELE 524 UNCOMPLICATED HERNIA AND VENTRAL HERNIA (OTHER THAN DIAPHRAGMATIC HERNIA)
49614	Repair of anterior abdominal hernia(s) (ie, epigastric, incisional, ventral, umbilical, spigelian), any approach (ie, open, laparoscopic, robotic), recurrent, including implantation of mesh or other prosthesis when performed, total length of defect(s); less than 3 cm, incarcerated or strangulated	See 49592	168 COMPLICATED HERNIAS; PERSISTENT HYDROCELE 524 UNCOMPLICATED HERNIA AND VENTRAL HERNIA (OTHER THAN DIAPHRAGMATIC HERNIA)
49615	Repair of anterior abdominal hernia(s) (ie, epigastric, incisional, ventral, umbilical, spigelian), any approach (ie, open, laparoscopic, robotic), recurrent, including implantation of mesh or other prosthesis when performed, total length of defect(s); 3 cm to 10 cm, reducible	See 49591	168 COMPLICATED HERNIAS; PERSISTENT HYDROCELE 524 UNCOMPLICATED HERNIA AND VENTRAL HERNIA (OTHER THAN DIAPHRAGMATIC HERNIA)
49616	Repair of anterior abdominal hernia(s) (ie, epigastric, incisional, ventral, umbilical, spigelian), any approach (ie, open, laparoscopic, robotic), recurrent, including implantation of mesh or other prosthesis when performed, total length of defect(s); 3 cm to 10 cm, incarcerated or strangulated	See 49592	168 COMPLICATED HERNIAS; PERSISTENT HYDROCELE 524 UNCOMPLICATED HERNIA AND VENTRAL HERNIA (OTHER THAN DIAPHRAGMATIC HERNIA)

Code	Code Description	Similar code	Recommended placement
49617	Repair of anterior abdominal hernia(s) (ie, epigastric, incisional, ventral, umbilical, spigelian), any approach (ie, open, laparoscopic, robotic), recurrent, including implantation of mesh or other prosthesis when performed, total length of defect(s); greater than 10 cm, reducible	See 49591	168 COMPLICATED HERNIAS; PERSISTENT HYDROCELE 524 UNCOMPLICATED HERNIA AND VENTRAL HERNIA (OTHER THAN DIAPHRAGMATIC HERNIA)
49618	Repair of anterior abdominal hernia(s) (ie, epigastric, incisional, ventral, umbilical, spigelian), any approach (ie, open, laparoscopic, robotic), recurrent, including implantation of mesh or other prosthesis when performed, total length of defect(s); greater than 10 cm, incarcerated or strangulated	See 49592	168 COMPLICATED HERNIAS; PERSISTENT HYDROCELE 524 UNCOMPLICATED HERNIA AND VENTRAL HERNIA (OTHER THAN DIAPHRAGMATIC HERNIA)
49621	Repair of parastomal hernia, any approach (ie, open, laparoscopic, robotic), initial or recurrent, including implantation of mesh or other prosthesis, when performed; reducible	Previously coded with recurrent incisional hernia (CPT 49654-49657 Laparoscopy, surgical, repair, incisional hernia, recurrent/non-recurrent) which were on lines 168, 524	168 COMPLICATED HERNIAS; PERSISTENT HYDROCELE 524 UNCOMPLICATED HERNIA AND VENTRAL HERNIA (OTHER THAN DIAPHRAGMATIC HERNIA)
49622	Repair of parastomal hernia, any approach (ie, open, laparoscopic, robotic), initial or recurrent, including implantation of mesh or other prosthesis, when performed; incarcerated or strangulated	See 49621	168 COMPLICATED HERNIAS; PERSISTENT HYDROCELE 524 UNCOMPLICATED HERNIA AND VENTRAL HERNIA (OTHER THAN DIAPHRAGMATIC HERNIA)
49623	Removal of total or near total non-infected mesh or other prosthesis at the time of initial or recurrent anterior abdominal hernia repair or parastomal hernia repair, any approach (ie, open, laparoscopic, robotic) (List separately in addition to code for primary procedure)	See 49591	168 COMPLICATED HERNIAS; PERSISTENT HYDROCELE 524 UNCOMPLICATED HERNIA AND VENTRAL HERNIA (OTHER THAN DIAPHRAGMATIC HERNIA)

Code	Code Description	Similar code	Recommended placement
55867	Laparoscopy, surgical prostatectomy, simple subtotal (including control of postoperative bleeding, vasectomy, meatotomy, urethral calibration and/or dilation, and internal urethrotomy), includes robotic assistance, when performed	55802 (Prostatectomy, perineal, subtotal) is on lines 327, 515, 585	327 FUNCTIONAL AND MECHANICAL DISORDERS OF THE GENITOURINARY SYSTEM INCLUDING BLADDER OUTLET OBSTRUCTION 515 CHRONIC PROSTATITIS, OTHER DISORDERS OF PROSTATE 585 BENIGN NEOPLASM OF MALE GENITAL ORGANS: TESTIS, PROSTATE, EPIDIDYMIS
69728	Removal, entire osseointegrated implant, skull; with magnetic transcutaneous attachment to external speech processor, outside the mastoid and involving a bony defect greater than or equal to 100 sq mm surface area of bone deep to the outer cranial cortex	Similar codes 69726 and 69727 are on lines 285,311,446	285 COMPLICATIONS OF A PROCEDURE ALWAYS REQUIRING TREATMENT 311 HEARING LOSS - AGE 5 OR UNDER 446 HEARING LOSS - OVER AGE OF FIVE
69729	Implantation, osseointegrated implant, skull; with magnetic transcutaneous attachment to external speech processor, outside of the mastoid and resulting in removal of greater than or equal to 100 sq mm surface area of bone deep to the outer cranial cortex	Similar codes 69714 and 69716 are on lines 311, 446	311 HEARING LOSS - AGE 5 OR UNDER 446 HEARING LOSS - OVER AGE OF FIVE
69730	Replacement (including removal of existing device), osseointegrated implant, skull; with magnetic transcutaneous attachment to external speech processor, outside the mastoid and involving a bony defect greater than or equal to 100 sq mm surface area of bone deep to the outer cranial cortex	Similar code 69717 is on lines 311, 446	311 HEARING LOSS - AGE 5 OR UNDER 446 HEARING LOSS - OVER AGE OF FIVE

Code	Code Description	Similar code	Recommended placement
76883	Ultrasound, nerve(s) and accompanying structures throughout their entire anatomic course in one extremity, comprehensive, including real-time cine imaging with image documentation, per extremity	Similar code 76882 (Ultrasound, limited, joint or other nonvascular extremity structure(s) (eg, joint space, peri-articular tendon[s], muscle[s], nerve[s], other soft-tissue structure[s], or soft-tissue mass[es]), real-time with image documentation) is on DIAGNOSTIC PROCEDURES	DIAGNOSTIC PROCEDURES
87468	Infectious agent detection by nucleic acid (DNA or RNA); Anaplasma phagocytophilum, amplified probe technique	Causes anaplasmosis, a tick bourne disease	DIAGNOSTIC PROCEDURES
87469	Infectious agent detection by nucleic acid (DNA or RNA); Babesia microti, amplified probe technique	Causes babesosis, a tick bourne disease	DIAGNOSTIC PROCEDURES
87478	Infectious agent detection by nucleic acid (DNA or RNA); Borrelia miyamotoi, amplified probe technique	Causes tickbourne relapsing fever	DIAGNOSTIC PROCEDURES
87484	Infectious agent detection by nucleic acid (DNA or RNA); Ehrlichia chaffeensis, amplified probe technique	Causes ehrlichiosis, a tick bourne disease	DIAGNOSTIC PROCEDURES
93569	Injection procedure during cardiac catheterization including imaging supervision, interpretation, and report; for selective pulmonary arterial angiography, unilateral (List separately in addition to code for primary procedure)	Similar codes 93563-93567 (Injection procedure during cardiac catheterization) are DIAGNOSTIC PROCEDURES	DIAGNOSTIC PROCEDURES
93573	Injection procedure during cardiac catheterization including imaging supervision, interpretation, and report; for selective pulmonary arterial angiography, bilateral (List separately in addition to code for primary procedure)	Similar codes 93563-93567 (Injection procedure during cardiac catheterization) are DIAGNOSTIC PROCEDURES	DIAGNOSTIC PROCEDURES

Code	Code Description	Similar code	Recommended placement
93574	Injection procedure during cardiac catheterization including imaging supervision, interpretation, and report; for selective pulmonary venous angiography of each distinct pulmonary vein during cardiac catheterization (List separately in addition to code for primary procedure)	Similar codes 93563-93567 (Injection procedure during cardiac catheterization) are DIAGNOSTIC PROCEDURES	DIAGNOSTIC PROCEDURES
93575	Injection procedure during cardiac catheterization including imaging supervision, interpretation, and report; for selective pulmonary angiography of major aortopulmonary collateral arteries (MAPCAs) arising off the aorta or its systemic branches, during cardiac catheterization for congenital heart defects, each distinct vessel (List separately in addition to code for primary procedure)	Similar codes 93563-93567 (Injection procedure during cardiac catheterization) are DIAGNOSTIC PROCEDURES	DIAGNOSTIC PROCEDURES
99418	Prolonged inpatient or observation evaluation and management service(s) time with or without direct patient contact beyond the required time of the primary service when the primary service level has been selected using total time, each 15 minutes of total time (List separately in addition to the code of the inpatient and observation Evaluation and Management service)		All lines with inpatient E&M codes

Code	Code Description	Similar code	Recommended placement
15778	Implantation of absorbable mesh or other prosthesis for delayed closure of defect(s) (ie, external genitalia, perineum, abdominal wall) due to soft tissue infection or trauma	See issues	502 CONDITIONS FOR WHICH INTERVENTIONS RESULT IN MARGINAL CLINICAL BENEFIT OR LOW COST-EFFECTIVENESS
22860	Total disc arthroplasty (artificial disc), anterior approach, including discectomy to prepare interspace (other than for decompression); second interspace, lumbar (List separately in addition to code for primary procedure)	See issues	662 CONDITIONS FOR WHICH CERTAIN INTERVENTIONS ARE UNPROVEN, HAVE NO CLINICALLY IMPORTANT BENEFIT OR HAVE HARMS THAT OUTWEIGH BENEFITS
30469	Repair of nasal valve collapse with low energy, temperature-controlled (ie, radiofrequency) subcutaneous/submucosal remodeling	See issues	662 CONDITIONS FOR WHICH CERTAIN INTERVENTIONS ARE UNPROVEN, HAVE NO CLINICALLY IMPORTANT BENEFIT OR HAVE HARMS THAT OUTWEIGH BENEFITS
43290	Esophagogastroduodenoscopy, flexible, transoral; with deployment of intragastric bariatric balloon	See issues	662 CONDITIONS FOR WHICH CERTAIN INTERVENTIONS ARE UNPROVEN, HAVE NO CLINICALLY IMPORTANT BENEFIT OR HAVE HARMS THAT OUTWEIGH BENEFITS
87467	Hepatitis B surface antigen (HBsAg), quantitative	See issues	198 CHRONIC HEPATITIS; VIRAL HEPATITIS
90678	Respiratory syncytial virus vaccine, preF, subunit, bivalent, for intramuscular use	See issues	EXCLUDED
92066	Orthoptic training; under supervision of a physician or other qualified health care professional	See issues	393 STRABISMUS WITHOUT AMBLYOPIA AND OTHER DISORDERS OF BINOCULAR EYE MOVEMENTS; CONGENITAL ANOMALIES OF EYE; LACRIMAL DUCT OBSTRUCTION IN CHILDREN
95919	Quantitative pupillometry with physician or other qualified health care professional interpretation and report, unilateral or bilateral	See issues	662 CONDITIONS FOR WHICH CERTAIN INTERVENTIONS ARE UNPROVEN, HAVE NO CLINICALLY IMPORTANT BENEFIT OR HAVE HARMS THAT OUTWEIGH BENEFITS

2023 CPT Code Review
Issues

1) Code: **15778**
    a. Code description: Implantation of absorbable mesh or other prosthesis for delayed closure of defect(s) (ie, external genitalia, perineum, abdominal wall) due to soft tissue infection or trauma
    b. Information: Biosynthetic prosthetics are those designed to allow for tissue ingrowth and wound healing before completely dissolving in a prescribed time period. Absorbable meshes made of Vicryl (Ethicon) or Dexon (Medtronic) were initially developed for hernia repair in infected fields; however, their use is limited by a prohibitive rate of hernia recurrence if used as a bridging repair. Examples of biologics include the human acellular dermal matrices AlloDerm (Allergan), AlloMax (Bard), and FlexHD (Ethicon).
    c. Similar codes:
        i. 15777 Implantation of biologic implant (eg, acellular dermal matrix) for soft tissue reinforcement (ie, breast, trunk)
            1. Line 502 CONDITIONS FOR WHICH INTERVENTIONS RESULT IN MARGINAL CLINICAL BENEFIT OR LOW COST-EFFECTIVENESS
    d. Current Prioritized List status: Relevant wound or surgical site dehiscence diagnosis codes are on lines 47, 131, 159, 205, 235, 285, and 385. Line 379 CHRONIC ULCER OF SKIN; VARICOSE VEINS WITH MAJOR COMPLICATIONS already has skin substitute codes attached with a guideline
        i. 47 DEEP ABSCESSES, INCLUDING APPENDICITIS AND PERIORBITAL ABSCESS
        ii. 131 CRUSH INJURIES OTHER THAN DIGITS; COMPARTMENT SYNDROME
        iii. 159 TOXIC EPIDERMAL NECROLYSIS AND STAPHYLOCOCCAL SCALDED SKIN SYNDROME; STEVENS-JOHNSON SYNDROME; ERYTHEMA MULTIFORME MAJOR; ECZEMA HERPETICUM
        iv. 205 SUPERFICIAL ABSCESSES AND CELLULITIS
        v. 207 DEEP OPEN WOUND, WITH OR WITHOUT TENDON OR NERVE INVOLVEMENT
        vi. 235 LIMB THREATENING VASCULAR DISEASE, INFECTIONS, AND VASCULAR COMPLICATIONS
        vii. 285 COMPLICATIONS OF A PROCEDURE ALWAYS REQUIRING TREATMENT
        viii. 385 SUPERFICIAL INJURIES WITH INFECTION
    e. Evidence:
        i. **Rosen 2022**, RCT comparing biologic vs synthetic mesh for repair of contaminated ventral hernias [CONSORT trial]
            1. N=253 patients with contaminated wound
                a. N=126 with synthetic mesh
                b. N=127 with biologic mesh
            2. Synthetic mesh significantly reduced the risk of hernia recurrence (site adjustment: HR 0.31; CI, 0.23-0.42, P ≤ .001) and (surgeon adjustment: HR, 0.31; 95% CI, 0.13-0.75; P = .009)

3. Comparable risks of surgical site occurrences requiring procedural intervention were found at each time point through the 2-year study period (biologic vs synthetic at 30 days, 27.6% vs 24.6%; P = .70; 6 months, 7.1% vs 4.8%; P = .61; 12 months, 1.6% vs 2.4%; P = .68; 24 months, 0.8% vs 1.6%; P = .62)
4. Overall, there were comparable rates of surgical site infection; however, the biologic mesh group tended to have a higher risk of deep surgical site infection than the synthetic group (14 [11%] vs 5 [4%], respectively; P = .06).
5. There were significantly more adverse events in the biologic vs the synthetic mesh group (84 [66.1%] vs 65 [51.6%], respectively; P = .03). Patients receiving synthetic mesh had a 14.5% (95% CI, 1.7-27.3) absolute risk reduction of having an adverse event compared with the biologic mesh group. Most adverse events were either wound morbidity or ileus
6. the 30-day adverse events in the biologic group tended to be more severe than the synthetic group (20.9 [95% CI, 0.0-28.2] vs 8.7 [95% CI, 0.0-22.6], respectively; P = .05)
7. There were no significant differences between the groups regarding QOL
8. Conclusion: In this randomized clinical trial, synthetic mesh added a substantial benefit over biologic mesh during single-stage ventral hernia repair in a clean-contaminated or contaminated surgical field in terms of reducing hernia recurrence risk at 2-year follow-up. Safety profiles were similar between the meshes at up to 2 years; however, there was a significant difference in the prespecified secondary end point of cost between the groups, with biologic mesh costing roughly 200 times as much as synthetic mesh and being the sole driver doubling the total 30-day median hospital costs.

ii. **Lak 2018**, mesh selection in abdominal wall reconstruction

1. Absorbable meshes made of Vicryl (Ethicon) or Dexon (Medtronic) were initially developed for hernia repair in infected fields; however, their use is limited by a prohibitive rate of hernia recurrence if used as a bridging repair. Biosynthetic prosthetics are those designed to allow for tissue ingrowth and wound healing before completely dissolving in a prescribed time period. Biologic prosthetics have been commonly derived from human, porcine, or bovine tissues and are decellularized in efforts to create a collagen scaffold to support native tissue ingrowth. Examples of biologics include the human acellular dermal matrices AlloDerm (Allergan), AlloMax (Bard), and FlexHD (Ethicon).
2. Management of contaminated wounds is challenging as placement of a permanent material into the field increases the risk of postoperative infection, bowel adhesions, mesh extrusion, mesh erosion, fistula formation, seroma development, and pain. The most efficacious

management strategy of a ventral hernia in a contaminated clinical situation has been debated and includes methods of staging the repair, primary facial closure alone, or use of a permanent, absorbable synthetic or biologic mesh

3. **It is important to note that there is no current indication for any reinforcement material (mesh) for use in a contaminated field. Therefore, any use of such material would be considered off-label.**
4. Two prospective cohort studies of biologic mesh use in repair of infected or contaminated ventral hernias were summarized (Repair of Infected or Contaminated ventral incisional Hernias (RICH) and the Complex Open Bioabsorbable Reconstruction of the Abdominal Wall (COBRA) studies)
    a. RICH examined Allergan, COBRA examined Bio-A (Gore)
    b. RICH: demonstrated a surgical-site occurrence rate of 66% and a surgical-site infection rate of 30%. By 24-month follow-up, the hernia recurrence was 28%.
    c. COBRA: In a 24-month follow-up, the surgical-site occurrence rate was 28%, and surgical-site infection rate was 18%. The overall recurrence rate was 17%.

iii. **Petro 2019**, review of long-acting resorbable meshes in abdominal wall reconstruction
    1. Biologic mesh—decellularized human or animal collagen that serves as a scaffold for tissue ingrowth—is typically regarded as a "safe" alternative in contaminated settings, but at $25–30/ cm2 adds a significant expense to the patient's care in exchange for widely variable recurrence rates

f. HERC staff summary:
    i. Use of absorbable mesh or biologic prosthesis appears to be a controversial topic in surgery. The evidence identified comes from contaminated surgical wounds rather than wounds from trauma or infection. The evidence indicates that absorbable mesh/biologic prostheses have higher rates of complications and hernia formation compared to non-absorbable mesh, and a trend toward higher infection rates. Other treatments are available, including wound vacuum therapy, traditional wound care, and non-absorbable mesh repair. However, staff literature review did not find comparison of more traditional wound care with closure with either absorbable or non-absorbable mesh, making the efficacy of absorbable mesh vs standard care not determinable. Of note, use of any type of mesh or prosthesis in an infected site is an off-label use of these products. Also of note, absorbable mesh/biologic prostheses have a much higher cost than non-absorbable mesh.

g. **HERC staff recommendation**:
    i. Place 15778 on the line 502 CONDITIONS FOR WHICH INTERVENTIONS RESULT IN MARGINAL CLINICAL BENEFIT OR LOW COST-EFFECTIVENESS
        1. Add an entry to GN172 as shown below

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

Line 502

The following interventions are prioritized on Line 502 CONDITIONS FOR WHICH INTERVENTIONS RESULT IN MARGINAL CLINICAL BENEFIT OR LOW COST-EFFECTIVENESS:

Procedure Code	Intervention Description	Rationale	Last Review
15778	Implantation of absorbable mesh or other prosthesis for delayed closure of defect(s) (ie, external genitalia, perineum, abdominal wall) due to soft tissue infection or trauma	More cost-effective treatments with lower complications rates are available	November 2022

2) Code **22860**
   a. Code description: Total disc arthroplasty (artificial disc), anterior approach, including discectomy to prepare interspace (other than for decompression); second interspace, lumbar
   b. Similar codes: Similar code 22857 (Total disc arthroplasty (artificial disc), anterior approach, including discectomy to prepare interspace (other than for decompression), single interspace, lumbar) is on lines 346 CONDITIONS OF THE BACK AND SPINE WITH URGENT SURGICAL INDICATIONS and 530 530 CONDITIONS OF THE BACK AND SPINE WITHOUT URGENT SURGICAL INDICATIONS.
   c. Information: artificial discs are covered based on GN101 ARTIFICIAL DISC REPLACEMENT. This guideline restricts coverage to a single level lumbar artificial disc replacement: "Replacement of a single disc for degenerative disc disease at one level confirmed by patient history and imaging." Coverage of artificial discs was last reviewed in January 2016.
   d. Evidence
      i. **NICE 2020**, evidence review for low back pain and sciatica
         1. N=5 RCTs, comparing artificial disc to other treatment (fusion or multidisciplinary rehabilitation)
            a. Unclear from study descriptions if any patients had multi-level artificial disc replacement
         2. Evidence from 1 study comparing disc replacement to anterior lumbar interbody fusion suggested clinical benefit of disc replacement for quality of life (SF-36 mental component) both at short and long term, but this was not demonstrated for the SF-36 physical component summary score (low to very low quality; n=577). Clinical benefit of disc replacement compared to posterior lumbar interbody fusion for quality of life (EQ-5D) at 1 year was also observed; however, this was not demonstrated at 2 years (1 study, low to very low quality; n=152). Evidence from the 2 studies also demonstrated no clinical difference

between disc replacement and spinal fusion for pain (back and leg pain VAS) or function (ODI) at both short and long term (low to very low quality; n=577, n=152).

3. In terms of adverse events, evidence from a single study showed greater numbers of adverse events for disc replacement compared to spinal fusion below 4 months (low to very low quality; n=577)
4. There was no clinical difference between the 2 procedures for the reoperation outcome at 2 years (2 studies; low to very low quality; n=577, n=152) and at 5 years (1 study; low to very low quality; n=152), while there was evidence of clinical benefit favoring disc replacement for device-related reoperations at 5 years (1 RCT; low to very low quality; n=152)
5. Summary: The guideline development group (GDG) noted that there were some signs of benefit from disc replacement compared to other interventions, but this evidence was very limited and not consistent across outcomes. Furthermore the GDG felt the risk of harms associated with disc replacement outweighed the potential benefits. The GDG were aware of the lack of long-term follow-up data for disc replacement surgery. The GDG expressed their concerns about this, particularly as disc replacement is often performed in younger age-groups in consideration of its claimed motion preservation benefits. However, it was highlighted that there is currently limited evidence of disc replacement benefits regarding motion and adjacent level degeneration compared to other surgical procedures, and the reported risks of disc replacement would often prevail over the benefits. As a result, the GDG agreed that the limited evidence of effectiveness alongside the above concerns meant it was appropriate to recommend against the use of disc replacement in people with low back pain with/without sciatica.

ii. **Scott-Young 2019**, patient reported outcomes after multilevel lumbar disc arthroplasty

1. N=122 patients with two level (120 patients) or three level (2 patient) artificial disc arthroplasty
    a. Surgery 1999-2009
    b. 24 month follow-up
2. VAS outcomes for both back and leg pain: At all stages of follow-up, a statistically significant difference from baseline can be seen ($P < 0.001$). By 12 months, the median VAS-B had improved by 88.75% to a score of 9/100
3. Conclusion: Multilevel lumbar disc arthroplasty surgery appears to be a suitable option for individuals with multilevel symptomatic DDD refractory to conservative management, when appropriate diagnosis, patient selection, surgical technique, and rehabilitation methods are followed.
4. Level of evidence: 4

e. Other payer policies
   i. NICE 2020: Do not offer disc replacement in people with low back pain.
   ii. CMS 2007: The Centers for Medicare and Medicaid Services (CMS) has determined that LADR is not reasonable and necessary for the Medicare population over sixty years of age. Therefore, Section 150.10 of the Medicare National Coverage Determination (NCD) Manual is amended to reflect the change from non-coverage for LADR with a specific implant to non-coverage for the LADR procedure for the Medicare population over sixty years of age. For Medicare beneficiaries sixty years of age and under, there is no national coverage determination, leaving such determinations to be made on a local basis.
   iii. United Healthcare 2022: only covers single level lumbar artificial disc
   iv. Aetna 2022: considers lumbar artificial discs experimental

f. HERC staff summary: since the last review in 2016, minimal new literature was identified that examined the outcomes of multiple level lumbar artificial disc placement. A recent NICE review concluded that there was insufficient evidence for even single level disc replacement. Other payers either recommend against any coverage (NICE) or only cover single level disc replacement. Multi-level replacement appears to continue to be experimental. https://www.nice.org.uk/guidance/ng59/resources/low-back-pain-and-sciatica-in-over-16s-assessment-and-management-pdf-1837521693637

g. **HERC staff recommendation**:
   i. Place CPT 22860 on line 662 CONDITIONS FOR WHICH CERTAIN INTERVENTIONS ARE UNPROVEN, HAVE NO CLINICALLY IMPORTANT BENEFIT OR HAVE HARMS THAT OUTWEIGH BENEFITS
   ii. Add an entry to GN173 as shown below

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

Line 662

The following Interventions are prioritized on Line 662 CONDITIONS FOR WHICH CERTAIN INTERVENTIONS ARE UNPROVEN, HAVE NO CLINICALLY IMPORTANT BENEFIT OR HAVE HARMS THAT OUTWEIGH BENEFITS:

Procedure Code	Intervention Description	Rationale	Last Review
22860	Total disc arthroplasty (artificial disc), anterior approach, including discectomy to prepare interspace (other than for decompression); second interspace, lumbar	Insufficient evidence of effectiveness	November 2022

3) Code **30469**
   a. Code description: Repair of nasal valve collapse with low energy, temperature-controlled (ie, radiofrequency) subcutaneous/submucosal remodeling

b. Information: The Aerin™ VivAer® procedure is a non-invasive, office-based procedure that employs low-dose radiofrequency (RF) energy to modify soft tissues of the nose with the intent of improving airflow for patients with nasal valve collapse.
c. Similar codes: Similar code 30468 (Repair of nasal valve collapse with subcutaneous/submucosal lateral wall implant(s)) is on lines 466, 506, and 577
    i. 466 CHRONIC SINUSITIS
    ii. 506 NASAL POLYPS, OTHER DISORDERS OF NASAL CAVITY AND SINUSES
    iii. 577 DEVIATED NASAL SEPTUM, ACQUIRED DEFORMITY OF NOSE, OTHER DISEASES OF UPPER RESPIRATORY TRACT
d. Evidence
    i. **Silvers 2021,** RCT of radiofrequency treatment vs sham for nasal valve obstruction
        1. All authors had funding from Aerin Medical
        2. N=119 patients
            a. N=77 patients in the radiofrequency arm, N=41 in the sham procedure arm
        3. Follow up 3 months
        4. At baseline, patients had a mean NOSE-scale score of 76.7 (95% confidence interval [CI], 73.8 to 79.5) and 78.8 (95% CI, 74.2 to 83.3) (p = 0.424) in the active treatment and sham-control arms, respectively. At 3 months, the responder rate was significantly higher in the active treatment arm (88.3% [95% CI, 79.2%-93.7%] vs 42.5% [95% CI, 28.5%-57.8%]; p < 0.001). The active treatment arm had a significantly greater decrease in NOSE-scale score (mean, −42.3 [95% CI, −47.6 to −37.1] vs −16.8 [95% CI, −26.3 to −7.2]; p < 0.001). Three adverse events at least possibly related to the device and/or procedure were reported, and all resolved.
        5. There was no significant difference in pain score immediately post-procedure (active treatment median [n = 76]: 5 mm [IQR, 0-14.5 mm]; sham-control median: 2 mm [IQR, 0-10.5 mm]; p = 0.235)
    ii. Three prospective cohort studies were identified (Yao 2021, Brehmer 2019, Jacobowitz 2019) with N=122, N=31 and N=50 respectively
e. Expert guidelines: none identified
f. Other payer policies
    i. Anthem BCBS 2022: Low-dose radiofrequency intranasal tissue remodeling as a treatment of nasal airway obstruction is considered investigational and not medically necessary**.**
    ii. Centene 2022: It is the policy of health plans affiliated with Centene Corporation that safety and efficacy have not been established for the following procedures for repair of nasal vestibular stenosis: A. Radiofrequency ablation (VivAer®)
g. HERC staff summary:
    i. Radiofrequency treatment of nasal valves is a new procedure with a very limited evidence base. Its efficacy at treating nasal obstruction due to nasal valve collapse cannot be determined from the limited evidence available.

h. **HERC staff recommendation**:
   i. Place CPT 30469 on line 662 CONDITIONS FOR WHICH CERTAIN INTERVENTIONS ARE UNPROVEN, HAVE NO CLINICALLY IMPORTANT BENEFIT OR HAVE HARMS THAT OUTWEIGH BENEFITS
   ii. Add an entry to GN173 as shown below

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

Line 662

The following Interventions are prioritized on Line 662 CONDITIONS FOR WHICH CERTAIN INTERVENTIONS ARE UNPROVEN, HAVE NO CLINICALLY IMPORTANT BENEFIT OR HAVE HARMS THAT OUTWEIGH BENEFITS:

Procedure Code	Intervention Description	Rationale	Last Review
30469	Repair of nasal valve collapse with low energy, temperature-controlled (ie, radiofrequency) subcutaneous/submucosal remodeling	Insufficient evidence of effectiveness	November 2022

4) Code: **43290**
   a. Code description: Esophagogastroduodenoscopy, flexible, transoral; with deployment of intragastric bariatric balloon
   b. From GUIDELINE NOTE 5, OBESITY AND OVERWEIGHT
      i. Pharmacological treatments and devices (e.g. gastric balloons, duodenal jejunal bypass liners, and vagus nerve blocking devices) for obesity are not intended to be included as services on this line or any other line on the Prioritized List.
   c. HERC staff recommendation:
      i. Place **43290** on lines 662 CONDITIONS FOR WHICH CERTAIN INTERVENTIONS ARE UNPROVEN, HAVE NO CLINICALLY IMPORTANT BENEFIT OR HAVE HARMS THAT OUTWEIGH BENEFITS
      ii. Modify GN 173 as shown below

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

Line 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
43290	Esophagogastroduodenoscopy, flexible, transoral; with deployment of intragastric bariatric balloon	Insufficient evidence of effectiveness	November 2022

5) Code: **87467**
    a. Code description: Hepatitis B surface antigen (HBsAg), quantitative
    b. Information:
        i. From LabCorp: Quantitative HBV surface antigen (HBsAg) testing is intended for use in individuals with a confirmed diagnosis of Hepatitis B Virus infection based on positive HBsAg, Anti-HBs antibody and/or Anti-core antigen (anti-HBc) antibody test results. Quantitative HBsAg testing has utility in assessing HBV replication in the absence and presence of antiviral therapy, which may inform monitoring treatment response and relapse in the setting of initial and prolonged antiviral therapy, respectively. Quantitative HBsAg testing is not intended for the diagnosis of HBV infection. The relationship between HBsAg levels and ongoing HBV replication and/or persistent infection has not been fully defined. HBV DNA viral load measurements reflect the extent of ongoing HBV replication. HBsAg levels reflect the transcription and trranslational expression of HBV DNA. The clinical ramifications of detectable levels of HBsAg in the absence of detectable levels of HBV DNA are the subject of ongoing investigation.
    c. Other codes of interest:
        i. ICD-10-CM B18.X (Chronic viral hepatitis B) is online 198 CHRONIC HEPATITIS; VIRAL HEPATITIS
    d. Evidence
        i. **Vachon 2021**, novel biomarkers of hepatitis B virus and their use in chronic hepatitis B patient management
            1. There are two types of therapies available for the treatment of hepatitis B infection: NA and peg-IFN. NAs include lamivudine, telbivudine, tenofovir disoproxil fumarate, adefovir, and entecavir
            2. While qualitative detection of HBsAg may be used to screen for and diagnose HBV infection, quantitative HBsAg (qHBsAg) measurement may better inform clinicians regarding response to treatment, prediction of SVR, and disease progression, among other clinical situations
            3. Serum HBsAg levels have been shown to correlate with other markers of HBV infection. During antiviral treatment, HBsAg levels correlate with serum HBV DNA and serum HBV RNA, although a stronger correlation is observed in HBeAg-positive patients than those who are HBeAg negative
            4. Quantitative HBsAg has also been used to predict treatment response in HBeAg-positive and -negative patients treated with peg-IFN with or without NA
            5. HBsAg levels have also been investigated as a predictor of chronic disease progression to fibrosis and HCC

e. Expert guidelines
    i. **NICE 2017** management of hepatitis B
        1. Monitor HBV DNA and quantitative HBsAg levels and HBeAg status before starting peginterferon alfa-2a at 12, 24 and 48 weeks after starting treatment to determine treatment response
        2. Monitor HBV DNA and quantitative HBsAg levels and HBeAg status before starting entecavir or lamivudine, 12, 24 and 48 weeks after starting treatment and then every 6 months to determine treatment response and medicines adherence
        3. Monitor HBV DNA and quantitative HBsAg levels and HBeAg status before starting tenofovir disoproxil, 12, 24 and 48 weeks after starting treatment and then every 6 months to determine treatment response and medicines adherence
        4. Further research should be undertaken to evaluate the clinical and cost effectiveness of hepatitis B surface antigen (HBsAg) quantitative assays in determining treatment duration in hepatitis B antigen (HBeAg) negative disease
f. HERC staff summary: Diagnosis of hepatitis B is done with qualitative HBsAg levels. Quantitative testing is recommended during treatment with antiviral therapy.
g. **HERC staff recommendation**:
    i. Place CPT 87467 on line 198 CHRONIC HEPATITIS; VIRAL HEPATITIS
        1. Can be used in the management of treatment of chronic hepatitis B but not in diagnosis of this condition

6) CPT **90678**
    h. Code description: Respiratory syncytial virus vaccine, preF, subunit, bivalent, for intramuscular use
    i. Similar codes: none
    j. Issue: there is currently no FDA approved vaccine for respiratory syncytial virus (RSV). RSV is a contagious virus and a common cause of respiratory illness. RSV can be potentially life-threatening for young infants, the immunocompromised, and older adults. Pfizer announced in September 2022 that it is seeking FDA approval for its RSV vaccine, which is designed to protect adults 60 years of age and older. Pfizer has also studied its vaccine in pregnant women as a method to prevent severe RSV infection in their babies up to 6 months. This vaccine has not yet been reviewed by the FDA. Jansson and Moderna are also developing vaccines against RSV. Per the CDC, there is no vaccine for RSV currently available.
    k. ACIP October 2022 meeting:
        i. RSV Older Adults: The Committee heard presentations from both GSK (RSVpreF3 vaccine) and Pfizer (RSVpreF vaccine) on their phase 3 clinical trials for RSV vaccines for adults ≥60. Both clinical trials presented today were conducted during the COVID-19 pandemic; no RSV associated deaths in trials. Efficacy point estimates against the primary outcomes in both trials exceeded 60% (82.6% GSK

against lower respiratory tract disease; 66.7%-85.7% against lower respiratory tract illness), but efficacy cannot be compared across trials. Data from only the first year will be available for consideration of the first policy recommendations; there is no established immunologic correlate of protection for RSV. Cases of Guillain-Barre syndrome (GBS) were reported in both trials (1 in GSK, 2 in Pfizer) The Committee felt that both vaccine candidates should be studied further in frailer, older adults 70+ or 80+, and there were concerns about GBS associated with the GSK product. Neither of these vaccines are ACIP recommended in the U.S., but the RSV-Adults ACIP Work Group will continue to consider safety and efficacy data into 2023.

l. HERC staff recommendation
    i. Place CPT **90678** on the EXCLUDED file
        1. Currently no approved vaccine for use with this code
        2. If an RSV vaccine is approved, HSD can move this code to a funded list and then HERC can reassess placement

7) CPT **92066**

m. Code description: Orthoptic training; under supervision of a physician or other qualified health care professional
n. Similar code: Similar code 92065 (Orthoptic training; performed by a physician or other qualified health care professional) is on line 393 STRABISMUS WITHOUT AMBLYOPIA AND OTHER DISORDERS OF BINOCULAR EYE MOVEMENTS; CONGENITAL ANOMALIES OF EYE; LACRIMAL DUCT OBSTRUCTION IN CHILDREN
o. Prior review: Opthoptic training was reviewed in 2017. From the 2017 HERC staff summary: "There is little evidence to support the use of vision therapy for any indication. The best available evidence (small case series) is for intermittent esotropia and exotropia. Current OAR limits vision therapy to children up through age 20 for 6 sessions without a PA, and for unlimited sessions with a PA, using only the CPT code specific for Orthoptic and/or pleoptic training (i.e. CPT 92065)." Based on this review, a new coding specification was added to the Prioritized List, that later became GN215.
p. Current Prioritized List status
q. **HERC staff recommendations**:
    i. Place 92066 on line 393 STRABISMUS WITHOUT AMBLYOPIA AND OTHER DISORDERS OF BINOCULAR EYE MOVEMENTS; CONGENITAL ANOMALIES OF EYE; LACRIMAL DUCT OBSTRUCTION IN CHILDREN
        1. Note: There may be additional benefits for children with different diagnoses through the requirements of EPSDT benefits.
    ii. Modify GN215 as shown below

GUIDELINE NOTE 215, ORTHOPTIC AND/OR PLEOPTIC TRAINING

Line 393

CPT 92065**, 92066** (Orthoptic and/or pleoptic training) is included on Line 393 only for pairing with ICD-10-CM H50.31 (Intermittent monocular esotropia), H50.32 (Intermittent alternating esotropia), H50.33 (Intermittent monocular exotropia), and H50.34 (Intermittent alternating exotropia).

8) CPT **95919**

r. Code description: Quantitative pupillometry with physician or other qualified health care professional interpretation and report, unilateral or bilateral

s. Information: Pupillary examination has been used as a basic measure in critically ill patients and is important for the prognosis and management of disease. Traditionally, pupillary measurements have been carried out in a subjective manner – by means of a pen flash-light to evaluate for reactivity and a pupil gauge for pupil size. Pupillometry refers to an objective way of measuring the diameter of the pupil. The NeurOptics NPi-100 Pupillometer is a hand-held infrared device that allows for objective measurement of pupillary light reflex and pupil size. Moreover, the numeric scale of the Neurological Pupil index (NPi), allows for a more rigorous interpretation and classification of the pupillary response. The Pupillometer and its NPi scale reduce subjectivity from the measurement by comparing the pupillary light reflex against normative data in the NPi model and automatically deriving whether the pupillary reflex falls within the normal range or outside of the normal range and provide a reliable way to quantitatively classify the pupillary light response.

t. Evidence

i. **NICE 2020**, NPi-2000 for pupillary light reflex in critical care patients, innovation briefing

1. N=6 observations studies (1,217 patients)
2. The evidence for the technology is of low methodological quality, and most of the studies are small in terms of patient numbers
3. The studies show that NPi-200 can predict poor outcomes in critically ill people. Further evidence comparing NPi-200 with standard care, with a large sample size is needed.

u. Expert guidelines: none found

v. Other payer policies

i. Aetna 2021

1. Aetna considers the use of quantitative pupillometry/pupillography experimental and investigational for all indications

w. HERC staff summary: Quantitative pupillometry appears to be an experimental test, and is far expensive than the standard of care (hand held pen-light)

x. HERC staff recommendation:

i. Place **95919** on lines 662 CONDITIONS FOR WHICH CERTAIN INTERVENTIONS ARE UNPROVEN, HAVE NO CLINICALLY IMPORTANT BENEFIT OR HAVE HARMS THAT OUTWEIGH BENEFITS

ii. Modify GN 173 as shown below

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

Line 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
95919	Quantitative pupillometry with physician or other qualified health care professional interpretation and report, unilateral or bilateral	Insufficient evidence of effectiveness	November 2022

JAMA Surgery | Original Investigation

Biologic vs Synthetic Mesh for Single-stage Repair of Contaminated Ventral Hernias
A Randomized Clinical Trial

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IMPORTANCE Biologic mesh is widely used for reinforcing contaminated ventral hernia repairs; however, it is expensive and has been associated with high rates of long-term hernia recurrence. Synthetic mesh is a lower-cost alternative but its efficacy has not been rigorously studied in individuals with contaminated hernias.

OBJECTIVE To determine whether synthetic mesh results in superior reduction in risk of hernia recurrence compared with biologic mesh during the single-stage repair of clean-contaminated and contaminated ventral hernias.

DESIGN, SETTING, AND PARTICIPANTS This multicenter, single-blinded randomized clinical trial was conducted from December 2012 to April 2019 with a follow-up duration of 2 years. The trial was completed at 5 academic medical centers in the US with specialized units for abdominal wall reconstruction. A total of 253 adult patients with clean-contaminated or contaminated ventral hernias were enrolled in this trial. Follow-up was completed in April 2021.

INTERVENTIONS Retromuscular synthetic or biologic mesh at the time of fascial closure.

MAIN OUTCOMES AND MEASURES The primary outcome was the superiority of synthetic mesh vs biologic mesh at reducing risk of hernia recurrence at 2 years based on intent-to-treat analysis. Secondary outcomes included mesh safety, defined as the rate of surgical site occurrence requiring a procedural intervention, and 30-day hospital direct costs and prosthetic costs.

RESULTS A total of 253 patients (median [IQR] age, 64 [55-70] years; 117 [46%] male) were randomized (126 to synthetic mesh and 127 to biologic mesh) and the follow-up rate was 92% at 2 years. Compared with biologic mesh, synthetic mesh significantly reduced the risk of hernia recurrence (hazard ratio, 0.31; 95% CI, 0.23-0.42; $P < .001$). The overall intent-to-treat hernia recurrence risk at 2 years was 13% (33 of 253 patients). Recurrence risk with biologic mesh was 20.5% (26 of 127 patients) and with synthetic mesh was 5.6% (7 of 126 patients), with an absolute risk reduction of 14.9% with the use of synthetic mesh (95% CI, −23.8% to −6.1%; $P = .001$). There was no significant difference in overall 2-year risk of surgical site occurrence requiring a procedural intervention between the groups (odds ratio, 1.22; 95% CI, 0.60-2.44; $P = .58$). Median (IQR) 30-day hospital direct costs were significantly greater in the biologic group vs the synthetic group ($44 936 [$35 877-$52 656] vs $17 289 [$14 643-$22 901], respectively; $P < .001$). There was also a significant difference in the price of the prosthetic device between the 2 groups (median [IQR] cost biologic, $21 539 [$20 285-$23 332] vs synthetic, $105 [$105-$118]; $P < .001$).

CONCLUSIONS AND RELEVANCE Synthetic mesh demonstrated superior 2-year hernia recurrence risk compared with biologic mesh in patients undergoing single-stage repair of contaminated ventral hernias, and both meshes demonstrated similar safety profiles. The price of biologic mesh was over 200 times that of synthetic mesh for these outcomes.

TRIAL REGISTRATION ClinicalTrials.gov Identifier: NCT02451176

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Mesh Selection in Abdominal Wall Reconstruction

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Summary: Selection of mesh for ventral hernia repair and abdominal wall reconstruction can be challenging. Since the adoption of a tension-free mesh repair, the recurrence rates and outcomes after ventral hernia repair have substantially improved. The market for medical prostheses is constantly changing, with new technology in development attempting to create the ideal mesh for each clinical scenario. Permanent mesh is typically used for clean wounds. The various mesh materials, density, and pore sizes are discussed. In addition, the materials commonly used for contaminated wounds (absorbable synthetic and biologic meshes) are described. The latest literature regarding the use of various mesh materials is reviewed and organized to help make an informed decision regarding the appropriate use of reinforcing material. (*Plast. Reconstr. Surg.* 142: 99S, 2018.)

Selection of mesh for ventral hernia repair and abdominal wall reconstruction can be challenging. Since the adoption of a tension-free mesh repair, the recurrence rates and outcomes after ventral hernia repair have substantially improved. The market for medical prostheses is constantly changing, with new technology in development attempting to create the ideal mesh for each clinical scenario. In efforts to break down the current literature regarding mesh selection, we will describe prosthetic and patient-related factors that may be considered in the decision-making process of what mesh is best for your patient.

PROSTHETIC MATERIAL

The choices for mesh for repair of ventral hernia are vast. For this article, the use of the term "mesh" will represent any material that is implanted to aid in the repair of a hernia. Meshes differ in many ways including material and composition. The 2 main types of mesh are synthetic and biologic. Within each of these types are variations that affect the tissue incorporation, strength, and resistance to infection.

Synthetic Prosthetics

Synthetic meshes may be permanent or absorbable. The most common materials used in permanent synthetic mesh manufacturing are polypropylene (PP), polyester (PET), and polytetrafluoroethylene (PTFE).[1] PP mesh is the most common mesh material. PP was the initial material used in mesh manufacturing and has proven to be a versatile material that could be modified to capitalize on its ideal characteristics. It is inert, hydrophobic, and resistant to enzymatic breakdown.[1] PP meshes are characterized as heavyweight or lightweight, which refers to the density of the material. Some examples of polypropylene mesh include Marlex (C.R. Bard, Inc., Murray Hill, N.J.), Prolene (Ethicon, Inc., Somerville, N.J.), and Parietene (Medtronic, Minneapolis, Minn.; Table 1). Polypropylene incites an inflammatory response leading to disorganized scar formation.[2] In specimens of removed mesh, this inflammatory process was demonstrated at the prosthetic-tissue interface.[3] This inflammatory process and subsequent collagen deposition are what is believed to be responsible for the resulting stiffness, relative lack of compliance, and mesh shrinkage after ventral hernia repair with polypropylene.[1]

PET meshes are those formed by a reaction of alcohol with carboxylic acid. Examples of PET meshes include Symbotex (Medtronic), Dacron, or Mersilene mesh (Ethicon; Table 1). PET mesh is known for being hydrophilic, strong, and durable. Although PET mesh has been used for decades, its

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A Current Review of Long-Acting Resorbable Meshes in Abdominal Wall Reconstruction

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Summary: Concern for chronic infection of a permanent synthetic material in contaminated and "high risk" ventral hernia repairs has led to the development and dissemination of slowly resorbable biosynthetic materials at a lower cost compared with biologic mesh counterparts. Here, we review the preclinical and clinical data available for each long-acting resorbable mesh, with a candid comparison to biologic and synthetic equivalents. (*Plast. Reconstr. Surg.* 142: 84S, 2018.)

For all but the smallest hernia defects, mesh reinforcement dramatically reduces recurrence by almost 50% at 10 years.[1,2] However, the concern for developing a chronic infection of a permanent synthetic material in contaminated and high-risk settings puts the surgeon in a difficult situation: forgo additional reinforcement and accept an inevitable recurrence or put the patient at risk of a chronic mesh infection that will eventually require mesh excision and another—likely more complex—repair.[3,4] This difficult yet common clinical scenario has stimulated innovation of alternative reinforcement types. Biologic mesh—decellularized human or animal collagen that serves as a scaffold for tissue ingrowth—is typically regarded as a "safe" alternative in contaminated settings, but at $25–30/cm^2 adds a significant expense to the patient's care in exchange for widely variable recurrence rates.[5–7] Although recent long-term data have shown the durability of biologics in nonbridged settings, one National Surgical Quality Improvement Program analysis of propensity matched patients found that operating room service and supply costs were an additional $14,000 when biologic mesh was used instead of a permanent synthetic.[8,9] Meanwhile, permanent synthetic meshes have been vetted to help characterize properties most susceptible to chronic infection such as a barrier coating, antibiotic impregnation, or multifilament weave.[10] Uncoated monofilament polypropylene is often heralded as most resilient to a bacterial burden, but even though some regard its use in contaminated settings as safe, risk for a chronic infection is not zero and long-term complications may not justify short-term cost savings.[4,11,12]

Long-acting resorbable (LAR, ie, biodegradable, bioabsorbable, biosynthetic) meshes are the most recent development in this arena. These products are composed of synthetic polymers that serve as a scaffold for host-tissue ingrowth.

Native collagen replaces the mesh as it slowly degrades, theoretically evading the potential for a chronic infection. Ultimately, the argument for LARs is that they provide the benefits of a biologic material at a lower cost. There are currently 3 LARs on the market:

- Tigr Matrix (TM; Novus Scientific, Uppsala, Sweden)
- Gore Bio-A (W. L. Gore and Associates, Inc., Flagstaff, Ariz.)
- Phasix Mesh (C. R. Bard, Inc./Davol Inc., Warwick, R.I.)

In order for the surgeon to make an assessment of these products' value, we will provide a summary of the preclinical and clinical data that exist for each LAR product. Long-term follow-up of hernia repairs with Bio-A and Phasix has just recently been published, making their candid appraisal a timely matter.

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Treatment of Peripheral Pulmonary Artery Stenosis

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Abstract: Peripheral pulmonary artery stenosis (PAS) is an abnormal narrowing of the pulmonary vasculature and can form anywhere within the pulmonary artery tree. PAS is a congenital or an acquired disease, and its severity depends on the etiology, location, and number of stenoses. Most often seen in infants and young children, some symptoms include shortness of breath, fatigue, and tachycardia. Symptoms can progressively worsen over time as right ventricular pressure increases, leading to further complications including pulmonary artery hypertension and systolic and diastolic dysfunctions. The current treatment options for PAS include simple balloon angioplasty, cutting balloon angioplasty, and stent placement. Simple balloon angioplasty is the most basic therapeutic option for proximally located PAS. Cutting balloon angioplasty is utilized for more dilation-resistant PAS vessels and for more distally located PAS. Stent placement is the most effective option seen to treat the majority of PAS; however, it requires multiple re-interventions for serial dilations and is generally reserved for PAS vessels that are resistant to angioplasty.

Key Words: peripheral pulmonary artery stenosis, simple balloon angioplasty, cutting balloon angioplasty, stent placement

(*Cardiology in Review* 2021;29: 115–119)

Peripheral pulmonary artery stenosis (PAS) is caused by the formation of obstructive lesions in the pulmonary artery (PA) and its branches. Most often seen in infants and young children, PAS is characterized by shortness of breath, fatigue, tachycardia, and often swelling of the feet, ankles, and abdomen. These symptoms can progressively worsen over time.[1] This condition must be differentiated from pulmonary valve stenosis, which is a stenosis of the valve itself, and not of the PA and its branches. Hemodynamically, a stenosis in the PA results in a decreased vascular cross-sectional area, which increases the impedance to blood flow exiting the heart. This in turn raises right ventricular (RV) pressure, which can cause endothelial damage to parallel healthy non-stenotic vessels in the PA tree. Additionally, as RV pressure increases, there can be RV hypertension which can further lead to pulmonary artery hypertension, all of which can lead to systolic and diastolic dysfunctions and eventually present as heart failure.

PAS is a congenital or an acquired disease and can be found unilaterally or bilaterally, and either as a single isolated lesion or multiple lesions along several levels of PA branches.[2–5] PAS may occur as a physiologically benign feature in infants or as a pathological feature present in patients with various congenital heart diseases. Congenital heart diseases where PAS has been observed include tetralogy of Fallot, pulmonary atresia, truncus arteriosus, pulmonary valve stenosis, ventricular septal defect, and patient ductus arteriosus. Up to 70% of patients with pulmonary atresia have some form of PAS, followed by 20% of patients with ventricular septal defect, and 10% of patients with tetralogy of Fallot.

Williams syndrome and Alagille syndrome, both genetic disorders, have been associated with PAS, with some evidence suggesting a link to a mutation in the elastin gene resulting in abnormalities in the pulmonary vessels.[6–9] There has also been some evidence of PAS development in infants whose mothers had contracted rubella while pregnant. Williams syndrome, Alagille syndrome, and congenital rubella syndrome have been shown to result in more complex and severe PAS with multiple lesions in the PA tree. Other disorders, such as Ehlers-Danlos syndrome and Noonan's syndrome, have also shown some link to the development of PAS in the child.

Acquired PAS is most often seen in patients following cardiac surgery to repair or improve congenitally malformed hearts.[2,10,11] Several procedures have been shown to lead to the development of PAS, including shunt placement, an arterial switch operation, pulmonary artery band placement, or aortic arch augmentation. Postoperative patients have an increased risk of unintended scar formation along the PA vasculature, twisting of the PA vessels, or external compression of the vessel. However, postoperatively acquired PAS is generally isolated, more proximally located, and therefore, more easily treated.

PAS can be categorized based on location. PAS may be proximal, lobar, or segmental and sub-segmental. Proximal PAS is commonly seen in congenital heart disease patients postoperatively and located just distally to the main PA. Segmental and sub-segmental PAS is located most distally and associated with congenital disorders such as Williams syndrome and Alagille syndrome, and are the most difficult to treat with numerous lesions at less accessible anatomical locations. Lobar PAS is found in between proximal and segmental PAS. The diagnosis of PAS may include an electrocardiogram, cardiac magnetic resonance imaging, cardiac catheterization, perfusion scan, and pulmonary angiography. Rotational angiography has been shown to be very effective in both the diagnosis and the analysis of the anatomy of the stenosis prior to treatment.[12,13] Indications for PAS intervention include (1) symptoms of PAS, (2) significantly elevated RV pressure, (3) significantly decreased pulmonary perfusion (<35%), and (4) an elevated pressure gradient across a PA branch (>20 mm Hg).[3,14] Early intervention for PAS is important as worsening of PAS can result in RV hypertension, pulmonary artery hypertension, and more vascular diseases. Due to the complicated etiology of PAS, the optimal therapeutic strategies depend on the pathology and the extent of the PA obstruction. These treatments are reviewed in this article.

TREATMENT OF PULMONARY ARTERY STENOSIS

Currently, simple balloon angioplasty, cutting balloon (CB) angioplasty, and stenting are the standard treatments for PAS. Prior to the development of balloon angioplasty in the early 1980s, surgical angioplasty was utilized to excise the stenosis directly. However, there were many challenges, including limited success in increasing the vessel diameter, limited accessibility to distally located stenoses,

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National Guideline Centre

Low back pain and sciatica in over 16s: assessment and management

Invasive treatments

NICE guideline NG59
Methods, evidence and recommendations
November 2016

Guideline updates

December 2020: in the recommendation on stopping opioid analgesics we added links to other NICE guidelines and resources that support discussion with patients about opioid prescribing and safe withdrawal management.

September 2020: NICE's original guidance on low back pain and sciatica in over 16s was published in 2016. It was partially updated in September 2020.

See the NICE website for the guideline recommendations and the evidence review for the 2020 update.

This document preserves evidence reviews and committee discussions for areas of the guideline that were not updated in 2020.

Final, 2016

Commissioned by the National Institute for Health and Care Excellence

Royal College of Physicians

26.5 Evidence statements

26.5.1 Clinical

26.5.1.1 Disc replacement versus spinal fusion (Low back pain with/without sciatica)

Evidence from 1 study comparing disc replacement to anterior lumbar interbody fusion suggested clinical benefit of disc replacement for quality of life (SF-36 mental component) both at short and long term, but this was not demonstrated for the SF-36 physical component summary score (low to very low quality; n=577). Clinical benefit of disc replacement compared to posterior lumbar interbody fusion for quality of life (EQ-5D) at 1 year was also observed ; however, this was not demonstrated at 2 years (1 study, low to very low quality; n=152). Evidence from the 2 studies also demonstrated no clinical difference between disc replacement and spinal fusion for pain (back and leg pain VAS) or function (ODI) at both short and long term (low to very low quality; n=577, n=152). Further evidence informing these outcomes, could not be analysed as the results were inadequately reported for analysis.

In terms of adverse events, evidence from a single study showed greater numbers of adverse events for disc replacement compared to spinal fusion below 4 months (low to very low quality; n=577).

There was no clinical difference between the 2 procedures for the reoperation outcome at 2 years (2 studies; low to very low quality; n=577, n=152) and at 5 years (1 study; low to very low quality; n=152), while there was evidence of clinical benefit favouring disc replacement for device-related reoperations at 5 years (1 RCT; low to very low quality; n=152).

26.5.1.2 Disc replacement versus 3-MBR (low back pain without sciatica)

Evidence from 1 study demonstrated a clinically important benefit of disc replacement when compared to 3-element MBR for quality of life (EQ-5D and SF-36 physical component) in the long-term but this was not demonstrated for the SF-36 mental component. A benefit of disc replacement was also shown for back pain severity in the long-term. There was no clinical difference for function in the short or longer term (low to very low quality; n=173).

26.5.2 Economic

- One cost-utility analysis found that total disc replacement was dominant (less costly and more effective) compared to spinal fusion in people with low back pain with or without sciatica. This study was partially applicable with potentially serious limitations.
- One cost-utility analysis found that total disc replacement was cost-effective compared to 3-element MBR (ICER: £9,544 per QALY gained). This study was partially applicable with potentially serious limitations.

26.6 Recommendations and link to evidence

Recommendations	The current recommendations can be found at https://www.nice.org.uk/guidance/ng59/chapter/Recommendations

Spine

SPINE Volume 45, Number 1, pp 18–25

CLINICAL CASE SERIES

OPEN

Patient-Reported Outcome Measures After Multilevel Lumbar Total Disc Arthroplasty for the Treatment of Multilevel Degenerative Disc Disease

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Study Design. Case series

Objective. The aim of this study was to assess the patient-reported outcome measures (PROMs) and patient satisfaction of multilevel lumbar total disc arthroplasty (TDA) for symptomatic multilevel degenerative disc disease (MLDDD).

Summary of Background Data. TDA has been shown to be safe and effective for the treatment of symptomatic single level degenerative disc disease. There is minimal PROMs data on the mid- to long-term outcomes of multilevel TDA constructs.

Methods. Prospectively collected PROMs were analyzed from patients receiving multilevel TDA for symptomatic MLDDD. Data were collected preoperatively and postoperatively at 3, 6, and 12 months, then yearly. PROMs included patient satisfaction, Visual Analog Score back and leg, Oswestry Disability Index, and Roland-Morris Disability Questionnaire.

Results. One hundred twenty-two patients (77 men, 45 women) who had preoperative and at least 24-month follow-up data were included. The average age was 42 ± 8.2 years (range 21–61) and mean follow-up 7.8 years (range 2–10). The majority received two-level TDA, except two patients (1.6%) who received three-level TDA. The two- to three-level TDA's were at the levels L3–4, L4–5, and L5-S1, whereas most two levels ($n = 110$, 90.2%) were at L4–5 and L5-S1; the remainder ($n = 10$, 8.2%) being at L3–4 and L4–5. Implants used were Charité (DePuy Spine, Raynham, MA) in 119 patients (240 levels) and InMotion (DePuy Spine) in 3 patients (6 levels). Improvement in pain and disability scores were both clinically and statistically significant ($P < 0.001$), and this improvement was sustained in those patients over the course of their follow-up. Ninety-two percent of patients reported good or excellent satisfaction with treatment at final review.

Conclusion. Multilevel TDA constructs for MLDDD demonstrate favorable and sustained clinical outcomes at mid- to long-term follow-up.

Key words: arthroplasty, artificial disc, back pain, bisegmental, degenerative disc disease, lumbar spine, motion preservation, multilevel disc arthroplasty, total disc replacement.

Level of Evidence: 4

Spine 2020;45:18–25

"Spinal pain" or "nonspecific low back pain" are symptoms influenced by structural, biomechanical, biochemical, medical, psychosocial, and compensable factors that can result in dilemmas of diagnosis and management of such complexity that treatment may be rendered ineffective. Distinct from "low back pain," degenerative disc disease (DDD) causing discogenic pain is a specific diagnosis and, therefore, can be treated non-operatively or, when conservative care fails, operatively.[1] The diagnosis is made from a combination of a clinical history, physical examination, radiological investigations, such as magnetic resonance imaging (MRI), and discriminating provocative discography with postdiscography computed tomography (CT) scans.[2,3] Other authors have also found electrophysiological studies,[4] MR spectroscopy[5,6] and SPECT scanning[7] adjunctive in supporting a diagnosis.

Basic science studies have confirmed the validity of the model of internal disc disruption and the DDD cascade,

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The device(s)/drug(s) is/are FDA-approved or approved by corresponding national agency for this indication.

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viruses

MDPI

Review

Novel Biomarkers of Hepatitis B Virus and Their Use in Chronic Hepatitis B Patient Management

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Abstract: Even though an approved vaccine for hepatitis B virus (HBV) is available and widely used, over 257 million individuals worldwide are living with chronic hepatitis B (CHB) who require monitoring of treatment response, viral activity, and disease progression to reduce their risk of HBV-related liver disease. There is currently a lack of predictive markers to guide clinical management and to allow treatment cessation with reduced risk of viral reactivation. Novel HBV biomarkers are in development in an effort to improve the management of people living with CHB, to predict disease outcomes of CHB, and further understand the natural history of HBV. This review focuses on novel HBV biomarkers and their use in the clinical setting, including the description of and methodology for quantification of serum HBV RNA, hepatitis B core-related antigen (HBcrAg), quantitative hepatitis B surface antigen (qHBsAg), including ultrasensitive HBsAg detection, quantitative anti-hepatitis B core antigen (qAHBc), and detection of HBV nucleic acid-related antigen (HBV-NRAg). The utility of these biomarkers in treatment-naïve and treated CHB patients in several clinical situations is further discussed. Novel HBV biomarkers have been observed to provide critical clinical information and show promise for improving patient management and our understanding of the natural history of HBV.

Keywords: hepatitis B virus; biomarker; qHBsAg; serum HBV RNA; pgRNA; quantitative anti-HBc; HBcrAg; NRAg

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1. Introduction

It is estimated that over 257 million people are chronically infected with hepatitis B virus (HBV) worldwide and over 880,000 annual deaths are the result of hepatitis B-related outcomes such as hepatocellular carcinoma (HCC) and liver cirrhosis [1]. Although childhood vaccination programs have been operational since the 1990s, a significant number of individuals worldwide live with the life-changing disease that is hepatitis B and therefore require monitoring of treatment response, viral activity, and disease progression to minimize their imminent risk of developing HBV-related liver disease. While qualitative detection of traditional markers such as HBV DNA, HBV e antigen (HBeAg), HBV surface antigen (HBsAg), and antibody to the HBV core antigen (AHBc) are used in monitoring of acute or chronic hepatitis B, these markers have limitations in predicting clinical outcomes of disease or antiviral treatment. Quantification of intrahepatic covalently closed circular DNA (cccDNA) is the gold standard for gaining a full understanding of HBV replicative and transcriptional activity; however, invasive procedures and a lack of standardization prevent this as a routine prognostic HBV biomarker. Quantification of novel and traditional serum HBV markers is being investigated as a surrogate of cccDNA, not only to circumvent the need for a liver biopsy to measure viral transcriptional activity, but also to provide additional information on the state of disease, allow for more refined guidance in the clinical management of hepatitis B, and improve our understanding of HBV natural history. Methods to detect and quantify novel serum markers of HBV have been developed

NICE National Institute for Health and Care Excellence

NICE guideline

Hepatitis B (chronic): diagnosis and management

Clinical guideline

Published: 26 June 2013
www.nice.org.uk/guidance/cg165

Your responsibility

The recommendations in this guideline represent the view of NICE, arrived at after careful consideration of the evidence available. When exercising their judgement, professionals and practitioners are expected to take this guideline fully into account, alongside the individual needs, preferences and values of their patients or the people using their service. It is not mandatory to apply the recommendations, and the guideline does not override the responsibility to make decisions appropriate to the circumstances of the individual, in consultation with them and their families and carers or guardian.

Local commissioners and providers of healthcare have a responsibility to enable the guideline to be applied when individual professionals and people using services wish to use it. They should do so in the context of local and national priorities for funding and developing services, and in light of their duties to have due regard to the need to eliminate unlawful discrimination, to advance equality of opportunity and to reduce health inequalities. Nothing in this guideline should be interpreted in a way that would be inconsistent with complying 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.

Contents

This guideline partially replaces TA96.

This guideline is the basis of QS65 and QS152.

Overview

This guideline covers assessing and managing chronic hepatitis B in children, young people and adults. It aims to improve care for people with hepatitis B by specifying which tests and treatments to use for people of different ages and with different disease severities.

Who is it for?

- Healthcare professionals
- Commissioners and providers
- People with chronic hepatitis B and their families and carers

Introduction

This guideline updates and replaces recommendations in NICE technology appraisal 96 and incorporates recommendations from NICE technology appraisals 96, 153, 154 and 173. See Update information for details.

Chronic hepatitis B describes a spectrum of disease usually characterised by the presence of detectable hepatitis B surface antigen (HBsAg) in the blood or serum for longer than 6 months. In some people, chronic hepatitis B is inactive and does not present significant health problems, but others may progress to liver fibrosis, cirrhosis and hepatocellular carcinoma (HCC). The progression of liver disease is associated with hepatitis B virus (HBV) DNA levels in the blood. Without antiviral treatment, the 5-year cumulative incidence of cirrhosis ranges from 8 to 20%. People with cirrhosis face a significant risk of decompensated liver disease if they remain untreated. Five-year survival rates among people with untreated decompensated cirrhosis can be as low as 15%. Chronic hepatitis B can be divided into e antigen- (HBeAg) positive or HBeAg-negative disease based on the presence or absence of e antigen. The presence of HBeAg is typically associated with higher rates of viral replication and therefore increased infectivity.

The goal of treatment for chronic hepatitis B is to prevent cirrhosis, HCC and liver failure. In clinical practice surrogate markers are used to monitor progression of disease and treatment response, and include normalisation of serum alanine aminotransferase (ALT) levels, decrease in inflammation scores with no worsening or improvement in fibrosis on liver biopsies, suppression of serum HBV DNA to undetectable levels, loss of HBeAg and seroconversion to HBe antibody (anti-HBe), and loss of HBsAg and seroconversion to HBs antibody (anti-HBs).

Antiviral therapy suppresses HBV replication and decreases hepatic inflammation and fibrosis, thereby reducing the likelihood of serious clinical disease. Since the introduction of effective treatment in the form of interferon alfa, several nucleoside and nucleotide analogues are now approved for use in adults with chronic hepatitis B, together with a pegylated form of interferon alfa. With multiple treatment options that are efficacious and safe, the key questions are which patients need immediate treatment and what sequence and combination of drug regimens should be used, and which patients can be monitored and delay treatment.

In this guideline we cover the following:

- information needs of people with chronic hepatitis B and their carers
- where children, young people and adults with chronic hepatitis B should be assessed
- assessment of liver disease, including the use of non-invasive tests and genotype testing
- criteria for offering antiviral treatment
- the efficacy, safety and cost effectiveness of currently available treatments
- selection of first-line therapy
- management of treatment failure or drug resistance
- whether there is a role for combination therapy
- when it is possible to stop treatment
- managing the care of pregnant and breastfeeding women and prevention of vertical transmission
- prophylactic treatment during immunosuppressive therapy
- monitoring for treatment response, severity of fibrosis and development of HCC.

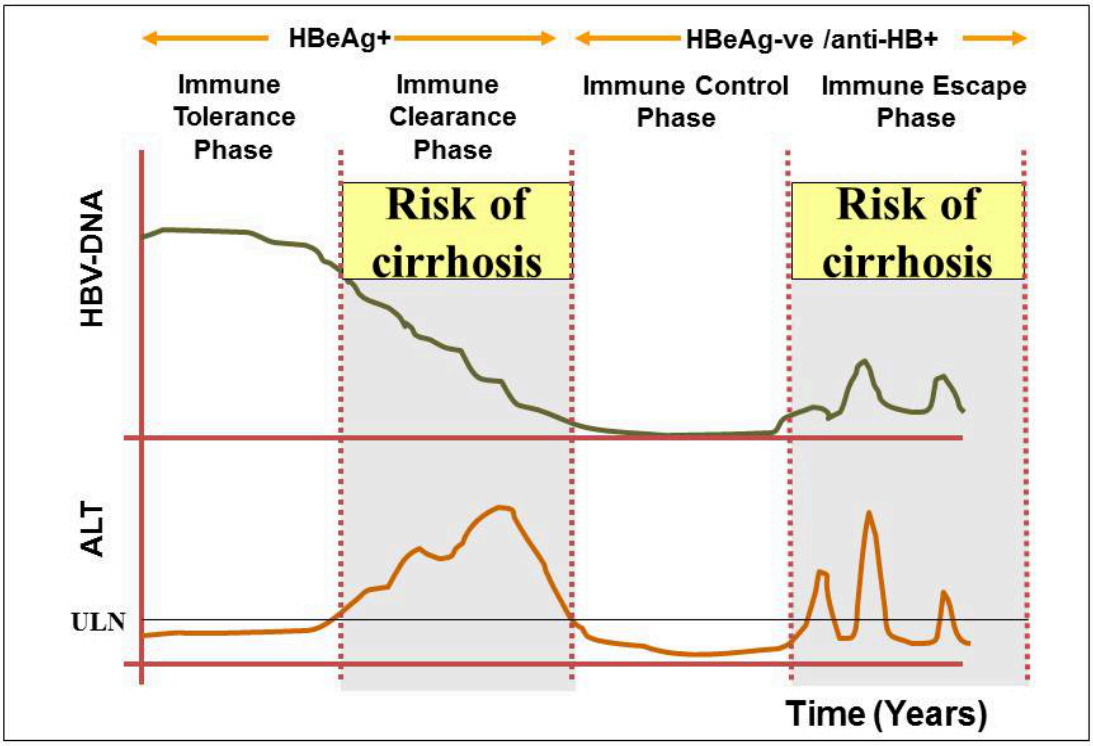
The spontaneous mutation rate of HBV DNA is high. Exposure of HBV to nucleoside or nucleotide analogues selects for mutations in the polymerase gene that confer resistance or decreased susceptibility to the drugs. The relative risk of drug resistance must be taken into account when considering treatment with nucleoside or nucleotide analogues, including the level of cross resistance between different agents.

Figure 1 depicts the natural history of chronic HBV infection. The immune-tolerance phase is seen in HBeAg-positive disease and is characterised by high levels of HBV replication with normal ALT levels and limited liver necroinflammation. Because there is minimal immune response to the virus it is unusual for spontaneous HBeAg loss to occur. This phase is commonly seen in children. It is followed by an immune-clearance or immune-reactive phase in which the immune system recognises and starts to clear the virus. ALT levels are typically elevated or fluctuating, and there is a higher risk of liver fibrosis. This tends to be the initial phase in people infected with HBV as adults. It lasts from weeks to

years and ends with HBeAg seroconversion.

With the loss of HBeAg the person may enter an immune-control phase with very low or undetectable HBV DNA levels, normal ALT and minimal fibrosis progression. However, some people may experience rising HBV DNA levels despite HBeAg negativity. This is caused by virions that do not express HBeAg because of genetic mutations. This immune-escape phase can lead to active necroinflammation and progression of fibrosis.

Figure 1. Natural history of chronic HBV infection



After Chu et al, Hepatology 1985;5:431-34 ULN: upper limit of normal of ALT

Substantial progress has been made in the treatment of chronic hepatitis B in the past decade but the appropriate time for starting treatment remains a topic of debate. Although currently available treatment is effective in suppressing HBV replication, it fails to eradicate the virus necessitating long treatment duration and perhaps lifelong treatment.

The guideline will assume that prescribers will use a drug's summary of product characteristics to inform decisions made with individual patients.

This guideline recommends some drugs for indications for which they do not have a UK marketing authorisation at the date of publication, if there is good evidence to support

that use. The prescriber should follow relevant professional guidance, taking full responsibility for the decision. The patient (or those with authority to give consent on their behalf) should provide informed consent, which should be documented. See the General Medical Council's Good practice in prescribing medicines – guidance for doctors for further information. Where recommendations have been made for the use of drugs outside their licensed indications ('off-label use'), these drugs are marked with a footnote in the recommendations.

Patient-centred care

This guideline offers best practice advice on the care of children, young people and adults with chronic hepatitis B.

Patients and healthcare professionals have rights and responsibilities as set out in the NHS Constitution for England – all NICE guidance is written to reflect these. Treatment and care should take into account individual needs and preferences. Patients should have the opportunity to make informed decisions about their care and treatment, in partnership with their healthcare professionals. If the patient is under 16, their family or carers should also be given information and support to help the child or young person to make decisions about their treatment. Healthcare professionals should follow the Department of Health's advice on consent. If someone does not have capacity to make decisions, healthcare professionals should follow the code of practice that accompanies the Mental Capacity Act and the supplementary code of practice on deprivation of liberty safeguards. In Wales, healthcare professionals should follow advice on consent from the Welsh Government.

NICE has produced guidance on the components of good patient experience in adult NHS services. All healthcare professionals should follow the recommendations in Patient experience in adult NHS services.

If a young person is moving between paediatric and adult services, care should be planned and managed according to the best practice guidance described in the Department of Health's Transition: getting it right for young people.

Adult and paediatric healthcare teams should work jointly to provide assessment and services to young people with chronic hepatitis B. Diagnosis and management should be reviewed throughout the transition process, and there should be clarity about who is the lead clinician to ensure continuity of care.

Terms used in this guidance

Chronic hepatitis B

Chronic hepatitis B is defined as persistence of hepatitis B surface antigen (HBsAg) for 6 months or more after acute infection with hepatitis B virus (HBV).

HBV DNA

HBV DNA level, or 'viral load', is an indicator of viral replication. Higher HBV DNA levels are usually associated with an increased risk of liver disease and hepatocellular carcinoma. HBV DNA level typically falls in response to effective antiviral treatment.

Hepatitis B surface antigen (HBsAg)

Hepatitis B surface antigen (HBsAg) is a viral protein detectable in the blood in acute and chronic hepatitis B infection.

HBsAg seroconversion

The development of antibodies against HBsAg is known as HBsAg seroconversion. It signifies clearance of HBsAg and resolution of the chronic infection.

Hepatitis B e antigen (HBeAg)

Hepatitis B e antigen (HBeAg) is an indicator of viral replication, although some variant forms of the virus do not express HBeAg (see 'HBeAg-negative chronic hepatitis B' below). Active infection can be described as HBeAg-positive or HBeAg-negative according to whether HBeAg is secreted.

HBeAg-negative chronic hepatitis B

HBeAg-negative hepatitis B is a form of the virus that does not cause infected cells to

secrete HBeAg. People can be infected with the HBeAg-negative form of the virus from the beginning, or the viral mutation can emerge later in the course of infection in people initially infected with the HBeAg-positive form of the virus.

HBeAg seroconversion

HBeAg seroconversion occurs when people infected with the HBeAg-positive form of the virus develop antibodies against the 'e' antigen. The seroconverted disease state is referred to as the 'inactive HBV carrier state' when HBeAg has been cleared, anti-HBe is present and HBV DNA is undetectable or less than 2000 IU/ml. Once seroconversion has taken place, most people remain in the inactive HBV carrier state (the immune-control phase; see figure 1). However, increasing HBV DNA and recurrent hepatitis after seroconversion indicate the emergence of the HBeAg-negative strain of the virus (the immune-escape phase; see figure 1).

Key priorities for implementation

The following recommendations have been identified as priorities for implementation.

Assessment and referral

- Arrange the following tests in primary care for adults who are hepatitis B surface antigen (HBsAg) positive:
  - hepatitis B e antigen (HBeAg)/antibody (anti-HBe) status
  - HBV DNA level
  - IgM antibody to hepatitis B core antigen (anti-HBc IgM)
  - hepatitis C virus antibody (anti-HCV)
  - hepatitis delta virus antibody (anti-HDV)
  - HIV antibody (anti-HIV)
  - IgG antibody to hepatitis A virus (anti-HAV)
  - additional laboratory tests including alanine aminotransferase (ALT) or aspartate aminotransferase (AST), gamma-glutamyl transferase (GGT), serum albumin, total bilirubin, total globulins, full blood count and prothrombin time
  - tests for hepatocellular carcinoma (HCC), including hepatic ultrasound and alpha-fetoprotein testing.
- Include the results of the initial tests with the referral (see recommendation 1.2.1).

Treatment sequence in adults with HBeAg-positive chronic hepatitis B and compensated liver disease

- Offer a 48-week course of peginterferon alfa-2a as first-line treatment in adults with HBeAg-positive chronic hepatitis B and compensated liver disease[1].

- Offer tenofovir disoproxil as second-line treatment to people who do not undergo HBeAg seroconversion or who relapse (revert to being HBeAg positive following seroconversion) after first-line treatment with peginterferon alfa-2a.
- Offer entecavir as an alternative second-line treatment to people who cannot tolerate tenofovir disoproxil or if it is contraindicated.

Treatment sequence in adults with HBeAg-negative chronic hepatitis B and compensated liver disease

- Offer a 48-week course of peginterferon alfa-2a as first-line treatment in adults with HBeAg-negative chronic hepatitis B and compensated liver disease[1].
- Offer entecavir or tenofovir disoproxil as second-line treatment to people with detectable HBV DNA after first-line treatment with peginterferon alfa-2a.

Women who are pregnant or breastfeeding

- Offer tenofovir disoproxil to women with HBV DNA greater than 10^7 IU/ml in the third trimester to reduce the risk of transmission of HBV to the baby[2].

Prophylactic treatment during immunosuppressive therapy

- In people who are HBsAg positive and have HBV DNA greater than 2000 IU/ml, offer prophylaxis with entecavir or tenofovir disoproxil[3].
  - Start prophylaxis before beginning immunosuppressive therapy and continue for a minimum of 6 months after HBeAg seroconversion and HBV DNA is undetectable.

- In people who are HBsAg positive and have HBV DNA less than 2000 IU/ml, offer prophylaxis:
  - consider lamivudine[3] if immunosuppressive therapy is expected to last less than 6 months
    - monitor HBV DNA monthly in people treated with lamivudine and change to tenofovir disoproxil if HBV DNA remains detectable after 3 months
  - consider entecavir or tenofovir disoproxil[3] if immunosuppressive therapy is expected to last longer than 6 months
  - start prophylaxis before beginning immunosuppressive therapy and continue for a minimum of 6 months after stopping immunosuppressive therapy.

[1] Avoid use of peginterferon alfa-2a in pregnancy unless the potential benefit outweighs risk. Women of childbearing potential must use effective contraception throughout therapy.

[2] At the time of publication (June 2013), tenofovir disoproxil did not have a UK marketing authorisation for this indication. The prescriber should follow relevant professional guidance, taking full responsibility for the decision. Informed consent should be obtained and documented. See the General Medical Council's Good practice in prescribing medicines – guidance for doctors for further information.

[3] At the time of publication (June 2013), entecavir, lamivudine and tenofovir disoproxil did not have a UK marketing authorisation for this indication. The prescriber should follow relevant professional guidance, taking full responsibility for the decision. Informed consent should be obtained and documented. See the General Medical Council's Good practice in prescribing medicines – guidance for doctors for further information.

1 Recommendations

The following guidance is based on the best available evidence. The full guideline gives details of the methods and the evidence used to develop the guidance.

The wording used in the recommendations in this guideline (for example, words such as 'offer' and 'consider') denotes the certainty with which the recommendation is made (the strength of the recommendation). See About this guideline for details.

In this guideline, children and young people are defined as aged up to 18 years. Please follow the recommendations for women who are pregnant for young people with chronic hepatitis B who are pregnant.

1.1 Patient information

1.1.1 Provide information on the following topics to people with chronic hepatitis B and to family members or carers (if appropriate) before assessment for antiviral treatment:

- the natural history of chronic hepatitis B, including stages of disease and long-term prognosis
- lifestyle issues such as alcohol, diet and weight
- family planning
- monitoring
- routes of hepatitis B virus (HBV) transmission
- the benefits of antiviral treatment, including reduced risk of serious liver disease and death and reduced risk of transmission of HBV to others
- treatment options and contraindications based on the patient's circumstances, including peginterferon alfa-2a and nucleoside or nucleotide analogues
- short- and long-term treatment goals

- causes of treatment failure, including non-adherence to prescribed medicines, and options for re-treatment
- risks of treatment, including adverse effects and drug resistance.

1.1.2 Offer a copy of the personalised care plan to people with chronic hepatitis B and to family members or carers (if appropriate) outlining proposed treatment and long-term management, for example, a copy of the hospital consultation summary.

1.1.3 Provide information on self-injection techniques to people beginning peginterferon alfa-2a or to family members or carers.

1.1.4 NICE has produced public health guidance on ways to promote and offer testing to people at increased risk of infection with hepatitis B. All healthcare professionals should follow the recommendations in Hepatitis B and C: ways to promote and offer testing to people at increased risk of infection (NICE public health guidance 43).

1.1.5 NICE has produced guidance on the components of good patient experience in adult NHS services. All healthcare professionals should follow the recommendations in Patient experience in adult NHS services (NICE clinical guidance 138).

1.2 Assessment and referral in primary care

Adults who are HBsAg positive

1.2.1 Arrange the following tests in primary care for adults who are hepatitis B surface antigen (HBsAg) positive:

- hepatitis B e antigen (HBeAg)/antibody (anti-HBe) status
- HBV DNA level
- IgM antibody to hepatitis B core antigen (anti-HBc IgM)
- hepatitis C virus antibody (anti-HCV)

- hepatitis delta virus antibody (anti-HDV)
- HIV antibody (anti-HIV)
- IgG antibody to hepatitis A virus (anti-HAV)
- additional laboratory tests including alanine aminotransferase (ALT) or aspartate aminotransferase (AST), gamma-glutamyl transferase (GGT), serum albumin, total bilirubin, total globulins, full blood count and prothrombin time
- tests for hepatocellular carcinoma (HCC), including hepatic ultrasound and alpha-fetoprotein testing.

1.2.2 Refer all adults who are HBsAg positive to a hepatologist or to a gastroenterologist or infectious disease specialist with an interest in hepatology.

1.2.3 Include the results of the initial tests with the referral (see recommendation 1.2.1).

Pregnant women who test HBsAg positive at antenatal screening

1.2.4 Refer pregnant women who are HBsAg positive to a hepatologist, or to a gastroenterologist or infectious disease specialist with an interest in hepatology, for assessment within 6 weeks of receiving the screening test result and to allow treatment in the third trimester (see recommendation 1.5.39).

Adults with decompensated liver disease

1.2.5 Refer adults who develop decompensated liver disease immediately to a hepatologist or to a gastroenterologist with an interest in hepatology. Symptoms of decompensated liver disease include (but are not limited to) ascites, encephalopathy and gastrointestinal haemorrhage.

Children and young people who are HBsAg positive

1.2.6 Arrange the following tests for children and young people who are HBsAg positive:

- HBeAg/anti-HBe status
- HBV DNA level
- anti-HBc IgM
- anti-HCV
- anti-HDV
- anti-HIV
- anti-HAV
- additional laboratory tests, including ALT or AST, GGT, serum albumin, total bilirubin, total globulins, full blood count and prothrombin time
- tests for HCC, including hepatic ultrasound and alpha-fetoprotein testing.

1.2.7 Refer all children and young people who are HBsAg positive to a paediatric hepatologist or to a gastroenterologist or infectious disease specialist with an interest in hepatology.

1.2.8 Include the results of the initial tests with the referral (see recommendation 1.2.6).

1.3 Assessment of liver disease in secondary specialist care

Adults with chronic hepatitis B

Please refer to recommendations 1.5.3 to 1.5.7 for detailed guidance on offering antiviral treatment.

1.3.1 Ensure all healthcare professionals who refer adults for non-invasive tests for liver disease are trained to interpret the results and aware of co-factors that influence liver elasticity (for example, fatty liver caused by obesity or alcohol misuse).

1.3.2 Discuss the accuracy, limitations and risks of the different tests for liver

disease with the patient.

1.3.3 Offer transient elastography as the initial test for liver disease in adults newly referred for assessment.

1.3.4 Offer antiviral treatment without a liver biopsy to adults with a transient elastography score greater than or equal to 11 kPa[4], in line with recommendation 1.5.6.

1.3.5 Consider liver biopsy to confirm the level of fibrosis in adults with a transient elastography score between 6 and 10 kPa[5]. Offer antiviral treatment in line with recommendations 1.5.3 to 1.5.7.

1.3.6 Offer liver biopsy to adults with a transient elastography score less than 6 kPa if they are younger than 30 years and have HBV DNA greater than 2000 IU/ml and abnormal ALT (greater than or equal to 30 IU/L for males and greater than or equal to 19 IU/L for females) on 2 consecutive tests conducted 3 months apart[6]. Offer antiviral treatment in line with recommendations 1.5.3 to 1.5.7.

1.3.7 Do not offer liver biopsy to adults with a transient elastography score less than 6 kPa who have normal ALT (less than 30 IU/L in males and less than 19 IU/L in females) and HBV DNA less than 2000 IU/ml as they are unlikely to have advanced liver disease or need antiviral treatment (see recommendations 1.5.3 to 1.5.7)[6].

1.3.8 Offer an annual reassessment of liver disease using transient elastography to adults who are not taking antiviral treatment.

Children and young people with chronic hepatitis B

1.3.9 Discuss the accuracy, limitations and risks of liver biopsy in determining the need for antiviral treatment with the child or young person and with parents or carers (if appropriate).

1.3.10 Consider liver biopsy to assess liver disease and the need for antiviral treatment in children and young people with HBV DNA greater than 2000 IU/ml and abnormal ALT (greater than or equal to 30 IU/L for males

and greater than or equal to 19 IU/L for females) on 2 consecutive tests conducted 3 months apart. Offer biopsy under a general anaesthetic to children who are too young to tolerate the procedure under a local anaesthetic.

1.4 Genotype testing

1.4.1 Do not offer genotype testing to determine initial treatment in people with chronic hepatitis B.

1.5 Antiviral treatment

Adults with chronic hepatitis B

Recommendations 1.5.8 to 1.5.12 are reproduced from existing NICE technology appraisals on options for the treatment of chronic hepatitis B, and 1.5.13 to 1.5.15 update guidance in NICE technology appraisal 96[7]. The GDG has reviewed the evidence and has made recommendations on treatment sequences and combination drug regimens (see recommendations 1.5.16 to 1.5.28).

Recommendations 1.5.8 to 1.5.43 do not apply to people with chronic hepatitis B who also have hepatitis C, hepatitis D or HIV.

1.5.1 Discuss treatment options, adverse effects and long-term prognosis with the patient before starting treatment.

1.5.2 Re-assess the person's risk of exposure to HIV before starting treatment and offer repeat testing if needed.

1.5.3 Offer antiviral treatment to adults aged 30 years and older who have HBV DNA greater than 2000 IU/ml and abnormal ALT (greater than or equal to 30 IU/L in males and greater than or equal to 19 IU/L in females) on 2 consecutive tests conducted 3 months apart.

1.5.4 Offer antiviral treatment to adults younger than 30 years who have HBV DNA greater than 2000 IU/ml and abnormal ALT (greater than or equal to 30 IU/L in males and greater than or equal to 19 IU/L in females) on 2

consecutive tests conducted 3 months apart if there is evidence of necroinflammation or fibrosis on liver biopsy or a transient elastography score greater than 6 kPa.

1.5.5 Offer antiviral treatment to adults who have HBV DNA greater than 20,000 IU/ml and abnormal ALT (greater than or equal to 30 IU/L in males and greater than or equal to 19 IU/L in females) on 2 consecutive tests conducted 3 months apart regardless of age or the extent of liver disease.

1.5.6 Offer antiviral treatment to adults with cirrhosis and detectable HBV DNA, regardless of HBeAg status, HBV DNA and ALT levels.

1.5.7 Consider antiviral treatment in adults with HBV DNA greater than 2000 IU/ml and evidence of necroinflammation or fibrosis on liver biopsy.

1.5.8 Peginterferon alfa-2a is recommended as an option for the initial treatment of adults with chronic hepatitis B (HBeAg-positive or HBeAg-negative), within its licensed indications. [This recommendation is from Adefovir dipivoxil and peginterferon alfa-2a for the treatment of chronic hepatitis B (NICE technology appraisal guidance 96).]

1.5.9 Entecavir, within its marketing authorisation, is recommended as an option for the treatment of people with chronic HBeAg-positive or HBeAg-negative hepatitis B in whom antiviral treatment is indicated. [This recommendation is from Entecavir for the treatment of chronic hepatitis B (NICE technology appraisal guidance 153).]

1.5.10 Tenofovir disoproxil, within its marketing authorisation, is recommended as an option for the treatment of people with chronic HBeAg-positive or HBeAg-negative hepatitis B in whom antiviral treatment is indicated. [This recommendation is from Tenofovir disoproxil fumarate for the treatment of hepatitis B (NICE technology appraisal guidance 173).]

1.5.11 Telbivudine is not recommended for the treatment of chronic hepatitis B. [This recommendation is from Telbivudine for the treatment of chronic hepatitis B (NICE technology appraisal guidance 154).]

1.5.12 People currently receiving telbivudine should have the option to continue therapy until they and their clinicians consider it appropriate to stop. [This recommendation is from Telbivudine for the treatment of chronic hepatitis B (NICE technology appraisal guidance 154).]

1.5.13 Do not offer adefovir dipivoxil for treatment of chronic hepatitis B.

1.5.14 People currently receiving adefovir dipivoxil should be offered the option to switch to a different treatment. Offer tenofovir disoproxil or entecavir, depending on previous antiviral exposure:

- offer tenofovir disoproxil to people with a history of lamivudine resistance.

1.5.15 Antiviral treatment should be initiated only by an appropriately qualified healthcare professional with expertise in the management of viral hepatitis. Continuation of therapy under shared-care arrangements with a GP is appropriate.

Treatment sequence in adults with HBeAg-positive chronic hepatitis B and compensated liver disease

1.5.16 Offer a 48-week course of peginterferon alfa-2a as first-line treatment in adults with HBeAg-positive chronic hepatitis B and compensated liver disease[8].

1.5.17 Consider stopping peginterferon alfa-2a 24 weeks after starting treatment if HBV DNA level has decreased by less than 2 $\log_{10}$ IU/ml and/or if HBsAg is greater than 20,000 IU/ml, and offer second-line treatment in line with recommendations 1.5.18 and 1.5.19.

1.5.18 Offer tenofovir disoproxil as second-line treatment to people who do not undergo HBeAg seroconversion or who relapse (revert to being HBeAg positive following seroconversion) after first-line treatment with peginterferon alfa-2a.

1.5.19 Offer entecavir as an alternative second-line treatment to people who cannot tolerate tenofovir disoproxil or if it is contraindicated.

1.5.20 Review adherence in people taking tenofovir disoproxil who have detectable HBV DNA at 48 weeks of treatment and, if appropriate, provide support in line with Medicines adherence (NICE clinical guidance 76).

- If HBV DNA remains detectable at 96 weeks, and there is no history of lamivudine resistance, consider adding lamivudine to tenofovir disoproxil.
- In people with a history of lamivudine resistance, consider adding entecavir to tenofovir disoproxil.

1.5.21 Consider stopping nucleoside or nucleotide analogue treatment 12 months after HBeAg seroconversion in people without cirrhosis.

1.5.22 Do not stop nucleoside or nucleotide analogue treatment 12 months after HBeAg seroconversion in people with cirrhosis.

Treatment sequence in adults with HBeAg-negative chronic hepatitis B and compensated liver disease

1.5.23 Offer a 48-week course of peginterferon alfa-2a as first-line treatment in adults with HBeAg-negative chronic hepatitis B and compensated liver disease[8].

1.5.24 Consider stopping peginterferon alfa-2a 24 weeks after starting treatment if HBV DNA level has decreased by less than 2 $\log_{10}$ IU/ml and HBsAg has not decreased, and consider second-line treatment in line with recommendation 1.5.25.

1.5.25 Offer entecavir or tenofovir disoproxil as second-line treatment to people with detectable HBV DNA after first-line treatment with peginterferon alfa-2a.

1.5.26 Consider switching from tenofovir disoproxil to entecavir, or from entecavir to tenofovir disoproxil, as third-line treatment in people who have detectable HBV DNA at 48 weeks of treatment.

1.5.27 Consider stopping nucleoside or nucleotide analogue treatment 12 months after achieving undetectable HBV DNA and HBsAg

seroconversion in people without cirrhosis.

1.5.28 Do not stop nucleoside or nucleotide analogue treatment after achieving undetectable HBV DNA and HBsAg seroconversion in patients with cirrhosis.

Children and young people with chronic hepatitis B and compensated liver disease

1.5.29 Discuss treatment options, adverse effects and long-term prognosis with the child or young person and with parents or carers (if appropriate) before starting treatment.

1.5.30 Re-assess the child or young person's risk of exposure to HIV before starting treatment and offer repeat testing if necessary.

1.5.31 Offer antiviral treatment if there is evidence of significant fibrosis (METAVIR stage greater than or equal to F2 or Ishak stage greater than or equal to 3) or abnormal ALT (greater than or equal to 30 IU/L for males and greater than or equal to 19 IU/L for females) on 2 consecutive tests conducted 3 months apart.

1.5.32 Consider a 48-week course of peginterferon alfa-2a as first-line treatment in children and young people with chronic hepatitis B and compensated liver disease[8],[9].

1.5.33 Consider stopping peginterferon alfa-2a 24 weeks after starting treatment if HBV DNA level has decreased by less than 2 $\log_{10}$ IU/ml and/or if HBsAg is greater than 20,000 IU/ml.

1.5.34 Consider a nucleoside or nucleotide analogue as second-line treatment in children and young people with detectable HBV DNA after first-line treatment with peginterferon alfa-2a[10].

Adults with decompensated liver disease

1.5.35 Manage decompensated liver disease in adults in conjunction with a liver transplant centre.

1.5.36 Do not offer peginterferon alfa-2a to people with chronic hepatitis B and decompensated liver disease.

1.5.37 Offer entecavir as first-line treatment in people with decompensated liver disease if there is no history of lamivudine resistance.

- Offer tenofovir disoproxil to people with a history of lamivudine resistance.
- Reduce the dose of tenofovir disoproxil in people with renal impairment, in line with guidance in the summary of product characteristics.

Women who are pregnant or breastfeeding

1.5.38 Discuss with pregnant women the benefits and risks of antiviral treatment for them and their baby.

1.5.39 Offer tenofovir disoproxil to women with HBV DNA greater than 10^7 IU/ml in the third trimester to reduce the risk of transmission of HBV to the baby[11].

1.5.40 Monitor quantitative HBV DNA 2 months after starting tenofovir disoproxil and ALT monthly after the birth to detect postnatal HBV flares in the woman.

1.5.41 Stop tenofovir disoproxil 4 to 12 weeks after the birth unless the mother meets criteria for long-term treatment (see recommendations 1.5.4 to 1.5.8).

1.5.42 Offer active and passive hepatitis B immunisation in infants and follow up in line with the guidance below:

- Hepatitis B antenatal screening and newborn immunisation programme: best practice guidance
- Immunisation against infectious disease (the Green book)
- Hepatitis B and C: ways to promote and offer testing. NICE public health guidance 43 (2012)

- Reducing differences in the uptake of immunisations. NICE public health guidance 21 (2009).

1.5.43 Advise women that there is no risk of transmitting HBV to their babies through breastfeeding if guidance on hepatitis B immunisation has been followed, and that they may continue antiviral treatment while they are breastfeeding.

Adults who are co-infected with hepatitis C

1.5.44 Offer peginterferon alfa and ribavirin in adults co-infected with chronic hepatitis B and C[8].

Adults who are co-infected with hepatitis D

1.5.45 Offer a 48-week course of peginterferon alfa-2a in people co-infected with chronic hepatitis B and hepatitis delta infection who have evidence of significant fibrosis (METAVIR stage greater than or equal to F2 or Ishak stage greater than or equal to 3)[8].

1.5.46 Consider stopping peginterferon alfa-2a if there is no decrease in HDV RNA after 6 months to 1 year of treatment. Otherwise, continue treatment and re-evaluate treatment response annually.

1.5.47 Stop treatment after HBsAg seroconversion.

Prophylactic treatment during immunosuppressive therapy

1.5.48 Perform the following tests in people who are HBsAg and/or anti-HBc positive before starting immunosuppressive therapy for autoimmune or atopic diseases, chemotherapy, bone marrow or solid organ transplantation:

- antibody to hepatitis B surface antigen (anti-HBs)
- plasma or serum HBV DNA level
- ALT.

1.5.49 In people who are HBsAg positive and have HBV DNA greater than 2000 IU/ml, offer prophylaxis with entecavir or tenofovir disoproxil[12].

- Start prophylaxis before beginning immunosuppressive therapy and continue for a minimum of 6 months after HBeAg seroconversion and HBV DNA is undetectable.

1.5.50 In people who are HBsAg positive and have HBV DNA less than 2000 IU/ml, offer prophylaxis.

- Consider lamivudine[12] if immunosuppressive therapy is expected to last less than 6 months.
  - Monitor HBV DNA monthly in people treated with lamivudine and change to tenofovir disoproxil if HBV DNA remains detectable after 3 months.
- Consider entecavir or tenofovir disoproxil[12] if immunosuppressive therapy is expected to last longer than 6 months.
- Start prophylaxis before beginning immunosuppressive therapy and continue for a minimum of 6 months after stopping immunosuppressive therapy.

1.5.51 In people who are HBsAg negative and anti-HBc positive (regardless of anti-HBs status) and are starting rituximab or other B cell-depleting therapies:

- offer prophylaxis with lamivudine[12]
- start prophylaxis before beginning immunosuppressive therapy and continue for a minimum of 6 months after stopping immunosuppressive therapy.

1.5.52 In people who are HBsAg negative, anti-HBc positive and anti-HBs negative and are not taking rituximab or other B cell-depleting therapies:

- monitor HBV DNA monthly and offer prophylaxis to people whose HBV DNA becomes detectable
  - consider lamivudine[12] in people with HBV DNA less than 2000 IU/ml and for whom immunosuppressive therapy is expected to last less than 6 months; change to tenofovir disoproxil if HBV DNA remains detectable after 6 months
  - consider entecavir or tenofovir disoproxil[12] in people with HBV DNA greater than 2000 IU/ml and for whom immunosuppressive therapy is expected to last longer than 6 months
  - continue antiviral therapy for a minimum of 6 months after stopping immunosuppressive therapy.

1.5.53 Do not offer prophylaxis to people who are HBsAg negative and anti-HBc and anti-HBs positive who are not taking rituximab or other B cell-depleting therapies.

1.6 Monitoring

Monitoring in people who do not meet criteria for antiviral treatment

Further information on the progression of chronic hepatitis B can be found in the Introduction (see Figure 1).

Adults with HBeAg-positive disease in the immune-tolerant and immune clearance phases

1.6.1 Monitor ALT levels every 24 weeks in adults with HBeAg-positive disease who are in the immune-tolerant phase (defined by active viral replication and normal ALT levels [less than 30 IU/L in males and less than 19 IU/L in females]).

1.6.2 Monitor ALT every 12 weeks on at least 3 consecutive occasions if there is an increase in ALT levels.

Adults with inactive chronic hepatitis B (immune-control phase)

1.6.3 Monitor ALT and HBV DNA levels every 48 weeks in adults with inactive chronic hepatitis B infection (defined as HBeAg negative on 2 consecutive tests with normal ALT [less than 30 IU/L in males and less than 19 IU/L in females] and HBV DNA less than 2000 IU/ml).

- Consider monitoring more frequently (for example, every 12–24 weeks) in people with cirrhosis who have undetectable HBV DNA.

Children and young people

1.6.4 Monitor ALT levels every 24 weeks in children and young people with HBeAg-positive disease who have normal ALT levels (less than 30 IU/L for males and less than 19 IU/L for females) and no evidence of significant fibrosis (METAVIR stage less than F2 or Ishak stage less than 3).

1.6.5 Review annually children and young people with HBeAg-negative disease who have normal ALT (less than 30 IU/L for males and less than 19 IU/L for females), no evidence of significant fibrosis (METAVIR stage less than F2 or Ishak stage less than 3) and HBV DNA less than 2000 IU/ml.

1.6.6 Review every 12 weeks children and young people with HBeAg-negative disease who have abnormal ALT (greater than or equal to 30 IU/L for males and greater than or equal to 19 IU/L for females) and HBV DNA greater than 2000 IU/ml.

Children, young people and adults with HBeAg or HBsAg seroconversion after antiviral treatment

1.6.7 In people with HBeAg seroconversion after antiviral treatment, monitor HBeAg, anti-HBe, HBV DNA level and liver function at 4, 12 and 24 weeks after HBeAg seroconversion and then every 6 months.

1.6.8 Monitor HBsAg and anti-HBs annually in people with HBsAg seroconversion after antiviral treatment and discharge people who are anti-HBs positive on 2 consecutive tests.

Monitoring in people taking antiviral treatment

Children, young people and adults taking peginterferon alfa-2a

1.6.9 Review injection technique and adverse effects weekly during the first month of treatment in people taking peginterferon alfa-2a[10].

1.6.10 Monitor full blood count, liver function (including bilirubin, albumin and ALT), renal function (including urea and electrolyte levels) and thyroid function (and in children, weight and height) before starting peginterferon alfa-2a and 2, 4, 12, 24, 36 and 48 weeks after starting treatment to detect adverse effects[10].

1.6.11 Monitor HBV DNA and quantitative HBsAg levels and HBeAg status before starting peginterferon alfa-2a at 12, 24 and 48 weeks after starting treatment to determine treatment response[10].

Children, young people and adults with compensated liver disease taking entecavir or lamivudine

1.6.12 Monitor full blood count, liver function (including bilirubin, albumin and ALT) and renal function (including urea and electrolyte levels) in people with compensated liver disease before starting entecavir or lamivudine, 4 weeks after starting treatment and then every 3 months to detect adverse effects[10].

1.6.13 Monitor HBV DNA and quantitative HBsAg levels and HBeAg status before starting entecavir or lamivudine, 12, 24 and 48 weeks after starting treatment and then every 6 months to determine treatment response and medicines adherence[10].

1.6.14 Monitor HBV DNA levels every 12 weeks in people with HBeAg-negative disease who have been taking lamivudine for 5 years or longer[10].

Children, young people and adults with compensated liver disease taking tenofovir disoproxil

1.6.15 Monitor full blood count, liver function (including bilirubin, albumin and

ALT), renal function (including urea and electrolyte levels and urine protein/creatinine ratio), and phosphate levels in people with compensated liver disease before starting tenofovir disoproxil, 4 weeks after starting treatment and then every 3 months to detect adverse effects[10].

1.6.16 Monitor HBV DNA and quantitative HBsAg levels and HBeAg status before starting tenofovir disoproxil, 12, 24 and 48 weeks after starting treatment and then every 6 months to determine treatment response and medicines adherence[10].

Children, young people and adults with decompensated liver disease who are taking entecavir or lamivudine

1.6.17 Monitor full blood count, liver function (including bilirubin, albumin and ALT), renal function (including urea and electrolyte levels and urine protein/creatinine ratio), blood clotting, HBV DNA level and HBeAg status in people with decompensated liver disease before starting entecavir or lamivudine and weekly after starting treatment to assess treatment response and adverse effects. When the person is no longer decompensated, follow the recommendations in 'Children, young people and adults with compensated liver disease taking entecavir or lamivudine'[10].

Children, young people and adults with decompensated liver disease who are taking tenofovir disoproxil

1.6.18 Monitor full blood count, liver function (including bilirubin, albumin and ALT), renal function (including urea and electrolyte levels and urine protein/creatinine ratio) and phosphate, blood clotting, HBV DNA level and HBeAg status in people with decompensated liver disease before starting tenofovir disoproxil and weekly after starting treatment to assess treatment response and adverse effects. When the person is no longer decompensated, follow the recommendations in 'Children, young people and adults with compensated liver disease taking tenofovir disoproxil'[10].

1.7 Surveillance testing for hepatocellular carcinoma in adults with chronic hepatitis B

1.7.1 Perform 6-monthly surveillance for HCC by hepatic ultrasound and alpha-fetoprotein testing in people with significant fibrosis (METAVIR stage greater than or equal to F2 or Ishak stage greater than or equal to 3) or cirrhosis.

1.7.2 In people without significant fibrosis or cirrhosis (METAVIR stage less than F2 or Ishak stage less than 3), consider 6-monthly surveillance for HCC if the person is older than 40 years and has a family history of HCC and HBV DNA greater than or equal to 20,000 IU/ml.

1.7.3 Do not offer surveillance for HCC in people without significant fibrosis or cirrhosis (METAVIR stage less than F2 or Ishak stage less than 3) who have HBV DNA less than 20,000 IU/ml and are younger than 40 years.

More information

You can also see this guideline in the NICE pathway on hepatitis B (chronic).

To find out what NICE has said on topics related to this guideline, see our web page on hepatitis.

See also the guideline committee's discussion and the evidence reviews (in the full guideline), and information about how the guideline was developed, including details of the committee.

[4] Adults with a transient elastography score greater than or equal to 11 kPa are very likely to have cirrhosis and confirmation by liver biopsy is not needed.

[5] The degree of fibrosis cannot be accurately predicted in adults with a transient elastography score between 6 to 10 kPa. Some people may choose to have a liver biopsy in these circumstances to confirm the extent of liver disease.

[6] Adults with a transient elastography score less than 6 kPa are unlikely to have significant fibrosis.

[7] Adefovir dipivoxil and peginterferon alfa-2a for the treatment of chronic hepatitis B (NICE technology appraisal guidance 96), Entecavir for the treatment of chronic hepatitis B (NICE technology appraisal guidance 153), Telbivudine for the treatment of chronic hepatitis B (NICE technology appraisal guidance 154) and Tenofovir disoproxil fumarate for the treatment of hepatitis B (NICE technology appraisal guidance 173).

[8] Avoid use of peginterferon alfa-2a in pregnancy unless the potential benefit outweighs risk. Women of childbearing potential must use effective contraception throughout therapy.

[9] At the time of publication (June 2013), peginterferon alfa-2a did not have a UK marketing authorisation for use in children for this indication. The prescriber should follow relevant professional guidance, taking full responsibility for the decision. Informed consent should be obtained and documented. See the General Medical Council's Good practice in prescribing medicines – guidance for doctors for further information.

[10] At the time of last review (October 2017), peginterferon alfa-2a did not have a UK marketing authorisation for use in children for this indication, tenofovir disoproxil did not have a UK marketing authorisation for use in children younger than 12 years for this indication and entecavir did not have a UK marketing authorisation for use in children younger than 2 years for this indication. The prescriber should follow relevant professional guidance, taking full responsibility for the decision. Informed consent should be obtained and documented. See the General Medical Council's Good practice in prescribing medicines – guidance for doctors for further information.

[11] At the time of publication (June 2013), tenofovir disoproxil did not have a UK marketing authorisation for this indication. The prescriber should follow relevant professional guidance, taking full responsibility for the decision. Informed consent should be obtained and documented. See the General Medical Council's Good practice in prescribing medicines – guidance for doctors for further information.

[12] At the time of publication (June 2013), entecavir, lamivudine and tenofovir disoproxil did not have a UK marketing authorisation for this indication. The prescriber should follow relevant professional guidance, taking full responsibility for the decision. Informed consent should be obtained and documented. See the General Medical Council's Good practice in prescribing medicines – guidance for doctors for further information.

2 Research recommendations

The Guideline Development Group has made the following recommendations for research, based on its review of evidence, to improve NICE guidance and patient care in the future.

2.1 Stopping antiviral treatment in HBeAg-negative disease

Further research should be undertaken to evaluate the clinical and cost effectiveness of hepatitis B surface antigen (HBsAg) quantitative assays in determining treatment duration in hepatitis B e antigen- (HBeAg) negative disease.

Why this is important

In HBeAg-positive disease, HBeAg seroconversion is a predictor of durable response to antiviral treatment and can be used as a milestone after which treatment can be stopped. At present, similar parameters have not been defined in HBeAg-negative disease. Quantitative HBsAg may have a role in determining treatment duration in this setting. Establishing threshold levels for HBsAg titre associated with durable off-treatment control in HBeAg-negative disease would transform current treatment strategies. People on long-term nucleoside or nucleotide analogues could safely stop treatment once they achieved a threshold level of HBsAg. Further research is needed to define these levels of HBsAg and to determine when treatment in HBeAg-negative disease can be safely stopped.

2.2 ALT values for children and young people

Further research should be undertaken to examine whether the upper limit of normal ALT values for adults (below 30 IU/L for males and below 19 IU/L for females) are appropriate for use in children and young people with chronic hepatitis B when making decisions on when to initiate treatment.

Why this is important

Recent studies have highlighted the imprecision of using biochemical activity as a measure of immune activity in children and young people with chronic hepatitis B. Researchers have

found T-cell exhaustion and even HBV-specific immune responses in children and young people considered to have immune-tolerant disease. These findings need to be validated in larger studies to see if upper limit of normal ALT values derived from adults accurately reflect disease activity in children and young people. Further research is needed to investigate whether there is a genuine state of immune tolerance in children and young people reflected in lower levels of biochemical activity and a lower upper limit of normal ALT value.

2.3 Long-term safety of tenofovir disoproxil in chronic hepatitis B

Further research should be undertaken to determine the long-term safety of tenofovir disoproxil, including the risk of clinically significant hypophosphataemia and related bone toxicity, in people with chronic hepatitis B. The cost effectiveness of routine monitoring for phosphate loss and bone disease in people with chronic hepatitis B who are receiving tenofovir disoproxil treatment needs further evaluation.

Why this is important

Tenofovir disoproxil is recommended as an option for treatment of people with chronic hepatitis B, and is typically prescribed for long-term use. Kidney dysfunction has been reported in people treated with tenofovir disoproxil, including rare cases of proximal renal tubular dysfunction that appear related to long-term exposure but are not well understood. Adverse renal effects such as hypophosphataemia may have an impact on bone architecture which could result in clinical problems such as fragility fractures. Monitoring for phosphate loss and bone disease could have a role in preventing clinically significant bone problems in people with chronic hepatitis B receiving long-term tenofovir disoproxil. However, the cost effectiveness and clinical utility of routine monitoring needs to be established before recommendations can be made about its use.

2.4 Prophylactic treatment in people receiving immunosuppressive therapy

Further research should be undertaken to determine whether long-term use of mild immunosuppressive agents for autoimmune and allergic problems presents a risk for reactivation of HBV infection in people with previous or current chronic hepatitis B,

including occult HBV infection. The cost effectiveness of routine tests for HBV in this population, including HBV DNA for occult HBV infection, and the need for prophylactic treatment with nucleoside or nucleotide analogues needs further evaluation.

Why this is important

Reactivation of HBV may occur spontaneously or arise during immunosuppression. Solid organ transplantation, chemotherapy and immunosuppressive drugs used to treat autoimmune diseases are key causes of HBV reactivation. Antiviral agents can be used as prophylaxis to prevent reactivation of HBV infection in people receiving immunosuppressive therapy but the optimal treatment and duration of therapy are unknown. Decision-making and cost-effectiveness studies are needed to determine optimal screening strategies to identify people at risk of HBV reactivation. People with occult HBV (including people coming from high endemicity regions) might carry a low, but not negligible, risk of viral reactivation. Prospective studies are needed to assess the risk of HBV reactivation in people receiving mild immunosuppressants or biological treatment for autoimmune diseases, to identify risk factors that predict HBV reactivation in this population, and evaluate treatment or pre-emptive strategies using existing nucleoside and nucleotide analogues.

Update information

October 2017: A footnote was changed to update the information on UK marketing authorisations for entecavir.

January 2014: A correction has been made to the units used for abnormal alanine aminotransferase (ALT) in men and women. The abnormal ALT levels should read greater than or equal to 30 IU/L for males and greater than or equal to 19 IU/L for females, not IU/ml. This has been changed in recommendations 1.3.6, 1.3.7, 1.3.10, 1.5.3–5, 1.5.31, 1.6.1, 1.6.3–6, and 2.2.

June 2013: Recommendations 1.5.13 to 1.5.15 in this guideline update and replace recommendations 1.2 to 1.4 on the use of adefovir dipivoxil for treating chronic hepatitis B in Adefovir dipivoxil and peginterferon alfa-2a for the treatment of chronic hepatitis B (NICE technology appraisal guidance 96). NICE technology appraisal guidance 153, 154, 173 and recommendation 1.1 of NICE technology appraisal guidance 96 have been incorporated into this guideline and remain extant.

Accreditation

NICE advice

NPi-200 for pupillary light reflex in critical care patients

Medtech innovation briefing
Published: 12 November 2020
www.nice.org.uk/guidance/mib235

Summary

- The **technology** described in this briefing is NPi-200. It is used to measure pupillary light reflex and pupil diameter in patients in critical care.
- The **innovative aspects** are that the neurological pupil index, a proprietary index developed from more than 600,000 normative data sets, allows pupil reactivity and other parameters to be trended over time, like other vital signs.
- The intended **place in therapy** would be as an alternative to manually checking pupillary response using a pen torch in critical care units.
- The **main points from the evidence** summarised in this briefing are from 6 observational studies including a total of 1,217 people in critical care units. They show that NPi-200 can measure additional parameters compared with standard care and predict poor outcomes in people who are critically ill.
- **Key uncertainties** around the evidence or technology are that only 1 comparative observational study was included, which did not report on patient outcomes and none of the studies were conducted in the UK.

- The **cost** of NPi-200 is £17.50 per patient, per 7-day stay in a critical care unit, with hourly observations (excluding VAT). The **resource impact** would be greater than standard care, which is around £1.50 for a pen torch.

The technology

NPi-200 (Neuroptics) is a handheld automated pupillometer that includes a camera and a colour touch screen. It provides precise, accurate and objective measurements of pupil size and pupillary light reflex (PLR), as well as other parameters including minimal pupil diameter, percentage change in pupil size and constriction velocity, and displays a video of the constriction response. Measurement takes around 3 seconds per eye. The NPi-200 is used with a disposable SmartGuard. The SmartGuard positions the NPi-200 at a consistent distance to perform the scan. SmartGuard is a single-patient-use device with smart-card technology that can store patient data for each patient for the length of their admission. The SmartGuard has an radio-frequency identification memory tag that can store up to 168 paired pupil measurements, which can be uploaded to the person's electronic medical record or downloaded to a computer for research purposes.

The SmartGuard reader is required for integrating the data into electronic medical records. A barcode scanner is available to avoid manual input of patient data.

Innovations

The company claims that, unlike manual PLR assessment, the NPi-200 expresses PLR in a numerical readout using the 'neurological pupil index' (NPi). The NPi is a proprietary index that is a numerical expression of the PLR on a scale from 0 to 4.9, where an NPi of 3 or higher is considered a healthy response. NPi was validated based on data from over 600,000 people with normal pupillary light reflexes. This allows an objective measurement to be taken so that, like other vital signs, changes from baseline can be recorded over time. The company also claims that a reduction in NPi of more than 0.7 can be used to predict neurological deterioration several hours before a person develops symptoms. A difference in NPi of 0.7 or more between pupils may be considered abnormal (anisocoria). The company claims that the early warning has a substantial unquantifiable benefit because it allows people to be treated earlier.

Current care pathway

Pupillary reactions are usually checked manually using a pen torch, which can lead to inter- and intra-observer variability. Pupil size is recorded in millimetres (1 mm to 9 mm) before light stimulus. Size charts are available, often printed on the side of the pen torch. To assess the PLR, the ambient light is dimmed and the person is asked to fixate on a distant target. The right eye is illuminated from the right side and the left from the left side. Direct pupillary response (the pupil constricts when the light is shone on to it) and a consensual response (the other pupil also constricts) is noted. Pupil size is measured, ideally with reference to a neurological observation chart. PLR is subjectively classed as brisk, sluggish or non-reactive.

A clinical expert said that it is often difficult to adequately dim the ambient light in the intensive therapy unit and people who are critically ill are usually unable to comply with requests to fixate on a distant target. Pen torch assessments are performed regularly by nurses as part of routine neurological assessments, and intermittently by junior doctors to confirm findings. Minimal training is required to use the pen torch, but experience is essential to accurately judge the speed of pupillary response and presence or absence of anisocoria.

The following publications have been identified as relevant to this care pathway:

- NICE's COVID-19 rapid guideline on managing COVID-19
- NICE's guideline on suspected neurological conditions: recognition and referral
- NICE's guideline on rehabilitation after critical illness in adults
- NICE's guideline on acutely ill adults in hospital: recognising and responding to deterioration.

Population, setting and intended user

NPi-200 is indicated for use in the clinical management of children and adults in critical care, specifically in neuro critical care, cardiac critical care, paediatric critical care and stroke units. The company states that it is important to establish a baseline reading as soon as possible for all critically ill people and that people at risk of neurological decline should be continually monitored.

The technology is used by clinicians and intensivists, in relevant tertiary settings. Because of their learned experiences across multiple disciplines, the technology is now becoming nurse-led in many locations.

The company states that the device is simple to use and requires minimal training. Key aspects of the training involve understanding and using the available data. Training is tailored to the users and can be one-to-one or group training, and can be provided face-to-face or online via Microsoft Teams. Training for key users for each commission is included in the purchase price. Training videos and materials are available.

Costs

Technology costs

The NPi-200 consists of 2 components, the NeurOptics NPi-200 automated pupillometer and the NeurOptics NPi-200 'SmartGuard'. The SmartGuard reader is necessary to integrate the data into the electronic medical record. The barcode scanner avoids the need for manual input of patient data.

- NeurOptics NPi-200 automated pupillometer: £4,155
- NeurOptics NPi-200 SmartGuard: £396 for 24
- Barcode scanner and charging cradle by socket: £475 to £595
- SmartGuard reader: £150 to £195.

The company states that the NeurOptics NPi-200 automated pupillometer has an initial cost of about £4,000, which over a 5-year period with a cohort of 800 patients per year amounts to £1.00 per patient. The NeurOptics NPi-200 SmartGuard costs £16.50 per device. Each SmartGuard has an inbuilt radio-frequency identification chip that stores up to 168 paired measurements, which is enough for hourly pupil examinations over a typical 7-day stay in critical care (336 data sets per £16.50 or £0.049 per data set). The total cost of the NeurOptics NPi-200 and SmartGuard per patient for a 7-day stay in a critical care unit is therefore £17.50, or £2.50 per day.

Costs of standard care

Pupillary reactions are usually taken manually using a pen torch. One expert said that a pen torch costs approximately £1.50 and that most staff purchase their own.

Resource consequences

The company states that the technology is currently used in 28 NHS trusts.

The company claims that the use of the automated pupillometry can save valuable nursing time.

The raw data obtained from the automated pupillometer can be included in patient notes and changes tracked over time like other vital signs.

Regulatory information

NPi-200 is a CE-marked class I medical device.

The following manufacturer field safety notices or medical device alerts for this technology have been identified:

NeurOptics NPi-200, MAUDE report number 6913426, September 2017. It was reported that the charger docking station had a design error, with the charger burning out within 60 days of operation. This was resolved in January 2018.

The Medicines and Healthcare products Regulatory Agency said that the complaint seems to be from a single device user and does not have an associated recall or other field safety corrective action from the manufacturer. The affected component is the power supply, which is likely to be different in the UK and therefore has limited relevance to the UK market.

Equality considerations

NICE is committed to promoting equality of opportunity, eliminating unlawful discrimination and fostering good relations between people with particular protected characteristics and others.

Older people and people with poor health or pre-existing conditions are more likely to be admitted to critical care units. NPi-200 is intended for use in critically ill people. Age and disability are protected characteristics under the Equality Act (2010).

Clinical and technical evidence

A literature search was carried out for this briefing in accordance with NICE's interim process and methods statement for the production of medtech innovation briefings. This briefing includes the most relevant or best available published evidence relating to the clinical effectiveness of the technology. Further information about how the evidence for this briefing was selected is available on request by contacting mibs@nice.org.uk.

Published evidence

There are 6 studies summarised in this briefing, including a total of 1,217 people.

All studies are observational, with 2 being multicentre studies and most studies investigating the prognostic value of the NPi-200. There are further studies that are not summarised here.

The clinical evidence and its strengths and limitations is summarised in the overall assessment of the evidence.

Overall assessment of the evidence

The evidence for the technology is of low methodological quality, and most of the studies are small in terms of patient numbers. For 2 of the studies it was unclear in which country the study took place, and none of the studies were done in the UK. Only 2 studies had a comparator, however they did not report on patient outcomes. The studies show that NPi-200 can predict poor outcomes in critically ill people. Further evidence comparing NPi-200 with standard care, with a large sample size is needed.

Robba et al. (2019)

Study size, design and location

A single-centre prospective observational study of 112 critically ill people.

Intervention and comparator(s)

Neurolight Algiscan (NL) and NPi-200 compared with standard pupillary light reflex (PLR).

Key outcomes

There was a significant correlation between the 2 automated pupillometry devices for pupil size, constriction to light stimulation and constriction velocity, but not for pupillary latency. The NL and the NPi-200 devices' mean bias for pupil size was -0.12 mm (limit of agreement [LoA] -1.29 mm to 1.06 mm), for pupil constriction -1.0% (LoA -9.3% to 7.2%), and for latency 0.02 ms (LoA 0.22 ms to 0.25 ms). There was a significant correlation between pupil size evaluated by clinical examination and by the NL or NPi-200 devices. The mean biases for pupil size measured using NL and NPi-200 and clinical examination were 0.16 mm (LoA -0.99 mm to 1.32 mm) and 0.21 mm (LoA 3.03 mm to 3.30 mm), respectively. Although there was significant correlation between NL and NPi-200 values and clinical examination of the PLR, the 2 devices were not always interchangeable, especially for the evaluation of pupillary latency.

Strengths and limitations

This study compares 2 automated pupillary devices to each other and to standard care (pen torch). The devices were used in random order. This study did not assess the effect of automated pupillary findings on patient outcomes. Furthermore, neurological pupil index (NPi) was not assessed as this was not available in both devices. It is unclear in which country the study took place.

Miroz et al. (2019)

Study size, design and location

A prognostic observational cohort study in Switzerland of 100 people who had been

sedated and were undergoing mechanically ventilated venoarterial extracorporeal membrane oxygenation (VA-ECMO) therapy.

Intervention and comparator(s)

NPi-200 pupillometer.

Key outcomes

Non-survivors (n=57) had significantly lower NPi than survivors at all time points (all p<0.01). Abnormal NPi (less than 3, at any time from 24 hours to 72 hours) was 100% specific for 90-day mortality, with no false positives. Adding the 12-hour PREDICT VA-ECMO score to the NPi provided the best prognostic performance (specificity 100%, 95% confidence interval [CI] 92 to 100; sensitivity 60%, 95% CI 46 to 72; area under the receiver operating characteristic curve [AUC] 0.82). Quantitative NPi alone had excellent predictive ability for poor outcome from day 1 after VA-ECMO insertion, with no false positives. Combining NPi and 12-hour PREDICT VA-ECMO score increased the sensitivity of outcome prediction, while maintaining 100% specificity.

Strengths and limitations

This is the first clinical study testing the role of automated pupillometry as a neuromonitoring tool for the early prediction of outcome in people receiving VA-ECMO. One of the authors is consultant to and a member of the scientific advisory board of NeurOptics.

Riker et al. (2019)

Study size, design and location

A prospective diagnostic accuracy study of 55 adults given targeted temperature management after initial cardiac arrest.

Intervention and comparator(s)

NPi-200 pupillometer.

Key outcomes

All 9 people with 1 or more non-reactive pupil (NPi=0) within 6 hours (range 2 hours) after recovery of spontaneous circulation (ROSC) died, and 86% (12 of 14) with sluggish pupils (NPi less than 3) had poor outcomes. Out of 29 people with normal pupil reactivity (NPi of 3 or more), 15 (52%) had poor outcomes. During targeted temperature management, 95% (20 of 21) of people with non-reactive pupils had poor outcomes, 64% (9 of 14) of people with sluggish pupils had poor outcomes, and 45% (9 of 20) of people with normal pupil reactivity had poor outcomes. Pupil size did not predict outcome, but NPi (AUC 0.72 [0.59 to 0.86]; p<0.001), PLR constriction percentage (AUC 0.75 [0.62 to 0.88]; p<0.001) and constriction velocity (AUC 0.78 [0.66 to 0.91]; p<0.001) at 6 hours predicted poor outcome. The best predictor of poor outcome in the first 6 hours after ROSC was an NPi less than 3.7. Very early after resuscitation from cardiac arrest, abnormal NPi and PLR measurements by pupillometer are predictive of poor outcome and are not usually associated with dilated pupils.

Strengths and limitations

It is possible that some results may present false positives. A convenience sample was taken. It is unclear in which country the study took place.

Oddo et al. (2018)

Study size, design and location

A prospective observational multicentre study of 456 comatose adults at day 1 and day 2 after cardiac arrest, in 10 European countries.

Intervention and comparator(s)

NPi-200 pupillometer compared with standard manual PLR (sPLR).

Key outcomes

Between day 1 and 3, an NPi of 2 or less had a 51% (95% CI 49 to 53) negative predictive value (NPV) and a 100% positive predictive value (PPV; 0% false-positive rate, 95% CI 0 to 2), with a 100% (95% CI 98 to 100) specificity and 32% (95% CI 27 to 38) sensitivity for the prediction of unfavourable outcome. Using the cut-off of abnormal NPi (less than 3)

increased sensitivity (38%, 95% CI 32 to 44) but at the expense of a lower specificity (96%, 95% CI 92 to 98; 6% false-positive rate). Compared with NPi, sPLR had significantly lower PPV and significantly lower specificity (p<0.001 at day 1 and day 2; p=0.06 at day 3). The combination of NPi of 2 or less with bilaterally absent somatosensory evoked potentials (SSEP; n=188 patients) provided higher sensitivity (58% [95% CI 49 to 67] compared with 48% [95% CI 39 to 57] for SSEP alone), with comparable specificity (100% [95% CI 94 to 100]).

Strengths and limitations

This study indicates that quantitative pupillometry had higher accuracy than sPLR in predicting poor outcome after cardiac arrest, with no false positives, and significantly higher specificity than standard manual pupillary examination.

Obling et al. (2019)

Study size, design and location

An observational study in Denmark of 221 resuscitated comatose people in 3 groups: out of hospital cardiac arrest (OHCA), in hospital cardiac arrest (IHCA) and other including with cardiac diagnoses.

Intervention and comparator(s)

NPi-200 pupillometer.

Key outcomes

Information about 30-day mortality was available for all people in the study. 135 people had OHCA and 51 (38%) people died within 30 days. The median NPi values were 4.10 (interquartile range [IQR] 0.60) in survivors compared to 2.80 (IQR 3.43) in people who did not survive (p<0.0001). Higher NPi values were independently associated with a lower 30-day mortality (odds ratio 0.15, 95% CI 0.06 to 0.29; p<0.0001), and the univariable model had an AUC of 0.87, with a maximal AUC cut-off level for NPi being 3.30 (sensitivity 69% and specificity 93%, PPV 85% and NPV 83%). For people with IHCA and other cardiac diagnoses, they found no association between NPi values and 30-day mortality, and the univariable models showed poor predictive values.

Strengths and limitations

This study highlights that automated infrared pupillometry is a promising prognostic tool in patients following resuscitation from OHCA.

Al-Obaidi et al. (2019)

Study size, design and location

A prospective observational multicentre replication study of 273 people (16,221 pupillary observations) in neurocritical care units in the US.

Intervention and comparator(s)

NPi-200 pupillometer.

Key outcomes

Analysis of t-test indicates statistically significant differences for all right and left mean pupilometer values, except right latency (p=0.3000) and repeated measure mixed model (p=0.0001). In people with increased intracranial pressure, mean pupilometer values for left NPi, pupil dilation, pupil size and constriction velocity were lower for both eyes compared with people with normal intracranial pressure. Values were higher in both eyes for people with increased intracranial pressure compared with normal intracranial pressure for right NPi (3.98 and 3.92 respectively; p=0.0300) and left latency (0.27 and 0.25 respectively; p<0.0001). Worsening measures of the PLR using automated pupillometry are associated with elevated intracranial pressure.

Strengths and limitations

The findings from this replication study confirm and extend those of McNett et al. (2018). The registry used in this study was partially funded by NeurOptics, the company that produced the pupillometer.

Recent and ongoing studies

- Establishing Normative Data for Pupillometer Assessments in Neuro-Intensive Care (ENDPANIC). ClinicalTrials.gov Identifier: NCT02804438. Status: recruiting. Indication: neuro-intensive care unit patients. Devices: NeurOptics NPi-200. Estimated completion date: September 2022. Country: US.
- Effects of Volatile and Intravenous Anesthetics on Pupillary Function. ClinicalTrials.gov Identifier: NCT03987529. Status: not yet recruiting. Indication: abnormal pupillary functions. Devices: NeurOptics NPi-200. Estimated completion date: February 2021. Country: South Korea.

The company states that it is aware of 2 further UK studies in development.

Expert comments

Comments on this technology were invited from relevant patient organisations and clinical experts working in the field. The comments received are individual opinions and do not represent NICE's view.

All 3 experts were familiar with and had used this technology before.

Level of innovation

All experts said that the NPi-200 is innovative compared with a pen torch. The technology is innovative because it offers an objective measure of pupil size and response and potential trends in intracranial pressure. One expert said that the metric can be compared against previous readings done by different professionals, reducing inter- and intra-observer variability. Experts were not aware of any other competing or alternative technologies available to the NHS.

Potential patient impact

All experts said that using NPi-200 provides an objective, standardised and accurate measure of pupil size and reactivity. Two experts also said that it has the potential to speed up the identification of patient deterioration and provide early intervention to neurological emergency. Experts noted that NPi-200 would be of benefit to people with

acute brain injury or neurological impairment. Another expert said that NPi-200 has the potential to improve outcomes in people with raised intracranial pressure and brain trauma. Finally, 1 expert said that the use of the NPi-200 has the potential to improve outcomes by identifying changes in a person's clinical condition that otherwise could have been missed.

One expert said that 20% of intensive treatment unit (ITU) admissions had their neurological pupil index (NPi) measurements taken at some point during their admission. Another expert noted that NPi can be used for 550 to 600 patients per annum in their intensive care unit.

Potential system impact

Two experts noted that NPi-200 will cost more than the relatively inexpensive pen torch. Two experts do not expect an impact on the number of staff, or a reduction in other equipment needed as nurses will still carry a pen torch for other reasons. One expert said that NPi-200 has the potential to reduce overall cost across the whole pathway through a potential reduction in CT scanning and a reduced length of stay. It may also lead to earlier decisions to carry out brainstem testing and potentially improve the possibility of organ donation. Two experts expect a quicker response to changes in pupil size and reactivity and reduced inter-observer variability. Early intervention in raised intracranial pressure may improve functional outcomes. One expert also said that this may lead to changes in patient management. One expert noted that the use of NPi-200 has changed clinical management in their ITU regarding the decision to perform CT scans, earlier brainstem testing, and changes in medical management such as increasing target mean arterial pressure in response to a decrease in NPi.

All experts said that a short training session of about 30 minutes is needed for staff. None of the experts were aware of any safety concerns surrounding this technology.

General comments

One expert said that they use NPi-200 regularly and that it is particularly useful for people who are unconscious or paralysed. However, it can be difficult to use in small infants who are not paralysed. Another expert said that nursing staff felt that the objective nature of the NPi-200 takes away a burden of responsibility when assessing pupils, which they know may influence patient management. Nursing staff also felt that more than 1 NPi-200 device is needed per unit.

Two experts noted that NPi-200 would be in addition to current standard care, while 1 expert said that NPi-200 has the potential to replace current standard care. No barriers to adoption have been identified by the experts, apart from 1 expert noting the cost could be an obstacle.

One expert said that NPi-200 has the potential to provide a reproducible metric that can be used to monitor depth of sedation, progression of illness or presence of raised intracranial pressure. Even though the evidence does not appear to address this, the benefits remain possible.

Two experts said that further research is needed to address the uncertainty in the evidence base, including research in children and research on intracranial pressure. One expert expressed the need for high quality randomised controlled trials to demonstrate clinically relevant benefits to support investment in the technology.

Expert commentators

The following clinicians contributed to this briefing:

- Dr Helen Turnham, consultant in paediatric critical care medicine, Oxford University Hospitals NHS Trust. Did not declare any interests.
- Dr Simon Raby, consultant in neurocritical care, Oxford University Hospitals NHS Trust. Did not declare any interests.
- Dr Anthony K Parsons, specialty lead for ICU and anaesthesia, Ashford and St. Peters NHS Foundation Trust. Did not declare any interests.

Development of this briefing

This briefing was developed by NICE. NICE's interim process and methods statement for the production of medtech innovation briefings sets out the process NICE uses to select topics, and how the briefings are developed, quality-assured and approved for publication.

Update information

Minor changes since publication

August 2022: Costings of the Smartguard device were updated throughout.

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IFAR: International Forum of Allergy & Rhinology

ORIGINAL ARTICLE

Temperature-controlled radiofrequency device treatment of the nasal valve for nasal airway obstruction: A randomized controlled trial

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Background: Nasal valve collapse is one of several causes of nasal obstruction. The safety and efficacy of a temperature-controlled radiofrequency (RF) device for the treatment of the nasal valve for nasal airway obstruction (NAO) has been established in single-arm studies. The objective of this trial was to compare active device treatment against a sham procedure (control).

Methods: In a prospective, multicenter, single-blinded, randomized controlled trial (RCT), patients were assigned to bilateral temperature-controlled RF treatment of the nasal valve (n = 77) or a sham procedure (n = 41), in which no RF energy was transferred to the device/treatment area. The device was applied to the mucosa over the lower lateral cartilage on the lateral nasal wall. The primary endpoint was responder rate at 3 months, defined as a ≥20% reduction in Nasal Obstruction Symptom Evaluation (NOSE)-scale score or ≥1 reduction in clinical severity category.

Results: At baseline, patients had a mean NOSE-scale score of 76.7 (95% confidence interval [CI], 73.8 to 79.5) and 78.8 (95% CI, 74.2 to 83.3) ($p = 0.424$) in the active treatment and sham-control arms, respectively. At 3 months, the responder rate was significantly higher in the active treatment arm (88.3% [95% CI, 79.2%-93.7%] vs 42.5% [95% CI, 28.5%-57.8%]; $p < 0.001$). The active treatment arm had a significantly greater decrease in NOSE-scale score (mean, −42.3 [95% CI, −47.6 to −37.1] vs −16.8 [95% CI, −26.3 to −7.2]; $p < 0.001$). Three adverse events at least possibly related to the device and/or procedure were reported, and all resolved.

Conclusion: This RCT shows temperature-controlled RF treatment of the nasal valve is safe and effective in reducing symptoms of NAO in short-term follow-up.

KEYWORDS
nasal valve, nasal valve collapse, nasal obstruction, radiofrequency, nasal congestion, NOSE scale, randomized controlled trial

2023 HCPCS Code Review

1) Vaccine counseling codes (G0310-G0315)
    a. Codes
        i. **G0310** - Immunization counseling by a physician or other qualified health care professional when the vaccine(s) is not administered on the same date of service, 5-15 minutes. (This code is used for Medicaid billing purposes.)
        ii. **G0311** - Immunization counseling by a physician or other qualified health care professional when the vaccine(s) is not administered on the same date of service, 16-30 minutes. (This code is used for Medicaid billing purposes.)
        iii. **G0312** - Immunization counseling by a physician or other qualified health care professional when the vaccine(s) is not administered on the same date of service for ages under 21, 5-15 minutes. (This code is used for Medicaid billing purposes.)
        iv. **G0313** - Immunization counseling by a physician or other qualified health care professional when the vaccine(s) is not administered on the same date of service for ages under 21, 16-30 minutes. (This code is used for Medicaid billing purposes.)
        v. **G0314** - Immunization counseling by a physician or other qualified health care professional for COVID-19, ages under 21, 16-30 minutes. (This code is used for the Medicaid EPSDT benefit).
        vi. **G0315** - Immunization counseling by a physician or other qualified health care professional for COVID-19, ages under 21, 5-15 minutes. (This code is used for the Medicaid EPSDT benefit).
    b. Information: Six new HCPCS codes were released in early 2022 by CMS for use in counseling patients and guardians regarding vaccines when the vaccine is not administered (for example, if a parent declines the vaccine). Currently, vaccine counseling is only included as part of the CPT code for vaccine administration. CMS intends that these new HCPCS codes be used for stand-alone vaccine counseling and is requiring coverage of the under-21 codes as part of the EPSDT benefit. These codes will be very useful to providers who spend extensive time in vaccine counseling but the patient/guardian decides to decline the vaccine. The under-21 versions of these codes were intended to be opened early this year per CMS directive. HSD opened these codes when HERC staff became aware of them, with the vaccine program staff approval.
    c. **HERC staff recommendation**:
        i. Add HCPCS G0310-G0315 to the Ancillary Procedures File
            1. This will allow use at any type of visit and with any visit diagnosis when vaccine counseling is done by a provider

2) Home COVID testing (K1034)
    a. Code: **K1034** Provision of covid-19 test, nonprescription self-administered and self-collected use, fda approved, authorized or cleared, one test count
    b. Information: CMS released a new HCPCS code for home COVID-19 tests in spring 2022. HSD has already opened this code to allow the testing required by the American Rescue Plan legislation. HSD staff report that the HCPCS code is in the Durable Medical Equipment file (similar to the Ancillary file).
    c. **HERC staff recommendation**:
        i. Affirm the placement of K1034 on the Ancillary File

3) Doula services (T1032-T1033)
    a. Codes
        i. **T1032** Services performed by a doula birth worker, per 15 minutes
        ii. **T1033** per diem
    b. Information: Two new HCPCS codes were released in October 2022 by CMS for use by doulas. A Doula is a birth companion who provides personal, nonmedical support to women and families throughout a woman's pregnancy, childbirth, and post-partum experience. OHA is currently paying for doula services using a modifier added to the CPT codes for vaginal or other types of delivery. Doulas are certified under the traditional health worker certification process by OHA and then added to the state registry. The certification requirements can be found at https://www.oregon.gov/oha/OEI/Pages/THW_birthdoulas.aspx. Currently, the rate is $350 per delivery, which includes two visits before delivery, delivery care, and two visits after delivery. If the doula is present for only the delivery, the rate is $150. Of note, Oregon just received CMS approval to increase birth doula rates from $350 up to $1500.
    c. HERC staff consulted with HSD staff and with the staff who administer the doula program, and the new HCPCS codes were recommended for addition to line 1 PREGNANCY. The doula community has asked for this coverage and adding this code to line 1 would align with OHA's goal of expanding access to doula care.
    d. **HERC staff recommendation**:
        i. Add HCPCS T1032-T1033 to line 1 PREGNANCY

DEPARTMENT OF HEALTH & HUMAN SERVICES
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SHO # 22-002

RE: Medicaid and CHIP Coverage of Stand-alone Vaccine Counseling

May 12, 2022

Dear State Health Official:

The Centers for Medicare & Medicaid Services (CMS) is issuing this guidance on Medicaid and Children's Health Insurance Program (CHIP) coverage and payment for "stand-alone vaccine counseling." The term "stand-alone vaccine counseling" refers to when a patient and/or caregiver receives counseling about a vaccine from a health care practitioner but the patient does not actually receive the vaccine dose at the same time as the counseling (i.e., there is no actual delivery or injection of a vaccine during the practitioner visit) because it is not appropriate to provide the vaccine dose at that time (such as when the patient and/or caregiver does not consent to the patient receiving the vaccine dose at that time).[1]

The policies discussed in this guidance generally apply beginning December 2, 2021, which was when they were first announced.[2] CMS shared further details with states on an all-state call on December 9, 2021.[3]

Overview

CMS interprets the Medicaid Early and Periodic Screening, Diagnostic, and Treatment (EPSDT) benefit to require states to provide coverage of stand-alone vaccine counseling to Medicaid beneficiaries under the age of 21 who are eligible for EPSDT.[4] This interpretation applies to stand-alone vaccine counseling related to all vaccines covered for beneficiaries eligible for EPSDT.

[1] When we refer to stand-alone vaccine counseling we do not mean that no other care or services are provided other than the vaccine counseling. Rather, we simply mean that the vaccine is not injected or delivered during the same practitioner visit as the counseling about the vaccine. Stand-alone vaccine counseling could be provided as a component of a practitioner visit in which other services are also rendered.
[2] https://www.cms.gov/newsroom/press-releases/biden-harris-administration-makes-100-federal-medicaid-matching-funds-available-state-expenditures.
[3] https://www.medicaid.gov/state-resource-center/downloads/vaccine-counseling-for-medicaid-chip-beneficiaries.pdf
[4] Unless stated otherwise, all references to Medicaid beneficiaries also include beneficiaries enrolled in Medicaid-expansion CHIPs.

Additionally, section 9811 of the American Rescue Plan Act of 2021 (Pub. L. No. 117-2) (ARP) requires state Medicaid programs to cover COVID-19 vaccine administration without cost-sharing and makes a 100 percent Federal Medical Assistance Percentage (FMAP) temporarily available for state Medicaid expenditures on COVID-19 vaccines and their administration.

CMS interprets the references in ARP section 9811 to the administration of a COVID-19 vaccine, including in section 1905(a)(4)(E) and (hh) of the Social Security Act (the Act), to include stand-alone COVID-19 vaccine counseling, when this counseling is covered for Medicaid beneficiaries under the age of 21 who are eligible for EPSDT.

State expenditures on stand-alone COVID-19 vaccine counseling are federally matched at 100 percent under the ARP only when this counseling is provided to Medicaid beneficiaries who are eligible both for EPSDT and the COVID-19 vaccination coverage required under the ARP. States have the option to cover stand-alone vaccine counseling for Medicaid beneficiaries who are not eligible for EPSDT. State expenditures on stand-alone COVID-19 vaccine counseling for beneficiaries not eligible for EPSDT, and state expenditures on stand-alone vaccine counseling related to vaccines other than COVID-19 vaccines, are federally matched at the otherwise applicable FMAP, not at the ARP 100 percent FMAP.

Because EPSDT is not a requirement in a separate CHIP, different policies apply in separate CHIPs, as discussed below.

Background

As of January 2022, Medicaid and CHIP enrollment totaled approximately 86.9 million individuals, including over 40.1 million children.[5] The number of children enrolled represents 47.3 percent of total Medicaid and CHIP enrollment. Medicaid beneficiaries currently have some of the lowest reported COVID-19 vaccination rates among those for whom the COVID-19 vaccines are recommended.[6]

Stand-alone vaccine counseling has been shown to help address vaccine hesitancy by helping beneficiaries and their families learn about vaccines from trusted health care providers. Coverage of stand-alone vaccine counseling could help states increase COVID-19 and other vaccination rates for Medicaid and CHIP beneficiaries, especially among children. Survey data have shown that a large percentage of parents are hesitant to have their children vaccinated, even when they have received the COVID-19 vaccination themselves, and that they are most comfortable having their children vaccinated by their trusted health care provider.[7] The American Academy of Pediatrics (AAP) recommends that providers address parental questions regarding vaccines and

[5] https://www.medicaid.gov/medicaid/program-information/medicaid-and-chip-enrollment-data/report-highlights/index html.
[6] https://www.commonwealthfund.org/blog/2021/how-can-states-improve-covid-19-vaccination-rates-in-medicaid
[7] https://www.medicaid.gov/state-resource-center/downloads/cmcs-all-state-call-11092021.pdf

notes the importance of counseling to address parental anxiety and misinformation.[8] This is particularly vital for parents of children with disabilities and chronic conditions, many of whom the Centers for Disease Control and Prevention (CDC) advises may be at higher risk than their peers for severe outcomes of COVID-19.[9] Additionally, data indicates that people from racial and ethnic minority groups are more likely to die from COVID-19 at younger ages than non-Hispanic white people.[10]

During the COVID-19 Public Health Emergency (PHE), there has been a decline in the number of all childhood vaccines provided to Medicaid and CHIP populations, except for influenza.[11] Vaccine counseling is an important tool available for all vaccinations, but is particularly important during the COVID-19 PHE, as families seek to have their children receive routine vaccinations and well-child visits.

Coverage of Stand-alone Vaccine Counseling

Medicaid Coverage of Stand-alone Vaccine Counseling

States have long had the option to cover stand-alone vaccine counseling in Medicaid. State expenditures on this counseling have historically been federally matched at the regularly applicable FMAP.

Coverage of Stand-alone Vaccine Counseling for Beneficiaries Eligible for EPSDT

As of December 2, 2021, CMS interprets the Medicaid EPSDT benefit to require states to provide coverage of stand-alone vaccine counseling to Medicaid beneficiaries under the age of 21 who are eligible for EPSDT. This interpretation is based on section 1905(r)(1)(B)(v) of the Act, under which states are required to cover "health education" as part of the EPSDT benefit. Under this updated interpretation of the EPSDT benefit, states **must** cover stand-alone vaccine counseling for all vaccines covered under EPSDT, including both COVID-19 and non-COVID-19 vaccines, regardless of the federal matching percentage for their expenditures on the stand-alone vaccine counseling. States may establish limits on the number of times stand-alone vaccine counseling is covered for a beneficiary eligible for EPSDT, as long as the limits can be exceeded based on medical necessity. Stand-alone vaccine counseling may also be covered when provided via telehealth, at state option.[12]

Coverage of Stand-alone COVID-19 Vaccine Counseling for Beneficiaries Eligible for EPSDT

Section 9811 of the ARP established a mandatory Medicaid benefit at section 1905(a)(4)(E) of the Act for COVID-19 vaccines and their administration and amended various sections of the

[8] https://publications.aap.org/pediatrics/article/138/3/e20162146/52702/Countering-Vaccine-Hesitancy
[9] https://www.cdc.gov/coronavirus/2019-ncov/hcp/clinical-care/underlyingconditions.html#accordion-1-card-
[10] https://www.cdc.gov/coronavirus/2019-ncov/hcp/clinical-care/underlyingconditions html#accordion-1-card-
[11] https://www.medicaid.gov/state-resource-center/downloads/covid-19-medicaid-data-snapshot-08-31-2021.pdf
[12] States generally have a great deal of flexibility with respect to covering Medicaid services provided via telehealth. See https://www.medicaid.gov/medicaid/benefits/downloads/medicaid-chip-telehealth-toolkit.pdf.

Act, including sections 1902(a)(10), 1905, 1916(a)(2), 1916(b)(2), 1916A(b)(3)(B), and 1937 of the Act.[13] Under the ARP's amendments, state Medicaid programs must cover COVID-19 vaccine administration without cost-sharing, for a specified period of time, and 100 percent FMAP is available for state Medicaid expenditures on COVID-19 vaccine administration.[14] The requirement to cover COVID-19 vaccines and their administration without cost-sharing generally applies beginning March 11, 2021 and ending on the last day of the first calendar quarter that begins one year after the last day of the COVID-19 PHE (referred to herein as the "ARP coverage period").[15] The applicable period for the 100 percent FMAP is slightly different, as discussed further below.

CMS's interpretation of the EPSDT benefit to include stand-alone vaccine counseling affects how CMS interprets the amendments made by the ARP. Specifically, as of December 2, 2021, CMS interprets the references in ARP section 9811 to the administration of a COVID-19 vaccine, including in section 1905(a)(4)(E) and (hh) of the Act, to include stand-alone COVID-19 vaccine counseling, when this counseling is covered for Medicaid beneficiaries under the age of 21 who are eligible both for EPSDT and the ARP COVID-19 vaccination coverage.[16] This means that states are required to cover this counseling for those beneficiaries, without cost-sharing. An overview of how CMS interprets the Medicaid statute to require coverage of this stand-alone COVID-19 vaccine counseling was provided to states on the CMS All-State Call held on December 9, 2021 and the corresponding presentation can be accessed on Medicaid.gov.[17]

Additionally, CMS will match state expenditures on stand-alone COVID-19 vaccine counseling for Medicaid beneficiaries who are eligible both for EPSDT and the ARP COVID-19 vaccination coverage at the 100 percent FMAP available under the ARP for state expenditures on COVID-19 vaccine administration. This 100 percent FMAP is available beginning on April 1, 2021 and ending on the last day of the first quarter that begins one year after the last day of the COVID-19 PHE (referred to herein as the "ARP FMAP period").[18]

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[13] For more information on the COVID-19 vaccination coverage requirements under the ARP, see section II of *Coverage and Reimbursement of COVID-19 Vaccines, Vaccine Administration, and Cost-Sharing under Medicaid, the Children's Health Insurance Program, and Basic Health Program* (Vaccine Toolkit), https://www.medicaid.gov/state-resource-center/downloads/covid-19-vaccine-toolkit.pdf.

[14] Nearly all Medicaid beneficiaries are eligible for this coverage, but there are a few limited exceptions. For example, persons eligible only for Medicaid coverage of Medicare premiums under sections 1902(a)(10)(E) or 1933 of the Act are not eligible for it. *See* ARP § 9811 generally, and, in particular, ARP § 9811(a)(2)(F) (adding clause XIX to the language following section 1902(a)(10)(G) of the Act).

[15] The optional COVID-19 group at section 1902(a)(10)(A)(ii)(XXIII) of the Act receives this coverage only through the last day of the COVID-19 PHE. No federal financial participation is available for any state expenditures on benefits for this group, including coverage of COVID-19 vaccinations, after the PHE ends.

[16] https://www.cms.gov/newsroom/press-releases/biden-harris-administration-makes-100-federal-medicaid-matching-funds-available-state-expenditures.

[17] https://www.medicaid.gov/state-resource-center/downloads/vaccine-counseling-for-medicaid-chip-beneficiaries.pdf

[18] For more information about the ARP 100 percent FMAP and the ARP FMAP period, see State Health Official (SHO) Letter #21-004 at https://www medicaid.gov/federal-policy-guidance/downloads/sho-21-004.pdf

After the ARP FMAP period expires, federal matching for state Medicaid expenditures on COVID-19 vaccine administration, including on stand-alone COVID-19 vaccine counseling for persons who are eligible both for EPSDT and the ARP COVID-19 vaccination coverage, will revert to the regularly applicable FMAP.

These policies **only** apply when stand-alone COVID-19 vaccine counseling is covered for persons who are eligible both for EPSDT and the ARP COVID-19 vaccination coverage.

Coverage of Stand-alone Vaccine Counseling for Beneficiaries Not Eligible for EPSDT

There is no benefit or coverage requirement comparable to EPSDT or its health education requirement for Medicaid beneficiaries age 21 and older. Additionally, some Medicaid beneficiaries under age 21 are not eligible for EPSDT. However, states continue to have the option to cover stand-alone vaccine counseling (including stand-alone vaccine counseling related to the COVID-19 vaccines) for Medicaid beneficiaries who are not eligible for EPSDT. State expenditures on stand-alone COVID-19 and other vaccine counseling for all Medicaid beneficiaries who are not eligible for EPSDT will be matched at the applicable FMAP, not at the ARP 100 percent FMAP.

CHIP Coverage of Stand-alone Vaccine Counseling

Section 9821 of the ARP added a mandatory COVID-19 vaccination benefit for separate CHIPs at section 2103(c)(11)(A) of the Act and amended section 2103(e)(2) of the Act. The changes require coverage of COVID-19 vaccines and their administration without cost-sharing for all separate CHIP enrollees, and apply during the same time period as the Medicaid coverage requirements under section 9811 of the ARP. Section 9821 of the ARP also amended the CHIP statute to provide for a 100 percent CHIP federal matching rate for state expenditures on COVID-19 vaccine administration during the ARP FMAP period.

Because EPSDT is not a requirement in a separate CHIP and there is no benefit or coverage requirement comparable to EPSDT or its health education requirement for individuals in a separate CHIP, CMS does not interpret the references to COVID-19 vaccine administration added to the CHIP statute under section 9821 of the ARP to include stand-alone vaccine counseling related to a COVID-19 vaccine for a beneficiary in a separate CHIP. Therefore, separate CHIPs are not required to cover stand-alone COVID-19 vaccine counseling for beneficiaries under age 21, and states will not receive 100 percent federal matching funds under section 9821 of the ARP for their expenditures on this stand-alone vaccine counseling. States may opt to cover stand-alone COVID-19 and other vaccine counseling for children and pregnant adults enrolled in a separate CHIP, but are not required to do so. Expenditures for this stand-alone vaccine counseling will be matched at the state's enhanced federal matching percentage for Title XXI beneficiaries, not at the 100 percent federal matching percentage for COVID-19 vaccine administration under section 9821 of the ARP. Even though states are not required to cover stand-alone vaccine counseling in a separate CHIP, the majority of states have elected to follow the AAP *Bright Futures* periodicity schedule for preventive pediatric health care, which emphasizes the importance of vaccine counseling as part of CHIP required well-baby/well-child

visits.[19]

Since CMS published its December 9, 2021 slide deck on this updated interpretation of the EPSDT benefit, states and other members of the public have asked about the federal matching rate for state expenditures on stand-alone COVID-19 vaccine counseling in Medicaid-expansion CHIPs. Beneficiaries enrolled in a Medicaid-expansion CHIP under 42 CFR § 435.118 or § 435.229 are eligible for EPSDT, and states are required to cover stand-alone vaccine counseling for all pediatric vaccines covered under EPSDT for all such Medicaid-expansion CHIP beneficiaries. State expenditures on stand-alone COVID-19 vaccine counseling for these Medicaid-expansion CHIP beneficiaries will be federally matched at the 100 percent federal matching rate for COVID-19 vaccine administration under section 9821 of the ARP during the ARP FMAP period. State expenditures on stand-alone vaccine counseling provided to these Medicaid-expansion CHIP beneficiaries about all other vaccines required under the EPSDT benefit (i.e., non-COVID-19 vaccines) will be federally matched at the state's enhanced federal medical assistance percentage for Title XXI beneficiaries, not at the ARP 100 percent federal matching rate.

Medicaid and CHIP Coverage of Visits During which Beneficiaries Receive Both Counseling about COVID-19 Vaccination and the COVID-19 Vaccine Itself

CMS considers all visits during which a COVID-19 vaccine is actually delivered or injected to include COVID-19 vaccine administration under the ARP, regardless of whether counseling about the COVID-19 vaccine is also provided during the same visit. States are required to cover any actual delivery of a COVID-19 vaccine, without cost-sharing, for *all* CHIP beneficiaries and for *all* Medicaid beneficiaries eligible for COVID-19 vaccine administration coverage under the ARP. States' expenditures on the COVID-19 vaccine delivery provided during such visits will be federally matched at 100 percent in both Medicaid and CHIP during the ARP FMAP period,[20] regardless of whether counseling about COVID-19 vaccination is also provided during the same visit, and regardless of whether the visit is provided to a person who is eligible for EPSDT.

Qualified Providers

States may have licensure and scope of practice laws governing who is authorized under state law to administer vaccinations. Additionally, some federal Medicaid and CHIP regulations defining benefits under which states might opt to cover vaccine administration expressly refer to state licensure or scope of practice laws, by requiring that services be prescribed, furnished, recommended, or provided by practitioners acting within their scope of practice as defined by state law. For example, 42 CFR § 440.60 requires that Medicaid "other licensed practitioner" services be provided by practitioners acting within the scope of practice as defined under state law, and 42 CFR § 440.130(c) requires that Medicaid preventive services be recommended by

[19] https://downloads.aap.org/AAP/PDF/periodicity_schedule.pdf; https://brightfutures.aap.org/Bright%20Futures%20Documents/BF4_POCKETGUIDE.pdf (see pp. 10-11).

[20] *See* SHO Letter #21-004 for CMS guidance about allocation methods states should follow to appropriately identify and report expenditures associated with COVID-19 vaccine administration in circumstances where states make a bundled payment to providers for services that include COVID-19 vaccine administration. https://www.medicaid.gov/federal-policy-guidance/downloads/sho-21-004.pdf.

practitioners acting within the scope of authorized practice under state law.

As is discussed in greater detail in *Coverage and Reimbursement of COVID-19 Vaccines, Vaccine Administration, and Cost-Sharing under Medicaid, the Children's Health Insurance Program, and Basic Health Program* (the Vaccine Toolkit), the Secretary of Health and Human Services (HHS) issued a declaration under the Public Readiness and Emergency Preparedness (PREP) Act that authorizes certain practitioners to administer COVID-19 vaccines, subject to certain conditions set forth in the declaration.[21] The HHS COVID-19 PREP Act declaration also authorizes certain pharmacy practitioners to administer childhood vaccines to children ages three (3) through 18.[22]

The HHS Office of the General Counsel and Department of Justice Office of Legal Counsel issued advisory opinions explaining that the PREP Act and the HHS COVID-19 PREP Act declaration preempt state laws that would otherwise prohibit or effectively prohibit licensed pharmacists from ordering and administering covered countermeasures described in the HHS COVID-19 PREP Act declaration.[23] Based on the reasoning set forth in these opinions, state laws are also preempted if they would prohibit or effectively prohibit persons authorized to administer COVID-19 or childhood vaccines under the HHS COVID-19 PREP Act declaration from doing so. This means that states cannot rely on state law to prevent persons from administering COVID-19 or childhood vaccines if they are authorized to do so under the HHS COVID-19 PREP Act declaration.

As explained in more detail in the Vaccine Toolkit, because the authorizations in the HHS COVID-19 PREP Act declaration preempt conflicting state law, if a person is authorized to administer COVID-19 or childhood vaccines under the HHS COVID-19 PREP Act declaration, a state may not deny Medicaid or CHIP reimbursement to that person for the vaccine administration on the basis of a state law that is preempted by the declaration. CMS also interprets references to practitioners' state-law scope of practice in federal Medicaid and CHIP laws and regulations as incorporating the PREP Act preemption of state law. In other words, if a state law is currently preempted by the PREP Act and HHS's COVID-19 PREP Act declaration and authorizations, CMS would interpret a reference to that state law in a federal Medicaid or

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[21] *See* Vaccine Toolkit, at section V, https://www.medicaid.gov/state-resource-center/downloads/covid-19-vaccine-toolkit.pdf. The Vaccine Toolkit contains citations to the HHS COVID-19 PREP Act declaration and related authorizations, but they are also available at https://aspr hhs.gov/legal/PREPact/Pages/default.aspx.

[22] *See* Third Amendment to Declaration Under the Public Readiness and Emergency Preparedness Act for Medical Countermeasures Against COVID-19, 85 Fed. Reg. 52,136 (Aug. 24, 2020), at https://www.govinfo.gov/content/pkg/FR-2020-08-24/pdf/2020-18542.pdf; Eighth Amendment to Declaration Under the Public Readiness and Emergency Preparedness Act for Medical Countermeasures Against COVID-19, 86 Fed. Reg. 41,977 (Aug. 4, 2021), https://www.federalregister.gov/documents/2021/08/04/2021-16681/eighth-amendment-to-declaration-under-thepublic-readiness-and-emergency-preparedness-act-for.

[23] Advisory Opinion 20-02 on the Public Readiness and Emergency Preparedness Act and the Secretary's Declaration under the Act, May 19, 2020, https://www hhs.gov/guidance/sites/default/files/hhs-guidance-documents/advisory-opinion-20-02-hhs-ogc-prep-act.pdf. See also Department of Justice Office of Legal Counsel Advisory Opinion for Robert P. Charrow, General Counsel of the Department of Health and Human Services, January 19, 2021, available at: https://www.justice.gov/sites/default/files/opinions/attachments/2021/01/19/2021-01-19-prep-act-preemption.pdf.

CHIP statute or regulation to refer instead to the federal law preempting the state law.

Additionally, consistent with Medicaid's freedom-of-choice of provider requirement at section 1902(a)(23)(A) of the Act, CMS will expect states to provide Medicaid coverage for COVID-19 and childhood vaccinations administered by anyone who is authorized to do so under the HHS COVID-19 PREP Act declaration, during any time period when the HHS COVID-19 PREP Act declaration authorizations are in effect and Medicaid coverage of the vaccinations is mandatory. States still must meet all other applicable federal requirements for covering the applicable benefit, such as reimbursing only those providers that are enrolled as Medicaid providers and covering vaccinations only for eligible individuals.[24]

The authorizations under the HHS COVID-19 PREP Act declaration to administer COVID-19 and childhood vaccines extend to stand-alone vaccine counseling related to these vaccines that is provided to Medicaid beneficiaries who are eligible for EPSDT. CMS has determined that this stand-alone vaccine counseling, when provided as part of the EPSDT mandate, is "vaccine administration." Thus, states cannot deny Medicaid payment for this stand-alone vaccine counseling to practitioners authorized to administer COVID-19 and childhood vaccines under the HHS COVID-19 PREP Act declaration on the basis that state law would not authorize the practitioner to administer the vaccine in question. Importantly, the age range for which a practitioner is authorized to administer a vaccine under the HHS COVID-19 PREP Act declaration may be broader than what is authorized under state law, and if so, the more restrictive state law would be preempted. State Medicaid programs are expected to give all provider types authorized to administer COVID-19 and childhood vaccinations under the HHS COVID-19 PREP Act declaration an opportunity to enroll as Medicaid providers and receive Medicaid payment—not only for actually delivering or injecting the vaccines, but also for stand-alone vaccine counseling about these types of vaccinations provided to beneficiaries eligible for EPSDT. It is also important to note that the HHS COVID-19 PREP Act declaration may be in effect for longer than the COVID-19 PHE.[25]

Providers who work in school-based settings might also be qualified providers of COVID-19 or childhood vaccine administration, and states would receive 100 percent FMAP during the ARP FMAP period in payments to these providers for COVID-19 vaccine administration, including for stand-alone COVID-19 vaccine counseling for beneficiaries eligible for EPSDT.

Payment and Claims

Within the parameters of section 1902(a)(30)(A) of the Act, states have flexibility to set payment rates for stand-alone vaccine counseling. States may establish separate payment rates for stand-alone vaccine counseling, or explore other payment methodologies to recognize additional costs

[24] See discussion in section V.C of the Vaccine Toolkit for more information and examples. Although the Vaccine Toolkit is focused on COVID-19 vaccinations, the same principles would apply with respect to the HHS COVID-19 PREP Act declaration authorizations related to administration of childhood vaccines. https://www medicaid.gov/state-resource-center/downloads/covid-19-vaccine-toolkit.pdf.

[25] See section XII of the HHS COVID-19 PREP Act declaration, at 87 Fed. Reg. 982, 988 (Jan. 7, 2022), https://www federalregister.gov/documents/2022/01/07/2022-00151/tenth-amendment-to-declaration-under-the-public-readiness-and-emergency-preparedness-act-for-medical.

associated with vaccine counseling that are not otherwise paid as part of the state's usual payment rate for vaccine administration or for a comprehensive office visit.

CMS encourages states to develop a payment methodology for stand-alone COVID-19 vaccine counseling that will enable them to identify and document which state expenditures can be claimed at 100 percent FMAP because CMS considers them to be COVID-19 vaccine administration under the ARP provisions. For example, states could explore establishing a new, additional COVID-19 vaccine administration payment rate that would apply only to stand-alone counseling about the COVID-19 vaccines provided to beneficiaries who are eligible both for EPSDT and the ARP COVID-19 vaccination coverage. Such a rate could be separate from, and/or in addition to, any rate for COVID-19 vaccine administration that a state might have developed for actual injection of the vaccines, provided that the state would not pay a provider twice for any costs already built into the state's existing rate for COVID-19 vaccine administration. Establishing a separate payment rate for this stand-alone COVID-19 vaccine counseling would enable states to make separate payments to providers for that counseling, and thus might help states identify and document which expenditures should be claimed at the ARP 100 percent FMAP during the ARP FMAP period. States could also modify existing billing codes designed to help states and other payers reimburse practitioners for stand-alone COVID-19 vaccine counseling (see Coding discussion below) to identify when stand-alone COVID-19 vaccine counseling was furnished to EPSDT-eligible beneficiaries.

States that choose not to establish separate payment rates and associated billing codes for stand-alone COVID-19 vaccine counseling provided to beneficiaries who are eligible both for EPSDT and the ARP COVID-19 vaccination coverage could reimburse for this mandatory coverage through existing payment methods such as the payment rate for a comprehensive office visit or the payment rate that the state has already established for vaccine administration. In such cases, however, states claiming the ARP 100 percent FMAP must still be able to determine when their expenditures on such payments can be matched at 100 percent FMAP during the ARP FMAP period. Not having a separate Healthcare Common Procedure Coding System (HCPCS) code, Current Procedural Terminology (CPT) code, or modifier for state expenditures on stand-alone COVID-19 vaccine counseling provided to beneficiaries who are eligible both for EPSDT and the ARP COVID-19 vaccination coverage could present significant challenges in determining which state expenditures can be matched at 100 percent FMAP during the ARP FMAP period. States that do not pay a separate fee or use a separate code for stand-alone COVID-19 vaccine counseling furnished to EPSDT-eligible beneficiaries will need to work directly with their practitioner communities to determine an approach to use to document and identify which state expenditures qualify for the 100 percent FMAP. Alternatively, states may opt not to claim the ARP 100 percent FMAP for this stand-alone COVID-19 vaccine counseling, if claiming that FMAP would be too administratively and/or operationally burdensome.

States currently covering stand-alone COVID-19 vaccine counseling for Medicaid beneficiaries who are eligible both for EPSDT and the ARP COVID-19 vaccination coverage will be able to retroactively adjust claims back to April 1, 2021, to receive the 100 percent FMAP for these expenditures during the ARP FMAP period. States that newly implement Medicaid coverage of stand-alone COVID-19 vaccine counseling for beneficiaries who are eligible both for EPSDT and the ARP COVID-19 vaccination coverage can claim the 100 percent FMAP for their

expenditures on this stand-alone COVID-19 vaccine counseling on or after April 1, 2021, and throughout the ARP FMAP period.

CMS will work to ensure appropriate oversight of states' claiming and allocation methodologies and will place special emphasis on state expenditures claimed at the ARP 100 percent FMAP while conducting quarterly and annual financial reviews.

State Plan Amendments (SPAs)

Medicaid SPAs

Stand-alone COVID-19 Vaccine Counseling for Beneficiaries Eligible for EPSDT

CMS released streamlined templates for states to utilize to make state plan changes related to COVID-19 vaccine administration, testing, and treatment under the ARP. [26] States must utilize these streamlined templates to comply with the required coverage and reimbursement for stand-alone COVID-19 vaccine counseling for beneficiaries eligible for EPSDT that is discussed in this SHO Letter during the ARP coverage period. States may seek waivers under section 1135 of the Act with respect to public notice timeframes, tribal consultation timeframes, and SPA effective dates when submitting SPAs using these templates, but only during the COVID-19 PHE. CMS cannot waive or modify statutory or regulatory requirements under section 1135 of the Act after the COVID-19 PHE ends. Unlike the current disaster relief SPA templates, these new templates will allow states to extend their coverage after the end of the COVID-19 PHE through the end of the ARP coverage period without submitting a second SPA when the PHE ends.

Stand-alone Vaccine Counseling for All Other Pediatric Vaccines for Beneficiaries Eligible for EPSDT

All states should already be covering EPSDT, which requires states to cover health education and all medically necessary services that could be covered under the benefits listed in section 1905(a) of the Act for eligible children under age 21. States in compliance with this requirement are not required to submit SPA coverage pages to specifically reflect that the required stand-alone vaccine counseling is covered as part of the EPSDT benefit. States that do not currently cover and reimburse for stand-alone vaccine counseling for all other pediatric vaccines covered under EPSDT for persons eligible for the EPSDT benefit will need to submit a reimbursement SPA. A comprehensive description of the payment methodology for stand-alone vaccine counseling must be included in the reimbursement section of the Medicaid state plan.

CHIP SPAs

There is no SPA required to cover stand-alone vaccine counseling in CHIP. Coverage and

[26] https://www.medicaid.gov/resources-for-states/spa-and-1915-waiver-processing/medicaid-spa-processing-tools-for-states/index.html

payment for stand-alone vaccine counseling in Medicaid-expansion CHIPs, including when covered for beneficiaries eligible for EPSDT, would be pursuant to the state's Medicaid state plan. CMS is available to provide technical assistance to states interested in covering stand-alone vaccine counseling. States should reach out to their CHIP project officer for more information.

Coding

States should alert Medicaid and CHIP providers to the American Medical Association (AMA) and AAP published codes for reporting stand-alone COVID-19 vaccine counseling. The AMA publishes codes for all vaccines (including COVID-19 vaccines).[27] The AAP also has information on billing codes that can be used for stand-alone COVID-19 vaccine counseling on its COVID-19 vaccine administration dedicated website.[28] In addition, the AAP has information on billing codes for pediatric vaccines and vaccine counseling.

To further assist states with coding for stand-alone vaccine counseling, CMS is developing new HCPCS codes that providers may use to bill for stand-alone vaccine counseling. CMS anticipates providing more information about these codes soon.

Conclusion

CMS is eager to work with states on the implementation of Medicaid and CHIP coverage for stand-alone vaccine counseling to help increase vaccination rates for COVID-19 and other diseases. CMS is committed to increasing vaccine confidence and the promotion of vaccinations for Medicaid and CHIP beneficiaries. If you have any questions regarding this letter or would like to request technical assistance, please contact your respective CMS State Lead.

Sincerely,

Daniel Tsai
Deputy Administrator and Director

[27] https://www.ama-assn.org/practice-management/cpt/covid-19-cpt-vaccine-and-immunization-codes and https://www.ama-assn.org/practice-management/cpt/covid-19-immunization-administration-and-em-visits.
[28] https://www.aap.org/en/pages/2019-novel-coronavirus-covid-19-infections/covid-19-vaccine-for-children/covid-19-vaccine-administration-getting-paid/

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Date: July 26, 2022

To: Fee-for-service (FFS) providers
Coordinated care organizations (CCOs)

From: Nathan Roberts, Traditional Programs manager
Dave Inbody, CCO Operations manager
Medicaid Programs

Subject: FFS reimbursement for self-administered COVID-19 test kits supplied by non-pharmacy providers, effective April 4, 2022

Effective immediately, the Oregon Health Authority (OHA) now allows the following providers to bill OHA for FDA-approved, self-collected COVID-19 home test kits supplied to FFS members on or after April 4, 2022:

- Clinic/group practices
- Critical access hospitals
- Federally Qualified Health Centers
- Home health agencies
- Hospital outpatient departments
- Independent laboratories
- Indian Health Service facilities
- Opioid treatment programs
- Physicians and other practitioners
- Rural health clinics
- Skilled nursing facilities

CCOs may choose to allow additional suppliers as described above. CCOs do not need to do this if pharmacies provide sufficient member access to COVID-19 home test kits.

OHA will cover up to 8 tests per month without prior authorization or a physician's order, at $12 per test.

What should you do?

Providers: To bill OHA for FDA-approved or cleared over the counter test kits:

- Use HCPCS K1034 for professional claims and revenue code 0300 for institutional claims.
- Bill one unit of K1034 for each test. If a package contains two tests, bill two units.
- Please adjust previously submitted claims as described in the Claim Adjustment Handbook.

CCOs: Determine if you will allow additional providers to supply COVID-19 home test kits.

Also refer to the updated Oregon Medicaid COVID-19 Provider Guide for coverage and billing details.

Questions?

Providers: If you have any questions about this announcement, contact Provider Services Unit at dmap.providerservices@dhsoha.state.or.us or call 800-336-6016 (Option 5).

CCOs: If you have questions, please contact your CCO Account Representative.

Thank you for your continued support of the Oregon Health Plan and the services you provide to our members.

Section 10.0

Previously Discussed Items

Hydrocele Repair in Adults

Plain Language Summary:
Background: Consideration for coverage for adults for swelling or fluid collection in the scrotum. Left unrepaired, this can result in a hernia.

Should OHP cover this treatment? Staff recommends extending coverage for repair to adults who have pain or functional limitations due to the fluid collection.

Question: Should there continue to be limitations on hydrocele repair to children through age 18?

Question source: Ombuds office

Issue: A hydrocele is a type of swelling in the scrotum that occurs when fluid collects in the thin sheath surrounding a testicle. Hydrocele is common in newborns and usually disappears without treatment by age 1. Older boys and adult men can develop a hydrocele due to inflammation or injury within the scrotum. Hydroceles can be asymptomatic or cause pain. A symptomatic hydrocele can be surgically removed. Non-repaired communicating hydroceles can lead to inguinal hernia formation.

Recently, the Ombuds office had a case involving a recent immigrant who had a hydrocele causing pain that had not been repaired in childhood. The guideline note limiting hydrocele repair led to a denial of repair for him.

The current guideline was adopted in 2007, when hernias of any type were not repaired in persons over the age of 18.

HERC staff have done a data review, and found multiple claims for hydrocele repair in adults, all of which were paid. There were 111 paid claims for patients over age 18 between 1/2018 and 1/2022.

All private payers cover repair of hydroceles regardless of age.

This topic was discussed at the October 2022 VBBS meeting. At that meeting, members requested consideration of criteria for coverage in adults similar to the criteria outlined in the hernia guideline, as hydroceles can develop into inguinal hernias. There was also a request to look at the evidence that hydrocele repair in adults is effective at relieving pain or other symptoms.

Current Prioritized List status
Line 168 COMPLICATED HERNIAS; PERSISTENT HYDROCELE
Treatment: REPAIR
ICD-10-CM
- N43.0 Encysted hydrocele
- N43.2 Other hydrocele
- N43.3 Hydrocele, unspecified
- P83.5 Congenital hydrocele

Line 545 HYDROCELE
Treatment: MEDICAL THERAPY, EXCISION
ICD-10-CM

N43.3 Hydrocele, unspecified
N43.4 Spermatocele of epididymis
N50.89 Other specified disorders of the male genital organs
P83.5 Congenital hydrocele

GUIDELINE NOTE 63, HYDROCELE REPAIR

Line 168

Excision of hydrocele is only covered for children age 18 and younger with hydroceles which persist after 18 months of age.

GUIDELINE NOTE 24, COMPLICATED HERNIAS

Lines 168,524

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

A) Causes symptoms of intestinal obstruction and/or strangulation; OR
B) Is incarcerated (defined as non-reducible by physical manipulation); OR
C) Causes pain and functional limitations as assessed and documented by a medical professional; OR
D) Affects the patient's ability to obtain or maintain gainful employment.

Repair of inguinal and femoral hernias in women and in children age 18 or younger are included on Line 168 due to the different natural history of disease in these populations.

Ventral hernias are included on Line 524. Incarcerated ventral hernias (including incarcerated abdominal incisional and umbilical hernias) are included on Line 524, because the chronic incarceration of large ventral hernias does not place the patient at risk for impending strangulation. Ventral hernias are defined as anterior abdominal wall hernias and include primary ventral hernias (epigastric, umbilical, Spigelian), paratomal hernias and most incisional hernias (ventral incisional hernias). ICD-10-CM K42.0, K43.0, K43.3, K43.6 and K46.0 are included on Line 524 when used to designate incarcerated abdominal incisional and umbilical hernias without intestinal obstruction or gangrene

Evidence

1) **Rioja 2011**, review of hydrocele in adults https://docslib.org/doc/12605449/surgery-illustrated-surgical-atlas-adult-hydrocele-and-spermatocele-bjuibju-international-jorge-rioja-francisco-m
    a. In the adult, a hydrocele is an accumulation of excessive secretion of the vaginal mucosa; exudates collect in the non-communicative vaginal cavities. In the young adult, a communicative hydrocele must be excluded, as its treatment is similar to pediatric herniorrhaphy
    b. Surgical treatment is the gold standard for adult hydrocele.
    c. Surgical treatment is indicated when functional problems are present such as pain, discomfort or disability due to the size, but not for aesthetics only
2) **Lundstrom 2019**, epidemiology of hydrocele and spermatocele; incidence, treatment and complications

a. Cystic intra-scrotal changes such as hydroceles and spermatoceles are common in general urological practice. Small studies suggests that 10% of healthy volunteers have a small or moderate amount of extra-testicular fluid and 30% have cystic structures in the epididymis.

b. In tropical regions, mainly low income countries, it is estimated that 25,000,000 men suffer from hydrocele, due to the infection of Wuchericia bancroftii

c. Treatment includes both surgery and aspiration with or without sclerotherapy

d. hydroceles in childhood are common but have a completely different pathogenesis [than in adults]

e. In Sweden, between 2004 and 2015 the overall annual incidence of hydro and spermatoceles as main or secondary complaint for in and outpatient visits at hospital-based specialties were 98.5/100,000 men (59.9 for hydroceles and 38.5 for spermatoceles) with variation between years. Overall treatment incidence was 17.3/100,000/year corresponding to treatment of [approximately] 20% of all men diagnosed with a cystic lesion in the scrotum

f. The evidence for the indications of treatment is lacking. Also, comparative treatment studies are scarce. A recent meta-analysis on the subject found only a total of 275 patients in studies comparing surgery vs sclerotherapy. Data in the current study is not sufficient to compare cure rates between treatments

g. Conclusion: The incidence of healthcare visits for fluid collections in the scrotum is near 100/100,000 and subsequent treatment rates are low, indicating that most scrotal cysts are minimally symptomatic

Hydrocele Repair in Adults

HERC staff summary

Hydroceles are common in adult men and have a different etiology than hydroceles in children. Hydroceles are common in men from lower income countries due to infection of Wuchericia bancroftii. Repair is only recommended when functional problems are present such as pain, discomfort or disability due to the size, but not for aesthetics only.

HERC staff recommendations:

1) Change the name of line 545 to UNCOMPLICATED HYDROCELE, SPERMATOCELE
2) Modify GN 63 as shown below

GUIDELINE NOTE 63, HYDROCELE REPAIR

Line 168,545

Excision of hydrocele is only included on line 168 ~~covered~~ for children age 18 and younger with hydroceles which persist after 18 months of age. Treatment of hydrocele in men over age 18 is included on line 168 only when the hydrocele causes pain and functional limitations as assessed and documented by a medical professional.

For children under 18 months of age and men over age 18 who do not meet the above criteria, treatment of hydroceles is included on line 545.

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ARTICLE

Epidemiology of hydrocele and spermatocele; incidence, treatment and complications

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ABSTRACT

Objectives: To estimate the incidence of men seeking specialized care and receiving treatment for hydro or spermatocele complaints. Also, to determine the risk of complications of treatment.

Materials and methods: The total number of men living in Sweden each year from 2005 to 2014 was used to calculate incidence and age distribution of adult (≥18 years) men seeking specialized healthcare with either hydro or spermatocele. This was done by using nationwide registries, mandatory by law. They contain information on primary or discharge diagnosis, procedure codes and antibiotic prescriptions. Also, complication rates comparing aspiration (with or without sclerotherapy) and conventional surgery were analysed.

Results: The incidence of men with either hydro or spermatocele diagnosis in specialized healthcare was ~100/100,000 men. The treatment incidence was 17/100,000 men. Orchiectomy was used as primary treatment in 2.4% of cases. The risk of experiencing a complication was clinically and statistically significantly increased with conventional surgery as compared with aspiration, 17.5% (1607/9174) vs 4.6% (181/3920), corresponding to relative risk of 3.79 (95% CI = 3.27–4.40). Hematoma and infections were the most common complications.

Conclusion: Hydro and spermatoceles are common, affecting elderly men. Aspiration seems advantageous with respect to complications and can be recommended due to the benign course of the disease. The indication for conventional surgery might be questioned such as the use of orchiectomy as primary treatment.

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KEYWORDS
Testicular hydrocele; spermatocele; incidence; postoperative complications

Cystic intra-scrotal changes such as hydroceles and spermatoceles are common in general urological practice. Small studies suggests that ~10% of healthy volunteers have a small or moderate amount of extra-testicular fluid and 30% have cystic structures in the epididymis [1]. However, no incidence study on symptomatic hydro- or spermatoceles is published from high-income countries. Nor is there a uniform definition of the disease or a clear indication for treatment, although experts suggest only to treat subjective symptoms [2].

In tropical regions, mainly low income countries, it is estimated that 25,000,000 men suffer from hydrocele, due to the infection of Wuchericia bancroftii [3]. Treatment includes both surgery and aspiration with or without sclerotherapy. However, complications of hydrocele treatment are common [4,5]. Thus, there is a need for information on the incidence numbers, numbers of treated patients, and the spectrum of complications of treatments, including uncommon adverse events.

The aim of this study was to examine the incidence of hydro and spermatoceles in adult men (≥18 years) and their treatments and possible side-effects.

Materials and methods

Design

A population-based cohort study with data from a high coverage, national register.

Patients

Data source

The NPR is a health register of all hospital-based healthcare in Sweden. It is mandatory by law to participate in this register and has a nearly complete capture rate of discharge diagnosis, International Classification of Diseases (ICD) codes from hospital-based specialties. Primary healthcare is not included in the register, but hospital outpatient clinics are. Validation shows that 85–95% of diagnoses are valid [6].

From NPR, it is possible to extract both primary diagnosis (the actual complaint of that visit) and secondary diagnosis (findings not directly related to the visit).

Also, in the NPR, surgical procedure codes are registered as Nordic Medico-Statistical Committee (NOMESCO) codes [7].

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Section 11.0

New Discussion Items

Plain Language Summary:
Background: Human growth hormone (HGH) fuels childhood growth and helps maintain tissues and organs throughout life. It's produced by the gland located at the brain's base (pituitary). Currently, OHP limits use of HGH to children who are not yet done growing. There are other important uses which should be considered for other conditions.

Should OHP cover this treatment? Staff recommends extensive changes to the current guideline to allow limited coverage of HGH for adults and allow individualized review for HGH needs for children.

Question: Should the growth hormone guideline be deleted or extensively modified?

Question source: advocates, OHA leadership, HERC staff, P&T staff

Issue: Over the past year, several concerns have arisen regarding Guideline Note 74 GROWTH HORMONE TREATMENT.

This medication has several different formulations which have indications applying to different pediatric populations, including endocrine disorders, developmental disorders and short stature. For adults they are indicated only for growth hormone deficiency, HIV wasting or cachexia and short bowel syndrome. The medication is sometimes also used off label as anti-aging therapy and for athletic performance or for bodybuilding. This latter use is illegal in the United States.

Diagnosis code ICD-10-CM E23.0 (hypopituitarism) can be used either for a serious conditions resulting in lack of growth hormone from pituitary disease or absence or a pituitary gland, in association with several developmental syndromes or in an attempt to obtain coverage for human growth hormone used for anti-aging therapy, athletic performance or body building.

Currently, GN74 restricts growth hormone (HGH) use to children "until adult height as determined by bone age is achieved." It also specifies the conditions under which E23.0 is above or below the funding line. As a result, use in adults with FDA approved HGH indications such as pituitary malformation, post-surgical pan hypopituitary dysfunction, or HIV cachexia is not covered under OHP, and some other potentially funded indications related to pediatric-onset endocrine or developmental syndromes are not covered after adult bone age is achieved.

In addition, during OHA's waiver renewal process, an issue was raised about coverage of HGH in an adolescent with closed growth plates who had Prader-Willi syndrome, a genetic multisystem disorder characterized during infancy by lethargy, hypotonia, a weak suck and feeding difficulties with poor weight gain and growth and other hormone deficiency. Treatment of Prader-Willi syndrome in children, as well as persons who have obtained adult height, is an FDA approved indication for certain formulations of HGH.

Currently, congenital pediatric short stature is expressly not covered as the ICD-10-CM code for this condition (E34.3 family) is on line 652 ENDOCRINE AND METABOLIC CONDITIONS WITH NO OR MINIMALLY EFFECTIVE TREATMENTS OR NO TREATMENT NECESSARY. However, this is another FDA approved indication for certain formulations of HGH.

Current Prioritized List status

GUIDELINE NOTE 74, GROWTH HORMONE TREATMENT

Lines 40,386,470,652

Treatment with growth hormone should continue only until adult height as determined by bone age is achieved. ICD-10-CM E23.0 (Hypopituitarism) is included on Lines 40 and 386 for conditions other than adult human growth hormone deficiency. ICD-10-CM E23.0 is included on Line 652 only for adult human growth hormone deficiency.

The current lines referenced in GN74 are 40 PANHYPOPITUITARISM, IATROGENIC AND OTHER PITUITARY DISORDERS, 386 PITUITARY DWARFISM, 470 GONADAL DYSFUNCTION, MENOPAUSAL MANAGEMENT and 652 ENDOCRINE AND METABOLIC CONDITIONS WITH NO OR MINIMALLY EFFECTIVE TREATMENTS OR NO TREATMENT NECESSARY

Expert guideline (Adults)

1) **Yuen 2019,** AMERICAN ASSOCIATION OF CLINICAL ENDOCRINOLOGISTS AND AMERICAN COLLEGE OF ENDOCRINOLOGY GUIDELINES FOR MANAGEMENT OF GROWTH HORMONE DEFICIENCY IN ADULTS
    a. Adult GHD is a well-defined clinical entity characterized by decreased lean body mass and increased fat mass, dyslipidemia, cardiac dysfunction, decreased fibrinolysis and premature atherosclerosis, decreased muscle strength and exercise capacity, decreased bone mineral density (BMD), increased insulin resistance, and impaired QoL
    b. It is recommended that adults with childhood onset growth hormone deficiency caused by structural pituitary or brain tumors be followed up closely during transition as these patients tend to have lower bone mineral density, impaired bone microarchitecture, and more adverse body composition abnormalities and cardiovascular risk markers than those with adult onset growth hormone deficiency (Grade A; BEL 1).
    c. In the U.S., off-label distribution or marketing of GH for the enhancement of athletic performance or to treat aging or aging-related conditions is illegal and punishable by imprisonment. Under no circumstances should rhGH be prescribed for sports or for “anti-aging” purposes (Grade A; BEL 1).

Other payer policies

1) Premara BCBS 2022
    a. Growth hormone* may be considered medically necessary in the treatment of adults who meet ALL criteria for the conditions listed below:
        i. AIDS wasting syndrome
        ii. Severe growth hormone deficiency
            1. Adult growth deficiency must be confirmed by a negative response to a growth hormone stimulation test (eg, serum GH levels of <5 ng/ml on stimulation testing with either of the following: glucagon or insulin).
            OR

2. Growth hormone deficiency may be assumed without a stimulation test if patient has had the pituitary removed or destroyed or has had panhypopituitarism since birth.
AND
3. Growth hormone therapy is prescribed by or in consultation with an endocrinologist

iii. Short bowel syndrome

b. Growth hormone is considered not medically necessary in the treatment of idiopathic short stature without growth hormone deficiency.

2) Cigna 2022

a. Growth Hormone Deficiency in an Adult or Transition Adolescent. Approve for 1 year if the individual meets the following criteria (A, B, C, and D):

A) The endocrinologist must certify that somatropin is not being prescribed for anti-aging therapy or to enhance athletic ability or for body building; AND

B) Individual must have a diagnosis of growth hormone deficiency that is one of the following (i or ii): [documentation required for all elements]

i. Childhood onset; OR

ii. Adult onset that results from one of the following: growth hormone deficiency alone or multiple hormone deficiencies (hypopituitarism) resulting from pituitary disease, hypothalamic disease, pituitary surgery, cranial radiation therapy, tumor treatment, traumatic brain injury, or subarachnoid hemorrhage; AND

C) Individual meets one of the following criteria (i, ii, or iii):

i. Individual (adult or transition adolescent) has known mutations, embryopathic lesions, congenital or genetic defects, or structural hypothalamic-pituitary defects; [documentation required] OR

ii. Individual meets the following criteria (a, b, and c):

a) Individual (adult onset or transition adolescent) has three or more of the following pituitary hormone deficiencies: Adrenocorticotropic hormone, thyroid-stimulation hormone, gonadotropin deficiency (luteinizing hormone and/or follicle stimulating hormone deficiency are counted as one deficiency), and prolactin [documentation required]; AND

b) The age and gender adjusted serum insulin-like growth factor-1 is below the lower limit of the normal reference range for the reporting laboratory [documentation required]; AND

Other causes of low serum insulin-like growth factor-1 have been excluded (e.g., malnutrition, prolonged fasting, poorly controlled diabetes mellitus, hypothyroidism, hepatic insufficiency, oral estrogen therapy); OR

Individual meets one of the following (a or b):

a) Adult. Individual has had a negative response to one of the following standard growth hormone stimulation tests (1, 2, 3, 4, 5, or 6) [documentation required for all elements]: Note: If the individual has had a previous trial of an arginine alone test with a peak response of ≤ 0.4 mcg/L, this would meet the criteria for a negative response to a growth hormone stimulation test.

(1) Insulin tolerance test (obtaining at least 3 growth hormone levels in at least a 60 minute timeframe [not including a level at timeframe zero], with adequate hypoglycemia being achieved) with peak response ≤ 5.0 mcg/L; OR
(2) Glucagon stimulation test (obtaining at least 3 growth hormone levels in at least 180 minute timeframe [not including a level at timeframe zero]) with peak response ≤ 3.0 mcg/L AND the individual's body mass index (BMI) is < 25 kg/m2; OR
(3) Glucagon stimulation test (obtaining at least 3 growth hormone levels in at least 180 minute timeframe [not including a level at timeframe zero]) with a peak response ≤ 3.0 mcg/L AND the individual's BMI is ≥ 25 kg/m2 and ≤ 30 kg/m2 with, according to the prescriber, a high pretest probability of growth hormone deficiency; OR
(4) Glucagon stimulation test (obtaining at least 3 growth hormone levels in at least 180 minute timeframe [not including a level at timeframe zero]) with a peak response ≤ 1.0 mcg/L AND the individual's BMI is ≥ 25 kg/m2 and ≤ 30 kg/m2 with, according to the prescriber, a low pretest probability of growth hormone deficiency; OR
(5) Glucagon stimulation test (obtaining at least 3 growth hormone levels in at least 180 minute timeframe [not including a level at timeframe zero]) with peak response ≤ 1.0 mcg/L AND the individual's BMI is > 30 kg/m2; OR
(6) Macrilen (macimorelin oral solution) test (obtaining at least 4 growth hormone levels in at least a 90 minute timeframe [not including a level at timeframe zero]) with peak responses < 2.8 ng/mL (2.8 mcg/L) AND the individual's BMI is ≤ 40 kg/m2. Note: The following formula can be used to calculate BMI: BMI equals body weight in kg divided by height meters squared (m2) [i.e., BMI = kg/m2]; OR

HERC staff summary:
Human growth hormone treatment is indicated in adults with childhood onset growth hormone deficiency caused by structural pituitary damage, brain tumors or clinically significant pituitary dysfunction when medically appropriate based on expert guidelines. Federal law requires the Oregon Health Plan to cover medically necessary medications for funded conditions according to FDA indications. For people under age 21, the Early and Periodic Screening, Diagnosis and Treatment Program as well as recent changes to HERC's Statement of Intent 4 requiring coverage of services which would benefit a child in terms of growth, development and ability to attend school, even if they appear in the unfunded region.

HERC staff recommends modifying the current guideline to clearly exclude use of these agents for anti-aging therapy, to enhance athletic ability or for body building, but to allow limited appropriate use in adults as well as children when prescribed according to FDA indications for funded conditions. In addition, the guideline would require consultation with an endocrinologist, as well as lab or historical evidence of lack of growth hormone.

HERC staff recommendations:

1) Remove GN74 from line 470 GONADAL DYSFUNCTION, MENOPAUSAL MANAGEMENT
2) Modify GN74 as shown below
    a. Alternative: delete guideline

GUIDELINE NOTE 74, GROWTH HORMONE TREATMENT

Lines 40,386,~~470,~~652

~~Treatment with growth hormone should continue only until adult height as determined by bone age is achieved. ICD-10-CM E23.0 (Hypopituitarism) is included on Lines 40 and 386 for conditions other than adult human growth hormone deficiency. ICD-10-CM E23.0 is included on Line 652 only for adult human growth hormone deficiency.~~

Treatment with growth hormone for ICD-10-CM E23.0 (Hypopituitarism) is included on Lines 40 and 386 for adults when

1 Prescribed by or in consultation with an endocrinologist; AND
2 Either
    i. Growth hormone deficiency is confirmed by a negative response to a growth hormone stimulation test (eg, serum GH levels of <5 ng/ml on stimulation testing with either of the following: glucagon or insulin); OR
    ii. patient has had the pituitary removed or destroyed or has had panhypopituitarism since birth; AND
3 The prescriber certifies that the growth hormone is not being prescribed for anti-aging therapy or to enhance athletic ability or body building

ICD-10-CM E23.0 is included on Line 652 only for adult human growth hormone deficiency that does not meet the above criteria.

Treatment of children and adolescents with growth hormone (for any indication) must be evaluated for medical appropriateness and medical necessity on a case-by-case basis. Therapy must be initiated by and continued in consultation with a pediatric endocrinologist.

FDA approved indications for various HGH agents

GENOTROPIN (somatropin) for injection, for subcutaneous use

Pediatric: Treatment of children with growth failure due to growth hormone deficiency, Prader-Willi syndrome, Small for Gestational Age, Turner syndrome, and Idiopathic Short Stature.

Adult: Treatment of adults with either adult onset or childhood onset GHD

HUMATROPE (somatropin) for injection, for subcutaneous use

Pediatric: Growth failure due to inadequate secretion of endogenous growth hormone; short stature associated with Turner syndrome; Idiopathic Short Stature, height standard deviation score <-2.25, and associated with growth rates unlikely to permit attainment of adult height in the normal range; short stature or growth failure in short stature homeobox-containing gene deficiency; short stature born small for gestational age with no catch-up growth by 2 years to 4 years of age.

Adult: Replacement of endogenous growth hormone in adults with growth hormone deficiency.

NORDITROPIN (somatropin) injection, for subcutaneous use

Pediatric: Treatment of pediatric patients with growth failure due to inadequate secretion of endogenous growth hormone, short stature associated with Noonan syndrome, short stature associated with Turner syndrome, short stature born small for gestational age with no catch-up growth by age 2 to 4 years, Idiopathic Short Stature, and growth failure due to Prader-Willi Syndrome.

Adult: Replacement of endogenous growth hormone in adults with growth hormone deficiency.

NUTROPIN (somatropin) injection, for subcutaneous use

Pediatric: Treatment of children with growth failure due to growth hormone deficiency, idiopathic short stature, Turner syndrome, and chronic kidney disease up to the time of renal transplantation.

Adult: Treatment of adults with either childhood-onset or adult-onset growth hormone deficiency.

OMNITROPE (somatropin) injection, for subcutaneous use

Pediatric: Treatment of children with growth failure due to growth hormone deficiency, Prader-Willi Syndrome, Small for Gestational Age, Turner syndrome, and Idiopathic Short Stature.

Adult: Treatment of adults with either adult onset or childhood onset growth hormone deficiency.

SAIZEN (somatropin) for injection, for subcutaneous use

Pediatric: Treatment of children with growth failure due to growth hormone deficiency.

Adult: Treatment of adults with either adult onset or childhood onset growth hormone deficiency.

SEROSTIM (somatropin) for injection, for subcutaneous use

Pediatric and Adult: Treatment of HIV patients with wasting or cachexia to increase lean body mass and body weight, and improve physical endurance.

SKYTROFA (lonapegsomatropin-tcgd) for injection, for subcutaneous use

Pediatric: treatment of pediatric patients 1 year and older who weigh at least 11.5 kg and have growth failure due to inadequate secretion of endogenous growth hormone.

Adult: N/A

ZOMACTON (somatropin) for injection, for subcutaneous use

Pediatric: Treatment of pediatric patients with growth failure due to inadequate secretion of endogenous growth hormone, short stature associated with Turner syndrome, idiopathic short stature, short stature or growth failure in short stature homeobox-containing gene deficiency, and short stature born small for gestational age with no catch-up growth by 2 years to 4 years.

Adult: Replacement of endogenous growth hormone in adults with growth hormone deficiency.

ZORBTIVE (somatropin) for injection, for subcutaneous use

Pediatric: N/A

Adult: Treatment of short bowel syndrome in adult patients receiving specialized nutritional support.

ABSTRACT

Objective: The development of these guidelines is sponsored by the American Association of Clinical Endocrinologists (AACE) Board of Directors and American College of Endocrinology (ACE) Board of Trustees and adheres with published AACE protocols for the standardized production of clinical practice guidelines (CPG).

Methods: Recommendations are based on diligent reviews of clinical evidence with transparent incorporation of subjective factors, according to established AACE/ACE guidelines for guidelines protocols.

Results: The Executive Summary of this 2019 updated guideline contains 58 numbered recommendations: 12 are Grade A (21%), 19 are Grade B (33%), 21 are Grade C (36%), and 6 are Grade D (10%). These detailed, evidence-based recommendations allow for nuance-based clinical decision-making that addresses multiple aspects of real-world care of patients. The evidence base presented in the subsequent Appendix provides relevant supporting information for the Executive Summary recommendations. This update contains 357 citations of which 51 (14%) are evidence level (EL) 1 (strong), 168 (47%) are EL 2 (intermediate), 61 (17%) are EL 3 (weak), and 77 (22%) are EL 4 (no clinical evidence).

Conclusion: This CPG is a practical tool that practicing endocrinologists and regulatory bodies can refer to regarding the identification, diagnosis, and treatment of adults and patients transitioning from pediatric to adult-care services with growth hormone deficiency (GHD). It provides guidelines on assessment, screening, diagnostic testing, and treatment recommendations for a range of individuals with various causes of adult GHD. The recommendations emphasize the importance of considering testing patients with a reasonable level of clinical suspicion of GHD using appropriate growth hormone (GH) cut-points for various GH–stimulation tests to accurately diagnose adult GHD, and to exercise caution interpreting serum GH and insulin-like growth factor-1 (IGF-1) levels, as various GH and IGF-1 assays are used to support treatment decisions. The intention to treat often requires sound clinical judgment and careful assessment of the benefits and risks specific to each individual patient. Unapproved uses of GH, long-term safety, and the current status of long-acting GH preparations are also discussed in this document. **(Endocr Pract. 2019;25:1191-1232)**

LAY ABSTRACT

This updated guideline provides evidence-based recommendations regarding the identification, screening, assessment, diagnosis, and treatment for a range of individuals with various causes of adult growth-hormone deficiency (GHD) and patients with childhood-onset GHD transitioning to adult care. The update summarizes the most current knowledge about the accuracy of available GH–stimulation tests, safety of recombinant human GH (rhGH) replacement, unapproved uses of rhGH related to sports and aging, and new developments such as long-acting GH preparations that use a variety of technologies to prolong GH action. Recommendations offer a framework for physicians to manage patients with GHD effectively during transition to adult care and adulthood. Establishing a correct diagnosis is essential before consideration of replacement therapy with rhGH. Since the diagnosis of GHD in adults can be challenging, GH–stimulation tests are recommended based on individual patient circumstances and use of appropriate GH cut-points. Available GH–stimulation tests are discussed regarding variability, accuracy, reproducibility, safety, and contraindications, among other factors. The regimen for starting and maintaining rhGH treatment now uses individualized dose adjustments, which has improved effectiveness and reduced reported side effects, dependent on age, gender, body mass index, and various other individual characteristics. With careful dosing of rhGH replacement, many features of adult GHD are reversible and side effects of therapy can be minimized. Scientific studies have consistently shown rhGH therapy to be beneficial for adults with GHD, including improvements in body composition and quality of life, and have demonstrated the safety of short- and long-term rhGH replacement.

Abbreviations:
AACE = American Association of Clinical Endocrinologists; **ACE** = American College of Endocrinology; **AHSG** = alpha-2-HS-glycoprotein; **AO-GHD** = adult-onset growth hormone deficiency; **ARG** = arginine; **BEL** = best evidence level; **BMD** = bone mineral density; **BMI** = body mass index; **CI** = confidence interval; **CO-GHD** = childhood-onset growth hormone deficiency; **CPG** = clinical practice guideline; **CRP** = C-reactive protein; **DM** = diabetes mellitus; **DXA** = dual-energy X-ray absorptiometry; **EL** = evidence level; **FDA** = Food and Drug Administration; **FD-GST** = fixed-dose glucagon stimulation test; **GeNeSIS** = Genetics and Neuroendocrinology of Short Stature International Study; **GH** = growth hormone; **GHD** = growth hormone deficiency; **GHRH** = growth hormone–releasing hormone; **GST** = glucagon stimulation test; **HDL** = high-density lipoprotein; **HypoCCS** = Hypopituitary Control and Complications Study; **IGF-1** = insulin-like growth factor-1; **IGFBP** = insulin-like growth factor–binding protein; **IGHD** = isolated growth hormone deficiency; **ITT** = insulin tolerance test; **KIMS** = Kabi International Metabolic Surveillance; **LAGH** = long-acting growth hormone; **LDL** = low-density lipoprotein; **LIF** = leukemia inhibitory factor; **MPHD** = multiple pituitary hormone deficiencies; **MRI** = magnetic resonance imaging; **P-III-NP** = procollagen

Eosinophilic Esophagitis

Plain Language Summary:
Background: Should a chronic inflammatory disorder that can make swallowing difficult and be painful be treated with a medicine used to treat certain disorders of the stomach and intestines, such as heartburn and ulcers (proton pump inhibitor (PPI) therapy)?

Should OHP cover this treatment? Staff recommends covering this treatment because studies show it is effective and has lower side effects then other treatments.

Question: Should eosinophilic esophagitis be moved to a line attached to the proton pump inhibitor therapy (PPI) guideline?

Question source: P&T staff

Issue: Eosinophilic esophagitis is a chronic inflammatory disorder characterized by symptoms of esophageal dysfunction and eosinophil-predominant inflammation. The symptoms of eosinophilic esophagitis resemble those of other esophagitis conditions, such as GERD. These include stomach/chest pain, dysphagia (difficulty swallowing), vomiting, poor appetite, and globus (a feeling of food being stuck in the throat). The eosinophil accumulation may be caused by immune hypersensitivity to particular foods, as well as a variety of genetic mutations found to increase predisposition to this condition. Eosinophilic esophagitis has historically been characterized by lack of response to anti-GERD therapy such as proton pump inhibitors (PPIs). Recently, it has been appreciated that some patients with pronounced esophageal eosinophilia can have complete responses to proton pump inhibitor (PPI) therapy, but the PPI appears to exert its effects by direct action rather than blockade of stomach acid alone. Standard treatment includes diet modification so that allergenic food is removed, most commonly milk, egg, soy, wheat, nuts and fish. Steroid medications are often used to control inflammation if dietary changes alone are not sufficient. In 2022, dupilumab (Dupixant) was approved by the U.S. Food and Drug Administration (FDA) to treat adults and children 12 years and older with eosinophilic esophagitis. This is the first FDA approved treatment for eosinophilic esophagitis.

P&T recently reviewed dupilumab for eosinophilic esophagitis. This review found that "Dupilumab was studied in one trial that lasted 24 weeks, in adults and children older than age 12. Patients who took dupilumab in the trial had better improvement in tissue taken from the esophagus when viewed under a microscope. More importantly, patients tended to feel better on dupilumab because they could swallow food better." P&T's recommendations were to revise PA criteria for dupilumab to allow coverage for treatment of eosinophilic esophagitis with dupilumab in patients aged 12 years of age and older who weigh at least 40 kg. The PA criteria for PPIs was then modified to allow PPI therapy for eosinophilic esophagitis for 1 year per PA cycle. This criteria was added per the American Gastroenterology Association guidance on treatment of eosinophilic esophagitis.

HERC/HSD history
Eosinophilic esophagitis was last reviewed in January, 2016 as part of a larger review of Barrett's esophagus and esophageal dysphagia. Until that time, eosinophilic esophagitis was on the upper and lower GERD lines. At the January 2016 meeting, the HERC added eosinophilic esophagitis to what is now line 378 ESOPHAGEAL STRICTURE; ACHALASIA to pair with esophageal dilation, and removed from the upper and lower GERD lines. From the meeting materials:

During the current review of this topic, HERC staff noted that eosinophilic esophagitis was included on the upper and lower GERD lines. However, review of the treatment of this condition finds that it is treated with allergy medications and dietary changes; it is resistant to PPI therapy in most cases as it is caused by some type of underlying allergic condition. This condition mainly becomes an issue when it causes narrowing of the esophagus; esophageal dilation is the mainstay of treatment for this. The esophageal dilation CPT codes are not included on the upper, covered GERD line.

Adopted changes:

1) Add K20.0 (Eosinophilic esophagitis) to line 383 ESOPHAGEAL STRICTURE; ACHALASIA and remove from lines 385 ESOPHAGITIS; ESOPHAGEAL AND INTRAESOPHAGEAL HERNIAS and 516 ESOPHAGITIS AND GERD; ESOPHAGEAL SPASM; ASYMPTOMATIC DIAPHRAGMATIC HERNIA
    a. Main therapy is medical (allergy medications, diet therapy) and esophageal dilation. Dilation CPT codes are available on line 383 but not lines 385 or 516

Current Prioritized List status

ICD-10-CM K20.0 (Eosinophilic esophagitis) is on line 378 ESOPHAGEAL STRICTURE; ACHALASIA

Most other esophagitis diagnosis codes are on lines 380 ESOPHAGITIS; GERD and 513 ESOPHAGITIS AND GERD; ESOPHAGEAL SPASM; ASYMPTOMATIC DIAPHRAGMATIC HERNIA, with placements and treatments governed by GN144.

DIAGNOSTIC GUIDELINE D12, UPPER ENDOSCOPY FOR GERD OR DYSPEPSIA SYMPTOMS
Upper endoscopy for uninvestigated dyspepsia or GERD symptoms is covered for:

Patients less than 50 years of age with persistent symptoms following advice on lifestyle modifications and completion of an appropriate course of twice daily PPI therapy or an H. pylori test and treat protocol.
Patients 50 years of age and older
Patients with “alarm symptoms” including, but not limited to, iron deficiency anemia or weight loss

Upper endoscopy is not covered for patients with previous upper endoscopy with non-malignant findings (other than Barrett’s esophagus) in the absence of significant new symptoms.

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 144, PROTON PUMP INHIBITOR THERAPY FOR GASTROESOPHAGEAL REFLUX DISEASE (GERD)

Lines 314,380,513

Short term treatment (up to 8 weeks) of GERD without Barrett's (ICD-10-CM K20.8, K20.9, K21.0, K21.9) with proton pump inhibitor therapy is included on Line 380. Long term treatment is included on Line 513.

Long term proton pump inhibitor therapy is included on Line 380 for Barrett's esophagus (ICD-10-CM K22.70) and on Line 314 for Barrett's esophagus with dysplasia (ICD-10-CM K22.71).

Eosinophilic Esophagitis

Evidence

1) **Lucendo 2016**, systematic review and meta-analysis of PPIs for treatment of eosinophilic esophagitis
    - **a.** N=33 studies (11 prospective cohort) with N=619 patients
        - **i.** N=13 retrospective cohort studies
        - **ii.** N=11 prospective cohort studies
        - **iii.** N=9 case series (1 to 66 patients)
    - **b.** An overall favorable clinical response after PPI treatment given at any dose was reported for 60.8% (95% CI, 48.38%–72.2%; I 2 ¼ 80.2%) of patients, with a similar benefit for children and adults (64.9% vs 56.2%). The overall effectiveness for inducing histologic remission of EoE (defined as the reduction of peak eosinophil counts to < 15 eosinophils/hpf) for any PPI administered at any dosage was 50.5% (95% CI, 42.2%–58.7%; I 2 ¼ 67.5%)
    - **c.** In conclusion, the present study proves that PPI therapy is an effective treatment that induces histologic and clinical remission in half of patients with symptomatic esophageal eosinophilia suggestive of EoE. Our results support the concept of PPIs as the first-line therapy in both children and adults for this subset of patients. Other effective alternatives, such as dietary or topical steroid therapy, likely might be set aside as second-line treatment, owing to long-term safety concerns (topical steroid therapy) and impairment of quality of life and nutritional inadequacy (dietary interventions).

Expert guidelines

1) **American Gastroenterological Association Guideline/Allergy Immunology Practice Parameters 2020**, clinical guidelines for the management of eosinophilic esophagitis (EoE)
    a. In patients with symptomatic esophageal eosinophilia, the AGA/JTF suggests using proton pump inhibition over no treatment. (Conditional recommendation, very low-quality evidence)
        i. Twenty-three observational studies that evaluated the histologic response to proton pump inhibitors (PPIs) reported an overall, unweighted histologic response rate of 42%. PPIs failed to induce histologic remission in approximately two-thirds of treated patients, compared with >85% of patients treated with placebo (RR, 0.66; 95% confidence interval [CI], 0.61e0.72).
        ii. It should be emphasized that direct comparison of the efficacy of PPI and other medical or dietary EoE therapies is limited because, up to this time, most trials in EoE have excluded patients with esophageal eosinophilia that responded to a PPI (formerly denoted as PPI-responsive esophageal eosinophilia).
    b. In patients with EoE, the AGA/JTF recommends topical glucocorticosteroids over no treatment. (Strong recommendation, moderate quality evidence)
    c. In patients with EoE, the AGA/JTF recommends topical glucocorticosteroids over no treatment. (Strong recommendation, moderate quality evidence)

Eosinophilic Esophagitis

HERC staff summary

Long term PPI therapy is effective in treatment approximately half of patients with eosinophilic esophagitis (EoE), based on observational studies. Long term therapy with PPIs is recommended by expert groups as a first line therapy for treating EoE. Other therapies for EoE include dietary restriction, which can impact quality of life and nutrition, and topical steroid therapy, which has a greater risk of side effects compared to PPI therapy. A newer therapy, dupilumab, was recently FDA approved for treatment of EoE. Of note, EoE patients need esophageal dilatation and upper endoscopy at higher frequency that patients with GERD; however, the esophageal stricture line has diagnosis codes for esophageal stricture which allows dilation if present.

HERC staff recommendations:

1) Add ICD-10-CM K20.0 (Eosinophilic esophagitis) to line 380 ESOPHAGITIS; GERD
    a. Remove K20.0 from line 378 ESOPHAGEAL STRICTURE; ACHALASIA
2) Modify GN144 as shown below
    a. Add eosinophilic esophagitis as a diagnosis eligible for long term PPI therapy
    b. Clarify the wording around coverage of GERD without Barrett's

GUIDELINE NOTE 144, PROTON PUMP INHIBITOR THERAPY FOR GASTROESOPHAGEAL REFLUX DISEASE (GERD)

Lines 314,380,513

Short term treatment (up to 8 weeks) of GERD without Barrett's (ICD-10-CM K20.8, K20.9, K21.0, K21.9) with proton pump inhibitor therapy is included on Line 380. Long term treatment of GERD without Barrett's with proton pump inhibitor therapy is included on Line 513.

Long term proton pump inhibitor therapy is included on Line 380 for Barrett's esophagus (ICD-10-CM K22.70) and eosinophilic esophagitis (ICD-10-CM K20.0) and on Line 314 for Barrett's esophagus with dysplasia (ICD-10-CM K22.71).

SYSTEMATIC REVIEWS AND META-ANALYSES

Fasiha Kanwal, Section Editor

Efficacy of Proton Pump Inhibitor Drugs for Inducing Clinical and Histologic Remission in Patients With Symptomatic Esophageal Eosinophilia: A Systematic Review and Meta-Analysis

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BACKGROUND & AIMS: **Proton pump inhibitor (PPI) therapy might lead to clinical and histologic remission in a significant proportion of patients with symptomatic esophageal eosinophilia (>15 eos/high-power field). We aimed to evaluate systematically the efficacy of PPI therapy for these patients.**

METHODS: **A search in MEDLINE, EMBASE, and SCOPUS databases, and the American Gastroenterological Association Institute, American College of Gastroenterology, and United European Gastroenterology meetings abstract books, was performed. Primary outcomes were clinical response and histologic remission (<15 eos/high-power field) after PPI therapy. Secondary outcomes were the influence on the response to PPIs of age group, study design/quality, PPI type, doses and interval dosing, and pH monitoring results. Data were pooled using a random-effects model.**

RESULTS: **Thirty-three studies (11 prospective studies) comprising 619 patients with symptomatic esophageal eosinophilia (188 children and 431 adults) were included. PPI therapy led to a clinical response in 60.8% (95% confidence interval, 48.38%–72.2%; $I^2 = 80.2$) and histologic remission in 50.5% (95% confidence interval, 42.2%–58.7%; $I^2 = 67.5$) of patients. No differences were observed regarding the study population (children vs adults), the type of publication, or its quality. PPIs were nonsignificantly more effective in prospective studies (52.6% vs 39.1%) administered twice daily compared with once daily (55.9% vs 49.7%), and with pathologic pH monitoring (65.4% vs 49.3%). A significant publication bias in favor of studies reporting histologic responses to PPIs was observed.**

CONCLUSIONS: **PPI therapy induces clinicohistologic remission in half of patients with symptomatic esophageal eosinophilia. This finding should be interpreted with caution because of poor-quality evidence, heterogeneity, and publication bias.**

Keywords: Eosinophilic Esophagitis; Proton Pump Inhibitors; Omeprazole; Esomeprazole; Lansoprazole; Rabeprazole; Systematic Review; Meta-Analysis.

Eosinophilic esophagitis (EoE) is a chronic immune-mediated inflammatory disorder, defined symptomatically by esophageal dysfunction and histologically by esophageal eosinophil–predominant inflammation.[1] Despite first characterized as a distinct clinicopathologic disorder 20 years ago,[2,3] EoE just recently has become recognized as the most prevalent cause of chronic esophageal symptoms among children and young adults.[4–6] Because the presence of esophageal eosinophilia is not specific, EoE consensus guidelines require clinical and/or histologic unresponsiveness to a 4- to 8-week proton pump inhibitor (PPI) trial, with other alternative causes of esophageal eosinophilia ruled out as well.[1,7–9] This requirement initially was introduced intending to eliminate gastroesophageal reflux disease (GERD) as an alternative cause of eosinophil infiltration.[7] However, it became clear that the relationship between esophageal eosinophilia, EoE, and GERD was much more complex,[10] so the description of a third diagnostic category, proton pump inhibitor esophageal eosinophilia (PPI-REE), was needed.

Abbreviations used in this paper: **CI, confidence interval; EoE, eosinophilic esophagitis; GERD, gastroesophageal reflux disease; hpf, high-power field; PPI, proton pump inhibitor; REE, responsive esophageal eosinophilia.**

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Practice Parameter

AGA institute and the joint task force on allergy-immunology practice parameters clinical guidelines for the management of eosinophilic esophagitis

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Guideline Panel included: Ikuo Hirano (chair), Yngve T. Falck-Ytter (co-chair, GRADE methodologist), Matthew A. Rank (co-chair, GRADE methodologist), Neil H. Stollman (member), Kenneth Wang (member), David R. Stukus (member), Matthew Greenhawt (member), Rajiv N. Sharaf (member), and Edmond S. Chan (member). Technical Review Panel included: Glenn Furuta (content expert), Evan Dellon (content expert), Jonathan Spergel (content expert), Seema Aceves (content expert), Matthew Greenhawt (content expert), Yngve Falck-Ytter (GRADE methodologist), Matthew A. Rank (GRADE methodologist), and Rajiv Sharaf (trainee GRADE methodologist).

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Table 2
GRADE Definitions on Quality of Evidence

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

histologic remission in approximately two-thirds of treated patients, compared with >85% of patients treated with placebo (RR, 0.66; 95% confidence interval [CI], 0.61–0.72). A high degree of inconsistency makes it difficult to provide a precise estimate of an absolute effect size and raises important concerns regarding variation in the criteria for patient selection, study design, as well as PPI duration, dosing, and formulation. Furthermore, most studies were noncomparative, single-arm, retrospective studies. Based on these factors, the strength of the recommendation was lowered. Nevertheless, a clinical benefit to the use of PPI monotherapy may be evident for certain patients. It is important to note that a European and an International consensus recommendation have recently removed the PPI trial from the diagnostic criteria of EoE.[7,8] After the exclusion of secondary causes of esophageal eosinophilia, symptomatic esophageal eosinophilia is now viewed as synonymous with EoE. PPIs are positioned as an effective, primary therapeutic option for certain patients with EoE. Based on their longstanding safety profile and ease of administration, patients may prefer to start with this form of therapy before trials of glucocorticosteroids or elimination diets. It should be emphasized that direct comparison of the efficacy of PPI and other medical or dietary EoE therapies is limited because, up to this time, most trials in EoE have excluded patients with esophageal eosinophilia that responded to a PPI (formerly denoted as PPI-responsive esophageal eosinophilia).

Question 2. Should Topical Glucocorticosteroids Be Used in Patients With Eosinophilic Esophagitis?

In patients with EoE, the AGA/JTF recommends topical glucocorticosteroids over no treatment. *(Strong recommendation, moderate quality evidence)*

Eight double-blind placebo-controlled studies enrolling 437 patients followed for a mean of 8 weeks compared treatment with topical budesonide or topical fluticasone to placebo.[2] It is of note that most of these studies required that patients first fail a PPI trial or excluded patients with known gastroesophageal reflux disease, which may not reflect routine clinical practice or the most current consensus-driven recommendations. Two of the trials used formulations of topical steroids developed specifically for esophageal delivery (tablet or liquid), whereas the remainder utilized ingested formulations designed for the treatment of asthma. As the result of a review process described in the technical guidelines, a single pooled estimate is presented here, despite many methodologic differences between these studies, including the relative potency and bioavailability of the agents used, method of administration, definition of response, dose, and differences that can occur in pediatric vs adult patients. All such factors may limit generalizability of this recommendation. Topical glucocorticosteroids failed to induce histologic remission in approximately one-third of treated patients, compared with >85% of patients treated with placebo (RR, 0.39; 95% CI, 0.26–0.58).[2] The certainty of this estimate is moderate; it was downgraded for inconsistency due to heterogeneity of the studies. In short-term studies of ≤3 months, there was no

Table 3
American Gastroenterological Institute and Joint Task Force on Allergy-Immunology Practice Parameters Guideline Recommendations on the Management of Eosinophilic Esophagitis

Recommendation	Strength of recommendation	Quality of evidence
1. Recommendation: In patients with symptomatic esophageal eosinophilia, the AGA/JTF suggests using proton pump inhibition over no treatment.	Conditional	Very low quality
2. In patients with EoE, the AGA/JTF recommends topical glucocorticosteroids over no treatment.	Strong	Moderate
3. In patients with EoE, the AGA/JTF suggests topical glucocorticosteroids rather than oral glucocorticosteroids.	Conditional	Moderate
4. In patients with EoE, the AGA/JTF suggests using elemental diet over no treatment.	Conditional	Moderate
Comment: Patients who put a higher value on avoiding the challenges of adherence to an elemental diet and the prolonged process of dietary reintroduction may reasonably decline this treatment option.		
5. In patients with EoE, the AGA/JTF suggests using an empiric, 6-food elimination diet over no treatment.	Conditional	Low
Comment: Patients who put a higher value on avoiding the challenges of adherence to diet involving elimination of multiple common food staples and the prolonged process of dietary reintroduction may reasonably decline this treatment option.		
6. In patients with EoE, the AGA/JTF suggests using an allergy testing-based elimination diet over no treatment.	Conditional	Very low quality
Comment: Due to the potential limited accuracy of currently available, allergy-based testing for the identification of specific food triggers for EoE, patients may prefer alternative medical or dietary therapies to an exclusively testing-based elimination diet.		
7. Recommendation: In patient with EoE in remission after short-term use of topical glucocorticosteroids, the AGA/JTF suggests continuation of topical glucocorticosteroids over discontinuation of treatment.	Conditional	Very low quality
Comments: Patients who put a high value on the avoidance of long-term topical steroid use and its possible associated adverse effects, and/or place a lower value on the prevention of potential long-term undesirable outcomes (ie, recurrent dysphagia, food impaction, and esophageal stricture), could reasonably prefer cessation of treatment after initial remission is achieved, provided clinical follow-up is maintained.		
8. Recommendation: In adult patients with dysphagia from a stricture associated with EoE, the AGA/JTF suggests endoscopic dilation over no dilation.	Conditional	Very low quality
Comment: Esophageal dilation does not address the esophageal inflammation associated with EoE.		
9. Recommendation: In patients with EoE, the AGA/JTF recommends using anti–IL-5 therapy for EoE only in the context of a clinical trial.	No recommendation	Knowledge gap
10. Recommendation: In patients with EoE, the AGA/JTF recommends using anti–IL-13 or anti–IL-4 receptor α therapy for EoE only in the context of a clinical trial.	No recommendation	Knowledge gap
11. Recommendation: In patients with EoE, the AGA/JTF suggests against the use of anti-IgE therapy for EoE.	Conditional	Very low quality
12–15. Recommendation: In patients with EoE the AGA/JTF suggest using montelukast, cromolyn sodium, immunomodulators, and anti-TNF for EoE only in the context of a clinical trial.	No recommendation	Knowledge gap

Botulinum Toxin for Strabismus

Plain Language Summary:
Background: Should Botox be used in eye conditions that cause the eye to turn either inward or outward?

Should OHP cover this treatment? Staff recommends not cover this treatment because there is insufficient evidence that it works.

Question: Should the guideline regarding botulinum toxin injection be clarified regarding the intent for coverage for strabismus, esotropia and related conditions?

Question source: Medical Management Committee case review

Issue: Strabismus is a deviation of the ocular alignment where one eye turns, which may be intermittent or constant. Strabismus can be further divided into esotropia (in-turning deviation), exotropia (out-turning deviation) or, less commonly, hypertropia (upturning deviation), hypotropia (downturning deviation) and cyclotropia (rotatory deviation). Strabismus can be caused by a variety of insults such as abnormal anatomical development of extraocular muscles or the orbit, impaired neurological input to extraocular muscles, uncorrected refractive error or hereditary factors. Sequelae to strabismus can include blurring of vision, diplopia (double vision), impaired depth (3-D) perception, and in younger children, amblyopia. Amblyopia is impaired vision in the deviating eye due to the lack of correct stimulation of that eye and results in permanent loss of vision if left untreated at a young age.

There are various treatments available for strabismus. Conservative options include prisms to realign the visual axes and orthoptic exercises to promote and establish binocular control of ocular alignment where both eyes can subsequently work as a pair. Invasive treatment options include surgery and botulinum toxin to individual extraocular muscles.

HSC/HERC history: botulinum toxin injection (67345)
2012 Ophthalmology review: did not look specifically at Botox
August 2014 botulinum toxin review: "In the treatment of strabismus, there is very low quality evidence, based on a systematic review with limited data that BoNT may be as effective as surgery for retreatment of acquired or infantile esotropia, but does not appear effective for acute 6th nerve palsy or adult horizontal strabismus." As a result of that review, CPT 67345 (Chemodenervation of extraocular muscle) was removed from line 397/372 AMBLYOPIA, as botulinum toxin is not FDA approved for amblyopia. A new coding specification was added to the two strabismus lines, which later was incorporated into the botulinum toxin guideline: "Chemodenervation with botulinum toxin injection (CPT 67345) is included on this line for the treatment of strabismus due to other neurological disorders (ICD-9 378.73 /ICD-10 H50.89)."
May 2018 P&T review: included only the 2017 Cochrane review of botulinum toxin for strabismus

Current Prioritized List status
CPT 67345 (351,393) is on lines 351 STRABISMUS DUE TO NEUROLOGIC DISORDER and 393 STRABISMUS WITHOUT AMBLYOPIA AND OTHER DISORDERS OF BINOCULAR EYE MOVEMENTS; CONGENITAL ANOMALIES OF EYE; LACRIMAL DUCT OBSTRUCTION IN CHILDREN

- ICD-10-CM H49.8 family (paralytic strabismus) and various ophthalmologic nerve palsies are on line 351
- ICD-10-CM H50.0 family (esotroptia) is on line 393
- ICD-10-CM H50.1 family (exotropia) is on line 393
- ICD-10-CM H50.3 family (esotroptia) is on line 393
- ICD-10-CM H50.60 (Mechanical strabismus, unspecified) and H50.69 (Other mechanical strabismus) are on line 393
- ICD-10-CM H50.89 (Other specified strabismus) is on line 393. Sub-diagnoses include strabismus in neuromuscular disorder

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.

Evidence

1) **Rowe 2017,** Cochrane review of botulinum toxin for the treatment of strabismus
    a. N=6 RCTs
    b. 2 trials (102 people) compared botulinum toxin with surgery in people with acquired or infantile esotropia.
        i. low-certainty evidence that children who received botulinum toxin may have a similar or slightly reduced chance of achieving ocular alignment (pooled risk ratio (RR) 0.91, 95% confidence interval (CI) 0.71 to 1.16), binocular single vision (RR 0.88, 95% CI 0.63 to 1.23), sensory fusion (RR 0.88, 95% CI 0.63 to 1.23) and stereopsis (RR 0.86, 95% CI 0.59 to 1.25) compared with children who received surgery.
    c. 1 trial of 30 adults comparing botulinum toxin with surgery in patients with horizontal strabismus found a reduced change of ocular alignment with botulinum toxin (RR 0.38, 95% CI 0.17 to 0.85; low-certainty evidence).
    d. 1 trial of people with acute onset sixth nerve palsy found that people treated with botulinum toxin may have a similar or slightly improved chance of ocular alignment in people compared with observation (RR 1.19, 95% CI 0.96 to 1.48; 47 participants, low-certainty evidence).
    e. 1 trial of adjuvant botulinum toxin in strabismus surgery found that it may increase the chances of ocular alignment compared with strabismus surgery alone (RR 1.83, 95% CI 0.41 to 8.11; 23 participants, very low-certainty evidence).
    f. Reported complications in people given botulinum toxin in the included trials included ptosis (range 9% to 41.66%) and vertical deviation (range 8.3% to 18.51%).
    g. Authors' conclusions: Most published literature on the use of botulinum toxin in the treatment of strabismus consists of retrospective studies, cohort studies or case reviews. Although these provide useful descriptive information, clarification is required as to the effective use of botulinum toxin as an independent treatment modality. Six RCTs on the therapeutic use of botulinum toxin in strabismus, graded as low and very low certainty evidence, have shown varying responses. These include a lack of evidence for effect of botulinum toxin on reducing visual symptoms in acute sixth nerve palsy, poor response in people with horizontal strabismus without binocular vision, similar or slightly reduced achievement of successful ocular alignment in children with esotropia and potential increased achievement of successful ocular alignment where surgery and botulinum toxin are combined. Further high quality trials using robust methodologies are required to botulinum toxin to alternative surgical interventions in strabismus cases with and without potential for binocular vision.

Expert guidelines

1) **American Academy of Ophthalmology 2017**, preferred practice pattern for esotropia and exotropia
    a. Treatment for esotropia includes the following:
        i. Correction of refractive errors
        ii. Bifocal eyeglasses
        iii. Prism therapy
        iv. Amblyopia treatment
        v. Extraocular muscle surgery
            1. Botulinum toxin injection

a. Favorable prognostic indicators include good vision in each eye, absence of restricted eye movement, a small to moderate angle of esotropia, and the potential for binocular vision. Such treatment may be an alternative to conventional extraocular muscle surgery in selected patients, but its value in managing infantile esotropia has not been definitively established.

2. Other pharmacologic agents

b. Treatment for exotropia includes
   i. Correction of refractive errors
   ii. Stimulating accommodative convergence (overcorrection of myopia or undercorrection of hyperopia)
   iii. Patching (antisuppression) therapy
   iv. Amblyopia treatment
   v. Prism therapy
   vi. Convergence exercises for convergence insufficiency exotropia
   vii. Extraocular muscle surgery
   viii. Botulinum toxin injection
      1. There is insufficient evidence to make treatment recommendations for botulinum toxin treatment for exotropia

Other payer policies

1) Aetna 2022

a. OnabotulinumtoxinA (Botox Brand of Botulinum Toxin Type A): Aetna considers onabotulinumtoxinA (Botox) medically necessary for any of the following conditions:
   i. A. Strabismus (including gaze palsies accompanying diseases, such as neuromyelitis optica and Schilder's disease), for deviations less than 50 prism diopters.
   ii. Note: Strabismus repair is considered cosmetic in adults with uncorrected congenital strabismus and no binocular fusion.

2) Cigna 2021

a. Botox is indicated for the treatment of strabismus and blepharospasm associated with dystonia, including benign essential blepharospasm or VII nerve disorders in patients 12 years of age and older

Botulinum Toxin for Strabismus

HERC staff summary

There is limited evidence for the treatment of strabismus with botulinum toxin. The American Academy of Ophthalmology has not found evidence for the use of botulinum toxin for treatment of exotropia and states that the value of botulinum toxin for the management of esotropia is not well established.

The current botulinum toxin guideline is consistent with the evidence and private payer policies; however, several housekeeping items need to be addressed.

HERC staff summary

1) Delete ICD-10-CM H50.89 (Other specified strabismus) from line 393 STRABISMUS WITHOUT AMBLYOPIA AND OTHER DISORDERS OF BINOCULAR EYE MOVEMENTS; CONGENITAL ANOMALIES OF EYE; LACRIMAL DUCT OBSTRUCTION IN CHILDREN
2) Add ICD-10-CM H50.89 (Other specified strabismus) to line 351 STRABISMUS DUE TO NEUROLOGIC DISORDER
    a. Sub-diagnoses include strabismus in neuromuscular disorder
3) Delete CPT 67345 Chemodenervation of extraocular muscle (currently on lines 351 and 393) from line 393 STRABISMUS WITHOUT AMBLYOPIA AND OTHER DISORDERS OF BINOCULAR EYE MOVEMENTS; CONGENITAL ANOMALIES OF EYE; LACRIMAL DUCT OBSTRUCTION IN CHILDREN
4) Modify GN 219 as shown below
    a. Does not contain the specified ICD-10-CM code

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).

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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:

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Line 526 CHRONIC ANAL FISSURE

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

Cochrane Library

Cochrane Database of Systematic Reviews

Botulinum toxin for the treatment of strabismus (Review)

Rowe FJ, Noonan CP

Rowe FJ, Noonan CP.
Botulinum toxin for the treatment of strabismus.
Cochrane Database of Systematic Reviews 2017, Issue 3. Art. No.: CD006499.
DOI: 10.1002/14651858.CD006499.pub4.

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[Intervention Review]

Botulinum toxin for the treatment of strabismus

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ABSTRACT

Background

The use of botulinum toxin as an investigative and treatment modality for strabismus is well reported in the medical literature. However, it is unclear how effective it is in comparison to other treatment options for strabismus.

Objectives

The primary objective was to examine the efficacy of botulinum toxin therapy in the treatment of strabismus compared with alternative conservative or surgical treatment options. This review sought to ascertain those types of strabismus that particularly benefit from the use of botulinum toxin as a treatment option (such as small angle strabismus or strabismus with binocular potential, i.e. the potential to use both eyes together as a pair). The secondary objectives were to investigate the dose effect and complication rates associated with botulinum toxin.

Search methods

We searched CENTRAL (which contains the Cochrane Eyes and Vision Trials Register) (2016, Issue 6), Ovid MEDLINE, Ovid MEDLINE In-Process and Other Non-Indexed Citations, Ovid MEDLINE Daily, Ovid OLDMEDLINE (January 1946 to July 2016), Embase (January 1980 to July 2016), Latin American and Caribbean Literature on Health Sciences (LILACS) (January 1982 to July 2016), the ISRCTN registry (www.isrctn.com/editAdvancedSearch), ClinicalTrials.gov (www.clinicaltrials.gov), and the World Health Organization (WHO) International Clinical Trials Registry Platform (ICTRP) (www.who.int/ictrp/search/en). We did not use any date or language restrictions in the electronic searches for trials. We last searched the electronic databases on 11 July 2016. We handsearched the British and Irish Orthoptic Journal, Australian Orthoptic Journal, proceedings of the European Strabismological Association (ESA), International Strabismological Association (ISA) and International Orthoptic Association (IOA) (www.liv.ac.uk/orthoptics/research/search.htm) and American Academy of Paediatric Ophthalmology and Strabismus meetings (AAPOS). We contacted researchers who are active in this field for information about further published or unpublished studies.

Selection criteria

We included randomised controlled trials (RCTS) of any use of botulinum toxin treatment for strabismus.

Data collection and analysis

Two review authors independently selected studies and extracted data. We used standard methods expected by Cochrane and assessed the certainty of the evidence using GRADE. We defined ocular alignment as an angle of deviation of less than or equal to 10 prism dioptres.

Main results

Six RCTs were eligible for inclusion. We judged the included studies as at a mixture of low, unclear and high risk of bias. We did not consider any of the included studies as at low risk of bias for all domains.

Two trials conducted in Spain (102 people, number of eyes not specified) compared botulinum toxin with surgery in children that required retreatment for acquired or infantile esotropia. These two studies provided low-certainty evidence that children who received botulinum toxin may have a similar or slightly reduced chance of achieving ocular alignment (pooled risk ratio (RR) 0.91, 95% confidence interval (CI) 0.71 to 1.16), binocular single vision (RR 0.88, 95% CI 0.63 to 1.23), sensory fusion (RR 0.88, 95% CI 0.63 to 1.23) and stereopsis (RR 0.86, 95% CI 0.59 to 1.25) compared with children who received surgery. One trial from Canada compared botulinum toxin with surgery in 30 adults (30 eyes) with horizontal strabismus and reported a reduced chance of ocular alignment with botulinum toxin (RR 0.38, 95% CI 0.17 to 0.85; low-certainty evidence).

One trial in the UK suggested that botulinum toxin may result in a similar or slightly improved chance of ocular alignment in people with acute onset sixth nerve palsy compared with observation (RR 1.19, 95% CI 0.96 to 1.48; 47 participants, low-certainty evidence).

Very low-certainty evidence from one trial from Brazil suggested that adjuvant botulinum toxin in strabismus surgery may increase the chances of ocular alignment compared with strabismus surgery alone (RR 1.83, 95% CI 0.41 to 8.11; 23 participants).

One trial from China of 47 participants (94 eyes) suggested that people receiving botulinum toxin combined with sodium hyaluronate may have a similar or slightly reduced chance of achieving ocular alignment compared with botulinum toxin alone (RR 0.81, 95% CI 0.36 to 1.82; low-certainty evidence).

Reported complications in people given botulinum toxin in the included trials included ptosis (range 9% to 41.66%) and vertical deviation (range 8.3% to 18.51%). Ptosis occurred less frequently when treated with botulinum toxin combined with sodium hyaluronate compared to botulinum toxin alone.

Authors' conclusions

Most published literature on the use of botulinum toxin in the treatment of strabismus consists of retrospective studies, cohort studies or case reviews. Although these provide useful descriptive information, clarification is required as to the effective use of botulinum toxin as an independent treatment modality. Six RCTs on the therapeutic use of botulinum toxin in strabismus, graded as low and very low-certainty evidence, have shown varying responses. These include a lack of evidence for effect of botulinum toxin on reducing visual symptoms in acute sixth nerve palsy, poor response in people with horizontal strabismus without binocular vision, similar or slightly reduced achievement of successful ocular alignment in children with esotropia and potential increased achievement of successful ocular alignment where surgery and botulinum toxin are combined. Further high quality trials using robust methodologies are required to compare the clinical and cost effectiveness of various forms of botulinum toxin (e.g. Dysport, Xeomin, etc), to compare botulinum toxin with and without adjuvant solutions and to compare botulinum toxin to alternative surgical interventions in strabismus cases with and without potential for binocular vision.

PLAIN LANGUAGE SUMMARY

Botulinum toxin for the treatment of strabismus

What is the aim of this review?
The aim of this Cochrane Review was to find out how well botulinum toxin works as a treatment for strabismus. Cochrane researchers collected and analysed all relevant studies to answer this question and included six studies.

Key messages
The evidence as to the benefits and harms of using botulinum toxin for strabismus is uncertain.

What was studied in the review?
Strabismus occurs when the eyes are not aligned. Usually one eye turns inwards or outwards. Less frequently one eye turns upwards or downwards. It is commonly known as "squint".

Strabismus can lead to blurred vision or double vision. In children it can affect the long term development of vision in the affected eye. There are many causes of strabismus. In most cases, there are problems with the muscles or nerves around the eye.

Doctors can use botulinum toxin to stop individual muscles around the eye working for a while. This may help the eyes become more aligned and may lead to less blurred or double vision. One problem with using botulinum toxin is that it can result in a droopy eyelid (ptosis).

What are the main results of the review?
The review shows that:

• using botulinum toxin in children requiring primary treatment or retreatment for strabismus may make no difference, or slightly reduce the chances of recovering correct alignment of the eyes compared with surgery (low-certainty evidence);

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esotropia and/or amblyopia.[98-101] (Refer to Table 3 in the Pediatric Eye Evaluations PPP, Section II. Comprehensive Ophthalmic Examination, for guidelines for correcting hyperopia in children.[89]) For children with esotropia, the threshold for prescribing hyperopic eyeglasses is lower than for children without esotropia. For example, eyeglasses are generally prescribed for +2.00 diopters (D) or more in children under 2 years of age, and +1.50 D or more for children over 2. For hyperopic patients, anisometropia is a risk factor for the development of accommodative esotropia.[18]

Choice of Therapy

Treatment should be considered for all forms of esotropia, and binocular alignment should be established as soon as possible, especially in young children, to maximize binocular potential,[71, 102] to prevent or facilitate treatment of amblyopia,[39, 103] and to restore normal appearance. Significant refractive errors should be corrected. Amblyopia treatment is usually started before surgery because this may alter the angle of strabismus[104] and/or increase the likelihood of good postoperative binocularity.[102, 105]

There is evidence that early surgical correction improves sensory outcomes for infantile esotropia, probably because the duration of constant esotropia is minimized.[70, 71, 75, 106-108] Given equal visual acuity in both eyes, there is no consensus among strabismus surgeons on unilateral versus bilateral surgery, nor is there good evidence supporting one approach over the other.[109]

Treatment for esotropia includes the following:

- Correction of refractive errors[11]
- Bifocal eyeglasses[110]
- Prism therapy[111, 112]
- Amblyopia treatment[105]
- Extraocular muscle surgery[113]
  - Botulinum toxin injection[114, 115]
  - Other pharmacologic agents

Treatment plans are formulated in consultation with the parent/caregiver and patient, if appropriate. The plans should be responsive to the preferences and expectations of the parent/caregiver and patient. The plans should account for the parent's/caregiver's and patient's perception of the existing alignment, which may differ from that of the ophthalmologist. It is important that the family/caregiver and ophthalmologist agree on the goals of treatment before surgery is performed. For patients for whom the potential for binocularity is poor, surgery to restore normal appearance may be an appropriate treatment.

Correction of Refractive Errors

Correction of significant refractive errors should be the initial treatment for children with esotropia.[46,115] (Refer to Table 3 in the Pediatric Eye Evaluations PPP, Section II. Comprehensive Ophthalmic Examination, for guidelines for correcting refractive errors in children.[89]) For patients with accommodative esotropia, realignment by cycloplegia-determined eyeglasses or contact lenses alone is successful in most cases.[46, 116] In general, a greater degree of hyperopia indicates a higher likelihood that the refractive error is an important etiologic factor of the esotropia. While children with developmental delay and strabismus may be less tolerant of eyeglasses, they may respond to correction of smaller amounts of ametropia. Additionally, children with a variable angle of esotropia or a greater deviation at near may respond to correction of even low hyperopia.

The aim of treatment is to correct hyperopia sufficiently to restore alignment, and in most cases a prescription is given to correct the full refractive error as determined after cycloplegia. Undercorrection of the hyperopia sometimes improves eyeglass wear, especially in older children. A manifest noncycloplegic refraction may be required to optimize visual acuity and binocular alignment in older children because correction of the full cycloplegic refractive error may blur their distance vision.

Improved alignment after prescribing eyeglasses may take several weeks. If the esotropia persists, the cycloplegic refraction should be repeated before considering surgery because additional hyperopic refractive error may be uncovered. A repeat refraction should also be

the total deviation and, as such, is used to quantify the amount of surgery, if required.[91] The simultaneous prism-and-cover test measures the manifest deviation and provides useful information for patients with fusional vergence, where the alignment under binocular viewing conditions is better than during alternate-cover testing.

MANAGEMENT

All forms of exotropia should be monitored and some require treatment. Young children with intermittent exotropia and good fusional control should be followed without surgery.[178] (*moderate evidence, strong recommendation*) Deviations that are present most or all of the time often require treatment. However, the optimal therapy for exotropia, the long-term benefit of early surgical correction, and the relative merits of bilateral versus unilateral surgery are not well established.[179] Amblyopia is uncommon in patients with intermittent exotropia, but, if present, should be treated.

Choice of Therapy

Current treatment practices are listed below. Some of these treatments are under evaluation in randomized trials.

- Correction of refractive errors
- Stimulating accommodative convergence (overcorrection of myopia or undercorrection of hyperopia)
- Patching (antisuppression) therapy
- Amblyopia treatment
- Prism therapy
- Convergence exercises for convergence insufficiency exotropia
- Extraocular muscle surgery
- Botulinum toxin injection[114]

Correction of Refractive Errors

In the setting of an exodeviation, corrective lenses should be prescribed for any clinically significant refractive error that causes reduced vision in one or both eyes.[178] Improved retinal-image clarity often improves the control of the exotropia.[180] Such refractive errors include myopia, high hyperopia, astigmatism, and significant anisometropia. In one study, myopia was found in more than 90% of exotropic patients by 20 years of age.[181] Correcting even mild amounts of myopia may be beneficial. Correction of mild to moderate amounts of hyperopia is not generally recommended for patients with intermittent exotropia because reducing accommodative convergence can worsen the control or size of the exodeviation. If hyperopic correction is necessary, the amount prescribed is the least amount needed to promote good vision while still promoting accommodative convergence to control the exodeviation. Such correction may be the full cycloplegic refraction,[180] but it is often less than the full amount.

Stimulating Accommodative Convergence

If fusional control of intermittent exotropia is suboptimal despite providing image clarity with refractive correction, it may be improved in many cases by increasing myopic correction in myopes, reducing hyperopic correction in hyperopes, or prescribing myopic correction in ametropes. In one multicenter pilot study, patients randomized to overminus therapy had better control of intermittent exotropia after 8 weeks, but the durability of the effect is uncertain.[182] Some patients, in particular older patients and adults, may not tolerate this therapy because of visual discomfort or decreased visual acuity. Studies suggest that overcorrecting minus-lens therapy stimulates accommodation without increasing myopia.[183, 184] It is most useful in patients with low-grade myopia and in those already wearing eyeglasses.

Patching Therapy

In some cases, part-time patching (e.g., 2 to 6 hours daily) may improve fusional control[185, 186] and/or reduce the angle of strabismus, particularly in the 3-to-10-year age

Acupuncture 2022 Review

Plain Language Summary:
Background: A procedure that inserts thin needles into the skin. Should OHP add more coverage for acupuncture for:

-Language problems following a stroke (post-stroke aphasia)
-Chronic pain in the muscles and trigger points (tender lumps under the skin), most commonly in the upper back, shoulder and neck (myofascial pain)
-A condition caused by the lack of blood that carries oxygen and nutrients to a part of the brain. It causes problems with reasoning, planning, judgment and memory (vascular dementia)
- A disorder that affects muscle and soft tissue characterized by chronic muscle pain, tenderness, fatigue and sleep disturbances (fibromyalgia)
-How soon a person can breastfeed their child after childbirth (rates of lactation within 24 hours after delivery)
-Hay fever (allergic rhinitis)
-A chronic, painful bladder condition where increased urinary urgency and frequency is seen (interstitial cystitis)

Should OHP cover this treatment? Staff recommends discussing treatment for fibromyalgia (line 531) because studies show a small, short term benefit. Other conditions did not have sufficient evidence that acupuncture is helpful.

Questions:

1) Should additional conditions be paired with acupuncture on the Prioritized List?
2) Should the diagnosis code for post-stroke depression be clarified in the acupuncture guideline?

Question sources:

1) Laura Ocker, LAc; Ali Jones
2) Holly Jo Hodges, CCO medical director

Issue: A new review of systematic reviews (Lu et al, 2022) found high or moderate certainty evidence that acupuncture is effective for treatment of post-stroke aphasia, myofascial pain, vascular dementia, fibromyalgia, rates of lactation within 24 hours after delivery, and allergic rhinitis.

Additionally, Ali Jones (member of the public) submitted a request to review acupuncture as a possible treatment for interstitial cystitis through the coverage guidance nomination process.

Acupuncture is currently paired with a variety of indications, governed by Guideline Note 92 ACUPUNCTURE.

Dr. Hodges is requesting that the diagnosis code for post stroke depression be clarified. Per the MODA behavioral health director, the best codes for use with this diagnosis are ICD-10-CM F06.31 (Mood disorder due to known physiological condition with depressive features) and F06.32 (Mood disorder due to known physiological condition with major depressive-like episode).

Current Prioritized List guideline

GUIDELINE NOTE 92, ACUPUNCTURE

Lines 1,4,5,64,65,92,111,112,114,125,129,133,135,157,158,191,199-201,208,210,214,215,229,234, 237,238,258,259,262,271,276,286,287,294,314-316,329,342,361,396,397,402,410,419,435,464,541, 559

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

Line 1 PREGNANCY

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

Hyperemesis gravidarum

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

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

Breech presentation

ICD-10-CM: O32.1

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

Back and pelvic pain of pregnancy

ICD-10-CM: O99.89

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

Line 4 SUBSTANCE USE DISORDER, Line 62 SUBSTANCE-INDUCED MOOD, ANXIETY, DELUSIONAL AND OBSESSIVE-COMPULSIVE DISORDERS, Line 65 SUBSTANCE-INDUCED DELIRIUM; SUBSTANCE INTOXICATION AND WITHDRAWAL

Acupuncture is included on these lines only when used as part of a program that offers patients a variety of evidence-based interventions including behavioral interventions, social support, and Medication Assisted Treatment (MAT), as appropriate.

Line 5 TOBACCO DEPENDENCE

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

Lines 92, 111, 112, 114, 125, 129, 133, 135, 157, 158, 191, 199, 200, 208, 210, 214, 215, 229, 234, 237, 238, 258, 259, 261, 262, 271, 276, 286, 287, 294, 314, 315, 316, 329, 342, 372, 396, 397, 419, 435 and 559

Acupuncture is paired only with the ICD-10 code G89.3 (Neoplasm related pain (acute) (chronic)) when there is active cancer and limited to 12 total sessions per year; patients may have additional visits authorized beyond these limits if medically appropriate.

Line 201 CHRONIC ORGANIC MENTAL DISORDERS INCLUDING DEMENTIAS

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

Line 361 SCOLIOSIS

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

Line 402 CONDITIONS OF THE BACK AND SPINE

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

Line 410 MIGRAINE HEADACHES

Acupuncture pairs on Line 410 for migraine (ICD-10-CM G43.0, G43.1, G43.5, G43.7, G43.8, G43.9), for up to 12 sessions per year.

Line 464 OSTEOARTHRITIS AND ALLIED DISORDERS

Acupuncture pairs on Line 464 for osteoarthritis of the knee only (ICD-10-CM M17), for up to 12 sessions per year.

*Line 541 TENSION HEADACHES

Acupuncture is included on Line 541 for treatment of tension headaches (ICD-10-CM G44.2), for up to 12 sessions per year.

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

*Below the current funding line.

Evidence

Post stroke aphasia

1) **Lu 2022**
    a. Zhang 2019 was the only systematic review of meta-analysis included in the analysis of post-stoke aphasia
        i. Included 8 RCTs, 243 patients in acupuncture group and 238 in control group
        ii. Acupuncture plus rehabilitation therapy vs rehabilitation therapy alone
        iii. Standard mean difference 1.01 (0.81, 1.2)
            1. There is no information presented on what scale or what outcome this measures
        iv. Moderate certainty of evidence of effectiveness
        v. No details given on length of follow up, quality of included studies or other specifics
2) **Zhang 2019** Acupuncture is effective in improving functional communication in post-stroke aphasia : A systematic review and meta-analysis of randomized controlled trials
    a. Not available in Medline
3) **Huang 2020** An overview of systematic reviews and meta-analyses on acupuncture for post-stroke aphasia
    a. Not available in Medline
4) **Deng 2022**: published protocol for a multi-center RCT to examine efficacy of acupuncture for post-stroke motor aphasia
    a. Acupuncture + language training vs sham acupuncture + language training
5) **Li 2021**: protocol for randomized, blinded, controlled multicenter trial to examine acupuncture for post-stroke aphasia

Myofascial pain/fibromyalgia

1) **Lu 2022**
    a. Yuan 2016 only systematic review included in analysis of myofascial pain
        i. Included 13 RCTs, 222 patients in acupuncture group and 192 in control group
        ii. Acupuncture vs sham acupuncture
        iii. Standard mean difference -1 (-1.43, -0.57)
            1. No information given on what this scale represents
        iv. Moderate certainty of evidence of effectiveness, large therapeutic effect
        v. Follow up less than 1 week after acupuncture
        vi. No details given on quality of included studies or other specifics
    b. Kim Jiwon 2019 only systematic review included in analysis of fibromyalgia
        i. 11 RCTs, 242 patients in the acupuncture group, 317 in the control group
        ii. Acupuncture vs western medicine
        iii. Standard mean difference -0.49 (-0.79, -0.2)
            1. No information given on what this scale represents
        iv. Moderate certainty of evidence of effectiveness, moderate therapeutic effect
2) **Zhang 2019,** Systematic review and meta-analysis of acupuncture for fibromyalgia
    a. N=12 RCTs
        i. Acupuncture vs sham acupuncture
        ii. N=12 to 164 patients
    b. Meta-analysis showed that acupuncture was significantly better than sham acupuncture for relieving pain (VAS 0-10 cm scale) (MD =-1.04, 95% CI [-1.70, –0.38], P=0.002, I2

=78%) and improving the quality of life (FIQ 0-80 point scale) (MD =-13.39, 95% CI [-21.69, –5.10], P=0.002, I 2 =82%), with low- to moderate-quality evidence in the short term. At follow-up in the long term, the effect of acupuncture was also superior to that of sham acupuncture. No serious adverse events were found during acupuncture.

   i. Note: minimal clinically important difference on the VAS scale is 1.37 cm
   ii. Note: minimal clinically important difference on the FIQ scale is 14

c. Two studies reported on pain intensity. Pool results indicated that there were no statistically significant differences in pain reduction between real MA and sham MA (MD =-1.23, 95% CI [–4.74, 2.27], P=0.49, I 2 =0%) with low quality of evidence
d. Four studies evaluated quality of life by using the FIQ score. The pooled results indicated that real acupuncture was significantly better than sham acupuncture in improving quality of life after treatment (MD =-13.39, 95% CI [-21.69, –5.10], P=0.002, I 2 =82%; Figure 3C). The quality of evidence was evaluated as low (downgraded because of inconsistency and imprecision)
e. Conclusion: Acupuncture therapy is an effective and safe treatment for patients with FM, and this treatment can be recommended for the management of FM.

3) **Deare 2013**, Cochrane review of acupuncture for fibromyalgia **https://www.cochranelibrary.com/cdsr/doi/10.1002/14651858.CD007070.pub2/epdf/full**
   a. N=9 trials (395 participants)
   b. Low quality evidence from one study (13 participants) showed electro-acupuncture (EA) improved symptoms with no adverse events at one month following treatment. Mean pain in the non-treatment control group was 70 points on a 100 point scale; EA reduced pain by a mean of 22 points (95% confidence interval (CI) 4 to 41), or 22% absolute improvement. Control group global well-being was 66.5 points on a 100 point scale; EA improved well-being by a mean of 15 points (95% CI 5 to 26 points). Control group stiffness was 4.8 points on a 0 to 10 point; EA reduced stiffness by a mean of 0.9 points (95% CI 0.1 to 2 points; absolute reduction 9%, 95% CI 4% to 16%). Fatigue was 4.5 points (10 point scale) without treatment; EA reduced fatigue by a mean of 1 point (95% CI 0.22 to 2 points), absolute reduction 11% (2% to 20%). There was no difference in sleep quality (MD 0.4 points, 95% CI -1 to 0.21 points, 10 point scale), and physical function was not reported.
   c. Moderate quality evidence from six studies (286 participants) indicated that acupuncture (EA or MA) was no better than sham acupuncture, except for less stiffness at one month. Subgroup analysis of two studies (104 participants) indicated benefits of EA. Mean pain was 70 points on 0 to 100 point scale with sham treatment; EA reduced pain by 13% (5% to 22%); (SMD -0.63, 95% CI -1.02 to -0.23). Global well-being was 5.2 points on a 10 point scale with sham treatment; EA improved well-being: SMD 0.65, 95% CI 0.26 to 1.05; absolute improvement 11% (4% to 17%). EA improved sleep, from 3 points on a 0 to 10 point scale in the sham group: SMD 0.40 (95% CI 0.01 to 0.79); absolute improvement 8% (0.2% to 16%). Low-quality evidence from one study suggested that MA group resulted in poorer physical function: mean function in the sham group was 28 points (100 point scale); treatment worsened function by a mean of 6 points (95% CI -10.9 to -0.7). Low-quality evidence from three trials (289 participants) suggested no difference in adverse events between real (9%) and sham acupuncture (35%); RR 0.44 (95% CI 0.12 to 1.63).
   d. Moderate quality evidence from one study (58 participants) found that compared with standard therapy alone (antidepressants and exercise), adjunct acupuncture therapy reduced pain at one month after treatment: mean pain was 8 points on a 0 to 10 point

scale in the standard therapy group; treatment reduced pain by 3 points (95% CI -3.9 to -2.1), an absolute reduction of 30% (21% to 39%).

e. Four studies reported no differences between acupuncture and control or other treatments described at six to seven months follow-up

f. Authors' conclusions There is low to moderate-level evidence that compared with no treatment and standard therapy, acupuncture improves pain and stiffness in people with fibromyalgia. There is moderate-level evidence that the effect of acupuncture does not differ from sham acupuncture in reducing pain or fatigue, or improving sleep or global well-being

Chronic pain

1) **NICE 2021** Evidence review of acupuncture for chronic pain
    a. Overall
        i. N=32 studies
            1. the majority of evidence was based on women with chronic neck pain or fibromyalgia
        ii. The majority of the evidence identified was of low to very low quality, with only a small amount of moderate quality evidence. The evidence was mainly downgraded due to risk of bias and imprecision. Risk of bias was often high due to attrition and selection bias. In the usual care comparisons there was a lack of blinding in the studies due to the nature of the intervention; this combined with the mostly subjective outcomes resulted in a high risk of performance bias.
        iii. Evidence of acupuncture versus sham acupuncture was based on 19 studies and showed a benefit of treatment in terms of pain and quality of life in the short term
        iv. Evidence of acupuncture versus usual care was based on 9 studies and showed a benefit of acupuncture (mainly for pain and quality of life), which was consistent to the sham comparison. There was evidence for all critical and important outcomes and the evidence quality was downgraded mainly due to risk of bias and imprecision, ranging from very low to moderate.
    b. Acupuncture vs sham acupuncture
        i. Pain reduction
            1. Very low quality evidence from 13 studies with 1230 participants showed a clinically important benefit of acupuncture compared to sham acupuncture at ≤3 months. Low quality evidence from 2 studies with 159 participants showed a clinically important benefit of acupuncture compared to sham acupuncture at ≤3 months.
            2. Low quality evidence from 4 studies with 376 participants showed no clinically important difference between acupuncture and sham acupuncture at >3 months. Moderate quality evidence from 2 studies with 159 participants showed a clinically important benefit of acupuncture compared to sham acupuncture at >3 months. Low quality evidence from 1 study with 61 participants showed no clinically important difference between acupuncture and sham acupuncture at >3 months
        ii. Quality of life

1. Low to moderate quality evidence from 2 studies with 210 participants showed a clinically important benefit of acupuncture compared to sham acupuncture at ≤3 months. Moderate quality evidence from 1 study with 158 participants showed sham acupuncture to have a clinically important improvement compared to acupuncture at ≤3 months. Very low quality evidence from 3 studies with 244 participants showed no clinically important difference between acupuncture and sham acupuncture at ≤3 months. Very low quality evidence from 2 studies with 168 participants showed a clinically important benefit of acupuncture compared to sham acupuncture at ≤3 months. Very low to low quality evidence from 1 study with 178 participants showed a clinically important benefit, clinically important harm and no clinically important difference of acupuncture compared to sham acupuncture at ≤3 months (various quality of life subscales). Moderate quality evidence from 2 studies with 159 participants showed a clinically important benefit of acupuncture compared to sham acupuncture at ≤3 months. Low quality evidence from 1 study with 72 participants showed a clinically important benefit of acupuncture compared to sham acupuncture at ≤3 months. Very low quality evidence from 1 study with 76 participants showed a clinically important benefit of sham acupuncture compared to verum acupuncture at >3 months. Low quality evidence from 1 study with 96 participants showed no clinically important difference between acupuncture and sham acupuncture at >3 months. Low quality evidence from 1 study with 153 participants showed a clinically important benefit of acupuncture compared to sham acupuncture at >3 months. Moderate quality evidence from 1 study with 159 participants showed a clinically important benefit of acupuncture compared to sham acupuncture at >3 months

iii. Physical function

1. Very low quality evidence from 1 study with 118 participants showed no clinically important difference between acupuncture and sham acupuncture at ≤3 months. Very low quality evidence from 1 study with 106 participants showed no clinically important difference between acupuncture and sham acupuncture at >3 months.

c. Acupuncture vs usual care

i. Pain reduction

1. Low quality evidence from 5 studies with 234 participants showed a clinically important benefit of acupuncture compared to usual care at ≤3 months. Low quality evidence from 2 studies with 384 participants showed no clinically important difference between acupuncture and usual care at ≤3 months. Moderate quality evidence from 1 study with 3162 participants showed a clinically important benefit of acupuncture compared to usual care at ≤3 months. Moderate quality evidence from 1 study with 344 participants showed no clinically important difference between acupuncture and usual care at >3 months.

ii. Quality of life

1. Moderate quality evidence from 1 study with 3213 participants showed a clinically important benefit of acupuncture compared to usual care at

≤3 months. Very low quality evidence from 1 study with 100 participants showed both a clinically important benefit and no clinically important difference between acupuncture and usual care at ≤3 months (various quality of life subscales). Low quality evidence from 1 study with 204 participants showed a clinically important benefit of acupuncture compared to usual care at >3 months.

iii. Physical function
    1. Very low quality evidence from 1 study with 45 participants showed no clinically important difference between acupuncture and usual care at ≤3 months. Very low quality evidence from 1 study with 100 participants showed a clinically important benefit of acupuncture compared to usual care at ≤3 months.

Vascular dementia

1) Lu 2022

a. Tong Li 2019 only systematic review included in analysis of vascular dementia
    i. Included 6 RCTs, 265 patients in acupuncture group and 265 in control group
    ii. Acupuncture vs western medicine
    iii. Standard mean difference 0.5 (0.29, 0.76)
    iv. Given moderate certainty of evidence of effectiveness, moderate therapeutic effect
    v. No details given on length of follow up, quality of included studies or other specifics

2) **Ma 2021**, review of systematic reviews of acupuncture for dementia

a. N=13 systematic reviews with meta-analyses
    i. 137 RCTs, 9012 patients
    ii. All conducted in China

b. The results suggested that acupuncture has beneficial effects on effectiveness, cognitive ability, and activities of daily living in the treatment of dementia for 4–24 weeks, although there was a high degree of heterogeneity. The quality of reports was rated “high” in one SR, “moderate” in five SRs, and “low” in seven SRs. The methodological quality of only one SR was “low,” and the rest were rated "very low." The quality of evidence was rated “high” in one SR, including the effectiveness rate, MMSE, ADAS-cog, HDS, MoCA and FAQ.

c. 9 SRs assessed the efficacy of acupuncture on the treatment of dementia (5094 patients, 79 RCTs). The pooled effects reported in these reviews were quite inconsistent. Two SRs had a high degree of heterogeneity, even after subgroup analysis. Four SRs showed no significant difference in acupuncture compared with western medicine.

d. Nine SRs assessed the cognitive performance of acupuncture in the treatment of dementia, with a total of 5210 patients and 75 RCTs enrolled. The pooled effects were not statistically significant in the subgroup analysis of four SRs. Three SRs showed moderate heterogeneity and two SRs showed high heterogeneity. Two SRs showed no statistical significance in acupuncture compared with western medicine.

e. Nine SRs assessed the quality of life of acupuncture in the treatment of dementia, with a total of 2302 patients and 34 RCTs enrolled. The pooled effects were not statistically significant in the subgroup analysis of four SRs. One SR showed moderate heterogeneity

and three SRs showed high heterogeneity. Three SRs showed no statistical significance in acupuncture compared with western medicine

f. Conclusion: Acupuncture showed potential therapeutic effects for patients with dementia, but the quality of the evidence was not high. Higher-quality RCTs are warranted to confirm the clinical effects of acupuncture in the treatment of dementia

3) **Su 2021** Systematic review and meta-analysis of acupuncture for vascular dementia
   a. N=48 RCTs (3,778 patients)
      i. Control groups included western medicine, usual care
   b. The pooled data demonstrated that acupuncture was more beneficial for a global cognitive function (measured by MMSE, HDS, MoCA, and ADAS-cog) [mean difference (MD) 1.86, 95% CI 1.19–2.54, $p < 0.01$] and activities of daily living (measured by ADL Scale and BI) (MD −3.08, 95% CI −4.81 to −1.35, $p < 0.01$) compared with western medicine (WM). The favorable results were also observed when acupuncture was combined with WM (MD 2.37, 95% CI 1.6–3.14, $p < 0.01$) or usual care (UC, MD 4.4, 95% CI 1.61–7.19, $p = 0.002$) in comparison with the corresponding control conditions. Meanwhile, the subgroup analysis did not indicate a statistical effect difference between manual acupuncture (MA) and electroacupuncture (EA) (inter-group I 2 < 50% and $p > 0.1$) when comparing acupuncture with WM. There were no significant differences in the occurrence of adverse events (AEs) between the acupuncture group and the control group ($p > 0.05$). Owing to the poor methodological quality and considerable heterogeneity among studies, the certainty of the evidence was low or very low.
   c. Conclusions: This review suggests that acupuncture as a monotherapy or an adjuvant therapy may play a positive role in improving the cognition and daily performance of VCI patients associated with few side effects

Breast feeding

1) Lu 2022
   a. Ying Tang 2017 only systematic review included in analysis of breastfeeding
      i. Included 5 RCTs, 279 patients in acupuncture group and 278 in control group
      ii. Acupuncture vs sham acupuncture
      iii. Relative risk 2.24 (1.58, 3.17)
      iv. Given moderate certainty of evidence of effectiveness, high therapeutic effect
      v. No details given on length of follow up, quality of included studies or other specifics
      vi. Original study not found in Medline search
2) **Bao 2022**, protocol published for systematic review and meta-analysis of acupuncture on breast feeding
3) No studies found in Medline when searching for acupuncture and lactation, breastfeeding

Allergic rhinitis

1) Lu 2022
   a. Jinzhang 2017 only systematic review included in analysis of breastfeeding
      i. Included 4 RCTs, 198 patients in acupuncture group and 194 in control group
      ii. Acupuncture vs sham acupuncture
      iii. Standard mean difference -0.47 (-0.67, -0.27)

iv. Given moderate certainty of evidence of effectiveness, moderate therapeutic effect
v. No details given on length of follow up, quality of included studies or other specifics

2) **He 2022**, systematic review and meta-analysis of acupuncture for allergic rhinitis
   a. N=30 trials (4413 patients)
      i. Sample sizes ranged from 24 to 981
      ii. The performance bias and attrition bias are serious in most studies that were included. Selection bias may also have affected the quality of the evidence.
   b. Acupuncture vs wait list
      i. N=3 studies
      ii. Data pooled from three studies also showed that acupuncture improved the life quality of patients, measured by Rhinoconjunctivitis Quality of Life Questionnaire (RQLQ) or Mini RQLQ (n=1112, SMD −0.95, 95% CI −1.17, −0.73)
   c. Acupuncture vs sham acupuncture
      i. N=4 trials
      ii. The post-intervention nasal symptoms score was lower in the acupuncture group than in the sham acupuncture group (RQLQ nasal symptom subscale: n=489, MD −0.60, 95% CI −1.16 to −0.04)
      iii. Evidence from three trials demonstrated that the acupuncture group had significantly improved life quality (RQLQ) compared to the sham acupuncture group (n=436, SMD −0.26 95% CI −0.44, −0.07)
   d. Acupuncture vs western medicine (cetirizine, loratadine, terfenadine, Tranilast capsules and desloratadine)
      i. N=17 trials
      ii. There was no difference for clinical response between these two groups (n=588, RR 1.10 95% CI 0.96, 1.26)
      iii. The difference in the quality of life between two groups was inconsistent
   e. Acupuncture in children
      i. Only two trials enrolled participants younger than 18 years old. Ng et al. found no difference between real acupuncture and sham acupuncture in the severity of nasal symptoms (n=72, MD −1.76, 95% CI −3.59 to 0.07)
      ii. Determined to have insufficient data
   f. Conclusion: Acupuncture may have an advantage over no intervention and sham acupuncture in improving nasal symptoms and quality of life for adults with AR. The effect of acupuncture and cetirizine or loratadine for AR may be similar. Additional trials are necessary to confirm these results.

Interstitial cystitis

1) **Verghese 2016**, systematic review of complementary therapies for bladder pain syndrome
   a. Acupuncture
      i. Cohort study (N=11 patients with bladder pain syndrome, 25 patients with overactive bladder) [Honjo et al]
         1. At the end of treatment there was a significant decrease in the 24-h frequency and VAS for pain ($p<0.001$). However, the results for the BPS and overactive bladder patients were presented together, preventing an assessment of symptoms in patients with BPS alone.

ii. Pilot study (N=7 patients) [Staack et al]
    1. acupuncture treatment with electric stimulation led to modest improvement in the urinary frequency, voiding difficulty and abdominal/genital pain
iii. Case series of 8 patients [Katayama et al]
    1. 38 % of women showed improvement in symptoms after 3 months

Other payer policies

1) Aetna 2022

a. Considers the following experimental (excerpts)
    i. Fibromyalgia
    ii. Myofascial pain
    iii. Vascular dementia

2) Cigna 2022

a. Covers acupuncture for chronic pain conditions
    i. Fibromyalgia or myofascial pain ICD-10-CM codes not included on covered list

HERC staff summary

Acupuncture appears to be a promising treatment modality for post-stroke aphasia and breastfeeding difficulties, but the quality of evidence is low and there appear to be ongoing RCTs in these areas. There is poor evidence based on low to very low quality studies to support the use of acupuncture for vascular dementia. Acupuncture was not superior to routine medical therapy in adults with allergic rhinitis; insufficient evidence was found to evaluate effectiveness as a treatment for allergic rhinitis in children. Very little evidence was found on acupuncture to treat interstitial cystitis.

There is moderate quality evidence that acupuncture improves pain and stiffness in fibromyalgia; however, this improvement has borderline clinical significance and is only short term. NICE found low to moderate quality evidence for effectiveness of acupuncture for the treatment of chronic pain (pain reduction and quality of life) in the short term (<3 months), with the majority of included studies in patients with fibromyalgia. However, the NICE review found no evidence of clinically important improvement with acupuncture over sham at more than 3 months.

HERC staff recommendation

1) Modify GN 92 as shown below
    a. Clarify that post-stroke depression refers to ICD-10-CM F06.31 (Mood disorder due to known physiological condition with depressive features) and F06.32 (Mood disorder due to known physiological condition with major depressive-like episode).
    b. Note: previously adopted change from October 2022 is shown under substance use disorder
2) Discuss adding acupuncture (CPT 97810-97814) to line 531 FIBROMYALGIA, CHRONIC FATIGUE SYNDROME, AND RELATED DISORDERS
    a. If acupuncture is added to this line, modify GN92 as shown below in purple

GUIDELINE NOTE 92, ACUPUNCTURE

Lines 1,4,5,64,65,92,111,112,114,125,129,133,135,157,158,191,199-201,208,210,214,215,229,234, 237,238,258,259,262,271,276,286,287,294,314-316,329,342,361,396,397,402,410,419,435,464, ***531,****541,559*

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

Line 1 PREGNANCY

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

Hyperemesis gravidarum

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

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

Breech presentation

ICD-10-CM: O32.1

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

Back and pelvic pain of pregnancy

ICD-10-CM: O99.89

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

Line 4 SUBSTANCE USE DISORDER, Line 62 SUBSTANCE-INDUCED MOOD, ANXIETY, DELUSIONAL AND OBSESSIVE-COMPULSIVE DISORDERS, Line 65 SUBSTANCE-INDUCED DELIRIUM; SUBSTANCE INTOXICATION AND WITHDRAWAL

Acupuncture is included on these lines only when used as part of a ~~program~~ documented broader treatment plan that offers patients a variety of evidence-based interventions including behavioral interventions, social support, and Medication Assisted Treatment (MAT), as appropriate.

Line 5 TOBACCO DEPENDENCE

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

Lines 92, 111, 112, 114, 125, 129, 133, 135, 157, 158, 191, 199, 200, 208, 210, 214, 215, 229, 234, 237, 238, 258, 259, 261, 262, 271, 276, 286, 287, 294, 314, 315, 316, 329, 342, 372, 396, 397, 419, 435 and 559

Acupuncture is paired only with the ICD-10 code G89.3 (Neoplasm related pain (acute) (chronic)) when there is active cancer and limited to 12 total sessions per year; patients may have additional visits authorized beyond these limits if medically appropriate.

Line 201 CHRONIC ORGANIC MENTAL DISORDERS INCLUDING DEMENTIAS

Acupuncture is paired with the treatment of post-stroke depression only (ICD-10-CM F06.31 or F06.32). Treatments may be billed to a maximum of 30 minutes face-to-face time and limited to 12 total sessions per year, with documentation of meaningful improvement; patients may have additional visits authorized beyond these limits if medically appropriate

Line 361 SCOLIOSIS

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

Line 402 CONDITIONS OF THE BACK AND SPINE

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

Line 410 MIGRAINE HEADACHES

Acupuncture pairs on Line 410 for migraine (ICD-10-CM G43.0, G43.1, G43.5, G43.7, G43.8, G43.9), for up to 12 sessions per year.

Line 464 OSTEOARTHRITIS AND ALLIED DISORDERS

Acupuncture pairs on Line 464 for osteoarthritis of the knee only (ICD-10-CM M17), for up to 12 sessions per year.

*Line 531 FIBROMYALGIA, CHRONIC FATIGUE SYNDROME, AND RELATED DISORDERS

Acupuncture is included on Line 531 for treatment of fibromyalgia (ICD-10-CM M79.7), for up to 12 sessions per year.

*Line 541 TENSION HEADACHES

Acupuncture is included on Line 541 for treatment of tension headaches (ICD-10-CM G44.2), for up to 12 sessions per year.

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

*Below the current funding line.

BMJ Open

Evidence mapping and overview of systematic reviews of the effects of acupuncture therapies

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ABSTRACT

Objective To provide a route map regarding systematic reviews (SRs) of acupuncture therapies that will meet two goals: (1) to identify areas in which more or better evidence is required and (2) to identify acupuncture applications that, although proven effective, remain underused in practice, and thus warrant more effective knowledge dissemination.

Eligibility criteria We included SRs that conducted meta-analyses (MAs) of randomised controlled trials (RCTs) for this overview.

Information sources We searched for SRs without language restrictions from January 2015 to November 2020 in four Chinese electronic databases and Epistemonikos database. And we also searched for newly published RCTs that were eligible for selected best SRs in PubMed, Medline, Cochrane Central Register of Controlled Trials, Embase and four Chinese electronic databases from its lasted search dates to November 2020.

Synthesis of results We reanalysed the selected MAs if new primary studies were added. We used random-effect model to calculate the overall effect.

Results Our search identified 120 SRs published in the last 5 years addressing acupuncture therapies across 12 therapeutic areas and 77 diseases and conditions. The SRs included 205 outcomes and involved 138 995 participants from 1402 RCTs. We constructed 77 evidence matrices, including 120 SRs and their included RCTs in the Epistemonikos database. Seventy-seven SRs represented the effect estimate of acupuncture therapies. Finally, we system summarised the areas of possible underutilisation of acupuncture therapies (high or moderate certainty evidence of large or moderate effects), and the areas of warranting additional investigation of acupuncture therapies (low or very low certainty evidence of moderate or large effects).

Conclusion The evidence maps and overview of SRs on acupuncture therapies identified both therapies with substantial benefits that may require more assertive evidence dissemination and promising acupuncture therapies that require further investigation.

STRENGTHS AND LIMITATIONS OF THIS STUDY

⇒ This study was the first evidence map for acupuncture therapies across all therapeutic areas to our knowledge.
⇒ This study includes a comprehensive search of eligible systematic reviews and randomised controlled trials and explicit eligibility criteria.
⇒ This study use of both a combination of evidence mapping and an overview approach provides readers with both a broad perspective of the evidence landscape and in-depth information on the certainty of evidence and the effect size on patient-important outcomes.
⇒ This study, in-depth collaboration with the Epistemonikos foundation, makes it possible for readers to have an overview of evidence and access the primary studies.
⇒ The limitation of this review is that we excluded studies investigating the effect of acupuncture as an adjunct therapy, and some diseases/conditions may be omitted.

INTRODUCTION

Clinicians and patients worldwide now make wide use of acupuncture, a form of traditional medicine.[1] According to a 2013 WHO report,[2] 103 of the WHO's member countries have approved the use of acupuncture. According to a 2013 survey conducted by the World Federation of Acupuncture-moxibustion Societies,[3] 183 (91%) of the 202 countries surveyed use acupuncture, while 178 (93%) of the 192 member countries of the United Nations have acupuncture practices, and 59 (31%) have partial or full insurance coverage.

Based on the extensive application of acupuncture in practice, in recent years[4] numerous systematic reviews (SRs) have explored the effects of acupuncture therapies. Despite the mass of evidence, acupuncture practice and related policies practice in different jurisdictions vary, including over-utilisation or underutilisation.[5] Cultural,

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ORIGINAL RESEARCH

Acupuncture therapy for fibromyalgia: a systematic review and meta-analysis of randomized controlled trials

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Purpose: Fibromyalgia (FM) can cause chronic widespread pain and seriously affect the quality of patient lives. Acupuncture therapy is widely used for pain management. However, the effect of acupuncture on FM is still uncertain. The aim of this review was to determine the effect and safety of acupuncture therapy on the pain intensity and quality of life in patients with FM.

Materials and methods: We searched PubMed, the Cochrane Library, Embase, the China National Knowledge Infrastructure, the Chinese Science and Technology Periodical Database, and the Chinese Biomedical Literature Database to collect randomized controlled trials (RCTs) of acupuncture for FM published before May 2018. A meta-analysis was performed according to the Cochrane systematic review method by using RevMan 5.3 software, and GRADE was used to evaluate the quality of the evidence.

Results: We identified 12 RCTs that compared acupuncture therapy to sham acupuncture or conventional medication. Meta-analysis showed that acupuncture was significantly better than sham acupuncture for relieving pain (MD =–1.04, 95% CI [–1.70, –0.38], P=0.002, I^2=78%) and improving the quality of life (MD =–13.39, 95% CI [–21.69, –5.10], P=0.002, I^2=82%), with low- to moderate-quality evidence in the short term. At follow-up in the long term, the effect of acupuncture was also superior to that of sham acupuncture. No serious adverse events were found during acupuncture.

Conclusion: Acupuncture therapy is an effective and safe treatment for patients with FM, and this treatment can be recommended for the management of FM.

Keywords: acupuncture, fibromyalgia, pain, quality of life, meta-analysis

Introduction

Fibromyalgia (FM) is characterized by widespread musculoskeletal pain,[1] is present in as much as 0.4% to 9.3% of the population,[2] and is often accompanied by fatigue, sleep difficulties, cognitive dysfunction, depressed mood, or depressive episodes.[3,4] FM can occur in all populations at every age, especially involving more middle-aged females than males.[5] A recent study reported that the annual medical cost of FM was more than 12,993 million euros (32.5% corresponded to health care costs and 67.5% to indirect costs attributable to productivity losses) in Spain.[6] Therefore, it is imperative to find effective therapies relieving pain and reducing social and economic burden.

The management of FM requires a multidimensional approach that includes patient education, behavioral therapy, exercise, and pain management.[7] Unfortunately, no effective treatments for FM are presently available. The most common pharmacological therapies for the pain management of FM include amitriptyline, anticonvulsants,

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Final

Chronic pain (primary and secondary) in over 16s: assessment of all chronic pain and management of chronic primary pain

[G] Evidence review for acupuncture for chronic primary pain

NICE guideline NG193

Intervention evidence review underpinning recommendation 1.2.5 and the research recommendation in the NICE guideline

April 2021

This evidence review was developed by the National Guideline Centre based at the Royal College of Physicians

Table 13: Incremental cost needed to make acupuncture cost effective

Estimates of QALY gain	Maximum incremental cost	Resource use that could be funded (hours of band 6 community staff time)	Resource use that could be funded (hours of band 7 community staff time)
Willich 2006 QALY gain = 0.024	£20,000*0.024 = £480	7.5 hours	6.2 hours
Essex 2017 QALY gain (complete case analysis) = 0.032	£20,000*0.032 = £640	9.9 hours	8.3 hours
Essex 2017 QALY gain (imputed data analysis) = 0.019	£20,000*0.019 = £380	5.9 hours	4.9 hours

Note: The number of appointments or hours of physio time have been rounded down to the nearest whole number.

The results of the threshold calculations in Table 13 show the range of hours of staff time that could be afforded, depending on the magnitude of the QALY, and based on UK staff costs. The committee discussed that each session of acupuncture is not usually an hour. Sometimes it can be as little as 10 minutes, although if traditional Chinese medicine is undertaken this can take an hour. Typically, the committee opinion was that although there might be variation in how acupuncture is delivered, there was some agreement that around 6 sessions of about 30 minutes might be considered a typical course that would be offered to patients. Using the lowest QALY estimate from Table 13, shows that this could afford around 5 hours of staff time, which would mean roughly 10 sessions of 30 minutes. Therefore 6 sessions of 30 minutes could be cost effective based on the above calculations.

1.6 Evidence statements

1.6.1 Clinical evidence statements

1.6.1.1 Acupuncture versus sham acupuncture

Pain reduction

Very low quality evidence from 13 studies with 1230 participants showed a clinically important benefit of acupuncture compared to sham acupuncture at ≤3 months. Low quality evidence from 2 studies with 159 participants showed a clinically important benefit of acupuncture compared to sham acupuncture at ≤3 months.

Low quality evidence from 4 studies with 376 participants showed no clinically important difference between acupuncture and sham acupuncture at >3 months. Moderate quality evidence from 2 studies with 159 participants showed a clinically important benefit of acupuncture compared to sham acupuncture at >3 months. Low quality evidence from 1 study with 61 participants showed no clinically important difference between acupuncture and sham acupuncture at >3 months

Quality of life

Low to moderate quality evidence from 2 studies with 210 participants showed a clinically important benefit of acupuncture compared to sham acupuncture at ≤3 months. Moderate quality evidence from 1 study with 158 participants showed sham acupuncture to have a clinically important improvement compared to acupuncture at ≤3 months. Very low quality evidence from 3 studies with 244 participants showed no clinically important difference

between acupuncture and sham acupuncture at ≤3 months. Very low quality evidence from 2 studies with 168 participants showed a clinically important benefit of acupuncture compared to sham acupuncture at ≤3 months. Very low to low quality evidence from 1 study with 178 participants showed a clinically important benefit, clinically important harm and no clinically important difference of acupuncture compared to sham acupuncture at ≤3 months (various quality of life subscales). Moderate quality evidence from 2 studies with 159 participants showed a clinically important benefit of acupuncture compared to sham acupuncture at ≤3 months. Low quality evidence from 1 study with 72 participants showed a clinically important benefit of acupuncture compared to sham acupuncture at ≤3 months.

Very low quality evidence from 1 study with 76 participants showed a clinically important benefit of sham acupuncture compared to verum acupuncture at >3 months. Low quality evidence from 1 study with 96 participants showed no clinically important difference between acupuncture and sham acupuncture at >3 months. Low quality evidence from 1 study with 153 participants showed a clinically important benefit of acupuncture compared to sham acupuncture at >3 months. Moderate quality evidence from 1 study with 159 participants showed a clinically important benefit of acupuncture compared to sham acupuncture at >3 months.

Physical function

Very low quality evidence from 1 study with 118 participants showed no clinically important difference between acupuncture and sham acupuncture at ≤3 months. Very low quality evidence from 1 study with 106 participants showed no clinically important difference between acupuncture and sham acupuncture at >3 months.

Psychological distress

Low quality evidence from 1 study with 50 participants showed a clinically important benefit of acupuncture compared to sham acupuncture at ≤3 months. Low quality evidence from 2 studies with 206 participants showed a clinically important benefit of acupuncture compared to sham acupuncture at ≤3 months. Low quality evidence from 1 study with 155 participants showed a clinically important benefit of acupuncture compared to sham acupuncture at >3 months.

Pain interference

No evidence identified

Pain self-efficacy

No evidence identified

Sleep

Low quality evidence from 1 study with 52 participants showed a clinically important benefit of acupuncture compared to sham acupuncture at ≤3 months. Moderate quality evidence from 1 study with 72 participants showed a clinically important benefit of acupuncture compared to sham acupuncture at ≤3 months. Moderate quality evidence from 1 study with 96 participants showed no clinically important difference between acupuncture and sham acupuncture at >3 months.

Discontinuation

Very low quality evidence from 17 studies with 1477 participants showed no clinically important difference between acupuncture and sham acupuncture at ≤3 months. Low quality evidence from 3 studies with 360 participants demonstrated that more people discontinued from acupuncture compared to sham acupuncture at >3 months.

1.6.1.2 Acupuncture versus usual care

Pain reduction

Low quality evidence from 5 studies with 234 participants showed a clinically important benefit of acupuncture compared to usual care at ≤3 months. Low quality evidence from 2 studies with 384 participants showed no clinically important difference between acupuncture and usual care at ≤3 months. Moderate quality evidence from 1 study with 3162 participants showed a clinically important benefit of acupuncture compared to usual care at ≤3 months.

Moderate quality evidence from 1 study with 344 participants showed no clinically important difference between acupuncture and usual care at >3 months.

Quality of life

Moderate quality evidence from 1 study with 3213 participants showed a clinically important benefit of acupuncture compared to usual care at ≤3 months. Very low quality evidence from 1 study with 100 participants showed both a clinically important benefit and no clinically important difference between acupuncture and usual care at ≤3 months (various quality of life subscales).

Low quality evidence from 1 study with 204 participants showed a clinically important benefit of acupuncture compared to usual care at >3 months.

Physical function

Very low quality evidence from 1 study with 45 participants showed no clinically important difference between acupuncture and usual care at ≤3 months. Very low quality evidence from 1 study with 100 participants showed a clinically important benefit of acupuncture compared to usual care at ≤3 months.

Psychological distress

Low quality evidence from 2 studies with 145 participants showed no clinically important difference between acupuncture and usual care at ≤3 months. Very low quality evidence from 1 study with 100 participants showed no clinically important difference between acupuncture and usual care at ≤3 months.

Pain self-efficacy

Very low quality evidence from 1 study with 294 participants showed a clinically important benefit of acupuncture compared to usual care at ≤3 months.

Pain interference

Very low quality evidence from 1 study with 100 participants showed a clinically important benefit of acupuncture compared to usual care at >3 months.

Sleep

Very low quality evidence from 1 study with 100 participants showed no clinically important difference between acupuncture and usual care at ≤3 months.

Discontinuation

Low quality evidence from 1 study with 66 participants showed no clinically important difference between acupuncture and usual care at ≤3 months.

1.6.1.3 Electro-acupuncture versus sham electro-acupuncture

1.6.1.4 Pain reduction

Very low quality evidence from 1 study with 61 participants showed no clinically important difference between electro-acupuncture and sham electro-acupuncture at ≤3 months. Very low quality evidence from 1 study with 61 participants showed no clinically important difference between electro-acupuncture and sham electro-acupuncture at >3 months.

Quality of life

Moderate quality evidence from 1 study with 163 participants showed no clinically important difference between electro-acupuncture and sham electro-acupuncture at ≤3 months. Low quality evidence from 1 study with 49 participants showed a clinically important benefit of electro-acupuncture compared to sham electro-acupuncture at ≤3 months. Moderate to low quality evidence from 1 study with 160 participants showed no clinically important difference between electro-acupuncture and sham electro-acupuncture at >3 months. Low quality evidence from 1 study with 49 participants showed no clinically important difference between electro-acupuncture and sham electro-acupuncture at >3 months.

Physical function

No evidence identified.

Psychological distress

No evidence identified.

Pain interference

Low quality evidence from 1 study with 49 participants showed a clinically important benefit of electro-acupuncture compared to sham electro-acupuncture at ≤3 months and >3 months.

Pain self-efficacy

No evidence identified.

Sleep

Very low quality evidence from 1 study with 55 participants showed no clinically important difference between electro-acupuncture and sham electro-acupuncture at ≤3 months.

Discontinuation

Low quality evidence from 6 studies with 444 participants showed a clinically important benefit of electro-acupuncture compared to sham electro-acupuncture at ≤3 months.

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Systematic review

Effects of acupuncture on dementia: An overview of systematic reviews

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ABSTRACT

Introduction: The published evidence on the effectiveness and safety of acupuncture on people with dementia has been inconsistent. This systematic review of overviews aims to summarize and evaluate the evidence from relevant systematic reviews (SRs) and meta-analyses to provide reliable evidence for future clinical treatment.

Methods: We searched PubMed, EMBASE, Web of Science, Cochrane Library, Cochrane Database of Systematic Reviews, DARE, Google Scholar, CNKI, VIP, CBM and Wangfang from the establishment of the databases to January 2020. The types of dementia based on pathology mainly include Alzheimer's disease (AD) and vascular dementia (VD). We included SRs of randomized controlled trials (RCTs) to assess the effect and safety of acupuncture on different outcomes in patients with dementia in our search. We assessed methodological quality of the included SRs using AMSTAR2, reporting quality using the PRISMA checklist, and quality of evidence of the outcomes using GRADE. Intraclass correlation coefficient (ICC) was used to test the consistency of the results of two evaluators.

Results: Thirteen SRs with meta-analyses met the inclusion criteria, including a total of 137 RCTs and 9012 participants. The results suggested that acupuncture has beneficial effects on effectiveness, cognitive ability, and activities of daily living in the treatment of dementia for 4–24 weeks, although there was a high degree of heterogeneity. Subgroup analysis showed that acupuncture was more effective in treating VD than AD. Further analyses also revealed that single acupuncture treatment was superior to combination treatments and that the safety of acupuncture was significantly higher than that of drug treatments. The quality of reports was rated "high" in one SR, "moderate" in five SRs, and "low" in seven SRs. The methodological quality of only one SR was "low," and the rest were rated "very low." The quality of evidence was rated "high" in one SR, including the effectiveness rate, MMSE, ADAS-cog, HDS, MoCA and FAQ.

Conclusion: Acupuncture showed potential therapeutic effects for patients with dementia, but the quality of the evidence was not high. Higher-quality RCTs are warranted to confirm the clinical effects of acupuncture in the treatment of dementia.

1. Introduction

Dementia is a chronic, acquired, and progressive cognitive impairment syndrome, which is characterized by slow cognitive decline in clinical practice and is common in people age 65 years and older. According to estimates from the World Alzheimer Report (2015), 46.8 million people worldwide have dementia, and this number is expected to increase to 74.7 million by 2030 and 131.5 million by 2050 [1]. It affects approximately 3% of people between the ages of 65 and 74, 19% between 75 and 84, and nearly half of those older than 85 years [2]. Therefore, dementia has become an important public health, economic, social, and political issue, receiving increased global attention.

Alzheimer's disease (AD) and vascular dementia (VD) are the two most common forms of dementia, accounting for 60–75% and 25% of all dementias, respectively [3,4]. Studies generally have focused on neurological characteristics and pathophysiological mechanisms, primarily identifying the deposition of amyloid A, oxidative stress, abnormal phosphorylation of Tau protein, and genetic inheritance as key risk factors [5,6].

Currently, no specific drugs can treat dementia or reverse the course of this disease. Existing therapeutics that target improvements in cognitive function mainly include acetylcholinesterase inhibitors (Donepezil,

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SYSTEMATIC REVIEW
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Effectiveness and Safety of Acupuncture for Vascular Cognitive Impairment: A Systematic Review and Meta-Analysis

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Background: Acupuncture may be a promising complementary therapy for vascular cognitive impairment (VCI) and has been extensively applied in China. However, its potential effects remain uncertain, and the clinical findings are inconsistent. This review aimed to systematically appraise the overall effectiveness and safety of acupuncture in treating VCI.

Methods: To investigate the effects of acupuncture on VCI from inception to February 28, 2021 using randomized clinical trials (RCTs), seven electro-databases [Cochrane Central Register of Controlled Trials (CENTRAL), PubMed, Embase, China National Knowledge Infrastructure (CNKI), Chinese Biomedical Literature Database (CBM), VIP, and Wanfang] were searched. Two independent investigators identified the eligible RCTs and extracted data into predesigned forms. The risk of bias (ROB) within each individual trial was evaluated using the Cochrane Collaboration's tool. Meta-analyses were conducted for calculating comparative effects in the RevMan software (version 5.3). The strength of attained evidence was rated using the online GRADEpro approach.

Results: A total of 48 RCTs involving 3,778 patients with VCI were included. The pooled data demonstrated that acupuncture was more beneficial for a global cognitive function [mean difference (MD) 1.86, 95% CI 1.19–2.54, $p < 0.01$] and activities of daily living (MD −3.08, 95% CI −4.81 to −1.35, $p < 0.01$) compared with western medicine (WM). The favorable results were also observed when acupuncture was combined with WM (MD 2.37, 95% CI 1.6–3.14, $p < 0.01$) or usual care (UC, MD 4.4, 95% CI 1.61–7.19, $p = 0.002$) in comparison with the corresponding control conditions. Meanwhile, the subgroup analysis did not indicate a statistical effect difference between manual acupuncture (MA) and electroacupuncture (EA) (inter-group $I^2 < 50\%$ and $p > 0.1$) when comparing acupuncture with WM. There were no significant differences in the occurrence of adverse events (AEs) between the acupuncture group and the control group ($p > 0.05$). Owing to the poor methodological quality and considerable heterogeneity among studies, the certainty of the evidence was low or very low.

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Conclusions: This review suggests that acupuncture as a monotherapy or an adjuvant therapy may play a positive role in improving the cognition and daily performance of VCI patients associated with few side effects. The difference in styles may not significantly influence its effectiveness. More rigorously designed and preregistered RCTs are highly desirable to verify the therapeutic benefits and determine an optimal acupuncture paradigm. The methodological and reporting quality of future researches should be enhanced by adhering to authoritative standardized statements.

Systematic Review Registration: [PROSPERO], identifier [No. CRD42017071820].

Keywords: Hasegawa's Dementia Scale, Montreal Cognitive Assessment, Alzheimer's Disease Assessment Scale-Cognitive Subscale, Barthel ADL Index, Functional Activities Questionnaire

INTRODUCTION

Next to Alzheimer's disease (AD), vascular cognitive impairment (VCI) is the second most frequent form of cognitive disorders, encompassing the full spectrum ranging from vascular subjective cognitive decline to vascular dementia, which is mainly caused by the diseased cerebral vasculature (O'Brien and Thomas, 2015; van der Flier et al., 2018). The prevalence of VCI is estimated at 1–1.5% in the global population above 65 years old (Jia et al., 2014; Rizzi et al., 2014), whereas the incidence of VCI increases with age, with the risk approximately doubling every 5.3 years, just slightly lower than that of AD (Jorm and Jolley, 1998). Meanwhile, VCI is also a serious challenge to healthcare providers and policymakers as the concomitant of the aging issue, which carries a heavy financial burden ranging from $17,000 to $55,200 per patient (Quentin et al., 2010; Zhou et al., 2019). The major underlying pathophysiology of VCI incorporates the interactions between vascular etiology, cerebral tissue dysfunction, white matter lesions, atrophy, and host factors such as age and education (Skrobot et al., 2016; Dichgans and Leys, 2017). Even though VCI is considered clinically and pathologically different from AD, VCI oftentimes coexists along with AD among older adults in the clinic (concurrent mixed dementia; Cechetto et al., 2008; Levine and Langa, 2011). In comparison to AD, the progress toward seeking available treatments for VCI has proven to be even more elusive and sluggish (O'Brien and Thomas, 2015). So far, the regulatory bodies and guideline groups have not approved any licensed drugs for effective disease modification in VCI. The present predominant strategy emphasizes symptomatic improvement and optimization of the quality of life for patients with VCI (Moniz-Cook et al., 2008; O'Brien and Thomas, 2015; National Collaborating Centre for Mental Health, 2018). More feasible therapeutic options for VCI are urgently needed.

Acupuncture, as an essential modality of traditional Chinese medicine (TCM), has been commonly practiced in the prevention and treatment of various diseases for millennia (Ulett et al., 1998). In recent decades, it receives increased attention from both the public and health professionals worldwide, even arousing the interest of major academic medical centers, especially for chronic disorders, which are difficult to be managed with conventional therapies (NIH Consensus Conference, 1998; Burke et al., 2006; World Health Organization, 2013). There are many categories of acupuncture approaches such as manual acupuncture (MA), electroacupuncture (EA), and scalp acupuncture (SA), which have turned out to be relatively less expensive with few adverse effects (Witt et al., 2009). As a non-pharmacological intervention with the intention to make patients recover to the postulated equilibrium state prior to illness (Endres et al., 2007), acupuncture has already been extensively used for VCI in plenty of Chinese medical institutions (Peng et al., 2007; Su et al., 2020a). A considerable number of emerging clinical trials demonstrated that acupuncture can serve as a promising treatment in improving the global cognitive status of patients with VCI (Chen et al., 2016, 2020; Yang et al., 2019). Meanwhile, various preclinical studies have also been conducted to explore the potential mechanisms of acupuncture *via* using the VCI animal model (Ye et al., 2017a; Du et al., 2018; Xiao et al., 2018). There may be multiple factors contributing to the neuroprotective effects of acupuncture, which can defer the pathological process of VCI. The underlying mechanisms of acupuncture are possibly reflected in protecting the neurons from oxidative stress, apoptosis, and neuroinflammation and in regulating glucose metabolism and neurotransmitters. In addition, another possible mechanism supporting the beneficial effect of acupuncture on VCI may be the enhancement of synaptic plasticity and blood vessel function (Ye et al., 2017b).

So far, systematic reviews (SRs) of acupuncture for VCI are relatively scant, whereas most of the existing randomized control trials (RCTs) are limited by the small sample size and study design flaws, which may bring about controversial results and cannot provide adequate evidence for further clinical applications. There was a Cochrane SR intending to appraise the efficacy and safety of acupuncture in treating VCI, which was firstly published in 2007 and updated in 2011 (Peng et al., 2007). However, due to its overcritical literature inclusion criteria, this SR did not include any RCTs and reached no valuable conclusion finally. Another SR published in 2017 only assessed the quality of reports concerning RCTs of SA for the treatment of VCI but did not synthesize the clinical outcomes (You et al., 2017). Given that there has been a further increase in newly published studies over the recent years since these two SRs have been published, it is of a strong necessity for us to conduct an updated SR and meta-analysis to re-evaluate its clinical benefits and safety.

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RESEARCH Open Access

Acupuncture for allergic rhinitis: a systematic review and meta-analysis

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Abstract

Background: In this study, we attempted to assess the efficacy and safety of acupuncture for allergic rhinitis (AR), and to test the robustness of the estimated effects.

Methods: The Cochrane methodology standard was followed to conduct this systematic review. Randomized controlled trials (RCTs) comparing acupuncture with other therapies for AR were included. Furthermore, trial sequential analysis was conducted to test the robustness of pooled results. Thirty trials with 4413 participants were included.

Results: Acupuncture improved the nasal symptoms on Total Nasal Symptom Score (TNSS) and quality of life measured by Rhinoconjunctivitis Quality of Life Questionnaire (RQLQ) in adults with AR, compared to acupuncture with no intervention. Acupuncture was also shown to be more effective than sham acupuncture for nasal symptom (RQLQ subscale, $n = 489$, MD −0.60, 95% CI −1.16 to −0.04) and quality of life (RQLQ, $n = 248$, −8.47 95% CI −14.91, −2.03). No clear difference was observed between acupuncture and cetirizine or loratadine. Interestingly, trial sequential analysis (TSA) failed to confirm the aforementioned results. The effect of acupuncture for children/adolescents with AR remains unclear due to insufficient data. The performance bias and attrition bias are serious in most studies that were included. Selection bias may also have affected the quality of the evidence.

Conclusion: Acupuncture may have an advantage over no intervention and sham acupuncture in improving nasal symptoms and quality of life for adults with AR. The effect of acupuncture and cetirizine or loratadine for AR may be similar. Additional trials are necessary to confirm these results.

Keywords: Acupuncture, Allergic rhinitis, Meta-analysis, Randomized controlled trials

Introduction

Allergic rhinitis (AR) is a symptomatic nasal disorder resulting from an IgE-mediated immunological reaction to allergen exposure [1]. As a worldwide health problem, AR is now estimated to affect nearly 1.4 billion people globally and continues to be on the rise [2]. Although AR is not a life-threatening illness, it underlies many complications such as bronchial asthma, sinusitis, nasal polyps, otitis media, and allergic conjunctivitis, which affect quality of life and work productivity [3, 4]. The current mainstream management of AR primarily includes allergen avoidance and pharmacotherapy such as topical steroids, oral antihistamines and immunotherapy [5]. These treatments are recommended by the National Guideline Clearinghouse (NGC) as they can rapidly relieve the nasal symptoms. Unfortunately, unpleasant side effects still limit their application. These include epistaxis, dry eyes, and sedation among others. Moreover, some patients prefer non-pharmacologic therapies [5].

Acupuncture was developed from Traditional Chinese Medicine (TCM) techniques. It utilizes acupuncture points, to stimulate lines of meridians that correspond to the flow of energy through the body [6]. Acupuncture

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REVIEW ARTICLE

Complementary therapies for bladder pain syndrome: a systematic review

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Abstract
Introduction and hypothesis Bladder pain syndrome is a difficult condition to treat. The purpose of this systematic review is to assess the effectiveness of various complementary therapies available for treatment.
Methods This review was conducted in adherence with Preferred Reporting Items for Systematic Reviews. Citations were retrieved using a comprehensive database search (from inception to July 2014: CINAHL, Cochrane, EMBASE, Medline and SIGEL and grey literature). Studies that fulfilled the inclusion criteria were selected. Eligibility consisted of women with bladder pain syndrome, an intervention of alternative/complementary therapies and an outcome of improvement of symptoms. Information regarding study characteristics and primary outcomes was collated. The Cochrane risk of bias scale was used to evaluate the quality of the studies included.
Results A total of 1,454 citations were identified, 11 studies fulfilled the inclusion criteria (4 randomised control trials [RCTs] and 7 prospective studies). The key interventions studied were acupuncture, relaxation therapy, physical therapy, hydrogen-rich therapy, diet and nitric oxide synthetase.
Conclusion Therapies with the potential for benefit in patients with bladder pain syndrome are dietary management, acupuncture and physical therapy. These findings were obtained from small studies and hence caution is advised. Robustly designed multicentre RCTs on these complementary therapies are needed to guide patients and clinicians.

Keywords Alternative or complementary therapies · Myofascial physical therapies · Acupuncture · Bladder pain syndrome

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Introduction

The European Society for the Study of Interstitial Cystitis/Bladder Pain Syndrome in 2008 defined bladder pain syndrome (BPS) as pelvic pain, pressure or discomfort perceived to be related to the bladder, lasting for at least 6 months, and accompanied by at least one other urinary symptom [1]. Urinary symptoms include the persistent urge to void or frequency, in the absence of other identifiable causes. The International Urogynaecological Association (IUGA) and the International Continence Society (ICS) produced a joint report on terminologies by Haylen et al. in 2010, defining bladder pain as a "complaint of supra pubic or retro-pubic pressure, discomfort or pain, associated with the bladder, generally aggravated by bladder filling. The symptom may persist or alleviate after voiding." [2]. An estimated 400,000 people in the UK suffer from BPS, the majority being women [3]. There is no definitive evidence to support an autoimmune, inflammatory, structural or infectious aetiology. Consequently, treating these patients is often challenging.

Intrauterine Devices as Treatment for Endometrial Cancer

Plain Language Summary:
Background: Should OHP cover an alternative treatment for cancer of the lining of the uterus?

Should OHP cover this treatment? Staff recommends covering this treatment for people who cannot have standard treatments (removal of the uterus and ovaries and/or radiation) or who want to be able to have a child in the future.

Question: Should IUD insertion procedure codes be added to the endometrial cancer line?

Question source: Medical Management Committee (MMC) of HSD

Issue: Progestin-containing intrauterine devices (IUDs) are included in the NCCN management of endometrial cancer for women who are not candidates for hysterectomy due to co-morbidities or desire for future fertility. Recently, MMC had a case in which a woman with significant co-morbidities was not able to have hysterectomy/oophorectomy nor pelvic radiation. IUD insertion was approved by exception. As this treatment is recommended in certain circumstances by NCCN, HERC staff recommend pairing IUD insertion with endometrial cancer so that these procedures can be approved without going through the exception process.

Evidence:

1) **Janda 2021**, FeMMe RCT of IUD for endometrial cancer
    a. N=154 patients
        i. Endometrial hyperplasia with atypia (EHA) for FIGO grade 1 endometrial adenocarcinoma (EAC)
        ii. BMI>30
        iii. Depth of myometrial invasion of <50% on MRI
        iv. CA125≤30 U/mL
        v. IUD with or without metformin (M) or weight loss (WL)
    b. After 6 months of treatment, the rate of pathologic complete response (pCR) was 61% (20/33, 95% CI: 42–77%) for OBS, 67% (22/33, 95% CI: 48–82%) for WL, and 57% (24/42, 95% CI: 41–72%) for M
    c. In summary, the feMMe trial demonstrates encouraging response rates for EHA and EAC to IUD therapy with or without metformin or weight loss

Expert guidelines

1) **NCCN 1.2022** Guideline for treatment of endometrial cancer
    a. Although the primary treatment of endometrial cancer is usually hysterectomy, continuous progestin-based therapy may be considered for highly selected patients with Grade 1, stage IA (noninvasive) disease who wish to preserve their fertility
    b. Continuous progestin-based therapy may include megestrol acetate, medroxyprogesterone, or an intrauterine device containing levonorgestrel. A durable complete response occurs in about 50% of patients
    c. For uterine-confined disease not suitable for primary surgery, EBRT and/or brachytherapy is the preferred treatment approach. Initial systemic therapy can also be considered for selected patients with uterine-confined tumors of endometrioid histology (eg, estrogen and progesterone receptor–positive [ER/PR-positive]). Patients

receiving hormonal therapy alone should be closely monitored by endometrial biopsy (eg, consider endometrial biopsies every 3–6 months). Progesterone-based therapy has been shown to provide some benefit with low toxicity in patients with low-grade tumors

HERC staff summary

The standard treatment for endometrial cancer is hysterectomy/oophorectomy with or without pelvic radiation. However, for women who are unable to undergo these therapies due to co-morbidities or due to a desire for fertility, progestin containing IUDs can be an alternative therapy.

HERC staff recommendation

1) Add 58300 (Insertion of intrauterine device (IUD)) to line 208 CANCER OF UTERUS

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Complete pathological response following levonorgestrel intrauterine device in clinically stage 1 endometrial adenocarcinoma: Results of a randomized clinical trial

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HIGHLIGHTS

- LNG-IUD is commonly used to treat patients with EHA or EAC.
- Complete response rates were 43% and 82%, for EAC and EHA, respectively.
- Pathological complete response was 61% for LNG-IUD alone.
- Pathological complete response was 67% for LNG-IUD plus weight loss.
- Pathological complete response was 57% for LNG-IUD plus metformin.

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ABSTRACT

Purpose. Intrauterine levonorgestrel (LNG-IUD) is used to treat patients with endometrial adenocarcinoma (EAC) and endometrial hyperplasia with atypia (EHA) but limited evidence is available on its effectiveness. The study determined the extent to which LNG-IUD with or without metformin (M) or weight loss (WL) achieves a pathological complete response (pCR) in patients with EAC or EHA.

Patients and methods. This phase II randomized controlled clinical trial enrolled patients with histologically confirmed, clinically stage 1 FIGO grade 1 EAC or EHA; a body mass index > 30 kg/m2; a depth of myometrial invasion of less than 50% on MRI; a serum CA125 ≤ 30 U/mL. All patients received LNG-IUD and were randomized

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Progestin/progesterone
Levonorgestrel intrauterine device
Metformin
Fertility preservation
Weight loss
Physical activity

to observation (OBS), M (500 mg orally twice daily), or WL (pooled analysis). The primary outcome measure was the proportion of patients developing a pCR (defined as absence of any evidence of EAC or EHA) after 6 months.

Results. From December 2012 to October 2019, 165 patients were enrolled and 154 completed the 6-months follow up. Women had a mean age of 53 years, and a mean BMI of 48 kg/m^2. Ninety-six patients were diagnosed with EAC (58%) and 69 patients with EHA (42%). Thirty-five participants were randomized to OBS, 36 to WL and 47 to M (10 patients were withdrawn). After 6 months the rate of pCR was 61% (95% CI 42% to 77%) for OBS, 67% (95% CI 48% to 82%) for WL and 57% (95% CI 41% to 72%) for M. Across the three treatment groups, the pCR was 82% and 43% for EHA and EAC, respectively.

Conclusion. Complete response rates at 6 months were encouraging for patients with EAC and EHA across the three groups.

Trial registration. U.S. National Library of Medicine, NCT01686126.

1. Introduction

Endometrial adenocarcinoma (EAC) is common, with an estimated global incidence of 382,069 new cases each year [1]. The growing incidence of EAC is likely due to ageing populations, and the increasing prevalence of obesity, which is a recognized risk factor for EAC and is estimated to cause at least 41% of new EACs [2–5]. Obesity is associated with low-grade EAC developing through endometrial hyperplasia with atypia (EHA).

Current standard treatment for EAC is total hysterectomy and bilateral salpingo-oophorectomy (THBSO) with or without surgical staging [6]. While surgical treatment is generally safe and effective, two groups of patients are poorly served by this strategy. Firstly, young women who wish to preserve childbearing capacity [7–9]. For these women, a THBSO will result in irrevocable loss of fertility [10]. Secondly, elderly, morbidly obese women and those with multiple medical comorbidities significantly increasing their risk for procedure-related adverse events, prolonged hospital stay, protracted recovery and high cost, even with enhanced postoperative care [11–13]. Therefore, professional societies, clinicians, and patients identified the development of effective, non-surgical treatments a research priority [14,15].

With the availability of intrauterine levonorgestrel (LNG-IUD), delivering progestins directly into the endometrial cavity without the adverse effects from systemic progestins became feasible [16]. Despite a lack of high-level evidence on the effectiveness of LNG-IUD, it is offered to EAC patients as a primary treatment option [17,18].

Metformin, has shown antiproliferative activity to reduce endometrial cancer cell growth in vitro [19–22]. Epidemiological evidence suggested it is associated with improved survival in women diagnosed with EAC [23–25]. Ongoing trials will determine the effectiveness of metformin in window of opportunity studies in EAC [26–28].

Obesity is potentially reversible through behavior-based weight loss interventions with or without weight loss medications [29] and while it reduces the risk of EAC [30] and increases overall survival in EAC patients [31], evidence that weight loss improves the likelihood of response to LNG-IUD is lacking.

The present trial investigated the effectiveness of LNG-IUD and whether metformin (M) or a weight loss (WL) intervention in addition to LNG-IUD improves the response rate in patients with EAC or EHA.

2. Methods

2.1. Trial design

The feMMe trial was an open label, three-arm randomized phase II clinical trial (NCT01686126). The initial and most recent trial protocol version are provided in Supplement 1. Ethics approvals were obtained from six Human Research Ethics Committees (HREC) in Australia and New Zealand and informed consent was obtained prior to randomization.

2.2. Participants

FeMMe trial methodology was reported previously [32,33]. In brief, the feMMe trial enrolled females over the age of 18 years with histologically confirmed EHA or FIGO grade 1 endometrioid EAC apparently confined to the uterus and with a BMI >30 kg/m2, who wished to maintain fertility or who were at high risk of surgical complications due to severe medical co-morbidities. A BMI of >30 kg/m2 was selected as previous data showed that these patients had increased risk of surgical complications when undergoing total hysterectomy [34]. Patients had to have a computed tomography or magnetic resonance imaging scan of the pelvis, abdomen and chest (chest X-ray was permitted) to confirm the absence of extrauterine disease. Patients with EAC had an MRI scan showing myometrial invasion of not more than 50%. Patients had to have a serum CA125 ≤ 30 U/mL at baseline [32,33]. Patients were considered ineligible if they had: ECOG score > 3; FIGO grade 2 or 3 endometrial cancer; histological cell type other than endometrioid; evidence of extrauterine disease on medical imaging; or received oral or intrauterine progestins prior to 12 weeks before planned randomization.

2.3. Interventions

All participants had a LNG-IUD inserted into the uterine cavity, releasing 52 mg of levonorgestrel at a rate of 20 microgram/24 h. Patients were randomly assigned to (i) Observation (OBS); (ii) weight loss intervention (WL); or (iii) oral metformin (M). Participants in the WL arm were provided with a voucher for a comprehensive six months subscription to Weight Watchers®, providing unlimited use of face-to-face and online support standardized dietary intervention [35]. Patients were encouraged to lose 7% body weight by 6 months and called monthly to assess adherence to the WL program, and encouragement to increase its active use. This was selected based on results from the Diabetes Intervention trial, which provided evidence that weight loss of 7% body weight induces a large biological effect (e.g. reduces incidence of diabetes by 58% [36], and incidence of hypertension by 26%) [37]. Participants assigned to the M arm had 500 mg of metformin orally, twice daily with meals (self-administered). This could be reduced to 250 mg tablets twice daily if the starting dose was not tolerated.

Patients had a HD&C or endometrial sampling at 3 and 6 months after randomization. Patients who developed progressive disease at 3 months were removed from the trial and treated as clinically appropriate. The endometrial sample taken at 6 months was used to assess the response to intervention. Other data collected at baseline included a detailed medical history including Charlson comorbidity score; sociodemographic characteristics; questionnaires on health-related quality of life, health services use, pelvic floor symptoms and dietary intake. These were repeated at 3 and 6 months.

Cochlear Implant Guideline

Plain Language Summary:
Background: Should OHP cover a device that provides a sense of sound for people who are deaf or severely hard of hearing (cochlear implants) for one-sided hearing loss or just for two-sided, as is currently covered? Also, should the current hearing loss criteria needed to qualify for a cochlear implant be updated to allow people with lower levels of hearing loss receive one?

1) A Medicaid director asked for a review of cochlear implants since the Centers for Medicaid and Medicare Services (CMS) updated the guidelines to include people with lower levels of hearing loss.

2) An organization requested cochlear implant coverage for single-sided hearing loss.

Should OHP change its coverage policy? Staff recommends OHP change coverage policy to include patients with lower levels of hearing loss but not include cochlear implants for single-sided hearing loss.

Question: Should the criteria for eligibility for cochlear implants be updated?

Question sources:

1) Holly Jo Hodges, CCO medical director
2) Cochlear

Issues:

1) CMS recently updated their coverage criteria for cochlear implants, reducing the hearing loss level required for eligibility. Dr. Hodges has requested a review of the current cochlear implant requirements in the Prioritized List guideline to see if the guideline needs to be updated in light of the new CMS guidance.
2) Cochlear is requesting review of lack of coverage of cochlear implants for single-sided deafness/unilateral hearing loss. Per Cochlear: "On January 10, 2022, the Food and Drug Administration (FDA) approved (P970051/S205) the Cochlear™ Nucleus® for the treatment of unilateral hearing loss (UHL)/single-sided deafness (SSD)… We are requesting you revise your cochlear implant medical coverage policy to include coverage for individuals with UHL/SSD candidates for surgical implantation." The company is specifically requesting expansion of coverage to:
    a. Individuals 5 years or older who have one ear with a severe to profound sensorineural hearing loss and obtain limited benefit from an appropriately fitted unilateral hearing device and one ear with normal or near normal hearing.
        i. In the ear to be implanted, a severe to profound sensorineural hearing loss is defined as a PTA at 500 Hz, 1000 Hz, 2000 Hz and 4000 Hz of > 80 dB HL.
        ii. In the contralateral ear, normal or near normal hearing is defined as a PTA at 500 Hz, 1000 Hz, 2000 Hz and 4000 Hz ≤ 30 dB HL.
    b. Limited benefit from an appropriately fit unilateral hearing device is defined as a score of less than or equal to 5% on a Consonant-Nucleus-Consonant (CNC) word test. For individuals between 5 years and 18 years of age, insufficient functional access to sound in the ear to be implanted must be determined by aided speech perception test scores of 5% or less on developmentally appropriate monosyllabic word lists when tested in the ear to be implanted alone.

c. Failed trial of at least 2 weeks wearing appropriately fit Contralateral Routing of Signal (CROS) hearing aid or another suitable hearing device.

A cochlear implant is an implanted electronic hearing device, designed to produce useful hearing sensations to a person with severe to profound nerve deafness by electrically stimulating nerves inside the inner ear.

Previous HSC/HERC review history

January 2005

Cochlear Implant: Criteria posted on OSHU website are the same as Medicare's, with the exception that for adults, the criteria is for test scores of 40% or less on open set sentence recognition. Current Medicare criteria is for test scores of 30% or less, though there is proposal to expand coverage to 40% or less, and 60% or less if the patient is enrolled in a clinical trial. Action: Adopt OHSU guidelines for cochlear implants.

Note: at this time, there were two cochlear implant guidelines, one for age 5 and older, one for under age 5

May 2013

Added a definition for profound sensorineural hearing loss for children age 5 and under: (defined as 91dB hearing loss or greater at 500, 1000 and 2000 Hz), and for post-linguistic adults: (defined as 71dB (decibels) hearing loss or greater at 500 Hz (hertz), 1000 Hz and 2000 Hz) and for prelinguistic adults: (defined as 91dB (decibels) hearing loss or greater at 500 Hz (hertz), 1000 Hz and 2000 Hz)

Allowed coverage of bilateral cochlear implants for all ages

March 2015

The two cochlear implant lines (over age 5 and age 5 and younger) were merged and the accompanying guidelines were merged into a single guideline and modified. Profound sensorineural hearing loss was defined as 71 dB hearing loss, and a definition was added regarding what was meant be "limited useful benefit for appropriately fitted hearing aids:" defined as a speech discrimination score of <30% on age appropriate testing for children and as scores of 40% or less on sentence recognition test in the best-aided listening condition for adults.

Specific notation was added to the unilateral hearing loss line clarifying that cochlear implants were not included for treatment of unilateral hearing loss.

Current Prioritized List status

CPT 69930 (Cochlear device implantation, with or without mastoidectomy) is on line 326 SENSORINEURAL HEARING LOSS Treatment: COCHLEAR IMPLANT

ICD-10-CM H90.3 (Sensorineural hearing loss, bilateral), H90.4X (Sensorineural hearing loss, unilateral), H90.A2X (Sensorineural hearing loss, unilateral, with restricted hearing on the contralateral side) and H90.A3X (Mixed conductive and sensorineural hearing loss, unilateral, with restricted hearing on the contralateral side) are on lines 311 HEARING LOSS - AGE 5 OR UNDER, 326 and 446 HEARING LOSS - OVER AGE OF FIVE

ICD-10-CM H90.6 (Mixed conductive and sensorineural hearing loss, bilateral) and H90.7 (Mixed conductive and sensorineural hearing loss, unilateral) are on lines 311 and 446

GUIDELINE NOTE 31, COCHLEAR IMPLANTATION

Line 326

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

A) Severe to profound sensorineural hearing loss in both ears (defined as 71dB hearing loss or greater at 500, 1000 and 2000 Hz)
B) Receive limited useful benefit from appropriately fitted hearing aids, defined as a speech discrimination score of <30% on age appropriate testing for children and as scores of 40% or less on sentence recognition test in the best-aided listening condition for adults
C) No medical contraindications
D) High motivation and appropriate expectations (both patient and family, when appropriate)

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

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.

Cochlear implant eligibility criteria, bilateral hearing loss

Expert guidelines

1) **American Academy of Otolaryngology-Head and Neck Surgery 2021**, Position Statement on general cochlear implantation candidacy
   a) https://www.entnet.org/resource/position-statement-cochlearimplants/#:~:text=The%20American%20Academy%20of%20Otolaryngology,with%20appropriately%20fit%20hearing%20aids.
   b) The American Academy of Otolaryngology-Head and Neck Surgery considers unilateral and bilateral cochlear implantation as appropriate treatment for adults and children over 9 months of age with moderate to profound hearing loss who have failed a trial with appropriately fit hearing aids.
      i) Definitions of moderate to profound not given
2) **American Academy of Otolaryngology-Head and Neck Surgery 2021**, Position Statement on pediatric cochlear implantation candidacy
   a) https://www.entnet.org/resource/position-statement-pediatric-cochlear-implantation-candidacy/
   b) There is ample evidence that early cochlear implantation of children with sensorineural hearing loss (SNHL) for whom hearing aids provide inadequate access to sound is advantageous. Early implantation improves auditory and language outcome and may be done safely.
   c) Children with bilateral severe to profound SNHL (4-frequency PTA > 80 dB HL or 2-frequency PTA > 85) will not receive adequate benefit from amplification and are candidates for bilateral cochlear implantation. Children with this degree of SNHL, including infants between 6 and 12 months, should receive cochlear implants as soon as practicable. Implantation below 12 months of age is correlated with better language outcome. Therefore, implantation should not be delayed by a hearing aid trial of an arbitrary prescribed length unsupported by current evidence. Infants below 12 months of age should have objective measures (auditory brainstem response/auditory steady state response testing) of SNHL with confirmatory audiometric results, when possible, prior to implantation.
   d) Children aged 12 months and older with a PTA between 65 and 85dB HL whose early aided auditory skill development and speech and language progress indicate a persistent, or widening, gap in age appropriate auditory and language skills are also eligible for implantation. The Pediatric Minimum Speech Test Battery is critical for providers working with this population to assess their functional benefit from amplification.
   e) For children to obtain the benefit of early implantation, referral of potentially eligible infants and children for candidacy evaluation should be a priority for professionals involved in diagnosis, audiological and medical management, and habilitation of childhood hearing loss. Pre- and post-cochlear implant auditory and spoken language habilitation therapy are essential services for this special population.

NICE 2019 https://www.nice.org.uk/guidance/ta566/resources/cochlear-implants-for-children-and-adults-with-severe-to-profound-deafness-pdf-82607085698245

1) Unilateral cochlear implantation is recommended as an option for people with severe to profound deafness who do not receive adequate benefit from acoustic hearing aids

a) For the purposes of this guidance, severe to profound deafness is defined as hearing only sounds that are louder than 80 dB HL (pure-tone audiometric threshold equal to or greater than 80 dB HL) at 2 or more frequencies (500 Hz, 1,000 Hz, 2,000 Hz, 3,000 Hz and 4,000 Hz) bilaterally without acoustic hearing aids.
b) Adequate benefit from acoustic hearing aids is defined for this guidance as:
    i) for adults, a phoneme score of 50% or greater on the Arthur Boothroyd word test presented at 70 dBA
    ii) for children, speech, language and listening skills appropriate to age, developmental stage and cognitive ability

2) Simultaneous bilateral cochlear implantation is recommended as an option for the following groups of people with severe to profound deafness who do not receive adequate benefit from acoustic hearing aids, as defined above:
    a) children
    b) adults who are blind or who have other disabilities that increase their reliance on auditory stimuli as a primary sensory mechanism for spatial awareness.
    c) Acquisition of cochlear implant systems for bilateral implantation should be at the lowest cost and include currently available discounts on list prices equivalent to 40% or more for the second implant.
3) Sequential bilateral cochlear implantation is not recommended as an option for people with severe to profound deafness.

Other payer policies

CMS 2022 Decision Memo regarding cochlear implantation https://www.cms.gov/medicare-coverage-database/view/ncacal-decision-memo.aspx?proposed=N&ncaid=306

a. We have concluded that the evidence is sufficient to determine that cochlear implantation may be covered for treatment of bilateral pre- or post-linguistic, sensorineural, moderate-to-profound hearing loss in individuals who demonstrate limited benefit from amplification. Limited benefit from amplification is defined by test scores of less than or equal to 60% correct in the best-aided listening condition on recorded tests of open-set sentence cognition. Patients must meet all of the following criteria.
    i. Diagnosis of bilateral moderate-to-profound sensorineural hearing impairment with limited benefit from appropriate hearing (or vibrotactile) aids;
    ii. Cognitive ability to use auditory clues and a willingness to undergo an extended program of rehabilitation; Freedom from middle ear infection, an accessible cochlear lumen that is structurally suited to implantation, and freedom from lesions in the auditory nerve and acoustic areas of the central nervous system;
    iii. No contraindications to surgery; and
    iv. The device must be used in accordance with Food and Drug Administration (FDA)-approved labeling.
b. CMS may also provide coverage of cochlear implants for beneficiaries not meeting the coverage criteria listed above when performed in the context of FDA-approved category B investigational device exemption clinical trials as defined at 42 CFR 405.201 or as a routine cost in clinical trials under section 310.1 of the National Coverage Determinations Manual titled Routine Costs in Clinical Trials.

c. We are expanding coverage by broadening the patient criteria and removing the requirement that for individuals with hearing test scores of > 40 % and ≤ 60 %

2) Aetna 2022

a. Aetna considers uniaural (monaural) or binaural (bilateral) cochlear implantation a medically necessary prosthetic for adults aged 18 years and older with bilateral, pre- or post-linguistic, sensorineural, moderate-to-profound hearing impairment who meet *both* of the following criteria
   i. Member has bilateral severe to profound sensorineural hearing loss determined by an air conduction pure tone average of 70 dB or greater at 500 Hz, 1000 Hz, and 2000 Hz; *and*
   ii. Member has limited benefit from appropriately fitted binaural hearing aids. Limited benefit from amplification is defined by test scores of 40 % correct or less in best-aided listening condition on open-set sentence cognition (e.g., Central Institute for the Deaf (CID) sentences, Hearing in Noise Test sentences (HINT), and consonant-nucleus-consonant (CNC) test.

b. Aetna considers uniaural (monaural) or binaural (bilateral) cochlear implantation a medically necessary prosthetic for infants and children with bilateral sensorineural hearing impairment who meet *all* of the following criteria:
   i. Child has profound, bilateral sensorineural hearing loss determined by an air conduction pure tone average of 70 dB or greater at 500 Hz, and 90 dB or greater at 1000 and 2000 Hz; *and*
   ii. Child has limited benefit from appropriately fitted binaural hearing aids. For children 4 years of age or younger, limited benefit is defined as failure to reach developmentally appropriate auditory milestones measured using the Infant-Toddler Meaningful Auditory Integration Scale, the Meaningful Auditory Integration Scale, or the Early Speech Perception test, or less than 20 % correct on open-set word recognition test (Multisyllabic Lexical Neighborhood Test) in conjunction with appropriate amplification and participation in intensive aural habilitation over a 3 to 6 month period. For children older than 4 years of age, limited benefit is defined as less than 12 % correct on the Phonetically Balanced-Kindergarten Test, or less than 30 % correct on the Hearing in Noise Test for children, the open-set Multi-syllabic Lexical Neighborhood Test (MLNT) or Lexical Neighborhood Test (LNT), depending on the child's cognitive ability and linguistic skills

Cochlear implants for unilateral hearing loss

Evidence

1) **Benchetrit 2021**, systematic review and meta-analysis of cochlear implantation of children with single-sided deafness
   a. N=12 studies (119 children)
      i. N=6 studies in the meta-analysis
      ii. All were case series (N=3-23 patients)
   b. Most children showed clinically meaningful improvement in speech perception in noise (39 of 49 children [79.6%]) and in quiet (34 of 42 children [81.0%]). Sound localization as measured by degrees of error from true location (mean difference [MD], –24.78°; 95% CI, –34.16° to –15.40°; I 2 = 10%) improved statistically significantly after cochlear implantation.

c. Cochlear implantation was associated with statistically significant improvements in all 3 domains (speech hearing, spatial hearing, and hearing quality)
d. Conclusion: This systematic review and meta-analysis found that cochlear implantation for children with SSD was associated with clinically meaningful improvements in audiological and patient-reported outcomes; shorter duration of deafness may lead to better outcomes. The heterogeneity and small sample sizes of the included studies emphasize the need for robust clinical studies.

Other payer policies

1) **Anthem BCBS 2022**: A cochlear implant is considered **not medically necessary** for unilateral deafness
2) **Aetna 2022**
    a. Aetna considers uniaural (monaural) cochlear implantation medically necessary for individuals aged 1 year and older with single sided deafness (SSD) or asymmetric hearing loss (AHL) who meet the following criteria:
        i. Persons with single-sided deafness (SSD) who have profound sensorineural hearing loss in one ear and normal hearing or mild sensorineural hearing loss in the other ear, who have obtained limited benefit from a one-month or longer trial of an appropriately fitted unilateral hearing aid in the ear to be implanted; *or*
        ii. Persons with asymmetric hearing loss (AHL) who have profound sensorineural hearing loss in one ear and mild to moderately severe sensorineural hearing loss in the other ear who have obtained limited benefit from a one-month or longer trial of an appropriately fitted unilateral hearing aid in the ear to be implanted.
    b. For adults 18 years of age or older with SSD or AHL, limited benefit from unilateral amplification is defined by aided speech perception test scores of 5 % correct or less on monosyllabic consonant-nucleus-consonant (CNC) words in quiet when tested in the ear to be implanted alone. For children and adolescents with SSD or AHL, insufficient functional access to sound in the ear to be implanted must be determined by aided speech perception test scores of 5% or less on developmentally appropriate monosyllabic word lists when tested in the ear to be implanted alone.
    c. Before implantation with a cochlear implant, individuals with SSD or AHL must have at least one month of experience wearing a hearing aid, a CROS hearing aid or other relevant device and not show any subjective benefit.
    d. For SSD and AHL indications, profound hearing loss is defined as having a PTA of 90 dB HL or greater at 500 Hz, 1000 Hz, 2000 Hz and 4000 Hz. Normal hearing is defined as having a PTA of up to 15 dB HL at 500 Hz, 1000 Hz, 2000 Hz and 4000 Hz. Mild hearing loss is defined as having a PTA of up to 30 dB HL at 500 Hz, 1000 Hz, 2000 Hz and 4000 Hz. Mild to moderately severe hearing loss is defined as having a PTA ranging from 31 to up to 55 dB HL at 500 Hz, 1000 Hz, 2000 Hz and 4000 Hz.

HERC staff summary

Specialty society and CMS guidelines have changed their definitions of what is considered "useful benefit" from hearing aids.

For children, the AAO-HNS 2021 position statement states that "implantation should not be delayed by a hearing aid trial of an arbitrary prescribed length unsupported by current evidence." The AAO-HNS now recommends cochlear implants for all children with >80 DB hearing loss and for children aged 12 months and older with between 65 and 85dB hearing loss whose early aided auditory skill development and speech and language progress indicate a persistent, or widening, gap in age appropriate auditory and language skills. A recent recommendation by NICE is similar to the AAO-HNS recommendation.

For adults, CMS has changed the definition of benefit from hearing aids to ≤ 60% correct in the best-aided listening condition on recorded tests of open-set sentence cognition (broadening this from ≤ 40 % correct).

CMS and AAO-HNS recommend consideration of cochlear implants for adults with moderate to profound hearing loss. Based on HERC staff review, there does not appear to be a standard definition of moderate, severe, and profound hearing loss. Currently, Prioritized List coverage is limited to severe to profound (>71 dB) hearing loss in both ears for both adults and children.

There is little evidence regarding treatment of single sided profound hearing loss with cochlear implants. Based on a 2021 systematic review and meta-analysis, the only data consists of small case series. Private payers are varied in their coverage for cochlear implants for unilateral hearing loss.

HERC staff recommendations:

1) Modify GN31 as shown below
2) Make no change in non-coverage of cochlear implants for unilateral hearing loss
    a. Children under age 21 will still require an individualized review prior to denial

GUIDELINE NOTE 31, COCHLEAR IMPLANTATION

Line 326

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

A) Children who are either
    1) Any age with severe to profound sensorineural hearing loss in both ears (defined as 4-frequency PTA > 80 dB HL or 2-frequency PTA > 85) ~~(defined as 4 frequency 71 dB hearing loss or greater at 500, 1000 and 2000 Hz~~), OR
    2) Aged 12 months an older with between 65 and 85 dB hearing loss in both ears whose early aided auditory skill development and speech and language progress indicate a persistent, or widening, gap in age appropriate auditory and language skills
B) Adults with bilateral severe to profound sensorineural hearing impairment (defined as >71 dB hearing loss in both ears) with limited benefit from appropriate hearing (or vibrotactile) aids. Limited benefit from amplification is defined by test scores of less than or equal to 60% correct in the best-aided listening condition on recorded tests of open-set sentence cognition
~~C) Receive limited useful benefit from appropriately fitted hearing aids, defined as a speech discrimination score of <30% on age appropriate testing for children and as scores of 40% or less on sentence recognition test in the best-aided listening condition for adults~~

D) No medical contraindications
E) High motivation and appropriate expectations (both patient and family, when appropriate)

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

JAMA Otolaryngology–Head & Neck Surgery | Original Investigation

Cochlear Implantation in Children With Single-Sided Deafness
A Systematic Review and Meta-analysis

Liliya Benchetrit, MD; Evette A. Ronner, BA; Samantha Anne, MS, MD; Michael S. Cohen, MD

IMPORTANCE In 2019, the US Food and Drug Administration approved cochlear implantation for children with single-sided deafness (SSD). The absence of robust clinical data specific to pediatric patients to guide shared decision-making and to identify potential advantages is a challenge in family counseling.

OBJECTIVE To evaluate the audiological and patient-reported outcomes in children who underwent cochlear implantation for SSD and to assess the association between time of implantation, subjective outcomes, and cochlear implant device use rates.

DATA SOURCE MEDLINE, Embase, Scopus, Cochrane, and PubMed were searched for English-language articles that were published in a peer-reviewed journal from database inception to February 18, 2020.

STUDY SELECTION Inclusion criteria were designed to capture studies that evaluated pediatric patients (1) younger than 18 years, (2) with a diagnosis of SSD for which they underwent a cochlear implantation, and (3) with at least 1 outcome of interest measured numerically: speech perception, sound localization, device use, and patient-reported outcomes. Of the 526 articles reviewed, 12 (2.3%) met the selection criteria.

DATA EXTRACTION AND SYNTHESIS The Meta-analyses Of Observational Studies in Epidemiology (MOOSE) reporting guidelines were followed. Data were pooled using fixed-effect and random-effect models. The following information was obtained from each article: study characteristics, patient characteristics, hearing loss and intervention characteristics, and outcomes.

MAIN OUTCOMES AND MEASURES Outcomes were (1) postoperative changes in speech perception (in quiet was measured as a proportion of correct responses, and in noise was measured as decibel signal to noise ratio for speech reception threshold) and sound localization (measured in degree of localization error), (2) patient-reported audiological outcomes (measured by the speech, spatial, and qualities of hearing scale), and (3) device use rates among children who received cochlear implantation for SSD.

RESULTS Twelve observational studies that evaluated 119 children (mean [SD] age, 6.6 [4.0] years) with SSD who received a cochlear implant were included. Most children showed clinically meaningful improvement in speech perception in noise (39 of 49 children [79.6%]) and in quiet (34 of 42 children [81.0%]). Long duration of deafness (>4 years in congenital SSD and >7 years in perilingual SSD) was the most commonly proposed reason for lack of improvement. Sound localization as measured by degrees of error from true location (mean difference [MD], −24.78°; 95% CI, −34.16° to −15.40°; I^2 = 10%) improved statistically significantly after cochlear implantation. Patients with acquired SSD and shorter duration of deafness compared with those with congenital SSD reported greater improvements in speech (MD, 2.27; 95% CI, 1.89-2.65 vs 1.58; 95% CI, 1.00-2.16) and spatial (MD, 2.95; 95% CI, 2.66-3.24 vs 1.68; 95% CI, 0.96-2.39) hearing qualities. The duration of deafness among device nonusers was statistically significantly longer than the duration of deafness among regular device users (median difference, 6.84; 95% CI, 4.02-9.58).

CONCLUSIONS AND RELEVANCE This systematic review and meta-analysis found that cochlear implantation for children with SSD was associated with clinically meaningful improvements in audiological and patient-reported outcomes; shorter duration of deafness may lead to better outcomes. These findings can guide future research efforts, refine cochlear implantation candidacy criteria, and aid in family counseling and shared decision-making.

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Supplemental content

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CPAP Titration

Plain Language Summary:
Background: An overnight sleep test used to correctly set the pressure (continuous positive airway pressure (CPAP)) on an in-home machine used to treat people with sleep apnea. The first test is covered on OHP. Should OHP cover repeat tests to adjust the CPAP device?

Should OHP cover this treatment? Staff recommends covering up to two repeat sleep tests per year when certain factors occur (for example: weight change, worsening health conditions related to sleep apnea) based on expert input.

Question: Should the obstructive sleep apnea diagnostic guideline be modified to specify when and how often repeat sleep studies for Continuous Positive Airway (CPAP) titration are covered?

Question source: Providence CCO

Issue: The current guideline for diagnosis of obstructive sleep apnea (OSA) lists criteria for when initial sleep studies are covered. Providence CCO reviewers are seeing multiple requests for CPAP titrations (CPT 95811) after a diagnostic sleep study. The CCO is requesting clarification of coverage for repeat sleep studies/CPAP titration studies.

Current Prioritized List status
Both of the following are on the DIAGNOSTIC PROCEDURES file:

CPT **95810** Polysomnography; age 6 years or older, sleep staging with 4 or more additional parameters of sleep, attended by a technologist

CPT **95811** Polysomnography; age 6 years or older, sleep staging with 4 or more additional parameters of sleep, with initiation of continuous positive airway pressure therapy or bilevel ventilation, attended by a technologist

DIAGNOSTIC GUIDELINE D8, DIAGNOSTIC TESTING FOR OBSTRUCTIVE SLEEP APNEA (OSA)
For adults over the age of 18 years:

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

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

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

For children age of 18 or younger:

A) Obstructive sleep apnea (OSA) must be diagnosed by

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

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

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

GUIDELINE NOTE 27, TREATMENT OF SLEEP APNEA

Line 202

For adults over the age of 18 years:

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

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

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

D) Surgery for sleep apnea in adults is not included on this line (due to lack of evidence of efficacy). Surgical codes are included on this line only for children who meet criteria below

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

For children age of 18 years or younger:

A) Adenotonsillectomy is an appropriate first line treatment for children with OSA. Adenoidectomy without tonsillectomy is only covered when a child with OSA has previously had a tonsillectomy,

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

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

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

D) CPAP will be covered for children through age 18 on an ongoing basis if:
   1) There is documentation of improvement in sleep disruption and daytime sleepiness and behavior problems with CPAP use, AND
   2) Annual re-evaluation for CPAP demonstrates ongoing clinical benefit and compliance with use, defined as use of CPAP for at least four hours per night on 70% of the nights in a consecutive 30 day period

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

Evidence

No reviews or expert guidelines were found regarding the frequency of repeat sleep studies. Sleep medicine specialists were consulted and recommended review of the American Academy of Sleep Medicine guidelines; however, no guidelines were found addressing repeat sleep studies.

Expert guidelines

1) **Choosing Wisely 2014**
   a. Don't perform positive airway pressure re-titration studies in asymptomatic, adherent sleep apnea patients with stable weight.
      i. Re-titration of positive airway pressure (PAP) is not indicated for adult obstructive sleep apnea patients with stable weight whose symptoms are well controlled by their current PAP treatment. Follow-up PSG or re-titration is indicated for adult patients who are again symptomatic despite the continued, proper use of PAP, especially if they have gained substantial weight (e.g. 10% of original weight) since the last titration study. A new diagnostic PSG or re-titration may be indicated for patients who have lost substantial weight, to determine whether PAP treatment is still necessary

Other payer policies

1) **Aetna 2022**
   a. It may be necessary to perform repeat sleep studies up to twice a year for *any* of the following indications:
      i. To determine whether positive airway pressure treatment (i.e., CPAP, bilevel positive airway pressure (BiPAP), demand positive airway pressure (DPAP), variable positive airway pressure (VPAP), or auto-titrating positive airway

pressure (AutoPAP)) continues to be effective in persons with new or persistent symptoms, after interrogation of current positive airway pressure device; *or*

ii. To determine whether positive airway pressure treatment settings need to be changed in persons with new or persistent symptoms, after interrogation of current positive airway pressure device. (**Note**: This criterion does not apply to AutoPAP devices, as these devices are automatically titrated and do not require manual adjustment of treatment settings.); *or*

iii. For persons with substantial weight loss (loss of 10 percent or more body weight) or some other change in their medical condition that would affect the need for continued positive airway pressure treatment (e.g., heart attack, stroke, heart failure), to determine whether continued treatment with positive airway pressure treatment is necessary; *or*

iv. To assess treatment response after upper airway surgical procedures and after initial treatment with oral appliances.

2) Cigna 2021

a. Repeat Titration study can be performed if any of the following criteria is met:
   i. OSA currently on CPAP
      1. Re-assessment of treatment results for an individual with known OSA currently on CPAP therapy can be performed when any of the following has occurred:
         a. Substantial weight gain (10% of body weight) with return of symptoms.
         b. BMI decreases by 10% and there is intolerance of PAP pressure
         c. Clinical response is insufficient despite treatment
         d. Symptoms return despite a good initial response to CPAP
         e. Development of hypertension or worsening of hypertension despite a minimum of three months of adherent PAP usage.
         f. New onset decompensated heart failure or new stroke or TIA in a patient adherent to PAP therapy
         g. PAP machine download with AHI ≥5/hr with return of symptoms
         h. Must demonstrate that recurrent or continued symptoms are not due to insufficient compliance (must be using PAP >70% of nights, 4+hrs/night with continued symptoms).
         i. Results of previous medically necessary sleep test were inadequate and not diagnostic due to limited sleep time or other specified variables.
         j. NOT to assess for the efficacy of PAP therapy in the absence of recurrent or changed symptoms
         k. NOT to supply new PAP equipment.

b. OSA currently treated with bi-level PAP, APAP, ASV Re-assessment of treatment results (with CPT® 95811) for a patient with known OSA currently treated with bilevel PAP, APAP, ASV can be performed when any of the following has occurred:
   i. Substantial weight gain (10% of body weight) with return of symptoms.
   ii. BMI decreases by 10% and there is intolerance of PAP pressure o Clinical response is insufficient despite treatment
   iii. Symptoms return despite a good initial response to CPAP. o PAP machine download with AHI ≥5/hr with return of symptoms or ≥15/hr with or without return of symptoms.

iv. Must demonstrate that recurrent or continued symptoms are not due to insufficient compliance (must be using PAP ≥70% of nights, 4+hrs/night with continued symptoms).
v. Results of previous medically necessary sleep test were inadequate and not diagnostic due to limited sleep time or other specified variables.
vi. NOT to assess for the efficacy of PAP therapy in the absence of recurrent or changed symptoms
vii. NOT to supply new PAP equipment.

3. Carecentrix 2021

a. A repeat PSG, HSAT, or Split Night Study to confirm the diagnosis of sleep disorders meets the definition of medical necessity when the member meets previously stated criteria for a PSG, HSAT, or Split Night as outlined above and at least ONE of the following conditions is met:
    i. Recent HSAT (less than 1 year old) confirmed to be non-diagnostic:
        1. A previous home sleep study was technically inadequate and there was a valid attempt to retest the member via HSAT OR
        2. A previous home sleep study failed to establish the diagnosis of OSA in a member with a high pretest probability of OSA.
    ii. Member has had a significant change in weight that has impacted signs/symptoms of obstructive sleep apnea, specifically weight gain or weight loss of greater than or equal to 10% of total body weight, when re-evaluation is warranted to modify therapy.
    iii. Reassessment of clinical indicators of obstructive sleep apnea to determine the effectiveness of treatment after surgical intervention:
        1. Tonsillectomy,
        2. Adenoidectomy,
        3. Uvulopalatoplasty (UPPP),
        4. Maxillomandibular Advancement Surgery (MMA)
        5. Other upper airway surgery/implantation for treatment of obstructive sleep apnea
    iv. Implementation and evaluation of a fabricated oral mandibular advancement appliance (OAT) by a qualified healthcare professional:
        1. Treatment efficacy of an oral mandibular appliance may be assessed using HSAT, OR
        2. An oral mandibular appliance may be adjusted manually during polysomnography to eliminate sleep disordered breathing in the sleep laboratory by a sleep technologist, and as prescribed by the qualified healthcare professional.
b. A repeat in-lab PAP titration (95811) meets the definition of medical necessity for a member who is known to have OSA when (1&2):
    i. A diagnostic sleep test has been submitted to confirm the diagnosis of OSA AND, any of the following:
        1. The member is documented to have a recurrence of OSA related symptoms, such as snoring, excessive daytime somnolence, fatigue, disrupted sleep, etc. or persistent elevation in AHI documented from PAP device download while adherent to PAP therapy (use ≥4 hours per night on 70% of nights during a consecutive thirty (30) day period),

2. The member has a 10% change in body weight which has resulted in a recurrence of OSA-related symptoms,
3. The member has upper airway surgery, which has resulted in a recurrence of OSA-related symptoms,
4. Significant oxygen desaturation found during diagnostic testing:
    a. O2 saturation <90% for greater than 15 % of recording time during a diagnostic home sleep apnea test or diagnostic facility based PSG, OR
    b. O2 saturation < 80% for greater than 1% of recording time during a diagnostic home sleep apnea test or diagnostic facility based PSG

ii. The member is not a candidate for APAP based on the presence of co-morbid medical conditions or concomitant sleep disorders

Expert input:

Dr. Derek Lam, OHSU sleep medicine

Dr. Lam agreed with the HERC staff recommended wording regarding repeat studies. He had some concerns about applying these criteria to children, but the section with the added wording only applies to adults aged 18 and over.

CPAP Titration

HERC staff summary

There is a dearth of data on how often sleep studies need to be performed for patients on CPAP. The American Academy of Sleep Medicine does not have a specific guideline regarding repeat sleep studies other than a statement that re-titration is not needed in asymptomatic, adherent patients with stable weight. Major insurers have similar criteria for repeat sleep studies: recurrence of OSA symptoms, weight change of 10% of body weight, new or worsening health conditions related to OSA, and to assess treatment response after upper airway surgical procedures and after initial treatment with oral appliances. Some major insurers limit repeat sleep studies to twice per year.

HERC staff recommendation:

1) Modify Diagnostic Guideline D8 as shown below

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

For adults over the age of 18 years:

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

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

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

D) Repeat sleep studies are covered up to twice a year when one of the following has occurred since the most recent test:
   1) recurrence of OSA symptoms
   2) weight change of more than 10% of body weight
   3) new or worsening health conditions related to OSA
   4) upper airway surgical procedures or initial treatment with oral appliances

For children age of 18 or younger:

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

B) Polysomnography and/or consultation with a sleep medicine specialist to support the diagnosis of OSA and/or to identify perioperative risk is recommended for
   1) high-risk children (i.e. children with cranio-facial abnormalities, neuromuscular disorders, Down syndrome, etc.)

2) children with equivocal indications for adenotonsillectomy (such as discordance between tonsillar size on physical examination and the reported severity of sleep-disordered breathing), children younger than three years of age

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

Apnea-Hypopnea Index Scoring for Sleep Apnea Evaluation

Plain Language Summary:
Background: Should a guideline about episodes of lack of oxygen during sleep be changed to spell out how a particular marker (apnea-hypopnea index (AHI)) is presented?

Should OHP cover this treatment? Staff recommends using a marker of over 4% AHI because the literature shows the effectiveness for a breathing machine (CPAP) is difficult to study and draw conclusions. Also, the Centers for Medicaid and Medicare Services (CMS) states it would not use under 4% without additional studies.

Question: Should the sleep apnea guideline be modified to specify how the apnea-hypopnea index (AHI) needs to be calculated and reported?

Question source: CCO medical directors

Issue: The severity of OSA is usually graded based on the number of disordered breathing events per hour of sleep. These are generally calculated as the apnea-hypopnea index (AHI), equal to number of "apneas" (cessation or near cessation of airflow) plus the number of "hypopneas" (reductions in airflow associated with certain physiologic consequences) per hour of sleep. The AHI thus becomes a measure of severity and can have implications for whether and what type of treatment is indicated. As the underlying criteria to determine AHI, the definition of hypopnea has a significant influence on how many patients are found to have an AHI high enough to qualify for a diagnosis of sleep apnea, and thus qualify for treatments such as CPAP. The CCO medical directors are asking for clarification of which method should be used for determination of eligibility for treatment of OSA (CPAP, surgery, etc.).

The most recent AASM manual for scoring of sleep and associated events (2020) recommends using a 3% oxygen desaturation as the definition of an AHI. Earlier AASM scoring manuals recommended a 4% oxygen desaturation, which is what CMS continues to recommend using.

As reported in Berry (2022): In 2001, the CMS accepted the use of an AHI based on a hypopnea defined by ≥ 30% drop in airflow associated with a ≥ 4% drop in the oxygen saturation (H4, AHI4). In 2007, the AASM Scoring Manual listed a recommended hypopnea definition consistent with H4 and an alternative definition based on a ≥ 50% drop in airflow for ≥ 10 seconds associated with a ≥ 3% desaturation or an arousal. In 2012, based on consensus, the Sleep Apnea Definition Task Force recommended a hypopnea definition based on a ≥ 30% drop in airflow for ≥ 10 seconds associated with a ≥ 3% drop in the oxygen saturation or an arousal (H3A), with the rationale that this would allow a wider spectrum of symptomatic patients to qualify for treatment. The AASM Scoring Manual subsequently included a recommended hypopnea definition (H3A, AHI3A) and an acceptable definition (H4, AHI4). AASM representatives met with CMS in both June 2013 and June 2018 to discuss the AASM's recommendation to use the more inclusive H3A definition, rather than the H4 hypopnea definition, in the national coverage determination for PAP therapy for OSA. Through the discussion, it was clear that CMS would require more published data concerning the long-term health consequences of hypopneas scored using the H3A definition before considering adopting this change.

HERC review history
The HERC reviewed sleep studies as part of a coverage guidance in 2013. There did not appear to be any discussion about how to define an AHI in the coverage guidance materials. The last review of diagnosis

of sleep apnea was in March 2018. The 2018 review noted the AASM 2017 guidelines, but did not specifically addresses the definition of hypopnea.

Current Prioritized List status

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

For adults over the age of 18 years:

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

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

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

For children age of 18 or younger:

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

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

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

GUIDELINE NOTE 27, TREATMENT OF SLEEP APNEA

Line 202

For adults over the age of 18 years:

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

B) CPAP coverage subsequent to the initial 12 weeks is based on documented patient tolerance, compliance, and clinical benefit. Compliance (adherence to therapy) is defined as use of CPAP for at least four hours per night on 70% of the nights during a consecutive 30-day period.
C) Mandibular advancement devices (oral appliances) are covered for those for whom CPAP fails or is contraindicated.
D) Surgery for sleep apnea in adults is not included on this line (due to lack of evidence of efficacy). Surgical codes are included on this line only for children who meet criteria below
E) Hypoglossal nerve stimulation for treatment of obstructive sleep apnea is not included on this line due to insufficient evidence of effectiveness and evidence of harm.

For children age of 18 years or younger:

A) Adenotonsillectomy is an appropriate first line treatment for children with OSA. Adenoidectomy without tonsillectomy is only covered when a child with OSA has previously had a tonsillectomy, when tonsillectomy is contraindicated, or when tonsillar hypertrophy is not present. More complex surgical treatments are only included on this line for children with craniofacial anomalies.
B) Intranasal corticosteroids are an option for children with mild OSA in whom adenotonsillectomy is contraindicated or for mild postoperative OSA.
C) CPAP is covered for a 3 month trial for children through age 18 who have
   1) undergone surgery or are not candidates for surgery, AND
   2) have documented residual sleep apnea symptoms (sleep disruption and/or significant desaturations) with residual daytime symptoms (daytime sleepiness or behavior problems)
D) CPAP will be covered for children through age 18 on an ongoing basis if:
   1) There is documentation of improvement in sleep disruption and daytime sleepiness and behavior problems with CPAP use, AND

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

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

Evidence

1) **AHRQ 2021 *DRAFT*** review of the effectiveness of CPAP for treatment of OSA
    a. Across 47 eligible studies, reporting and choice of criteria to define sleep study breathing measures and OSA were highly inconsistent. The majority of studies did not explicitly report full criteria or definitions. For example, only 41 percent of studies fully explicitly reported apnea and hypopnea definitions…Most studies citing published criteria to define sleep study measures (26/30) cited some version of the American Academy of Sleep Medicine (AASM) criteria. However, there was no discernable consistency in choice of a threshold and citation of a specific AASM version. Of interest was whether the different definitions of sleep measures used had an impact on study findings regarding clinical effect of CPAP. However, as described below, there were no discernable differences across studies, so we could not assess the impact of the variable definitions.
    b. Based on RCT data alone, there is low SoE that CPAP use does not affect the risk of all-cause mortality, stroke, myocardial infarction, composite CV outcomes, driving accidents, and incident diabetes
    c. There is low SoE that CPAP does not yield clinically meaningful changes in depression and anxiety symptoms, cognitive function, or QoL.
    d. Conclusion: The effect of CPAP on most long-term clinical outcomes is unclear, due to insufficient evidence from sparse studies and/or highly imprecise estimates. Additional studies are needed before we have a clear understanding of the potential effects of CPAP on long-term outcomes for patients with OSA
2) **Korotinsky 2016**, comparison of AASM vs CMS definition of AHI and eligibility for CPAP treatment
    a. N=112 patients, prospective cohort study
    b. For the entire cohort, median AHI by AASM criteria was 21.8 (IQR 7.9–33.7) and that by CMS criteria was 12.3 (IQR 3.0– 28.9) (P = .002). AHI was greater by both AASM and CMS criteria for those ≥65 years old than for younger patients. The difference in median AHI measured by AASM and CMS criteria was significant for subjects < .001), but not for subjects ≥65 (P = .184).
    c. According to CMS treatment criteria, AHI ≥ 15 qualifies patients for treatment with CPAP with no further comorbid conditions. For the younger patients (N = 85), 42 (49.4 %) qualified by AASM scoring, compared with 28 (32.9 %) by CMS scoring (P = .043). For the older patients (N = 27), 23 (85.2 %) qualified by AASM scoring, compared with 10 (37.0 %) by CMS scoring criteria (P < .001).
    d. Conclusion: In Medicare age subjects, applying more stringent rules for scoring hypopneas did not change the proportion eligible for CPAP treatment. However, in younger subjects, applying the CMS criteria, even with specified comorbid conditions, would have resulted in fewer being eligible for treatment according to CMS criteria
3) **Wimms 2020**, MERGE trial of CPAP vs standard care for people with mild sleep apnea
    a. N=115 CPAP vs N=118 standard care: all qualified under the 3% criteria
        i. 3 month follow up
        ii. Intention to treat analysis
        iii. Scoring of hypopnea was done using both the AASM 2012 criteria (3%) and the AASM 2007 criteria (4%)
        iv. ResMed Ltd sponsored the trial
    b. N=95 patients who qualified only under the 3% criteria (AASM 2012 criteria)
        i. N=50 CPAP vs N=45 standard care

ii. Participants in the very mild OSA group (normal using AASM 2007 scoring criteria and mild using AASM 2012 scoring criteria) were symptomatic, with a baseline mean ± SD ESS of 10·3 ± 4·7, FSS of 37·9 ± 13·8, and ISI of 12·8 ± 6·1. They were shown to significantly improve when provided with CPAP treatment
iii. CPAP patients in this group had statistically significant improvement in Epworth Sleepiness Scale (ESS) and Fatigue severity scale (FSS) scores, and in HADS: depression index
    1. Clinically meaningful change in the ESS is between -2 and -3
        a. The reported change in ESS was -2.0 (CI -3.0 to -1.1) which falls outside a clinically meaningful change
    2. Clinically meaningful change in the FSS is 0.45 points
        a. The reported change in FSS was -7.8 (CI -10.6 to -5.1) which indicates a clinically meaningful change
iv. CPAP patients had inconsistent improvement in SF-36 subscales
    1. Vitality, physical role, general health, social functioning, emotional role and mental health were all statistically improved
    2. Clinically meaningful change in SF-36 is defined as a change in 5 points
        a. Clinically meaningful change of >5 beyond the confidence interval was only reported in SF-36 vitality
v. No data was presented on any differences between the group who only met criteria using the 4% cut off vs the group that met the cutoff with either scale (i.e. sex, age, comorbidities)

c. Author conclusion: Patients with mild obstructive sleep apnea diagnosed using AASM 2007 scoring criteria showed similar significant improvements in QoL measures to patients diagnosed using AASM 2012 criteria. Subgroup analysis of the 95 participants on the mildest end of the disease spectrum (ie, patients diagnosed with mild obstructive sleep apnea using the 2012 criteria, but classed as normal with the 2007 criteria) also showed a significant improvement in vitality score and other QoL measures when comparing CPAP treatment with standard car

Expert input:

Kim Hutchinson, MD OHSU sleep medicine

It is important to honor the 3% desaturation because many patients (particularly thinner and younger) do not desaturation as significantly as older, larger patients.

When these home studies are negative, we often end up ordering a more costly in-lab polysomnogram, which is a more sensitive test for picking up sleep apnea. Not honoring the 3% desaturation would result in many more in-lab diagnostic studies, resulting in higher costs and treatment delays.

Apnea-Hypopnea Index Scoring for Sleep Apnea Evaluation

HERC staff summary

The definition of hypopnea in the AHI calculation for sleep studies has a major effect on the number of patients who are diagnosed with obstructive sleep apnea. Using the higher cut off criteria (4% oxygen desaturation), the group that would not qualify for CPAP is mainly younger patients (under age 65). AHRQ has concluded that the variation in definition of hypopnea makes the literature on the effectiveness of CPAP for OSA very difficult to analyze. Only one RCT is available that differentiates patients based on hypopnea definition (3% vs 4%). On subgroup analysis of this mild OSA study population (only diagnosed by the 3% definition), there was very little clinically meaningful change in the measured outcomes with or without CPAP treatment. CMS currently defines hypopnea using the 4% oxygen desaturation definition: "CMS would require more published data concerning the long-term health consequences of hypopneas scored using the H3A definition [3% oxygen desaturation qualifying as a hypopnic event] before considering adopting this change."

Staff will review the final AHRQ report on CPAP when it is available to determine if any other coverage changes should be recommended.

HERC staff recommendation

1) Modify GN27 as shown below

GUIDELINE NOTE 27, TREATMENT OF SLEEP APNEA

Line 202

For adults over the age of 18 years:

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

B) CPAP coverage subsequent to the initial 12 weeks is based on documented patient tolerance, compliance, and clinical benefit. Compliance (adherence to therapy) is defined as use of CPAP for at least four hours per night on 70% of the nights during a consecutive 30-day period.
C) Mandibular advancement devices (oral appliances) are covered for those for whom CPAP fails or is contraindicated.
D) Surgery for sleep apnea in adults is not included on this line (due to lack of evidence of efficacy). Surgical codes are included on this line only for children who meet criteria below
E) Hypoglossal nerve stimulation for treatment of obstructive sleep apnea is not included on this line due to insufficient evidence of effectiveness and evidence of harm.

Apnea-Hypopnea Index Scoring for Sleep Apnea Evaluation

For children age of 18 years or younger:

A) Adenotonsillectomy is an appropriate first line treatment for children with OSA. Adenoidectomy without tonsillectomy is only covered when a child with OSA has previously had a tonsillectomy, when tonsillectomy is contraindicated, or when tonsillar hypertrophy is not present. More complex surgical treatments are only included on this line for children with craniofacial anomalies.

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

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

D) CPAP will be covered for children through age 18 on an ongoing basis if:
   1) There is documentation of improvement in sleep disruption and daytime sleepiness and behavior problems with CPAP
      use, AND
   2) Annual re-evaluation for CPAP demonstrates ongoing clinical benefit and compliance with use, defined as use of CPAP
      for at least four hours per night on 70% of the nights in a consecutive 30 day period

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

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SPECIAL ARTICLES

A transition to the American Academy of Sleep Medicine–recommended hypopnea definition in adults: initiatives of the Hypopnea Scoring Rule Task Force

Richard B. Berry, MD[1]; Alexandre R. Abreu, MD[2]; Vidya Krishnan, MD, MHS[3]; Stuart F. Quan, MD[4,5]; Patrick J. Strollo Jr, MD[6]; Raman K. Malhotra, MD[7]

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The American Academy of Sleep Medicine (AASM) recommends that hypopneas be identified using a definition that is based on a ≥ 30% decrease in airflow associated with a ≥ 3% reduction in the oxygen saturation or an arousal (H3A) for diagnosis of obstructive sleep apnea (OSA) in adults. This conflicts with the Centers for Medicare & Medicaid Services definition, which requires a ≥ 4% decrease in the oxygen saturation to identify a hypopnea (H4) and does not acknowledge arousals. In 2018, the AASM Board of Directors constituted a Hypopnea Scoring Rule Task Force with a mandate to "create a strategy for adoption and implementation of the AASM recommended adult hypopnea scoring criteria among members, payers and device manufacturers." The task force initiated several activities including a survey of AASM-accredited sleep facilities and discussions with polysomnography software vendors. Survey results indicated that most sleep facilities scored polysomnograms using only the Centers for Medicare & Medicaid Services definition. Vendors indicated that they could easily support dual scoring. Informal testing among task force members' sleep facilities confirmed there would be little additional work if dual scoring was performed. The task force convened several meetings of a working group of OSA content experts and interested parties, with the purpose of creating research recommendations to study the impact on relevant clinical outcomes using the different definitions of hypopnea. Several possible prospective and retrospective approaches were discussed with emphasis on the group of patients diagnosed with OSA based on an apnea-hypopnea index using H3A but not H4. Based on the deliberations of the working group, the Hypopnea Scoring Rule Task Force submitted recommendations to the AASM Foundation concerning research project strategies for potential grant funding. Further discussions within the Hypopnea Scoring Rule Task Force focused on developing advocacy initiatives among patient stakeholder groups to change payer policy.

Keywords: sleep scoring, hypopnea, apnea-hypopnea index

Citation: Berry RB, Abreu AR, Krishnan V, Quan SF, Strollo PJ Jr, Malhotra RK. A transition to the American Academy of Sleep Medicine–recommended hypopnea definition in adults: initiatives of the Hypopnea Scoring Rule Task Force. *J Clin Sleep Med.* 2022;18(5):1419–1425.

INTRODUCTION

The purpose of this article is to inform the American Academy of Sleep Medicine (AASM) membership and medical providers taking care of patients with obstructive sleep apnea (OSA) of the rationale for creation of a Hypopnea Scoring Rule Task Force (HSRTF), the activities and findings of the task force, and recommendations for future research concerning the recommended adult hypopnea definition (H3A; see **Table 1**) and its impact on patient care.

RATIONALE FOR CREATION OF THE HSRTF

In 2018, the AASM Board of Directors released a position statement with the recommendation that respiratory events associated with arousal be used in the evaluation of suspected OSA.[1] The AASM Board of Directors felt that many sleep facilities and providers were solely counting respiratory events associated with a ≥ 4% oxygen desaturation based on the current AASM Scoring Manual "acceptable" hypopnea definition for adults (H4; **Table 1**).[2] This approach may result in missing a diagnosis of OSA in symptomatic patients who otherwise would be diagnosed based on the recommended hypopnea definition (H3A; **Table 1**) and would potentially benefit from treatment. The "recommended" hypopnea definition (H3A) in the current version of the AASM Scoring Manual defines a hypopnea in adults based on a ≥ 30% drop in airflow for ≥ 10 seconds associated with an arousal or a ≥ 3% oxygen desaturation.[2] Such a definition allows a wider spectrum of symptomatic patients with OSA to qualify for positive airway pressure (PAP) and other treatments compared with one based solely on a ≥ 4% desaturation. The goal is not to diagnose more patients with OSA but to allow the option for treatment of symptomatic patients not diagnosed under the H4 definition. The Centers for Medicare & Medicaid Services (CMS) and many insurance providers require use of a hypopnea rule based on 4% desaturations (H4). The existence of these 2 hypopnea

Draft Technology Assessment

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Continuous Positive Airway Pressure Treatment for Obstructive Sleep Apnea

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Continuous Positive Airway Pressure Treatment for Obstructive Sleep Apnea

Structured Abstract

Background. Obstructive sleep apnea (OSA) is a disorder characterized by periods of airflow cessation (apnea) or reduced airflow (hypopnea) during sleep. The diagnosis and severity of OSA, and response to therapy, are typically assessed using the apnea-hypopnea index (AHI). However, no standard definition of this measure exists, and whether AHI (and associated measures) are valid surrogate measure of clinical outcomes is unknown. OSA is commonly treated with the use of continuous positive airway pressure (CPAP) devices during sleep. The efficacy of CPAP, including for Food and Drug Administration (FDA) clearance/approval, has been based on changes in AHI, but the long-term effect of CPAP on clinical outcomes and the role of disease severity (as measured by AHI) or sleepiness symptoms on the putative effect of CPAP are unclear.

Methods. We searched Medline, Embase, Cochrane databases, CINAHL, and ClinicalTrials.gov from January 2010 through November 18, 2019; we screened reference lists of the 2011 Agency for Healthcare Research and Quality (AHRQ) OSA report and other systematic reviews for earlier studies. We included randomized controlled trials (RCT) and adjusted nonrandomized comparative studies (NRCS) of CPAP and other comparative studies that reported both changes in potential intermediate or surrogate measures (e.g., AHI) and effects on clinical outcomes. All studies had to report effects on long-term (≥6 or 12 months) clinical outcomes in adults with OSA.

Results. The 47 identified studies used highly inconsistent criteria to define breathing measures (apneas, hypopneas, and oxygen desaturation). Definitions of respiratory disturbance events (e.g., apneas, hypopneas) and criteria to define or categorize severity of OSA are highly inconsistent across studies, despite frequent claims of using standard national or international definitions. Possible differences in study findings based on heterogeneity of OSA and sleep study measures could not be elucidated. Among the 25 studies that compared CPAP and no CPAP (n=23) or sham CPAP (n=2), 12 were RCTs and 13 NRCSs; 14 were analyzed as intention-to-treat (ITT) and 11 compared CPAP users to nonusers (either never-users or noncompliant users). All outcomes of interest were addressed by RCTs; the NRCSs mostly addressed composite cardiovascular (CV) outcomes and death.

RCTs provide low strength of evidence (SoE) that CPAP does not affect the risk of all-cause mortality (summary effect size [ES] 0.87, 95% confidence interval [CI] 0.58 to 1.29), stroke (summary ES 0.96, 95% CI 0.59 to 1.29), myocardial infarction (summary ES 1.06, 95% CI 0.72 to 1.56), or composite CV outcomes (ES range 0.42 to 1.10 across studies, all statistically nonsignificant). Regarding all-cause mortality, NRCSs were consistent with RCTs in direction of association. When NRCSs were combined with the RCTs there was low SoE that CPAP reduces risk of mortality (ES 0.66, 95% CI 0.60 to 0.73); although this conclusion may be most applicable to older adults and longer-term followup. RCTs provided insufficient evidence regarding risk of CV death, but combined with a NRCS, there is low SoE of no effect of CPAP (ES 0.97, 95% CI 0.62 to 1.53). NRCSs did not alter conclusions regarding other CV-related

outcomes. Insufficient evidence exists regarding effect of CPAP on the risk of transient ischemic attack, angina, coronary artery revascularization, congestive heart failure, and atrial fibrillation.

Regarding other assessed outcomes, CPAP does not affect the risk of driving accidents or the risk of incident diabetes (both low SoE). CPAP does not result in clinically significant changes in depression or anxiety scores, executive cognitive function measures, or nonspecific quality of life measures (all low SoE). There is insufficient evidence regarding the effect of CPAP on incident hypertension, functional status measures, male or female sexual function, or days of work missed.

Insufficient evidence exists regarding possible differences in the effect of CPAP on various outcomes based on patient characteristics (such as disease severity or comorbidities), different diagnostic criteria, or whether studies were analyzed as ITT or "as-treated". No study reported within-study correlations among outcomes (e.g., the association between the effects of CPAP on AHI and on all-cause mortality).

Eligible studies provided insufficient evidence about adverse events due to CPAP use. Adverse events reported in the Food and Drug Administration database mostly related to inadequate humidification, user errors, or device malfunction. No deaths were attributed to CPAP use.

No studies have evaluated the validity of intermediate or surrogate measures (such as change in AHI) as predictors of long-term clinical outcomes, including surrogacy or mediation analyses. Studies did not compare the concordance of different polysomnography and symptom measures with clinical outcomes. Across the 15 studies that reported both changes in intermediate or surrogate measures and effects on clinical outcomes, data were too sparse to allow adequate cross-study evaluation of concordance between any specific measure and clinical outcome.

Conclusions. Studies are highly inconsistent as to how they define breathing measures during sleep studies and OSA itself. Insufficient evidence exists to assess the validity of AHI as a surrogate or intermediate outcome for long-term clinical outcomes. Until such validation has been conducted, it cannot be assumed that changes (e.g., improvements) in intermediate or surrogate outcomes are correlated with long-term clinical outcomes.

The published evidence mostly does not support that CPAP prescription affects long-term, clinically important outcomes. Specifically, with low SoE RCTs do not demonstrate that CPAP affects all-cause mortality, various CV outcomes, clinically important changes in psychosocial measures, or other clinically important outcomes. When NRCSs are combined with the RCTs there is the suggestion that CPAP reduces the risks of all-cause mortality (low SoE); other conclusions are not changed. The low SoE for these outcomes suggests that we have limited confidence that the summary estimates are close to the true effect.

Studies did not adequately address whether effects of CPAP vary based on disease severity (e.g., as assessed by AHI), symptoms (e.g., as assessed by sleepiness scales), other patient characteristics, different features or modes or CPAP, or different criteria or definitions of sleep measures or OSA diagnosis.

Additional studies are needed before we have a clear understanding of the potential effects of CPAP on long-term outcomes for patients with OSA, whether any particular group of patients may benefit to a greater or lesser degree from CPAP treatment or whether of AHI (and/or other breathing measures) are valid intermediate or surrogate measures of clinical outcomes.

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SLEEP BREATHING PHYSIOLOGY AND DISORDERS • ORIGINAL ARTICLE

Comparison of American Academy of Sleep Medicine (AASM) versus Center for Medicare and Medicaid Services (CMS) polysomnography (PSG) scoring rules on AHI and eligibility for continuous positive airway pressure (CPAP) treatment

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Abstract
Background Obstructive sleep apnea (OSA) is an important clinical condition. Eligibility for treatment usually depends on disease severity, measured as the apnea-hypopnea index (AHI), equal to the sum of apneas plus hypopneas per hour of sleep. There is divergence on scoring rules for hypopneas between the recommendations of the American Academy of Sleep Medicine (AASM) and the Center for Medicare Services (CMS), the latter being more restrictive. Thus, patients could be eligible for treatment under AASM rules, but not under CMS rules.
Methods Sleep laboratory records of 112 consecutive patients were reviewed (85 < 65, 27 ≥ 65 years old). AHI was calculated both by AASM and by CMS criteria. Information on demographics, and important comorbidities, was also reviewed.
Results AHI was lower in younger patients using CMS criteria. However, differences in AHI using the two sets of criteria were not significantly different in the older patients. Incorporating all criteria for eligibility (severity, presence of certain comorbid conditions) for treatment, we found that fewer younger patients would be eligible using CMS criteria, but among the older patients, eligibility for treatment was the same whether AASM or CMS criteria were used.
Conclusions Use of CMS criteria for scoring hypopneas results in lower estimates of OSA severity, with fewer younger patients eligible for treatment. However, among Medicare age patients, the rate of treatment eligibility was the same whether AASM or CMS scoring rules were used.

Keywords Sleep apnea · American Academy of Sleep Medicine · Centers for Medicare Services · Hypopnea criteria

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Introduction

Obstructive sleep apnea (OSA) is a prevalent condition associated with poor sleep, hyper-somnolence, daytime fatigue, as well as increased risk for motor vehicle accidents and cardiovascular disease [1]. OSA increases the risk of developing hypertension, heart failure, and stroke [2, 3]. In men, severe OSA significantly increases the risk of fatal and non-fatal cardiovascular events. Treatment with continuous positive airway pressure (CPAP) has been shown to reduce this risk and to reduce death from cardiovascular diseases [4]. The impact of untreated OSA has important health care utilization and cost implications. For example, one study showed that untreated OSA patients consume significantly more healthcare resources for treatment of cardio-respiratory diseases compared to subjects without OSA [5]. Therefore, diagnosing and treating OSA would have a considerable beneficial medical and public health impact [6].

The severity of OSA is usually graded based on the number of disordered breathing events per hour of sleep. These are generally calculated as the apnea-hypopnea index (AHI), equal to number of "apneas" (cessation or near cessation of airflow) plus the number of "hypopneas" (reductions in airflow associated with certain physiologic consequences) per hour of sleep. The AHI thus becomes a measure of severity

Continuous positive airway pressure versus standard care for the treatment of people with mild obstructive sleep apnoea (MERGE): a multicentre, randomised controlled trial

Alison J Wimms, Julia L Kelly*, Christopher D Turnbull, Alison McMillan, Sonya E Craig, John F O'Reilly, Annabel H Nickol, Emma L Hedley, Meredith D Decker, Leslee A Willes, Peter M A Calverley, Adam V Benjafield, John R Stradling, Mary J Morrell, on behalf of the MERGE trial investigators†*

Summary

Background The evidence base for the treatment of mild obstructive sleep apnoea is limited and definitions of disease severity vary. The MERGE trial investigated the clinical effectiveness of continuous positive airway pressure in patients with mild obstructive sleep apnoea.

Methods MERGE, a multicentre, parallel, randomised controlled trial enrolled patients (≥18 years to ≤80 years) with mild obstructive sleep apnoea (apnoea-hypopnoea index [AHI] ≥5 to ≤15 events per h using either AASM 2007 or AASM 2012 scoring criteria) from 11 UK sleep centres. Participants were assigned (1:1) to either 3 months of continuous positive airway pressure plus standard care (sleep counselling), or standard care alone, by computer-generated randomisation; neither participants nor researchers were blinded. The primary outcome was a change in the score on the Short Form-36 questionnaire vitality scale in the intention-to-treat population of patients with mild obstructive sleep apnoea diagnosed using the American Academy of Sleep Medicine 2012 scoring criteria. The study is registered with ClinicalTrials.gov, NCT02699463.

Findings Between Nov 28, 2016 and Feb 12, 2019, 301 patients were recruited and randomised. 233 had mild obstructive sleep apnoea using AASM 2012 criteria and were included in the intention-to-treat analysis: 115 were allocated to receive continuous positive airway pressure and 118 to receive standard care. 209 (90%) of these participants completed the trial. The vitality score significantly increased with a treatment effect of a mean of 10·0 points (95% CI 7·2–12·8; p<0·0001) after 3 months of continuous positive airway pressure, compared with standard care alone (9·2 points [6·8 to 11·6] *vs* –0·8 points [–3·2 to 1·5]). Using the ANCOVA last-observation-carried-forward analysis, a more conservative estimate, the vitality score also significantly increased with a treatment effect of a mean of 7·5 points (95% CI 5·3 to 9·6; p<0·0001) after 3 months of continuous positive airway pressure, compared with standard care alone (7·5 points [6·0 to 9·0] *vs* 0·0 points [–1·5 to 1·5]). Three serious adverse events occurred (one allocated to the continuous positive airway pressure group) and all were unrelated to the intervention.

Interpretation 3 months of treatment with continuous positive airway pressure improved the quality of life in patients with mild obstructive sleep apnoea. These results highlight the need for health-care professionals and providers to consider treatment for patients with mild obstructive sleep apnoea.

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See Comment page 322

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See Online for appendix

Introduction

Nearly 1 billion adults aged 30–69 years are estimated to have obstructive sleep apnoea globally, with about 40% of these people having moderate-to-severe disease (apnoea-hypopnoea index [AHI] ≥15 events per h) and 60% mild disease (AHI ≥5 to <15 events per h).[1] Despite this high prevalence, clinical management—including access to treatment—varies widely across the spectrum of obstructive sleep apnoea disease severity and from country to country.

In 2009, the UK Health Technology Assessment Programme, which produces information for the National Institute for Health and Care Excellence, reported that there was clear evidence for the benefit of continuous positive airway pressure (CPAP)—compared with placebo, conservative treatment, or usual care—in patients with moderate-to-severe obstructive sleep apnoea with symptoms of sleepiness.[2] The report also concluded that in patients with mild disease, further investigations of the effectiveness of treatment were needed. Similar reviews undertaken by the American Thoracic Society in 2016 and the American Academy of Sleep Medicine (AASM) in 2019 drew similar conclusions.[3,4] These reviews suggested that future studies should focus on capturing improvements in the diversity of symptoms reported by patients with mild obstructive sleep apnoea, such as reduced energy, feelings of general tiredness, fatigue and poor sleep,

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Supplementary appendix

This appendix formed part of the original submission and has been peer reviewed. We post it as supplied by the authors.

Supplement to: Wimms AJ, Kelly JL, Turnbull CD, et al ,on behalf of the MERGE trial investigators. Continuous positive airway pressure versus standard care for the treatment of people with mild obstructive sleep apnoea (MERGE): a multicentre, randomised controlled trial. *Lancet Respir Med* 2019; published online Dec 2. https://doi.org/10.1016/S2213-2600(19)30402-3.

3. RESULTS

3.1. Recruitment

Recruitment took place between 28th of November 2016 and 12th February 2019. The CONSORT (Consolidated Standards of Reporting Trials) diagram shows the flow of patients through the trial (MERGE manuscript: Figure 1).

In total, 513 individuals were screened as potential participants. Of these, 354/ 513 (69%) were eligible and subsequently 301/354 (85%) were randomised. Data collected on the screening logs enabled the 212 non-randomised individuals to be grouped into the following categories:

Ineligible:

- AHI >15 using AASM 2007 criteria: n = 47/ 212 (22%)
- AHI <5 using AASM 2012 criteria: n = 78/ 212 (37%)
- Central sleep apnoea predominant: n = 1/212 (0.5%)
- Sleep study inadequate for analysis: n = 33/ 212 (16%)

Eligible:

- Declined prior to visit one: n = 51/212 (24%)
- Declined after CPAP trial n=2/212 (1%)

From the 301 participants who were randomised into the MERGE study, 233/301 (77%) were included in the primary analysis population (mild OSA as per AASM 2012 scoring criteria), and 209/233 (90%) of these participants completed the trial.

3.2. Description of patient movement when re-scoring with AASM 2007 and AASM 2012 scoring criteria

When scoring was performed using AASM 2007 criteria, 205 patients were classified as mild OSA (AHI 5-15) and 96 patients were classified as normal (AHI <5). When these patients were re-scored according to AASM 2012 scoring criteria 95/96 (99%) had mild OSA (AHI <5), despite being previously classified as normal using the AASM 2007 scoring criteria; one patient remained classified as normal (Section 3·8).

Of those patients who were classified as mild OSA using 2007 criteria, 138/205 (67%) remained in the mild OSA group, and 67/205 (33%) became moderate OSA using AASM 2012 criteria. Figure S1 summarizes the movement between classifications of these patients. Table S1 describes the median and IQR of the AHI in each group.

3.3. Manual vs. automated scoring

No significant difference was found between the AHI scored using an automated algorithm, programmed according to AASM 2012 criteria, compared to the AHI scored following manual by the independent central scorer: AHI median (IQR) automated algorithm: 11·5 (8·0-15·4) vs independent scorer: 11·3 (8·2–15·4) events/hour, p = 0·44.

3.4. Reason for referral

Patients' reasons for referral to their NHS sleep centre were documented on case report forms, and are summarised in Table S2. The most common reason for referral was snoring (85·4% of the CPAP group, 77·4% of the Standard Care group) and witnessed apnoeas (52·4% of the CPAP group, 51·9% of the Standard Care group).

3.5. Self-reported medical history

The self-reported medical history of each patient was documented on case report forms, and is summarised in Table S3. The most frequently reported conditions were hypertension (33·0% of the CPAP group, 23·7% of the Standard Care group), and depression (23·5% of the CPAP group, 32·2% of the Standard Care group).

3.6. Sensitivity analyses of the primary outcome

The primary outcome was the change in the Vitality scale of the SF-36 questionnaire from baseline to 3 months in subjects with mild OSA per AASM 2012 criteria. A significant treatment effect was seen in both the primary repeated measures analysis and the ANCOVA LOCF sensitivity analysis (Table S4).

The relationship between change in primary outcome (change in Vitality score) and screening AHI per AASM 2012 criteria, baseline QoL scores and average CPAP usage during the study was examined graphically and using the ANCOVA LOCF approach. There was no correlation between AHI and Vitality score at baseline. No pattern of association was observed between the changes in the Vitality score from baseline to 3 months and the severity of the disease (baseline AHI) or the hours of CPAP usage. Additionally, baseline QoL scores for ESS, FSS, FOSQ, and ISI were unrelated to change in Vitality score. Baseline HADS Depression score was a statistically significant covariate in the ANCOVA LOCF model; however, the resulting treatment effect was similar to the ANCOVA model not including HADS baseline scores and there was no strong pattern of association.

3.7. Changes in QoL in patients with mild OSA diagnosed using ASSM 2007 criteria

Mild OSA, diagnosed using AASM 2007 scoring criteria, showed similar significant improvements in QoL measures to those seen in the primary analysis of the participants diagnosed using the AASM 2012 scoring criteria. Outcomes are shown in Table S5.

3.8. Changes in QoL in patients with very mild OSA

Participants in the very mild OSA group (normal using AASM 2007 scoring criteria and mild using AASM 2012 scoring criteria) were symptomatic, with a baseline mean ± SD ESS of 10·3 ± 4·7, FSS of 37·9 ± 13·8, and ISI of 12·8 ± 6·1. They were shown to significantly improve when provided with CPAP treatment (Table S6). This patient group is most at risk of being denied treatment for OSA, particularly if the clinic only diagnoses sleep apnoea using the AASM 2007 scoring criteria.

3.9. CPAP adherence and centralised support

The median (IQR) CPAP usage over three months was 4:00 hours:minutes (1:36–5:44). The group median (IQR) of each individual's median pressure was 7·3 (6·2–8.8) cmH2O, (95th percentile 10·1 (8·6–11·8) cmH2O) with a residual AHI of 1·5 (0·8–2·5) events/hour; the median mask leak was 1·6 (0·4–4·1) L/min.

All MERGE trial participants received a three-day phone call/ email from the trial Sleep Therapist. Further to the 3-day call, 99/ 115 (86%) of participants assigned to the CPAP group, had additional contact with a trial Sleep Therapist, the median number of contacts was 5 (IQR 2–8).

3.10. Serious adverse events

Three serious adverse events were recorded during the study, and are summarised in Table S7. None of these events were assessed as being related to the treatment device.

3.11. Data sharing

Requests for access to deidentified data can be made to the corresponding author of the paper and will be assessed for approval by an oversight committee from the MERGE trial.

Plain Language Summary:
Background: Should an imaging test (PET Scan) used to look at cancer be used to look at types of cancer?

Should OHP cover this treatment? Staff recommends extending this test for additional types of cancer (diagnosis and staging) because studies show its use is effective at helping decide on treatment.

Question: Should the covered indications for PET scan be expanded?

Question source: Mary Engrav, CCO medical director

Issue: PET scans are a nuclear medicine study that can be used to evaluate the extent of a cancer for initial determination of treatment or when there is suspicion that the cancer has returned. Diagnostic Guideline D22 PET SCANS limits coverage of PET scans to certain cancers where there is evidence of benefit, either in assisting in diagnosis, prognosis, guiding treatment, or evaluating recurrence.

Dr. Engrav requested consideration of PET scans for multiple other cancers based on requests from community oncologists.

HSC/HERC history
PET scans have been extensively reviewed over the past 20 years. The most recent changes were adding PET scan coverage for initial staging of breast cancer in 2018, and expanding this indication to monitoring treatment of metastatic breast cancer in 2021. PET scan coverage was added for use in management of active therapy of classic Hodgkin's lymphoma in 2021. Coverage for Alzheimer's disease for patients being considered for treatment with aducanumab or similar FDA approved medications for treatment of Alzheimer's disease was added in 2021.

Current Prioritized List status

DIAGNOSTIC GUIDELINE D22, PET SCANS
***Diagnosis**:*
PET Scans are covered for diagnosis only when:

A) The PET scan is for evaluation of either:
   1) Solitary pulmonary nodules and non-small cell lung cancer, OR
   2) Evaluation of cervical lymph node metastases when CT or MRI do not demonstrate an obvious primary tumor, AND
B) The PET scan will
   1) Avoid an invasive diagnostic procedure, OR
   2) Assist in determining the optimal anatomic location to perform an invasive diagnostic procedure.

***Initial staging**:*
PET scans are covered for the initial staging when:

A) The staging is for one of the following cancers/situations:

1) Cervical cancer only when initial MRI or CT is negative for extra-pelvic metastasis
2) Head and neck cancer when initial MRI or CT is equivocal
3) Colon cancer
4) Esophageal cancer
5) Solitary pulmonary nodule
6) Non-small cell lung cancer
7) Lymphoma
8) Melanoma
9) Breast cancer ONLY when metastatic disease is suspected AND standard imaging results are equivocal or suspicious; AND

B) Clinical management of the patient will differ depending on the stage of the cancer identified and either:
1) the stage of the cancer remains in doubt after standard diagnostic work up, OR
2) PET replaces one or more conventional imaging studies when they are insufficient for clinical management of the patient.

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

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

Restaging:
Restaging is covered only when:
A) the cancer has staging covered above OR for thyroid cancer if recurrence is suspected and l131 scintography is negative, AND
B) initial therapy has been completed, AND
C) the PET scan is conducted for
1) detecting residual disease, or
2) detecting suspected recurrence, or
3) determining the extent of a known recurrence.

Other indications:
PET scans are covered for preoperative evaluation of the brain in patients who have intractable seizures and are candidates for focal surgery. PET scans are covered for patients being considered for treatment with aducanumab or similar FDA approved medications for treatment of Alzheimer's disease.

Non-covered conditions/situations:
A) PET scans are NOT covered to monitor tumor response during the planned course of therapy for any cancer other than classic Hodgkin's lymphoma or the limited indication described above for metastatic breast cancer.
B) PET scans are NOT covered for routine follow up of cancer treatment or routine surveillance in asymptomatic patients.
C) PET scans are NOT covered for cardiac evaluation.

Evidence

a. **Fuchs 2019**, Evidence-based indications for PET or PET/CT
    a. There is a (relative) consensus that there is sufficient evidence for sub-indications in eight indications in favor of PET or PET–CT examinations (in Table 2 highlighted green). The first six were already determined in the 2015 report—(1) bronchial carcinoma (update: mainly pretreatment, contradictory in re-staging and response control and in therapy monitoring), (2) colon carcinoma, (3) malignant lymphoma, (4) malignant melanoma (update: contradictory for diagnosis of recurrence), (5) mamma carcinoma (treatment response, for diagnosis of recurrence), and (6) head–neck tumors (in 2015 report: CUP, thyroid carcinoma; update: mainly for diagnosis of recurrence)— while two new treatment areas were added by the update: (7) myeloma and (8) neuroendocrine tumors.
        i. Note: current PET coverage on the Prioritized List does not include all subtypes of bronchial carcinoma (specifically small cell lung cancer), myeloma or neuroendocrine tumors. Only limited coverage is included for thyroid cancer

Expert guidelines

1) **NCCN 1.2022** Neuroendocrine and adrenal tumors
    a. Initial diagnosis:
        i. Because most neuroendocrine tumors (NETs) overexpress high-affinity receptors for somatostatin, a peptide hormone generated by the hypothalamus that blocks the release of growth hormones, somatostatin receptor (SSR)- based imaging may be considered in the initial evaluation of patients with NETs. Such imaging can provide useful information on overall tumor burden and location; additionally, positive imaging confirms the presence of SSRs, which can have therapeutic implications. A major advance in imaging NETs came with the 2016 FDA approval of PET/CT imaging using the radiolabeled somatostatin analog gallium-68 (68Ga) DOTATATE. Several studies have shown the diagnostic utility, safety, specificity, and high sensitivity of 68Ga-DOTATATE PET/CT.69-73 A systematic review and meta-analysis of 22 studies determined that 68Ga-DOTATATE had a pooled sensitivity and specificity of 91% and 94%, respectively, for the initial diagnosis of NETs. One study even showed that it was able to more correctly identify patients for peptide receptor radiotherapy than 111indium-diethylenetriaminepentaacetic acid (111In-DPTA) scintigraphy. The 2018 Appropriate Use Criteria for Somatostatin Receptor PET Imaging in NETs recommends the use of SSR PET over 111In-DPTA scintigraphy. Unless otherwise indicated, the preferred SSR-based imaging in this discussion includes SSR-PET/CT or SSR-PET/MRI imaging using 68Ga-DOTATATE, 68Ga-DOTATOC, or 64Cu-DOTATATE. SSR scintigraphy using 111In-octreotide (with SPECT/CT) is appropriate only if SSR-PET is not available. SSR-PET imaging is more sensitive than SSR scintigraphy for determining SSR status
    b. Surveillance of resected NETs
        i. Surveillance of bronchopulmonary and GI NETs should include complete patient history and physical (H&P) examination and a multiphasic CT or an MRI scan with contrast (usually abdominal with or without pelvis). For patients with primary lung and thymic tumors, chest CT scans with or without contrast are recommended

ii. SSR-based imaging or 18F-fluorodeoxyglucose (FDG)-PET/CT scans (for high-grade tumors) are not routinely recommended for surveillance after definitive resection, but may be indicated to assess disease location and disease burden for comparison in cases of subsequent possible recurrence.

2) **NCCN 2.2022** Thyroid cancer
   a. Post-treatment iodine-131 imaging
      i. PET scan is indicated for patients with a negative whole body scan who have suspected structural disease based on other imaging methods and/or elevated Tg to a degree that would indicate distant metastasis
   b. Evaluating recurrent disease
      i. When recurrent disease is suspected based on progressively rising Tg values (basal or stimulated) and negative imaging studies (including PET scans), RAI therapy can be considered using an empirically determined dose of greater than or equal to 100 mCi of iodine-131
   c. Hurthle cell carcinoma
      i. Iodine-131 therapy (100–150 mCi) may be considered after thyroidectomy for patients with rising or newly elevated Tg levels who have negative scans (including FDG-PET)
      ii. Since Hürthle cell carcinoma tends to be non–iodine-avid, negative scans that were done without single-photon emission CT (SPECT) are likely to have missed distant structural disease. Therefore, if Tg is high and/or pathology is high-risk, then FDG-PET is indicated.
   d. Anaplastic thyroid cancer
      i. PET/CT or MRI scans are recommended to accurately stage the patient.
3) **NCCN 1.2023** Multiple myeloma
   a. Initial imaging for diagnostic work up:
      i. Whole-body imaging with low-dose CT or FDG PET/CT is recommended for initial diagnostic workup of patients suspected of having MM or solitary plasmacytoma
      ii. whole-body FDG PET/CT is the first choice for initial evaluation of solitary extraosseous plasmacytoma
   b. Imaging for follow-up
      i. Imaging studies with MRI without contrast, whole-body low-dose CT and/or CT and/or whole-body FDG PET/CT are recommended annually or as clinically indicated. The NCCN Panel recommends considering using the same imaging modality used during the initial workup for the follow-up assessments.
      ii. Residual focal lesions detected by either FDG PET/CT or MRI have been shown to be of adverse prognostic significance.
4) **NCCN 1.2023** Small cell lung cancer
   a. Initial diagnosis
      i. PET scans can increase staging accuracy in patients with SCLC, because SCLC is a highly metabolic disease. PET/CT is superior to PET alone. Approximately 19% of patients who undergo PET are upstaged from limited-stage to extensive-stage disease, whereas only 8% are downstaged from extensive-stage to limited-stage disease. For most metastatic sites, PET/CT is superior to CT imaging… Changes in management based on PET staging were reported in approximately 27% of patients, mainly because of alterations in the planned radiation field as a result of improved detection of intrathoracic sites of disease. Although PET/CT seems

to improve staging accuracy in SCLC, pathologic confirmation is still required for PET/CT-detected lesions that would alter the stage

b. Follow up/surveillance
    i. PET/CT is not recommended for routine follow-up

HERC staff summary

Evidence based reviews and expert guidelines support use of PET for initial staging of neuroendocrine tumors, multiple myeloma, and small cell lung cancer and in certain clinical scenarios with thyroid cancer. PET scans are not recommended for routine surveillance after treatment for any of these cancers.

HERC staff recommendation

1) Modify Diagnostic guideline D22 as shown below

DIAGNOSTIC GUIDELINE D22, PET SCANS

Diagnosis:

PET Scans are covered for diagnosis only when:

A) The PET scan is for evaluation of either:
   1) Solitary pulmonary nodules, small cell lung cancer and non-small cell lung cancer, OR
   2) Evaluation of cervical lymph node metastases when CT or MRI do not demonstrate an obvious primary tumor, AND

B) The PET scan will
   1) Avoid an invasive diagnostic procedure, OR
   2) Assist in determining the optimal anatomic location to perform an invasive diagnostic procedure.

Initial staging:

PET scans are covered for the initial staging when:

A) The staging is for one of the following cancers/situations:
   1) Cervical cancer only when initial MRI or CT is negative for extra-pelvic metastasis
   2) Head and neck cancer when initial MRI or CT is equivocal
   3) Colon cancer
   4) Esophageal cancer
   5) Solitary pulmonary nodule
   6) Non-small cell lung cancer
   7) Lymphoma
   8) Melanoma
   9) Breast cancer ONLY when metastatic disease is suspected AND standard imaging results are equivocal or suspicious
   10) Small cell lung cancer
   11) Neuroendocrine tumors
   12) Multiple myeloma
   13) Thyroid cancers; AND

B) Clinical management of the patient will differ depending on the stage of the cancer identified and either:
   1) the stage of the cancer remains in doubt after standard diagnostic work up, OR
   2) PET replaces one or more conventional imaging studies when they are insufficient for clinical management of the patient.

Monitoring:

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

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

Restaging:
Restaging is covered only when:
A) the cancer has staging covered above ~~OR for thyroid cancer if recurrence is suspected and I131 scintography is negative~~, AND
B) initial therapy has been completed, AND
C) the PET scan is conducted for
    1) detecting residual disease, or
    2) detecting suspected recurrence, or
    3) determining the extent of a known recurrence.

Other indications:
PET scans are covered for preoperative evaluation of the brain in patients who have intractable seizures and are candidates for focal surgery. PET scans are covered for patients being considered for treatment with aducanumab or similar FDA approved medications for treatment of Alzheimer's disease.

Non-covered conditions/situations:
A) PET scans are NOT covered to monitor tumor response during the planned course of therapy for any cancer other than classic Hodgkin's lymphoma or the limited indication described above for metastatic breast cancer.
B) PET scans are NOT covered for routine follow up of cancer treatment or routine surveillance in asymptomatic patients.
C) PET scans are NOT covered for cardiac evaluation.

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SYSTEMATIC REVIEW

Evidence-based indications for the planning of PET or PET/CT capacities are needed

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Abstract

Purpose To identify evidence-based indications for PET/PET–CT scans in support of facilities planning and to describe a pilot project in which this information was applied for an investment decision in an Austrian region. The study updates a Health Technology Assessment (HTA) report (2015) on oncological indications, extending it to neurological indications and inflammatory disorders.

Methods A systematic literature search to identify HTA reports, evidence-based guidelines, and systematic reviews/meta-analyses (SR/MA) was performed, supplemented by a manual search for professional society recommendations and explicit "not-to-do's". A needs-assessment was conducted in the context of the pilot study on investing in an additional PET–CT scanner in the Austrian region of Carinthia.

Results Overall recommendations for indications as well as non-recommendations for the three areas (oncology, neurology, and inflammatory disorders) were compiled from the 2015 PET–HTA report and expanded for a final total of ten HTA, comprising 234 (positive and negative) recommendations from professional societies and databases, and supplemented by findings from 23 SR/MA. For the investment decision pilot study in Carinthia, 1762 PET scans were analyzed; 77.8% were assigned to the category "recommended evidence-based indications" (54.7%), "not recommended" (1.8%) or "contradictory recommendations" (21.3%). The remaining could not be assigned to any of the three categories.

Conclusions The piloting of PET capacity planning using evidence-based information is a first of its kind in the published literature. On one hand, the high number of PET scans that could not be ascribed to any of the categories identified limits to the instructive power of the study to use evidence-based indication lists as the basis for a needs-assessment investment planning. On the other hand, this study reveals how there is a need to improve indication coding for enhanced capacity planning of medical services. Overall recommendations identified can serve as needs-based and evidence-based decision support for PET/PET–CT service provision.

Keywords Evidence-based planning · Needs-based planning · PET/PET–CT · Oncology · Neurology · Inflammatory disorders · Advanced diagnostics

Introduction

Europe is one of the largest markets for the fast-growing sector of medical devices (MDs) and diagnostic procedures, which encompass a broad and heterogeneous range of technologies. Due to the rising costs associated with introducing of new MDs and procedures into the healthcare system, payers have started to pay more attention to the effectiveness and financial implications of such new technologies. In this context, health technology assessment (HTA) has gained increasing recognition at the European level as a decision support tool [1].

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