Health Evidence Review Commission's Value-based Benefits Subcommittee

November 9, 2017

8:00 AM - 1:00 PM

Wilsonville Training Center
Community Health Education Center, Room 111-112
29373 SW Town Center Loop E, Wilsonville,
Oregon, 97070

Section 1.0

Call to Order

AGENDA
VALUE-BASED BENEFITS SUBCOMMITTEE
November 9, 2017
8:00am - 1:00pm
Wilsonville Training Center, Rooms 111-112
29353 SW Town Center Loop E
Wilsonville, Oregon 97070
A working lunch will be served at approximately 12:00 PM
All times are approximate

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

II. Staff report – Ariel Smits, Cat Livingston, Darren Coffman **8:05 AM**
- **A.** Retreat update
- **B.** Update on outgoing and incoming members

III. Straightforward/Consent agenda – Ariel Smits **8:15 AM**
- **A.** Straightforward/consent table
- **B.** Fecal incontinence 2013 error
- **C.** Massage in the medical back pain guideline

IV. Advisory panel reports **8:25 AM**
- **A.** Genetics Advisory Panel report
    - A. 2018 CPT code placement
    - B. Family history cancer codes
    - C. Breast cancer genetic testing panels
    - D. Non-Prenatal Genetic Testing Guideline

V. 2018 CPT codes **9:00 AM**
- **A.** Straightforward code placements
- **B.** Issues for discussion
    - A. Intraoperative radiation therapy for breast cancer
    - B. Bone marrow aspirate for spinal fusion
    - C. Cryoablation for pulmonary tumors
    - D. Total artificial heart
    - E. Varicose vein ablation with foam sclerosant or cyanoacrylate
    - F. Absorbable perirectal spacer
    - G. Nerve repair with nerve allografts
    - H. Oncology tests
    - I. Gene expression profiling for breast and prostate cancer
    - J. Prostate promoter methylation profiling
    - K. Serum allergy testing
    - L. Home INR monitoring

M. Photodynamic therapy of premalignant lesions of the skin and adjacent mucosa

VI. Previous discussion items **10:45 AM**

A. Updates to the line 500/660 titles and associated guideline notes
B. Barium enema as a colon cancer screening modality
C. Tobacco cessation guideline

VII. New discussion items **11:30 AM**

A. Severe inflammatory skin disease
B. Medication assisted treatment for opioid dependence
C. Implantable buprenorphine for opioid dependence
D. Enzyme replacement therapy guideline
E. Fibrosure addition to liver fibrosis testing guideline

VIII. Coverage guidances **11:50 AM**

A. Opportunistic salpingectomy for ovarian cancer prevention

IX. Previous discussion items **12:30 PM**

A. Eteplirsen (Exondys 51) follow up discussion

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 September 28, 2017

For specific coding recommendations and guideline wording, please see the text of the 09/28/2017 VbBS minutes.

RECOMMENDED CODE MOVEMENT (effective 1/1/2018 unless otherwise noted)

- Add the 2018 CDT codes to various lines as recommended by the Oral Health Advisory Panel.
- Add the medication deflazacort for Duchenne muscular dystrophy to an unfunded line due to low cost-effectiveness.
- Add the medication eteplirsen for Duchenne muscular dystrophy to an unfunded line due to lack of evidence of effectiveness *[note: this recommendation was not approved by HERC].*
- Add the procedure code for delayed insertion of testicular prostheses to all lines with the code for immediate insertion after orchiectomy.
- Add procedure codes for open capsulorrhaphy to a funded line. The procedure code for thermal capsulorrhaphy was added to an unfunded line.
- Add various types of transcutaneous neurostimulators to the unfunded line for interventions with no evidence of effectiveness. The statement in the medical back line guideline regarding lack of coverage for TENS was removed.
- Add limited coverage for physical therapy for interstitial cystitis to a funded line with a guideline limiting to experienced therapists.
- Make several changes to diagnosis codes for peripheral nerve injuries.
- As part of the 2020 Biennial review, the peripheral nerve injury line was deleted as it is duplicative of the deep open wound line in terms of diagnoses and procedures included. The guideline regarding peripheral nerve injuries was associated with the deep open wound line.
- Add various procedure codes for graphs, flaps and pedicles to the Ancillary File with the intent to cover these services only when the major surgery that they are a portion of is a covered procedure.
- Add several colon cancer screening procedure codes to the funded preventive services line.
- Made various straightforward coding and guideline note changes.

ITEMS CONSIDERED BUT NO RECOMMENDATIONS FOR CHANGES MADE

- Edits to the tobacco cessation guideline regarding specifics of nicotine replacement products included for coverage were discussed but tabled to a future meeting.
- There was discussion about prioritization of iliotibial band syndrome and staff was directed to research this further and bring back to a future meeting.

RECOMMENDED GUIDELINE CHANGES (effective 1/1/2018 unless otherwise noted)

- Add a new statement of intent regarding the role of the Prioritized List in coverage.
- Edit the preventive services guideline to specify which colon cancer screening modalities are included on line 3.
- Add several colon cancer screening modalities to the guideline for services with minimal clinical effectiveness.

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VALUE-BASED BENEFITS SUBCOMMITTEE
Clackamas Community College
Wilsonville Training Center, Rooms 111-112
Wilsonville, Oregon
September 28, 2017
8:00 AM – 1:00 PM

Members Present: Kevin Olson, MD, Chair; David Pollack, MD; Susan Williams, MD (via phone); Mark Gibson; Irene Croswell, RPh; Holly Jo Hodges, MD; Vern Saboe, DC.

Members Absent: Gary Allen, DMD.

Staff Present: Darren Coffman; Ariel Smits, MD, MPH; Cat Livingston, MD, MPH; Denise Taray, RN; Daphne Peck.

Also Attending: Kim Wentz, MD, MPH and Robb Cowie (OHA); Adam Obley, MD, MPH and Craig Mosbaek, MPH (OHSU Center for Evidence-based Policy); Sarah Servid (OSU College of Pharmacy); Jenn McNary; Mike Donabedian and Lisa Borland (Sarepta Pharmaceuticals); Jamie Saukko; Hannah Cain; Erika Finanger, MD (OHSU pediatric neurology); two reporters from KATU (names unavailable).

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

  The meeting was called to order at 8:00 am and roll was called. Minutes from the August 10, 2017 VbBS meeting were reviewed and approved.

  Smits reported on the first meeting of the Chronic Pain Task Force. The majority of that meeting was framing the problem and guiding staff on what data and other resources were needed for the next meeting, which is tentatively scheduled for January, 2018.

  Coffman discussed the upcoming HERC retreat, which will orient new members and assess strengths and areas for improvement in the HERC work with the Prioritized List, coverage guidances, and the new process for prioritization of certain medications. He asked for any specific thoughts or feedback from members prior to the meeting.

- **Topic: Straightforward/Consent Agenda**

  Discussion: There was no discussion about the consent agenda items other than the tobacco cessation guideline.

  Hodges raised concerns about the tobacco cessation guideline; specifically, that it went into too much detail. She was particularly concerned about the requirement to cover nicotine sprays, which have limited evidence of effectiveness and are more likely to result in addiction to the spray. She was concerned about patients using the products for more than 6 months. She felt that the edits added unneeded complication. Hodges said the CCO metric on tobacco cessation already requires offering all these products, making the guideline note change unnecessary.

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The decision was to table the tobacco cessation guideline edits. HERC staff will work with P&T and HSD staff regarding the specific nicotine replacement products and bring this topic back in November.

Recommended Actions:

1) Remove 20552 and 20553 (Injection(s); single or multiple trigger point(s)) from line 425 ACUTE PERIPHERAL MOTOR AND DIGITAL NERVE INJURY
2) Add 26460 (Tenotomy, extensor, hand or finger, open, each tendon) to line 292 NEUROLOGICAL DYSFUNCTION IN POSTURE AND MOVEMENT CAUSED BY CHRONIC CONDITIONS
3) Add 10030 (Image-guided fluid collection drainage by catheter (eg, abscess, hematoma, seroma, lymphocele, cyst), soft tissue (eg, extremity, abdominal wall, neck), percutaneous) to line 422 COMPLICATIONS OF A PROCEDURE USUALLY REQUIRING TREATMENT
4) Add 29130 (Application of finger splint; static) to line 441 MALUNION AND NONUNION OF FRACTURE
5) Add 28300 (Osteotomy; calcaneus (eg, Dwyer or Chambers type procedure), with or without internal fixation) to line 355 CLOSED FRACTURE OF EXTREMITIES (EXCEPT MINOR TOES)
6) Add 29894 (Arthroscopy, ankle (tibiotalar and fibulotalar joints), surgical; with removal of loose body or foreign body) to line 355 CLOSED FRACTURE OF EXTREMITIES (EXCEPT MINOR TOES)
7) Add 37184 and (Primary percutaneous transluminal mechanical thrombectomy, noncoronary, non-intracranial, arterial or arterial bypass graft, including fluoroscopic guidance and intraprocedural pharmacological thrombolytic injection(s)) to line 285 COMPLICATIONS OF A PROCEDURE ALWAYS REQUIRING TREATMENT
8) Add 37211 (Transcatheter therapy, arterial infusion for thrombolysis, any method, including radiological supervision and interpretation, initial treatment day) and 37212 (venous) to line 285 COMPLICATIONS OF A PROCEDURE ALWAYS REQUIRING TREATMENT
9) Add 96150-96153 (Health and behavior intervention) to lines
    a. 10 GALACTOSEMIA
    b. 13 CONGENITAL HYPOTHYROIDISM
    c. 14 PHENYLKETONURIA (PKU)
    d. 15 CONGENITAL INFECTIOUS DISEASES
    e. 33 SPINA BIFIDA
    f. 44 COARCTATION OF THE AORTA
    g. 48 CHRONIC RESPIRATORY DISEASE ARISING IN THE NEONATAL PERIO...
    h. 64 CONGENITAL ANOMALIES OF UPPER ALIMENTARY TRACT, EXCLUDING...
    i. 67 VENTRICULAR SEPTAL DEFECT
    j. 77 PATENT DUCTUS ARTERIOSUS…
    k. 87 CONGENITAL ANOMALIES OF GENITOURINARY SYSTEM
    l. 89 DISCORDANT CARDIOVASCULAR CONNECTIONS
    m. 101 CONGENITAL ANOMALIES OF DIGESTIVE SYSTEM…
    n. 103 POISONING BY INGESTION…
    o. 105 TETRALOGY OF FALLOT…
    p. 111 CONGENITAL HEART BLOCK…
    q. 130 TOTAL ANOMALOUS PULMONARY VENOUS CONNECTION
10) Add L08.9 (Local infection of the skin and subcutaneous tissue, unspecified) to lines 206 SUPERFICIAL ABSCESSES AND CELLULITIS and 385 SUPERFICIAL INJURIES WITH INFECTION and remove from line 625 BENIGN NEOPLASMS OF SKIN AND OTHER SOFT TISSUES
11) Remove the following ICD-10 codes from line 2 BIRTH OF AN INFANT
    a. P39.2 Neonatal urinary tract infection

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b. P39.4 Neonatal skin infection
c. P39.8 Other specified infections specific to the perinatal period
d. P 39.9 Infection specific to the perinatal period, unspecified

12) Add 58150, 58180, 58260-58262, 58290-58291, 58541-58544, and 58550-58573 (various hysterectomy codes) to line 1 PREGNANCY
13) Add 62143 (Replacement of bone flap or prosthetic plate of skull) to line 196 SUBARACHNOID AND INTRACEREBRAL HEMORRHAGE/HEMATOMA; CEREBRAL ANEURYSM; COMPRESSION OF BRAIN
14) Add 77332-77334 (Treatment devices, design and construction) to lines 440 TRIGEMINAL AND OTHER NERVE DISORDERS and 458 CENTRAL PTERYGIUM AFFECTING VISION
15) Reverse the August 2017 VbBS/HERC decision to remove CPT 95250 and 95251 (Glucose monitoring by SQ device) from line 8 TYPE 1 DIABETES MELLITUS
16) Add a coding specification to line 8 TYPE 1 DIABETES MELLITUS as shown below
    a. "CPT 95250 and 95251 are included on this line for services related to real-time CGM but not to retrospective (professional) CGM."
17) Affirm the addition of the entry to GN172 regarding CPT 95250 and 95251 as shown in the August, 2017 VbBS and HERC minutes
18) Modify GN144 as shown in Appendix A
19) HERC staff will work with P&T and HSD staff regarding the tobacco cessation guideline and bring that topic back to a future meeting.

MOTION: To approve the recommendations stated in the consent agenda with the exception of the changes to the tobacco cessation guideline. CARRIES 7-0.

- **Topic: Oral Health Advisory Panel (OHAP) report**

Discussion: Smits introduced the OHAP CDT code placement recommendations. There was no discussion.

Recommended Actions:
1) Place the 2018 CDT codes as shown in Appendix B
2) Remove D7980 (SIALOLITHOTOMY) from line 323 SIALOADENITIS, ABSCESS, FISTULA OF SALIVARY GLANDS

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

- **Topic: Consideration for prioritization on lines 500/660, Services with Minimal or No Clinical Benefit and/or Low Cost Effectiveness, for deflazacort and eteplirsen for Duchenne muscular dystrophy**

Discussion: Olsen started by introducing a background of the new work of the VbBS on drug prioritization. Coffman reviewed the process discussion. Typically drugs have not been specifically prioritized. He reviewed the two new lines (500 and 660) for services not recommended for coverage. Gibson pointed out the history of the VbBS to place treatments with poor evidence on low priority lines. There is a lot of precedent for evaluating evidence and making hard decisions to rank something low on the Prioritized List.

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Smits reviewed the summary document. Sarah Servid from the OSU College of Pharmacy provided background information regarding the drug review.

Dr. Erika Finanger from OHSU answered questions about Duchenne muscular dystrophy (DMD). She also provider some information about an ongoing trail of eteplirsen; this ongoing study (N=75) is a 48 week trial of eteplirsen with control patients who are DMD patients with other exon skipping mutations (not exon 51) but who thought to be generally clinically similar to the exon 51 patients with standard of care therapy. Finanger said her clinical experience is that her patients on eteplirsen are not losing ability to ambulate, unlike similar untreated patients.

The Sarepta Pharmaceuticals representatives clarified that eteplirsen has FDA approval. However, if no data is brought back to the FDA showing clinical efficacy in 4-5 years, approval will be withdrawn.

Public testimony:
Jenn McNary, an advocate for DMD and mother of 2 sons with DMD: Her 2 sons were in the eteplirsen trials. One son in an eteplirsen study while still ambulatory is still ambulatory at 16 yrs. Son who was not ambulatory in the study has had some muscular improvement and does not require ventulatory assistance at age 19. Slowing the disease down has been very significant for their family. Interviews from families were recorded at an FDA hearing and she urged the VbBS/HERC members to review these interviews. Ms. McNary noted that in regards to the question about what level of dystrophin is clinically significant, that patients with exon 45 skipping DMD have higher levels of dystrophin and have milder disease progression and walk 2 years longer than DMD patients with exon 51 mutations. These exon 45 mutation patients have dystrophin levels that are similar to eteplirsen results for exon 51 patients.

Mike Donabedian: Sarepta Pharmaceuticals. Meeting materials contain inaccuracies. He said there are estimated to be 3-4 patients with exon 51 skipping on OHP. *(This was noted in the P&T report and verbally corrected by HERC staff.)* Other drugs are still in clinical development, and are anticipated will treat approximately 6-8 additional patients. He also complained that the VbBS limit of 3 minutes of testimony does not meet the criteria of "meaningful engagement." When asked about critical access programs, he said there is a critical access program available on a case-by-case basis. He would not comment on whether the 3-4 OHP patients would be eligible for such a critical access program through his company. He also could not comment about the availability of the drug through ongoing clinical trials.

Lisa Borland: Sarepta Pharmaceuticals. FDA approval of eteplirsen is not conditional, it is full and final. She discussed the accelerated approval pathway at the FDA. Eteplirsen was approved by FDA based on dystrophin levels as a surrogate endpoint considered reasonably likely to impact clinical outcomes. There is evidence in medical literature that slightly higher dystrophin levels can prolong time to loss of ambulation (different mutations other than exon 51 skipping resulting in higher dystrophin levels). Eteplirsen is the only FDA approved treatment that targets the underlying cause of DMD. Gibson asked about any other drug that has an automatic removal of approval without confirmatory study. Borland replied that the FDA requirement for confirmatory study is not unique to eteplirsen.

Jamie Saukko: mother of a son with DMD who is 2 yrs old. This is the only medication to treat her son. No clinical trials are available to her son. She feels that treating her son at 2 would result in a

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more significant improvement due to lack of muscle harm to date. She has not seen DMD patients walking as long as the eteplirsen patients she has heard about. Her brother and her uncle had DMD and died in their early 20's. She also testified in support of coverage for deflazacort—her son is too young for steroids, but she thinks patients should have drug choices if needed.

Hannah Cain: Duchenne advocate, mother of DMD son. Son just diagnosed last month at age 6. She is battling for the right to an FDA approved drug for her son. Her son will have progressive symptoms, and these will have a great impact on her family. Eteplirsen can improve his quality of life and extend his life. She also noted that, based on expert opinion, deflazacort is superior to prednisone.

Dr. Erika Finanger: deflazacort has a significant cost difference compared to prednisone. She has patients on both types of steroids. She notes that a small increase in weight gain can have a very significant impact in her patients. If there is large weight gain with prednisone, she changes to deflazacort. Patients need to be on steroids for significant clinical benefit and if they cannot tolerate prednisone, they need effective alternatives. She noted that eteplirsen went through an established FDA approval process. She agrees on the need for further study on the effectiveness of eteplirsen. She did note that the researchers need to use surrogate outcome in the eteplirsen studies as finding other outcomes takes a very long time and is likely not feasible.

Gibson asked about any dose response difference between the 30 and 50 mg/kg doses. Borland answered that no difference was seen in dystrophen levels at 30 and 50 mg/kg.

In response to a question about side effects, Servid clarified that the studies on deflazacort were of too poor quality to conclusively determine any difference in side effects compared to prednisone.

Pollack and Olson commented on the need for the committee to consider the entire OHP population and limited resources. They expressed compassion for the DMD community and the need for improved care for that condition. Williams thanked all the advocates and parents for coming and engaging in our process. She urged them to continue their advocacy efforts, and urged them to consider spending efforts to affect the pricing of these medications. Gibson also thanked the advocates, parents and clinical experts, for taking time and effort to assist the committee. He noted that future research may show higher quality evidence of clinical benefit. He urged continuing advocation of the families and experts with the VbBS and HERC.

Recommended Actions:

1) Prioritize deflazacort (Emflaza) for Duchenne muscular dystrophy to line 500 and add an entry to GN172 as shown in Appendix A
2) Prioritize eteplirsen (Exondys 51) to line 660 and add an entry to GN173 as shown in Appendix A

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

Note: Please see September 28, 2017 HERC minutes for further discussion and changes to these recommendations

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- **Topic: Testicular prostheses**

Discussion: There was no discussion about this topic.

Recommended Actions:

1) Add CPT 54660 (Insertion of testicular prosthesis (separate procedure)) to the following lines:
    a. 112 CANCER OF TESTIS
    b. 208 DEEP OPEN WOUND, WITH OR WITHOUT TENDON OR NERVE INVOLVEMENT
    c. 259 CANCER OF PENIS AND OTHER MALE GENITAL ORGANS
    d. 312 GENDER DYSPHORIA/TRANSEXUALISM
    e. 327 FUNCTIONAL AND MECHANICAL DISORDERS OF THE GENITOURINARY SYSTEM INCLUDING BLADDER OUTLET OBSTRUCTION
    f. 329 CANCER OF PROSTATE GLAND
    g. 467 GONADAL DYSFUNCTION, MENOPAUSAL MANAGEMENT

MOTION: To recommend the code changes as presented. CARRIES 6-0. *(Absent: Hodges)*

- **Topic: Capsulorrhaphy for recurrent shoulder dislocation**

Discussion: Smits introduced the staff summary. Williams noted that CPT 29806 (Arthroscopy, shoulder, surgical; capsulorrhaphy) had not been included in the staff recommendations. This code is already on line 359, but needs to be removed from line 417. This modification was accepted.

Recommended Actions:

1) Add open capsulorrhaphy (CPT 23462-23466) to line 359 DEFORMITY/CLOSED DISLOCATION OF MAJOR JOINT AND RECURRENT JOINT DISLOCATIONS
    a. CPT 23462, Capsulorrhaphy, anterior, any type; with coracoid process transfer
    b. CPT 23465, Capsulorrhaphy, glenohumeral joint, posterior, with or without bone block
    c. CPT 23466, Capsulorrhaphy, glenohumeral joint, any type multi-directional instability
2) Remove CPT 23462-23466 (open capsulorrhaphy) and 29806 (Arthroscopy, shoulder, surgical; capsulorrhaphy) from line 417 DISORDERS OF SHOULDER, INCLUDING SPRAINS/STRAINS GRADE 4 THROUGH 6
3) Add HCPCS S2300 (Arthroscopy, shoulder, surgical; with thermally-induced capsulorrhaphy) to line 500 CONDITIONS FOR WHICH CERTAIN TREATMENTS RESULT IN MARGINAL CLINICAL BENEFIT OR LOW COST-EFFECTIVENESS with an entry in GN172 as shown in Appendix A

MOTION: To approve the code and guideline note changes as amended. CARRIES 7-0.

- **Topic: Transcutaneous neurostimulators**

Discussion: There was no discussion about this topic.

Recommended Actions:

1) Add CPT 64550, 97014 and 97032 and HCPCS E0720, E0730, and G0283 (Transcutaneous electrical nerve stimulation [TENS]; electrical stimulation) to line 660 CONDITIONS FOR WHICH

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CERTAIN TREATMENTS HAVE NO CLINICALLY IMPORTANT BENEFIT OR HAVE HARMS THAT OUTWEIGH BENEFITS; UNPROVEN TREATMENTS

2) Add CPT 0278T (Transcutaneous electrical modulation pain reprocessing (e.g, scrambler therapy), each treatment session (includes placement of electrodes)) to line 660
3) Delete the following sentence from GUIDELINE NOTE 56, NON-INTERVENTIONAL TREATMENTS FOR CONDITIONS OF THE BACK AND SPINE as shown in Appendix A

~~Transcutaneous electrical nerve stimulation (TENS; CPT 64550, 97014 and 97032) is not included on the Prioritized List for any condition due to lack of evidence of effectiveness.~~

4) Modify the entry to GN173 adopted in May, 2017 as shown in Appendix A

MOTION: To approve the code and guideline note changes as presented. CARRIES 7-0.

- **Topic: Physical therapy for interstitial cystitis**

Discussion: There was no discussion about this topic.

Recommended Actions:

1) Add pelvic physical therapy to line 327 FUNCTIONAL AND MECHANICAL DISORDERS OF THE GENITOURINARY SYSTEM INCLUDING BLADDER OUTLET OBSTRUCTION
    a. Add CPT 97140 Manual therapy techniques (e.g., mobilization/manipulation, manual lymphatic drainage, manual traction), one or more regions, each 15 minutes
    b. Add CPT 97161-97164 Physical therapy evaluation or reevaluation
    c. Adopt a new guideline note for line 327 as shown in Appendix C

MOTION: To recommend the code and guideline note changes as presented. CARRIES 7-0.

- **Topic: Acute peripheral nerve injury**

Discussion: Smits reviewed the summary document. Saboe raised the question about coverage of nerve entrapment syndromes. It was determined that the topic under review was regarding acute nerve injury, from trauma, etc. It was decided that HERC staff would review placement of nerve entrapment and bring back as a future topic.

Recommended Actions:

1) Interim modification (effective January 1, 2018)
    a. Add peripheral nerve injury ICD-10 codes below to lines 507 PERIPHERAL NERVE DISORDERS Tx MEDICAL TREATMENT and 534 PERIPHERAL NERVE DISORDERS Tx SURGICAL TREATMENT:
        i. S44.00xA-S44.42xA / S54.00xA-S54.22xA / S64.00xA-S64.498A (Injury of ulnar nerve, Injury of median nerve, Injury of radial nerve, Injury of axillary nerve, Injury of musculocutaneous nerve)
        ii. S74.0 (Injury of sciatic nerve at hip and thigh level)
        iii. S74.1 (Injury of femoral nerve at hip and thigh level)
        iv. S94.00xA-S94.22xA (Injury of lateral plantar nerve, Injury of medial plantar nerve, Injury of deep peroneal nerve).

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b. Revise GN133 as shown in Appendix A

2) Biennial Review 2020 (effective January 1, 2020):
   a. Delete line 425 ACUTE PERIPHERAL MOTOR AND DIGITAL NERVE INJURY
   b. Add ICD-10 G57.2 (Lesion of femoral nerve) to line 208 DEEP OPEN WOUND, WITH OR WITHOUT TENDON OR NERVE INVOLVEMENT
   c. Modify GN133 as shown in Appendix A

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

- **Topic: SOI on role of Prioritized List in coverage**

Discussion: There was no discussion about this topic.

Recommended Actions:
1) Adopt a new Statement of Intent regarding the role of the Prioritized List in coverage as shown in Appendix C

MOTION: To recommend the adoption of a new statement of intent as presented. CARRIES 7-0.

- **Topic: Graphs, flaps and pedicles**

Discussion: There was no discussion about this topic.

Recommended Actions:
1) Remove the CPT codes in the following table from all lines on the Prioritized List
   a. Advise HSD to add these codes to the Ancillary Procedures List

CPT code	Code Description
14000-14302	Adjacent tissue transfer or rearrangement, various locations and types
15040	Harvest of skin for tissue cultured skin autograft, 100 sq cm or less
15050	Pinch graft, single or multiple, to cover small ulcer, tip of digit, or other minimal open area (except on face), up to defect size 2 cm diameter
15100	Split-thickness autograft, trunk, arms, legs; first 100 sq cm or less, or 1% of body area of infants and children (except 15050)
15101	…each additional 100 sq cm, or each additional 1% of body area of infants and children, or part thereof
15110	Epidermal autograft, trunk, arms, legs; first 100 sq cm or less, or 1% of body area of infants and children
15111	…each additional 100 sq cm, or each additional 1% of body area of infants and children, or part thereof
15115	Epidermal autograft, face, scalp, eyelids, mouth, neck, ears, orbits, genitalia, hands, feet, and/or multiple digits; first 100 sq cm or less, or 1% of body area of infants and children

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CPT code	Code Description
15116	…each additional 100 sq cm, or each additional 1% of body area of infants and children, or part thereof
15120	Split-thickness autograft, face, scalp, eyelids, mouth, neck, ears, orbits, genitalia, hands, feet, and/or multiple digits; first 100 sq cm or less, or 1% of body area of infants and children (except 15050)
15121	…each additional 100 sq cm, or each additional 1% of body area of infants and children, or part thereof
15130	Dermal autograft, trunk, arms, legs; first 100 sq cm or less, or 1% of body area of infants and children
15131	…each additional 100 sq cm, or each additional 1% of body area of infants and children, or part thereof
15135	Dermal autograft, face, scalp, eyelids, mouth, neck, ears, orbits, genitalia, hands, feet, and/or multiple digits; first 100 sq cm or less, or 1% of body area of infants and children
15136	…each additional 100 sq cm, or each additional 1% of body area of infants and children, or part thereof (List separately in addition to code for primary procedure)
15150	Tissue cultured skin autograft, trunk, arms, legs; first 25 sq cm or less
15151	…additional 1 sq cm to 75 sq cm
15152	…each additional 100 sq cm, or each additional 1% of body area of infants and children, or part thereof
15155	Tissue cultured skin autograft, face, scalp, eyelids, mouth, neck, ears, orbits, genitalia, hands, feet, and/or multiple digits; first 25 sq cm or less
15156	…additional 1 sq cm to 75 sq cm
15157	…each additional 100 sq cm, or each additional 1% of body area of infants and children, or part thereof
15200	Full thickness graft, free, including direct closure of donor site, trunk; 20 sq cm or less
15201	…each additional 20 sq cm, or part thereof
15220	Full thickness graft, free, including direct closure of donor site, scalp, arms, and/or legs; 20 sq cm or less
15221	…each additional 20 sq cm, or part thereof
15240	Full thickness graft, free, including direct closure of donor site, forehead, cheeks, chin, mouth, neck, axillae, genitalia, hands, and/or feet; 20 sq cm or less
15241	…each additional 20 sq cm, or part thereof
15260	Full thickness graft, free, including direct closure of donor site, nose, ears, eyelids, and/or lips; 20 sq cm or less
15261	…each additional 20 sq cm, or part thereof
15570	Formation of direct or tubed pedicle, with or without transfer; trunk
15572	…, arms, or legs
15574	…forehead, cheeks, chin, mouth, neck, axillae, genitalia, hands or feet
15576	Formation of direct or tubed pedicle, with or without transfer; eyelids, nose, ears, lips, or intraoral
15600	Delay of flap or sectioning of flap (division and inset); at trunk
15610	…at scalp, arms or legs
15620	…at forehead, cheeks, chin, neck, axillae, genitalia, hands, or feet
15630	..at eyelids, nose, ears, or lips

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CPT code	Code Description
15650	Transfer, intermediate, of any pedicle flap (eg, abdomen to wrist, Walking tube), any location
15731	Transfer, intermediate, of any pedicle flap (eg, abdomen to wrist, Walking tube), any location
15732	Muscle, myocutaneous, or fasciocutaneous flap; head and neck (eg, temporalis, masseter muscle, sternocleidomastoid, levator scapulae)
15734	Muscle, myocutaneous, or fasciocutaneous flap; trunk
15736	Muscle, myocutaneous, or fasciocutaneous flap; upper extremity
15738	Muscle, myocutaneous, or fasciocutaneous flap; lower extremity
15740	Flap; island pedicle requiring identification and dissection of an anatomically named axial vessel
15750	Flap; neurovascular pedicle
15756	Free muscle or myocutaneous flap with microvascular anastomosis
15757	Free skin flap with microvascular anastomosis
15758	Free fascial flap with microvascular anastomosis
15760	Graft; composite (eg, full thickness of external ear or nasal ala), including primary closure, donor area
15770	Graft; derma-fat-fascia
20900	Bone graft, any donor area; minor or small (eg, dowel or button)
20902	Bone graft, any donor area; major or large
20920	Fascia lata graft; by stripper
20922	Fascia lata graft; by incision and area exposure, complex or sheet
20924	Tendon graft, from a distance (eg, palmaris, toe extensor, plantaris)
20926	Tissue grafts, other (eg, paratenon, fat, dermis)

MOTION: To recommend the code changes as presented. CARRIES 7-0.

- **Topic: Iliotibial (IT) band syndrome**

Discussion: Smits introduced the summary document. Williams asked for clarification about whether adding IT band syndrome to a nonfunded line would result in loss of medical coverage (physical therapy, etc.) for this condition. The answer was found to be dependent on how GN98 was interpreted. If GN98 is interpreted strictly, then IT band syndrome would never meet GN98 criteria and would always be considered on the lower line and therefore could not get medical therapy outside of primary care office visits. IF GN98 is only applied to surgical therapy, then IT band syndrome medical therapy would be on a funded line and medical therapy covered. Saboe spoke about how chiropractic treatment is highly effective for this condition. The subcommittee wanted PT and chiropractic care for IT band syndrome covered; however, it was noted that similar minor injuries and overuse syndromes (sprains and strains) have no coverage. HERC staff was charged with looking at the coverage of minor sprains/strains/overuse syndromes, as well as the intent of GN98 (does it apply only to surgery or to all treatment of conditions on the lines attached to it?). GN98 likely needs clarification about applying to just surgery or both surgical and medical interventions. Line 376 treatment description also needs to be examined and "repair" changed to a more appropriate description. HERC staff will also look at line 605 prioritization.

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Recommended Actions:

1) HERC staff will investigate GN98, line 376 and line 608, and readdress the questions raised at a future meeting.

- **Topic: Coverage Guidance—Colon cancer screening modalities**

Discussion: Obley reviewed the evidence for colon cancer screening modalities. Shaffer introduced the summary document for proposed Prioritized List changes based on this review.

A member asked about the statement in one of the public comments that CT colonography detects lesions missed by blood tests. Obley said that this is correct; the SEPT9 test is a blood test and has a low sensitivity and is not recommended for coverage. It is not detecting precancerous tumors that would be found by colonoscopy. Obley also clarified that radiation doses have declined as CT technology improves. He also said that some of the incidental findings would not require followup, according to the commenter. There were also questions about the radiation dose with CT colonography. Obley said he is not an expert in this area but that some believe that each additional dose of radiation increases risk, even if the dose is relatively small. Livingston said a chest x-ray is 0.1 millisieverts. A CT scan of the abdomen and pelvis is 15 millisieverts. Wentz asked how much of the sensitivity is dependent on the person doing the colonoscopy or reading the CT colonography. Obley confirmed that experience matters and one study purportedly showing the superiority of CT colonography had been criticized for using only experienced radiologists, with a broader mix of experience levels for the gastroenterologists performing the colonoscopies. In response to another question about this study's results he said that it would be a highly divergent view that anything other than colonoscopy represents the gold standard.

There was also brief discussion of comments from the American College of Radiology regarding the HERC's process. The policies and rules they cite are not applicable to the HERC as it is not a federal body and does not develop clinical guidelines, but coverage policy.

The group discussed the so-called camera pill. It is not recommended or studied for colorectal cancer screening. Smits said that it is only covered for investigation of GI bleeding when the source of the bleeding is not identified by other tests.

Pollack asked about the preparation for the colonoscopy, saying it's the part people are averse to and that the Commission needs to consider this, as colonoscopy is still required after positive findings on other tests examined in this coverage guidance.

Another member asked about the finding that FOBT (fecal occult blood testing) and sigmoidoscopy are the only tests that reduce colon cancer specific mortality. However, large observational trials on colonoscopy suggest a benefit in right-sided cancers, enough so that sigmoidoscopy is falling out of favor. Obley said Dr. Lieberman in Portland is conducting a randomized trial of colonoscopy versus FIT testing to answer the question. Shaffer said that, in its submitted comments, the Medical Imaging and Technology Alliance expressed support for CT colonography based on a similar argument, as it is more sensitive than FOBT. While this is true, HTAS looked at this argument in the context of already having colonoscopy as an accepted test.

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The members discussed sigmoidoscopy. It can be done by a primary care provider, especially in rural areas, but colonoscopy is generally preferred as it examines the entire colon.

The subcommittee discussed Cologuard, also known as FIT-DNA or mt-sDNA. Olson asked about the definition of advanced adenoma. Obley said it is based on polyp size. There was little discussion on this intervention, SEPT9 blood testing or chromoscopy.

In discussion of application to the Prioritized List, Livingston suggested that the word "chromoscopy" be added to guideline note 172 even though it does not have a HCPCS code.

Shaffer said that CT colonography and mt-sDNA are both a part of the HEDIS colorectal cancer screening metric adopted by OHA as a CCO incentive metric. Even though the services would be unfunded, if a member received such a service it would count toward the performance measure. Hodges said she didn't see this as the concern of the HERC and said her CCO would educate providers that the other screenings are not covered. The subcommittee discussed that OHA adopted a national quality measure and that it is sometimes hesitant to modify national measures because it causes administrative difficulties, and that if a member had a noncovered screening, it might be good for that to be counted. Hodges said such patients should be provided a more effective screening, rather than a less effective test not approved by HERC.

Obley clarified that there was a randomized controlled trial comparing CT colonography without cathartic bowel preparation versus colonoscopy. A higher proportion of patients invited to CT colonography underwent testing. Nevertheless, the polyp/cancer detection rate was the same between the two groups of patients invited to testing, as colonoscopy was more sensitive when the patients actually attended testing. You could make a case that CT colonography is not worth the extra cost when it results in a similar yield. In addition, all the patients who screened positive with CT colonography had to have a colonoscopy.

Gibson asked about the meeting materials that were originally sent, which included a recommendation for CT colonography for patients who couldn't undergo colonoscopy. Shaffer explained that these materials had been corrected; HTAS had considered that recommendation but decided not to recommend CT colonography as it could displace more effective techniques and because patients who couldn't undergo colonoscopy might have little benefit from colonography since a follow-up colonoscopy would be necessary after positive findings.

The staff recommendations were accepted as presented, with the exception of adding chromoscopy to the GN172 entry to call out that it is non-covered.

Recommended Actions:

1) Add the following CPT codes to line 3 PREVENTION SERVICES WITH EVIDENCE OF EFFECTIVENESS
    a. 44392 (Colonoscopy through stoma; with removal of tumor(s), polyp(s), or other lesion(s) by hot biopsy forceps)
    b. 44394 (Colonoscopy through stoma; with removal of tumor(s), polyp(s), or other lesion(s) by snare technique)
    c. 45333 (Sigmoidoscopy, flexible; with removal of tumor(s), polyp(s), or other lesion(s) by hot biopsy forceps)
    d. 45338 (Sigmoidoscopy, flexible; with removal of tumor(s), polyp(s), or other lesion(s) by snare technique)

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2) Add the following HCPCS codes to line 3 PREVENTION SERVICES WITH EVIDENCE OF EFFECTIVENESS and advise HSD to remove from the Ancillary File
    a. G0104 (Colorectal cancer screening; flexible sigmoidoscopy)
    b. G0105 (Colorectal cancer screening; colonoscopy on individual at high risk)
    c. G0106 (Colorectal cancer screening; alternative to g0104, screening sigmoidoscopy, barium enema)
    d. G0120 (Colorectal cancer screening; alternative to g0105, screening colonoscopy, barium enema)
    e. G0121 (Colorectal cancer screening; colonoscopy on individual not meeting criteria for high risk)
    f. G0122 (Colorectal cancer screening; barium enema)
3) Revise Guideline Note 106 as shown in Appendix A
4) Add CPT 74263 (Computed tomographic (CT) colonography, screening, including image postprocessing), 81528 (Oncology (colorectal) screening, quantitative real-time target and signal amplification of 10 DNA markers (KRAS mutations, promoter methylation of NDRG4 and BMP3) and fecal hemoglobin, utilizing stool, algorithm reported as a positive or negative result), and 81327 (SEPT9 (Septin9) (eg, colorectal cancer) methylation analysis) to line 500 and add an entry to GN172 as shown in Appendix A

MOTION: To approve the recommended changes as amended to the Prioritized List based on the draft Colorectal Cancer Screening Modalities coverage guidance scheduled for review by HERC at their September 2017 meeting. CARRIES 7-0.

Note: The barium enema CRC screening code placement recommendation was not accepted by HERC and will be reconsidered at a future VbBS meeting.

- **Public Comment:**

  No additional public comment was received.

- **Issues for next meeting:**
  - -Tobacco cessation guideline
  - -IT band syndrome prioritization

- **Next meeting:**

  The next meeting will be held on November 9, 2017 at Clackamas Community College, Wilsonville Training Center, Wilsonville Oregon, Rooms 111-112.

- **Adjournment:**

  The meeting adjourned at 12:35 PM.

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Appendix A
Revised Guideline Notes

Effective January 1, 2018

GUIDELINE NOTE 56, NON-INTERVENTIONAL TREATMENTS FOR CONDITIONS OF THE BACK AND SPINE

Lines 366,407

Patients seeking care for back pain should be assessed for potentially serious conditions ("red flag" symptoms requiring immediate diagnostic testing), as defined in Diagnostic Guideline D4. Patients lacking red flag symptoms should be assessed using a validated assessment tool (e.g. STarT Back Assessment Tool) in order to determine their risk level for poor functional prognosis based on psychosocial indicators.
For patients who are determined to be low risk on the assessment tool, the following services are included on these lines:

- Office evaluation and education,
- Up to 4 total visits, consisting of the following treatments: OMT/CMT, acupuncture, and PT/OT. Massage, if available, may be considered.
- First line medications: NSAIDs, acetaminophen, and/or muscle relaxers. Opioids may be considered as a second line treatment, subject to the limitations on coverage of opioids in Guideline Note 60 OPIOIDS FOR CONDITIONS OF THE BACK AND SPINE. See evidence table.

For patients who are determined to be medium- or high risk on the validated assessment tool, as well as patients undergoing opioid tapers as in Guideline Note 60 OPIOIDS FOR CONDITIONS OF THE BACK AND SPINE, the following treatments are included on these lines:

- Office evaluation, consultation and education
- Cognitive behavioral therapy. The necessity for cognitive behavioral therapy should be re-evaluated every 90 days and coverage will only be continued if there is documented evidence of decreasing depression or anxiety symptomatology, improved ability to work/function, increased self-efficacy, or other clinically significant, objective improvement.
- Prescription and over-the-counter medications; opioid medications subject to the limitations on coverage of opioids in Guideline Note 60 OPIOIDS FOR CONDITIONS OF THE BACK AND SPINE. See evidence table.
- The following evidence-based therapies, when available, are encouraged: yoga, massage, supervised exercise therapy, intensive interdisciplinary rehabilitation. HCPCS S9451 is only included on Line 407 for the provision of yoga or supervised exercise therapy.
- A total of 30 visits per year of any combination of the following evidence-based therapies when available and medically appropriate. These therapies are only included on these lines if provided by a provider licensed to provide the therapy and when there is documentation of measurable clinically significant progress toward the therapy plan of care goals and objectives using evidence based objective tools (e.g. Oswestry, Neck Disability Index, SF-MPQ, and MSPQ).
    1) Rehabilitative therapy (physical and/or occupational therapy), if provided according to Guideline Note 6 REHABILITATIVE AND HABILITATIVE THERAPIES. Rehabilitation services provided under this guideline also count towards visit totals in Guideline Note 6
    2) Chiropractic or osteopathic manipulation
    3) Acupuncture

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Appendix A
Revised Guideline Notes

Mechanical traction (CPT 97012) is not included on these lines, due to evidence of lack of effectiveness for treatment of back and neck conditions. ~~Transcutaneous electrical nerve stimulation (TENS; CPT 64550, 97014 and 97032) is not included on the Prioritized List for any condition due to lack of evidence of effectiveness.~~

The development of this guideline note was informed by HERC coverage guidances on Low Back Pain Non-Pharmacologic, Non-Invasive Intervention, Low Back Pain, Pharmacological and Herbal Therapies. See http://www.oregon.gov/oha/HPA/CSI-HERC/Pages/Evidence-based-Reports.aspx.

GUIDELINE NOTE 106, PREVENTIVE SERVICES

Lines 3,625

Included on Line 3 are the following preventive services:

1. US Preventive Services Task Force (USPSTF) "A" and "B" Recommendations in effect and issued prior to January 1, 2016.
   http://www.uspreventiveservicestaskforce.org/Page/Name/uspstf-a-and-b-recommendations/
   a. USPSTF "D" recommendations are not included on this line or any other line of the Prioritized List.
2. American Academy of Pediatrics (AAP) Bright Futures Guidelines:
   http://brightfutures.aap.org. Periodicity schedule available at http://www.aap.org/en-us/professional-resources/practice-support/Periodicity/Periodicity%20Schedule_FINAL.pdf.
   a. Screening for lead levels is defined as blood lead level testing and is indicated for Medicaid populations at 12 and 24 months. In addition, blood lead level screening of any child between ages 24 and 72 months with no record of a previous blood lead screening test is indicated.
3. Health Resources and Services Administration (HRSA) Women's Preventive Services - Required Health Plan Coverage Guidelines as retrieved from http://www.hrsa.gov/womensguidelines/ on 1/1/2017.
4. Immunizations as recommended by the Advisory Committee on Immunization Practices (ACIP):
   http://www.cdc.gov/vaccines/schedules/hcp/index.html

Colorectal cancer screening is included on Line 3 for average-risk adults aged 50 to 75, using one of the following screening programs:

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

Colorectal cancer screening for average-risk adults aged 76 to 85 is covered only for those who (1) are healthy enough to undergo treatment if colorectal cancer is detected, and (2) do not have comorbid conditions that would significantly limit their life expectancy.

The development of this guideline note was informed by a HERC coverage guidance. See [link]

Effective January 1, 2018

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Appendix A
Revised Guideline Notes

GUIDELINE NOTE 133, ACUTE PERIPHERAL MOTOR AND DIGITAL NERVE INJURY

Lines 208,425,~~483,~~507,~~519,~~534

Repair of acute (<6 months) peripheral nerve injuries are included on Line 208 and 425. Non-surgical medical care of these injuries are included on Line 507 ~~483~~. Surgical repair of c~~C~~hronic nerve injuries are included on Line~~s 507, 519 and~~ 534.

GUIDELINE NOTE 144, PROTON PUMP INHIBITOR THERAPY FOR GASTROESOPHAGEAL REFLUX DISEASE (GERD)

Lines 314,385,516

Short term treatment (up to 8 weeks) of GERD without Barrett's (ICD-10 K20.8, K20.9, K21.0, K21.9) with proton pump inhibitor therapy is included on Line 385. Long term treatment is included on Line 516.

Long term proton pump inhibitor therapy is included on line 385 for Barrett's esophagus (ICD-10 K22.70)~~.~~ and on line 314 for Barrett's esophagus with dysplasia (ICD-10 K22.71).

GUIDELINE NOTE ~~168~~172, ~~TREATMENTS~~ INTERVENTIONS WITH MARGINAL CLINICAL BENEFIT OR LOW COST-EFFECTIVENESS FOR CERTAIN CONDITIONS

The following treatments are prioritized on Line 500 CONDITIONS FOR WHICH CERTAIN TREATMENTS RESULT IN MARGINAL CLINICAL BENEFIT OR LOW COST-EFFECTIVENESS for the conditions listed here:

CONDITION	CPT/HCPCS code	~~TREATMENT~~ INTERVENTION	Rationale	Date of last Review
Recurrent shoulder dislocation or any other shoulder condition	S2300	Arthroscopy, shoulder, surgical; with thermally-induced capsulorrhaphy	More effective treatments are available	September, 2017
Duchenne Muscular Dystrophy		Deflazacort (Emflaza)	Marginal benefit/low cost-effectiveness compared to equally effective but much less expensive alternative corticosteroids	September, 2017
Colorectal cancer screening	74263, 81528, 81327	Screening CT Colonography FIT-DNA (Cologuard) mSEPT9, Chromoscopy	Insufficient evidence for use in population screening	September, 2017

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

The following treatments are prioritized on Line 660, CONDITIONS FOR WHICH CERTAIN TREATMENTS ARE UNPROVEN, HAVE NO CLINICALLY IMPORTANT BENEFIT OR HAVE HARMS THAT OUTWEIGH BENEFITS, for the conditions listed here:

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Appendix A
Revised Guideline Notes

CONDITION	CPT/HCPCS Code	TREATMENT	Rational	Date of last Review
All conditions ~~Chronic pain, anxiety, depression, insomnia, all other indications~~	64550, 97014, 97032, 0278T E0720, E0730, and G0283	Transcutaneous electrical nerve stimulation [TENS]; Scrambler therapy; Cranial electrical stimulation; all similar transcutaneous electrical neurostimulation therapies	No clinically important benefit (CES) or insufficient evidence of effectiveness (all other) for chronic pain; insufficient evidence of effectiveness for all other indications	September, 2017
Duchenne Muscular Dystrophy		*Eteplirsen (Exondys 51)*	*No clinically important benefit*	*September, 2017*

Note: please seen September 28, 2017 HERC minutes for further discussion and changes to the eteplirsen guideline recommendations

Effective January 1, 2020

GUIDELINE NOTE 133, ACUTE PERIPHERAL MOTOR AND DIGITAL NERVE INJURY

Lines 208,507,534

Repair of acute (<6 months) peripheral nerve injuries are included on Line 208 ~~and 425~~. Non-surgical medical care of these injuries are included on Line 507 ~~483~~. Surgical repair of c~~C~~hronic nerve injuries are included on Line~~s 507, 519 and~~ 534.

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APPENDIX B
CDT CODES

CDT Code	Code description	Proposed Placement
D0411	HbA1c in-office point of service testing	Diagnostic Procedures File
D5511	repair broken complete denture base, mandibular	451 DENTAL CONDITIONS (EG. MISSING TEETH, PROSTHESIS FAILURE) Treatment REMOVABLE PROSTHODONTICS (E.G. FULL AND PARTIAL DENTURES, RELINES)
D5512	repair broken complete denture base, maxillary	451
D5611	repair resin partial denture base, mandibular	451
D5612	repair resin partial denture base, maxillary	451
D5621	repair cast partial framework, mandibular	451
D5622	repair cast partial framework, maxillary	451
D6096	remove broken implant retaining screw	344 DENTAL CONDITIONS (EG. SEVERE CARIES, INFECTION) Treatment: ORAL SURGERY (I.E. EXTRACTIONS AND OTHER INTRAORAL SURGICAL PROCEDURES)
D6118	implant/abutment supported interim fixed denture for edentulous arch – mandibular	616 DENTAL CONDITIONS (EG. MISSING TEETH) Treatment: IMPLANTS (I.E. IMPLANT PLACEMENT AND ASSOCIATED CROWN OR PROSTHESIS)
D6119	implant/abutment supported interim fixed denture for edentulous arch – maxillary	616
D7296	corticotomy – one to three teeth or tooth spaces, per quadrant	615 DENTAL CONDITIONS (EG. MALOCCLUSION)
D7297	corticotomy four or more teeth or tooth spaces, per quadrant	615 DENTAL CONDITIONS (EG. MALOCCLUSION)
D7979	non – surgical sialolithotomy	498 SIALOLITHIASIS, MUCOCELE, DISTURBANCE OF SALIVARY SECRETION, OTHER AND UNSPECIFIED DISEASES OF SALIVARY GLANDS
D8695	removal of fixed orthodontic appliance(s) - other than at conclusion of treatment	267 Dental conditions (time sensitive events) Tx Urgent dental services
D9222	deep sedation/general anesthesia – first 15 minutes	Ancillary Procedures File
D9239	intravenous moderate (conscious) sedation/analgesia- first 15 minutes	Ancillary Procedures File

APPENDIX B
CDT CODES

CDT Code	Code description	Proposed Placement
D9995	teledentistry – synchronous; real-time encounter	54 DENTAL CONDITIONS (EG. INFECTION, PAIN, TRAUMA)
D9996	teledentistry – asynchronous; information stored and forwarded to dentist for subsequent review	54 DENTAL CONDITIONS (EG. INFECTION, PAIN, TRAUMA)

Appendix C
New Statements of Intent and Guideline Notes

STATEMENT OF INTENT XXX, ROLE OF THE PRIORITIZED LIST IN COVERAGE

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

The Commission recognizes that a condition and treatment pairing above the funding line does not necessarily mean that the service will be covered by the Oregon Health Plan (OHP). There may be other restrictions that apply, such as the service not being medically necessary or appropriate for an individual member. Likewise, the absence of a treatment and condition pairing above the funding line is not meant to be an absolute exclusion from coverage. Coverage may still be authorized under applicable federal and state laws, and Oregon's Medicaid State Plan and Waiver for an individual member. For example, OAR 410-141-0480 (Oregon Health Plan Benefit Package of Covered Services) includes services such as, but not limited to, the following:

- Diagnostic services, subject to the List's diagnostic guideline notes when applicable;
- Ancillary services (such as hospitalization, durable medical equipment, certain medications and anesthesia) provided for conditions appearing above the funding line, subject to the List's ancillary guideline notes when applicable; and
- Services paired with an unfunded condition which is causing or exacerbating a funded condition, the treatments for the funded condition are not working or contraindicated, and treatment of the unfunded condition would improve the outcome of treating the funded condition (the "Comorbidity Rule" OAR 410-141-0480(8)(a through b))

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

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

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

GUIDELINE NOTE XXX, PELVIC PHYSICAL THERAPY FOR INTERSTITIAL CYSTITIS

Line 327

Pelvic physical therapy (CPT 97140 and 97161-97164) is included on this line only for treatment of interstitial cystitis in patients who present with pelvic floor tenderness. Such pelvic PT is only included on this line when provided by professionals trained and experienced in pelvic floor therapy and as limited in Guideline Note 6 REHABILITATIVE AND HABILITATIVE THERAPIES.

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Section 3.0

Consent Agenda-

Straightforward Items

Consent Agenda Issues—November, 2017

Code	Code Description	Line(s) Involved	Issue	Recommendation(s)
77301	Intensity modulated radiotherapy plan, including dose-volume histograms for target and critical structure partial tolerance specifications	286 CANCER OF VAGINA, VULVA, AND OTHER FEMALE GENITAL ORGANS	HSD requested that 77301 pair with vulvar cancers. 77301 is currently on 30+ lines with radiation therapy. Dr. Olson and Dr. McWilliams (oncology) concur that is should be covered.	Add 77301 to line 286
T1016	Case management, each 15 minutes	40+ lines	Multiple requests have been made to add T1016 to various lines. Federal rules regarding T1016 indicate that it can be used for any medical or mental health condition. Similar code T1017 (Targeted case management, each 15 minutes) is in Ancillary File.	Remove T1016 from all current lines on the Prioritized List. Advise HSD to add T1016 to the Ancillary Procedures File.
26480	Transfer or transplant of tendon, carpometacarpal area or dorsum of hand; without free graft, each tendon	376 DISRUPTIONS OF THE LIGAMENTS AND TENDONS OF THE ARMS AND LEGS, EXCLUDING THE KNEE, RESULTING IN SIGNIFICANT INJURY/IMPAIRMENT	A provider requested that 26480 be covered for repair of tendon rupture. Similar codes appear on line 376. 26480 is on lines 208,285,359,415,425,503,525	Add 26480 to line 376
21556	Excision, tumor, soft tissue of neck or anterior thorax, subfascial (eg, intramuscular); less than 5 cm)	287 CANCER OF ORAL CAVITY, PHARYNX, NOSE AND LARYNX	A provider requested that 21556 pair with D37.032 (Neoplasm of uncertain behavior of the submandibular salivary glands). 21556 is on lines 200,230,276,287,400,541,556. Line 287 has all other CPT codes in the 21552-21558 series (excision, tumor, soft tissue of neck).	Add 21556 to line 287

Consent Agenda Issues—November, 2017

Code	Code Description	Line(s) Involved	Issue	Recommendation(s)
97530	Therapeutic activities, direct (one-on-one) patient contact (use of dynamic activities to improve functional performance), each 15 minutes	507 PERIPHERAL NERVE DISORDERS	HSD requested that 97530 pair with G57.23 (Lesion of femoral nerve, bilateral lower limbs). 97530 is on 60+ lines.	Add 97530 to line 507
97535	Self-care/home management training (eg, activities of daily living (ADL) and compensatory training, meal preparation, safety procedures, and instructions in use of assistive technology devices/adaptive equipment) direct one-on-one contact, each 15 minutes	30 EPILEPSY AND FEBRILE CONVULSIONS	HSD requested that 97535 pair with epilepsy diagnoses. 97535 is on lines 50+ lines.	Add 97535 to line 30
92133 92134 92226	Scanning computerized ophthalmic diagnostic imaging, posterior segment, with interpretation and report, unilateral or bilateral; optic nerve Scanning computerized ophthalmic diagnostic imaging, posterior segment, with interpretation and report, unilateral or bilateral; retina Ophthalmoscopy, extended, with retinal drawing (eg, for retinal detachment, melanoma), with interpretation and report; subsequent	19 HYDROCEPHALUS AND BENIGN INTRACRANIAL HYPERTENSION	HSD requested that 92133, 92134 and 92226 pair with G93.2 (Benign intracranial hypertension). Most other ophthalmology codes appear on line 19. All 3 CPT codes appear on 50+ lines.	Add 92133, 92134, and 92226 to line 19

Consent Agenda Issues—November, 2017

Code	Code Description	Line(s) Involved	Issue	Recommendation(s)
62160	Neuroendoscopy, intracranial, for placement or replacement of ventricular catheter and attachment to shunt system or external drainage	196 SUBARACHNOID AND INTRACEREBRAL HEMORRHAGE/HEMATOMA; CEREBRAL ANEURYSM; COMPRESSION OF BRAIN	HSD requested that 62160 pair with cerebral edema. Other shunt creation codes are present on line 196	Add 62160 to line 196
63173	Laminectomy with drainage of intramedullary cyst/syrinx; to peritoneal or pleural space	527 CONDITIONS OF THE BACK AND SPINE WITHOUT URGENT SURGICAL INDICATIONS	HSD requested that 63173 pair with G95.0 (Syringomyelia and syringobulbia). 63173 is only on line 150 CERVICAL VERTEBRAL DISLOCATIONS/FRACTURES, OPEN OR CLOSED; OTHER VERTEBRAL DISLOCATIONS/FRACTURES, OPEN OR UNSTABLE; SPINAL CORD INJURIES WITH OR WITHOUT EVIDENCE OF VERTEBRAL INJURY	Add 63173 to line 527
29085	Application, cast; hand and lower forearm (gauntlet)	441 MALUNION AND NONUNION OF FRACTURE	HSD requested that 29085 pair with non-union of hand fracture. 29085 is on lines 132,355,359,376	Add 29085 to line 441
49324 49325	Laparoscopy, surgical; with insertion of tunneled intraperitoneal catheter Laparoscopy, surgical; with revision of previously placed intraperitoneal cannula or catheter, with removal of intraluminal obstructive material if performed	285 COMPLICATIONS OF A PROCEDURE ALWAYS REQUIRING TREATMENT	HSD requested that 49324 and 49325 pair with Breakdown or other mechanical complication of intraperitoneal dialysis catheter. These codes are on 10 lines.	Add 49324 and 49325 to line 285

Consent Agenda Issues—November, 2017

Code	Code Description	Line(s) Involved	Issue	Recommendation(s)
92626 92627	Evaluation of auditory rehabilitation status; first hour each additional 15 minutes	311 HEARING LOSS - AGE 5 OR UNDER 444 HEARING LOSS - OVER AGE OF FIVE	HSD requested that 92626 pair with H90.71 (Mixed conductive and sensorineural hearing loss, unilateral, right ear, with unrestricted hearing on the contralateral side). 92626 and 92627 are on line 326 SENSORINEURAL HEARING LOSS	Add 92626 and 92627 to lines 311 and 444
92567 92552	Tympanometry (impedance testing) Pure tone audiometry (threshold); air only	3 PREVENTION SERVICES WITH EVIDENCE OF EFFECTIVENESS	HSD requested that 92567and 92552 be paired with various diagnoses. Until 2011, 92552 and 92567 were Diagnostic. With the creation of the new Prevention lines, they was added to the upper prevention lines with other hearing tests. However, tympanometry and pure tone audiometry are diagnostic tests is used to determine if there is an infection or fluid in the inner ear or to determine hearing loss, not for hearing screening. 92551 (Screening test, pure tone, air only) is the screening test for hearing. Similar audiometry tests are diagnostic.	Remove 92552 and 92567 from line 3 Advise HSD to add 92552 and 92567 to the Diagnostic Workup File

Consent Agenda Issues—November, 2017

Code	Code Description	Line(s) Involved	Issue	Recommendation(s)
35286 35700	Repair blood vessel with graft other than vein; lower extremity Reoperation, femoral-popliteal or femoral (popliteal)-anterior tibial, posterior tibial, peroneal artery, or other distal vessels, more than 1 month after original operation	349 NON-LIMB THREATENING PERIPHERAL VASCULAR DISEASE	HSD requested that I70.2 (Atherosclerosis of native arteries of extremities) pair with 35286 and 35700. 35286 is on lines 69,78,189,280. 35700 is on lines 79,285	Add 35286 and 35700 to line 349
13160	Secondary closure of surgical wound or dehiscence, extensive or complicated	349 NON-LIMB THREATENING PERIPHERAL VASCULAR DISEASE	HSD requested that 13160 pair with I70.2 (Atherosclerosis of native arteries of extremities). 13160 is on lines 208,230,243,276,285,422,622	Add 13160 to line 349
H0038	Self-help/peer services, per 15 minutes	65 SUBSTANCE-INDUCED DELIRIUM; SUBSTANCE INTOXICATION AND WITHDRAWAL	A provider requested pairing of H0038 with F15.23 (Other stimulant dependence with withdrawal). BHAP agrees with the placement of H0038 on line 65. H0038 is on 40+ mental health lines.	Add H0038 to line 65
52310	Cystourethroscopy, with removal of foreign body, calculus, or ureteral stent from urethra or bladder (separate procedure); simple	100 END STAGE RENAL DISEASE, Tx: RENAL TRANSPLANT	HSD requested that 52310 be added to line 100. A ureteral stent is frequently left in place after transplant and requires later removal. 52310 is on lines 49,80,180,285,327,352	Add 52310 to line 100
11300-11313	Shaving of epidermal or dermal lesion	243,276,321,600,622,625	HSD requested that 11300-11313 be made diagnostic. These types of shaves are becoming standard of care for biopsying skin lesions, rather than punch biopsies.	Remove 11300-11313 from all lines on the Prioritized List Advise HSD to add 11300-11313 to the Diagnostic Workup File

Consent Agenda Issues—November, 2017

Code	Code Description	Line(s) Involved	Issue	Recommendation(s)
62270	Spinal puncture, lumbar, diagnostic	Ancillary File	Currently, 62270 is Ancillary, when it should be diagnostic.	Advise HSD to move 62270 from the Ancillary File to the Diagnostic Workup File

Fecal Incontinence Topic Errors

Issue: as part of the 2013 ICD-10 General Surgery review, a series of coding changes were made to place surgical treatments of fecal incontinence on an uncovered, low priority line. However, multiple codes that were not suggested for movement to that line were added in error. These codes all appear on multiple other lines, except for two codes that had been diagnostic or ancillary. These codes were moved in error and should be removed from line 526 DISORDERS OF FUNCTION OF STOMACH AND OTHER FUNCTIONAL DIGESTIVE DISORDERS.

Below is the table from the 2013 document including only the lines with the error. Note: the "current lines" refer to the 2013 Prioritized List.

CODE	DESCRIPTION	CURRENT PRIORITIZED LIST PLACEMENT	Appropriate for pairing with fecal incontinence? YES/NO
44208	Laparoscopy, surgical; colectomy, partial, with anastomosis, with coloproctostomy (low pelvic anastomosis) with colostomy	35,48,78,84,111,163,165, 173,191,339,503,667	NO
44322	Colostomy or skin level cecostomy; with multiple biopsies (eg, for congenital megacolon) (separate procedure)	111,165	NO
44604	Suture of large intestine (colorrhaphy) for perforated ulcer, diverticulum, wound, injury or rupture (single or multiple perforations); without colostomy	84,88,97,111,240,593	NO
44605	Suture of large intestine (colorrhaphy) for perforated ulcer, diverticulum, wound, injury or rupture (single or multiple perforations); with colostomy	84,88,97,111,240	NO
45805	Closure of rectovesical fistula; with colostomy	35 REGIONAL ENTERITIS, IDIOPATHIC PROCTOCOLITIS, ULCERATION OF INTESTINE	NO
45825	Closure of rectourethral fistula; with colostomy	35 REGIONAL ENTERITIS, IDIOPATHIC PROCTOCOLITIS, ULCERATION OF INTESTINE	NO
50810	Ureterosigmoidostomy, with creation of sigmoid bladder and establishment of abdominal or perineal colostomy, including intestine anastomosis	30 VESICOURETERAL REFLUX	NO
57307	Closure of rectovaginal fistula; abdominal approach, with concomitant colostomy	323 FISTULA INVOLVING FEMALE GENITAL TRACT	NO
88304	Level III - Surgical pathology, gross and microscopic examination Abortion, induced Abscess Aneurysm - arterial/ventricular Anus, tag Appendix, other than incidental Artery, atheromatous plaque Bartholin's gland cyst Bone fragment(s), other than pathologi	DMAP Diagnostic Procedure File	NO
99505	Home visit for stoma care and maintenance including colostomy and cystostomy	DMAP Ancillary Codes File	N/A

HERC staff recommendations:

1) Remove 44208, 44322, 44604, 44605, 45805, 45825, 50810, 57307, 88304, and 99505 from line 526 DISORDERS OF FUNCTION OF STOMACH AND OTHER FUNCTIONAL DIGESTIVE DISORDERS
    a. Advise HSD to add 88304 to the Diagnostic Procedure File
    b. Advise HSD to add 99505 to the Ancillary Procedure File

Massage for Back Pain

Question: what if any limits should be placed on massage for back pain diagnoses?

Question source: OHA Hearings Division; Alison Little, MD, MPH, CCO medical director

Issue: the medical back pain guideline lists massage as a therapy that should be "encouraged" when available. It is not listed as included in the 30 visit limit for PT/OT/chiropractic/acupuncture services. The hearings division had a case where a patient was denied massage therapy as s/he was over his/her 30 visit limit. The HERC heard that some CCOs would not be able to provide massage services, and so did not initially want to include them in the 30 visit limit as it would then appear that these were services that must be covered. However, there was no intent for unlimited massage for back conditions.

The only CPT code for massage, 97124 (Therapeutic procedure, 1 or more areas, each 15 minutes; massage, including effleurage, petrissage and/or tapotement (stroking, compression, percussion)) is a PT service and should be included in the 30 visit maximum.

HERC staff recommendation:

1) Modify GN56 as shown below
    a. Add massage into the 4 visit total for services provided for low risk patients. The evidence supports no therapy for these patients; services were added due to the HERC's decision that this group should have access to a limited package of services
    b. Remove "encouraged" and replace with "may be provided" for high risk patients
    c. Specify that CPT 97124 is a PT service included in the 30 visit limit

GUIDELINE NOTE 56, NON-INTERVENTIONAL TREATMENTS FOR CONDITIONS OF THE BACK AND SPINE

Lines 361,401

Patients seeking care for back pain should be assessed for potentially serious conditions ("red flag" symptoms requiring immediate diagnostic testing), as defined in Diagnostic Guideline D4. Patients lacking red flag symptoms should be assessed using a validated assessment tool (e.g. STarT Back Assessment Tool) in order to determine their risk level for poor functional prognosis based on psychosocial indicators.

For patients who are determined to be low risk on the assessment tool, the following services are included on these lines:

- Office evaluation and education,
- Up to 4 total visits, consisting of the following treatments: OMT/CMT, acupuncture, and PT/OT. Massage, if available, may be ~~considered~~ provided as part of these 4 total visits.
- First line medications: NSAIDs, acetaminophen, and/or muscle relaxers. Opioids may be considered as a second line treatment, subject to the limitations on coverage of opioids in GUIDELINE NOTE 60 OPIOIDS FOR CONDITIONS OF THE BACK AND SPINE. See evidence table.

For patients who are determined to be medium- or high risk on the validated assessment tool, as well as patients undergoing opioid tapers as in GUIDELINE NOTE 60 OPIOIDS FOR CONDITIONS OF THE BACK AND SPINE, the following treatments are included on these lines:

- Office evaluation, consultation and education
- Cognitive behavioral therapy. The necessity for cognitive behavioral therapy should be re-evaluated every 90 days and coverage will only be continued if there is documented evidence of decreasing depression or anxiety symptomatology, improved ability to work/function, increased self-efficacy, or other clinically significant, objective improvement.

- Prescription and over-the-counter medications; opioid medications subject to the limitations on coverage of opioids in GUIDELINE NOTE 60 OPIOIDS FOR CONDITIONS OF THE BACK AND SPINE. See evidence table.
- The following evidence-based therapies, when available, ~~are encouraged~~ may be provided: yoga, massage, supervised exercise therapy, intensive interdisciplinary rehabilitation. HCPCS S9451 is only included on Line 401 for the provision of yoga or supervised exercise therapy.
- A total of 30 visits per year of any combination of the following evidence-based therapies when available and medically appropriate. These therapies are only included on these lines if provided by a provider licensed to provide the therapy and when there is documentation of measurable clinically significant progress toward the therapy plan of care goals and objectives using evidence based objective tools (e.g. Oswestry, Neck Disability Index, SF-MPQ, and MSPQ).
    1) Rehabilitative therapy (physical and/or occupational therapy), if provided according to GUIDELINE NOTE 6 REHABILITATIVE AND HABILITATIVE THERAPIES. Rehabilitation services provided under this guideline also count towards visit totals in GUIDELINE NOTE 6. CPT 97124 is included in this category.
    2) Chiropractic or osteopathic manipulation
    3) Acupuncture

Mechanical traction (CPT 97012) is not included on these lines, due to evidence of lack of effectiveness for treatment of back and neck conditions.

The development of this guideline note was informed by HERC coverage guidances on Low Back Pain Non-Pharmacologic, Non-Invasive Intervention, Low Back Pain, Pharmacological and Herbal Therapies. See http://www.oregon.gov/oha/HPA/CSI-HERC/Pages/Evidence-based-Reports.aspx.

GUIDELINE NOTE 56, NON-INTERVENTIONAL TREATMENTS FOR CONDITIONS OF THE BACK AND SPINE (CONT'D)

Evidence Table of Effective Treatments for the Management of Low Back Pain

Intervention Category*	Intervention	Acute < 4 Weeks	Subacute & Chronic > 4 Weeks
Self-care	Advice to remain active	●	●
	Books, handout	●	●
	Application of superficial heat	●	
Nonpharmacologic therapy	Spinal manipulation	●	●
	Exercise therapy		●
	Massage		●
	Acupuncture		●
	Yoga		●
	Cognitive-behavioral therapy		●
	Progressive relaxation		●
Pharmacologic therapy (Carefully consider risks/harms)	Acetaminophen	●	●
	NSAIDs	●(▲)	●(▲)
	Skeletal muscle relaxants	●	
	Antidepressants (TCA)		●
	*Benzodiazepines***	●(▲)	●(▲)
	*Tramadol, opioids***	●(▲)	●(▲)
Interdisciplinary therapy	Intensive interdisciplinary rehabilitation		●

- ● Interventions supported by grade B evidence (at least fair-quality evidence of moderate benefit, or small benefit but no significant harms, costs, or burdens). No intervention was supported by grade "A" evidence (good-quality evidence of substantial benefit).

▲ *Carries greater risk of harms than other agents in table.*

NSAIDs = nonsteroidal anti-inflammatory drugs; TCA = tricyclic antidepressants.

*These are general categories only. Individual care plans need to be developed on a case by case basis. For more detailed information please see: http://www.annals.org/content/147/7/478.full.pdf

**Associated with significant risks related to potential for abuse, addiction and tolerance. This evidence evaluates effectiveness of these agents with relatively short term use studies. Chronic use of these agents may result in significant harms.

Section 4.0

GAP report

code	long_code_description	Recommended Placement
81105	Human Platelet Antigen 1 genotyping (HPA-1), ITGB3 (integrin, beta 3 [platelet glycoprotein IIIa], antigen CD61 [GPIIIa]) (eg, neonatal alloimmune thrombocytopenia [NAIT], post-transfusion purpura), gene analysis, common variant, HPA-1a/b (L33P)	Diagnostic Workup File
81106	Human Platelet Antigen 2 genotyping (HPA-2), GP1BA (glycoprotein Ib [platelet], alpha polypeptide [GPIba]) (eg, neonatal alloimmune thrombocytopenia [NAIT], post-transfusion purpura), gene analysis, common variant, HPA-2a/b (T145M)	Diagnostic Workup File
81107	Human Platelet Antigen 3 genotyping (HPA-3), ITGA2B (integrin, alpha 2b [platelet glycoprotein IIb of IIb/IIIa complex], antigen CD41 [GPIIb]) (eg, neonatal alloimmune thrombocytopenia [NAIT], post-transfusion purpura), gene analysis, common variant, HPA	Diagnostic Workup File
81108	Human Platelet Antigen 4 genotyping (HPA-4), ITGB3 (integrin, beta 3 [platelet glycoprotein IIIa], antigen CD61 [GPIIIa]) (eg, neonatal alloimmune thrombocytopenia [NAIT], post-transfusion purpura), gene analysis, common variant, HPA-4a/b (R143Q)	Diagnostic Workup File
81109	Human Platelet Antigen 5 genotyping (HPA-5), ITGA2 (integrin, alpha 2 [CD49B, alpha 2 subunit of VLA-2 receptor] [GPIa]) (eg, neonatal alloimmune thrombocytopenia [NAIT], post-transfusion purpura), gene analysis, common variant (eg, HPA-5a/b (K505E))	Diagnostic Workup File
81110	Human Platelet Antigen 6 genotyping (HPA-6w), ITGB3 (integrin, beta 3 [platelet glycoprotein IIIa, antigen CD61] [GPIIIa]) (eg, neonatal alloimmune thrombocytopenia [NAIT], post-transfusion purpura), gene analysis, common variant, HPA-6a/b (R489Q)	Diagnostic Workup File
81111	Human Platelet Antigen 9 genotyping (HPA-9w), ITGA2B (integrin, alpha 2b [platelet glycoprotein IIb of IIb/IIIa complex, antigen CD41] [GPIIb]) (eg, neonatal alloimmune thrombocytopenia [NAIT], post-transfusion purpura), gene analysis, common variant, HP	Diagnostic Workup File
81112	Human Platelet Antigen 15 genotyping (HPA-15), CD109 (CD109 molecule) (eg, neonatal alloimmune thrombocytopenia [NAIT], post-transfusion purpura), gene analysis, common variant, HPA-15a/b (S682Y)	Diagnostic Workup File

code	long_code_description	Recommended Placement
81230	CYP3A4 (cytochrome P450 family 3 subfamily A member 4) (eg, drug metabolism), gene analysis, common variant(s) (eg, *2, *22)	660 CONDITIONS FOR WHICH CERTAIN TREATMENTS HAVE NO CLINICALLY IMPORTANT BENEFIT OR HAVE HARMS THAT OUTWEIGH BENEFITS
81231	CYP3A5 (cytochrome P450 family 3 subfamily A member 5) (eg, drug metabolism), gene analysis, common variants (eg, *2, *3, *4, *5, *6, *7)	660 CONDITIONS FOR WHICH CERTAIN TREATMENTS HAVE NO CLINICALLY IMPORTANT BENEFIT OR HAVE HARMS THAT OUTWEIGH BENEFITS
81232	DPYD (dihydropyrimidine dehydrogenase) (eg, 5-fluorouracil/5-FU and capecitabine drug metabolism), gene analysis, common variant(s) (eg, *2A, *4, *5, *6)	660 CONDITIONS FOR WHICH CERTAIN TREATMENTS HAVE NO CLINICALLY IMPORTANT BENEFIT OR HAVE HARMS THAT OUTWEIGH BENEFITS
81238	F9 (coagulation factor IX) (eg, hemophilia B), full gene sequence	Diagnostic Workup File
81247	G6PD (glucose-6-phosphate dehydrogenase) (eg, hemolytic anemia, jaundice), gene analysis; common variant(s) (eg, A, A-)	Diagnostic Workup File
81248	G6PD (glucose-6-phosphate dehydrogenase) (eg, hemolytic anemia, jaundice), gene analysis; known familial variant(s)	Diagnostic Workup File
81249	G6PD (glucose-6-phosphate dehydrogenase) (eg, hemolytic anemia, jaundice), gene analysis; full gene sequence	Diagnostic Workup File
81258	HBA1/HBA2 (alpha globin 1 and alpha globin 2) (eg, alpha thalassemia, Hb Bart hydrops fetalis syndrome, HbH disease), gene analysis; known familial variant	Diagnostic Workup File
81259	HBA1/HBA2 (alpha globin 1 and alpha globin 2) (eg, alpha thalassemia, Hb Bart hydrops fetalis syndrome, HbH disease), gene analysis; full gene sequence	Diagnostic Workup File
81269	HBA1/HBA2 (alpha globin 1 and alpha globin 2) (eg, alpha thalassemia, Hb Bart hydrops fetalis syndrome, HbH disease), gene analysis; duplication/deletion variants	Diagnostic Workup File

code	long_code_description	Recommended Placement
81283	IFNL3 (interferon, lambda 3) (eg, drug response), gene analysis, rs12979860 variant	660 CONDITIONS FOR WHICH CERTAIN TREATMENTS HAVE NO CLINICALLY IMPORTANT BENEFIT OR HAVE HARMS THAT OUTWEIGH BENEFITS
81328	SLCO1B1 (solute carrier organic anion transporter family, member 1B1) (eg, adverse drug reaction), gene analysis, common variant(s) (eg, *5)	660 CONDITIONS FOR WHICH CERTAIN TREATMENTS HAVE NO CLINICALLY IMPORTANT BENEFIT OR HAVE HARMS THAT OUTWEIGH BENEFITS
81335	TPMT (thiopurine S-methyltransferase) (eg, drug metabolism), gene analysis, common variants (eg, *2, *3)	660 CONDITIONS FOR WHICH CERTAIN TREATMENTS HAVE NO CLINICALLY IMPORTANT BENEFIT OR HAVE HARMS THAT OUTWEIGH BENEFITS
81346	TYMS (thymidylate synthetase) (eg, 5-fluorouracil/5-FU drug metabolism), gene analysis, common variant(s) (eg, tandem repeat variant)	660 CONDITIONS FOR WHICH CERTAIN TREATMENTS HAVE NO CLINICALLY IMPORTANT BENEFIT OR HAVE HARMS THAT OUTWEIGH BENEFITS
81361	HBB (hemoglobin, subunit beta) (eg, sickle cell anemia, beta thalassemia, hemoglobinopathy); common variant(s) (eg, HbS, HbC, HbE)	Diagnostic Workup File
81362	HBB (hemoglobin, subunit beta) (eg, sickle cell anemia, beta thalassemia, hemoglobinopathy); known familial variant(s)	Diagnostic Workup File
81363	HBB (hemoglobin, subunit beta) (eg, sickle cell anemia, beta thalassemia, hemoglobinopathy); duplication/deletion variant(s)	Diagnostic Workup File
81364	HBB (hemoglobin, subunit beta) (eg, sickle cell anemia, beta thalassemia, hemoglobinopathy); full gene sequence	Diagnostic Workup File
81448	Hereditary peripheral neuropathies (eg, Charcot-Marie-Tooth, spastic paraplegia), genomic sequence analysis panel, must include sequencing of at least 5 peripheral neuropathy-related genes (eg, BSCL2, GJB1, MFN2, MPZ, REEP1, SPAST, SPG11, SPTLC1)	Diagnostic Workup File

Comments

Comments

Comments

2018 Genetic CPT Code Review

1. Human Platelet Antigen genotyping (HPA-1) (CPT **81105-81112**)
    a. Background: testing used to screen for neonatal immunization during pregnancy, assess risk of neonatal alloimmune thrombocytopenia in future pregnancies, and assess risk of post-transfusion purpura and thrombocytopenia. These tests are used to screen both mother and father when a neonate is suspected of having neonatal alloimmune thrombocytopenia (NAIT) or when there is reason to suspect a high risk of NAIT in a pregnancy (mother's sister has an affected pregnancy, mother had posttransfusion purpura in the past). Neonatal alloimmune thrombocytopenia (NAIT) is a rare syndrome caused by maternal IgG antibody directed against a fetal platelet antigen inherited from the father. Approximately 1 in 1000 pregnancies is affected, with about half of the cases occurring in first pregnancies. Although HPA-1a (PlA1) is the dominant human platelet alloantigen (HPA) incompatibility causing NAIT, a significant number of cases are caused by other HPA incompatibilities
        i. Testing may be helpful to
            1. Screen for neonatal immunization during pregnancy when parents had prior affected pregnancy or when unexplained intracranial hemorrhage is detected
            2. Assess risk of NAIT in future pregnancies
            3. Assess risk of posttransfusion purpura and thrombocytopenia
    b. Was previously billed under CPT 81400 Molecular pathology procedure, Level 1 (eg, identification of single germline variant [eg, SNP] by techniques such as restriction enzyme digestion or melt curve analysis)
    c. **Arnsberg 2015**, review of human platelet antigen genetic testing
        i. Part of diagnosis of NAIT
        ii. Also used to screen pregnancies at risk of NAIT
        iii. Some work being done on population screening in the future for at risk pregnancies
    d. GAP discussion: Karen Haller agrees with the staff proposal, based on her clinical experience with families requesting this after neonatal stroke.
    e. GAP/HERC staff recommendation:
        i. Add CPT 81105-81112 to the Diagnostic Workup File

2. CYP3A4 (cytochrome P450 family 3 subfamily A member 4) (eg, drug metabolism), gene analysis, common variant(s) (eg, *2, *22) (CPT **81230)** and CYP3A5 (cytochrome P450 family 3 subfamily A member 5) (eg, drug metabolism), gene analysis, common variants (eg, *2, *3, *4, *5, *6, *7) (CPT **81231**)
    a. Background: Cytochrome P450 represents a major set of drug-metabolizing enzymes. Although there are many P450 genes, three (2C9, 2D6 and 2C19) are responsible for the metabolism of most commonly used drugs. They are highly polymorphic and vary between individuals. This can lead to variability in response to drug therapy. Certain medications, such as certain antipsychotics, antidepressants, and anticoagulants, are more likely to have their efficacy and side effects affected by cytochrome P450 polymorphisms

b. Private insurers have variable coverage. Those that do cover this test do so for selected drugs only
    i. Aetna covers this test for patients prescribed clopidogel (Plavix), tetrabenazine (Zenazine), and eliglustat (Cerdelga) but not for beta blockers, donepezil (Aricept), coumadin, tamoxifen, PPIs, antipsychotics, and SSRIs
    ii. Cigna does not cover cytochrome testing for P3A4 or P3A5 mutations
c. Literature: no recent (<9 or 10 yrs old) review of general utility of these tests was found. Reviews are of specific genetic testing for specific drugs, and found variable evidence for coverage of this type of testing depending on the drug
d. Similar codes are on the current Services Recommended for Non-Coverage due to lack of clinical utility (reviewed by GAP in late 2011 and HSC in December 2011) and are noted to not have coverage in the Non-Prenatal Genetic Testing Guideline
    i. 81225 (CYP2C19 (cytochrome P450, family 2, subfamily C, polypeptide 19) (eg, drug metabolism), gene analysis, common variants (eg, *2, *3, *4, *8, *17))
    ii. 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))
    iii. 81227 (CYP2C9 (cytochrome P450, family 2, subfamily C, polypeptide 9) (eg, drug metabolism), gene analysis, common variants (eg, *2, *3, *5, *6))
e. GAP discussion: GAP members agreed that the entire category of these codes should not be covered at this time. Use of these tests might be appropriate in very rare cases; but these cases could be handled as an exception.
f. GAP/HERC staff recommendation:
    i. Add CPT 81230 and 81231 (CYP3A4/5 gene analysis) to line 660 CONDITIONS FOR WHICH CERTAIN TREATMENTS HAVE NO CLINICALLY IMPORTANT BENEFIT OR HAVE HARMS THAT OUTWEIGH BENEFITS
        1. No proven clinical benefit

3. DPYD (dihydropyrimidine dehydrogenase) (eg, 5-fluorouracil/5-FU and capecitabine drug metabolism), gene analysis (CPT **81232**) and TYMS (thymidylate synthetase) (eg, 5-fluorouracil/5-FU drug metabolism), gene analysis, common variant(s) (CPT **81346**)
    a. Background: Genetic polymorphisms in the genes coding for dihydropyrimidine dehydrogenase (DPYD), a key enzyme in 5-FU metabolism, may result in enzyme products with different activity levels, resulting in 5-FU excess, the accumulation of 5-FU anabolic products, and severe toxicity. Between 3 to 5 out of every 100 people (3 to 5%) have partial DPD deficiency. TYMS mutations similarly result in 5-fluorouracil and capecitabine toxicity.
    b. Evidence
        i. **Meulendijks 2016**, review of DPYD testing
            1. DPYD testing has limited sensitivity to identify DPD deficient patients but high diagnostic accuracy when patients are identified as having a deleterious mutation
        ii. Rosmarin 2014

1. In conclusion, we have found that four specific germline *TYMS* and *DPYD* variants predict capecitabine toxicity. Although our analysis suggests that the polymorphisms may be predictive of toxicity in other FU monotherapy regimens, the data are currently less clear and these regimens are used uncommonly. We found no good evidence of polymorphisms that predict toxicity in patients on FU combination therapies, although no data were available for rare *DPYD* variants in this context.

iii. Campbell 2016

1. Polymorphisms of DPYD and TYMS, but not MTHFR, were statistically significantly associated with FU-induced toxicity (although only DPYD had clinical significance).
2. Full text not available

c. Private insurers no not currently cover these tests
   i. Aetna does not cover DPYD or TYMS testing for treatment with 5-fluorouracil/5-FU or capecitabine
   ii. Cigna does not cover DPYD testing for treatment with 5-fluorouracil/5-FU or capecitabine. No policy found on TYMS testing
   iii. The NHS does not cover DPYD testing unless a patient has severe side effects to fluorouracil or capecitabine because "But these tests only find about a quarter of people who are likely to have bad side effects."

d. GAP discussion: Agreed with staff recommendation for non-coverage

e. GAP/HERC staff recommendation:
   i. Add CPT 81232 and 81346 (5-fluorouracil/5-FU gene analysis) to line 660 CONDITIONS FOR WHICH CERTAIN TREATMENTS HAVE NO CLINICALLY IMPORTANT BENEFIT OR HAVE HARMS THAT OUTWEIGH BENEFITS
      1. No proven clinical benefit

4. F9 (coagulation factor IX) (eg, hemophilia B), full gene sequence (CPT **81238**)
   a. Background: The *F9* gene provides instructions for making a protein called coagulation factor IX. Coagulation factors are a group of related proteins that are essential for the formation of blood clots. Mutations in the *F9* gene cause a type of hemophilia called hemophilia B. Mutations that completely eliminate the activity of coagulation factor IX result in severe hemophilia. Mutations that reduce but do not eliminate the protein's activity usually cause mild or moderate hemophilia.
   b. Evidence:
      i. **De Brasi 2014**
         1. The aim of molecular genetic analysis in families with hemophilia is to identify the causative mutation in an affected male as this provides valuable information for the patient and his relatives. For the patient, mutation identification may highlight inhibitor development risk or discrepancy between different factor VIII assays. For female relatives, knowledge of the familial mutation can facilitate carrier status determination and prenatal diagnosis

c. GAP discussion: Agreed with staff recommendation
d. GAP/HERC staff recommendation:
    i. Add CPT 81238 to the Diagnostic Workup File

5. G6PD (glucose-6-phosphate dehydrogenase) (eg, hemolytic anemia, jaundice), gene analysis (CPT **81247-81249**)
    a. Background: G6PD deficiency may cause neonatal jaundice, acute hemolysis, or severe chronic non-spherocytic hemolytic anemia. Genetic testing is not routinely done but can be ordered as follow up to an enzyme test(s) that indicates a deficiency to determine which G6PD mutation(s) are present. At this time, more than 440 G6PD gene variations have been identified and can cause deficiencies of varying severity depending on the mutation(s) and on the individual person. Some mutations do not change the G6PD enzyme activity. The World Health Organization has classified the G6PD mutations into five groups based on the enzyme levels and their impact on the affected person's health. However, only the most common G6PD mutations are identified during testing. Per Mayo Labs, the genetic test is useful for aiding in the diagnosis of G6PD deficiency, differentiation of heterozygous females with skewed X-inactivation from homozygous and compound heterozygous females, determining definitive diagnosis of carrier status in females, evaluation of neonates (particularly males) with unexplained jaundice, and Identifying individuals at risk of drug-induced acute hemolytic anemia related to G6PD deficiency
    b. Similar codes are Diagnostic (these are enzyme activity tests, not genetic tests)
        i. CPT 82955 (Glucose-6-phosphate dehydrogenase (G6PD); quantitative)
        ii. CPT 82960 (Glucose-6-phosphate dehydrogenase (G6PD); screen)
    c. The CDC lists three indications for G6PD genetic testing in their genetic database, all Tier 2 evidence: prior to using dapsone, succimer, polyethylene glycol and sodium nitrate. These tests are all ranked Tier 2 due to "FDA label mentions biomarkers."
    d. GAP discussion: The GAP members agreed with the staff recommendation for adding these codes to the Diagnostic Workup File. The members felt that this test would be rarely needed; most testing is on enzyme activity rather than the genetic test. This test is used infrequently in prenatal testing. Stevens requested that there be some restrictions on the appropriate use of this code if possible. GAP members were unable to identify any restrictions, and suggested asking Dr. Thomas about additional input about any restrictions or qualifiers that might be needed. Haller will talk to the prenatal testing professionals and get back to staff with any input from that group. Once staff has input from Dr. Thomas and the prenatal genetic professionals, staff will formulate a final recommendation and will circulate to GAP members via email for final approval.
    e. From Dr. Greg Thomas (pediatric metabolic specialist):
        i. I don't think genetic testing should be routinely used to make a diagnosis of G6PD deficiency. In most cases the quantitative enzyme activity, in combination with the clinical history, and possibly family history, should be adequate to make the diagnosis. I can imagine a few situations where genetic testing might be helpful. In acute hemolysis with an elevated retic count the enzyme level will

be increased and it might be difficult to know if an enzyme deficiency was the original cause of the hemolysis. If it was clinically important to know if a deficiency was present, e.g. need to use a particular oxidant medication, or in chronic hemolytic anemias where the retic count is always increased, gene testing could be done. Gene testing could also be helpful for carrier testing. In heterozygous females there may be so few G6PD deficient RBCs present (all were hemolyzed) that the enzyme level could be normal. The only way to diagnose the carrier state would be by gene analysis.

ii. Recommendations for possible limitations to put into the non-prenatal genetic testing guideline:
    1. No gene testing done before enzyme activity testing is done. If the enzyme activity if low the diagnosis is made. If the enzyme activity is normal then whether gene testing is indicated will depend on the clinical situation.
    2. If a there is a known familial variant, gene testing could be done for genetic counseling (code 81248).
    3. Testing for common variants (code 81247) should probably be covered for those cases of acute hemolysis where there is an urgent clinical reason to know if a deficiency is present. If there is no urgency then the patient could be supported and followed and when the hemolysis has resolved and the patient is back to baseline, then the enzyme activity could be tested. Or in situations where the enzyme activity could be unreliable, e.g. female carrier with extreme Lyonization.
    4. Reserve testing the whole gene sequence (code 81249) for situations where the enzyme activity is difficult to interpret for various reasons and common variants have not been found.

f. GAP/HERC staff recommendation:
    i. Add CPT 81247-81249 to the Diagnostic Workup File
    ii. Adopt the following clause for the non-prenatal genetic testing guideline:

i) 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
    (ii) There is an urgent clinical reason to know if a deficiency is present, e.g. in a case of acute hemolysis; OR
    (iii) In situations where the enzyme activity could be unreliable, e.g. female carrier with extreme Lyonization.

ii) 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.

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

6. HBA1/HBA2 (alpha globin 1 and alpha globin 2) (eg, alpha thalassemia, Hb Bart hydrops fetalis syndrome, HbH disease), gene analysis (CPT **81258, 81259, 81269**)
    a. Background: Alpha thalassemias result from deletions of each of the alpha genes as well as deletions of both HBA2 and HBA1. This test identifies hemoglobin variants that are not easily diagnosed by electrophoresis/HPLC and can determine the cause of non-deletional alpha-thalassemia. Indications for testing include identification of hemoglobin variants detected by electrophoresis or HPLC, differential diagnosis of microcytic anemia, evaluation of nondeletional Hemoglobin H disease, evaluation of a relative of an individual with a known alpha-globin mutation and prenatal diagnosis of nondeletional alpha-thalassemia in pregnancies at risk for Hb H hydrops fetalis syndrome
    b. Similar code is Diagnostic
        i. CPT 81257, HBA1/HBA2 (alpha globin 1 and alpha globin 2) (eg, alpha thalassemia, Hb Bart hydrops fetalis syndrome, HbH disease), gene analysis; common deletions or variant (eg, Southeast Asian, Thai, Filipino, Mediterranean, alpha3.7, alpha4.2, alpha20.5, Constant Spring)
    c. GAP discussion: Agreed with staff recommendation
    d. GAP/HERC staff recommendation:
        i. Add CPT 81258, 81259, 81269 to the Diagnostic Workup File

7. IFNL3 (interferon, lambda 3) (eg, drug response), gene analysis, rs12979860 variant (CPT **81283**)
    a. Background: Single-nucleotide polymorphisms (SNPs) around the interferon lambda 3 (IFNL3; also known as interleukin 28B; IL28B) gene are associated with spontaneous hepatitis C virus (HCV) clearance, and improved response to treatment with peg-interferon and ribavirin
    b. Evidence:
        i. **FDA 2001,** package insert for Pegintron
            1. A single nucleotide polymorphism near the gene encoding interferon-lambda-3 (*IL28B rs12979860*) was associated with variable SVR rates. The *rs12979860* genotype was categorized as CC, CT and TT. In the pooled analysis of Caucasian, African-American, and Hispanic subjects from these trials (n=1587), SVR rates by *rs12979860* genotype were as follows: CC 66% vs. CT 30% vs. TT 22%. The genotype frequencies differed depending on racial/ethnic background, but the relationship of SVR to *IL28B* genotype was consistent across various racial/ethnic groups
            2. This information is given to assist in predicting treatment outcomes to therapy with peg-interferon and ribavirin combination medications
    c. GAP discussion: Stevens suggested covering this test if the test saved the cost of the medications to treat hepatitis C. Staff will research whether this test is being used in clinical protocols that allow waiting on treating hepatitis C in patients with such mutations. Staff will also discuss this test with hepatology. HERC staff will send final recommendation to GAP. It was suggested the HECR staff check CDC for genetic testing

recommendations for many of the tests discussed today as there are evidence based reviews being done by the CDC on many of these tests.

i. Further staff review finds that this genetic test predicts response to old hepatitis C treatment regimens, which are no longer standard of care. This test is not relevant to current standard of care and therefore is recommended for non-coverage

d. GAP/HERC staff recommendation:
   i. Add CPT 81283 to line 660 CONDITIONS FOR WHICH CERTAIN TREATMENTS HAVE NO CLINICALLY IMPORTANT BENEFIT OR HAVE HARMS THAT OUTWEIGH BENEFITS
      1. No proven clinical benefit

8. SLCO1B1 (solute carrier organic anion transporter family, member 1B1) (eg, adverse drug reaction), gene analysis, common variant(s) (eg, *5) (CPT **81328**)
   a. Background: genetic variations in this gene are associated with response to simvastatin. Clinical guidelines exist that can guide dosing of simvastatin based on SLCO1B1 gene variant using genotyping or whole exome sequencing.
   b. Evidence
      i. **Nelson 2016**, effects of genetics on drug efficacy
         1. SLCO1B1 effect size on statin metabolism: 0.15%
      ii. **Carr 2013**, proof of concept study on SLCO1B1 genetic variants on prediction of statin myelopathy
         1. SLCO1B1 c.521T>C single-nucleotide polymorphism to be a significant risk factor (P = 0.009), with an odds ratio (OR) per variant allele of 2.06 (1.32-3.15) for all myopathy and 4.09 (2.06-8.16) for severe myopathy (CPK > 10x ULN, and/or rhabdomyolysis; n = 23). Meta-analysis showed an association between c.521C>T and simvastatin-induced myopathy, although power for other statins was limited
   c. GAP discussion: no comments
   d. Preliminary HERC staff recommendation:
      i. Add CPT 81328 to line 660 CONDITIONS FOR WHICH CERTAIN TREATMENTS HAVE NO CLINICALLY IMPORTANT BENEFIT OR HAVE HARMS THAT OUTWEIGH BENEFITS
         1. No proven clinical benefit

9. TPMT (thiopurine S-methyltransferase) (eg, drug metabolism), gene analysis (CPT **81335**)
   a. Background: Thiopurine s-methyltransferase (TPMT) is an enzyme that is involved in the metabolism of medications called thiopurines that are used in the treatment of inflammatory bowel disease (IBD). Genotyping tests (eg, PRO-PredictRx) and phenotyping tests (eg, PRO-Predict EnzAct) for TPMT enzyme activity can be used to help make treatment decisions involving thiopurine medications such as azathioprine and 6-mercaptopurine in IBD.

b. Evidence
    i. Coenen 2015
        1. Screening for variants in TPMT did not reduce the proportions of patients with hematologic ADRs during thiopurine treatment for IBD
c. GAP discussion: no discussion
d. GAP/HERC staff recommendation:
    i. Add CPT 81335 to line 660 CONDITIONS FOR WHICH CERTAIN TREATMENTS HAVE NO CLINICALLY IMPORTANT BENEFIT OR HAVE HARMS THAT OUTWEIGH BENEFITS
        1. No proven clinical benefit

10. HBB (hemoglobin, subunit beta) (eg, sickle cell anemia, beta thalassemia, hemoglobinopathy) (CPT **81361-81364**)
    a. Background: HBB is a globin protein, which along with alpha globin (HBA), makes up the most common form of hemoglobin in adult humans, the HbA. Mutations in the gene produce several variants of the proteins which are implicated with genetic disorders such as sickle-cell disease and beta thalassemia. Indications for genetic testing are confirmation of 3 common hemoglobin (Hb) variants (HbS, HbC, and HbE) detected by hemoglobin electrophoresis or high-performance liquid chromatography (HPLC) and prenatal diagnosis when both parents are known carriers of HbS, HbC, or HbE
    b. GAP discussion: all agreed
    c. GAP/HERC staff recommendation:
        i. Add CPT 81361-81364 to the Diagnostic Workup File

11. Hereditary peripheral neuropathies (eg, Charcot-Marie-Tooth, spastic paraplegia), genomic sequence analysis panel, must include sequencing of at least 5 peripheral neuropathy-related genes (eg, BSCL2, GJB1, MFN2, MPZ, REEP1, SPAST, SPG11, SPTLC1) (CPT **81148**)
    a. Background: Hereditary neuropathies are a collection of inherited disorders affecting the peripheral nervous system. The hereditary neuropathies are divided into four major subcategories: hereditary motor and sensory neuropathy, hereditary sensory neuropathy, hereditary sensory and autonomic neuropathy, and hereditary motor neuropathy. Charcot-Marie-Tooth disease, is of the most common types of the hereditary motor and sensory neuropathies. Clinical presentation typically includes sensory symptoms like pain in the feet and hands, motor symptoms such as weakness in the lower leg and feet muscles. The estimated prevalence of hereditary neuropathies is about 1 in 2500 individuals. A myriad of genes are associated with hereditary neuropathies. Genetic testing has therefore become an important tool in the diagnosis of neuropathies. This test is indicated for confirmation of clinical diagnosis of neuropathies.
    b. GAP discussion: Keller noted that CMT is generally first tested the few common variants, then use this type of test if the common variants are negative. Stevens suggested adding a restriction to use only if the common genes have been tested first.

The GAP members felt that that would be appropriate for CMT but not for spastic paraplegia. There was concern that some providers may use this as a primary test, which is inappropriate. There was discussion about putting in a restriction that this is only covered after primary testing is done and negative, but this was not accepted. The final decision was to make diagnostic and readdress if this code is found to be misused.

c. GAP/HERC staff recommendation:
    i. Add CPT 81148 to the Diagnostic Workup File

Highlights

Genetic Advisory Panel
Conference Call hosted at:
Lincoln Building
421 SW Oak Ave., Ste. 775, Portland, OR
10/11/2017
10:00 AM-12:00 PM

Members Present: Karen Kovak; Sue Richards, PhD; Cary Harding, MD

Staff Present: Ariel Smits, MD, MPH; Jason Gingerich

Also Attending: Summer Lee Cox, OHA; Karen Heller and Devki Saraiya, Myriad Genetics; Carl Stevens, MD, CareOregon

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Review of New Genetics CPT Codes for 2018/Review of the Non-prenatal and Prenatal Genetic Testing Guidelines

Non-prenatal genetic testing guideline
There was discussion about the best way to indicated which genetic CPT codes are suggested for non-coverage. To date, these codes have been listed in the non-prenatal genetic testing guideline under a section for "codes not covered in any circunstance." GAP members noted that the non-prenatal genetic testing guideline was becoming very long and unwieldy. HERC staff reviewed the new lines 500 and 660 for services of marginal or no clinical benefit on the Prioritized List. Placement on these new lines would be another way to deal with genetic CPT codes intended for non-coverage due to experimental nature of the test or lack of perceived clinical benefit. The GAP members agreed that these new lines would allow more consistency on the Prioritized List for indicating procedures that are non-covered; members requested that staff remove the list of non-covered CPT codes from the non-prenatal genetic testing guideline and add all of these codes to line 660. Staff will look at the previous codes and see if any might actually be more appropriate for line 500 and, if so, will send updated recommendations to GAP members via email.

Additional suggested edits from staff to update the NCCN references were accepted; however it was noted that the NCCN guideline on high risk for breast or ovarian cancer guidelines had been updated last week and the proposed guideline reference update was therefore already out of date. It also appears that the high risk for colon cancer guideline was updated the day prior to the GAP meeting. Staff will locate these NCCN updates and cite these most recent versions on the non-prentatal genetic testing guideline.

Prenatal Genetic testing guidline:
No discussion or suggestions

The following recommendations were suggested for staff to present to the Value-based Benefits Subcommittee at their November 9, 2017 meeting:

1) CPT **81105-81112 (**Human Platelet Antigen genotyping (HPA-1))

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    a. GAP discussion: Karen Haller agrees with the staff proposal, based on her clinical experience with families requesting this after neonatal stroke.
    a. Recommendation to VbBS: Add CPT 81105-81112 to the Diagnostic Workup File
2. CPT **81230** and **81231 (**Cytochrome P450 gene analysis for evaluation of drug metabolism (HPA-2), GP1BA (glycoprotein Ib [platelet], alpha polypeptide [GPIba]) (eg, neonatal alloimmune thrombocytopenia [NAIT], post-transfusion purpura), gene analysis, common variant, HPA-2a/b (T145M))
    a. GAP discussion: GAP members agreed that the entire category of these codes should not be covered at this time. Use of these tests might be appropriate in very rare cases; but these cases could be handled as an exception.
    b. Recommendation to VbBS: Add CPT 81230 and 81231 to line 660 CONDITIONS FOR WHICH CERTAIN TREATMENTS HAVE NO CLINICALLY IMPORTANT BENEFIT OR HAVE HARMS THAT OUTWEIGH BENEFITS
3. CPT **81232** (DPYD (dihydropyrimidine dehydrogenase) (eg, 5-fluorouracil/5-FU and capecitabine drug metabolism), gene analysis) and CPT **81246 (**TYMS (thymidylate synthetase) (eg, 5-fluorouracil/5-FU drug metabolism), gene analysis, common variant(s))
    a. GAP discussion: Agreed with staff recommendation for non-coverage
    b. Recommendation to VbBS: Add CPT 81232 and 81346 to line 660 CONDITIONS FOR WHICH CERTAIN TREATMENTS HAVE NO CLINICALLY IMPORTANT BENEFIT OR HAVE HARMS THAT OUTWEIGH BENEFITS
4. CPT **81238 (**F9 (coagulation factor IX) (eg, hemophilia B), full gene sequence)
    a. GAP discussion: Agreed with staff recommendation
    b. Recommendation to VbBS: Add CPT 81238 to the Diagnostic Workup File
5. CPT **81247-81249 (**G6PD (glucose-6-phosphate dehydrogenase) (eg, hemolytic anemia, jaundice), gene analysis)
    a. GAP discussion: The GAP members agreed with the staff recommendation. The members felt that this test would be rarely needed; most testing is on enzyme activity rather than the genetic test. This test is used infrequently in prenatal testing. Stevens requested that there be some restrictions on the appropriate use of this code if possible. GAP members were unable to identify any restrictions, and suggested asking Dr. Thomas about additional input about any restrictions or qualifiers that might be needed. Haller will talk to the prenatal testing professionals and get back to staff with any input from that group. Once staff has input from Dr. Thomas and the prenatal genetic profressional, staff will formulate a final recommendation and will circulate to GAP members via email for final approval.
    b. Recommendation to VbBS: Add CPT 81247-81249 to the Diagnostic Workup File, with any appropriate restrictions suggested by experts added to the non-prenatal genetic testing guideline
6. CPT **81258, 81259, 81269 (**HBA1/HBA2 (alpha globin 1 and alpha globin 2) (eg, alpha thalassemia, Hb Bart hydrops fetalis syndrome, HbH disease), gene analysis)
    a. GAP Discussion: Agreed with staff recommendation
    b. Recommendation to VbBS: Add CPT 81258, 81259, 81269 to the Diagnostic Workup File
7. CPT **81283 (**IFNL3 (interferon, lambda 3) (eg, drug response), gene analysis, rs12979860 variant)

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a. GAP discussion: Stevens suggested covering this test if the test saved the cost of the medications to treat hepatitis C. Staff will research whether this test is being used in clinical protocols that allow waiting on treating hepatitis C in patients with such mutations. Staff will also discuss this test with hepatology. HERC staff will send final recommendation to GAP. It was suggested the HECR staff check CDC for genetic testing recommendations for many of the tests discussed today as there are evidence-based reviews being done by the CDC on many of these tests.
b. Recommendation to VbBS: Add CPT 81283 to line 660 CONDITIONS FOR WHICH CERTAIN TREATMENTS HAVE NO CLINICALLY IMPORTANT BENEFIT OR HAVE HARMS THAT OUTWEIGH BENEFITS, pending any input from hepatology or literature review on the use of this testing

8. CPT **81328 (**SLCO1B1 (solute carrier organic anion transporter family, member 1B1) (eg, adverse drug reaction), gene analysis, common variant(s) (eg, *5))
    a. GAP discussion: no discussion
    b. Recommendation to VbBS: Add CPT 81328 to line 660 CONDITIONS FOR WHICH CERTAIN TREATMENTS HAVE NO CLINICALLY IMPORTANT BENEFIT OR HAVE HARMS THAT OUTWEIGH BENEFITS
9. CPT **81335 (**TPMT (thiopurine S-methyltransferase) (eg, drug metabolism), gene analysis)
    a. GAP discussion: no discussion
    b. Recommendation to VbBS: Add CPT 81335 to line 660 CONDITIONS FOR WHICH CERTAIN TREATMENTS HAVE NO CLINICALLY IMPORTANT BENEFIT OR HAVE HARMS THAT OUTWEIGH BENEFITS
10. CPT **81361-81364 (**HBB (hemoglobin, subunit beta) (eg, sickle cell anemia, beta thalassemia, hemoglobinopathy))
    a. GAP discussion: no discussion
    b. Recommendation to VbBS: Add CPT 81361-81364 to the Diagnostic Workup File
11. CPT **81148 (**Hereditary peripheral neuropathies (eg, Charcot-Marie-Tooth, spastic paraplegia), genomic sequence analysis panel, must include sequencing of at least 5 peripheral neuropathy-related genes (eg, BSCL2, GJB1, MFN2, MPZ, REEP1, SPAST, SPG11, SPTLC1)
    a. GAP discussion: Keller noted that CMT is generally first tested for the few common variants, then use this type of test if the common variants are negative. Stevens suggested adding a restriction to use only if the common genes have been tested first. The GAP members felt that that would be appropriate for CMT but not for spastic paraplegia. There was concern that some providers may use this test as a primary test, which is inappropriate. There was discussion about putting in a restriction that this is only covered after primary testing is done and negative, but this was not accepted. The final decision was to make diagnostic and readdress if this code is found to be misused.
    b. Recommendation to VbBS: Add CPT 81148 to the Diagnostic Workup File

Family history genetic codes for diagnostic testing

Smits reviewed the summary document. There was little discussion regarding most of the code movement discussion. However, GAP members disagreed with HERC staff and felt that ICD-10 Z80.41 (Family history of malignant neoplasm of ovary) should be added to line 195 CANCER OF BREAST; AT HIGH RISK OF BREAST CANCER. The discussion was mainly centered around the fact that the existing diagnosis (Z15.02 Genetic susceptibility to malignant neoplasm of ovary) on the high risk for breast

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cancer line requires a patient to have an identified genetic mutation that increases ovarian cancer risk. However, there are many families where no specific gene has been identified, but there is still a strong family history of breast and ovarian cancer and these family members could be considered for oophorectomy based on family history alone. These patients would use Z80.41 as their diagnostic code rather than Z15.02.

Recommendations to VbBS:

1) Add ICD-10 Z80.41 (Family history of malignant neoplasm of ovary) to line 195 CANCER OF BREAST; AT HIGH RISK OF BREAST CANCER
    a. Leave on line 3 PREVENTIVE SERVICES WITH EVIDENCE OF EFFECTIVENESS
2) Advise HSD to add the following codes to the Diagnostic Work up File to be used for diagnostic testing and remove from the Informational File

Z81.0	Family history of intellectual disabilities
Z82.41	Family history of sudden cardiac death
Z82.79	Family history of other congenital malformations, deformations and chromosomal abnormalities
Z82.62	Family history of osteoporosis
Z82.79	Family history of other congenital malformations, deformations and chromosomal abnormalities
Z84.81	Family history of carrier of genetic disease

Breast cancer genetic testing panels

Smits reviewed the summary document and staff recommendations. Cox stated that the Oregon Genetics Program at OHA supports the use of panel testing with a genetic counseling requirement. The GAP members agreed that panel testing for breast cancer genetic susceptibility was standard practice among genetic counselors, and members expressed concern with not keeping up to date with standard of care if the current lack of coverage with panels is continued. There was acknowledgement that there would be an increased cost as well as an access issue if genetic counseling was made a requirement prior to such testing.

There was discussion about whether a single gene (e.g. BRCA1) should be required first and be negative prior to panel testing. The group noted that the panels are in many cases less expensive or equivalently priced to single gene tests; therefore single gene testing prior to panel testing would likely not be cost effective. Keller also noted that it is becoming difficult to find a lab that will test for a single gene in today's environment. There was discussion about the concern for panels finding results of uncertain significance, particularly with the larger panels. There was discussion about whether the cost of the genetic counseling to deal with any results of uncertain significance that are obtained from panel testing would raise the cost of panel testing/counseling up beyond the cost of single tests. Stevens noted that the CPT code most often used for panel testing is 81479 (Unlisted molecular pathology procedure), which has variable pricing depending on the lab and the panel size. Also, the costs of the individual tests and panels are difficult to determine as they are proprietary between insurer and lab. It was noted that BRCA1/2 testing will only identify 10% of patients with a high risk gene. With panel testing of common genes, about 50% of patients with a high risk gene will be identified.

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Stevens noted that at his CCO, they approve most panel testing if the initial gene testing is negative because the consequences of missing a high risk genetic result are too large. However, he noted that these panels are approved as part of an exceptions process. He suggested keeping the panels non-covered and allowing the exceptions process to continue for case-by-case approval. The GAP members were uncomfortable with this, as different CCOs might have very different approval criteria.

The general concensus was that panel testing should be covered. The GAP members could not decide if there should be a requirement for genetic counseling pre and post testing, due to cost and access issues. Also, certain common gene tests do not need genetic counseling to interpret—most providers with some training can interpret these tests for patients competently. There was discussion about requiring that any covered panel contain a certain number of genes which the NCCN genetic guideline for high risk for breast cancer calls out as changing clinical management. Thre was discussion about also putting a maximum number of genes in the guideline to minimize results of uncertain significant. HERC staff note that the current NCCN high risk breast cancer guideline listed 20+ genes that affected managment, and GAP members noted that other genes for high risk for colon cancer should also be included.

There was discussion of requiring that the panel not cost more than the sum of CPT 81211 (BRCA1, BRCA2 (breast cancer 1 and 2) (eg, hereditary breast and ovarian cancer) gene analysis; full sequence analysis and common duplication/deletion variants in BRCA1 (ie, exon 13 del 3.835kb, exon 13 dup 6kb, exon 14-20 del 26kb, exon 22 del 510bp, exon 8-9 del 7.1kb)) and 81213 (BRCA1, BRCA2 (breast cancer 1 and 2) (eg, hereditary breast and ovarian cancer) gene analysis; uncommon duplication/deletion variants).

The final recommendation of the GAP was to allow breast cancer genetic panel testing, with some type of guideline that would read approximately as follows:

> Hereditary breast cancer-related disorders genomic sequence analysis panels (CPT 81432, 81433, 81479) are included if cost is no more than testing for the sum of CPT 81211 and 81213, include at least 5 genes that the current NCCN guideline on breast/ovarian/colon cancer genetics provides specific guidance on clinical management and include no more than 40 genes total.

HERC staff will work on this proposed wording and send a draft to the CCO medical director guideline workgroup to see if such a guideline would be feasible, and obtain any suggested edits. The final wording of this guideline will be sent to GAP members via email for a final decision.

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Determination of human platelet antigen typing by molecular methods: Importance in diagnosis and early treatment of neonatal alloimmune thrombocytopenia

Suzanne A. Arinsburg,[1] Beth H. Shaz,[2,3] Connie Westhoff,[2,4] and Melissa M. Cushing[5]*

Neonatal alloimmune thrombocytopenia (NAIT) is the most common cause of severe thrombocytopenia and intracranial hemorrhage in the perinatal period. While the gold standard for making a diagnosis of NAIT is detection of a human platelet antigen (HPA)-specific antibody in maternal serum, together with identifying an incompatibility between the parents for the cognate HPA antigen, platelet genotyping is the gold standard method for HPA typing. Platelet genotyping is critical in screening at-risk fetuses for the presence of the HPA corresponding to the maternal antibody. In addition, platelet genotyping may play a role in population screening to identify women at risk for sensitization, and thus, fetuses at risk for NAIT. The most commonly used methods of platelet genotyping are sequence-specific primer-polymerase chain reaction (PCR-SSP), restriction fragment length polymorphism-PCR (PCR-RFLP), and TaqMan real-time PCR. PCR-SSP and PCR-RFLP are relatively inexpensive and technically simple methods, but they are not easily automated and require expertise for reliable interpretation of results. Newer methods that allow for multiplexing, automation, and easily interpretable results, such as bead arrays, are currently in development and available for research purposes. Am. J. Hematol. 87:525–528, 2012. **© 2011 Wiley Periodicals, Inc.**

Introduction

Neonatal alloimmune thrombocytopenia (NAIT) is the most common cause of moderate and severe thrombocytopenia in the fetus or an otherwise healthy newborn [1,2]. The reported incidence from prospective screening studies ranges from 1:1,000 to 1:2,000 live births [3–5].

Pathophysiology

Maternal alloimmunization results from incompatibility between maternal human platelet antigens (HPAs) and paternally inherited fetal HPA. Maternal alloimmunization generally occurs during or shortly after delivery of the first incompatible infant [6–8]. Maternal IgG traverses the placenta coating fetal platelets leading to removal by the fetal reticuloendothelial system resulting in potentially severe thrombocytopenia. The incompatibility can occur in one of two ways: mother has a common HPA type, but father expresses an uncommon (low-frequency) antigen, or more often, the mother is missing a common (high-frequency) antigen that is inherited from the father. In both scenarios, maternal antibody develops to the foreign paternal antigen expressed by the fetus. Maternal antibody to a common high-frequency HPA is readily detected by serological methods.

Incompatibility in HPA-1 accounts for approximately 80% of all cases of NAIT and almost all cases of severe NAIT in whites. NAIT due to anti-HPA-1a is rare in other races [9]. Approximately 2% of whites are negative for HPA-1a, though only about 10% of HPA-1a negative women become immunized after exposure during pregnancy [7]. Alloimmunization is associated with the presence of HLA-DRB3*0101 allele. Other HLA associations have also been reported [4,5,7,8]. Alloimmunization to HPA-5b is reported to account for almost all of the remaining NAIT cases in whites. Approximately 1% of whites are negative for HPA-5b. Alloimmunization to anti-HPA-4b is the predominant cause in individuals of Japanese descent. HLA associations with anti-HPA-4b have yet to be determined [10]. NAIT resulting from incompatibility in other HPAs is relatively rare [11]. Additionally, rare cases of NAIT have been attributed to antibodies against ABO blood group antigens and Class I HLA antigens [12–14].

Clinical Presentation

The diagnosis of NAIT is usually suspected in an otherwise healthy infant with unexpected petechiae, purpura, and/or bleeding, but the most severe consequence of NAIT is intracranial hemorrhage (ICH; Refs. 2,15, and 16). ICH occurs in about 10% of affected neonates with the majority occurring in utero [5,7,17]. About 10% of ICH cases are fatal, and about 20% have neurologic sequelae [9]. Importantly, the majority of NAIT cases are asymptomatic, and only about 30–40% of neonates born to immunized women will develop severe thrombocytopenia [3–5,7].

Recurrence rates in subsequent pregnancies with incompatible fetuses are nearly 100%, with subsequent pregnancies usually more severely affected than the first [18]. Eighty percent of ICH recurrence rates have been reported in subsequent pregnancies [19]. Genotyping the parents helps to evaluate the risk to subsequent fetuses. If the father is a heterozygote, or zygosity cannot be determined, then amniocytes are needed to determine the fetal genotype and consequent risk [20].

Human Platelet Antigens

Currently, 28 HPAs have been completely characterized [21], but new low-frequency alleles continue to be identified [22]. HPAs are found on platelet glycoproteins involved with platelet activation, most commonly GPIIb/IIIa [10]. They are

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Conflict of interest: Nothing to report

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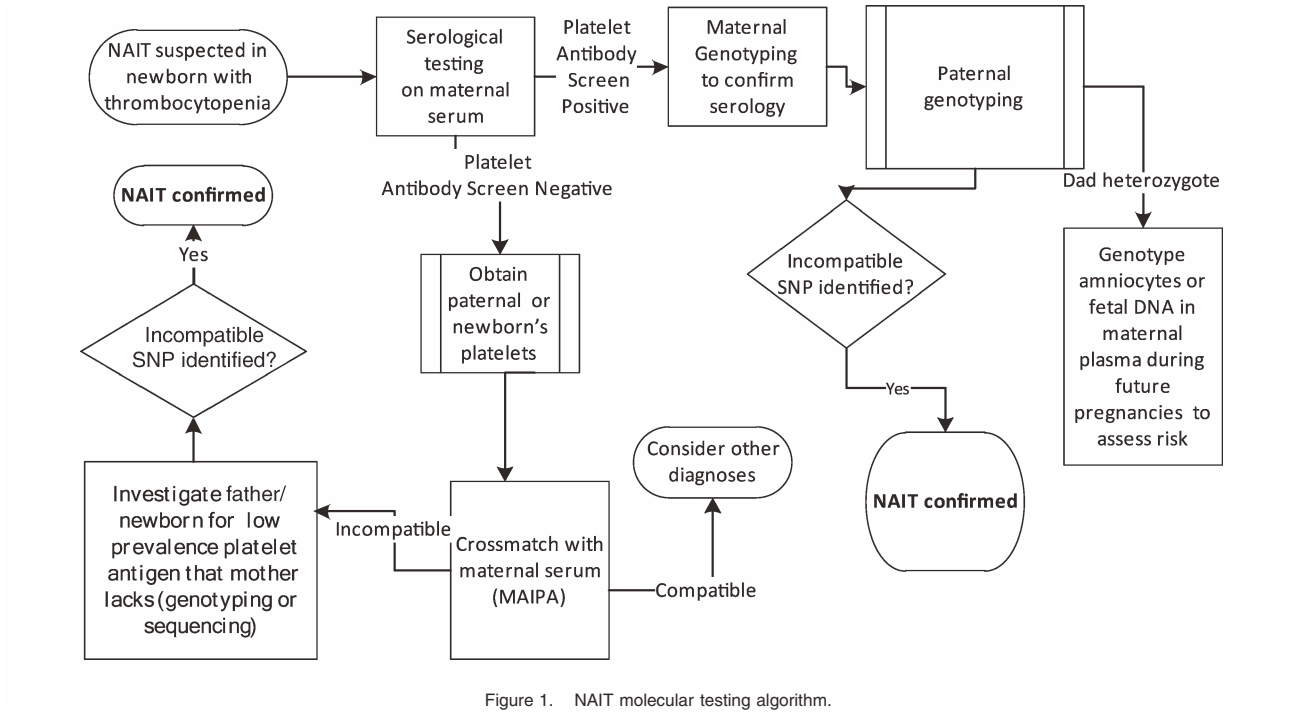

Figure 1. NAIT molecular testing algorithm.

expressed as early as 16-weeks gestational age [23]. The antigenic nature of these glycoproteins is due to amino acid substitutions that result from single nucleotide polymorphisms (SNP; Ref. 24).

Laboratory Investigation

The diagnosis of NAIT is based on demonstrating HPA incompatibility between the biologic mother and father of a thrombocytopenic neonate and identification of a maternal antibody specific for the incompatible antigen. HPA typing was originally performed by serologic methods [22,25]. Identification of the genetic basis for HPAs allowed for the development of molecular assays for platelet genotyping. Figure 1 provides an algorithm for NAIT diagnosis using serologic and molecular methods. Platelet genotyping may be used to confirm the HPA status of the mother, and if possible, to type a paternal sample in addition to or in lieu of serologic typing. Platelet genotyping is also critical in screening an at-risk fetus for the presence of the HPA corresponding to the maternal antibody, if the father is a heterozygote for the target HPA. The latter testing can be done on amniocytes. However, successful noninvasive fetal HPA genotyping using DNA extracted from maternal plasma has been reported [26] and is predicted to become more readily available.

Assays for Platelet Genotyping

The most commonly used methods by reference laboratories, sequence-specific primer-polymerase chain reaction (PCR-SSP), restriction fragment length polymorphism-PCR (PCR-RFLP), TaqMan real-time PCR (Applied Biosystems, Foster City, CA), and newer high-throughput methods will be discussed (Refs. 22 and 27; Table I).

PCR-SSP

PCR-SSP, also known as allele-specific PCR, uses two reactions with two sets of primers: one primer is specific for each allele (allele-specific primer) and is paired with a second common primer to control for PCR efficiency [25,27]. The basis of this method is the reduction in the efficiency of *Taq* polymerase to amplify DNA when there is a 3′ terminal nucleotide mismatch between the target DNA and the allele-specific primer. The HPA genotype is identified by the presence or absence of DNA bands after gel electrophoresis of the PCR products [28]. This method is a relatively simple and inexpensive procedure for HPA genotyping.

PCR-RFLP

PCR-RFLP relies on the loss or gain of a restriction enzyme recognition site at the polymorphic site in the target gene. The region of the gene encoding the polymorphism is amplified by PCR and then subjected to digestion with a specific restriction enzyme. Restriction fragments are separated according to their lengths by gel electrophoresis. After gel electrophoresis, the use of a UV transilluminator allows visualization of the DNA and fragment pattern interpretation. Like PCR-SSP, this method is relatively simple and inexpensive, but it requires an additional digestion step and cannot be automated. One potential disadvantage of this technique is that smaller fragments produced by the restriction enzyme will produce only faint bands with electrophoresis, but this can be avoided by careful choice of primers. Additionally, control of reaction parameters specific to the restriction enzyme is required to prevent incomplete digestion and thus, false results [25].

TaqMan Real-Time PCR

TaqMan real-time PCR assay allows for the quantification or identification of the PCR amplification product in real time. In this assay, the SSP (TaqMan probe) that binds to the SNP of interest has a reporter dye (fluorophore) attached to the 5′ end and a quencher attached to the 3′ end. The quencher prevents the reporter dye from fluorescing by fluorescence resonance energy transfer. The SSP binds to the DNA and is extended by *Taq* polymerase. The 5′ nuclease activity of *Taq* polymerase will displace the reporter dye from the 5′ end of the TaqMan probe, as it extends the SSP in the 5′ to 3′ direction. This event will allow the reporter to fluoresce due to the decreased proximity to the quencher. Fluorescence detection is directly proportional to the release of the reporter and the amount of the target DNA present. Each cycle of PCR will increase

TABLE I. Advantages and Limitations of Molecular Methods of Platelet Genotyping

	Advantages	Limitations
PCR-SSP	Technically simple Relatively inexpensive	Requires precise primer design Requires two reactions per assay sample Difficult to automate Subjective interpretation
PCR-RFLP	Technically simple Relatively inexpensive Easier primer design Less strict PCR reaction parameters	SNP must create an allele-specific digestion site Requires additional digestion step Cannot be automated Subjective interpretation
TaqMan	Does not require additional handling after amplification	Probes expensive
Real-time PCR Assay	Automated allele discrimination Can be multiplexed Easily interpreted	Requires test-specific technical expertise
Bead arrays	Relatively automated Medium throughput Can be multiplexed Relatively fast	Expensive Requires test-specific technical expertise Research use only at present
All methods	Fresh platelets are not required Potential for automation (newer methods) No reliance on antisera	Require test-specific technical expertise (newer methods) Mutations in the probe primer regions may result in false negatives Paternal low-frequency HPAs may not be detected

the fluorescent signal detected allowing for quantification of the amount of PCR product produced [22,25]. The major advantages of this technique are the ability to automate the process and detect homozygosity and heterozygosity in the biallelic HPA systems using two different allele-specific probes with different reporter dyes [29]. This method does not require additional handling after amplification, and allele discrimination is automated reducing potential sources of error [25].

High-Throughput Methods

The development of rapid high-throughput methods that allow for multiplexing or amplification of multiple target loci in one assay and automation could be particularly useful for screening pregnant women or platelet donors for HPA type. A recent article by Kamphuis et al. provides an excellent review on screening in pregnancy for NAIT [17]. These methods decrease the risk of human error seen in both the technical aspects and the interpretation necessary with other assays. However, these methods often employ the use of expensive computer software, instruments, and reagents [22]. High-throughput platforms are only available for research purposes at this time.

Bead arrays are multiplex high-throughput platforms that allow for HPA typing of known antigens using capture allele-specific probes affixed to beads labeled with fluorescent dyes. In some assays, multiple beads may be used at one time each targeting a different SNP. Target DNA fragments are allowed to anneal to the capture probes and are then elongated using fluorescent labeled nucleotides. The beads are either affixed to a microchip or analyzed by flow cytometry, and fluorescence patterns are analyzed to determine HPA type [30,31].

Multiplex SNP genotyping with oligonucleotide extension is another high-throughput method. This was used by Shehata et al. [32] to prospectively screen 750 plateletpheresis donors for HPA genotype. Mass-scale high-throughput multiplex polymerase chain reaction for human platelet antigen single-nucleotide polymorphism was utilized for screening of apheresis platelet donors. Briefly, multiplex PCR primers were designed to flank HPA SNPs. After PCR, the amplified fragments were annealed to single-base extension probes. The probes were a hybrid oligonucleotide, one portion annealed to the PCR-amplified target immediately proximal to the SNP of interest, and the tag portion immobilized the annealed complex to a microchip for laser activation and fluorescence.

High-throughput HPA identification systems are valuable to blood centers in order to screen platelet donors. Identification of HPA negative donors (and their associated products) enables antigen negative platelet transfusions to the thrombocytopenic fetus and neonate. However, it is most common for the mother to donate platelets for her baby as her platelets would lack the offending antigen. The mother's platelets must be washed to remove the platelet antibody prior to transfusion.

Advantages of Platelet Genotyping

There are multiple advantages to genotyping HPAs over serologic methods. First, fresh platelets are not required. Genomic DNA can be obtained from multiple sources including white blood cells, amniocytes, and buccal smears. Second, typing for low-frequency HPAs for which antisera is unavailable is possible. Lastly, automated and multiplex methods are available, decreasing the risk of error and time needed to perform these assays. While the gold standard for making a diagnosis of NAIT is detection of an HPA-specific antibody in maternal serum together with identifying an incompatibility between the parents for the cognate HPA antigen, platelet genotyping is the gold standard method for HPA typing. [22].

Limitations of Platelet Genotyping

There are some limitations and pitfalls in the use of molecular methods for platelet genotyping. Prior to the use of any particular method, DNA must be isolated that is free of contamination in a sufficient quantity and quality. Precautions must be in place to prevent contamination with DNA from other sources, as false positive results may occur. This is of particular importance when typing fetal cells obtained by amniocentesis or percutaneous umbilical blood sampling as maternal DNA may contaminate the sample. Additionally, DNA quality must be ensured by prevention of contamination with nucleases leading to false negative results. PCR reaction parameters must be optimized and tightly controlled for the primers chosen for each reaction. Quality controls to monitor DNA quality, contamination, and reaction parameters must be in place [25].

Molecular results must be interpreted carefully. Differences between genotype and expected phenotype have been identified for some of the HPAs including HPA-1 [33,34]. Unknown polymorphisms near the SNP of interest can affect primer annealing and hybridization leading to false negative results. Point mutations leading to the expression

of rare low-frequency HPA are difficult to identify, and the respective antibody or antigen mismatch may be missed by either serological or molecular methods [25].

Further characterization of DNA polymorphisms associated with NAIT is necessary but difficult due to the rarity of these cases. Multiple case reports recognizing NAIT due to familial or rare low-frequency antigens have been reported [35–38]. When there is a high index of clinical suspicion and there is no maternal/paternal mismatch identified for the most frequently implicated HPAs, a serologic crossmatch of maternal serum with paternal platelets—most often by monoclonal antibody-specific immobilization of platelet antigens (MAIPA)—may be utilized. MAIPA is an enzyme immunoassay that is performed by immobilizing a paternal HPA of interest with murine monoclonal antibodies on a microtiter plate. Maternal serum is added to allow maternal antiplatelet antibodies, if present, to bind to the immobilized paternal HPA [39]. If the father is not available, some reference laboratories have advocated for maintaining a panel of reference DNA and allele-specific cell lines expressing recombinant low-prevalence HPA for NAIT diagnosis when the diagnosis cannot be made by the aforementioned methods [37]. In addition, the cost of cloning and sequencing has decreased dramatically recently and can be considered, when all other methods fail.

Future Directions

Continued development of high-throughput automated methods will potentially allow for the implementation of screening to identify HPA-1a, -4b, or -5b negative women or potential platelet donors [22,40]. New strategies will be developed to identify cases of maternal immunization to previously unreported low-frequency paternal HPA, when routine genotyping or phenotyping has failed.

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Laboratory-Clinic Interface

Improving safety of fluoropyrimidine chemotherapy by individualizing treatment based on dihydropyrimidine dehydrogenase activity – Ready for clinical practice?

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ABSTRACT

Fluoropyrimidines remain the cornerstone of treatment for different types of cancer, and are used by an estimated two million patients annually. The toxicity associated with fluoropyrimidine therapy is substantial, however, and affects around 30% of the patients, with 0.5–1% suffering fatal toxicity. Activity of the main 5-fluorouracil (5-FU) metabolic enzyme, dihydropyrimidine dehydrogenase (DPD), is the key determinant of 5-FU pharmacology, and accounts for around 80% of 5-FU catabolism. There is a consistent relationship between DPD activity and 5-FU exposure on the one hand, and risk of severe and potentially lethal fluoropyrimidine-associated toxicity on the other hand. Therefore, there is a sound rationale for individualizing treatment with fluoropyrimidines based on DPD status in order to improve patient safety.

The field of individualized treatment with fluoropyrimidines is now rapidly developing. The main strategies that are available, are based on genotyping of the gene encoding DPD (*DPYD*) and measuring of pretreatment DPD phenotype. Clinical validity of additional approaches, including genotyping of *MIR27A* has also recently been demonstrated.

Here, we critically review the evidence on clinical validity and utility of strategies available to clinicians to identify patients at risk of developing severe and potentially fatal toxicity as a result of DPD deficiency. We evaluate the advantages and limitations of these methods when used in clinical practice, and discuss for which strategies clinical implementation is currently justified based on the available evidence and, in addition, which additional data will be required before implementing other, as yet less developed strategies.

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Introduction

5-Fluorouracil (5-FU) and its oral prodrugs capecitabine and tegafur play a key role in the treatment of colorectal, gastric, and breast cancer, and an estimated two million patients are treated with fluoropyrimidines annually [1–3]. While the majority of patients can be treated safely, a substantial proportion experiences severe, sometimes lethal, fluoropyrimidine-associated toxicity. In phase III studies of fluoropyrimidine monotherapy around 30% of the colorectal cancer patients treated with 5-FU or capecitabine experienced severe (CTC-AE grade $\geqslant 3$) treatment-related toxicity. Moreover, typically 10–20% of the patients is hospitalized for toxicity during treatment, and 0.5–1% suffers fatal toxicity [4–7]. Thus, fluoropyrimidine-associated toxicity is a well-recognized clinical problem which has a substantial impact on patients' quality of life.

In 1985, Tuchman et al. reported on a patient with familial pyrimidinemia (elevated serum uracil and thymine concentrations) who experienced severe, almost lethal, toxicity upon treatment with 5-FU [8]. This report provided the first evidence that a genetic defect in pyrimidine catabolism could be associated with fluoropyrimidine-associated toxicity. Diasio and colleagues

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ORIGINAL REPORT

Genetic Markers of Toxicity From Capecitabine and Other Fluorouracil-Based Regimens: Investigation in the QUASAR2 Study, Systematic Review, and Meta-Analysis

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See accompanying editorial on page 989

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ABSTRACT

Purpose
Fluourouracil (FU) is a mainstay of chemotherapy, although toxicities are common. Genetic biomarkers have been used to predict these adverse events, but their utility is uncertain.

Patients and Methods
We tested candidate polymorphisms identified from a systematic literature search for associations with capecitabine toxicity in 927 patients with colorectal cancer in the Quick and Simple and Reliable trial (QUASAR2). We then performed meta-analysis of QUASAR2 and 16 published studies (n = 4,855 patients) to examine the polymorphisms in various FU monotherapy and combination therapy regimens.

Results
Global capecitabine toxicity (grades 0/1/2 *v* grades 3/4/5) was associated with the rare, functional *DPYD* alleles 2846T>A and *2A (combined odds ratio, 5.51; $P = .0013$) and with the common *TYMS* polymorphisms 5′VNTR2R/3R and 3′UTR 6bp ins-del (combined odds ratio, 1.31; $P = 9.4 \times 10^{-6}$). There was weaker evidence that these polymorphisms predict toxicity from bolus and infusional FU monotherapy. No good evidence of association with toxicity was found for the remaining polymorphisms, including several currently included in predictive kits. No polymorphisms were associated with toxicity in combination regimens.

Conclusion
A panel of genetic biomarkers for capecitabine monotherapy toxicity would currently comprise only the four *DPYD* and *TYMS* variants above. We estimate this test could provide 26% sensitivity, 86% specificity, and 49% positive predictive value—better than most available commercial kits, but suboptimal for clinical use. The test panel might be extended to include additional, rare *DPYD* variants functionally equivalent to *2A and 2846A, though insufficient evidence supports its use in bolus, infusional, or combination FU. There remains a need to identify further markers of FU toxicity for all regimens.

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INTRODUCTION

Fluorouracil (FU) is the backbone of chemotherapy for colorectal cancer and many other solid tumors. Three methods are used to deliver FU: bolus infusional intravenous administration, and oral capecitabine, a prodrug that undergoes preferential conversion to FU in malignant tissue. Oxaliplatin or irinotecan can be added to FU in combination regimens that include infusional fluorouracil, leucovorin, and oxaliplatin (FOLFOX)[1]; capecitabine plus oxaliplatin (XELOX)[2]; and fluorouracil, leucovorin, and irinotecan (FOLFIRI).[3] Depending on the regimen used, 10% to 30% of patients suffer

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substantial FU toxicities (grade ≥ 3), typically diarrhea, nausea and vomiting, mucositis/stomatitis, myelosuppression, and hand-foot syndrome (HFS). Overall, FU causes 0.5% to 1.0% mortality (grade 5).[4,5] Consequently, attention has focused on the identification of biomarkers or assays predictive of FU toxicity.[6,7]

FU metabolism involves many enzyme reactions and intermediates (Data Supplement [online only]). Although measurement of enzyme activities could be used for toxicity prediction, these assays may be too cumbersome and expensive for routine, large-scale use. After initial reports linking severe dihydropyrimidine dehydrogenase (DPYD) deficiency with lethal FU use,[8] many genetic polymorphisms and rare variants in FU metabolism genes have been reported to influence the risk of adverse events.[9-11] In theory, by testing a panel of polymorphisms, FU toxicities can be predicted and dose modifications considered. However, the existing published data are limited by inconsistency in reporting and testing toxicities, pooling of patients on different FU schedules, and combined analysis of functionally distinct polymorphisms within the same gene. Several polymorphisms lacking validation may have been included in commercial FU toxicity kits.

Given the uncertainty regarding which genetic variants are truly predictive of adverse events from FU, we have examined associations between candidate polymorphisms and capecitabine toxicity in patients from the Quick and Simple and Reliable trial (QUASAR2). We have then performed a meta-analysis combining these data with those from previously published studies, both of capecitabine and other FU schedules.

PATIENTS AND METHODS

A synopsis of the methods used is presented here. Full details are provided in the Data Supplement.

The QUASAR2 study was the basis of our analysis of genetic markers of capecitabine toxicity. QUASAR2 is a phase III randomized trial of adjuvant capecitabine ± bevacizumab after resection of stage II/III colorectal cancer. We obtained data from 927 patients from the QUASAR2 trial for common FU-related toxicities—diarrhea, nausea and vomiting, mucositis/stomatitis, neutropenia, thrombocytopenia, and HFS. Adverse toxicity events were categorized as high (Common Terminology Criteria for Adverse Events grades 3, 4, or 5 during any treatment cycle) or low (grades 0, 1, or 2). A global toxicity measure was derived based on the presence of any grade 3/4/5 event (high) or absence of any such event (low).

From a systematic literature review (Data Supplement), we identified 36 FU-pathway polymorphisms potentially suitable for analysis (Table 1; Data Supplement). QUASAR2 genotypes were derived from Illumina (San Diego, CA) SNP arrays, individual polymorphism typing assays, or genetic imputation as long as high-quality results were obtained (Data Supplement). Twenty-one polymorphisms were included in the final analysis, after quality control and the exclusion of variants in strong pairwise linkage disequilibrium. They were *CES2*823C>G, *CES2*rs11568314, *CES2*rs11568311, *CES2*rs2241409, *CDA*−451C>T, CDA*2, *UMPS*638G>C, *TYMP*rs470119, *TYMP*S471L, *TYMS*5′VNTR2R/3R, *TYMS*3′UTR 6bp ins-del, *MTHFR*677C>T, *MTHFR*1298A>C, *DPYD*85T>C, *DPYD*496A>G, *DPYD*1236G>A, *DPYD*1601G>A, *DPYD*1627A>G, *DPYD**2A, *DPYD*2194G>A, and *DPYD*2846T>A.

For meta-analysis of genetic predictors of FU toxicity, studies were identified by systematic review.[6,9-35] Sixteen studies fulfilled our inclusion criteria.[9-11,13,18,19,21,23,24,26,28-31,33,35] We did not perform formal, combined analyses across regimens (Data Supplement). For every polymorphism in the meta-analysis (those analyzed for QUASAR2 plus *CES2*6046G>A, *CES2*6320G>A, *CDA*−205C>G, *CDA*rs602950, *CDA*943insC, *CDA*575C>T, *CDA*794G>A, *CDA*771 C>G, *UMPS*1336A>G, *TYMP*A324A, *TYMS*5′VNTR3RG>C, *DPYD*623G>A, *DPYD*1109delTA, *DPYD*1679T>G, and *DPYD*2858G>C), we performed an allelic test of association with global toxicity (grades 0/1/2 *v* 3/4/5) in each set of patients who had received the same regimen. For each FU regimen, meta-analyses assessing the relationship between toxicity (global and individual) and each individual polymorphism were performed using the metan command in STATA (STATA, College Station, TX). SEs and log(risk ratio) from each study were combined using the Mantel-Haenszel method.

For certain variants in *TYMS* and *DPYD,* we performed haplotype and/or set-based tests. The *TYMS*5′VNTR repeat haplotype with the G>CSNP in the second repeat was analyzed by a binary model based on the total number of USF1/USF2 binding sites across both alleles (0 to 2 *v* 3 to 4).[36] The *TYMS*5′VNTR (2R *v* 3R) and 3′UTR polymorphisms, which are in moderate linkage disequilibrium, were analyzed in combination by logistic regression conditioned on study, formal haplotype analysis, and a score test in which toxicity was regressed on the number of *TYMS* toxicity risk alleles (0 to 4) summed from the 3′UTR and 5′VNTR polymorphisms. For *DPYD*, we grouped rare variants with effects on enzyme function (*DPYD**2A and 2846T>A) for analysis.

For our primary investigation of global toxicity, we used a false discovery rate of $q < 0.05$,[37] corresponding to $P < .0065$ for the QUASAR2 analysis, $P < .0033$ for the capecitabine meta-analyses, and $P < .0048$ for the noncapecitabine meta-analyses. We refer to associations that achieve $q < 0.05$ as formally significant and those that achieve $P < .05$ as nominally significant. We also applied these thresholds to assessment of individual toxicities, because these are not independent of global toxicity.

RESULTS

Testing Candidate FU-Toxicity Variants in QUASAR2

Of 927 patients on the QUASAR2 study, 301 developed grade ≥ 3 global toxicity. The most frequent specific grade ≥ 3 toxicity was HFS (n = 206), followed by diarrhea (n = 97), and neutropenia (n = 19). Two patients died as a result of capecitabine-related toxicity; one as a result of respiratory failure second to neutropenia and the other as a result of neutropenic colitis and left ventricular hypertrophy. Three of the 21 polymorphisms were significantly associated with global G3+ toxicity at $q < 0.05$: *TYMS*5′VNTR2R (odds ratio [OR], 1.49; $P = 7.2 \times 10^{-5}$), *TYMS*3′UTR6bp ins (OR, 1.36; $P = .0051$), and *DPYD*2846A (OR, 9.35; $P = .0043$; Table 2). We found no formally significant effect of the other 18 previously reported FU variants on global or specific toxicities (Data Supplement).

The 5′VNTR and 3′UTR*TYMS* polymorphisms are in moderate linkage disequilibrium ($r^2 = 0.17$; $D' = 0.64$). In logistic regression analysis incorporating both variants, only the 5′VNTR polymorphism remained significantly associated with toxicity (Table 2). However, there was modest evidence from the logistic regression analysis that the 3′UTR genotype might have some independent association with toxicity (OR, 1.22; $P = .10$; Table 2), and a regression model with both 5′VNTR and 3′UTR had a slightly better fit to the data than a model with 5′VNTR alone (Aikake information criterion, 1,142 *v* 1,143). To capture the combined signal from the 5′VNTR and 3′UTR polymorphisms, we also tested a quantitative *TYMS* risk score (count, 0 to 4; according to the number of high-risk alleles per patient). The risk score was approximately normally distributed ($P = .76$, Shapiro-Wilk test) and strongly predicted global FU toxicity ($OR_{per\ count}$, 1.33; $P = 1.7 \times 10^{-5}$; Table 2; $OR_{score\ 3\ or\ 4\ v\ score\ 0}$, 2.91; 95% CI, 1.43 to 5.94; $P =$

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Table 1. The 36 Previously Studied FU-Toxicity Variants From Systematic Review

Functional Category	Gene Symbol (alias/synonym)	Gene Function	Included Polymorphisms	rsID or hg18 Coordinate	MAF (%)	Past	Kit	Studies
Pro-drug activation	*CES2*	First of three steps in converting capecitabine to FU	823 (830) C/G 5′UTR	rs11075646	8	Y		2
			Intronic SNP	rs11568314	6			1
			Intronic SNP	rs11568311	7			1
			6046G>A; R270H	rs8192924	1			1
			6320 G/A	chr16:65532174	0.8			1
			Intronic SNP	rs2241409	16			1
	CDA (*CDD*)	Second of three steps in converting capecitabine to FU	-451C>T	rs532545	34	Y		1
			-205C>G	rs603412	50			1
			5′UTR SNP rs602950	rs602950	35			1
			943insC	rs3215400	42	Y		2
			CDA*2; 79A>C; K27Q	rs2072671	34			2
			575 C/T	chr1:20817782	40			1
			794 G/A	chr1:20817822	6			1
			771 C/G	chr1:20817978	46			1
	UMPS (*OPRT*)	Conversion of FU to FUMP	638G>C (Gly213Ala)	rs1801019	20			1
			1336A>G (Ile446Val)	rs3772809	0.6			1
	TYMP (*TP*)	Conversion of FU to FUDR	Intronic SNP rs470119	rs470119	39			1
			A324A	rs131804	40			1
			S471L	rs11479	14			1
5-FU target	*TYMS* (*TS*)	Necessary for DNA synthesis; target of FU	5′VNTR 3R G/C SNP	rs2853542	50	Y		10
			5′VNTR 2R/3R	rs45445694	47	Y	Y	18
			3′UTR 1494indel6b	rs16430	31	Y	Y	18
	MTHFR	Lowers levels of folate-derived TYMS cofactor	677C>T; A222V	rs1801133	32	Y	Y	18
			1298A>C; E429A	rs1801131	33	Y	Y	14
Catabolism	*DPYD* (*DPD*)	First catabolic step of activated drug (up to 80%, mostly in liver)	*9A; 85T>C; C29R	rs1801265	23	Y	Y	6
			496A>G; M166V	rs2297595	9		Y	4
			623G>A; R208Q	chr1:97937552	ND			1
			1109delTA	chr1:97831380	ND			1
			1236G>A; E412E	rs56038477	2			3
			*4A; 1601G>A; S534N	rs1801158	2		Y	3
			*5; 1627A>G; I543V	rs1801159	20			4
			*13; 1679T>G; I560S	rs55886062	0.1		Y	1
			*2A; IVS14+1G>A	rs3918290	0.4	Y	Y	9
			*6; 2194G>A; V732I	rs1801160	3			3
			2846T>A; D949V	rs67376798	0.6	Y	Y	6
			2858G>C; C953S	chr1:97320523	ND			1

NOTE. Polymorphisms have been described in various ways and these names are all shown, together with their dbSNP ID (rs number) or, where absent from dbSNP, by chromosomal location in genome build hg18. Past refers to previously published associations at $P < .1$ for increased FU toxicity. Kit refers to inclusion in a commercially available kit for predicting FU toxicity. Studies refer to the number of eligible, published studies that have analyzed this polymorphism for an association with FU toxicity (excluding QUASAR2).

Abbreviations: dbSNP ID, database of SNPs identifier; DPYD, dihydropyrimidine dehydrogenase; FU, fluourouracil; MAF, minor allele frequency; ND, not determined; QUASAR2, Quick and Simple and Reliable 2 trial; Y, yes.

.0032), providing a slightly improved fit (Aikake information criterion, 1,140) to the data.

We then analyzed the individual toxicities underlying the significant associations with global toxicity. The *TYMS* polymorphisms (score test) seemed to have similar effects on HFS (OR, 1.30; $P = .00052$) and diarrhea (OR, 1.24; $P = .038$), but the former toxicity was more common and hence contributed more to the global measure (Table 2). In contrast, the effects of *DPYD*2846A seemed more marked for diarrhea (OR, 3.14; $P = .093$) than for HFS (OR, 1.31; $P = .69$; Table 2).

Meta-Analysis of FU-Toxicity Variants

Effect of variants on toxicity from capecitabine monotherapy. Fifteen variants were analyzed for associations with global capecitabine toxicity (Data Supplement). The four studies additional to QUASAR2 comprised up to 382 patients. For *TYMS* and *DPYD2A*, the conclusions from the QUASAR2 analysis were maintained in the meta-analysis (Table 2; Fig 1). We found no good evidence of an association between any other polymorphism and G3+ toxicity (Data Supplement).

Effect of variants on toxicity from infusional FU monotherapy. Fifteen variants were analyzed (Data Supplement), of which seven were present in single studies only. Only *TYMS* 5′VNTR2R met the formal significance threshold for association with global G3+ toxicity in the meta-analysis (OR, 1.45; 95% CI, 1.13 to 1.85; $P = .0035$; Data Supplement). In an analysis adjusted for the 3′UTR6bp ins-del variant (Data Supplement), the 5′VNTR polymorphism remained associated with toxicity (OR, 1.53; 95% CI, 1.14 to 2.04; $P = .0040$). The *TYMS* risk score was only nominally associated with toxicity ($OR_{per\ count}$, 1.22; 95% CI, 1.02 to 1.45; $P = .031$).

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Table 2. Associations Between Selected *DPYD* and *TYMS* Variants and Capecitabine-Related Toxicity

Polymorphism and Toxicity	QUASAR2 Analyses					All Capecitabine Analyses						
	No. of Patients	TAF	OR	95% CI	*P*	No. of Studies	No. of Patients	OR	95% CI	*P*	*P*-het	
*TYMS*5′VNTR2R/3R (*2-repeat allele*)												
Global	918	0.47	1.48	1.22 to 1.80	.000079	5	1,300	1.36	1.15 to 1.60	.00028	.17	Meta
Diarrhea	918	0.47	1.29	0.96 to 1.74	.093	5	1,309	1.12	0.87 to 1.45	.38	.29	
HFS	916	0.47	1.44	1.15 to 1.79	.0013	5	1,306	1.33	1.10 to 1.60	.0029	.23	
*TYMS*3′UTR6bpins-del (*6bp-insertion allele*)												
Global	474	0.69	1.67	1.23 to 2.22	.00084	4	738	1.35	1.07 to 1.70	.012	.024	Meta
Diarrhea	474	0.69	1.49	0.94 to 2.38	.085	4	745	1.11	0.79 to 1.58	.54	.007	
HFS	473	0.69	1.47	1.06 to 2.08	.021	4	743	1.43	1.09 to 1.87	.0091	.34	
5′VNTR adjusted for 3′UTR												
Global	474	0.47	1.24	0.93 to 1.67	.15	2	602	1.27	0.98 to 1.64	.068	—	Pooled
Diarrhea	474	0.47	1.08	0.70 to 1.67	.72	2	602	1.11	0.76 to 1.61	.59	—	
HFS	474	0.47	1.26	0.91 to 1.75	.17	2	602	1.20	0.90 to 1.58	.21	—	
3′UTR adjusted for 5′VNTR												
Global	474	0.69	1.56	1.11 to 2.18	.010	2	602	1.42	1.06 to 1.89	.017	—	Pooled
Diarrhea	474	0.69	1.47	0.88 to 2.45	.14	2	602	1.19	0.78 to 1.81	.43	—	
HFS	474	0.69	1.37	0.94 to 1.98	.10	2	602	1.40	1.02 to 1.93	.038	—	
TYMS score test (*No. of high-risk alleles*)												
Global	474	0.58	1.38	1.16 to 1.64	.00031	2	602	1.33	1.15 to 1.55	.00018	.46	Meta
Diarrhea	474	0.58	1.24	0.96 to 1.61	.096	2	602	1.14	0.92 to 1.42	.24	.20	
HFS	474	0.58	1.31	1.08 to 1.59	.0063	2	602	1.29	1.09 to 1.52	.0030	.73	
*DPYD**2A [*exon skipping allele (A)*]												
Global	905	0.004	2.78	0.62 to 12.5	.18	2	1,035	3.02	0.78 to 11.7	.11	.83	Meta
Diarrhea	905	0.004	1.41	0.17 to 11.8	.75	2	1,035	3.14	0.71 to 13.8	.13	.18	
HFS	903	0.004	2.67	0.59 to 12.0	.20	2	1,033	1.98	0.52 to 7.54	.32	.46	
*DPYD*2846T>A (*A allele*)												
Global	881	0.006	9.35	2.01 to 43.4	.0043							
Diarrhea	881	0.006	3.14	0.82 to 11.9	.093							
HFS	879	0.006	1.31	0.35 to 4.96	.69							
DPYD combined allelic model (*2846A or *2AA allele*)												
Global	863	0.005	5.51	1.95 to 15.5	.0013							
Diarrhea	863	0.005	2.48	0.81 to 7.60	.11							
HFS	861	0.005	1.76	0.66 to 4.71	.26							

NOTE. Fixed-effect meta-analysis and pooled logistic regression analysis results stratified by study are shown for ≥ grade 3 *v* grade 0-2 toxicity. Test alleles are shown in italics.

Abbreviations: DPYD, dihydropyrimidine dehydrogenase; HFS, hand-and-foot syndrome; meta, meta-analysis; OR, odds ratio; *P*-het, *P* value for heterogeneity test; S, No. of studies; TAF, frequency of the putative toxicity-associated allele.

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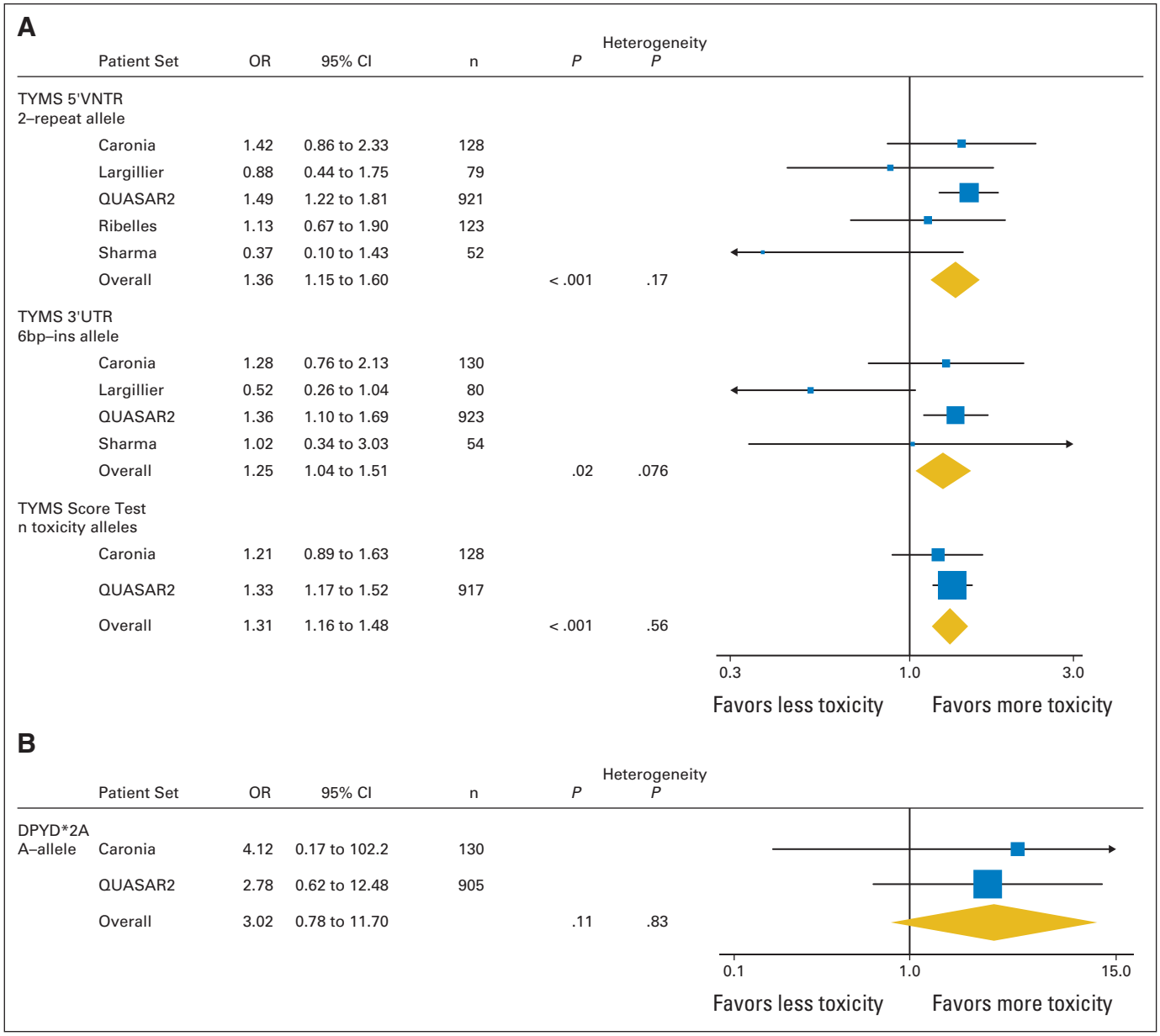

Fig 1. Forest plots of meta-analyses of selected (A) *TYMS* and (B) *DPYD* polymorphisms associated with global capecitabine toxicity. The analyses shown are for global grade ≥ 3 *v* grade 0 to 2 toxicities under a fixed-effects model. *DPYD*2846 is not shown because data were only available for the Quick and Simple and Reliable (QUASAR2) study. Horizontal lines show the 95% CIs. The size of the square is directly proportional to the amount of information contributed by the trial. The diamonds represent overall odds ratio (OR) for the included studies, with the center denoting the OR and the extremities the 95% CI.

Analysis of individual adverse events suggested that the increased toxicity with the *TYMS*5′VNTR2R allele was primarily owing to diarrhea (OR, 1.45; 95% CI, 1.01 to 2.08; $P = .042$).

Although it did not reach the formal significance level for association, a substantial increased risk of global G3+ toxicity was suggested for the *DPYD**2A polymorphism (OR, 6.71; 95% CI, 1.66 to 27.1; $P = .0075$), mainly because of diarrhea (OR, 7.71; 95% CI, 1.61 to 36.9; $P = .011$). In a single-study analysis, the *DPYD*2846A allele showed a trend to greater G3+ toxicity, though this did not reach significance (OR, 3.09; 95% CI, 0.28 to 34.4; $P = .36$). None of the other FU-toxicity variants analyzed showed significant associations with infusional FU toxicity.

Effect of variants on toxicity from bolus FU monotherapy. The only polymorphism significantly associated with global G3+ toxicity as a result of bolus FU was the *TYMS*3′UTR6bp ins allele (OR, 1.98; 95% CI, 1.15 to 3.40; $P = .00038$), principally because of mucositis (OR, 2.03; 95% CI, 1.34 to 3.08; $P = .00086$; Data Supplement). However, this association was not significant after adjusting for 5′VNTR alleles (Data Supplement). The *TYMS* risk score was a weaker predictor (OR, 1.35; 95% CI, 1.06 to 1.71; $P = .014$).

Although the *DPYD**2A variant did not meet the formal level of significance for association with global G3+ toxicity (OR, 3.84; 95% CI, 0.95 to 15.6; $P = .059$), a substantial and significant increase in G3+ neutropenia was evident in patients who carried

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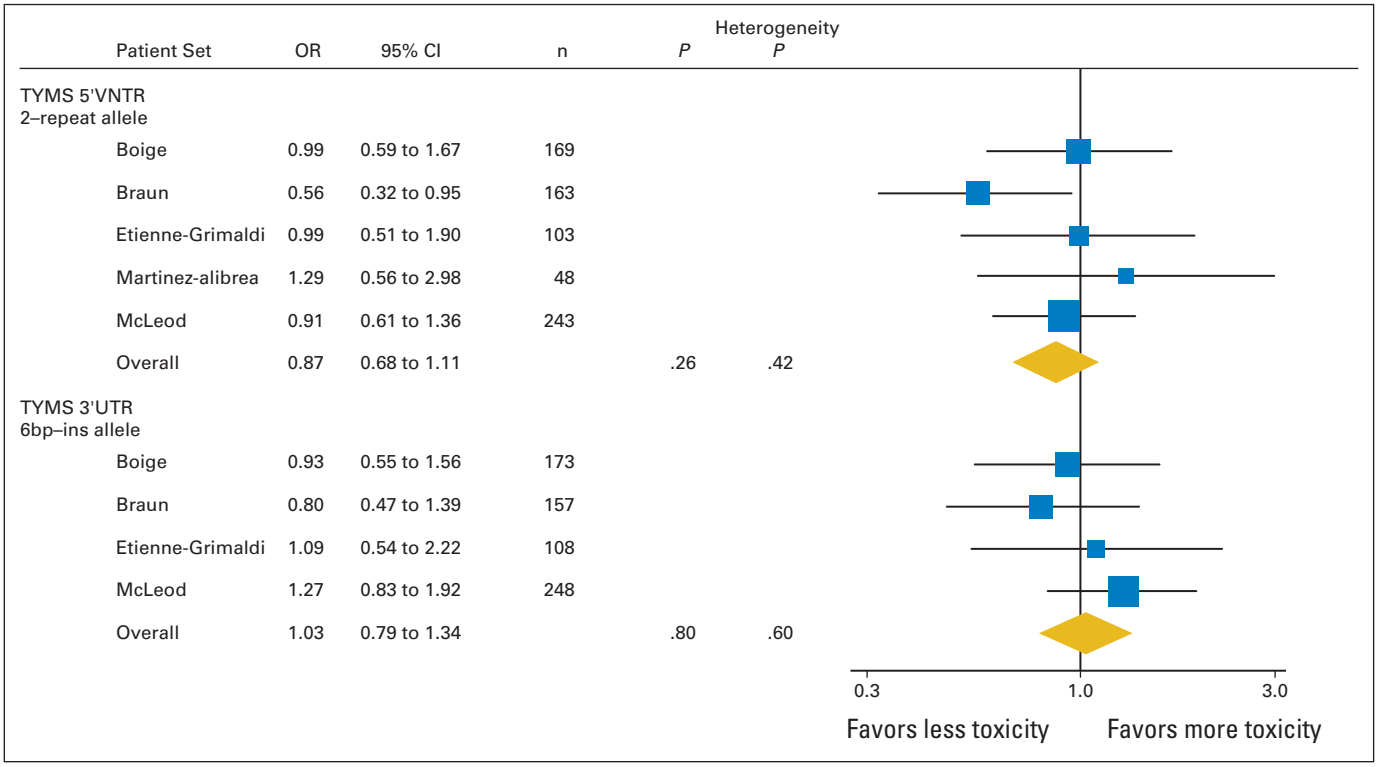

Fig 2. Forest plot of *TYMS* polymorphisms meta-analyzed in infusional fluorouracil, leucovorin, and oxaliplatin patients. Horizontal lines show the 95% CIs. The size of the square is directly proportional to the amount of information contributed by the trial. The diamonds represent overall odds ratios (OR) for the included studies, with the center denoting the OR and the extremities the 95% CI.

this variant (OR, 12.9; 95% CI, 3.13 to 53.3; $P = .0004$). As for infusional FU, patients who carried the *DPYD*2846A allele had trends to all types of toxicity. No other variant was significantly associated with bolus FU toxicity.

Combined Analysis of Rare DPYD *Alleles With Evidence of Effects on Enzyme Function*

For alleles within a single gene that have equivalent functional effects causally related to toxicity, it is justifiable to combine these into one functional class for predictive testing. For *DPYD*, some rare variants have been proposed to cause *DPYD* deficiency syndrome (Online Mendelian Inheritance in Man No. 274270).[38,39] Of these, a few have been shown to reduce DPYD activity in vitro,[40] whereas others have lesser functional evidence from in vivo reports.[41,42] Among variants found in our patient sets, we found good published evidence of functionality for *DPYD*2846A and *2A,[38,39] but not for *9A (85T>C) or Ile370Val (1108A>G), despite these having previously been reported as causing *DPYD* deficiency (Data Supplement). We therefore performed an analysis of *DPYD*2846T>A and *2A rare alleles as a group (presence of either variant *v* no either variant). We found a formally significant association with global toxicity for capecitabine (OR, 5.51; 95% CI, 1.95 to 15.51; $P = .0013$; data from QUASAR2 alone; Table 2) and nominally significant associations in the analyses for infusional ($P = .042$) and bolus ($P = .0068$) monotherapies (Data Supplement). All of these associations were stronger than when either of the variants was considered alone. We noted that of the two patients who died from capecitabine-related toxicity in QUASAR2, one carried *DPYD*2846A and the other, *2A.

Prediction of Toxicity in FU Combination Therapy Regimens

None of the polymorphisms analyzed was associated with global or any specific toxicity in the combination therapy regimens (FOLFOX; CAPOX [capecitabine and oxaliplatin]; FOLFIRI; irinotecan, leucovorin, and fluorouracil [IFL or FLIRI]; Data Supplement). We note that *DPYD**2A was invariant and *DPYD*2846T>A was not analyzed in the available datasets. Figure 2 shows the results from meta-analysis of the two main *TYMS* polymorphisms in studies using FOLFOX, the largest combination therapy data set.

Performance of Panels of Polymorphisms for Predicting FU Toxicity

There are currently three commercially available kits for predicting FU toxicity (Data Supplement). These kits contain a total of 17 polymorphisms that fall into three categories: evidence of toxicity prediction in our analysis (n = 4), present in our analysis but without good evidence of predictive ability (n = 5), or absent from our analysis (n = 8). Of the variants that are absent from our analysis, five are rare *DPYD* variants with evidence of harmful effects on enzyme function [1679(*13), 1897(*3), 295-298del(*7), 703(*8), and 2983(*10); Data Supplement].[38,39]

In QUASAR2, we assessed the prediction of global toxicity by each kit, following the instructions as closely as possible, and using a binary classification of risk (no/low *v* moderate/intermediate/high). Owing to the inclusion of some common polymorphisms, two kits classified almost all patients as at-raised-risk of toxicity. One kit, however, provided better discrimination, with an area under the

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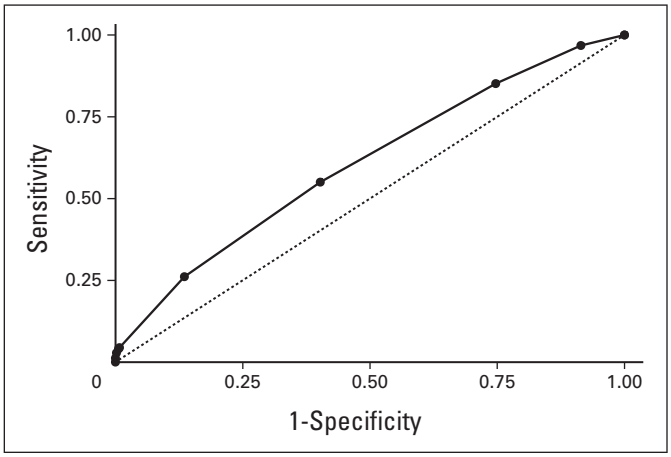

Fig 3. Receiver operating characteristic (ROC) analysis of the *TYMS* score test and *DPYD* group test for predicting global capecitabine toxicity in the Quick and Simple and Reliable (QUASAR2) trial capecitabine patients. Two sensitivity/specificity cut points are marked. Cut points at the bottom-left of the plot corresponds to the maximum proportion of patients correctly classified, with a sensitivity of 4.4%, specificity of 99%, positive predictive value of 73% (PPV; 95% CI, 45% to 91%), and negative predictive value of 68% (NPV; 95% CI, 64% to 71%), largely owing to rare *DPYD* variants. The other cut point (64% correctly classified) affects more patients as a result of utilizing *TYMS* genotypes and corresponds to a sensitivity of 26%, specificity of 86%, PPV of 49% (95% CI, 40% to 58%), and NPV of 70% (95% CI, 66% to 74%).

concentration-time curve of 0.56, 31% sensitivity, 82% specificity, 46% positive predictive value, and 70% negative predictive value (Data Supplement).

We then assessed whether we could improve on the performance of the kits using our *DPYD* combined rare functional alleles test and the *TYMS* score test (Fig 3; Data Supplement). Although no fully independent data set was available for cross-validation, we minimized bias by applying effect size estimates from Caronia et al[33] to QUASAR2 in a logistic regression model. Area under the concentration-time curve was 0.61. At our preferred ln(OR) cutoff of 0.762, sensitivity was 26%, specificity was 86%, positive predictive value was 49%, and negative predictive value was 70%.

DISCUSSION

We have provided the most comprehensive analysis to date of FU toxicity pharmacogenetics. We found that few genetic variants had convincing evidence of an association with toxicity. Of 36 previously assessed polymorphisms, only four—*TYMS* 5′VNTR 2R/3R, *TYMS* 3′UTR 6bpins-del, *DPYD* 2846TA, and *DPYD* *2A—were formally associated with global G3+ toxicity in our analysis. Even so, associations were only present in FU monotherapy regimens. The best evidence came from capecitabine monotherapy in the adjuvant setting although, even here, *TYMS*3′UTR6bp ins-del showed evidence of interstudy heterogeneity and we therefore relied on the larger capecitabine studies for our conclusions regarding this polymorphism. Studies of bolus and infusional FU generally supported the *TYMS* and *DPYD* data, although formally significant associations were less common. We found that formal cross-regimen analysis was not justifiable.

The *TYMS* risk alleles are common in the northern European population. We found the two *TYMS* polymorphisms to be partially independent toxicity predictors and both seem to provide useful information. Despite some inconsistent evidence that the *TYMS* alleles affect mRNA expression levels,[36,43] they have not been shown to cause clinically significant differences in TYMS activity or thymidine incorporation into nucleic acids. Because the identity of the functional *TYMS* variation that causes toxicity is unknown, we have proposed the use of an ad hoc test in which each individual has a score of 0 to 4 according to the number of high-risk alleles they carry at the 5′VNTR and 3′UTR polymorphisms. The score test was a good predictor of global toxicity for capecitabine (OR, 1.33 per allele), with weaker evidence for infusional and bolus FU monotherapy.

For *DPYD*, the two variants associated with toxicity are rare, but for patients with *2A or 2846A, the risk is relatively high (OR, 5.51). We have proposed a group test in which, on the basis of enzyme function, patients carrying either *DPYD*2846A or *DPYD**2A are classed as being variant or wildtype. It is likely that other rare *DPYD* variants with functional effects equivalent to 2846A or *2A could be included in this test (Data Supplement).

Evidence of an association with toxicity was weak for the remaining polymorphisms. Some of these (*DPYD*1627A>G, *DPYD*85T>C, *DPYD*496A>G, *TYMS*5′VNTRG>C, *MTHFR*677C>T, *MTHFR*1298A>C, *CDA*−451C>T, *CES2*823C>G, and the *TYMP* polymorphisms) have common alleles (MAF > 8%). Power to detect an association for these SNPs was approximately 75% to 100%, assuming an odds ratio of 1.5 per allele, and all but modest effects could therefore be excluded where sample sizes were relatively large. For other polymorphisms (eg, *DPYD*1601G>A, *DPYD*1236G>A, *DPYD*2194G>A, *CDA*943insC, and most *CES2* polymorphisms), minor allele frequencies were low or sample sizes small, leading to suboptimal power (approximately 20% to 40%) to detect an association. The case for these as markers of toxicity remains unproven.

Several factors limited our ability to identify polymorphisms associated with FU toxicity. First, the different incidences of individual toxicity phenotypes among FU-based regimens required that we stratify the meta-analyses by FU regimen. This conservative approach decreased power, but prevented us from falsely combining data for toxicity events resulting from different sources. This method also required a larger number of tests, though most were not independent and we corrected for false discovery. Second, in the meta-analysis, there was a little evidence of publication bias; eight of 28 studies failed to provide ORs, and the absence of individual patient data meant that covariate-adjusted analyses were not generally possible. Third, there was no large capecitabine study to validate QUASAR2. Fourth, studies used different genotyping methods, although there was only good evidence of deviation from Hardy-Weinberg equilibrium in two *TYMS* 3′UTR data sets, which were subsequently excluded.

In conclusion, we have found that four specific germline *TYMS* and *DPYD* variants predict capecitabine toxicity. Although our analysis suggests that the polymorphisms may be predictive of toxicity in other FU monotherapy regimens, the data are currently less clear and these regimens are used uncommonly. We found no good evidence of polymorphisms that predict toxicity in patients on FU combination therapies, although no data were available for rare *DPYD* variants in this context. The lack of an association between either of the *TYMS* polymorphisms and toxicity in combination regimens is interesting and might reflect reduced FU dosage in these regimens, overlapping toxicities between drugs, confounding of FU toxicity by other more serious and/or early-onset toxicities, or suboptimal patient set sizes.

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Our findings strongly suggest the exclusion of several unwarranted polymorphisms from the currently available FU toxicity tests, leading to better performance at lower cost. Even then, a genetic test comprising the validated polymorphisms—two *TYMS* variants and functional *DPYD* variants—provides only modest predictive power. For genetic tests to be used in clinical practice, there is a need to identify and characterize additional FU toxicity variants. If such variants were added to the panel of polymorphisms identified in our study, a genetic test might well provide the ability to closely monitor patients who are at increased risk of toxicity or to increase FU dosage in those who are at low risk of toxicity.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

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Genetic testing in bleeding disorders

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Summary

The aim of molecular genetic analysis in families with haemophilia is to identify the causative mutation in an affected male as this provides valuable information for the patient and his relatives. For the patient, mutation identification may highlight inhibitor development risk or discrepancy between different factor VIII assays. For female relatives, knowledge of the familial mutation can facilitate carrier status determination and prenatal diagnosis. Recent advances in understanding mutations responsible for haemophilia and methods for their detection are presented. For reporting of such mutations, participation in external quality assessment ensures that essential patient and mutation details are routinely included and that pertinent information is incorporated in the interpretation.

Keywords

external quality assessment; haemophilia A; haemophilia B; genetic analysis; intrachromosomal inversion; missing mutations

Introduction

In families with haemophilia, identification of the underlying mutation(s) in an affected male followed by its analysis in female relatives “at risk” is the method of choice for clarification of carrier status and for prenatal diagnosis. In other inherited bleeding

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disorders, genetic analysis can help with the diagnosis when the phenotype is unclear and can provide differential diagnosis between similar disorders. Establishing the underlying mutation may also enable prediction of the risk of inhibitor development.

Haemophilia A (HA) and haemophilia B (HB) are X-linked recessively inherited coagulopathies that manifest in hemizygous males with worldwide frequencies of 1:5,000 and 1:25,000, respectively. Although heterozygous female carriers only rarely express symptoms, haemophilia carrier diagnosis provides valuable information for genetic counselling. This article describes advances in understanding of the genetics of haemophilia, particularly those made by laboratories in Argentina and Germany and it then discusses the requirement for and utility of external quality assessment (EQA) for bleeding disorder genetic analysis.

Haemophilia genetic analysis; the Argentinian experience. De Brasi

Since 1995, the Argentinian Molecular Genetics of Haemophilia Laboratory has pursued two intertwined objectives: molecular diagnosis including establishing new approaches to investigate *F8*/*F9* DNA markers and mutations and to study the genotype-phenotype relationship in an Argentinian series of haemophilia patients and carriers.

In 1993, the most common recurrent mutation in haemophilia A, the *F8* intron 22 inversion (Inv22) was described, which is implicated in 35–50% of severe-HA cases regardless of ethnic/geographic origin. Using Southern blotting, molecular diagnosis of Inv22 has been available in Argentina since 1995. Shortly after the second recurrent inversion affecting *F8;* intron 1 (Inv1) was described, our series was reported along with a review of the literature estimating that Inv1 causes less than 3% of severe-HA in Argentina [1]. Inv22 originates from homologous recombination between a 9.5 kb sequence located within *F8* intron 22 (*int22h*-1) to one of two oppositely oriented extragenic copies of *int22h* (*int22h*-2 and *int22h*-3) located by the Xq-telomere. Similarly, Inv1 originates from homologous recombination between intra- and extragenic 900bp homologs. Inv22 and Inv1 are occasionally associated with DNA gain/loss or altered DNA sequence, making their genotyping challenging. Liu et al developed a rapid analysis of Inv22 based on long distance-PCR (LD-PCR) [2]. Our variant of inverse-PCR (inverse shifting-PCR, IS-PCR) that avoids PCR amplification through the *int22h* region was devised in 2004. In this technique, genomic DNA is digested with *Bcl*I restriction enzyme, and self-ligated producing *Bcl*I-DNA circles that provide the target sequence for conventional PCR analysis [3]. The finished sequence of the human X-chromosome indicated that *int22h*-2 and *int22h*-3 are inversely oriented to one another and it became clear that only one of these sequences generates inversions through head-to-head pairing with *int22h*-1. The other copy may generate deletions (Del22) or duplications (Dup22) but not inversions by recombining with equally oriented *int22h*-1. To support experimental evidence that Inv22 type I results from recombination between *int22h*-1 and *int22h*-3 and type II between *int22h*-1 and *int22h*-2, Bagnall et al hypothesized a non-deleterious 68kb inversion mediated by large inverted repeats (50kb) exchanging *int22h*-2/*int22h*-3 locations [4]. To distinguish these genomic variants including haemophilia-causing Inv22 and Del22, and non-causing Dup22, Bagnall et al [5] developed a LD-PCR-based approach. Our laboratory modified the

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previous IS-PCR-based approach, which now enables genotyping of Inv1 and Inv22 from the same template [6] and is applicable to *chorionic villus* extracted-DNA for prenatal diagnosis [7]. El-Hattab et al found that hemizygous Dup22 and Del22 associate with intellectual disability and *in utero* male lethality, respectively [8]. The extreme severity of Del22 in males resulting from loss of several genes suggests that reliable Del22 genotyping should be supported by detecting both of the specific juxtaposed sequences of Del22, and the specific DNA loss associated with the ~0.5Mb deletion [9].

Non inversion HA- and HB-causative mutations include large deletions of an exon or more that are detected by a consistent absence of contiguous exon-specific PCR products. These mutations can be characterised by PCR amplification across deletion junctions, and include both those caused by non-homologous and by homeologous recombination, e.g. that between equally oriented AluSx sequences in introns 4 and 10 of *F8* [10]. For genotyping small *F8* and *F9* mutations, high-resolution conformation sensitive gel electrophoresis (CSGE) on 37 and 8 amplimers respectively, followed by Sanger sequencing of the selected exon(s) showing anomalous CSGE-patterns detects mutations in the majority of subjects. These procedures allowed characterisation of insertions/deletions of 1–10bp (indels) mostly associated with frameshifts, and nucleotide substitutions predicting missense, nonsense or RNA splicing defects [11, 12]. Once a proband's sequence variant has been determined, the genotype-phenotype correlation can be investigated following the Clinical Molecular Genetics Society Practice Guideline for Unclassified Variants [13] along with 3D-structural modelling [14].

In conclusion, the characterisation of causative haemophilia mutations is essential to provide the best information for carrier and prenatal diagnosis, for genetic counselling and to predict phenotypic characteristics, such as genotype-specific inhibitor risks.

Missing mutations in Hemophilia A. El Maarri, Pezeshkpoor & Oldenburg

In almost all HA patients, the deficiency of factor VIII (FVIII) activity can be traced to mutations in *F8*. With advances in molecular diagnostic techniques and particularly in sequencing technology in the last decade, it has become possible to sequence all *F8* exons in all patients, for an affordable cost even in small clinics. Therefore, it was expected that the molecular defect in *F8* would be detected in every HA patient. However, it became clear that this was not the case. At that point, different centers started to characterize these patients and document their clinical phenotypes.

For such "mutation-negative" cases, the first step in the investigation is to verify the HA phenotype. This question can been addressed in two ways; firstly, to verify that only FVIII levels are decreased in these patients; secondly, to exclude combined FV/FVIII deficiency that may be caused by mutations in *LMAN1* or *MCFD2* that may alter the secretion pathways of both FVIII and factor V. In addition, defects in *VWF* should be excluded, as any sub-optimal binding of FVIII to its plasma carrier (VWF) would lead to reduced FVIII activity as observed in von Willebrand disease type 2N. Finally, the two *F8* inversions and deletions, duplications and exonic mutations are excluded by established tests [5, 6]. Only

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after all the above possibilities are excluded is further detailed analysis described below recommended.

The first molecular clue to identify the genetic defects in mutation-negative patients was described in 2008 [15]. Large duplications were identified in some of these patients [16]. Such duplications of entire exons escape detection when individual exons are sequenced. Therefore these duplications are only efficiently detected by multiplex ligation-dependent probe amplification (MLPA) [15], or possibly by array comparative genomic hybridization.

In 2011, Castaman et al identified intronic mutations lying deep in *F8* introns causing abnormal *F8* splicing leading to a decrease in the levels of normally spliced *F8* mRNA [17]. They identified these mutations based on their effect on ectopic *F8* mRNA only after sequencing the neighboring genomic regions. Recently we developed a detailed protocol for detecting the molecular defects in “mutation negative" patients [18, 19]. A systematic stepwise investigation to detect all possible changes in the *F8* locus is proposed. The first step is to exclude gross rearrangements caused by gross duplications, recombinations or inversions. Such rearrangements could leave the exons intact but in the wrong order. Such rearrangements can be excluded by the long-range (LR) amplification of overlapping amplicons that cover the whole *F8* genomic locus. Using this strategy, one patient with a rearranged genomic structure due to recombination between inverted repeats was identified [20]. The second step is to search for abnormal splicing by RT-PCR that covers all exon-exon boundaries. Once abnormal splicing is detected then the involved intronic regions surrounding the breakpoints are sequenced to identify the intronic mutations involved [17]. If no mutation is detected then a third step is to sequence all the LR-PCR products using a massively parallel sequencing approach (next generation sequencing). The advantage of this approach is the rapid identification of all variants in the locus at once [19]. Novel variants can then be further investigated for their effect on splicing (that may have been missed by previous RT-PCR) or for enhancer/silencer effect by functional assays. By undertaking these steps, mutations are expected to be identified in a proportion of previous “mutation negative” cases.

Quality assurance in genetic testing; David Perry on behalf of UK NEQAS BC

In contrast to phenotypic data, the results of genotypic assays are unequivocal with no borderline values. Accordingly, there is an acceptance of the accuracy of such data by referring physicians. However, several studies have shown that mutation detection in common with any analytical test has an intrinsic error rate [21, 22]. A failure to correctly identify a mutation or to interpret its significance can have major implications for an individual and their family members.

In the UK, participation in a recognised EQA scheme is a requirement for laboratory accreditation and a number of such schemes exist, coordinated through UK National External Quality Assessment Service (NEQAS). The only EQA scheme for the genetics of the heritable bleeding disorders in the EU is that administered by UK NEQAS for Blood Coagulation (UK NEQAS BC).

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In 1998, UK NEQAS BC established a pilot scheme to assess the performance of laboratories in genetic testing [23]. In 2003, a Special Advisory Group (SAG) on Haemophilia Molecular Genetics for UK NEQAS BC was established, with the remit of developing a robust EQA scheme for both UK and international participants. The scheme was designed to address three fundamental aspects of genetic testing: 1. The correct identification of the patient and their reason for referral; 2. The correct identification of the causative genetic mutation(s); 3. The interpretation and reporting of genetic data in the context of the any relevant clinical and family data.

Between 2003–2013, 18 exercises were undertaken (Table 1), the most recent was circulated in June 2013 (Exercise 22). The disorders and underlying genetic mutations evaluated by UK NEQAS have been chosen to reflect the routine workload in molecular genetics laboratories. Ten exercises have involved analysis of the *F8* gene of which three were for the Inv22, one for Inv1 and the remainder various sequence variations. Four exercises involved analysis of *F9*, two for a promoter mutation (not associated with HB Leiden) and two for missense mutations. Finally, three exercises involved analysis of missense mutations within *VWF*.

A formalised template for scoring reports was introduced in 2003. This template was employed to introduce a degree of objectivity to a subjective assessment process. The template is based upon recommendations of the UK Clinical Molecular Genetics Society (CMGS) best practice guidelines on report writing [24] with a maximum score of 2 marks for each of three sections; namely clerical accuracy, genotyping and interpretation. In each category, information considered “essential” or “recommended” has a different weighting and this weighting is established in advance of the laboratory report assessment. A score of <1 in any one category constitutes a “fail” in that exercise. Reports are scored independently by four experienced individuals and a consensus subsequently reached. Laboratories that are registered with the scheme who either fail to submit a report or do so outside the allocated turnaround time of 6 weeks (chosen to reflect UKHCDO recommendations) will also fail. A fail in any exercise generates a letter from the Director of UK NEQAS BC with the offer of assistance. Each participating laboratory is assigned a unique identification number that allows the continuing performance of each lab to be reviewed. The identification of participating labs is unknown to the reviewers.

All participating laboratories use the mutation nomenclature system proposed by the Human Gene Variation Society (HGVS) [25] that requires all sequence variations to be defined in relation to a specified reference sequence and the “A” nucleotide of the ATG-translation initiation codon to be numbered as +1 with the protein sequence representing the primary translation product numbered from the initiator methionine and therefore, includes signal peptide sequence. For some genes and proteins, this requires renumbering and makes reference to previously described mutations challenging. Laboratories are, therefore, encouraged to include legacy nomenclature as a number of published mutations including some of those listed in the on-line locus specific mutation databases remain in the “legacy” format.

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Of the 18 exercises circulated between 2004 and 2013, 13 involved the use of whole blood and five DNA derived from immortalised cell lines. Whole blood samples distributed internationally yield sufficient quantity and quality of DNA for analysis even when transport delays of several days occur.

The majority of laboratories in each exercise achieve full marks, and failing is unusual. Reasons for failing an exercise include clerical inaccuracies (e.g., a failure to include unique identifiers for each individual(s)); genotyping errors (e.g. incorrectly numbering the mutation or predicted amino acid substitution; failing to identify a mutation that was present; identifying a second mutation that was not present), and finally interpretation errors. Many of the errors that have led to a fail were based upon incorrect interpretation, e.g. failure to answer the clinical question; incorrectly assigning carrier status (or not) to an “at-risk” female; failing to establish the significance of a novel mutation and failing to consider the possibility of mosaicism.

The aim of EQA schemes is to highlight problems and deficiencies in laboratory procedures. This EQA scheme has led to a more uniform inclusion of information into reports and a standardised use of mutation nomenclature. There are currently 27 laboratories registered for this scheme: 24 in the EU of which 12 are in the UK and three in non-EU countries. The scheme has received very positive feedback from participants and is seen as a fundamental part of good laboratory practice.

Summary

The article has demonstrated the continuing development of molecular genetic analysis of hemophilia directed towards identifying the causative mutation in virtually all patients and for mutations identified, that participation in an EQA scheme promotes reporting and interpretation of the effect of these mutations to a recognized international standard.

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Table 1

A summary of the exercises circulated between 2004 and 2012

Exercise Number	Year	Gene	Mutation	Material
4	2004	Paper Exercise – *F8* Intron 22 Inversion		N/A
5	2004	*F8*	Intron 1 inversion	Whole blood
6	2005	*F8*	Exon 14 2bp deletion	Whole blood
7	2005	*F8*	Intron 22 inversion	Whole blood
8	2006	*F8*	Exon 19 missense mutation	Cell line DNA
9	2006	*F9*	Promoter mutation	Whole blood
10	2007	*VWF*	Exon 28 missense mutation	Whole blood
11	2007	*F8*	Exon 25 missense mutation	Whole blood
12	2008	*F8*	Exon 19 missense mutation	Cell line DNA
13	2008	*F9*	Promoter mutation	Whole blood
14	2009	*F8*	Exon 8 missense mutation	Whole blood
15	2009	*VWF*	Exon 28 missense mutation	Whole blood
16	2010	*F8*	Intron 22 inversion	Cell line DNA
17	2010	*VWF*	Exon 46 missense mutation	Whole blood
18	2011	*F9*	Exon 8 missense mutation	Whole Blood
19	2011	*F8*	Intron 22 inversion	Cell line DNA
20	2012	*F8*	Exon 14 nt duplication	Whole Blood
21	2012	*F9*	Missense mutation	Whole Blood
22	2013	*F8*	Intron 1 inversion	Cell line DNA

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

PEGINTRON® (peginterferon alfa-2b) injection, for subcutaneous use
Initial U.S. Approval: 2001

WARNING: RISK OF SERIOUS DISORDERS AND RIBAVIRIN-ASSOCIATED EFFECTS
***See full prescribing information for complete boxed warning*.**

- **May cause or aggravate fatal or life-threatening neuropsychiatric, autoimmune, ischemic, and infectious disorders. Monitor closely and withdraw therapy with persistently severe or worsening signs or symptoms of the above disorders. (5.2)**

Use with Ribavirin

- **Ribavirin may cause birth defects and fetal death; avoid pregnancy in female patients and female partners of male patients. (5.1)**

----------INDICATIONS AND USAGE----------
PegIntron is an antiviral indicated for treatment of Chronic Hepatitis C (CHC) in patients with compensated liver disease. (1.1)

---------- DOSAGE AND ADMINISTRATION ----------
- PegIntron is administered by subcutaneous injection. (2)

	PegIntron Dose (Adults)*	PegIntron Dose (Pediatric Patients)	REBETOL Dose* (Adults)	REBETOL Dose (Pediatric Patients)
PegIntron Combination Therapy (2.1)	1.5 mcg/kg/ week	60 mcg/m^2/ week	800-1400 mg orally daily with food	15 mg/kg/day orally with food in 2 divided doses

*Refer to Tables 1-7 of the Full Prescribing Information.

- Dose reduction is recommended in patients experiencing certain adverse reactions or renal dysfunction. (2.3, 2.5)

---------- DOSAGE FORMS AND STRENGTHS ----------
Injection: 50 mcg per 0.5 mL, 80 mcg per 0.5 mL, 120 mcg per 0.5 mL, 150 mcg per 0.5 mL in single-use vial (with 5 mL diluent) and single-use pre-filled pens (3)

----------CONTRAINDICATIONS----------
- Known hypersensitivity reactions, such as urticaria, angioedema, bronchoconstriction, anaphylaxis, Stevens-Johnson syndrome, and toxic epidermal necrolysis to interferon alpha or any other product component. (4)
- Autoimmune hepatitis. (4)
- Hepatic decompensation (Child-Pugh score greater than 6 [class B and C]) in cirrhotic CHC patients before or during treatment. (4)

Additional contraindications for combination therapy with ribavirin:

- Pregnant women and men whose female partners are pregnant. (4, 8.1)
- Hemoglobinopathies (e.g., thalassemia major, sickle-cell anemia). (4)
- Creatinine clearance less than 50 mL/min. (4)

---------- WARNINGS AND PRECAUTIONS----------
- Birth defects and fetal death with ribavirin: Patients must have a negative pregnancy test prior to therapy, use at least 2 forms of contraception, and undergo monthly pregnancy tests. (5.1)

Patients exhibiting the following conditions should be closely monitored and may require dose reduction or discontinuation of therapy:

- Hemolytic anemia with ribavirin. (5.1)
- Neuropsychiatric events. (5.2)
- History of significant or unstable cardiac disease. (5.3)
- Hypothyroidism, hyperthyroidism, hyperglycemia, diabetes mellitus that cannot be effectively treated by medication. (5.4)
- New or worsening ophthalmologic disorders. (5.5)
- Ischemic and hemorrhagic cerebrovascular events. (5.6)
- Severe decreases in neutrophil or platelet counts. (5.7)
- History of autoimmune disorders. (5.8)
- Pancreatitis and ulcerative or hemorrhagic/ischemic colitis and pancreatitis. (5.9, 5.10)
- Pulmonary infiltrates or pulmonary function impairment. (5.11)
- Child-Pugh score greater than 6 (class B and C). (4, 5.12)
- Increased creatinine levels in patients with renal insufficiency. (5.13)
- Serious, acute hypersensitivity reactions and cutaneous eruptions. (5.14)
- Dental/periodontal disorders reported with combination therapy. (5.16)
- Hypertriglyceridemia may result in pancreatitis (e.g., triglycerides greater than 1000 mg/dL). (5.17)
- Weight loss and growth inhibition reported during combination therapy in pediatric patients. Long-term growth inhibition (height) reported in some patients. (5.18)
- Peripheral neuropathy when used in combination with telbivudine. (5.19)

---------- ADVERSE REACTIONS ----------
Most common adverse reactions (greater than 40%) in adult patients receiving either PegIntron or PegIntron/REBETOL are injection site inflammation/reaction, fatigue/asthenia, headache, rigors, fevers, nausea, myalgia and anxiety/emotional lability/irritability (6.1). Most common adverse reactions (greater than 25%) in pediatric patients receiving PegIntron/REBETOL are pyrexia, headache, neutropenia, fatigue, anorexia, injection-site erythema, vomiting (6.1).

To report SUSPECTED ADVERSE REACTIONS, contact Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc., at 1-877-888-4231 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

----------DRUG INTERACTIONS----------
- Drugs metabolized by CYP450: Caution with drugs metabolized by CYP1A2 (e.g., caffeine) or CYP2D6 (e.g., thioridazine). (7.1)
- Methadone: Dosage reduction may be necessary. (7.1)
- Nucleoside analogues: Closely monitor for toxicities. Discontinue nucleoside reverse transcriptase inhibitors or reduce dose or discontinue interferon, ribavirin, or both with worsening toxicities. (7.2)
- Didanosine: Concurrent use with REBETOL is not recommended. (7.2)

---------- USE IN SPECIFIC POPULATIONS ----------
- Ribavirin Pregnancy Registry (8.1)
- Pediatrics: safety and efficacy in pediatrics less than 3 years old have not been established. (8.4)
- Geriatrics: neuropsychiatric, cardiac, pulmonary, GI, and systemic (flu-like) adverse reactions may be more severe. (8.5)
- Organ transplant: safety and efficacy have not been studied. (8.6)
- HIV or HBV co-infection: safety and efficacy have not been established. (8.7)

See 17 for PATIENT COUNSELING INFORMATION and Medication Guide.

Revised: 05/2017

FULL PRESCRIBING INFORMATION: CONTENTS*

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

FULL PRESCRIBING INFORMATION

WARNING: RISK OF SERIOUS DISORDERS AND RIBAVIRIN-ASSOCIATED EFFECTS

Alpha interferons, including PegIntron, may cause or aggravate fatal or life-threatening neuropsychiatric, autoimmune, ischemic, and infectious disorders. Patients should be monitored closely with periodic clinical and laboratory evaluations. Patients with persistently severe or worsening signs or symptoms of these conditions should be withdrawn from therapy. In many, but not all cases, these disorders resolve after stopping PegIntron therapy *[see Warnings and Precautions (5) and Adverse Reactions (6.1)].*

Use with Ribavirin

Ribavirin may cause birth defects and death of the unborn child. Extreme care must be taken to avoid pregnancy in female patients and in female partners of male patients. Ribavirin causes hemolytic anemia. The anemia associated with ribavirin therapy may result in a worsening of cardiac disease. *[See ribavirin labeling.]*

1 INDICATIONS AND USAGE

1.1 Chronic Hepatitis C (CHC)

PegIntron®, as part of a combination regimen, is indicated for the treatment of Chronic Hepatitis C (CHC) in patients with compensated liver disease.

- PegIntron in combination with REBETOL® (ribavirin) and an approved Hepatitis C Virus (HCV) NS3/4A protease inhibitor is indicated in adult patients with HCV genotype 1 infection (see labeling of the specific HCV NS3/4A protease inhibitor for further information).
- PegIntron in combination with REBETOL is indicated in patients with genotypes other than 1, pediatric patients (3-17 years of age), or in patients with genotype 1 infection where use of an HCV NS3/4A protease inhibitor is not warranted based on tolerability, contraindications or other clinical factors.

PegIntron monotherapy should only be used in the treatment of CHC in patients with compensated liver disease if there are contraindications to or significant intolerance of REBETOL and is indicated for use only in previously untreated adult patients. Combination therapy provides substantially better response rates than monotherapy *[see Clinical Studies (14.1, 14.2)]*.

2 DOSAGE AND ADMINISTRATION

2.1 PegIntron Combination Therapy

Adults

The recommended dose of PegIntron is 1.5 mcg/kg/week. The volume of PegIntron to be injected depends on the strength of PegIntron and patient's body weight *(see **Table 1**)*.

The recommended dose of REBETOL for use with PegIntron is 800 to 1400 mg orally based on patient body weight. REBETOL should be taken with food. REBETOL should not be used in patients with creatinine clearance less than 50 mL/min.

See labeling of the specific HCV NS3/4A protease inhibitor for information regarding dosing regimen and administration of the protease inhibitor in combination with PegIntron and ribavirin.

Duration of Treatment – Treatment with PegIntron/REBETOL of Interferon Alpha-naïve Patients

The treatment duration for patients with genotype 1 is 48 weeks. Discontinuation of therapy should be considered in patients who do not achieve at least a 2 $\log_{10}$ drop or loss of HCV-RNA at 12 weeks, or if HCV-RNA remains detectable after 24 weeks of therapy. Patients with genotype 2 and 3 should be treated for 24 weeks.

Duration of Treatment – Re-treatment with PegIntron/REBETOL of Prior Treatment Failures

For patients with genotype 1 infection, PegIntron and REBETOL without an HCV NS3/4A protease inhibitor should only be used if there are contraindications, significant intolerance or other clinical factors that would not warrant use of an HCV NS3/4A protease inhibitor. The treatment duration for patients who previously failed therapy is 48 weeks, regardless of HCV genotype. Re-treated patients who fail to achieve undetectable HCV-RNA at Week 12 of therapy, or whose HCV-RNA remains detectable after 24 weeks of therapy, are highly unlikely to achieve SVR and discontinuation of therapy should be considered *[see Clinical Studies (14.1)].*

Table 1: Recommended PegIntron Combination Therapy Dosing (Adults)

Body Weight kg (lbs)	PegIntron REDIPEN Pre-filled pen or Vial Strength to Use	Amount of PegIntron to Administer (mcg)	Volume* of PegIntron to Administer (mL)	REBETOL Daily Dose	REBETOL Number of Capsules
<40 (<88)	50 mcg per 0.5 mL	50	0.5	800 mg/day	2 x 200 mg capsules A.M. 2 x 200 mg capsules P.M.
40-50 (88-111)	80 mcg per 0.5 mL	64	0.4	800 mg/day	2 x 200 mg capsules A.M. 2 x 200 mg capsules P.M.
51-60 (112-133)		80	0.5	800 mg/day	2 x 200 mg capsules A.M. 2 x 200 mg capsules P.M.
61-65 (134-144)	120 mcg per 0.5 mL	96	0.4	800 mg/day	2 x 200 mg capsules A.M. 2 x 200 mg capsules P.M.
66-75 (145-166)		96	0.4	1000 mg/day	2 x 200 mg capsules A.M. 3 x 200 mg capsules P.M.
76-80 (167-177)		120	0.5	1000 mg/day	2 x 200 mg capsules A.M. 3 x 200 mg capsules P.M.
81-85 (178-187)				1200 mg/day	3 x 200 mg capsules A.M. 3 x 200 mg capsules P.M.
86-105 (188-231)	150 mcg per 0.5 mL	150	0.5	1200 mg/day	3 x 200 mg capsules A.M. 3 x 200 mg capsules P.M.
>105 (>231)	†	†	†	1400 mg/day	3 x 200 mg capsules A.M. 4 x 200 mg capsules P.M.

* When reconstituted as directed.
† For patients weighing greater than 105 kg (greater than 231 pounds), the PegIntron dose of 1.5 mcg/kg/week should be calculated based on the individual patient weight. This may require combinations of various PegIntron dose strengths and volumes.

Pediatric Patients

Dosing for pediatric patients is determined by body surface area for PegIntron and by body weight for REBETOL. The recommended dose of PegIntron is 60 mcg/m^2/week subcutaneously in combination with 15 mg/kg/day of REBETOL orally in 2 divided doses *(see **Table 2**)* for pediatric patients ages 3 to 17 years. Patients who reach their 18th birthday while receiving PegIntron/REBETOL should remain on the pediatric dosing regimen. The treatment duration for patients with genotype 1 is 48 weeks. Patients with genotype 2 and 3 should be treated for 24 weeks.

Table 2: Recommended REBETOL* Dosing in Combination Therapy (Pediatrics)

Body Weight kg (lbs)	REBETOL Daily Dose	REBETOL Number of Capsules
<47 (<103)	15 mg/kg/day	Use REBETOL oral solution†
47-59 (103-131)	800 mg/day	2 x 200 mg capsules A.M. 2 x 200 mg capsules P.M.
60-73 (132-162)	1000 mg/day	2 x 200 mg capsules A.M. 3 x 200 mg capsules P.M.
>73 (>162)	1200 mg/day	3 x 200 mg capsules A.M. 3 x 200 mg capsules P.M.

*REBETOL to be used in combination with PegIntron 60 mcg/m^2 weekly.
† REBETOL oral solution may be used for any patient regardless of body weight.

2.2 PegIntron Monotherapy

The recommended dose of PegIntron regimen is 1 mcg/kg/week subcutaneously for 1 year administered on the same day of the week. Discontinuation of therapy should be considered in patients who do not achieve at least a 2 $\log_{10}$ drop or loss of HCV-RNA at 12 weeks of therapy, or whose HCV-RNA levels remain detectable after 24 weeks of therapy. The volume of PegIntron to be injected depends on patient weight *(see **Table 3**)*.

Table 3: Recommended PegIntron Monotherapy Dosing

Body Weight kg (lbs)	PegIntron REDIPEN Pre-filled pen or Vial Strength to Use	Amount of PegIntron to Administer (mcg)	Volume of PegIntron to Administer (mL)*
≤45 (≤100)	50 mcg per 0.5 mL	40	0.4
46-56 (101-124)		50	0.5
57-72 (125-159)	80 mcg per 0.5 mL	64	0.4
73-88 (160-195)		80	0.5
89-106 (196-234)	120 mcg per 0.5 mL	96	0.4
107-136 (235-300)		120	0.5
137-160 (301-353)	150 mcg per 0.5 mL	150	0.5

* When reconstituted as directed.

2.3 Dose Reduction

If a serious adverse reaction develops during the course of treatment discontinue or modify the dosage of PegIntron and REBETOL until the adverse event abates or decreases in severity *[see Warnings and Precautions (5)]*. If persistent or recurrent serious adverse events develop despite adequate dosage adjustment, discontinue treatment. For guidelines for dose modifications and discontinuation based on depression or laboratory parameters see **Tables 4** and **5**. Dose reduction of PegIntron in adult patients on PegIntron/REBETOL combination therapy is accomplished in a two-step process from the original starting dose of 1.5 mcg/kg/week, to 1 mcg/kg/week, then to 0.5 mcg/kg/week, if needed. Dose reduction in patients on PegIntron monotherapy is accomplished by reducing the original starting dose of 1 mcg/kg/week to 0.5 mcg/kg/week. Instructions for dose reductions in adults are outlined in **Tables 6** (Monotherapy: REDIPEN/Vial) and **7** (Combination therapy: REDIPEN/Vial).

In the adult combination therapy Study 2, dose reductions occurred in 42% of subjects receiving PegIntron 1.5 mcg/kg plus REBETOL 800 mg daily, including 57% of those subjects weighing 60 kg or less. In Study 4, 16% of subjects had a dose reduction of PegIntron to 1 mcg/kg in combination with REBETOL, with an additional 4% requiring the second dose reduction of PegIntron to 0.5 mcg/kg due to adverse events *[see Adverse Reactions (6.1)]*.

Dose reduction in pediatric patients is accomplished by modifying the recommended dose in a 2-step process from the original starting dose of 60 mcg/m^2/week, to 40 mcg/m^2/week, then to 20 mcg/m^2/week, if needed *(see **Tables 4** and **5**).* In the pediatric combination therapy trial, dose reductions occurred in 25% of subjects receiving PegIntron 60 mcg/m^2 weekly plus REBETOL 15 mg/kg daily.

Table 4: Guidelines for Modification or Discontinuation of PegIntron or PegIntron/REBETOL and for Scheduling Visits for Patients with Depression

Depression Severity*	Initial Management (4-8 weeks)		Depression Status		
	Dose Modification	Visit Schedule	Remains Stable	Improves	Worsens
Mild	No change	Evaluate once weekly by visit or phone	Continue weekly visit schedule	Resume normal visit schedule	See moderate or severe depression
Moderate	Adults: Adjust Dose* Pediatrics: Decrease dose to 40 mcg/m^2/week, then to 20 mcg/m^2/week, if needed	Evaluate once weekly (office visit at least every other week)	Consider psychiatric consultation. Continue reduced dosing	If symptoms improve and are stable for 4 weeks, may resume normal visit schedule. Continue reduced dosing or return to normal dose	See severe depression
Severe	Discontinue PegIntron/REBETOL permanently	Obtain immediate psychiatric consultation	Psychiatric therapy as necessary		

* See DSM-IV for definitions. For patients on PegIntron/REBETOL combination therapy: 1st dose reduction of PegIntron is to 1 mcg/kg/week, 2nd dose reduction (if needed) of PegIntron is to 0.5 mcg/kg/week. For patients on PegIntron monotherapy: decrease PegIntron dose to 0.5 mcg/kg/week.

Table 5: Guidelines for Dose Modification and Discontinuation of PegIntron or PegIntron/REBETOL Based on Laboratory Parameters in Adults and Pediatrics

Laboratory Parameters	Reduce PegIntron Dose (see note 1) if:	Reduce ribavirin Daily Dose (see note 2) if:	Discontinue Therapy if:
WBC	1.0 to <1.5 x 10^9/L	N/A	<1.0 x 10^9/L

Laboratory Parameters	Reduce PegIntron Dose (see note 1) if:	Reduce ribavirin Daily Dose (see note 2) if:	Discontinue Therapy if:
Neutrophils	0.5 to <0.75 x 10^9/L	N/A	<0.5 x 10^9/L
Platelets	25 to <50 x 10^9/L (adults)	N/A	<25 x 10^9/L (adults)
	50 to <70 x 10^9/L (pediatrics)	N/A	<50 x 10^9/L (pediatrics)
Creatinine	N/A	N/A	>2 mg/dL (pediatrics)
Hemoglobin in patients without history of cardiac disease	N/A	8.5 to <10 g/dL	<8.5 g/dL
	Reduce PegIntron Dose by Half and the Ribavirin Dose by 200 mg/day if:		
Hemoglobin in patients with history of cardiac disease*†	≥2 g/dL decrease in hemoglobin during any four week period during treatment		<8.5 g/dL or <12 g/dL after four weeks of dose reduction

Note 1: *Adult patients on combination therapy*: 1st dose reduction of PegIntron is to 1 mcg/kg/week. If needed, 2nd dose reduction of PegIntron is to 0.5 mcg/kg/week.
Adult patients on PegIntron monotherapy: decrease PegIntron dose to 0.5 mcg/kg/week.
Pediatric patients: 1st dose reduction of PegIntron is to 40 mcg/m^2/week, 2nd dose reduction of PegIntron is to 20 mcg/m^2/week.

Note 2: *Adult patients*: 1st dose reduction of ribavirin is by 200 mg/day (except in patients receiving the 1400 mg, dose reduction should be by 400 mg/day). If needed, 2nd dose reduction of ribavirin is by an additional 200 mg/day. Patients whose dose of ribavirin is reduced to 600 mg daily receive one 200 mg capsule in the morning and two 200 mg capsules in the evening.
Pediatric patients: 1st dose reduction of ribavirin is to 12 mg/kg/day, 2nd dose reduction of ribavirin is to 8 mg/kg/day.

* Pediatric patients who have pre-existing cardiac conditions and experience a hemoglobin decrease greater than or equal to 2 g/dL during any 4-week period during treatment should have weekly evaluations and hematology testing.

† These guidelines are for patients with stable cardiac disease. Patients with a history of significant or unstable cardiac disease should not be treated with PegIntron /REBETOL combination therapy *[see Warnings and Precautions (5.3)].*

Table 6: Reduced PegIntron Dose (0.5 mcg/kg) for (1 mcg/kg) Monotherapy in Adults

Body Weight kg (lbs)	PegIntron REDIPEN/Vial		
	Strength to Use	Amount to Administer (mcg)	Volume* to Administer (mL)
≤45 (≤100)	50 mcg per 0.5 mL†	20	0.2
46-56 (101-124)	50 mcg per 0.5 mL†	25	0.25
57-72 (125-159)	50 mcg per 0.5 mL	30	0.3
73-88 (160-195)	50 mcg per 0.5 mL	40	0.4
89-106 (196-234)	50 mcg per 0.5 mL	50	0.5
107-136 (235-300)	80 mcg per 0.5 mL	64	0.4
≥137 (≥301)	80 mcg per 0.5 mL	80	0.5

* When reconstituted as directed.
† Must use vial. Minimum delivery for REDIPEN 0.3 mL.

Table 7: Two-Step Dose Reduction of PegIntron REDIPEN/Vial in Combination Therapy in Adults

First Dose Reduction to PegIntron 1 mcg/kg				Second Dose Reduction to PegIntron 0.5 mcg/kg			
Body weight kg (lbs)	**PegIntron REDIPEN/Vial Strength to Use**	**Amount of PegIntron (mcg) to Administer**	**Volume (mL) † of PegIntron to Administer**	**Body weight kg (lbs)**	**PegIntron REDIPEN/ Vial Strength to Use**	**Amount of PegIntron (mcg) to Administer**	**Volume (mL) † of PegIntron to Administer**
<40 (<88)	50 mcg per 0.5 mL	35	0.35	<40 (<88)	50 mcg per 0.5 mL*	20	0.2
40-50 (88-111)		45	0.45	40-50 (88-111)		25	0.25
51-60 (112-133)		50	0.5	51-60 (112-133)	50 mcg per 0.5 mL	30	0.3
61-75 (134-166)	80 mcg per 0.5 mL	64	0.4	61-75 (134-166)		35	0.35
76-85 (167-187)		80	0.5	76-85 (167-187)		45	0.45
86-104 (188-230)	120 mcg per 0.5 mL	96	0.4	86-104 (188-230)		50	0.5
105-125 (231-275)		108	0.45	105-125 (231-275)	80 mcg per 0.5 mL	64	0.4
>125 (>275)	150 mcg per 0.5 mL	135	0.45	>125 (>275)		72	0.45

* Must use vial. Minimum delivery for REDIPEN 0.3 mL.
† When reconstituted as directed.

2.4 Discontinuation of Dosing

Adults

See labeling of the specific HCV NS3/4A protease inhibitor for information regarding discontinuation of dosing based on treatment futility.

In HCV genotype 1, interferon-alfa-naïve patients receiving PegIntron, alone or in combination with REBETOL, discontinuation of therapy is recommended if there is not at least a 2 $\log_{10}$ drop or loss of HCV-RNA at 12 weeks of therapy, or if HCV-RNA levels remain detectable after 24 weeks of therapy. Regardless of genotype, previously treated patients who have detectable HCV-RNA at Week 12 or 24, are highly unlikely to achieve SVR and discontinuation of therapy is recommended.

Pediatrics (3-17 years of age)

It is recommended that patients receiving PegIntron/REBETOL combination (excluding those with HCV genotype 2 and 3) be discontinued from therapy at 12 weeks if their treatment Week 12 HCV-RNA dropped less than 2 $\log_{10}$ compared to pretreatment or at 24 weeks if they have detectable HCV-RNA at treatment Week 24.

2.5 Renal Function

In patients with moderate renal dysfunction (creatinine clearance 30-50 mL/min), the PegIntron dose should be reduced by 25%. Patients with severe renal dysfunction (creatinine clearance 10-29 mL/min), including those on hemodialysis, should have the PegIntron dose reduced by 50%. If renal function decreases during treatment, PegIntron therapy should be discontinued. When PegIntron is administered in combination with REBETOL, subjects with impaired renal function or those over the age of 50 should be more carefully monitored with respect to the development of anemia. PegIntron/REBETOL should not be used in patients with creatinine clearance less than 50 mL/min.

2.6 Preparation and Administration

A patient should self-inject PegIntron only if the physician determines that it is appropriate and the patient agrees to medical follow-up as necessary and has been trained in proper injection technique *[see illustrated FDA-approved Medication Guide and Instructions for Use for directions on injection site preparation and injection instructions].*

Reconstitute PegIntron Powder for Solution with 0.7 mL of Sterile Water for Injection, USP. The Sterile Water for Injection supplied contains 5 mL and is intended for single use only. Discard the unused portion. The reconstituted solution should be visually inspected for discoloration and particulate matter prior to administration. Do not use the solution if it is discolored or not clear, or if particulates are present.

DO NOT REUSE THE VIAL OR PRE-FILLED PEN; DISCARD THE UNUSED PORTION. Pooling of unused portions of some medications has been linked to bacterial contamination and morbidity.

3 DOSAGE FORMS AND STRENGTHS

- Single-use vial: 5 mL diluent vial: 50 mcg per 0.5 mL, 80 mcg per 0.5 mL, 120 mcg per 0.5 mL, 150 mcg per 0.5 mL.
- REDIPEN® single-use pre-filled pen: 50 mcg per 0.5 mL, 80 mcg per 0.5 mL, 120 mcg per 0.5 mL, 150 mcg per 0.5 mL.

4 CONTRAINDICATIONS

PegIntron is contraindicated in patients with:

- known hypersensitivity reactions, such as urticaria, angioedema, bronchoconstriction, anaphylaxis, Stevens-Johnson syndrome, and toxic epidermal necrolysis to interferon alpha or any other component of the product
- autoimmune hepatitis
- hepatic decompensation (Child-Pugh score greater than 6 [class B and C]) in cirrhotic CHC patients before or during treatment

PegIntron/ribavirin combination therapy is additionally contraindicated in:

- women who are pregnant. Ribavirin may cause fetal harm when administered to a pregnant woman. Ribavirin is contraindicated in women who are or may become pregnant. If ribavirin is used during pregnancy, or if the patient becomes pregnant while taking ribavirin, the patient should be apprised of the potential hazard to her fetus *[see Use in Specific Populations (8.1)].*
- men whose female partners are pregnant
- patients with hemoglobinopathies (e.g., thalassemia major, sickle-cell anemia)
- patients with creatinine clearance less than 50 mL/min

5 WARNINGS AND PRECAUTIONS

Patients should be monitored for the following serious conditions, some of which may become life threatening. Patients with persistently severe or worsening signs or symptoms should be withdrawn from therapy.

5.1 Use with Ribavirin

Pregnancy

Ribavirin may cause birth defects and death of the unborn child. Ribavirin therapy should not be started until a report of a negative pregnancy test has been obtained immediately prior to planned initiation of therapy. Patients should use at least 2 forms of contraception and have monthly pregnancy tests during treatment and during the 6-month period after treatment has been stopped *[see Contraindications (4) and ribavirin labeling].*

Anemia

Ribavirin caused hemolytic anemia in 10% of PegIntron/REBETOL-treated subjects within 1 to 4 weeks of initiation of therapy. Complete blood counts should be obtained pretreatment and at Week 2 and Week 4 of therapy or more frequently if clinically indicated. Anemia associated with ribavirin therapy may result in a worsening of cardiac disease. Decrease in dosage or discontinuation of ribavirin may be necessary *[see Dosage and Administration (2.3)* and *ribavirin labeling]*.

5.2 Neuropsychiatric Events

Life-threatening or fatal neuropsychiatric events, including suicide, suicidal and homicidal ideation, depression, relapse of drug addiction/overdose, and aggressive behavior sometimes directed towards others have occurred in patients with and without a previous psychiatric disorder during PegIntron treatment and follow-up. Psychoses, hallucinations, bipolar disorders, and mania have been observed in patients treated with interferon alpha.

PegIntron should be used with caution in patients with a history of psychiatric disorders. Treatment with interferons may be associated with exacerbated symptoms of psychiatric disorders in patients with co-occurring psychiatric and substance use disorders. If treatment with interferons is initiated in patients with prior history or existence of psychiatric condition or with a history of substance use disorders, treatment considerations should include the need for drug screening and periodic health evaluation, including psychiatric symptom monitoring. Early intervention for re-emergence or development of neuropsychiatric symptoms and substance use is recommended.

Patients should be advised to report immediately any symptoms of depression or suicidal ideation to their prescribing physicians. Physicians should monitor all patients for evidence of depression and other psychiatric symptoms. If patients develop psychiatric problems, including clinical depression, it is recommended that the patients be carefully monitored during treatment and in the 6-month follow-up period. If psychiatric symptoms persist or worsen, or suicidal or homicidal ideation or aggressive behavior towards others is identified, discontinue treatment with PegIntron and follow the patient closely, with psychiatric intervention as appropriate. In severe cases, PegIntron should be stopped immediately and psychiatric intervention instituted *[see Dosage and Administration (2.3)]*. Cases of encephalopathy have been observed in some patients, usually elderly, treated at higher doses of PegIntron.

5.3 Cardiovascular Events

Cardiovascular events, which include hypotension, arrhythmia, tachycardia, cardiomyopathy, angina pectoris, and myocardial infarction, have been observed in patients treated with PegIntron. PegIntron should be used cautiously in patients with cardiovascular disease. Patients with a history of myocardial infarction and arrhythmic disorder who require PegIntron therapy should be closely monitored *[see Warnings and Precautions (5.15)]*. Patients with a history of significant or unstable cardiac disease should not be treated with PegIntron/ribavirin combination therapy *[see ribavirin labeling]*.

5.4 Endocrine Disorders

PegIntron causes or aggravates hypothyroidism and hyperthyroidism. Hyperglycemia has been observed in patients treated with PegIntron. Diabetes mellitus, including cases of new onset Type 1 diabetes, has been observed in patients treated with alpha interferons, including PegIntron. Patients with these conditions who cannot be effectively treated by medication should not begin PegIntron therapy. Patients who develop these conditions during treatment and cannot be controlled with medication should not continue PegIntron therapy.

5.5 Ophthalmologic Disorders

Decrease or loss of vision, retinopathy including macular edema, retinal artery or vein thrombosis, retinal hemorrhages and cotton wool spots, optic neuritis, papilledema, and serous retinal detachment may be induced or aggravated by treatment with peginterferon alfa-2b or other alpha interferons. All patients should receive an eye examination at baseline. Patients with preexisting

ophthalmologic disorders (e.g., diabetic or hypertensive retinopathy) should receive periodic ophthalmologic exams during interferon alpha treatment. Any patient who develops ocular symptoms should receive a prompt and complete eye examination. Peginterferon alfa-2b treatment should be discontinued in patients who develop new or worsening ophthalmologic disorders.

5.6 Cerebrovascular Disorders

Ischemic and hemorrhagic cerebrovascular events have been observed in patients treated with interferon alfa-based therapies, including PegIntron. Events occurred in patients with few or no reported risk factors for stroke, including patients less than 45 years of age. Because these are spontaneous reports, estimates of frequency cannot be made, and a causal relationship between interferon alfa-based therapies and these events is difficult to establish.

5.7 Bone Marrow Toxicity

PegIntron suppresses bone marrow function, sometimes resulting in severe cytopenias. PegIntron should be discontinued in patients who develop severe decreases in neutrophil or platelet counts *[see Dosage and Administration (2.3)]*. Ribavirin may potentiate the neutropenia induced by interferon alpha. Very rarely alpha interferons may be associated with aplastic anemia.

5.8 Autoimmune Disorders

Development or exacerbation of autoimmune disorders (e.g., thyroiditis, thrombotic thrombocytopenic purpura, idiopathic thrombocytopenic purpura, rheumatoid arthritis, interstitial nephritis, systemic lupus erythematosus, and psoriasis) has been observed in patients receiving PegIntron.

PegIntron should be used with caution in patients with autoimmune disorders.

5.9 Pancreatitis

Fatal and nonfatal pancreatitis has been observed in patients treated with alpha interferon. PegIntron therapy should be suspended in patients with signs and symptoms suggestive of pancreatitis and discontinued in patients diagnosed with pancreatitis.

5.10 Colitis

Fatal and nonfatal ulcerative or hemorrhagic/ischemic colitis have been observed within 12 weeks of the start of alpha interferon treatment. Abdominal pain, bloody diarrhea, and fever are the typical manifestations. PegIntron treatment should be discontinued immediately in patients who develop these signs and symptoms. The colitis usually resolves within 1 to 3 weeks of discontinuation of alpha interferons.

5.11 Pulmonary Disorders

Dyspnea, pulmonary infiltrates, pneumonia, bronchiolitis obliterans, interstitial pneumonitis, pulmonary hypertension, and sarcoidosis, some resulting in respiratory failure or patient deaths, may be induced or aggravated by PegIntron or alpha interferon therapy. Recurrence of respiratory failure has been observed with interferon rechallenge. PegIntron combination treatment should be suspended in patients who develop pulmonary infiltrates or pulmonary function impairment. Patients who resume interferon treatment should be closely monitored.

Because of the fever and other "flu-like" symptoms associated with PegIntron administration, it should be used cautiously in patients with debilitating medical conditions, such as those with a history of pulmonary disease (e.g., chronic obstructive pulmonary disease).

5.12 Hepatic Failure

Chronic Hepatitis C (CHC) patients with cirrhosis may be at risk of hepatic decompensation and death when treated with alpha interferons, including PegIntron. Cirrhotic CHC patients co-infected with HIV receiving highly active antiretroviral therapy (HAART) and alpha interferons with or without ribavirin appear to be at increased risk for the development of hepatic decompensation compared to patients not receiving HAART. During treatment, patients' clinical status and hepatic function should be closely monitored, and PegIntron treatment should be immediately discontinued if decompensation (Child-Pugh score greater than 6) is observed *[see Contraindications (4)]*.

5.13 Patients with Renal Insufficiency

Increases in serum creatinine levels have been observed in patients with renal insufficiency receiving interferon alpha products, including PegIntron. Patients with impaired renal function should be closely monitored for signs and symptoms of interferon toxicity, including increases in serum creatinine, and PegIntron dosing should be adjusted accordingly or discontinued *[see Clinical Pharmacology (12.3) and Dosage and Administration (2.3)]*. PegIntron monotherapy should be used with caution in patients with creatinine clearance less than 50 mL/min; the potential risks should be weighed against the potential benefits in these patients. Combination therapy with ribavirin must not be used in patients with creatinine clearance less than 50 mL/min *[see ribavirin labeling]*.

5.14 Hypersensitivity

Serious, acute hypersensitivity reactions (e.g., urticaria, angioedema, bronchoconstriction, anaphylaxis) and cutaneous eruptions (Stevens-Johnson syndrome, toxic epidermal necrolysis) have been rarely observed during alpha interferon therapy. If such a reaction develops during treatment with PegIntron, discontinue treatment and institute appropriate medical therapy immediately. Transient rashes do not necessitate interruption of treatment.

5.15 Laboratory Tests

PegIntron alone or in combination with ribavirin may cause severe decreases in neutrophil and platelet counts, and hematologic, endocrine (e.g., TSH), and hepatic abnormalities. Transient elevations in ALT (2- to 5-fold above baseline) were observed in 10% of subjects treated with PegIntron, and were not associated with deterioration of other liver functions. Triglyceride

levels are frequently elevated in patients receiving alpha interferon therapy including PegIntron and should be periodically monitored.

Patients on PegIntron or PegIntron/REBETOL combination therapy should have hematology and blood chemistry testing before the start of treatment and then periodically thereafter. In the adult clinical trial, complete blood counts (including hemoglobin, neutrophil, and platelet counts) and chemistries (including AST, ALT, bilirubin, and uric acid) were measured during the treatment period at Weeks 2, 4, 8, and 12, and then at 6-week intervals, or more frequently if abnormalities developed. In pediatric subjects, the same laboratory parameters were evaluated with additional assessment of hemoglobin at treatment Week 6. TSH levels were measured every 12 weeks during the treatment period. HCV-RNA should be measured periodically during treatment *[see Dosage and Administration (2.1, 2.2, 2.4)]*.

Patients who have pre-existing cardiac abnormalities should have electrocardiograms done before treatment with PegIntron/ribavirin.

5.16 Dental and Periodontal Disorders

Dental and periodontal disorders have been reported in patients receiving PegIntron/REBETOL combination therapy. In addition, dry mouth could have a damaging effect on teeth and mucous membranes of the mouth during long-term treatment with the combination of REBETOL and PegIntron. Patients should brush their teeth thoroughly twice daily and have regular dental examinations. If vomiting occurs, patients should be advised to rinse out their mouth thoroughly afterwards.

5.17 Triglycerides

Elevated triglyceride levels have been observed in patients treated with interferon alpha, including PegIntron therapy. Hypertriglyceridemia may result in pancreatitis *[see Warnings and Precautions (5.9)]*. Elevated triglyceride levels should be managed as clinically appropriate. Discontinuation of PegIntron therapy should be considered for patients with symptoms of potential pancreatitis, such as abdominal pain, nausea, or vomiting, and persistently elevated triglycerides (e.g., triglycerides greater than 1000 mg/dL).

5.18 Impact on Growth — Pediatric Use

Data on the effects of PegIntron plus REBETOL on growth come from an open-label trial in 107 subjects, 3 through 17 years of age, in which weight and height changes are compared to US normative population data. In general, the weight and height gain of pediatric subjects treated with PegIntron plus REBETOL lags behind that predicted by normative population data for the entire length of treatment. Severely inhibited growth velocity (less than 3rd percentile) was observed in 70% of the subjects while on treatment. Following treatment, rebound growth and weight gain occurred in most subjects. Long-term follow-up data in pediatric subjects, however, indicates that PegIntron in combination therapy with REBETOL may induce a growth inhibition that results in reduced adult height in some patients *[see Adverse Reactions (6.1)].*

5.19 Peripheral Neuropathy

Peripheral neuropathy has been reported when alpha interferons were given in combination with telbivudine. In one clinical trial, an increased risk and severity of peripheral neuropathy was observed with the combination use of telbivudine and pegylated interferon alfa-2a as compared to telbivudine alone. The safety and efficacy of telbivudine in combination with interferons for the treatment of chronic hepatitis B has not been demonstrated.

6 ADVERSE REACTIONS

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 clinical practice.

Clinical trials with PegIntron alone or in combination with REBETOL have been conducted in over 6900 subjects from 3 to 75 years of age.

Serious adverse reactions have occurred in approximately 12% of subjects in clinical trials with PegIntron with or without REBETOL *[see Warnings and Precautions (5)]*. The most common serious events occurring in subjects treated with PegIntron and REBETOL were depression and suicidal ideation *[see Warnings and Precautions (5.2)],* each occurring at a frequency of less than 1%. The most common fatal events occurring in subjects treated with PegIntron and REBETOL were cardiac arrest, suicidal ideation, and suicide attempt *[see Warnings and Precautions (5.2, 5.3)]*, all occurring in less than 1% of subjects.

Greater than 96% of all subjects in clinical trials experienced one or more adverse events. The most commonly reported adverse reactions in adult subjects receiving either PegIntron or PegIntron/REBETOL were injection-site inflammation/reaction, fatigue/asthenia, headache, rigors, fevers, nausea, myalgia, and emotional lability/irritability. The most common adverse events in pediatric subjects, ages 3 and older, were pyrexia, headache, vomiting, neutropenia, fatigue, anorexia, injection-site erythema, and abdominal pain.

Adults

Study 1 compared PegIntron monotherapy with INTRON® A monotherapy. Study 2 compared combination therapy of PegIntron/REBETOL with combination therapy with INTRON A/REBETOL. In these clinical trials, nearly all subjects experienced one or more adverse reactions. Study 3 compared a PegIntron/weight-based REBETOL combination to a PegIntron/flat dose REBETOL regimen. Study 4 compared two PegIntron (1.5 mcg/kg/week and 1 mcg/kg/week) doses in combination with REBETOL and a third treatment group receiving Pegasys® (180 mcg/week)/Copegus® (1000-1200 mg/day).

Adverse reactions that occurred in Studies 1 and 2 at greater than 5% incidence are provided in **Table 8** by treatment group. Due to potential differences in ascertainment procedures, adverse reaction rate comparisons across trials should not be made. **Table 9** summarizes the treatment-related adverse reactions in Study 4 that occurred at a greater than or equal to 10% incidence.

Table 8: Adverse Reactions Occurring in Greater than 5% of Subjects

	*Percentage of Subjects Reporting Adverse Reactions**			
	Study 1		**Study 2**	
Adverse Reactions	**PegIntron 1 mcg/kg (N=297)**	**INTRON A 3 MIU (N=303)**	**PegIntron 1.5 mcg/kg/ REBETOL (N=511)**	**INTRON A/ REBETOL (N=505)**
Application Site				
Injection Site Inflammation/Reaction	47	20	75	49
Autonomic Nervous System				
Dry Mouth	6	7	12	8
Increased Sweating	6	7	11	7
Flushing	6	3	4	3
Body as a Whole				
Fatigue/Asthenia	52	54	66	63
Headache	56	52	62	58
Rigors	23	19	48	41
Fever	22	12	46	33
Weight Loss	11	13	29	20
Right Upper Quadrant Pain	8	8	12	6
Chest Pain	6	4	8	7
Malaise	7	6	4	6
Central/Peripheral Nervous System				
Dizziness	12	10	21	17
Endocrine				
Hypothyroidism	5	3	5	4
Gastrointestinal				
Nausea	26	20	43	33
Anorexia	20	17	32	27
Diarrhea	18	16	22	17
Vomiting	7	6	14	12
Abdominal Pain	15	11	13	13
Dyspepsia	6	7	9	8
Constipation	1	3	5	5
Hematologic Disorders				
Neutropenia	6	2	26	14
Anemia	0	0	12	17
Leukopenia	<1	0	6	5
Thrombocytopenia	7	<1	5	2
Liver and Biliary System				
Hepatomegaly	6	5	4	4
Musculoskeletal				
Myalgia	54	53	56	50
Arthralgia	23	27	34	28
Musculoskeletal Pain	28	22	21	19
Psychiatric				
Insomnia	23	23	40	41
Depression	29	25	31	34
Anxiety/Emotional Lability/Irritability	28	34	47	47
Concentration Impaired	10	8	17	21
Agitation	2	2	8	5
Nervousness	4	3	6	6
Reproductive, Female				
Menstrual Disorder	4	3	7	6

	*Percentage of Subjects Reporting Adverse Reactions**			
	Study 1		**Study 2**	
Adverse Reactions	**PegIntron 1 mcg/kg (N=297)**	**INTRON A 3 MIU (N=303)**	**PegIntron 1.5 mcg/kg/ REBETOL (N=511)**	**INTRON A/ REBETOL (N=505)**
Resistance Mechanism				
Viral Infection	11	10	12	12
Fungal Infection	<1	3	6	1
Respiratory System				
Dyspnea	4	2	26	24
Coughing	8	5	23	16
Pharyngitis	10	7	12	13
Rhinitis	2	2	8	6
Sinusitis	7	7	6	5
Skin and Appendages				
Alopecia	22	22	36	32
Pruritus	12	8	29	28
Rash	6	7	24	23
Skin Dry	11	9	24	23
Special Senses, Other				
Taste Perversion	<1	2	9	4
Vision Disorders				
Vision Blurred	2	3	5	6
Conjunctivitis	4	2	4	5

*Subjects reporting one or more adverse reactions. A subject may have reported more than one adverse reaction within a body system/organ class category.

Table 9: Treatment-Related Adverse Reactions (Greater than or Equal to 10% Incidence) By Descending Frequency

Adverse Reactions	*Percentage of Subjects Reporting Treatment-Related Adverse Reactions* Study 4		
	PegIntron 1.5 mcg/kg with REBETOL	**PegIntron 1 mcg/kg with REBETOL**	**Pegasys 180 mcg with Copegus**
	(N=1019)	**(N=1016)**	**(N=1035)**
Fatigue	67	68	64
Headache	50	47	41
Nausea	40	35	34
Chills	39	36	23
Insomnia	38	37	41
Anemia	35	30	34
Pyrexia	35	32	21
Injection Site Reactions	34	35	23
Anorexia	29	25	21
Rash	29	25	34
Myalgia	27	26	22
Neutropenia	26	19	31
Irritability	25	25	25
Depression	25	19	20
Alopecia	23	20	17
Dyspnea	21	20	22
Arthralgia	21	22	22
Pruritus	18	15	19
Influenza-like Illness	16	15	15
Dizziness	16	14	13
Diarrhea	15	16	14
Cough	15	16	17
Weight Decreased	13	10	10
Vomiting	12	10	9
Unspecified Pain	12	13	9
Dry Skin	11	11	12
Anxiety	11	11	10
Abdominal Pain	10	10	10
Leukopenia	9	7	10

The adverse reaction profile in Study 3, which compared PegIntron/weight-based REBETOL combination to a PegIntron/flat-dose REBETOL regimen, revealed an increased rate of anemia with weight-based dosing (29% vs. 19% for weight-based vs. flat-dose regimens, respectively). However, the majority of cases of anemia were mild and responded to dose reductions.

The incidence of serious adverse reactions was comparable in all trials. In the PegIntron monotherapy trial (Study 1) the incidence of serious adverse reactions was similar (about 12%) in all treatment groups. In Study 2, the incidence of serious adverse reactions was 17% in the PegIntron/REBETOL groups compared to 14% in the INTRON A/REBETOL group. In Study 3, there was a similar incidence of serious adverse reactions reported for the weight-based REBETOL group (12%) and for the flat-dose REBETOL regimen.

In many but not all cases, adverse reactions resolved after dose reduction or discontinuation of therapy. Some subjects experienced ongoing or new serious adverse reactions during the 6-month follow-up period.

There have been 31 subject deaths that occurred during treatment or during follow-up in these clinical trials. In Study 1, there was 1 suicide in a subject receiving PegIntron monotherapy and 2 deaths among subjects receiving INTRON A monotherapy (1 murder/suicide and 1 sudden death). In Study 2, there was 1 suicide in a subject receiving PegIntron/REBETOL combination therapy, and 1 subject death in the INTRON A/REBETOL group (motor vehicle accident). In Study 3, there were 14 deaths, 2 of which were probable suicides, and 1 was an unexplained death in a person with a relevant medical history of depression. In Study 4, there were 12 deaths, 6 of which occurred in subjects receiving PegIntron/REBETOL combination therapy; 5 in the PegIntron 1.5 mcg/REBETOL arm (N=1019) and 1 in the PegIntron 1 mcg/REBETOL arm (n=1016); and 6 of which occurred in subjects receiving Pegasys/Copegus (N=1035). There were 3 suicides that occurred during the off-treatment follow-up period in subjects who received PegIntron (1.5 mcg/kg)/REBETOL combination therapy.

In Studies 1 and 2, 10% to 14% of subjects receiving PegIntron, alone or in combination with REBETOL, discontinued therapy compared with 6% treated with INTRON A alone and 13% treated with INTRON A in combination with REBETOL. Similarly in Study 3, 15% of subjects receiving PegIntron in combination with weight-based REBETOL and 14% of subjects receiving PegIntron and flat-dose REBETOL discontinued therapy due to an adverse reaction. The most common reasons for discontinuation of therapy were related to known interferon effects of psychiatric, systemic (e.g., fatigue, headache), or gastrointestinal adverse reactions. In Study 4, 13% of subjects in the PegIntron 1.5 mcg/REBETOL arm, 10% in the PegIntron 1 mcg/REBETOL arm, and 13% in the Pegasys 180 mcg/Copegus arm discontinued therapy due to adverse events.

In Study 2, dose reductions due to adverse reactions occurred in 42% of subjects receiving PegIntron (1.5 mcg/kg)/REBETOL and in 34% of those receiving INTRON A/REBETOL. The majority of subjects (57%) weighing 60 kg or less receiving PegIntron (1.5 mcg/kg)/REBETOL required dose reduction. Reduction of interferon was dose-related (PegIntron 1.5 mcg/kg more than PegIntron 0.5 mcg/kg or INTRON A), 40%, 27%, 28%, respectively. Dose reduction for REBETOL was similar across all three groups, 33% to 35%. The most common reasons for dose modifications were neutropenia (18%) or anemia (9%). Other common reasons included depression, fatigue, nausea, and thrombocytopenia. In Study 3, dose modifications due to adverse reactions occurred more frequently with weight-based dosing (WBD) compared to flat dosing (29% and 23%, respectively). In Study 4, 16% of subjects had a dose reduction of PegIntron to 1 mcg/kg in combination with REBETOL, with an additional 4% requiring the second dose reduction of PegIntron to 0.5 mcg/kg due to adverse events, compared to 15% of subjects in the Pegasys/Copegus arm, who required a dose reduction to 135 mcg/week with Pegasys, with an additional 7% requiring a second dose reduction to 90 mcg/week with Pegasys.

In the PegIntron/REBETOL combination trials the most common adverse reactions were psychiatric, which occurred among 77% of subjects in Study 2 and 68% to 69% of subjects in Study 3. These psychiatric adverse reactions included most commonly depression, irritability, and insomnia, each reported by approximately 30% to 40% of subjects in all treatment groups. Suicidal behavior (ideation, attempts, and suicides) occurred in 2% of all subjects during treatment or during follow-up after treatment cessation *[see Warnings and Precautions (5.2)]*. In Study 4, psychiatric adverse reactions occurred in 58% of subjects in the PegIntron 1.5 mcg/REBETOL arm, 55% of subjects in the PegIntron 1 mcg/REBETOL arm, and 57% of subjects in the Pegasys 180 mcg/Copegus arm.

PegIntron induced fatigue or headache in approximately two-thirds of subjects, with fever or rigors in approximately half of the subjects. The severity of some of these systemic symptoms (e.g., fever and headache) tended to decrease as treatment continued. In Studies 1 and 2, application site inflammation and reaction (e.g., bruise, itchiness, and irritation) occurred at approximately twice the incidence with PegIntron therapies (in up to 75% of subjects) compared with INTRON A. However, injection-site pain was infrequent (2-3%) in all groups. In Study 3, there was a 23% to 24% incidence overall for injection-site reactions or inflammation.

In Study 2, many subjects continued to experience adverse reactions several months after discontinuation of therapy. By the end of the 6-month follow-up period, the incidence of ongoing adverse reactions by body class in the PegIntron 1.5/REBETOL group was 33% (psychiatric), 20% (musculoskeletal), and 10% (for endocrine and for GI). In approximately 10% to 15% of subjects, weight loss, fatigue, and headache had not resolved.

Individual serious adverse reactions in Study 2 occurred at a frequency less than or equal to 1% and included suicide attempt, suicidal ideation, severe depression; psychosis, aggressive reaction, relapse of drug addiction/overdose; nerve palsy (facial, oculomotor); cardiomyopathy, myocardial infarction, angina, pericardial effusion, retinal ischemia, retinal artery or vein thrombosis, blindness, decreased visual acuity, optic neuritis, transient ischemic attack, supraventricular arrhythmias, loss of consciousness; neutropenia, infection (sepsis, pneumonia, abscess, cellulitis); emphysema, bronchiolitis obliterans, pleural effusion, gastroenteritis, pancreatitis, gout, hyperglycemia, hyperthyroidism and hypothyroidism, autoimmune thrombocytopenia with or without purpura, rheumatoid arthritis, interstitial nephritis, lupus-like syndrome, sarcoidosis, aggravated psoriasis; urticaria, injection-site necrosis, vasculitis, and phototoxicity.

Subjects receiving PegIntron/REBETOL as re-treatment after failing a previous interferon combination regimen reported adverse reactions similar to those previously associated with this regimen during clinical trials of treatment-naïve subjects.

Pediatric Subjects

In general, the adverse-reaction profile in the pediatric population was similar to that observed in adults. In the pediatric trial, the most prevalent adverse reactions in all subjects were pyrexia (80%), headache (62%), neutropenia (33%), fatigue (30%), anorexia (29%), injection-site erythema (29%), and vomiting (27%). The majority of adverse reactions reported in the trial were mild or moderate in severity. Severe adverse reactions were reported in 7% (8/107) of all subjects and included injection-site pain (1%),

pain in extremity (1%), headache (1%), neutropenia (1%), and pyrexia (4%). Important adverse reactions that occurred in this subject population were nervousness (7%; 7/107), aggression (3%; 3/107), anger (2%; 2/107), and depression (1%; 1/107). Five subjects received levothyroxine treatment; three with clinical hypothyroidism and two with asymptomatic TSH elevations. Weight and height gain of pediatric subjects treated with PegIntron plus REBETOL lagged behind that predicted by normative population data for the entire length of treatment. Severely inhibited growth velocity (less than 3rd percentile) was observed in 70% of the subjects while on treatment.

Dose modifications were required in 25% of subjects, most commonly for anemia, neutropenia, and weight loss. Two subjects (2%; 2/107) discontinued therapy as the result of an adverse reaction.

Adverse reactions that occurred with a greater than or equal to 10% incidence in the pediatric trial subjects are provided in **Table 10**.

Table 10: Percentage of Pediatric Subjects with Treatment-related Adverse Reactions (in At Least 10% of All Subjects)

System Organ Class Preferred Term	All Subjects N=107
Blood and Lymphatic System Disorders	
Neutropenia	33%
Anemia	11%
Leukopenia	10%
Gastrointestinal Disorders	
Abdominal Pain	21%
Abdominal Pain Upper	12%
Vomiting	27%
Nausea	18%
General Disorders and Administration Site Conditions	
Pyrexia	80%
Fatigue	30%
Injection-site Erythema	29%
Chills	21%
Asthenia	15%
Irritability	14%
Investigations	
Weight Decreased	19%
Metabolism and Nutrition Disorders	
Anorexia	29%
Decreased Appetite	22%
Musculoskeletal and Connective Tissue Disorders	
Arthralgia	17%
Myalgia	17%
Nervous System Disorders	
Headache	62%
Dizziness	14%
Skin and Subcutaneous Tissue Disorders	
Alopecia	17%

Ninety-four of 107 subjects enrolled in a 5 year long-term follow-up trial. The long-term effects on growth were less in those subjects treated for 24 weeks than those treated for 48 weeks. Twenty-four percent of subjects (11/46) treated for 24 weeks and 40% of subjects (19/48) treated for 48 weeks had a >15 percentile height-for-age decrease from pre-treatment to the end of the 5 year long-term follow-up compared to pre-treatment baseline percentiles. Eleven percent of subjects (5/46) treated for 24 weeks and 13% of subjects (6/48) treated for 48 weeks were observed to have a decrease from pre-treatment baseline of >30 height-for-age percentiles to the end of the 5 year long-term follow-up. While observed across all age groups, the highest risk for reduced height at the end of long-term follow-up appeared to correlate with initiation of combination therapy during the years of expected peak growth velocity *[see Warnings and Precautions (5.18)]*.

Laboratory Values
Adults

Changes in selected laboratory values during treatment with PegIntron alone or in combination with REBETOL treatment are described below**. Decreases in hemoglobin, neutrophils, and platelets may require dose reduction or permanent discontinuation from therapy** *[see Dosage and Administration (2.3) and Warnings and Precautions (5.1, 5.7)]***.**

Hemoglobin. Hemoglobin levels decreased to less than 11 g/dL in about 30% of subjects in Study 2. In Study 3, 47% of subjects receiving WBD REBETOL and 33% on flat-dose REBETOL had decreases in hemoglobin levels less than 11 g/dL. Reductions in hemoglobin to less than 9 g/dL occurred more frequently in subjects receiving WBD compared to flat dosing (4% and 2%, respectively). In Study 2, dose modification was required in 9% and 13% of subjects in the PegIntron/REBETOL and INTRON A/REBETOL groups. In Study 4, subjects receiving PegIntron (1.5 mcg/kg)/REBETOL had decreases in hemoglobin levels to between 8.5 to less than 10 g/dL (28%) and to less than 8.5 g/dL (3%), whereas in subjects receiving Pegasys 180 mcg/Copegus these decreases occurred in 26% and 4% of subjects, respectively. Hemoglobin levels became stable by treatment Weeks 4 to 6 on average. The typical pattern observed was a decrease in hemoglobin levels by treatment Week 4 followed by stabilization and a plateau, which was maintained to the end of treatment. In the PegIntron monotherapy trial, hemoglobin decreases were generally mild and dose modifications were rarely necessary *[see Dosage and Administration (2.3)]*.

Neutrophils. Decreases in neutrophil counts were observed in a majority of subjects treated with PegIntron alone (70%) or as combination therapy with REBETOL in Study 2 (85%) and INTRON A/REBETOL (60%). Severe potentially life-threatening neutropenia (less than 0.5 x 10^9/L) occurred in 1% of subjects treated with PegIntron monotherapy, 2% of subjects treated with INTRON A/REBETOL, and in approximately 4% of subjects treated with PegIntron/REBETOL in Study 2. Two percent of subjects receiving PegIntron monotherapy and 18% of subjects receiving PegIntron/REBETOL in Study 2 required modification of interferon dosage. Few subjects (less than 1%) required permanent discontinuation of treatment. Neutrophil counts generally returned to pretreatment levels 4 weeks after cessation of therapy *[see Dosage and Administration (2.3)]*.

Platelets. Platelet counts decreased to less than 100,000/mm^3 in approximately 20% of subjects treated with PegIntron alone or with REBETOL and in 6% of subjects treated with INTRON A/REBETOL. Severe decreases in platelet counts (less than 50,000/mm^3) occur in less than 4% of subjects. Patients may require discontinuation or dose modification as a result of platelet decreases *[see Dosage and Administration (2.3)]*. In Study 2, 1% or 3% of subjects required dose modification of INTRON A or PegIntron, respectively. Platelet counts generally returned to pretreatment levels 4 weeks after the cessation of therapy.

Triglycerides. Elevated triglyceride levels have been observed in patients treated with interferon alphas, including PegIntron *[see Warnings and Precautions (5.17)].*

Thyroid Function. Development of TSH abnormalities, with or without clinical manifestations, is associated with interferon therapies. In Study 2, clinically apparent thyroid disorders occurred among subjects treated with either INTRON A or PegIntron (with or without REBETOL) at a similar incidence (5% for hypothyroidism and 3% for hyperthyroidism). Subjects developed new-onset TSH abnormalities while on treatment and during the follow-up period. At the end of the follow-up period, 7% of subjects still had abnormal TSH values *[see Warnings and Precautions (5.4)].*

Bilirubin and Uric Acid. In Study 2, 10% to 14% of subjects developed hyperbilirubinemia and 33% to 38% developed hyperuricemia in association with hemolysis. Six subjects developed mild to moderate gout.

Pediatric Subjects

Decreases in hemoglobin, white blood cells, platelets, and neutrophils may require dose reduction or permanent discontinuation from therapy *[see Dosage and Administration (2.3)]***.** Changes in selected laboratory values during treatment of 107 pediatric subjects with PegIntron/REBETOL combination therapy are described in **Table 11.** Most of the changes in laboratory values in this trial were mild or moderate.

Table 11: Selected Laboratory Abnormalities during Treatment Phase with PegIntron Plus REBETOL in Previously Untreated Pediatric Subjects

Laboratory Parameter*	All Subjects (N=107)
Hemoglobin (g/dL)	
9.5 to <11.0	30%
8.0 to <9.5	2%
WBC (x 10^9/L)	
2.0-2.9	39%
1.5 to <2.0	3%
Platelets (x 10^9/L)	
70-100	1%
50 to <70	—
25 to <50	1%
Neutrophils (x 10^9/L)	
1.0-1.5	35%
0.75 to <1.0	26%
0.5 to <0.75	13%
<0.5	3%
Total Bilirubin	
1.26-2.59 x ULN†	7%
Evidence of Hepatic Failure	—

* The table summarizes the worst category observed within the period per subject per laboratory

test. Only subjects with at least one treatment value for a given laboratory test are included.
† ULN=Upper limit of normal.

6.2 Immunogenicity

As with all therapeutic proteins, there is potential for immunogenicity. Approximately 2% of subjects receiving PegIntron (32/1759) or INTRON A (11/728) with or without REBETOL developed low-titer (less than or equal to 160) neutralizing antibodies to PegIntron or INTRON A. The clinical and pathological significance of the appearance of serum-neutralizing antibodies is unknown. The incidence of antibody formation is highly dependent on the sensitivity and specificity of the assay. Additionally, the observed incidence of antibody (including neutralizing antibody) positivity in an assay may be influenced by several factors, including assay methodology, sample handling, timing of sample collection, concomitant medications, and underlying disease. For these reasons, comparison of the incidence of antibodies to PegIntron with the incidence of antibodies to other products may be misleading.

6.3 Postmarketing Experience

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

Blood and Lymphatic System Disorders
Pure red cell aplasia, thrombotic thrombocytopenic purpura
Cardiac Disorders
Palpitations
Ear and Labyrinth Disorders
Hearing loss, vertigo, hearing impairment
Endocrine Disorders
Diabetic ketoacidosis, diabetes
Eye Disorders
Vogt-Koyanagi-Harada syndrome, serous retinal detachment
Gastrointestinal Disorders
Aphthous stomatitis
General Disorders and Administration Site Conditions
Asthenic conditions (including asthenia, malaise, fatigue)
Immune System Disorders
Cases of acute hypersensitivity reactions (including anaphylaxis, angioedema, urticaria); Stevens-Johnson syndrome, toxic epidermal necrolysis, systemic lupus erythematosus, erythema multiforme
Infections and Infestations
Bacterial infection including sepsis, Hepatitis B virus reactivation in HCV/HBV co-infected patients
Metabolism and Nutrition Disorders
Dehydration, hypertriglyceridemia
Musculoskeletal and Connective Tissue Disorders
Rhabdomyolysis, myositis
Nervous System Disorders
Seizures, memory loss, peripheral neuropathy, paraesthesia, migraine headache
Psychiatric Disorders
Homicidal ideation
Respiratory, Thoracic, and Mediastinal Disorders
Pulmonary hypertension, pulmonary fibrosis
Renal and Urinary Disorders
Renal failure, renal insufficiency
Skin and Subcutaneous Tissue Disorders
Psoriasis
Vascular Disorders
Hypertension, hypotension

7 DRUG INTERACTIONS

7.1 Drugs Metabolized by Cytochrome P-450

Peginterferon alfa-2b inhibits CYP1A2 and CYP2D6 activity. Drugs with a narrow therapeutic range metabolized by CYP1A2 (caffeine) or CYP2D6 (thioridazine) should be administered with caution when coadministered with PegIntron (**Table 12**). *[See Clinical Pharmacology (12.3).]*

Table 12: Established and Other Potentially Significant Drug Interactions: Alterations in Dose or Regimen May Be Recommended Based on Drug Interaction Studies or Predicted Interaction

Drugs	Effect on Concentration	Clinical Comment
Antiretroviral Agents: Nucleoside Reverse Transcriptase Inhibitors (NRTIs): zidovudine	↔ zidovudine	Monitor blood cell count and suppressive effect on bone marrow function when zidovudine is coadministered with PegIntron.
Immunosuppressants: e.g., cyclosporine	Effect on immunosuppressants unknown	Therapeutic monitoring of the immunosuppressive agents is recommended upon coadministration

sirolimus tacrolimus		with PegIntron.
Narcotic Analgesics: methadone	↑ methadone	Methadone dosage may need to be reduced when coadministered with PegIntron.
Neuroleptics: thioridazine	↑ thioridazine	Monitor for thioridazine adverse events when coadministered with PegIntron.
Xanthines: theophylline	↑ theophylline	Monitor for theophylline adverse events when coadministered with PegIntron.

7.2 Use with Ribavirin (Nucleoside Analogues)

Hepatic decompensation (some fatal) has occurred in cirrhotic HIV/HCV co-infected patients receiving combination antiretroviral therapy for HIV and interferon alpha and ribavirin. Adding treatment with alpha interferons alone or in combination with ribavirin may increase the risk in this patient subset. Patients receiving interferon with ribavirin and nucleoside reverse transcriptase inhibitors (NRTIs) should be closely monitored for treatment- associated toxicities, especially hepatic decompensation and anemia. Discontinuation of NRTIs should be considered as medically appropriate *[see labeling for individual NRTI product]*. Dose reduction or discontinuation of interferon, ribavirin, or both should also be considered if worsening clinical toxicities are observed, including hepatic decompensation (e.g., Child-Pugh greater than 6).

Stavudine, Lamivudine, and Zidovudine

In vitro studies have shown ribavirin can reduce the phosphorylation of pyrimidine nucleoside analogues such as stavudine, lamivudine, and zidovudine. In a trial with another pegylated interferon alpha, no evidence of a pharmacokinetic or pharmacodynamic (e.g., loss of HIV/HCV virologic suppression) interaction was seen when ribavirin was co-administered with zidovudine, lamivudine, or stavudine in HIV/HCV co-infected subjects *[see Clinical Pharmacology (12.3)]*.

HIV/HCV co-infected subjects who were administered zidovudine in combination with pegylated interferon alpha and ribavirin developed severe neutropenia (ANC less than 500) and severe anemia (hemoglobin less than 8 g/dL) more frequently than similar subjects not receiving zidovudine *(see **Table 12**)*.

Didanosine

Co-administration of ribavirin and didanosine is not recommended. Reports of fatal hepatic failure, as well as peripheral neuropathy, pancreatitis, and symptomatic hyperlactatemia/lactic acidosis have been reported in clinical trials *[see Clinical Pharmacology (12.3)]***.**

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

PegIntron Monotherapy

Pregnancy Category C: Nonpegylated interferon alfa-2b has been shown to have abortifacient effects in *Macaca mulatta* (rhesus monkeys) at 15 and 30 million IU/kg (estimated human equivalent of 5 and 10 million IU/kg, based on body surface area adjustment for a 60-kg adult). PegIntron should be assumed to also have abortifacient potential. There are no adequate and well-controlled trials in pregnant women. PegIntron therapy is to be used during pregnancy only if the potential benefit justifies the potential risk to the fetus. Therefore, PegIntron is recommended for use in fertile women only when they are using effective contraception during the treatment period.

Use with Ribavirin

Pregnancy Category X: Significant teratogenic and/or embryocidal effects have been demonstrated in all animal species exposed to ribavirin. Ribavirin therapy is contraindicated in women who are pregnant and in the male partners of women who are pregnant *[see Contraindications (4) and ribavirin labeling]***.**

A Ribavirin Pregnancy Registry has been established to monitor maternal-fetal outcomes of pregnancies in female patients and female partners of male patients exposed to ribavirin during treatment and for 6 months following cessation of treatment. Physicians and patients are encouraged to report such cases by calling 1-800-593-2214.

8.3 Nursing Mothers

It is not known whether the components of PegIntron and/or ribavirin are excreted in human milk. Studies in mice have shown that mouse interferons are excreted in breast milk. Because of the potential for adverse reactions from the drug in nursing infants, a decision must be made whether to discontinue nursing or discontinue the PegIntron and ribavirin treatment, taking into account the importance of the therapy to the mother.

8.4 Pediatric Use

Safety and effectiveness in pediatric patients below the age of 3 years have not been established. Clinical trials in pediatric subjects less than 3 years of age are not considered feasible due to the small proportion of patients in this age group requiring treatment for CHC.

Long-term follow-up data in pediatric subjects indicates that PegIntron in combination with REBETOL may induce a growth inhibition that results in reduced height in some patients *[see Warnings and Precautions (5.18) and Adverse Reactions (6.1)]*.

8.5 Geriatric Use

In general, younger patients tend to respond better than older patients to interferon-based therapies. Clinical trials of PegIntron alone or in combination with REBETOL did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently than younger subjects. Treatment with alpha interferons, including PegIntron, is associated with neuropsychiatric, cardiac, pulmonary, GI, and systemic (flu-like) adverse effects. Because these adverse reactions may be more severe in the elderly, caution should be exercised in the use of PegIntron in this population. This drug is known to be substantially excreted by the kidney. Because elderly patients are more likely to have decreased renal function, the risk of toxic reactions to this drug may be greater in patients with impaired renal function *[see Clinical Pharmacology (12.3)]*. When using PegIntron/ ribavirin therapy, refer also to the ribavirin labeling.

8.6 Organ Transplant Recipients

The safety and efficacy of PegIntron alone or in combination with ribavirin for the treatment of hepatitis C in liver or other organ transplant recipients have not been studied. In a small (n=16) single-center, uncontrolled case experience, renal failure in renal allograft recipients receiving interferon alpha and ribavirin combination therapy was more frequent than expected from the center's previous experience with renal allograft recipients not receiving combination therapy. The relationship of the renal failure to renal allograft rejection is not clear.

8.7 HIV or HBV Co-infection

The safety and efficacy of PegIntron/ ribavirin for the treatment of patients with HCV co-infected with HIV or HBV have not been established.

10 OVERDOSAGE

There is limited experience with overdosage. In the clinical trials, a few subjects accidentally received a dose greater than that prescribed. There were no instances in which a participant in the monotherapy or combination therapy trials received more than 10.5 times the intended dose of PegIntron. The maximum dose received by any subject was 3.45 mcg/kg weekly over a period of approximately 12 weeks. The maximum known overdosage of ribavirin was an intentional ingestion of 10 g (fifty 200 mg capsules). There were no serious reactions attributed to these overdosages. In cases of overdosing, symptomatic treatment and close observation of the patient are recommended.

11 DESCRIPTION

PegIntron, peginterferon alfa-2b, is a covalent conjugate of recombinant alfa-2b interferon with monomethoxy polyethylene glycol (PEG). The average molecular weight of the PEG portion of the molecule is 12,000 daltons. The average molecular weight of the PegIntron molecule is approximately 31,000 daltons. The specific activity of peginterferon alfa-2b is approximately 0.7 x 10^8 IU/mg protein.

Interferon alfa-2b is a water-soluble protein with a molecular weight of 19,271 daltons produced by recombinant DNA techniques. It is obtained from the bacterial fermentation of a strain of *Escherichia coli* bearing a genetically engineered plasmid containing an interferon gene from human leukocytes.

PegIntron is supplied in both vials and the REDIPEN single-use pre-filled pen for subcutaneous use.

Vials

Each vial contains either 74 mcg, 118.4 mcg, 177.6 mcg, or 222 mcg of PegIntron as a white to off-white tablet-like solid that is whole/in pieces or as a loose powder, and 1.11 mg dibasic sodium phosphate anhydrous, 1.11 mg monobasic sodium phosphate dihydrate, 59.2 mg sucrose, and 0.074 mg polysorbate 80. Following reconstitution with 0.7 mL of the supplied Sterile Water for Injection USP, each vial contains PegIntron at strengths of either 50 mcg per 0.5 mL, 80 mcg per 0.5 mL, 120 mcg per 0.5 mL, or 150 mcg per 0.5 mL.

REDIPEN single-use pre-filled pen

REDIPEN pre-filled pen is a dual-chamber glass cartridge containing lyophilized PegIntron as a white to off-white tablet or powder that is whole or in pieces in the sterile active chamber and a second chamber containing Sterile Water for Injection USP. Each PegIntron REDIPEN pre-filled pen contains either 67.5 mcg, 108 mcg, 162 mcg, or 202.5 mcg of PegIntron, and 1.013 mg dibasic sodium phosphate anhydrous, 1.013 mg monobasic sodium phosphate dihydrate, 54 mg sucrose, and 0.0675 mg polysorbate 80. Each cartridge is reconstituted to allow for the administration of up to 0.5 mL of solution. Following reconstitution, each REDIPEN pre-filled pen contains PegIntron at strengths of either 50 mcg per 0.5 mL, 80 mcg per 0.5 mL, 120 mcg per 0.5 mL, or 150 mcg per 0.5 mL for a single use. Because a small volume of reconstituted solution is lost during preparation of PegIntron, each REDIPEN pre-filled pen contains an excess amount of PegIntron powder and diluent to ensure delivery of the labeled dose.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Pegylated recombinant human interferon alfa-2b is an inducer of the innate antiviral immune response *[see Microbiology (12.4)].*

12.2 Pharmacodynamics

The pharmacodynamic effects of peginterferon alfa-2b include inhibition of viral replication in virus-infected cells, the suppression of cell cycle progression/cell proliferation, induction of apoptosis, anti-angiogenic activities, and numerous immunomodulating activities, such as enhancement of the phagocytic activity of macrophages, activation of NK cells, stimulation of cytotoxic T-lymphocytes, and the upregulation of the Th1 T-helper cell subset.

PegIntron raises concentrations of effector proteins such as serum neopterin and 2'5' oligoadenylate synthetase, raises body temperature, and causes reversible decreases in leukocyte and platelet counts. The correlation between the *in vitro* and *in vivo* pharmacologic and pharmacodynamic and clinical effects is unknown.

12.3 Pharmacokinetics

Following a single subcutaneous dose of PegIntron, the mean absorption half-life ($t_{½\ k_a}$) was 4.6 hours. Maximal serum concentrations (C_{max}) occur between 15 and 44 hours postdose, and are sustained for up to 48 to 72 hours. The C_{max} and AUC measurements of PegIntron increase in a dose-related manner. After multiple dosing, there is an increase in bioavailability of PegIntron. Week 48 mean trough concentrations (320 pg/mL; range 0, 2960) are approximately 3-fold higher than Week 4 mean trough concentrations (94 pg/mL; range 0, 416). The mean PegIntron elimination half-life is approximately 40 hours (range 22-60 hours) in patients with HCV infection. The apparent clearance of PegIntron is estimated to be approximately 22 mL/hr·kg. Renal elimination accounts for 30% of the clearance.

Pegylation of interferon alfa-2b produces a product (PegIntron) whose clearance is lower than that of nonpegylated interferon alfa-2b. When compared to INTRON A, PegIntron (1 mcg/kg) has approximately a 7-fold lower mean apparent clearance and a 5-fold greater mean half-life, permitting a reduced dosing frequency. At effective therapeutic doses, PegIntron has approximately 10-fold greater C_{max} and 50-fold greater AUC than interferon alfa-2b.

Renal Dysfunction

Following multiple dosing of PegIntron (1 mcg/kg subcutaneously given every week for 4 weeks) the clearance of PegIntron is reduced by a mean of 17% in subjects with moderate renal impairment (creatinine clearance 30-49 mL/min) and by a mean of 44% in subjects with severe renal impairment (creatinine clearance 10-29 mL/min) compared to subjects with normal renal function. Clearance was similar in subjects with severe renal impairment not on dialysis and subjects who are receiving hemodialysis. The dose of PegIntron for monotherapy should be reduced in patients with moderate or severe renal impairment *[see Dosage and Administration (2.3)* and *REBETOL labeling]*. REBETOL should not be used in patients with creatinine clearance less than 50 mL/min *[see REBETOL labeling, WARNINGS]*.

Gender

During the 48-week treatment period with PegIntron, no differences in the pharmacokinetic profiles were observed between male and female subjects with chronic hepatitis C infection.

Geriatric Patients

The pharmacokinetics of geriatric subjects (65 years of age and older) treated with a single subcutaneous dose of 1 mcg/kg of PegIntron were similar in C_{max}, AUC, clearance, or elimination half-life as compared to younger subjects (28-44 years of age).

Pediatric Patients

Population pharmacokinetics for PegIntron and REBETOL (capsules and oral solution) were evaluated in pediatric subjects with chronic hepatitis C between 3 and 17 years of age. In pediatric patients receiving PegIntron 60 mcg/m^2/week subcutaneously, exposure may be approximately 50% higher than observed in adults receiving 1.5 mcg/kg/week subcutaneously. The pharmacokinetics of REBETOL (dose-normalized) in this trial were similar to those reported in a prior trial of REBETOL in combination with INTRON A in pediatric subjects and in adults.

Effect of Food on Absorption of Ribavirin

Both AUC_{tf} and C_{max} increased by 70% when REBETOL capsules were administered with a high-fat meal (841 kcal, 53.8 g fat, 31.6 g protein, and 57.4 g carbohydrate) in a single-dose pharmacokinetic trial *[see Dosage and Administration (2.1)]*.

Drug Interactions

Table 13: Effect of PegIntron on Coadministered Drugs

Coadministered Drug	Dose of PegIntron	Study Population	Geometric Mean Ratio (Ratio with/without PegIntron)	
			AUC (90% CI)	C_{max} (90% CI)
Caffeine (CYP1A2 substrate)	1.5 mcg/kg/week (4 weeks)	Chronic Hepatitis C Subjects (N=22)	1.39 (1.27, 1.51)	1.02 (0.95, 1.09)
	1 mcg/kg/week (4 weeks)	Healthy Subjects (N=24)	1.18 (1.07, 1.31)	1.12 (1.05, 1.19)
	3 mcg/kg/week (2 weeks)	Healthy Subjects (N=13)	1.36 (1.25-1.49)	1.16 (1.10-1.24)
Tolbutamide (CYP2C9 substrate)	1.5 mcg/kg/week (4 weeks)	Chronic Hepatitis C Subjects (N=22)	1.1* (0.94, 1.28)	NA
	1 mcg/kg/week (4 weeks)	Healthy Subjects (N=24)	0.90* (0.81, 1.00)	NA
	3 mcg/kg/week (2 weeks)	Healthy Subjects (N=13)	0.95 (0.89-1.01)	0.99 (0.92-1.07)
Dextromethorphan hydrobromide (CYP2D6 and CYP3A substrate)	1.5 mcg/kg/week (4 weeks)	Chronic Hepatitis C Subjects (N=22)	0.96† (0.73, 1.26)	NA
	1 mcg/kg/week (4 weeks)	Healthy Subjects (N=24)	2.03* (1.55, 2.67)	NA
Desipramine (CYP2D6 substrate)	3 mcg/kg/week (2 weeks)	Healthy Subjects (N=13)	1.30 (1.18-1.43)	1.08 (1.00-1.16)
Midazolam (CYP3A4 substrate)	1.5 mcg/kg/week (4 weeks)	Chronic Hepatitis C Subjects (N=24)	1.07 (0.91, 1.25)	1.12 (0.94, 1.33)
	1 mcg/kg/week	Healthy Subjects	1.07	1.33

	(4 weeks)	(N=24)	(0.99, 1.16)	(1.15, 1.53)
	3 mcg/kg/week (2 weeks)	Healthy Subjects (N=13)	1.18 (1.06-1.32)	1.24 (1.07-1.43)
Dapsone (N-acetyltransferase substrate)	1.5 mcg/kg/week (4 weeks)	Chronic Hepatitis C Subjects (N=24)	1.05 (1.02, 1.08)	1.03 (1.00, 1.06)

* Calculated from urine data collected over an interval of 48-hours.
†Calculated from urine data collected over an interval of 24 hours

Methadone

The pharmacokinetics of concomitant administration of methadone and PegIntron were evaluated in 18 PegIntron-naïve chronic hepatitis C subjects receiving 1.5 mcg/kg PegIntron subcutaneously weekly. All subjects were on stable methadone maintenance therapy receiving greater than or equal to 40 mg/day prior to initiating PegIntron. Mean methadone AUC was approximately 16% higher after 4 weeks of PegIntron treatment as compared to baseline. In 2 subjects, methadone AUC was approximately double after 4 weeks of PegIntron treatment as compared to baseline *[see Drug Interactions (7.1)]*.

Use with Ribavirin

Zidovudine, Lamivudine, and Stavudine

Ribavirin has been shown *in vitro* to inhibit phosphorylation of zidovudine, lamivudine, and stavudine. However, in a trial with another pegylated interferon in combination with ribavirin, no pharmacokinetic (e.g., plasma concentrations or intracellular triphosphorylated active metabolite concentrations) or pharmacodynamic (e.g., loss of HIV/HCV virologic suppression) interaction was observed when ribavirin and lamivudine (n=18), stavudine (n=10), or zidovudine (n=6) were co-administered as part of a multi-drug regimen to HIV/HCV co-infected subjects *[see Drug Interactions (7.2)]*.

Didanosine

Exposure to didanosine or its active metabolite (dideoxyadenosine 5'- triphosphate) is increased when didanosine is co-administered with ribavirin, which could cause or worsen clinical toxicities *[see Drug Interactions (7.2)]*.

12.4 Microbiology

Mechanism of Action

The biological activity of PegIntron is derived from its interferon alfa-2b moiety. Peginterferon alfa-2b binds to and activates the human type 1 interferon receptor. Upon binding, the receptor subunits dimerize, and activate multiple intracellular signal transduction pathways. Signal transduction is initially mediated by the JAK/STAT activation, which may occur in a wide variety of cells. Interferon receptor activation also activates NFκB in many cell types. Given the diversity of cell types that respond to interferon alfa-2b, and the multiplicity of potential intracellular responses to interferon receptor activation, peginterferon alfa-2b is expected to have pleiotropic biological effects in the body.

The mechanism by which ribavirin contributes to its antiviral efficacy in the clinic is not fully understood. Ribavirin has direct antiviral activity in tissue culture against many RNA viruses. Ribavirin increases the mutation frequency in the genomes of several viruses and ribavirin triphosphate inhibits HCV polymerase in a biochemical reaction.

Antiviral Activity

The anti-HCV activity of interferon was demonstrated in cell culture using self-replicating HCV-RNA (HCV replicon cells) or HCV infection and resulted in an effective concentration (EC_{50}) value of 1 to 10 IU/mL.

The antiviral activity of ribavirin in the HCV-replicon is not well understood and has not been defined because of the cellular toxicity of ribavirin.

Resistance

HCV genotypes show wide variability in their response to pegylated recombinant human interferon/ribavirin therapy. Genetic changes associated with the variable response have not been identified.

Cross-resistance

There is no reported cross-resistance between pegylated/nonpegylated interferons and ribavirin.

12.5 Pharmacogenomics

A retrospective genome-wide association analysis[1,2] of 1671 subjects (1604 subjects from Study 4 *[see Clinical Studies (14.1)]* and 67 subjects from another clinical trial) was performed to identify human genetic contributions to anti-HCV treatment response in previously untreated HCV genotype 1 subjects. A single nucleotide polymorphism near the gene encoding interferon-lambda-3 (*IL28B rs12979860*) was associated with variable SVR rates. The *rs12979860* genotype was categorized as CC, CT and TT. In the pooled analysis of Caucasian, African-American, and Hispanic subjects from these trials (n=1587), SVR rates by *rs12979860* genotype were as follows: CC 66% vs. CT 30% vs. TT 22%. The genotype frequencies differed depending on racial/ethnic background, but the relationship of SVR to *IL28B* genotype was consistent across various racial/ethnic groups *(see **Table 14**)*. Other variants near the *IL28B* gene (e.g., *rs8099917* and *rs8103142*) have been identified; however, they have not been shown to independently influence SVR rates during treatment with pegylated interferon alpha therapies combined with ribavirin.[1]

Table 14: SVR Rates by *IL28B* Genotype*

Population	CC	CT	TT
Caucasian	69% (301/436)	33% (196/596)	27% (38/139)
African-American	48% (20/42)	15% (22/146)	13% (15/112)

Hispanic	56% (19/34)	38% (21/56)	27% (7/26)

* The SVR rates are the overall rates for subjects treated with PegIntron 1.0 mcg/kg/REBETOL, PegIntron 1.5 mcg/kg/REBETOL and Pegasys 180 mcg/Copegus according to self-reported race/ethnicity.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenesis and Mutagenesis

PegIntron has not been tested for its carcinogenic potential. Neither PegIntron nor its components, interferon or methoxypolyethylene glycol, caused damage to DNA when tested in the standard battery of mutagenesis assays, in the presence and absence of metabolic activation.

Use with Ribavirin: See ribavirin labeling for additional warnings relevant to PegIntron therapy in combination with ribavirin.

Impairment of Fertility

PegIntron may impair human fertility. Irregular menstrual cycles were observed in female cynomolgus monkeys given subcutaneous injections of 4239 mcg/m^2 PegIntron alone every other day for 1 month (approximately 345 times the recommended weekly human dose based upon body surface area). These effects included transiently decreased serum levels of estradiol and progesterone, suggestive of anovulation. Normal menstrual cycles and serum hormone levels resumed in these animals 2 to 3 months following cessation of PegIntron treatment. Every other day dosing with 262 mcg/m^2 (approximately 21 times the weekly human dose) had no effects on cycle duration or reproductive hormone status. The effects of PegIntron on male fertility have not been studied.

14 CLINICAL STUDIES

14.1 Chronic Hepatitis C in Adults

PegIntron Monotherapy — Study 1

A randomized trial compared treatment with PegIntron (0.5, 1, or 1.5 mcg/kg once weekly subcutaneously) to treatment with INTRON A (3 million units 3 times weekly subcutaneously) in 1219 adults with chronic hepatitis from HCV infection. The subjects were not previously treated with interferon alpha, had compensated liver disease, detectable HCV-RNA, elevated ALT, and liver histopathology consistent with chronic hepatitis. Subjects were treated for 48 weeks and were followed for 24 weeks post-treatment.

Seventy percent of all subjects were infected with HCV genotype 1, and 74 percent of all subjects had high baseline levels of HCV-RNA (more than 2 million copies per mL of serum), two factors known to predict poor response to treatment.

Response to treatment was defined as undetectable HCV-RNA and normalization of ALT at 24 weeks post-treatment. The response rates to the 1 and 1.5 mcg/kg PegIntron doses were similar (approximately 24%) to each other and were both higher than the response rate to INTRON A (12%) *(see **Table 15**)*.

Table 15: Rates of Response to Treatment – Study 1

	A PegIntron 0.5 mcg/kg (N=315)	B PegIntron 1 mcg/kg (N=298)	C INTRON A 3 MIU three times weekly (N=307)	B - C (95% CI) Difference between PegIntron 1 mcg/kg and INTRON A
Treatment Response (Combined Virologic Response and ALT Normalization)	17%	24%	12%	11 (5, 18)
Virologic Response*	18%	25%	12%	12 (6, 19)
ALT Normalization	24%	29%	18%	11 (5, 18)

* Serum HCV is measured by a research-based quantitative polymerase chain reaction assay by a central laboratory.

Subjects with both viral genotype 1 and high serum levels of HCV-RNA at baseline were less likely to respond to treatment with PegIntron. Among subjects with the two unfavorable prognostic variables, 8% (12/157) responded to PegIntron treatment and 2% (4/169) responded to INTRON A. Doses of PegIntron higher than the recommended dose did not result in higher response rates in these subjects. Subjects receiving PegIntron with viral genotype 1 had a response rate of 14% (28/199) while subjects with other viral genotypes had a 45% (43/96) response rate.

Ninety-six percent of the responders in the PegIntron groups and 100% of responders in the INTRON A group first cleared their viral RNA by Week 24 of treatment *[see Dosage and Administration (2.1)]*.

The treatment response rates were similar in men and women. Response rates were lower in African-American and Hispanic subjects and higher in Asians compared to Caucasians. Although African Americans had a higher proportion of poor prognostic factors compared to Caucasians, the number of non-Caucasians studied (9% of the total) was insufficient to allow meaningful conclusions about differences in response rates after adjusting for prognostic factors.

Liver biopsies were obtained before and after treatment in 60% of subjects. A modest reduction in inflammation compared to baseline that was similar in all 4 treatment groups was observed.

PegIntron/REBETOL Combination Therapy — Study 2

A randomized trial compared treatment with two PegIntron/REBETOL regimens [PegIntron 1.5 mcg/kg subcutaneously once weekly/REBETOL 800 mg orally daily (in divided doses); PegIntron 1.5 mcg/kg subcutaneously once weekly for 4 weeks then

0.5 mcg/kg subcutaneously once weekly for 44 weeks/REBETOL 1000 or 1200 mg orally daily (in divided doses)] with INTRON A [3 MIU subcutaneously thrice weekly/REBETOL 1000 or 1200 mg orally daily (in divided doses)] in 1530 adults with chronic hepatitis C. Interferon-naïve subjects were treated for 48 weeks and followed for 24 weeks post-treatment. Eligible subjects had compensated liver disease, detectable HCV-RNA, elevated ALT, and liver histopathology consistent with chronic hepatitis.

Response to treatment was defined as undetectable HCV-RNA at 24 weeks post-treatment. The response rate to the PegIntron 1.5 mcg/kg plus REBETOL 800 mg dose was higher than the response rate to INTRON A/REBETOL *(see **Table 16**)*. The response rate to PegIntron 1.5→0.5 mcg/kg/REBETOL was essentially the same as the response to INTRON A/REBETOL (data not shown).

Table 16: Rates of Response to Treatment – Study 2

	PegIntron 1.5 mcg/kg once weekly REBETOL 800 mg daily	INTRON A 3 MIU three times weekly REBETOL 1000/1200 mg daily
Overall response *†	52% (264/511)	46% (231/505)
Genotype 1	41% (141/348)	33% (112/343)
Genotype 2-6	75% (123/163)	73% (119/162)

* Serum HCV-RNA is measured with a research-based quantitative polymerase chain reaction assay by a central laboratory.
† Difference in overall treatment response (PegIntron/REBETOL vs. INTRON A/REBETOL) is 6% with 95% confidence interval of (0.18, 11.63) adjusted for viral genotype and presence of cirrhosis at baseline. Response to treatment was defined as undetectable HCV-RNA at 24 weeks post-treatment.

Subjects with viral genotype 1, regardless of viral load, had a lower response rate to PegIntron (1.5 mcg/kg)/REBETOL (800 mg) compared to subjects with other viral genotypes. Subjects with both poor prognostic factors (genotype 1 and high viral load) had a response rate of 30% (78/256) compared to a response rate of 29% (71/247) with INTRON A/REBETOL.

Subjects with lower body weight tended to have higher adverse reaction rates *[see Adverse Reactions (6.1)]* and higher response rates than subjects with higher body weights. Differences in response rates between treatment arms did not substantially vary with body weight.

Treatment response rates with PegIntron/REBETOL were 49% in men and 56% in women. Response rates were lower in African American and Hispanic subjects and higher in Asians compared to Caucasians. Although African Americans had a higher proportion of poor prognostic factors compared to Caucasians, the number of non-Caucasians studied (11% of the total) was insufficient to allow meaningful conclusions about differences in response rates after adjusting for prognostic factors in this trial.

Liver biopsies were obtained before and after treatment in 68% of subjects. Compared to baseline, approximately two-thirds of subjects in all treatment groups were observed to have a modest reduction in inflammation.

PegIntron/REBETOL Combination Therapy — Study 3

In a large United States community-based trial, 4913 subjects with chronic hepatitis C were randomized to receive PegIntron 1.5 mcg/kg subcutaneously once weekly in combination with a REBETOL dose of 800 to 1400 mg (weight-based dosing [WBD]) or 800 mg (flat) orally daily (in divided doses) for 24 or 48 weeks based on genotype. Response to treatment was defined as undetectable HCV-RNA (based on an assay with a lower limit of detection of 125 IU/mL) at 24 weeks post-treatment.

Treatment with PegIntron 1.5 mcg/kg and REBETOL 800 to 1400 mg resulted in a higher sustained virologic response compared to PegIntron in combination with a flat 800 mg daily dose of REBETOL. Subjects weighing greater than 105 kg obtained the greatest benefit with WBD, although a modest benefit was also observed in subjects weighing greater than 85 to 105 kg *(see **Table 17**)*. The benefit of WBD in subjects weighing greater than 85 kg was observed with HCV genotypes 1-3. Insufficient data were available to reach conclusions regarding other genotypes. Use of WBD resulted in an increased incidence of anemia *[see Adverse Reactions (6.1)]*.

Table 17: SVR Rates by Treatment and Baseline Weight – Study 3

Treatment Group	Subject Baseline Weight			
	<65 kg (<143 lb)	65-85 kg (143-188 lb)	>85-105 kg (>188-231 lb)	>105 kg (>231 lb)
WBD*	50% (173/348)	45% (449/994)	42% (351/835)	47% (138/292)
Flat	51% (173/342)	44% (443/1011)	39% (318/819)	33% (91/272)

* *P*=0.01, primary efficacy comparison (based on data from subjects weighing 65 kg or higher at baseline and utilizing a logistic regression analysis that includes treatment [WBD or Flat], genotype and presence/absence of advanced fibrosis, in the model).

A total of 1552 subjects weighing greater than 65 kg in Study 3 had genotype 2 or 3 and were randomized to 24 or 48 weeks of therapy. No additional benefit was observed with the longer treatment duration.

PegIntron/REBETOL Combination Therapy — Study 4

A large randomized trial compared the safety and efficacy of treatment for 48 weeks with two PegIntron/REBETOL regimens [PegIntron 1.5 mcg/kg and 1 mcg/kg subcutaneously once weekly both in combination with REBETOL 800 to 1400 mg PO daily (in two divided doses)] and Pegasys 180 mcg subcutaneously once weekly in combination with Copegus 1000 to 1200 mg PO daily (in two divided doses) in 3070 treatment-naïve adults with chronic hepatitis C genotype 1. In this trial, lack of early virologic response (undetectable HCV-RNA or greater than or equal to 2 $\log_{10}$ reduction from baseline) by treatment Week 12 was the criterion for discontinuation of treatment. SVR was defined as undetectable HCV-RNA (Roche COBAS TaqMan assay, a lower limit of quantitation of 27 IU/mL) at 24 weeks post-treatment *(see **Table 18**)*.

Table 18: SVR Rates by Treatment – Study 4

	PegIntron 1.5 mcg/kg/ REBETOL	**PegIntron 1 mcg/kg/ REBETOL**	**Pegasys 180 mcg/Copegus**
SVR	40% (406/1019)	38% (386/1016)	41% (423/1035)

Overall SVR rates were similar among the three treatment groups. Regardless of treatment group, SVR rates were lower in subjects with poor prognostic factors. Subjects with poor prognostic factors randomized to PegIntron (1.5 mcg/kg)/REBETOL or Pegasys/Copegus, however, achieved higher SVR rates compared to similar subjects randomized to PegIntron 1 mcg/kg/REBETOL. For the PegIntron 1.5 mcg/kg plus REBETOL dose, SVR rates for subjects with and without the following prognostic factors were as follows: cirrhosis (10% vs. 42%), normal ALT levels (32% vs. 42%), baseline viral load greater than 600,000 IU/mL (35% vs. 61%), 40 years of age and older (38% vs. 50%), and African American race (23% vs. 44%). In subjects with undetectable HCV-RNA at Week 12 who received PegIntron (1.5 mcg/kg)/REBETOL, the SVR rate was 81% (328/407).

PegIntron/REBETOL Combination Therapy in Prior Treatment Failures — Study 5

In a noncomparative trial, 2293 subjects with moderate to severe fibrosis who failed previous treatment with combination alpha interferon/ribavirin were re-treated with PegIntron, 1.5 mcg/kg subcutaneously, once weekly, in combination with weight adjusted ribavirin. Eligible subjects included prior nonresponders (subjects who were HCV-RNA positive at the end of a minimum 12 weeks of treatment) and prior relapsers (subjects who were HCV-RNA negative at the end of a minimum 12 weeks of treatment and subsequently relapsed after post-treatment follow-up). Subjects who were negative at Week 12 were treated for 48 weeks and followed for 24 weeks post-treatment. Response to treatment was defined as undetectable HCV-RNA at 24 weeks post-treatment (measured using a research-based test, limit of detection 125 IU/mL). The overall response rate was 22% (497/2293) (99% CI: 19.5, 23.9). Subjects with the following characteristics were less likely to benefit from re-treatment: previous nonresponse, previous pegylated interferon treatment, significant bridging fibrosis or cirrhosis, and genotype 1 infection.

The re-treatment sustained virologic response rates by baseline characteristics are summarized in **Table 19.**

Table 19: SVR Rates by Baseline Characteristics of Prior Treatment Failures

HCV Genotype/ Metavir Fibrosis Score	Overall SVR by Previous Response and Treatment			
	Nonresponder		Relapser	
	alfa interferon/ribavirin % (number of subjects)	peginterferon (2a and 2b combined)/ribavirin % (number of subjects)	alfa interferon/ribavirin % (number of subjects)	peginterferon (2a and 2b combined)/ribavirin % (number of subjects)
Overall	18 (158/903)	6 (30/476)	43 (130/300)	35 (113/344)
HCV 1	13 (98/761)	4 (19/431)	32 (67/208)	23 (56/243)
F2	18 (36/202)	6 (7/117)	42 (33/79)	32 (23/72)
F3	16 (38/233)	4 (4/112)	28 (16/58)	21 (14/67)
F4	7 (24/325)	4 (8/202)	26 (18/70)	18 (19/104)
HCV 2/3	49 (53/109)	36 (10/28)	67 (54/81)	57 (52/92)
F2	68 (23/34)	56 (5/9)	76 (19/25)	61 (11/18)
F3	39 (11/28)	38 (3/8)	67 (18/27)	62 (18/29)
F4	40 (19/47)	18 (2/11)	59 (17/29)	51 (23/45)
HCV 4	17 (5/29)	7 (1/15)	88 (7/8)	50 (4/8)

Achievement of an undetectable HCV-RNA at treatment Week 12 was a strong predictor of SVR. In this trial, 1470 (64%) subjects did not achieve an undetectable HCV-RNA at treatment Week 12, and were offered enrollment into long-term treatment trials, due to an inadequate treatment response. Of the 823 (36%) subjects who were HCV-RNA undetectable at treatment Week 12, those infected with genotype 1 had an SVR of 48% (245/507), with a range of responses by fibrosis scores (F4-F2) of 39-55%. Subjects infected with genotype 2/3 who were HCV-RNA undetectable at treatment Week 12 had an overall SVR of 70% (196/281), with a range of responses by fibrosis scores (F4-F2) of 60-83%. For all genotypes, higher fibrosis scores were associated with a decreased likelihood of achieving SVR.

14.2 Chronic Hepatitis C in Pediatrics

PegIntron/REBETOL Combination Therapy — Pediatric Trial

Previously untreated pediatric subjects 3 to 17 years of age with compensated chronic hepatitis C and detectable HCV-RNA were treated with REBETOL 15 mg/kg/day plus PegIntron 60 mcg/m^2 once weekly for 24 or 48 weeks based on HCV genotype and baseline viral load. All subjects were to be followed for 24 weeks post-treatment. A total of 107 subjects received treatment, of which 52% were female, 89% were Caucasian, and 67% were infected with HCV genotype 1. Subjects infected with genotype 1, 4 or genotype 3 with HCV-RNA greater than or equal to 600,000 IU/mL received 48 weeks of therapy while those infected with genotype 2 or genotype 3 with HCV-RNA less than 600,000 IU/mL received 24 weeks of therapy. The trial results are summarized in **Table 20**.

Table 20: SVR Rates by Genotype and Treatment Duration – Pediatric Trial

	All Subjects N=107	
	24 Weeks	48 Weeks
	Virologic Response N*† (%)	Virologic Response N*† (%)
Genotype		
All	26/27 (96.3)	44/80 (55.0)
1	—	38/72 (52.8)
2	14/15 (93.3)	—
3‡	12/12 (100)	2/3 (66.7)
4	—	4/5 (80.0)

* Response to treatment was defined as undetectable HCV-RNA at 24 weeks post-treatment.

† N = number of responders/number of subjects with given genotype, and assigned treatment duration.

‡ Subjects with genotype 3 low viral load (less than 600,000 IU/mL) were to receive 24 weeks of treatment while those with genotype 3 and high viral load were to receive 48 weeks of treatment.

15 REFERENCES

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2. Thompson, A.J., Muir, A.J., Sulkowski, M.S., Ge, D., Fellay, J., Shianna, K.V., Urban, T., Afdhal, N.H., Jacobson, I.M., Esteban, R., Poordad, F., Lawitz, E.J., McCone, J., Shiffman, M.L., Galler, G.W., Lee, W.M., Reindollar, R., King, J.W., Kwo, P.Y., Ghalib, R.H., Freilich, B., Nyberg, L.M., Zeuzem, S., Poynard, T., Vock, D.M., Pieper, K.S., Patel, K., Tillmann, H.L., Noviello, S., Koury, K., Pedicone, L.D., Brass, C.A., Albrecht, J.K., Goldstein, D.B., McHutchison, J.G., Interlukin-28B polymorphism improves viral kinetics and is the strongest pretreatment predictor of sustained virologic response in genotype 1 hepatitis C virus, Gastroenterology 2010;139:120-129.

16 HOW SUPPLIED/STORAGE AND HANDLING

PegIntron REDIPEN

Each PegIntron REDIPEN Package Contains:	
A box containing one 50 mcg per 0.5 mL PegIntron REDIPEN and 1 BD needle and 2 alcohol swabs.	(NDC 0085-1323-01)
A box containing one 80 mcg per 0.5 mL PegIntron REDIPEN and 1 BD needle and 2 alcohol swabs.	(NDC 0085-1316-01)
A box containing one 120 mcg per 0.5 mL PegIntron REDIPEN and 1 BD needle and 2 alcohol swabs.	(NDC 0085-1297-01)
A box containing one 150 mcg per 0.5 mL PegIntron REDIPEN and 1 BD needle and 2 alcohol swabs.	(NDC 0085-1370-01)

Each PegIntron REDIPEN PAK 4 Contains:	
A box containing four 50 mcg per 0.5 mL PegIntron REDIPEN Units, each containing 1 BD needle and 2 alcohol	(NDC 0085-1323-02)

swabs.	
A box containing four 80 mcg per 0.5 mL PegIntron REDIPEN Units, each containing 1 BD needle and 2 alcohol swabs.	(NDC 0085-1316-02)
A box containing four 120 mcg per 0.5 mL PegIntron REDIPEN Units, each containing 1 BD needle and 2 alcohol swabs.	(NDC 0085-1297-02)
A box containing four 150 mcg per 0.5 mL PegIntron REDIPEN Units, each containing 1 BD needle and 2 alcohol swabs.	(NDC 0085-1370-02)

PegIntron Vials

Each PegIntron Package Contains:	
A box containing one 50 mcg per 0.5 mL vial of PegIntron Powder for Injection and one 5 mL vial of Diluent (Sterile Water for Injection USP), 2 BD Safety Lok syringes with a safety sleeve and 2 alcohol swabs.	(NDC 0085-4353-01)
A box containing one 80 mcg per 0.5 mL vial of PegIntron Powder for Injection and one 5 mL vial of Diluent (Sterile Water for Injection USP), 2 BD Safety Lok syringes with a safety sleeve and 2 alcohol swabs.	(NDC 0085-4354-01)
A box containing one 120 mcg per 0.5 mL vial of PegIntron Powder for Injection and one 5 mL vial of Diluent (Sterile Water for Injection USP), 2 BD Safety Lok syringes with a safety sleeve and 2 alcohol swabs.	(NDC 0085-4355-01)
A box containing one 150 mcg per 0.5 mL vial of PegIntron Powder for Injection and one 5 mL vial of Diluent (Sterile Water for Injection USP), 2 BD Safety Lok syringes with a safety sleeve and 2 alcohol swabs.	(NDC 0085-4356-01)

Storage

PegIntron REDIPEN single-use pre-filled pen

PegIntron REDIPEN pre-filled pen should be stored at 2-8°C (36-46°F).

After reconstitution, the solution should be used immediately, but may be stored up to 24 hours at 2-8°C (36-46°F). The reconstituted solution contains no preservative, and is clear and colorless. **DO NOT FREEZE. Keep away from heat.**

PegIntron Vials

PegIntron should be stored at 25°C (77°F); excursions permitted to 15-30°C (59-86°F) [see USP Controlled Room Temperature]. After reconstitution with supplied diluent, the solution should be used immediately but may be stored up to 24 hours at 2-8°C (36-46°F). The reconstituted solution contains no preservative, and is clear and colorless. **DO NOT FREEZE. Keep away from heat.**

Disposal Instructions

Patients should be thoroughly instructed in the importance of proper disposal. After preparation and administration of PegIntron for Injection, patients should be advised to use a puncture-resistant container for the disposal of used syringes, needles, and the REDIPEN pre-filled pen. The full container should be disposed of in accordance with state and local laws. Patients should also be cautioned against reusing or sharing needles, syringes, or the REDIPEN pre-filled pen.

17 PATIENT COUNSELING INFORMATION

- Advise the patient to read the FDA-approved patient labeling (Medication Guide and Instructions for Use)

A patient should self-inject PegIntron only if it has been determined that it is appropriate, the patient agrees to medical follow-up as necessary, and training in proper injection technique has been given to him/her.

Pregnancy

Patients must be informed that REBETOL (ribavirin) may cause birth defects and death of the unborn child. Extreme care must be taken to avoid pregnancy in female patients and in female partners of male patients during treatment with combination PegIntron/ribavirin therapy and for 6 months post-therapy. Combination PegIntron/ribavirin therapy should not be initiated until a report of a negative pregnancy test has been obtained immediately prior to initiation of therapy. It is recommended that patients undergo monthly pregnancy tests during therapy and for 6 months post-therapy *[see Contraindications (4), Use in Specific Populations (8.1),* and *ribavirin labeling]*.

HCV Transmission

Inform patients that there are no data regarding whether PegIntron therapy will prevent transmission of HCV infection to others. Also, it is not known if treatment with PegIntron will cure hepatitis C or prevent cirrhosis, liver failure, or liver cancer that may be the result of infection with the hepatitis C virus.

Laboratory Evaluations, Hydration, "Flu-like" Symptoms

Patients should be advised that laboratory evaluations are required before starting therapy and periodically thereafter *[see Warnings and Precautions (5.15)]*. It is advised that patients be well hydrated, especially during the initial stages of treatment. "Flu-like" symptoms associated with administration of PegIntron may be minimized by bedtime administration of PegIntron or by use of antipyretics.

Patients developing fever, cough, shortness of breath or other symptoms of a lung problem during treatment with PegIntron may need to have a chest X-ray or other tests to adequately treat them.

Instructions for Use

Patients receiving PegIntron should be directed in its appropriate preparation, handling, measurement, and injection, and referred to the Instructions for Use for PegIntron Powder for Solution and PegIntron REDIPEN Single-use Pre-filled pen.

Patients should be instructed that the Sterile Water for Injection vial supplied with PegIntron Powder for Solution contains an excess amount of diluent (5 mL) and only 0.7 mL should be withdrawn to reconstitute PegIntron Powder for Solution. The vial of Sterile Water for Injection is intended for single use only. Discard the unused portion of the sterile water. Do not save or reuse.

Patients should be directed to store PegIntron before mixing as follows:

- PegIntron REDIPEN single-use pre-filled pens: store in the refrigerator between 36-46°F (2-8°C)
- PegIntron Powder for Solution: store at room temperature between 59-86°F (15-30°C)

Patients should be instructed on the importance of site selection for self-administering the injection, as well as the importance on rotating the injection sites.

Manufactured by:
Merck Sharp & Dohme Corp., a subsidiary of **Merck & Co., Inc.,** Whitehouse Station, NJ 08889, USA
U.S. License Number 0002

For patent information: www.merck.com/product/patent/home.html

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MEDICATION GUIDE
PegIntron® (peg-In-tron)
(Peginterferon alfa-2b)
for injection, for subcutaneous use

Read this Medication Guide before you start taking PegIntron®, and each time you get a refill. There may be new information. This information does not take the place of talking with your healthcare provider about your medical condition or your treatment.

If you are taking PegIntron with REBETOL (ribavirin) with or without an approved hepatitis C virus (HCV) protease inhibitor, also read the Medication Guides for those medicines.

PegIntron, by itself or in combination with other approved medicines, is a treatment for some people who are infected with hepatitis C virus.

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

PegIntron can cause serious side effects that:

- **may cause death, or**
- **may worsen certain serious diseases that you may already have.**

Tell your healthcare provider right away if you have any of the symptoms listed below while taking PegIntron. If symptoms get worse, or become severe and continue, your healthcare provider may tell you to stop taking PegIntron permanently. In many, but not all, people, these symptoms go away after they stop taking PegIntron.

1. **Mental health problems, including suicide**. PegIntron may cause you to develop mood or behavior problems that may get worse during treatment with PegIntron or after your last dose, including:
   - irritability (getting upset easily)
   - depression (feeling low, feeling bad about yourself, or feeling hopeless)
   - acting aggressive, being angry or violent
   - thoughts of hurting yourself or others, or suicide
   - former drug addicts may fall back into drug addiction or overdose

   If you have these symptoms, your healthcare provider should carefully monitor you during treatment with PegIntron and for 6 months after your last dose.
2. **Heart problems.** Some people who take PegIntron may get heart problems, including:
   - low blood pressure
   - fast heart rate or abnormal heart beat
   - trouble breathing or chest pain
   - heart attacks or heart muscle problems (cardiomyopathy)
3. **Stroke or symptoms of a stroke. Symptoms may include weakness, loss of coordination, and numbness.** Stroke or symptoms of a stroke may happen in people who have some risk factors **or** no known risk factors for a stroke.
4. **New or worsening autoimmune problems.** Some people taking PegIntron develop autoimmune problems (a condition where the body's immune cells attack other cells or

organs in the body), including rheumatoid arthritis, systemic lupus erythematosus, and psoriasis. In some people who already have an autoimmune problem, it may get worse during your treatment with PegIntron.

5. **Infections.** Some people who take PegIntron may get an infection. Symptoms may include:
   - fever
   - chills
   - bloody diarrhea
   - burning or pain with urination
   - urinating often
   - coughing up mucus (phlegm) that is discolored (for example, yellow or pink)

PegIntron in combination with REBETOL (ribavirin) may cause birth defects or the death of your unborn baby. Do not take PegIntron and ribavirin combination therapy if you or your sexual partner is pregnant or plan to be come pregnant. Do not become pregnant within 6 months after discontinuing PegIntron and ribavirin combination therapy. You must use 2 forms of birth control when you take PegIntron and ribavirin and for the 6 months after treatment.

- Females must have a pregnancy test before starting PegIntron and ribavirin combination therapy, every month while on the combination therapy, and every month for the 6 months after the last dose of combination therapy.
- If you or your female sexual partner becomes pregnant while taking PegIntron and ribavirin combination therapy or within 6 months after you stop taking the combination therapy, tell your healthcare provider right away. You or your healthcare provider should contact the Ribavirin pregnancy registry by calling 1-800-593-2214. The Ribavirin pregnancy registry collects information about what happens to mothers and their babies if the mother takes ribavirin while she is pregnant.

While taking PegIntron, you should see a healthcare provider regularly for check-ups and blood tests to make sure that your treatment is working, and to check for side effects.

What is PegIntron?

PegIntron is a prescription medicine that is used:

- with REBETOL (ribavirin) and an approved hepatitis C virus (HCV) protease inhibitor to treat chronic (lasting a long time) hepatitis C infection in adults.
- with REBETOL (ribavirin) to treat chronic (lasting a long time) hepatitis C infection in people 3 years and older with stable liver problems.
- alone, sometimes to treat adults who have chronic (lasting a long time) hepatitis C infection with stable liver problems and who can not take REBETOL (ribavirin).

People with hepatitis C have the virus in their blood and in their liver. PegIntron reduces the amount of virus in the body and helps the body's immune system fight the virus. REBETOL (ribavirin) is a drug that helps to fight the viral infection but does not work when used by itself to treat chronic hepatitis C.

It is not known if PegIntron use for longer than 1 year is safe and will work.

It is not known if PegIntron use in children younger than 3 years old is safe and will work.

Who should not take PegIntron?

Do not take PegIntron:

- if you have had a serious allergic reaction to another alpha interferon or to any of the ingredients in PegIntron. See the end of this Medication Guide for a complete list of ingredients. Ask your healthcare provider if you are not sure.
- if you have certain types of hepatitis (autoimmune hepatitis).
- if you have certain other liver problems.
- with REBETOL (ribavirin) if you are pregnant, planning to get pregnant, or breastfeeding. See "What is the most important information I should know about PegIntron?"

Talk to your healthcare provider before taking PegIntron if you have any of these conditions.

What should I tell my healthcare provider before taking PegIntron?

Before you take PegIntron, see **"What is the most important information I should know about PegIntron?**", and tell your healthcare provider if you:

- are being treated for a mental illness or had treatment in the past for any mental illness, including depression and thoughts of hurting yourself or others
- have or ever had any problems with your heart, including heart attack or high blood pressure
- have any kind of autoimmune disease (where the body's immune system attacks the body's own cells), such as psoriasis, systemic lupus erythematosus, rheumatoid arthritis
- have or ever had bleeding problems or a blood clot
- have or ever had low blood cell counts
- have ever been addicted to drugs or alcohol
- have cirrhosis or other liver disease (other than hepatitis C infection)
- have or had lung disease such as chronic obstructive pulmonary disease (COPD)
- have thyroid problems
- have diabetes
- have colitis (inflammation of your intestine)
- have a condition that suppresses your immune system, such as cancer
- have hepatitis B infection
- have HIV infection
- have kidney problems
- have high blood triglyceride levels (fat in your blood)
- have an organ transplant and are taking medicine that keeps your body from rejecting your transplant (suppresses your immune system)
- have any other medical conditions
- are pregnant or plan to become pregnant. PegIntron may harm your unborn baby. You should use effective birth control during treatment with PegIntron. Talk to your healthcare provider about birth control choices for you during treatment with PegIntron. Tell your healthcare provider if you become pregnant during treatment with PegIntron.
- are breastfeeding or plan to breastfeed. It is not known if PegIntron passes into your breast milk. You and your healthcare provider should decide if you will use PegIntron or breastfeed.

Tell your healthcare provider about all the medicines you take, including prescription and non-prescription medicines, vitamins, and herbal supplements. PegIntron and certain other medicines may affect each other and cause side effects.

Especially tell your healthcare provider if you take the anti-hepatitis B medicine telbivudine (Tyzeka).

Know the medicines you take. Keep a list of them and show it to your healthcare provider and pharmacist when you get a new medicine.

How should I take PegIntron?

- Take PegIntron exactly as your healthcare provider tells you to. Your healthcare provider will tell you how much PegIntron to take and when to take it. Do not take more than your prescribed dose.
- Take your prescribed dose of PegIntron every week, on the same day of each week and at the same time.
- PegIntron is given as an injection under your skin (subcutaneous injection). Your healthcare provider should show you how to prepare and measure your dose of PegIntron, and how to inject yourself before you use PegIntron for the first time.
- You should not inject PegIntron until your healthcare provider has shown you how to use PegIntron the right way.
- PegIntron comes as a:
    - o powder in a single-use vial
    - o single-use REDIPEN

  Your healthcare provider will prescribe the PegIntron that is right for you. See the Instructions for Use that comes with your PegIntron for detailed instructions for preparing and injecting a dose of PegIntron.
- If you miss a dose of PegIntron, take the missed dose as soon as possible during the same day or the next day, then continue on your regular dosing schedule. If several days go by after you miss a dose, check with your healthcare provider about what to do.
- Do not inject more than 1 dose of PegIntron in one week without talking to your healthcare provider.
- If you take too much PegIntron, call your healthcare provider right away. Your healthcare provider may examine you more closely, and do blood tests.
- Your healthcare provider should do blood tests before you start PegIntron, and regularly during treatment to see how well the treatment is working and to check you for side effects.

What are the possible side effects of PegIntron?

PegIntron may cause serious side effects including:

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

- **Serious eye problems.** PegIntron may cause eye problems that may lead to vision loss or blindness. You should have an eye exam before you start taking PegIntron. If you have eye problems or have had them in the past, you may need eye exams while you are taking PegIntron. Tell your healthcare provider or eye doctor right away if you have any vision changes while taking PegIntron.

- **Blood problems**. PegIntron can affect your bone marrow and cause low white blood cell and platelet counts. In some people, these blood counts may fall to dangerously low levels. If your blood counts become very low, you can get infections, and problems with bleeding and bruising.
- **Swelling of your pancreas (pancreatitis) or intestines (colitis).** Symptoms may include:
    - severe stomach area (abdomen) pain
    - severe back pain
    - nausea and vomiting
    - bloody diarrhea
    - fever
- **Lung problems including:**
    - trouble breathing
    - pneumonia
    - inflammation of lung tissue
    - new or worse high blood pressure of the lungs (pulmonary hypertension). This can be severe and may lead to death.

    You may need to have a chest X-ray or other tests if you develop fever, cough, shortness of breath or other symptoms of a lung problem during treatment with PegIntron.
- **Severe liver problems, or worsening of liver problems, including liver failure and death**. Symptoms may include:
    - nausea
    - loss of appetite
    - tiredness
    - diarrhea
    - yellowing of your skin or the white part of your eyes
    - bleeding more easily than normal
    - swelling of your stomach area (abdomen)
    - confusion
    - sleepiness
    - you cannot be awakened (coma)

- **Thyroid problems.** Some people develop changes in their thyroid function. Symptoms of thyroid changes include:
    - problems concentrating
    - feeling cold or hot all of the time
    - weight changes
    - skin changes
- **Blood sugar problems.** Some people may develop high blood sugar or diabetes. If you have high blood sugar or diabetes that is not controlled before starting PegIntron, talk to your healthcare provider before you take PegIntron. If you develop high blood sugar or diabetes while taking PegIntron, your healthcare provider may tell you to stop PegIntron and prescribe a different medicine for you. Symptoms of high blood sugar or diabetes may include:
    - increased thirst
    - tiredness

- urinating more often than normal
- increased appetite
- weight loss
- your breath smells like fruit

- **Serious allergic reactions and skin reactions. Symptoms may include:**
  - itching
  - swelling of the face, eyes, lips, tongue, or throat
  - trouble breathing
  - anxiousness
  - chest pain
  - feeling faint
  - skin rash, hives, sores in your mouth, or your skin blisters and peels

- **Growth problems in children.** Weight loss and slowed growth are common in children during combination treatment with PegIntron and REBETOL. Most children will go through a growth spurt and gain weight after treatment stops. Some children may not reach the height that they were expected to have before treatment. Talk to your healthcare provider if you are concerned about your child's growth during treatment with PegIntron and REBETOL.

- **Nerve problems.** People who take PegIntron or other alpha interferon products with telbivudine (Tyzeka) can develop nerve problems such as continuing numbness, tingling, or burning sensation in the arms or legs (peripheral neuropathy). Call your healthcare provider if you have any of these symptoms.

- **Dental and gum problems.**

Tell your healthcare provider right away if you have any of the symptoms listed above.

The most common side effects of PegIntron include:

- **Flu-like symptoms.** Symptoms may include: headache, muscle aches, tiredness, and fever. Some of these symptoms may be decreased by injecting your PegIntron dose at bedtime. Talk to your healthcare provider about which over-the-counter medicines you can take to help prevent or decrease some of these symptoms.
- **Tiredness.** Many people become very tired during treatment with PegIntron.
- **Appetite problems**. Nausea, loss of appetite, and weight loss can happen with PegIntron.
- **Skin reactions**. Redness, swelling, and itching are common at the site of injection.
- **Hair thinning**.

Tell your healthcare provider if you have any side effect that bothers you or that does not go away.

These are not all of the possible side effects of PegIntron. For more information, ask your healthcare provider or pharmacist.

Call your doctor for medical advice about side effects. You may report side effects to FDA at 1–800–FDA–1088.

How should I store PegIntron?

- Before mixing, store PegIntron single-use REDIPEN in the refrigerator between 36°F to 46°F (2°C to 8°C).
- Before mixing, store PegIntron vials at room temperature between 68°F to 77°F (20°C to 25°C).
- Keep PegIntron away from heat.
- After mixing, use PegIntron right away or store it in the refrigerator for up to 24 hours between 36°F to 46°F (2°C to 8°C).
- Do not freeze PegIntron.
- **Keep PegIntron and all medicines out of the reach of children.**

General Information about PegIntron

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

This Medication Guide summarizes the most important information about PegIntron. If you would like more information, ask your healthcare provider. You can ask your healthcare provider or pharmacist for information about PegIntron that was written for healthcare professionals.

For more information, go to www.PegIntron.com or call 1-800-526-4099.

What are the ingredients in PegIntron?

Active ingredients: peginterferon alfa-2b

Inactive ingredients: dibasic sodium phosphate anhydrous, monobasic sodium phosphate dihydrate, sucrose, polysorbate 80. Sterile water for injection is supplied as a diluent.

This Medication Guide has been approved by the U.S. Food and Drug Administration.

Manufactured by:
Merck Sharp & Dohme Corp., a subsidiary of **Merck & Co., Inc.,** Whitehouse Station, NJ 08889, USA

U.S. License Number 0002

Revised: 05/2017

For patent information: www.merck.com/product/patent/home.html

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usmg-mk4031-mf-1602r020

Instructions for Use

PegIntron® (peg-In-tron)

(Peginterferon alfa-2b)

Powder for Injection

This Instructions for Use is only for use with the single-use vials of Powder for injection. If your healthcare provider prescribes the REDIPEN Pre-filled Pen for you, use only those Instructions for Use.

Be sure that you read, understand and follow these instructions before injecting PegIntron. Your healthcare provider should show you how to prepare, measure, and inject PegIntron properly using a vial before you use it for the first time. Ask your healthcare provider if you have any questions.

Important:

- Make sure that you have:
    - the correct strength of PegIntron vial prescribed by your healthcare provider.
    - the correct syringe and needle to use with PegIntron. Your healthcare provider should tell you what syringes and needles to use to inject PegIntron.
- Throw away the syringe and needle after you use it. Do not re-use your syringes and needles. See "Disposal of the used needles, syringes and vials" in this Instructions for Use.
- The vial of mixed PegIntron should be used right away. Do not mix more than 1 vial of PegIntron at a time. If you do not use the vial of the prepared solution right away, store it in a refrigerator and use within 24 hours. See the end of these Instructions for Use for information about "How should I store PegIntron?"

Before starting, collect all of the supplies that you will need to use for preparing and injecting PegIntron. For each injection you will need a PegIntron vial package that contains:

- 1 vial of PegIntron powder for injection
- 1 vial of sterile water for injection (diluent)
- 2 single-use disposable syringes (BD Safety Lok syringes with a safety sleeve)
- 2 alcohol swabs

You will also need:

- 1 cotton ball or gauze

- 1 sharps disposal container for throwing away your used syringes, needles, and vials.

How should I prepare a dose of PegIntron?

Before you inject PegIntron, the powder must be mixed with 0.7 mL of the sterile water for injection (diluent) that comes in the PegIntron vial package.

1. Find a clean, well-lit, flat work surface.
2. Get 1 of your PegIntron vial packages. Check the date printed on the PegIntron carton. Make sure that the expiration date has not passed. Do not use your PegIntron vial packages if the expiration date has passed. The medicine in the PegIntron vial should look like a white to off-white tablet that is whole, or in pieces, or powdered.

   If you have already mixed the PegIntron solution and stored it in the refrigerator, take it out of the refrigerator before use and allow the solution to come to room temperature. See the Medication Guide section “How should I store PegIntron?”

3. Wash your hands well with soap and water, rinse and towel dry (See Figure A). Keep your work area, your hands, and injection site clean to decrease the risk of infection.

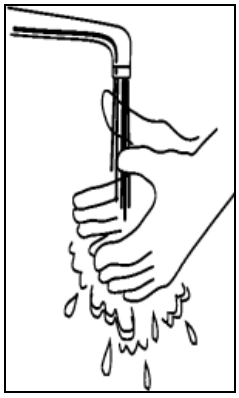

Figure A

The disposable syringes have needles that are already attached and cannot be removed. Each syringe has a clear plastic safety sleeve that is pulled over the needle for disposal after use. The safety sleeve should remain tight against the flange while using the syringe and moved over the needle only when ready for disposal. (See Figure B)

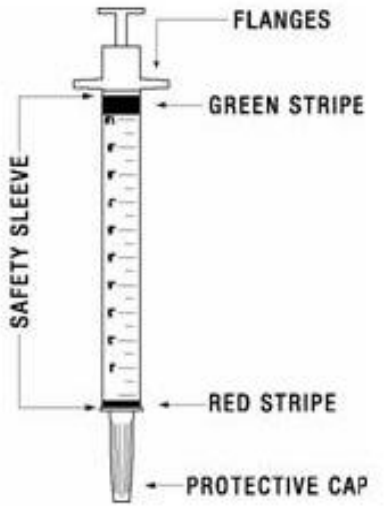

Figure B

4. Remove the protective wrapper from one of the syringes provided. Use the syringe for steps 4 through 15. Make sure that the syringe safety sleeve is sitting against the flange. (See Figure B)

5. Remove the protective plastic cap from the tops of both the sterile water for injection (diluent) and the PegIntron vials (See Figure C). Clean the rubber stopper on the top of both vials with an alcohol swab.

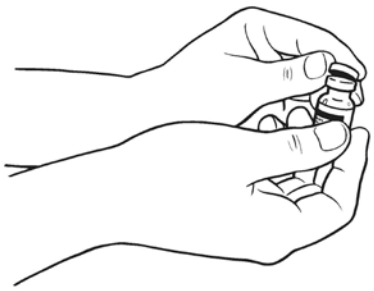

Figure C

6. Carefully remove the protective cap straight off of the needle to avoid damaging the needle point.

7. Fill the syringe with air by pulling back on the plunger to 0.7 mL. (See Figure D)

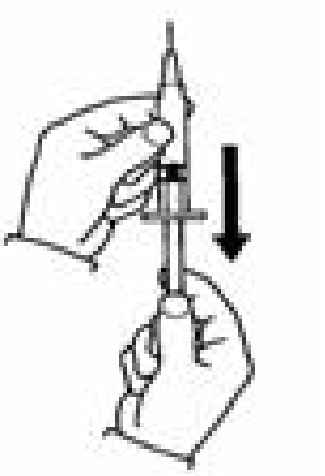

Figure D

8. Hold the diluent vial upright. Do not touch the cleaned top of the vial with your hands.
   - Push the needle through the center of the rubber stopper of the diluent vial. (See Figure E)
   - Slowly inject all the air from the syringe into the air space above the diluent in the vial. (See Figure F)

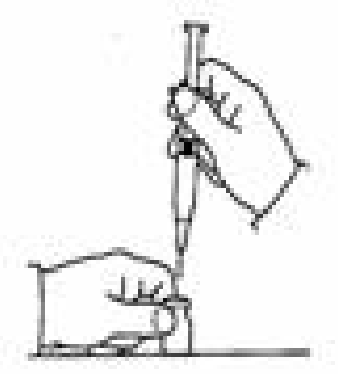

Figure E

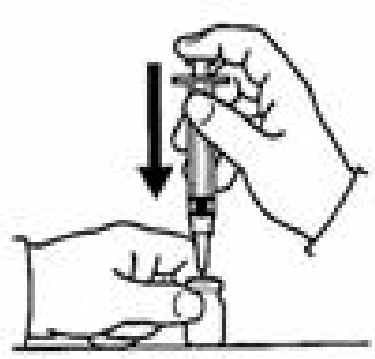

Figure F

9. Turn the vial upside down and make sure the tip of the needle is in the liquid.

10. Withdraw only 0.7 mL of diluent by pulling the plunger back to the 0.7 mL mark on the side of the syringe. (See Figure G)

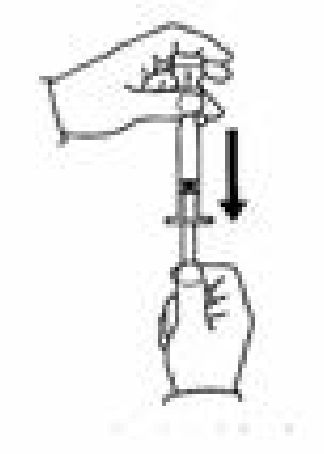

Figure G

11. With the needle still inserted in the vial, check the syringe for air bubbles.
    - If there are any air bubbles, gently tap the syringe with your finger until the air bubbles rise to the top of the syringe.
    - Slowly push the plunger up to remove the air bubbles.
    - If you push diluent back into the vial, slowly pull back on the plunger to draw the correct amount of diluent back into the syringe.

12. Remove the needle from the vial (See Figure H). Do not let the syringe touch anything.

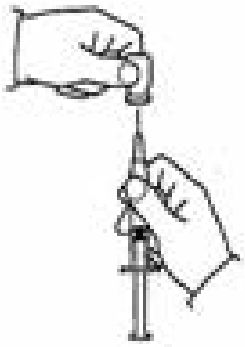

Figure H

13. Throw away any diluent that is left over in the vial.

14. Insert the needle through the center of the rubber stopper of the PegIntron powder vial. Do not touch the cleaned rubber stopper.
    - Place the needle tip, at an angle, against the side of the vial. (See Figure I)
    - Slowly push the plunger down to inject the 0.7 mL diluent. The stream of diluent should run down the side of the vial.

- To prevent bubbles from forming, do not aim the stream of diluent directly on the medicine in the bottom of the vial.

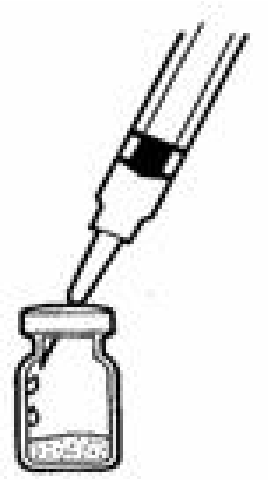

Figure I

15. Remove the needle from the vial.
    - Firmly grasp the safety sleeve and pull it over the exposed needle until you hear a click (See Figure J). The green stripe on the safety sleeve will completely cover the red stripe on the needle. Throw away the syringe, needle, and vial in the sharps disposal container (See “Disposal of the used needles, syringes, and vials”).

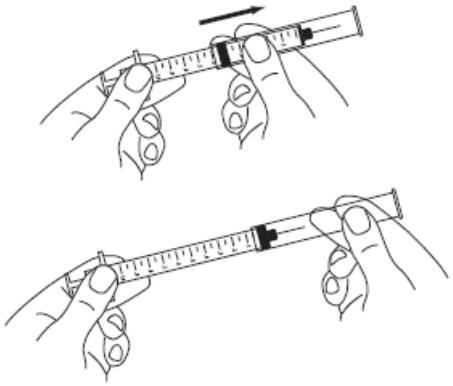

Figure J

16. Gently swirl the vial in a gentle circular motion, until the PegIntron is completely dissolved (mixed together). (See Figure K)
    - Do not shake the vial. If any powder remains undissolved in the vial, gently turn the vial upside down until all of the powder is dissolved.
    - The solution may look cloudy or bubbly for a few minutes. If air bubbles form, wait until the solution settles and all bubbles rise to the top.

Figure K

17. After the PegIntron completely dissolves, the solution should be clear, colorless and without particles. It is normal to see a ring of foam or bubbles on the surface.

    Do not use the mixed solution if you see particles in it, or it is not clear and colorless. Throw away the syringe, needle, and vial in the sharps disposal container (See the section "Disposal of the used needles, syringes, and vials"). Then, repeat steps 1 through 17 with a new vial of PegIntron and diluent to prepare a new syringe.

18. After the PegIntron powder completely dissolves, clean the rubber stopper again with an alcohol swab before you withdraw your dose.

19. Unwrap the second syringe provided. You will use it to give yourself the injection.

    - Carefully remove the protective cap from the needle. Fill the syringe with air by pulling the plunger to the number on the side of the syringe (mL) that matches your prescribed dose. (See Figure L)

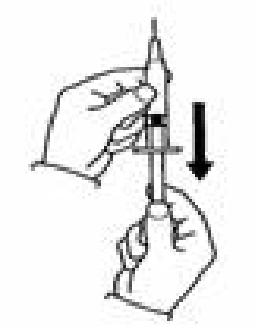

Figure L

    - Hold the PegIntron vial upright. Do not touch the cleaned top of the vial with your hands. (See Figure M)

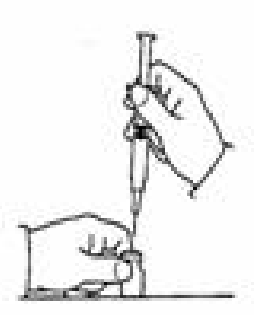

Figure M

- Insert the needle into the vial containing the PegIntron solution. Inject the air into the center of the vial. (See Figure N)

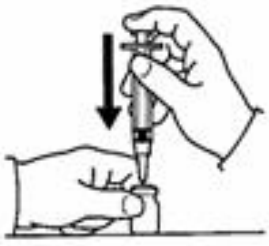

Figure N

20. Turn the PegIntron vial upside down. Be sure the tip of the needle is in the PegIntron solution.
    - Hold the vial and syringe with one hand. Be sure the tip of the needle is in the PegIntron solution. With the other hand, slowly pull the plunger back to fill the syringe with the exact amount of PegIntron into the syringe your healthcare provider told you to use. (See Figure O)

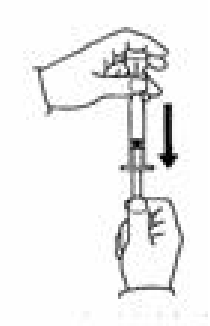

Figure O

21. Check for air bubbles in the syringe. If you see any air bubbles, hold the syringe with the needle pointing up. Gently tap the syringe until the air bubbles rise. Then, slowly push the plunger up to remove any air bubbles. If you push

solution into the vial, slowly pull back on the plunger again to draw the correct amount of PegIntron back into the syringe. When you are ready to inject the medicine, remove the needle from the vial. (See Figure P)

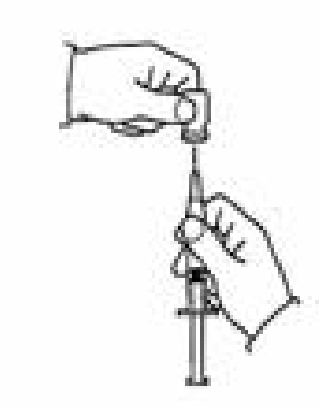

Figure P

How should I choose a site for injection?

The best sites for giving yourself an injection are those areas with a layer of fat between the skin and muscle, like your thigh, the outer surface of your upper arm, and abdomen (See Figure Q). Do not inject yourself in the area near your belly-button (navel) or waistline. If you are very thin, you should only use the thigh or outer surface of the arm for injection.

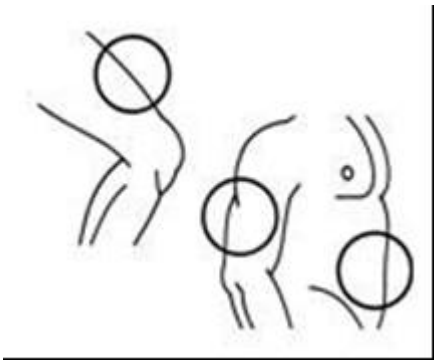

Figure Q

You should use a different site each time you inject PegIntron to avoid soreness at any one site. **Do not inject PegIntron solution into an area where the skin is irritated, red, bruised, infected or has scars, stretch marks, or lumps.**

How should I inject a dose of PegIntron?

22. Clean the skin where the injection is to be given with an alcohol swab. Wait for the area to dry.

- Make sure the safety sleeve of the syringe is pushed firmly against the syringe flange so that the needle is fully exposed.

23. With one hand, pinch a fold of skin. With your other hand, pick up the syringe and hold it like a pencil.

- Insert the needle into the pinched skin at a 45- to 90-degree angle with a quick dart-like motion. (See Figure R)

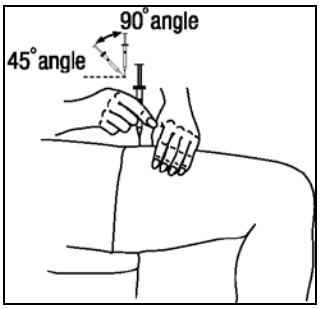

Figure R

- After the needle is inserted, remove the hand that you used to pinch your skin. Use it to hold the syringe barrel.
- Pull the plunger of the syringe back very slightly.
- **If no blood is present in the syringe**, inject the medicine by gently pressing the plunger all the way down the syringe barrel, until the syringe is empty.
- **If blood comes into the syringe**, the needle has entered a blood vessel. Do not inject.
    - Withdraw the needle and throw away the syringe and needle in the sharps disposal container. (See “Disposal of the used needles, syringes, and vials”)
    - Then, repeat steps 1 through 23 with a new vial of PegIntron and diluent to prepare a new syringe, and inject the medicine at a new site.

24. When the syringe is empty, pull the needle out of the skin.

- Place a cotton ball or gauze over the injection site and press for several seconds. Do not massage the injection site.
- If there is bleeding, cover it with a bandage.

25. After injecting your dose:

- Firmly grasp the safety sleeve and pull it over the exposed needle until you hear a click, and the green stripe on the safety sleeve covers the red stripe on the needle. (See Figure S)

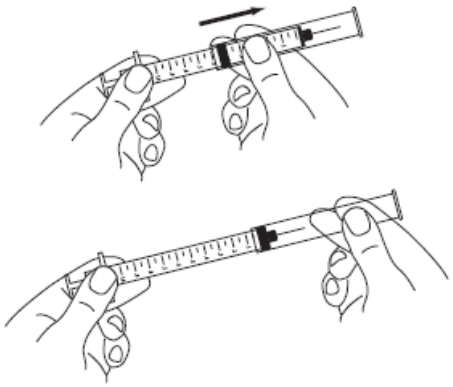

Figure S

Disposal of the used needles, syringes, and vials

- Put your used needles, syringes and vials in a FDA-cleared sharps disposal container right away after use. **Do not throw away (dispose of) loose needles, syringes and vials in your household trash.**
- If you do not have a FDA-cleared sharps disposal container, you may use a household container that is:
  - made of a heavy-duty plastic,
  - can be closed with a tight-fitting, puncture-resistant lid, without sharps being able to come out,
  - upright and stable during use,
  - leak-resistant, and
  - properly labeled to warn of hazardous waste inside the container.
- When your sharps disposal container is almost full, you will need to follow your community guidelines for the right way to dispose of your sharps disposal container. There may be state or local laws about how you should throw away used syringes and needles. For more information about safe sharps disposal, and for specific information about sharps disposal in the state that you live in, go to the FDA's website at: http://www.fda.gov/safesharpsdisposal.
- Do not dispose of your used sharps disposal container in your household trash unless your community guidelines permit this. Do not recycle your used sharps disposal container.

Always keep the sharps disposal container out of the reach of children.

How should I store PegIntron?

- Before mixing, store PegIntron vials at room temperature, between 68°F to 77°F (20°C to 25°C).
- After mixing, use PegIntron right away or store it in the refrigerator for up to 24 hours between 36°F to 46°F (2°C to 8°C).
- Do not freeze PegIntron.
- Keep PegIntron away from heat.

Keep PegIntron and all medicines out of the reach of children.

This Instructions for Use has been approved by the U.S. Food and Drug Administration.

Manufactured by:

Merck Sharp & Dohme Corp., a subsidiary of **Merck & Co., Inc.,** Whitehouse Station, NJ 08889, USA.

U.S. License Number 0002

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For patent information: www.merck.com/product/patent/home.html

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usifu-mk4031-pwi-1602r004

Instructions for Use

PegIntron® (peg-In-tron)

(peginterferon alfa-2b)

Powder for Injection

This Instructions for Use is only for use with the single-use vials of Powder for injection. If your healthcare provider prescribes the REDIPEN Pre-filled Pen for you, use only those Instructions for Use.

Be sure that you read, understand and follow these instructions before injecting PegIntron. Your healthcare provider should show you how to prepare, measure, and inject PegIntron properly using a vial before you use it for the first time. Ask your healthcare provider if you have any questions.

Important:

- Make sure that you have:
    - the correct strength of PegIntron vial prescribed by your healthcare provider.
    - the correct syringe and needle to use with PegIntron. Your healthcare provider should tell you what syringes and needles to use to inject PegIntron.
- Throw away the syringe and needle after you use it. Do not re-use your syringes and needles. See "How should I dispose of the used syringes, needles, and vials?" at the end of this Instructions for Use.
- The vial of mixed PegIntron should be used right away. Do not mix more than 1 vial of PegIntron at a time. If you do not use the vial of the prepared solution right away, store it in a refrigerator and use within 24 hours. See the end of these Instructions for Use for information about "How should I store PegIntron?"

Before starting, collect all of the supplies that you will need to use for preparing and injecting PegIntron. For each injection you will need a PegIntron vial package that contains:

- 1 vial of PegIntron powder for injection
- 1 vial of sterile water for injection (diluent). The vial contains an excess amount of sterile water (5 mL). You will only need to withdraw 0.7 mL to prepare your single dose.
- 2 single-use disposable syringes (BD Safety Lok syringes with a safety sleeve)
- 2 alcohol swabs

You will also need:

- 1 cotton ball or gauze
- 1 sharps disposal container for throwing away (dispose of) your used syringes, needles, and vials. See “How should I dispose of the used syringes, needles, and vials?” at the end of this Instructions for Use.

How should I prepare a dose of PegIntron?

Before you inject PegIntron, the powder must be mixed with 0.7 mL of the sterile water for injection (diluent) that comes in the PegIntron vial package.

1. Find a clean, well-lit, flat work surface.
2. Get 1 of your PegIntron vial packages. Check the date printed on the PegIntron carton. Make sure that the expiration date has not passed. Do not use your PegIntron vial packages if the expiration date has passed. The medicine in the PegIntron vial should look like a white to off-white tablet that is whole, or in pieces, or powdered.

   If you have already mixed the PegIntron solution and stored it in the refrigerator, take it out of the refrigerator before use and allow the solution to come to room temperature. See the Medication Guide section “How should I store PegIntron?”

3. Wash your hands well with soap and water, rinse and towel dry (See Figure A). Keep your work area, your hands, and injection site clean to decrease the risk of infection.

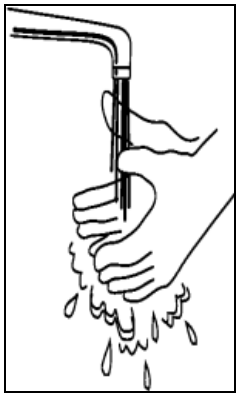

Figure A

The disposable syringes have needles that are already attached and cannot be removed. Each syringe has a clear plastic safety sleeve that is pulled over the needle for disposal after use. The safety sleeve should remain tight against the flange while using the syringe and moved over the needle only when ready for disposal. (See Figure B)

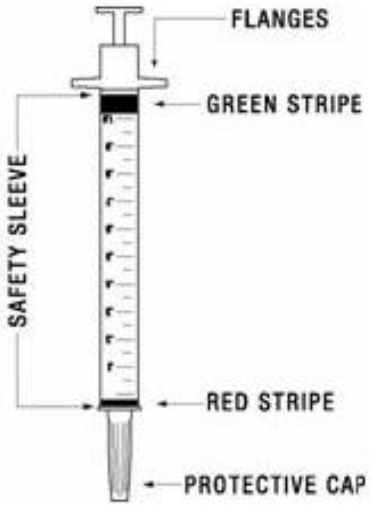

Figure B

4. Remove the protective wrapper from one of the syringes provided. Use the syringe for steps 4 through 15. Make sure that the syringe safety sleeve is sitting against the flange. (See Figure B)

5. Remove the protective plastic cap from the tops of both the sterile water for injection (diluent) and the PegIntron vials (See Figure C). Clean the rubber stopper on the top of both vials with an alcohol swab.

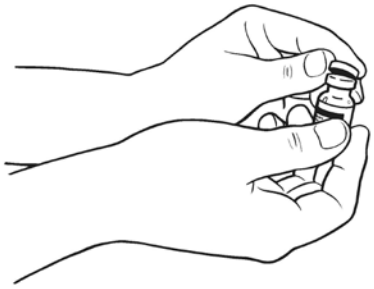

Figure C

6. Carefully remove the protective cap straight off of the needle to avoid damaging the needle point.

7. Fill the syringe with air by pulling back on the plunger to 0.7 mL. (See Figure D)

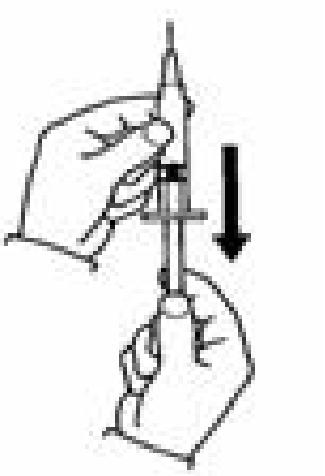

Figure D

8. Hold the diluent vial upright. Do not touch the cleaned top of the vial with your hands.
   - Push the needle through the center of the rubber stopper of the diluent vial. (See Figure E)
   - Slowly inject all the air from the syringe into the air space above the diluent in the vial. (See Figure F)

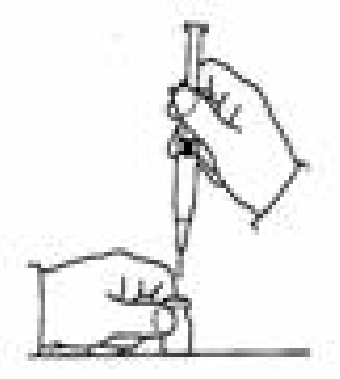

Figure E

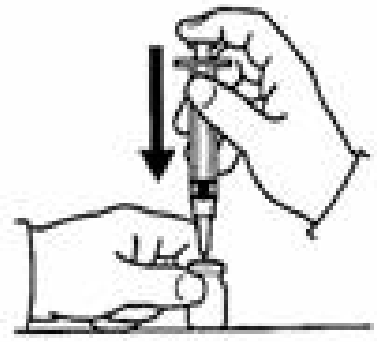

Figure F

9. Turn the vial upside down and make sure the tip of the needle is in the liquid.
   - Important: The sterile water for injection vial contains an excess amount of sterile water (5 mL). **You will only need to withdraw 0.7 mL to prepare your single dose.**

10. Withdraw only 0.7 mL of diluent by pulling the plunger back to the 0.7 mL mark on the side of the syringe. (See Figure G)

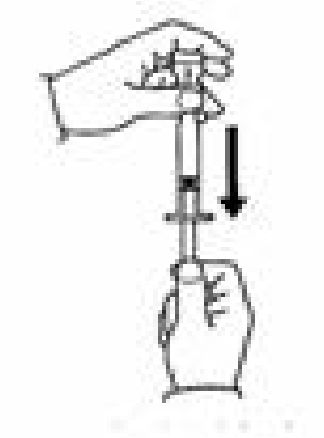

Figure G

11. With the needle still inserted in the vial, check the syringe for air bubbles.
    - If there are any air bubbles, gently tap the syringe with your finger until the air bubbles rise to the top of the syringe.
    - Slowly push the plunger up to remove the air bubbles.
    - If you push diluent back into the vial, slowly pull back on the plunger to draw the correct amount of diluent back into the syringe.

12. Remove the needle from the vial (See Figure H). Do not let the syringe touch anything.

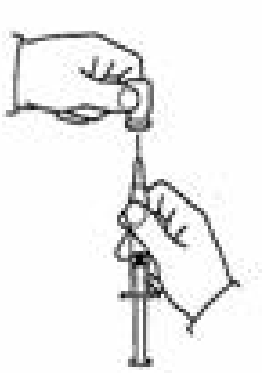

Figure H

13. Throw away the diluent that is left over in the vial. Do not save any leftover diluent or use it again. See “How should I dispose of the used syringes, needles, and vials?” at the end of this Instructions for Use.

14. Insert the needle through the center of the rubber stopper of the PegIntron powder vial. Do not touch the cleaned rubber stopper.
    - Place the needle tip, at an angle, against the side of the vial. (See Figure I)

- Slowly push the plunger down to inject the 0.7 mL diluent. The stream of diluent should run down the side of the vial.
- To prevent bubbles from forming, do not aim the stream of diluent directly on the medicine in the bottom of the vial.

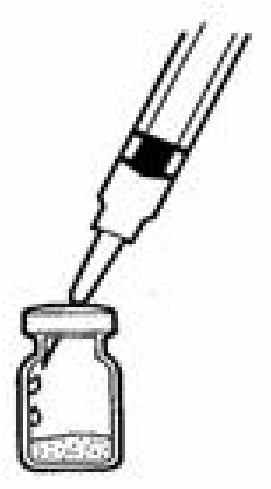

Figure I

15. Remove the needle from the vial.
    - Firmly grasp the safety sleeve and pull it over the exposed needle until you hear a click (See Figure J). The green stripe on the safety sleeve will completely cover the red stripe on the needle. Dispose of the syringe, needle, and vial in the sharps disposal container (See “How should I dispose of the used syringes, needles, and vials?”).

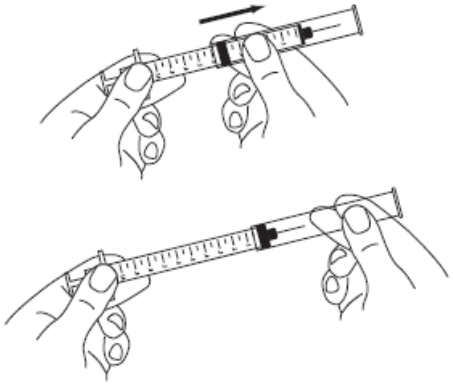

Figure J

16. Gently swirl the vial in a gentle circular motion, until the PegIntron is completely dissolved (mixed together). (See Figure K)
    - Do not shake the vial. If any powder remains undissolved in the vial, gently turn the vial upside down until all of the powder is dissolved.
    - The solution may look cloudy or bubbly for a few minutes. If air bubbles form, wait until the solution settles and all bubbles rise to the top.

Figure K

17. After the PegIntron completely dissolves, the solution should be clear, colorless and without particles. It is normal to see a ring of foam or bubbles on the surface.

    Do not use the mixed solution if you see particles in it, or it is not clear and colorless. Dispose of the syringe, needle, and vial in the sharps disposal container (See "How should I dispose of the used syringes, needles, and vials?"). Then, repeat steps 1 through 17 with a new vial of PegIntron and diluent to prepare a new syringe.

18. After the PegIntron powder completely dissolves, clean the rubber stopper again with an alcohol swab before you withdraw your dose.

19. Unwrap the second syringe provided. You will use it to give yourself the injection.

    - Carefully remove the protective cap from the needle. Fill the syringe with air by pulling the plunger to the number on the side of the syringe (mL) that matches your prescribed dose. (See Figure L)

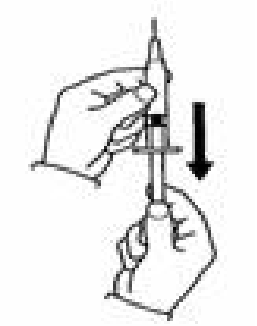

Figure L

    - Hold the PegIntron vial upright. Do not touch the cleaned top of the vial with your hands. (See Figure M)

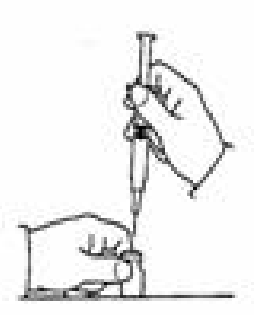

Figure M

- Insert the needle into the vial containing the PegIntron solution. Inject the air into the center of the vial. (See Figure N)

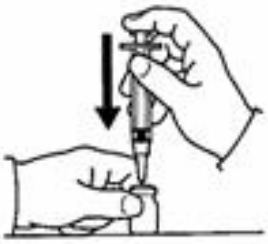

Figure N

20. Turn the PegIntron vial upside down. Be sure the tip of the needle is in the PegIntron solution.
    - Hold the vial and syringe with one hand. Be sure the tip of the needle is in the PegIntron solution. With the other hand, slowly pull the plunger back to fill the syringe with the exact amount of PegIntron into the syringe your healthcare provider told you to use. (See Figure O)

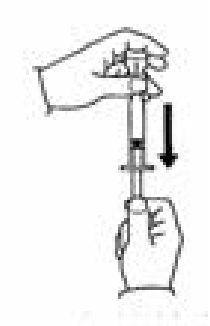

Figure O

21. Check for air bubbles in the syringe. If you see any air bubbles, hold the syringe with the needle pointing up. Gently tap the syringe until the air bubbles rise. Then, slowly push the plunger up to remove any air bubbles. If you push

solution into the vial, slowly pull back on the plunger again to draw the correct amount of PegIntron back into the syringe. When you are ready to inject the medicine, remove the needle from the vial. (See Figure P)

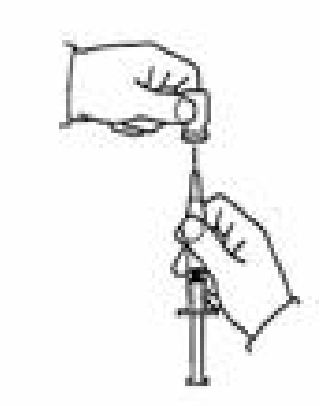

Figure P

How should I choose a site for injection?

The best sites for giving yourself an injection are those areas with a layer of fat between the skin and muscle, like your thigh, the outer surface of your upper arm, and abdomen (See Figure Q). Do not inject yourself in the area near your belly-button (navel) or waistline. If you are very thin, you should only use the thigh or outer surface of the arm for injection.

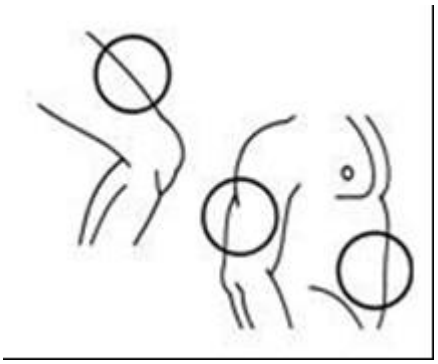

Figure Q

You should use a different site each time you inject PegIntron to avoid soreness at any one site. **Do not inject PegIntron solution into an area where the skin is irritated, red, bruised, infected or has scars, stretch marks, or lumps.**

How should I inject a dose of PegIntron?

22. Clean the skin where the injection is to be given with an alcohol swab. Wait for the area to dry.

- Make sure the safety sleeve of the syringe is pushed firmly against the syringe flange so that the needle is fully exposed.

23. With one hand, pinch a fold of skin. With your other hand, pick up the syringe and hold it like a pencil.

- Insert the needle into the pinched skin at a 45- to 90-degree angle with a quick dart-like motion. (See Figure R)

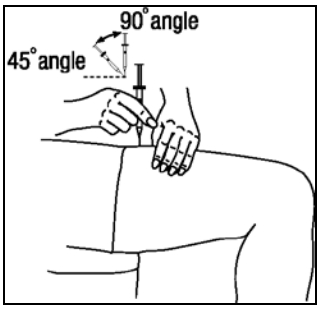

Figure R

- After the needle is inserted, remove the hand that you used to pinch your skin. Use it to hold the syringe barrel.
- Pull the plunger of the syringe back very slightly.
- **If no blood is present in the syringe**, inject the medicine by gently pressing the plunger all the way down the syringe barrel, until the syringe is empty.
- **If blood comes into the syringe**, the needle has entered a blood vessel. Do not inject.
    - Withdraw the needle and dispose of the syringe and needle in the sharps disposal container. (See "How should I dispose of the used syringes, needles, and vials?" at the end of this Instructions for Use.)
    - If there is bleeding, cover the injection site with a bandage.
    - Then, repeat steps 1 through 23 with a new vial of PegIntron and diluent to prepare a new syringe, and inject the medicine at a new site.

24. When the syringe is empty, pull the needle out of the skin.

- Place a cotton ball or gauze over the injection site and press for several seconds. Do not massage the injection site.
- If there is bleeding, cover it with a bandage.

25. After injecting your dose:

- Firmly grasp the safety sleeve and pull it over the exposed needle until you hear a click, and the green stripe on the safety sleeve covers the red stripe on the needle. (See Figure S)

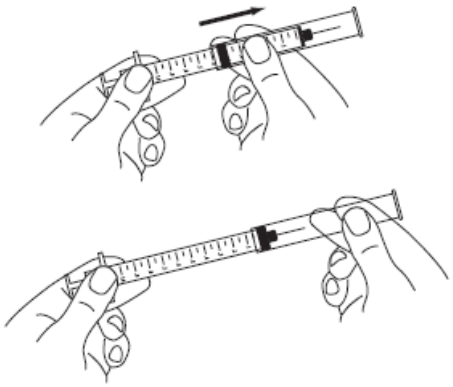

Figure S

26. Dispose of used syringes, needles, and vials in the sharps disposal container. (See "How should I dispose of the used syringes, needles, and vials?" below).

How should I dispose of the used syringes, needles, and vials?

- Put your used needles, syringes and vials in a FDA-cleared sharps disposal container right away after use. **Do not throw away (dispose of) loose needles, syringes and vials in your household trash.**
- If you do not have a FDA-cleared sharps disposal container, you may use a household container that is:
  - made of a heavy-duty plastic,
  - can be closed with a tight-fitting, puncture-resistant lid, without sharps being able to come out,
  - upright and stable during use,
  - leak-resistant, and
  - properly labeled to warn of hazardous waste inside the container.
- When your sharps disposal container is almost full, you will need to follow your community guidelines for the right way to dispose of your sharps disposal container. There may be state or local laws about how you should throw away used syringes and needles. For more information about safe sharps disposal, and for specific information about sharps disposal in the state that you live in, go to the FDA's website at: http://www.fda.gov/safesharpsdisposal.

- Do not dispose of your used sharps disposal container in your household trash unless your community guidelines permit this. Do not recycle your used sharps disposal container.

Always keep the sharps disposal container out of the reach of children.

How should I store PegIntron?

- Before mixing, store PegIntron vials at room temperature, between 68°F to 77°F (20°C to 25°C).
- After mixing, use PegIntron right away or store it in the refrigerator for up to 24 hours between 36°F to 46°F (2°C to 8°C).
- Do not freeze PegIntron.
- Keep PegIntron away from heat.

Keep PegIntron and all medicines out of the reach of children.

This Instructions for Use has been approved by the U.S. Food and Drug Administration.

Manufactured by:

Merck Sharp & Dohme Corp., a subsidiary of **Merck & Co., Inc.,** Whitehouse Station, NJ 08889, USA

U.S. License Number 0002

Revised: 05/2017

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For patent information: www.merck.com/product/patent/home.html

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usifu-mk4031-pwi-5mL-1602r001

Instructions for Use

PegIntron® (peg-In-tron)

(Peginterferon alfa-2b)

REDIPEN® single-use pre-filled pen

This Instructions for Use is only for use with the REDIPEN single-use pre-filled pen.

Be sure that you read, understand, and follow these instructions before injecting PegIntron. Your healthcare provider should show you how to prepare and inject PegIntron properly using the REDIPEN single-use pre-filled pen before you use it for the first time. Ask your healthcare provider if you have any questions.

Important:

- Make sure that you have the correct strength of REDIPEN pre-filled pen prescribed by your healthcare provider.
- Throw away REDIPEN after you use it. **Do not re-use your pre-filled pen or needle.** See "**Disposal of used needles and pre-filled pens**" in this Instructions for Use.

Before starting, collect all of the supplies that you will need to use for preparing and injecting PegIntron. For each injection you will need a package that contains:

- 1 PegIntron REDIPEN single-use pre-filled pen
- 1 disposable needle
- 2 alcohol swabs
- dosing tray (the dosing tray is the bottom half of the REDIPEN package)

- You will need gauze or a cotton ball to press to the injection site after injecting. You will also need 1 sharps disposal container for throwing away your used pre-filled pen. See "**Disposal of used needles and pre-filled pens**" in this Instructions for Use.

The REDIPEN single-use pre-filled pen should only be used with the injection needle that comes in the package. If you use other needles, the pen may not work the right way.

- Figures A and B below show the different parts of the REDIPEN single-use pre-filled pen and the injection needle. Figure C below shows the dosing tray with the pre-filled pen. The parts of the pre-filled pen you need to know are:

Figure A

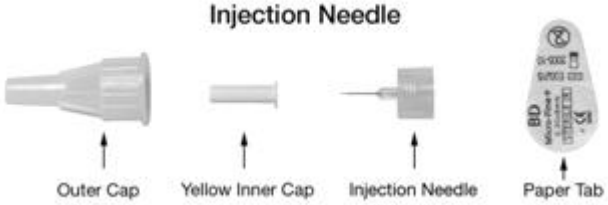

Figure B

Figure C

How should I prepare a dose of PegIntron using the REDIPEN single-use pre-filled pen?

1. Find a clean, well-lit, flat work surface.
2. Take the pre-filled pen out of the refrigerator and allow the medicine to come to room temperature. Look at the date printed on the carton to make sure that the expiration date has not passed. Do not use if the expiration date has passed.
3. After taking the pre-filled pen out of the carton, look in the window of the pre-filled pen and make sure the PegIntron in the cartridge holder window is a white to off-white tablet that is whole, or in pieces, or powdered.

4. Wash your hands well with soap and water. It is important to keep your work area, your hands, and the injection site clean to decrease the risk of infection. See Figure D.

Figure D

Mix the PegIntron

5. **Place the pre-filled pen upright** in the dosing tray on a hard, flat, non-slip surface with the dosing button down. See Figure E. You may want to hold the pre-filled pen using the grip.

Figure E

6. To mix the powder and the liquid, keep the pre-filled pen upright in the dosing tray and press the top half of the pre-filled pen downward toward the hard, flat, non-slip surface **until you hear the "click" sound.** See Figure F. When you hear the click, you will notice in the window that both dark stoppers are now touching. The dosing button should be flat with the pen body.

Figure F

7. Wait several seconds for the powder to completely dissolve. Do not shake. If the solution does not dissolve, gently turn the pre-filled pen upside down two times. See Figure G.

Figure G

8. Keep the pre-filled pen **UPRIGHT**, with the dosing button down. Look through the pre-filled pen window to see that the mixed PegIntron solution is completely dissolved. The solution should be clear and colorless **before use**. It is normal to see some small bubbles in the pre-filled pen window, near the top of the solution. Do not use the REDIPEN pre-filled pen if the solution is discolored, or is not clear, or if it has particles in it.

9. Place the pre-filled pen back into the dosing tray provided in the packaging. See Figure H. The dosing button will be on the bottom.

Figure H

Attach the Needle

10. Before you attach the needle to the pre-filled pen, wipe the rubber membrane of the pre-filled pen with an alcohol swab.

11. Remove the protective paper tab from the injection needle, but do not remove either the outer cap or the yellow inner cap from the injection needle.

12. Keep the pre-filled pen upright in the dosing tray and push the injection needle straight into the pre-filled pen rubber membrane. Screw the needle onto the pre-filled pen by turning it in a clockwise direction. See Figure I.
    - Remember to leave the needle caps in place when you attach the needle to the pre-filled pen. Pushing the needle through the rubber membrane "primes" the needle and allows the extra liquid and air in the pen to be removed.

Figure I

NOTE: Some fluid will trickle out. This is **normal**. The dark stoppers move up and you will no longer see the fluid in the window once the needle is successfully primed.

- Remove the outer clear needle cap on the pre-filled pen, but leave the yellow cap on. See Figure J.

Figure J

How should I set the dose prescribed by my healthcare provider?

Dial the Dose

13. Holding the pre-filled pen firmly, pull the dosing button out as far as it will go. See Figure K. You will see a dark band.

    Do not push the dosing button in until you are ready to self-inject the PegIntron dose.

Figure K

14. Turn the dosing button until your prescribed dose is lined up with the dosing tab. See Figure L. The dosing button will turn freely. If you have trouble dialing your dose, check to make sure the dosing button has been pulled out **as far** as it will go. See Figure M.

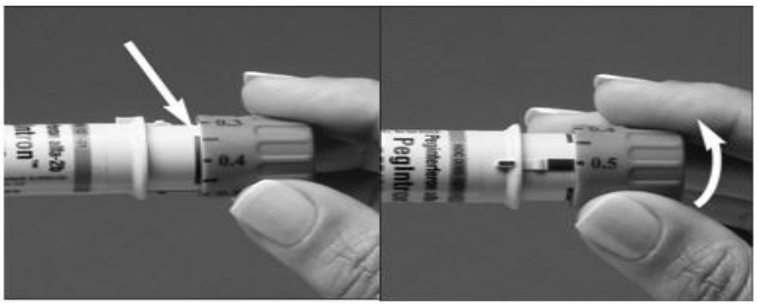

Figure L **Figure M**

15. Carefully lay the pre-filled pen down on the dosing tray or on a hard, flat, non-slip surface. Do not remove the yellow needle cap and do not push the dosing button in until you are ready to self-inject the PegIntron dose.

Choosing an Injection Site

The best sites for giving yourself an injection are those areas with a layer of fat between the skin and muscle, like your thigh, the outer surface of your upper arm, and abdomen. See Figure N. Do not inject yourself in the area near your belly-button (navel) or waistline. If you are very thin, you should only use the thigh or outer surface of the arm for injection.

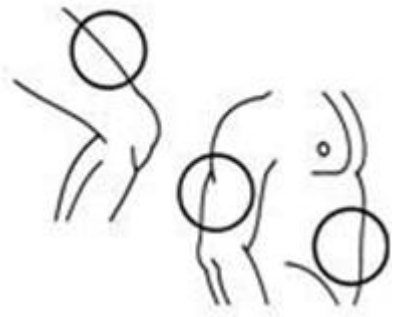

Figure N

You should use a different site each time you inject PegIntron to avoid soreness at any one site. Do not inject PegIntron into an area where the skin is irritated, red, bruised, infected, or has scars, stretch marks, or lumps.

How should I Inject a dose of PegIntron?

16. Clean the skin where the injection is to be given with the second alcohol swab provided, and wait for the skin to dry.

17. There may be some liquid around the yellow inner needle cap. See Figure O. This is normal.

Figure O

18. Remove the **yellow** inner needle cap when the injection site is dry. See Figure P. You are now ready to inject.

Figure P

19. Hold the pre-filled pen with your fingers wrapped around the pen body barrel and your thumb on the dosing button. See Figure Q.

Figure Q

20. With your other hand, pinch the skin in the area you have cleaned for injection.

21. Insert the needle into the pinched skin at an angle of 45° to 90°. See Figure R.

Figure R

22. Press the dosing button down slowly and firmly until you can not push it any further. Keep your thumb pressed down on the dosing button for an additional 5 seconds to make sure that you get the complete dose.

23. Slowly release the dosing button and remove the needle from your skin.

24. Gently press the injection site with a small bandage or sterile gauze if needed for a few seconds but do not massage the injection site. If there is bleeding, cover with an adhesive bandage. Do not recap the needle and do not reuse the pre-filled pen.

Disposal of the used needles and pre-filled pens

- Put your used needles and pre-filled pens in a FDA-cleared sharps disposal container right away after use. **Do not throw away (dispose of) loose needles and pre-filled pens in your household trash.**
- If you do not have a FDA-cleared sharps disposal container, you may use a household container that is:
    - made of a heavy-duty plastic,
    - can be closed with a tight-fitting, puncture-resistant lid, without sharps being able to come out,
    - upright and stable during use,
    - leak-resistant, and
    - properly labeled to warn of hazardous waste inside the container.
- When your sharps disposal container is almost full, you will need to follow your community guidelines for the right way to dispose of your sharps disposal container. There may be state or local laws about how you should throw away used needles, syringes and pre-filled pens. For more information about safe sharps disposal, and for specific information about sharps disposal in the state that you live in, go to the FDA's website at: http://www.fda.gov/safesharpsdisposal.
- Do not dispose of your used sharps disposal container in your household trash unless your community guidelines permit this. Do not recycle your used sharps disposal container.

Always keep the sharps disposal container out of the reach of children.

How should I store PegIntron REDIPEN pre-filled pen?

- Before mixing, store PegIntron REDIPEN pre-filled pen in the refrigerator between 36°F to 46°F (2°C to 8°C).
- After mixing, use PegIntron right away or store it in the refrigerator for up to 24 hours between 36°F to 46°F (2°C to 8°C).
- Do not freeze PegIntron.
- Keep PegIntron away from heat.

Keep PegIntron and all medicines out of reach of children.

This Instructions for Use has been approved by the U.S. Food and Drug Administration.

Manufactured by:

Merck Sharp & Dohme Corp., a subsidiary of **Merck & Co., Inc.**, Whitehouse Station, NJ 08889, USA

U.S. License Number 0002

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For patent information: www.merck.com/product/patent/home.html

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The genetics of drug efficacy: opportunities and challenges

Matthew R. Nelson[1], Toby Johnson[2]*, Liling Warren[3,4], Arlene R. Hughes[5], Stephanie L. Chissoe[6], Chun-Fang Xu[2] and Dawn M. Waterworth[1]*

Abstract | Lack of sufficient efficacy is the most common cause of attrition in late-phase drug development. It has long been envisioned that genetics could drive stratified drug development by identifying those patient subgroups that are most likely to respond. However, this vision has not been realized as only a small proportion of drugs have been found to have germline genetic predictors of efficacy with clinically meaningful effects, and so far all but one were found after drug approval. With the exception of oncology, systematic application of efficacy pharmacogenetics has not been integrated into drug discovery and development across the industry. Here, we argue for routine, early and cumulative screening for genetic predictors of efficacy, as an integrated component of clinical trial analysis. Such a strategy would identify clinically relevant predictors that may exist at the earliest possible opportunity, allow these predictors to be integrated into subsequent clinical development and provide mechanistic insights into drug disposition and patient-specific factors that influence response, therefore paving the way towards more personalized medicine.

One of the challenges for contemporary drug discovery and development is providing regulators, physicians, patients and payers with evidence that differentiates a new drug from the current standard-of-care treatments. This can be particularly challenging in disease areas where combination therapy is common and a wide range of drugs are already available, such as cardiovascular disease, type 2 diabetes, respiratory diseases, some infectious diseases and cancers. A new drug may be differentiated by superior efficacy, a more convenient dosing regimen or route of administration, a lower risk of adverse effects, or a combination of these or other advantages. One challenge to demonstrating efficacy is a lack of detailed understanding of inter-individual variability in drug response, which may involve differing concentrations of a drug reaching relevant tissues, differences in interactions between a drug and its target (or targets), or differences in the underlying causes or biological pathways perturbed by disease. Historically, a 'one-size-fits-all' approach has been common in drug development. Inevitably, a range of responses occur, and the overall drug effect observed in any given clinical trial reflects this mixture. There are a number of scientific efforts to understand the factors that affect drug response so that the best treatments can be given to each patient to maximize benefit and minimize potential harms — this is broadly referred to as personalized medicine. In addition to the benefit for patients, substantial efficiencies and savings could be made by drug developers. Earlier identification of genetic predictors could enable more efficient trials, with parallel rather than sequential development of companion diagnostics.

It has long been expected that genetics would play a major part in explaining inter-individual variability in drug response, a field known as pharmacogenetics. The impact of variation in genes involved in ADME (drug absorption, distribution, metabolism and excretion) on drug exposure (pharmacokinetics) is well established and has been studied since the 1950s[1]; such effects are noted in approved labelling information for many drugs[2]. Some high-profile successes of ADME pharmacogenetics in identifying predictors of drug toxicity[3], along with the occasionally high variability in drug response, created expectations that the human genome era would give rise to extensive genotype-based personalized medicine[4]. Progress so far has largely fallen short of those expectations, except for a few common cancers for which some drugs are indicated only for patients with specific tumour genomic alterations. However, outside of oncology, it is unclear whether the current lack of genetic predictors to guide treatment decisions is due to the paucity of well-powered genetic studies conducted for drug response, or due to a lack of genetic factors that actually influence drug response. In a recent review of the pharmacogenetics literature, Ioannidis[5] (who shook up the disease genetics field in 2001 with a similar review)[6]

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SLCO1B1 Genetic Variant Associated With Statin-Induced Myopathy: A Proof-of-Concept Study Using the Clinical Practice Research Datalink

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This study aimed to determine whether patients with statin-induced myopathy could be identified using the United Kingdom Clinical Practice Research Datalink, whether DNA could be obtained, and whether previously reported associations of statin myopathy with the *SLCO1B1* c.521T>C and COQ2 rs4693075 polymorphisms could be replicated. Seventy-seven statin-induced myopathy patients (serum creatine phosphokinase (CPK) > 4× upper limit of normal (ULN)) and 372 statin-tolerant controls were identified and recruited. Multiple logistic regression analysis showed the *SLCO1B1* c.521T>C single-nucleotide polymorphism to be a significant risk factor ($P = 0.009$), with an odds ratio (OR) per variant allele of 2.06 (1.32–3.15) for all myopathy and 4.09 (2.06–8.16) for severe myopathy (CPK > 10× ULN, and/or rhabdomyolysis; $n = 23$). *COQ2* rs4693075 was not associated with myopathy. Meta-analysis showed an association between c.521C>T and simvastatin-induced myopathy, although power for other statins was limited. Our data replicate the association of *SLCO1B1* variants with statin-induced myopathy. Furthermore, we demonstrate how electronic medical records provide a time- and cost-efficient means of recruiting patients with severe adverse drug reactions for pharmacogenetic studies.

The UK Clinical Practice Research Datalink (CPRD), formerly the General Practice Research Database, is a computerized database of anonymized longitudinal medical records from primary care. In March 2011 there were more than 12 million patient records contributing more than 64 million years of prospectively collected data; the number of records is to be increased to 52 million with the transition to CPRD.[1] The information collected includes patient demographics, medical diagnoses, prescription information, referrals, and health outcomes. Although the database has been widely used in observational studies, including reports on clinical epidemiology, disease patterns, drug utilization, and outcomes research, resulting in more than 800 publications, it has never been used to obtain patient samples for biomarker analysis.

To determine whether the CPRD could be used for biomarker analysis, we focused on the pharmacogenetics of statin-induced myopathy. This was chosen as the paradigm for several reasons: first, statins (inhibitors of 5-hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA) reductase) are widely used, being the cornerstone of therapy for hyperlipidemia, with proven efficacy for both primary and secondary prevention of atherosclerotic arterial disease.[2] Although generally well tolerated, a few patients develop muscle-related adverse effects, ranging from muscle pains without any elevation of plasma creatine kinase (CK)—a biomarker for muscle injury—to rhabdomyolysis, in which CK is elevated to > 10 times the upper limit of normal (ULN), which may be associated with renal impairment.[3] A systematic review of 21 clinical trials[4] suggested that mild muscle pain, myopathy, and rhabdomyolysis attributable to statin therapy occurred at an incidence of 190, 5, and 1.6 per 100,000 patient years, respectively.

Second, functional variation of the hepatic uptake transporter SLCO1B1 has been implicated in statin-induced myopathy. A genome-wide association study of 85 patients with incipient (CK level >3× ULN and >5× baseline) or definite myopathy

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(muscle symptoms with CK > 10× ULN) and 90 controls who were receiving 80 mg/day simvastatin showed a strong association with a noncoding single-nucleotide polymorphism (SNP; rs4363657).[5] This was subsequently found to be in nearly complete linkage disequilibrium with a nonsynonymous c. 521T>C SNP (rs4149056) that encodes a valine to arginine amino acid substitution at residue 147 (p.V147L) and defines the *SLCO1B1*5* allele. This variant has subsequently been associated with statin-induced myopathy in a number of other studies.[6–8] The incidence of statin-induced myopathy has been reported to be 19% in individuals without any *5 alleles, 27% in heterozygous individuals, and 50% in *5/*5 homozygous individuals.[8]

Recent studies have also suggested that variation in the coenzyme Q2 (COQ2) homologue gene may also predispose individuals to statin-induced myopathy. Puccetti *et al.* demonstrated an association between both rosuvastatin- and atorvastatin-induced myopathy and the rs4693075 polymorphism in the *COQ2* gene.[9] An association of another *COQ2* variant (rs4693570) and statin-induced myalgia has also been described.[10] Variants of the *COQ2* loci are directly involved in CoQ deficiency,[10] a postulated mechanism of statin-induced myopathy.[11,12]

Third, in randomized controlled trials, the incidence of statin-induced myopathy is very low. For example, of 6,031 patients receiving 80 mg simvastatin, the SEARCH (Study of the Effectiveness of Additional Reductions in Cholesterol and Homocysteine) study[5] identified just 49 (0.8%) patients who had developed myopathy (defined muscle symptoms with CPK > 10× ULN). Thus, it is important to explore other methods for recruiting patients from particular electronic records, in which the use of individual drugs is usually much higher than that in trials, and it represents real-world clinical practice, in which the incidence of severe adverse reactions is higher. This article thus describes the process by which the CPRD was used to identify and recruit a cohort of statin-receiving patients with and without an increase in CPK levels in the presence or absence of muscle symptoms. We have then undertaken genotyping for *SLCO1B1* and *COQ2* variants.

RESULTS

Statin-induced myopathy case recruitment

A total of 76 cases were recruited between June 2010 and November 2011, and a total of 372 controls were recruited from the General Practice Research Database between June 2010 and April 2012. Clinical data are summarized in **Table 1**. Within the first phase of recruitment (June 2010 onward), a total of 520 potential cases of statin-induced myopathy were identified on the patient list of recruited general practice clinics. Of these, 223 (42%) were deemed suitable by the physician for inclusion. As of November 2011, 76 (34%) patients had provided adequate biological samples (blood or saliva) to the receiving laboratory. Full recruitment statistics for the 36-month study period will be subsequently reported in a future publication.

Demography

At the time of the reported event, 59 of 76 (78%) myopathy patients were receiving simvastatin; 11 (14%) were on atorvastatin, and 6 (8%) were using other statins (cerivastatin, pravastatin, rosuvastatin, or fluvastatin). In the control cohort, 222 of 372 (60%) were receiving simvastatin at the time of recruitment, 30% were on atorvastatin, and 10% received other statins (**Table 1**). Univariate binary logistic regression analyses (**Table 1**) showed borderline statistically significant differences between cases and controls in terms of the statin type ($P = 0.075$) and previous history of type 2 diabetes ($P = 0.046$), asthma ($P = 0.080$), and hypertension ($P = 0.087$). These four variables were all adjusted for in the SNP-association analyses. There was no difference in the use of CYP3A4 inhibitors between cases and controls.

SNP analysis

Both SNPs conformed to Hardy–Weinberg equilibrium ($P > 0.0001$). The two SNPs were successfully genotyped in 99.7% (rs4693075) and 100% (rs4149056) of individuals. For logistic regression analysis of *COQ2* rs4693075, 371 controls were included. On comparing the SNP model including the *SLCO1B1* c.521T>C SNP (rs4149056) with the baseline model, the likelihood ratio test gave a significant *P* value (**Table 2**) both when incorporating all statin-induced myopathy cases (76 cases, 372 controls; $P = 0.005$) and when limiting the analysis to just patients with severe myopathy (23 cases, 372 controls; $P = 0.0003$). Limiting analysis to only those individuals receiving atorvastatin ($n = 121$) demonstrated no significant association between *SLCO1B1* c.521T>C (rs4149056) and risk of either myopathy ($P = 0.613$) or severe myopathy ($P = 0.507$). However, in patients receiving simvastatin ($n = 281$), statistically significant associations between c.521T>C (rs4149056) and risk of both myopathy ($P = 0.014$) and severe myopathy ($P = 0.0004$) were observed. Addition of the *COQ2* rs4693075 to the baseline model did not give a statistically significant *P* value for either all myopathy ($P = 0.358$) or severe myopathy ($P = 0.937$).

Binary logistic regression (**Table 2**) demonstrated a significant risk per *SLCO1B1* c.521 C allele for all myopathy cases regardless of prescribed statin ($n = 76$; odds ratio (OR) = 2.08 (1.35–3.23), $P = 0.005$). This translates to an OR of 4.32 (1.82–10.43) for risk of all myopathy for CC carriers as compared with TT carriers. For cases with severe myopathy ($n = 18$), an even higher risk per C allele was observed (OR = 4.47 (1.84–10.84)), translating to an OR of 19.98 (3.38–117.50) in CC individuals vs. that in TT individuals.

Limiting this analysis to individuals receiving simvastatin only demonstrated a similar risk to that observed for all statins, with a per-C-allele OR for all myopathy ($n = 59$) of 2.13 (1.29–3.54; $P = 0.014$). For simvastatin-induced severe myopathy ($n = 18$), the OR was 4.97 (2.16–11.43). Stratification of simvastatin patients (all myopathy) into those receiving <40 mg/day ($n = 24$) or ≥40 mg/day ($n = 35$) showed an increased risk for c.521C-allele carriers in the ≥40-mg/day group (OR = 3.23 (1.74–5.99), $P = 0.0002$)), whereas no significant risk was observed in the <40-mg group (OR = 1.03 (0.45–2.36), $P > 0.05$). For severe myopathy in patients receiving ≥40 mg/day simvastatin ($n = 13$), the OR per-C-allele was 6.28 (2.38–16.60; $P = 0.0004$). In patients

Table 1 Case–control comparison of nongenetic clinical variables

Variable	Controls ($n = 372$)	Cases ($n = 76$)	*P* value
Statin at index			
Simvastatin	222 (60%)	59 (75%)	**0.075**
Atorvastatin	110 (30%)	11 (14%)	
Rosuvastatin	21 (6%)	2 (3%)	
Fluvastatin	6 (2%)	1 (1%)	
Pravastatin	12 (3%)	3 (4%)	
Ceruvastatin	1 (<1%)	0 (0%)	
Mean daily dose, mg/day (SD)*	30.6 (±15.7)	33.2 (±15.7)	0.219
Mean age, years (SD)*	71.2 (±8.7)	69.9 (±10.4)	0.222
Gender	64% M/36% F	71% M/29% F	0.238
Mean BMI*	28.5 (±4.9)	29.3 (±5.4)	0.215
Smoking status[a]			
Nonsmoker	142 (41%)	28 (39%)	0.654
Ex-smoker	150 (43%)	34 (48%)	
Smoker	57 (16%)	9 (13%)	
Comedications in 6 months before index			
Antihypertensives	304 (82%)	60 (79%)	0.628
CYP3A4 inhibitors[b]	47 (12%)	12 (16%)	0.459
Known statin interactor (non-CYP3A4 substrate)[c]	24 (6%)	7 (9%)	0.454
Oral corticosteroids	15 (4%)	3 (4%)	1.000
Occurrence in previous 6 months or 2 weeks after index			
Cramps	1 (<1%)	1 (1%)	0.311
Myocardial infarction	2 (<1%)	1 (1%)	0.428
Renal failure	8 (2%)	4 (5%)	0.129
Trauma	1 (<1%)	1 (1%)	0.311
Previous history (any time before index)			
Type 2 diabetes	93 (25%)	28 (37%)	**0.046**
Alcohol dependence	21 (6%)	2 (3%)	0.396
Asthma	40 (11%)	14 (18%)	**0.080**
Atrial fibrillation	30 (8%)	10 (13%)	0.183
Chronic obstructive pulmonary disease	27 (7%)	5 (7%)	1.000
Hypertension	246 (66%)	42 (55%)	**0.087**
Hyperthyroidism	6 (2%)	2 (3%)	0.628
Hypothyroidism	26 (7%)	8 (11%)	0.339

All comparison analyses were undertaken using a χ^2 test, except those variables marked *, for which an independent-samples *t*-test was applied. Values in bold indicate $P < 0.1$ where variables were carried forward for inclusion in the binary logistic regression base model.

BMI, body mass index; F, female; M, male.

[a]Indicates missing data (23 tolerant, 5 myopathy). [b]CYP3A4-interacting comedications were amiodarone, cyclosporine, azole antifungals, macrolide antibiotics, protease inhibitors, and calcium channel blockers. A definitive list of drugs is given in **Supplementary Table S1** online. [c]Non-CYP3A4-interacting comedications recorded were fenofibrate, gemfibrozil, digoxin, warfarin, and nicotinic acid.

receiving <40 mg/day ($n = 5$), no significant association was observed with severe myopathy (OR = 1.84 (0.34–9.86)).

Meta-analysis

A total of seven studies, including our own, were included in the initial meta-analysis of myopathy risk for *SLCO1B1* c.521C carriage for any statin (**Figure 1**). The overall OR for myopathy risk was 2.18 (1.39–3.43). Limiting the analysis to those studies ($n = 4$) reporting genotype frequency in patients receiving simvastatin, the combined OR was marginally higher at 3.25 (1.72–6.12). Three studies reported frequencies of *SLCO1B1* in atorvastatin-receiving patients. The combined OR for myopathy was not significant at 1.54 (0.80–2.97).

DISCUSSION

The recruitment of patients with severe adverse drug reactions to pharmacogenomic studies is complicated by the facts that these reactions are rare and there is no systematic process for identifying patients. The use of electronic health records therefore represents an opportunity to undertake such studies, but, to date, electronic health records have not been used to identify patients with severe and rare phenotypes. Part of the problem here is that the phenotypes in the databases may be inadequate, leading to capture of heterogeneous patient groups and thus the identification of no or weak associations. It is well known that phenotype standardization is crucial in order to disentangle the signals from noise.[13]

To evaluate whether electronic health care record databases can be used to recruit patients with severe adverse drug reactions, we first chose CPRD as the database to undertake this feasibility study because of the quality of data contained within, which has resulted in a large number of important drug safety findings (http://www.cprd.com). We then chose statin-induced myopathy as the paradigm adverse drug reaction. Although statin-induced myopathy can present with many different clinical manifestations,[3] and indeed previous pharmacogenetic studies have used different end points (**Figure 1**), our inclusion criteria were simple, based on an increase in CPK levels. A previous study in Scotland using electronic records used a composite definition of intolerance based on increases greater than 50% from baseline in alanine transaminase and/or 1–3× ULN in CPK, with an accompanying prescription change.[7] This perhaps represents a milder intolerance phenotype as compared with our definition of CPK > 4× ULN. The utility of our approach is shown by the fact that over a period of 16 months, after administrative startup, we were able to recruit 76 patients with statin-induced myopathy, of whom 23 were of a more severe phenotype, denoted by CPK > 10× ULN or rhabdomyolysis. The CPRD (as of October 2009) recorded 127,268 individuals receiving a statin with a concurrent CK measurement recorded. Of those, 953 (0.75%) had CK > 4× ULN concurrent with statin prescription (T.v.S., unpublished data), an incidence comparable with that reported previously.[4]

Our results show that the rs4149056 SNP in *SLCO1B1* is associated with statin-induced myopathy. This is in accordance with previous findings,[5–8] confirming the utility of our approach.

Table 2 Multiple logistic regression analysis of statin-induced myopathy risk and *SLCO1B1* p.V174A and *COQ2* rs4693075 genetic variants

			SLC01B1 p.V174A					*COQ2* rs4693075				
			Genotype frequency					Genotype frequency				
		n	T/T	T/C	C/C	*P*	Per C-allele OR (95% CI)	G/G	G/C	C/C	*P*	Per C-allele OR (95% CI)
All statins (*n* = 448)	Tolerant[a]	372	0.70	0.27	0.03	—	—	0.40	0.45	0.15	—	—
	All myopathy	76	0.53	0.39	0.08	0.005	2.08 (1.35–3.23)	0.34	0.45	0.21	0.358	1.27 (0.90–1.81)
	Severe myopathy	23	0.35	0.44	0.21	**0.0003**	4.47 (1.84–10.84)	0.44	0.39	0.17	0.937	0.99 (0.54–1.82)
Simvastatin only (*n* = 281)	Tolerant	222	0.66	0.32	0.02	—	—	0.43	0.41	0.16	—	—
	All myopathy	59	0.49	0.42	0.09	0.014	2.13 (1.29–3.54)	0.37	0.42	0.21	0.643	1.20 (0.81–1.78)
	<40 mg/day	24	0.63	0.37	0.00	0.997	1.03 (0.45–2.36)	0.42	0.42	0.16	0.956	1.09 (0.61–1.96)
	≥40 mg/day	35	0.40	0.46	0.14	**0.0002**	3.23 (1.74–5.99)	0.34	0.43	0.23	0.543	1.32 (0.81–2.14)
	Severe myopathy	18	0.28	0.50	0.22	**0.0004**	4.97 (2.16–11.43)	0.42	0.41	0.17	0.975	1.08 (0.56–2.09)
	<40 mg/day	5	0.40	0.60	0.00	0.778	1.84 (0.34–9.86)	0.80	0.20	0.00	0.215	0.22 (0.03–1.74)
	≥40 mg/day	13	0.23	0.46	0.31	**0.0004**	6.28 (2.38–16.60)	0.23	0.54	0.23	0.516	1.57 (0.73–3.37)
Atorvastatin only (*n* = 121)	Tolerant	110	0.78	0.2	0.02	—	—	0.36	0.53	0.11	—	—
	All myopathy	11	0.64	0.36	0.00	0.613	1.91 (0.56–6.54)	0.38	0.45	0.17	0.595	1.61 (0.60–4.33)
	Severe myopathy	3	1.00	0.00	0.00	0.507	N/A	0.67	0.00	0.33	0.956	0.86 (0.13–5.70)

Statistically significant associations ($P < 0.05$) are shown in bold. Allele frequencies for tolerant and myopathy phenotypes are also shown.

CI, confidence interval; N/A, not available; OR, odds ratio.

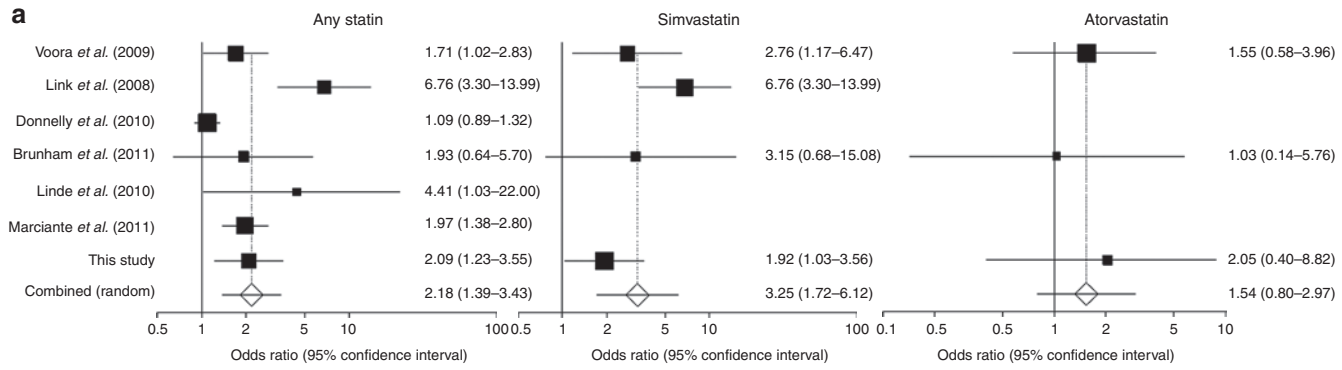
[a]Denotes one missing genotype for tolerant group for *COQ2* rs4693075 analysis.

We have shown that possession of at least one copy of the C-allele (CT/CC) is a significant risk factor for statin-induced myopathy (CK > 4× ULN), with an observed OR per C allele of 2.09 (1.27–3.45). The risk per C allele of severe myopathy (CK > 10× ULN/rhabdomyolysis; *n* = 23) was greater still, with an OR of 4.47 (1.84–10.84).

Our data replicate those of Link *et al.*,[5] who recruited cases and controls from a randomized trial setting, showing that our cases recruited through CPRD, an observational database, are comparable. However, our cases differ from those recruited by Link *et al.* in two important aspects: (i) the observations first made by Link *et al.* were in patients receiving 80 mg/day simvastatin, whereas the mean daily dose in this study was lower (33.4 ± 19.7 mg); and (ii) only 78% of our cases with myopathy were on simvastatin, with 22% receiving other statins, including atorvastatin (in 14% of cases). Limiting the analysis to those receiving simvastatin only demonstrated an association between *SLCO1B1* c.521T>C and both all myopathy cases (OR = 1.92 (1.08–3.42)) and those with severe myopathy (OR = 4.99 (1.72–14.50)). However, the association was observed only in those patients receiving ≥40 mg/day simvastatin (**Table 2**), indicating the importance of dose–genotype interaction. Despite the differences, the per-C-allele OR of 4.5 for high-dose (80 mg/day) simvastatin-induced myopathy (defined as CK > 3× ULN) by Link *et al.*[5] was highly comparable with that observed in our study for the equivalent phenotype (CK > 4× ULN) with ≥40 mg/day simvastatin (4.97; 95% confidence interval: 2.16–11.43).

Atorvastatin was the second most common drug implicated in our case group, reflecting its usage in comparison with simvastatin. However, unlike in simvastatin-treated patients, there was no significant association between the *SLCO1B1* c.521T>C variant and either myopathy or severe myopathy in atorvastatin-treated patients. This is consistent with a previous study that showed that the association was stronger for simvastatin than for atorvastatin.[6] Our meta-analysis of studies in Caucasians, including our data (**Figure 1**), also shows that there was a higher risk with simvastatin (OR = 3.25 (1.72–6.12)) than with atorvastatin (OR = 1.54 (0.80–2.97)), regardless of daily dose, in carriers of the *SLCO1B1* polymorphism. Pathophysiologically, this would be consistent with the fact that this polymorphism has the greatest effect on simvastatin (area under the curve is 221% higher in patients with the c.521CC genotype than in patients with the c.521TT genotype) but also has a smaller effect on atorvastatin (mean increase in area under the curve of 173%), and a very small, if any, effect on the other statins.[14] We did not have enough patients treated with the other statins to undertake any meaningful drug-specific analyses.

Recent studies[9,15] have shown that variation in the *COQ2* gene also predisposes an individual to statin-induced myopathy. However, we could not replicate the association with the COQ2 rs4693075 polymorphism in our patient group. Previous studies included patients mainly receiving atorvastatin and rosuvastatin.[9] In our study, just 13 (17%) of the statin-intolerant patients and 4 (16%) of the severe myopathy cases were receiving either atorvastatin or rosuvastatin. As such, we did not have sufficient statistical power to test this particular hypothesis. On the basis of the minor allele frequency of 0.35 observed in our atorvastatin-tolerant patients, we would require 135 cases and controls in



b

Study	Statin intolerance phenotype definition	Statin	Dose (mg/day)
Voora *et al.* (2009[8])	Composite of any side-effect, myalgia or CK > 3xULN	Atorvastatin Simvastatin Pravastatin	10 for 8 weeks then 80 20 for 8 weeks then 80 10 for 8 weeks then 40
Link *et al.* (2008[5])	"Incipient": CK > 3xULN, 5x baseline and ALT > 1.7x baseline "Definite": Muscle symptoms + CK > 10xULN	Simvastatin	80
Donnelly *et al.* (2010[7])	CK 1–3x ULN and/or abnormal ALT, accompanying prescription change	Various	<10 to >160
Brunham *et al.* (2012[6])	CK > 10x ULN	Simvastatin Atorvastatin	10–80 mean: 31 ± 23 (cases), 36 ± 25 (controls)
Linde *et al.* (2010[20])	Myalgia-self reported	Various	<10 to >80
Marciante *et al.* (2011[21])	Muscle pain or weakness + CK > 10x ULN	Cerivastatin	Mean: 0.6 (± 0.2)
This study	CK > 4x ULN	Simvastatin	10–80 mean: 33 ± 20 (cases), 31 ± 29 (controls)

Figure 1 (**a**) Forest plot showing meta-analysis of all previously published studies of *SLCO1B1* c.521T>C association with statin-induced myopathy, including data from this study. Analysis was restricted to studies on Caucasian populations. (**b**) Details of the studies included in the analysis. ALT, alanine transaminase; ULN, upper limit of normal.

order to have a study with 80% power to detect an OR of 2 and a significance value of 0.05.

The percentage of suitable statin-induced myopathy patients, identified within general practices, from whom biological samples were ultimately received (34%) was actually better than we had expected (20–25%). A previous study using spontaneous reports under the UK yellow card scheme to obtain biological samples from patients with terodiline-induced cardiotoxicity demonstrated a success rate of 25%.[16] Of course, we need to strive for higher recruitment rates for future studies, but interest in taking part in research studies by medical professionals is always tempered by the lack of time available. However, it should also be noted that a huge amount of time was saved through the more rapid identification of cases using the database, which would not have been possible through manual case-note searching.

In conclusion, there are clear time and cost benefits in using electronic patient records, such as the CPRD, for recruiting patients for genetic studies, particularly for rare phenotypes, such as statin-induced myopathy. There are also clinical benefits because the recruited patients will be from a real-world setting, and hence the effects of clinical factors such as concomitant medications can be evaluated. The electronic Medical Records and Genomics (eMERGE) network has already demonstrated the applicability of electronic medical records to identifying genomic loci associated with a population trait, white blood cell counts.[17] Others have applied a similar methodology to the identification of patients for pharmacogenetic studies of drugs such as warfarin.[18] In terms of the clinical utility of the genetic association between the *SLCO1B1* polymorphism and statin-induced myopathy, there is now convincing evidence for simvastatin, but not for other statins, for which more studies are needed. A recent Clinical Pharmacogenetics Implementation Consortium guideline has made some recommendations regarding dosing and choice of statin in patients with the variant *SLCO1B1* genotype.[19]

METHODS

Study design

Patient identification and recruitment. From a cohort of ~600,000 patients receiving statins identified in the CPRD (http://www.cprd.com), a case–control design was used to identify suitable patients for the study. Participation was restricted to Caucasians ≥18 years of age and with the first-ever statin prescription at least 1 year after the start of CPRD data collection. Potential cases were selected from the database if they discontinued their implicated statin therapy and demonstrated an increase in CPK > 4× ULN.

Potential controls were selected if they had been receiving statins for at least 3 months with no previous above-normal serum CPK measurements. General practitioners were contacted with a list of potential cases and/or controls identified from their practices. After being given the opportunity to decline involvement, they were first asked to review the list and remove any patients they considered unsuitable. They were then asked to contact suitable patients by letter requesting participation. Consenting case patients were randomized and invited to provide either a saliva sample (by post) or a blood sample (by visit to the practice). Controls provided only blood samples. All samples were then forwarded to the University of Liverpool for processing. To preserve anonymity, patient and practice identifier codes were used throughout the recruitment process, and all patient contact was through the general practitioner only.

Study approval. Ethical approval was obtained from the National Research Ethics Committee North West 2—Liverpool Central, and approval to use the CPRD data was obtained from the Independent Scientific Advisory

Committee at the Medicines and Healthcare Products Regulatory Agency. In addition, site-specific approval to contact the GP practices was obtained for each of the 138 primary-care trusts across the United Kingdom. Local informed consent was obtained from all study subjects or their guardians in accordance with the Declaration of Helsinki.

DNA extraction and genotyping

Genomic DNA was extracted from 5 ml of whole blood or 2 ml of saliva (collected using the Oragene DNA Sampling kit, DNAGenotek, Ontario, Canada) using the Chemagic Magnetic Module 1 system per the manufacturer's protocol (Chemagen Biopolymer-Technologie, Baesweiler, Germany).

A total of 448 individuals were genotyped for the rs4149056 SNP in *SLCO1B1* and rs4693075 in *COQ2* using commercially available TaqMan real-time PCR SNP genotyping assays with 1× Genotyping Master Mix (both from Applied Biosystems, Carlsbad, CA). Subsequently, 20 ng of genomic DNA per reaction was genotyped according to the manufacturer's protocol using an ABI 7900HT real-time PCR system (Applied Biosystems, Carlsbad, CA); Ten percent of the samples were run in duplicate to ensure concordance of genotype.

Statistical analysis

A univariate analysis of association between all nongenetic variables considered to be of *a priori* interest and case–control status was first undertaken. The χ^2 test was used for categorical variables and Student's *t*-test for continuous variables. Any variable demonstrating a statistically significant association ($P < 0.10$) was carried forward and adjusted for in the SNP association analyses.

To test for association with each SNP in turn, two multiple logistic regression models were fitted. The first (the baseline model) included all univariately significant ($P < 0.10$) nongenetic variables. The second (the SNP model) was the same but also included a covariate to represent the SNP (either rs4149056 or rs4693075). An additive effect of the variant allele was assumed. Homozygote wild type was coded as "0," heterozygote as "1," and homozygote variant allele as "2".

To test for association with the SNP, the likelihood ratio test was used to compare the SNP model with the baseline model. A P value <0.025 (0.05 corrected for two tests of associations using the Bonferroni approach) was assumed to represent statistical significance of the SNP.

Sensitivity analyses were undertaken by separately limiting cases to those classified as having either plasma CK > 10× ULN or rhabdomyolysis ($n = 23$; termed "severe myopathy"). All statistical analyses were undertaken using SPSS version 17.0.

Meta-analysis

A search of PubMed (http://www.ncbi.nlm.nih.gov/pubmed accessed January 2012) using the search terms "SLCO1B1" and "statin" yielded 108 publications, of which 96 were original research articles. Inspection of titles and abstracts identified six research articles that defined the frequency of the SLCO1B1 rs4149056 polymorphism in an entirely, or predominantly, Caucasian population of statin-induced myopathy. Studies were included regardless of the suspect statin investigated, dose, and myopathy phenotype observed (as described in **Figure 1b**). Due to the high degree of heterogeneity among the included studies ($I^2 = 84.1\%$), a DerSimonian-Laird random effects model was applied to the meta-analysis in StatsDirect version 2.6.8 (StatsDirect, Altrincham, UK)

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

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AUTHOR CONTRIBUTIONS

D.F.C. and H.O. wrote the manuscript. T.v.S., G.M., and M.P. designed the research. D.F.C., J.C., M.H., and H.O. performed the research. D.F.C, H.O., A.L.J., G.M., T.v.S., and M.P. analyzed the data.

CONFLICT OF INTEREST

The authors declared no conflict of interest.

Study Highlights

WHAT IS THE CURRENT KNOWLEDGE ON THE TOPIC?

✓ Genetic factors may predispose certain individuals to statin-induced myopathy. Many such adverse drug reactions are rare, and large, costly prospective clinical studies are required to recruit sufficient cohorts for pharmacogenetic analysis purposes.

WHAT QUESTION DOES THIS STUDY ADDRESS?

✓ Using statin-induced myopathy as a paradigm, this study assessed how electronic patient medical records held in the CPRD could be used to identify, recruit, and obtain DNA samples from adverse drug reaction cases and controls. Replication of the *SLCO1B1* c.521T>C polymorphism association with statin-induced myopathy was used to validate this recruitment protocol for pharmacogenetic studies.

WHAT THIS STUDY ADDS TO OUR KNOWLEDGE

✓ The use of the CPRD is a more cost- and time-effective method for the recruitment of patients for pharmacogenetic studies in comparison with traditional prospective recruitment methods.

HOW THIS MIGHT CHANGE CLINICAL PHARMACOLOGY AND THERAPEUTICS

✓ Use of electronic medical records such as those contained in the CPRD could prove valuable in identifying and recruiting patients with a number of rare adverse drug reactions for pharmacogenetics studies and facilitate future identification of predisposing genetic biomarkers.

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Identification of Patients With Variants in *TPMT* and Dose Reduction Reduces Hematologic Events During Thiopurine Treatment of Inflammatory Bowel Disease

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See editorial on page 850.

BACKGROUND & AIMS: More than 20% of patients with inflammatory bowel disease (IBD) discontinue thiopurine therapy because of severe adverse drug reactions (ADRs); leukopenia is one of the most serious ADRs. Variants in the gene encoding thiopurine S-methyltransferase (TPMT) alter its enzymatic activity, resulting in higher levels of thiopurine metabolites, which can cause leukopenia. We performed a prospective study to determine whether genotype analysis of *TPMT* before thiopurine treatment, and dose selection based on the results, affects the outcomes of patients with IBD. **METHODS:** In a study performed at 30 Dutch hospitals, patients were assigned randomly to groups that received standard treatment (control) or pretreatment screening (intervention) for 3 common variants of *TPMT* (*TPMT**2, *TPMT**3A, and *TPMT**3C). Patients in the intervention group found to be heterozygous carriers of a variant received 50% of the standard dose of thiopurine (azathioprine or 6-mercaptopurine), and patients homozygous for a variant received 0%–10% of the standard dose. We compared, in an intention-to-treat analysis, outcomes of the intervention (n = 405) and control groups (n = 378) after 20 weeks of treatment. Primary outcomes were the occurrence of hematologic ADRs (leukocyte count $< 3.0*10^9$/L or reduced platelet count $< 100*10^9$/L) and disease activity (based on the Harvey–Bradshaw Index for Crohn's disease [n = 356] or the partial Mayo score for ulcerative colitis [n = 253]). **RESULTS:** Similar proportions of patients in the intervention and control groups developed a hematologic ADR (7.4% vs 7.9%; relative risk, 0.93; 95% confidence interval, 0.57–1.52) in the 20 weeks of follow-up evaluation; the groups also had similar mean levels of disease activity ($P = .18$ for Crohn's disease and $P = .14$ for ulcerative colitis). However, a significantly smaller proportion of carriers of the *TPMT* variants in the intervention group (2.6%) developed hematologic ADRs compared with patients in the control group (22.9%) (relative risk, 0.11; 95% confidence interval, 0.01–0.85). **CONCLUSIONS:** Screening for variants in *TPMT* did not reduce the proportions of patients with hematologic ADRs during thiopurine treatment for IBD. However, there was a 10-fold reduction in hematologic ADRs among variant carriers who were identified and received a dose reduction, compared with variant carriers who did not, without differences in treatment efficacy. ClinicalTrials.gov number: NCT00521950.

Keywords: Leukocyte; Adverse Event; Pharmacogenetic; Side Effect.

Thiopurines are effective to induce and maintain long-term remission in up to 70% of patients with inflammatory bowel disease (IBD) (Crohn's disease [CD] and ulcerative colitis [UC]).[1] Azathioprine and 6-mercaptopurine are inactive prodrugs that need to undergo intracellular conversion to pharmacologically active 6-thioguanine nucleotides before exerting their cytotoxic action on (overactive) immune cells. Thiopurine S-methyltransferase (TPMT) metabolizes thiopurines to inactive metabolites, leaving less

*Authors share co-first authorship; §Authors share co-senior authorship.

Abbreviations used in this paper: ADR, adverse drug reaction; CD, Crohn's disease; CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; HBI, Harvey–Bradshaw Index; IBD, inflammatory bowel disease; RBC, red blood cell; TOPIC, Thiopurine response Optimization by Pharmacogenetic testing in Inflammatory bowel disease Clinics; TPMT, thiopurine S-methyltransferase; UC, ulcerative colitis.

Most current article

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CLINICAL AT

Family History Diagnoses for Diagnostic Testing

Questions:
1) Should certain family history diagnosis codes be added to the diagnostic work up file?
2) Should the diagnosis code for family history of malignant neoplasm of ovary be added to the high risk for breast cancer line?

Question source:
1) Tracy Muday, MD CCO medical director
2) Primary Health CCO

Issue: Certain "Z" codes for family history are on lines on the Prioritized List or on the Diagnostic Workup File (DWF). Certain codes in this series are on the Informational File, meaning they cannot be used for code pairing with CPT codes for genetic testing or other procedures. These codes are all listed in the ICD-10 manual as possible primary billing codes. These codes might be used for prenatal genetic testing, preconception testing, or testing an individual for an inheritable disease such as Huntington's disease.

The following codes are all currently informational:

ICD-10 Code	Code Description	Possible use(s)
Z81.0	Family history of intellectual disabilities	prenatal screening
Z82.41	Family history of sudden cardiac death	used for cardiac screening for teens/young adults (might be a secondary code)
Z82.79	Family history of other congenital malformations, deformations and chromosomal abnormalities	prenatal screening
Z82.62	Family history of osteoporosis	used for early DEXA (would be secondary to screening for osteoporosis code)
Z82.79	Family history of other congenital malformations, deformations and chromosomal abnormalities	prenatal screening
Z84.81	Family history of carrier of genetic disease	preconception screening, prenatal screening, other genetic testing for conditions like Huntington's Disease

Dr. Muday requested that ICD-10 Z80.41 (Family history of malignant neoplasm of ovary) be considered for addition to line 195 CANCER OF BREAST; AT HIGH RISK OF BREAST CANCER to pair with oophorectomy codes. ICD-10 Z80.41 is already on line 3 PREVENTION SERVICES WITH EVIDENCE OF EFFECTIVENESS. ICD-10 Z15.02 Genetic susceptibility to malignant neoplasm of ovary is on line 195 CANCER OF BREAST; AT HIGH RISK OF BREAST CANCER and is a more precise code to use for genetic carriers of mutations such as BRCA. HERC staff initially recommended against placement of ICD-10 Z80.41 on the high risk for breast cancer line as a more specific code (ICD-10 Z15.02) was already on this line. However, GAP members disagreed with HERC staff and felt that ICD-10 Z80.41 (Family history of malignant neoplasm of ovary) should be added to line 195 CANCER OF BREAST; AT HIGH RISK OF BREAST CANCER. The discussion was mainly around the fact that the existing diagnosis (ICD-10 Z15.02 Genetic susceptibility to malignant neoplasm of ovary) on the high risk for breast cancer line requires a patient

to have an identified genetic mutation which increases ovarian cancer risk. However, there are many families where no specific gene has been identified, but there is still a strong family history of breast and ovarian cancer and these family members could be considered for oophorectomy based on family history alone. These patients should use ICD-10 Z80.41 as their diagnosis code rather than ICD-10 Z15.02. The GAP recommendation for VBBS was to add ICD-10 Z80.41 to line 195.

GAP/HERC staff recommendations:

1) Advise HSD to add the following codes to the Diagnostic Work up File to be used for diagnostic testing and remove from the Informational File

Z81.0	Family history of intellectual disabilities
Z82.41	Family history of sudden cardiac death
Z82.79	Family history of other congenital malformations, deformations and chromosomal abnormalities
Z82.62	Family history of osteoporosis
Z82.79	Family history of other congenital malformations, deformations and chromosomal abnormalities
Z84.81	Family history of carrier of genetic disease

2) Add Z80.41 (Family history of malignant neoplasm of ovary) to line 195 CANCER OF BREAST; AT HIGH RISK OF BREAST CANCER

Breast Cancer Genetic Testing Panels

Question: Should genetic testing panels be covered for screening for breast cancer gene mutations? If so, with what restrictions?

Question source: HERC staff, VBBS, GAP, Myriad Genetics

Issue: Genetic testing panels for breast cancer genes were discussed at the 2015 and 2016 GAP meetings. At the 2015 GAP meeting, the GAP suggested that such panels be made diagnostic; however, at the November, 2015 VBBS meeting, the VBBS felt that such panels contained non-evidence based tests and elected to not cover them. This was discussed again at the 2016 GAP meeting, and HERC staff was directed to review updated NCCN guidelines. This was done, and at the November, 2016 VBBS meeting, the updated NCCN guidelines were found to have insufficient guidance on this topic. This field was noted to be rapidly evolving and HERC staff was directed to discuss this topic again at the 2017 GAP meeting.

At the October, 2017 GAP meeting, GAP members unanimously found that breast cancer gene panel testing was now standard of care. The panel testing is generally the same price or cheaper than single gene testing. There is ongoing concern with results of uncertain significance, particularly with the larger gene panels. There is also ongoing concern with the cost and lack of access to genetic counseling prior to such testing. The GAP recommended that breast cancer gene panel testing be covered with restrictions to be placed in the Non-Prenatal Genetic Testing Guideline to read similar to the following:

> Hereditary breast cancer-related disorders genomic sequence analysis panels (CPT 81432, 81433, 81479) included if cost no more than testing for the sum of CPT 81211 and 81213, include at least 5 genes that the current NCCN guideline on breast/ovarian/colon cancer genetics provides specific guidance on clinical management and include no more than 40 genes total.

This wording has been reviewed by the OHP medical directors' guideline workgroup who had the following comments:

1) The suggested guideline limited the panel to no more than the cost of CPT 81211 and 81213. Several medical directors and a geneticist were concerned about this clause. There was concern that an appropriate panel may cost slightly more but not be allowed. Also, there was concern that a patient might have to use a certain lab for clinical reasons or insurance reasons; not allowing that lab's panel to be covered due to cost might prevent a patient from having access to testing.
2) Most commenters agreed with the requirement for the panel to cover at least 5 genes with NCCN guidelines for management. There was a comment that other genes (other than for breast/ovarian/colorectal cancer) may be considered for inclusion based on the personal and/or family history of cancer.
3) One commenter was concerned about the arbitrary gene number limit, and requested that the extent of the panel be at the providers discretion, based on the patient's personal and family history

Nicoleta Voian, a cancer geneticist at Providence, provided the following feedback:

Many genetics providers use panels for multiple reasons:

1) Many genes may be candidates for a person's phenotype (e.g. breast cancer) or for the family history. Offering a gene panel testing increases the chances to capture a mutation in

a gene for which there are no testing guidelines, but there may be medical management guidelines(e.g. PALB2)

2) There are individuals who carry more than one gene mutation (e.g. BRCA2 mutation and CHEK2 mutation). If the patient's genetic testing would only include BRCA1/2 gene analysis the CHEK2 would have been missed. There are guidelines for medical management for CHEK2 mutations carriers.

Ms. Voian felt that genetic counseling should be required prior to panel testing to allow professional expertise on the best type of panel to order. Genetic counseling should also be required after the testing to help interpret the results, discuss the medical management based on the identified mutation, and advise on testing other family members.

The final form of the wording for inclusion in the non-prenatal genetic testing guideline approved by the GAP is as follows:

1) Hereditary breast cancer-related disorders genomic sequence analysis panels (CPT 81432, 81433, 81479) are only covered if the panel test
   a) Includes at least 5 genes that the NCCN Clinical Practice Guidelines in Oncology - Genetic/Familial High-Risk Assessment: Colorectal V3.2017 (10/10/17) and/or NCCN Clinical Practice Guidelines in Oncology - Genetic/Familial High-Risk Assessment: Breast and Ovarian V1.2018 (10/3/17) include(s) with specific guidance on clinical management; and,
   b) Includes no more than a reasonable number of genes (e.g. 40 genes total).

Current Prioritized List status:

81432-81433 (Breast and ovarian cancer syndrome testing): Services Recommended for Non-coverage File

81432: Hereditary breast cancer-related disorders (eg, hereditary breast cancer, hereditary ovarian cancer, hereditary endometrial cancer); genomic sequence analysis panel, must include sequencing of at least 10 genes, always including BRCA1, BRCA2, CDH1, MLH1, MSH2, MSH6, PALB2, PTEN, STK11, and TP53

81433: Hereditary breast cancer-related disorders (eg, hereditary breast cancer, hereditary ovarian cancer, hereditary endometrial cancer); duplication/deletion analysis panel, must include analyses for BRCA1, BRCA2, MLH1, MSH2, and STK11

81479: Unlisted molecular pathology procedure: Suspend for Review

From the 2015 GAP minutes:

1) Breast cancer syndrome genetic testing:
   a. Specific tests
      i. 81162 BRCA1, BRCA2 (breast cancer 1 and 2) (eg, hereditary breast and ovarian cancer) gene analysis; full sequence analysis and full duplication/deletion analysis
      ii. 81432: Hereditary breast cancer-related disorders (eg, hereditary breast cancer, hereditary ovarian cancer, hereditary endometrial cancer); geonomic sequence analysis panel, must include sequencing of at least 14 genes, including ATM,

BRCA1, BRCA2,BRIP1, CDH1, MLH1, MSH2, MSH6, NBN, PALB2, PTEN, RAD51C, STK11 AND TP53

iii. 81433: Hereditary breast cancer-related disorders (eg, hereditary breast cancer, hereditary ovarian cancer, hereditary endometrial cancer) duplication/deletion analysis panel, must include analyses for BRCA1, BRCA2, MLH1, MSH2, AND STK1

b. Discussion: NCCN guideline contains a table of recommended genetic tests--some of the tests included in the panels above are listed as evidence based, others do not have evidence support. However, the NCCN table has the caveat that even those tests without evidence to support their use might be useful in specific clinical situations. There was discussion about using panel testing versus using customized testing for certain genes. The advisory panel felt that panels are useful in some situations, and the more specific testing might be all that is indicated in other situations. However, the panel tests are frequently the same price as more specific tests. GAP felt that the panel tests above may be more cost effective that singling out the specific tests called out by NCCN as evidence based. Myriad representatives testified that 81432 and 81433 are not priced by Medicare and therefore will likely not be billable for 2016. A miscellaneous genetic testing CPT code is likely to be used instead.

c. Suggested staff recommendation to VbBS: Add all to the Diagnostic Procedures File and add to the Non-Prenatal Genetic Testing Guideline D1

From the November, 2016 VBBS meeting minutes:

81432-81433 (Breast and ovarian cancer syndrome testing) were discussed. There was considerable discussion regarding coverage of panels versus BRCA genes alone. The VbBS felt that the panels contained many genetic mutations without evidence that finding these mutations would be meaningful or would affect treatment plans or monitoring. The group decided to only cover the BRCA mutation code (81162) and to place the panels (81432-81433) on the Services Recommended for Non-Coverage Table. These codes were not added to the Non-Prenatal Genetic Testing Guideline as had been suggested in the meeting materials.

From the 2016 GAP minutes:

Karen Heller from Myriad commented on the 2015 GAP decision to not cover breast cancer genetic panel tests, due to the fact that many of the genes on these panels do not affect management. Myriad has a panel of 28 genes (MyRisk) that all affect management. Heller reported that literature has been published about the change in medical management with the MyRisk study. One study showed 52% of patients had a change in management. Another study showed 91% of patients had change in management. Myriad will supply this literature to HERC staff.

Kovak replied that there is emerging data on panel testing. NCCN guidelines have changed several times over the past year regarding evidence of different individual genes affecting management. NCCN recommends taking into account family history and getting a genetics professional involved. In her opinion, some genes beyond BRCA should be covered, but not all patients need a panel. She felt that this was an important issue to look at and a rapidly changing field.

There was discussion about having HERC staff look at NCCN breast cancer genetic testing guidelines and the available literature and consider adding coverage for panel testing. There was additional

discussion about how to limit the use of panel tests that include genes that do not affect management. There was a general consensus that such testing should be done for a limited group of patients with genetics input. There are quite variable panels depending on the lab. The general thought was that the tests felt to have a high probability of affecting management by NCCN should be covered.

HERC staff will research the NCCN breast cancer genetic testing guidelines and will develop proposed wording for the non-prenatal genetic testing guideline to limit the use of such panels to those containing NCCN determined genes with a high probability of changing management. HERC staff will also consult with oncology experts. Any proposed guideline change will be circulated to GAP members for comment prior to discussion at the November VbBS/HERC meetings.

From the November, 2016 VBBS meeting minutes:

There was some discussion about breast cancer gene panel testing. GAP had recommended that HERC staff review NCCN guidelines; staff reviewed this guideline and found no strong guidance. After staff conferred with HERC leadership, staff determined that there is no clear guidance but that this is a rapidly evolving field. The plan is to have GAP review this at their meeting next year.

From NCCN 1.2018

Multi-Gene Testing

- Patients with a personal or family history suggestive of a single inherited cancer syndrome are most appropriately managed by genetic testing for that specific syndrome. When more than one gene can explain an inherited cancer syndrome, then multi-gene testing may be more efficient and/or cost-effective
- There may be a role for multi-gene testing in individuals who have tested negative (indeterminate) for a single syndrome, but whose personal or family history remains suggestive of an inherited susceptibility
- As commercially available tests differ in the specific genes analyzed (as well as classification of variants and many other factors), choosing the specific laboratory and test panel is important
- Multi-gene testing can include “intermediate” penetrant (moderate-risk) genes. For many of these genes, there is limited data on the degree of cancer risk and there are no clear guidelines on risk management for carriers of mutations. Not all genes included on available multi-gene tests are necessarily clinically actionable.
- In many cases, the information from testing for moderate penetrance genes does not change risk management compared to that based on family history alone
- There is increased likelihood of finding variants of unknown significance when testing for mutations in multiple genes
- Multigene testing is ideally offered in the context of professional genetic expertise for pre- and post-test counseling

NICE 2013 (updated 2017) Familial Breast Cancer:

- Recommend screening for specific genes
- Does not comment on gene panel testing

Breast Cancer Genetic Testing Panels

Randall 2017, consensus statement of the American Society for Gynecologic Oncology

1) Panel testing may be particularly useful in women with significant family history who have previously tested negative for germline BRCA1 and BRCA2 mutations or those who test negative for mutations in Lynch syndrome genes. In addition, panel testing facilitates more robust identification of women at increased risk of ovarian cancer who could potentially benefit from risk-reducing surgery. Although less is known about the exact penetrance of mutations in non-BRCA hereditary ovarian cancer genes, a recent NCCN Guideline revision lists RAD51C, RAD51D, and BRIP1 mutations, in addition to BRCA1, BRCA2, and Lynch gene mutations, as candidates for risk-reducing surgery at age 45–50. In this update, risk was not considered increased for ATM, CDH1, CHEK2, or NF1 mutations, and remains uncertain for NBN and PALB2 mutations. Panel testing has the disadvantages of a higher rate of variant of uncertain significance (VUS) results that are confusing to patients and families and do not currently inform treatment or risk management decisions and of finding deleterious mutations in unexpected genes. The likelihood of VUS results increases with the number of genes on a panel test, varies by laboratory, and can be as high as 25–41%

ACOG 2017, Practice Bulletin on Breast and Ovarian Cancer Syndromes

1) The two main genetic testing options for hereditary breast and ovarian cancer syndrome are *BRCA* mutation testing and multigene panel testing that includes *BRCA* and other genetic mutations. The choice of testing strategy will depend on whether or not there is a known mutation in the family
2) Multigene panel testing may be useful when more than one gene may be associated with an inherited cancer syndrome or when a patient has a personal or family history that is consistent with an inherited cancer susceptibility, but single-gene testing has not identified a pathogenic variant
3) Multigene panel tests should be offered by a health care provider with cancer genetics expertise and after genetic counseling and informed consent.
4) An important consideration for multigene panel testing is the increased complexity and uncertainty of the results and how this affects interpretation, patient counseling, and medical management. Because panel testing involves the simultaneous testing of multiple genes and can include genes that confer moderate or uncertain risk, there is an increased likelihood of finding variants of uncertain significance for which there are limited (or no) data on associated cancer risk to guide appropriate management

Other policies:

1) Aetna does not cover breast cancer gene panels except in very specific clinical situations (generally patients with breast cancer prior to beginning certain treatment protocols)
2) Cigna and Anthem do not cover breast cancer gene panels

HERC staff summary: The GAP and major stakeholders, including the Oregon Genetics Group of OHA, recommend coverage of breast cancer genetic panels with soft restrictions on the total number of genes included and with a requirement that at least 5 of the genes being among those included in the NCCN breast/ovarian/colon cancer genetic guidelines as affecting clinical management.

Breast Cancer Genetic Testing Panels

HERC staff recommendations:

1) Add breast cancer genetic panel testing (CPT 81432-81433) to the Diagnostic Work Up File
    a. 81432: Hereditary breast cancer-related disorders (eg, hereditary breast cancer, hereditary ovarian cancer, hereditary endometrial cancer); genomic sequence analysis panel, must include sequencing of at least 10 genes, always including BRCA1, BRCA2, CDH1, MLH1, MSH2, MSH6, PALB2, PTEN, STK11, and TP53
    b. 81433: Hereditary breast cancer-related disorders (eg, hereditary breast cancer, hereditary ovarian cancer, hereditary endometrial cancer); duplication/deletion analysis panel, must include analyses for BRCA1, BRCA2, MLH1, MSH2, and STK11
2) Add an entry to the Non-Prenatal Genetic Testing Guideline as shown below
    a. Hereditary breast cancer-related disorders genomic sequence analysis panels (CPT 81432, 81433, 81479) are only covered if the panel test
        i. Includes at least 5 genes that the NCCN Clinical Practice Guidelines in Oncology - Genetic/Familial High-Risk Assessment: Colorectal V3.2017 (10/10/17) and/or NCCN Clinical Practice Guidelines in Oncology - Genetic/Familial High-Risk Assessment: Breast and Ovarian V1.2018 (10/3/17) include(s) with specific guidance on clinical management; and,
        ii. Includes no more than a reasonable number of genes (e.g. 40 genes total).

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Society Position Statements/White Papers

Multi-disciplinary summit on genetics services for women with gynecologic cancers: A Society of Gynecologic Oncology White Paper

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HIGHLIGHTS

- The Society of Gynecologic Oncology convened a multidisciplinary Genetics Summit.
- The benefits and challenges of genetic risk assessment were discussed.
- Minimum standards for genetic risk assessment are suggested.
- Suggestions for further research and educational efforts are communicated.

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ABSTRACT

Objective. To assess current practice, advise minimum standards, and identify educational gaps relevant to genetic screening, counseling, and testing of women affected by gynecologic cancers.

Methods. The Society of Gynecologic Oncology (SGO) organized a multidisciplinary summit that included representatives from the American College of Obstetricians and Gynecologists (ACOG), the American Society Clinical Oncology (ASCO), the National Society of Genetic Counselors (NSGC), and patient advocacy groups, BrightPink and Facing our Risk of Cancer Empowered (FORCE). Three subject areas were discussed: care delivery models for genetic testing, barriers to genetic testing, and educational opportunities for providers of genetic testing.

Results. The group endorsed current SGO, National Comprehensive Cancer Network (NCCN), and NSGC genetic testing guidelines for women affected with ovarian, tubal, peritoneal cancers, or DNA mismatch repair deficient endometrial cancer. Three main areas of unmet need were identified: timely and universal genetic testing for women with ovarian, fallopian tube, and peritoneal cancers; education regarding minimum standards for genetic counseling and testing; and barriers to implementation of testing of both affected individuals as well as cascade testing of family members. Consensus building among all stakeholders resulted in an action plan to address gaps in education of gynecologic oncology providers and delivery of cancer genetics care.

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1. Introduction

The discipline of cancer genetics developed outside the scope of gynecologic oncology practice, complicating the integration of genetic counseling and testing into gynecologic cancer care. Several aspects of

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Society of Gynecologic Oncology

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Clinical Management Guidelines for Obstetrician–Gynecologists

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Committee on Practice Bulletins–Gynecology, Committee on Genetics, Society of Gynecologic Oncology. This Practice Bulletin was developed by the American College of Obstetrician and Gynecologists' Committee on Practice Bulletins–Gynecology and Committee on Genetics in collaboration with Susan C. Modesitt, MD, and Karen Lu, MD, and by the Society of Gynecologic Oncology in collaboration with Lee-may Chen, MD, and C. Bethan Powell, MD.

Hereditary Breast and Ovarian Cancer Syndrome

Hereditary breast and ovarian cancer syndrome is an inherited cancer-susceptibility syndrome characterized by multiple family members with breast cancer, ovarian cancer, or both. Based on the contemporary understanding of the origins and management of ovarian cancer and for simplicity in this document, ovarian cancer also refers to fallopian tube cancer and primary peritoneal cancer. Clinical genetic testing for gene mutations allows more precise identification of those women who are at an increased risk of inherited breast cancer and ovarian cancer. For these individuals, screening and prevention strategies can be instituted to reduce their risks. Obstetrician–gynecologists play an important role in the identification and management of women with hereditary breast and ovarian cancer syndrome. If an obstetrician–gynecologist or other gynecologic care provider does not have the necessary knowledge or expertise in cancer genetics to counsel a patient appropriately, referral to a genetic counselor, gynecologic or medical oncologist, or other genetics specialist should be considered (1). More genes are being discovered that impart varying risks of breast cancer, ovarian cancer, and other types of cancer, and new technologies are being developed for genetic testing. This Practice Bulletin focuses on the primary genetic mutations associated with hereditary breast and ovarian cancer syndrome, BRCA1 *and* BRCA2*, but also will briefly discuss some of the other genes that have been implicated.*

Background

BRCA1 *and* BRCA2

Germline mutations in the *BRCA1* and *BRCA2* (*BRCA*) genes account for most cases of hereditary breast and ovarian cancer syndrome. Approximately 9–24% of cases of epithelial ovarian cancer (2–5) and approximately 4.5% of cases of breast cancer (6) are due to germline mutations in *BRCA1* and *BRCA2*. *BRCA1* is found on chromosome 17 and *BRCA2* is on chromosome 13 (7, 8). Both *BRCA* genes are tumor suppressor genes that encode proteins that function in the DNA repair process (9, 10). Individuals with hereditary breast and ovarian cancer syndrome inherit one defective allele in *BRCA1* or *BRCA2* from their father or mother, but they have a second, functional allele. If the second allele becomes nonfunctional as a result of a somatic mutation, cancer can develop. This is called the "two-hit hypothesis" (11).

Founder BRCA *Mutations*

In the general population, it is estimated that approximately 1 in 300 to 1 in 800 individuals carry a mutation in *BRCA1* or *BRCA2* (12). In certain populations founded by a small ancestral group, a specific mutation in *BRCA1* or *BRCA2* may occur more frequently, and is often referred to as a founder mutation. These founder mutations in *BRCA1* and *BRCA2* have been identified in Ashkenazi (Central and Eastern European) Jews, French Canadians, and Icelanders, among other groups.

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Updates to the Non-Prenatal Genetic Testing Guideline

Issue: Several edits are suggested for Diagnostic Guideline D1 and to GN169 after discussion at the October, 2017 Genetics Advisory Group meeting.

1) Update the references to NCCN guidelines to the most recent versions
2) Add a section regarding breast cancer genetic panel coverage requirements
3) Add a section regarding G6PD genetic testing coverage requirements
4) Remove the CPT codes listed as having non-coverage in Section F and place them on line 660 CONDITIONS FOR WHICH CERTAIN INTERVENTIONS HAVE NO CLINICALLY IMPORTANT BENEFIT OR HAVE HARMS THAT OUTWEIGH BENEFITS. A new sentence is added to refer readers to Guideline Note 173, INTERVENTIONS THAT HAVE NO CLINICALLY IMPORTANT BENEFIT OR HAVE HARMS THAT OUTWEIGH BENEFITS FOR CERTAIN CONDITIONS; UNPROVEN INTERVENTIONS for a list of these codes.
5) Modify GN173 INTERVENTIONS THAT HAVE NO CLINICALLY IMPORTANT BENEFIT OR HAVE HARMS THAT OUTWEIGH BENEFITS FOR CERTAIN CONDITIONS; UNPROVEN INTERVENTIONS to add the codes previously in Section F as shown below.

DIAGNOSTIC GUIDELINE D1, NON-PRENATAL GENETIC TESTING GUIDELINE

A) Genetic tests are covered as diagnostic, unless they are listed below in section F1 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 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.
    1) 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 V3.2017 (10/10/17) ~~V2.2016 (9/26/16)~~ www.nccn.org.

b) Breast and ovarian cancer syndrome genetic testing services (CPT 81162, 81211-81217) for women without a personal history of breast, ovarian and other associated cancers should be provided to high risk women 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 and Ovarian. V1.2018 (10/3/17) ~~V1.2017 (9/19/16).~~ www.nccn.org.

c) Breast and ovarian cancer syndrome genetic testing services (CPT 81162, 81211-81217) for women with a personal history of breast, ovarian, and other associated cancers and for men with breast cancer should be provided according to the NCCN Clinical Practice Guidelines in Oncology. Genetic/Familial High-Risk Assessment: Breast and Ovarian. V1.2018 (10/3/17) ~~V1.2017 (9/19/16).~~ www.nccn.org.

d) PTEN (Cowden syndrome) services (CPT 81321-81323) should be provided as defined by the NCCN Clinical Practice Guidelines in Oncology. Colorectal Screening. V3.2017 (10/10/17) ~~V2.2016 (9/26/16)~~ www.nccn.org.

2) 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.

i) "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.

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

3) 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 81211) 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).

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

5) Hereditary breast cancer-related disorders genomic sequence analysis panels (CPT 81432, 81433, 81479) are only included if the panel test

a) Includes at least 5 genes that the NCCN Clinical Practice Guidelines in Oncology - Genetic/Familial High-Risk Assessment: Colorectal V3.2017 (10/10/17) and/or NCCN Clinical Practice Guidelines in Oncology - Genetic/Familial High-Risk Assessment: Breast and Ovarian V1.2018 (10/3/17) include(s) with specific guidance on clinical management; and,

b) Includes no more than a reasonable number of genes (e.g. 40 genes total).

E) 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, Cytogenomic constitutional microarray analysis for copy number variants for chromosomal abnormalities: 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 81229, Cytogenomic constitutional microarray analysis for copy number variants for chromosomal abnormalities; plus cytogenetic constitutional microarray analysis for single nucleotide polymorphism (SNP) variants for chromosomal abnormalities: 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; only if (a) consanguinity and recessive disease is suspected, or (b) uniparental disomy is suspected, or (c) another mechanism is suspected that is not detected by the copy number variant test alone.
3) CPT 81243, 81244, 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.
4) A visit with the appropriate specialist (often genetics, developmental pediatrics, or child neurology), including physical exam, medical history, and family history is covered. Physical exam, medical history, and family history by the appropriate specialist, prior to any genetic testing is often the most cost-effective strategy and is encouraged.

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 HAVE NO CLINICALLY IMPORTANT BENEFIT OR HAVE HARMS THAT OUTWEIGH BENEFITS FOR CERTAIN CONDITIONS; UNPROVEN INTERVENTIONS
2) ~~The following tests are not covered:~~
   a) ~~CPT 81225, CYP2C9 (cytochrome P450, family 2, subfamily C, polypeptide 9) (eg, drug metabolism), gene analysis, common variants (eg, *2, *3, *5, *6)~~
   b) ~~CPT 81226, CYP2D6 (cytochrome P450, family 2, subfamily D, polypeptide 6) (eg, drug metabolism), gene analysis, common variants (eg, *2, *3, *4, *5, *6, *9, *10, *17, *19, *29, *35, *41, *1XN, *2XN, *4XN).~~
   c) ~~CPT 81227, CYP2C9 (cytochrome P450, family 2, subfamily C, polypeptide 9) (eg, drug metabolism), gene analysis, common variants (eg, *2, *3, *5, *6)~~
   d) ~~CPT 81287, MGMT (O-6-methylguanine-DNA methyltransferase) (eg, glioblastoma multiforme), methylation analysis~~
   e) ~~CPT 81291, MTHFR (5,10-methylenetetrahydrofolate reductase) (eg, hereditary hypercoagulability) gene analysis, common variants (eg, 677T, 1298C)~~
   f) ~~CPT 81330, SMPD1(sphingomyelin phosphodiesterase 1, acid lysosomal) (eg, Niemann-Pick disease, Type A) gene analysis, common variants (eg, R496L, L302P, fsP330)~~
   g) ~~CPT 81350, UGT1A1 (UDP glucuronosyltransferase 1 family, polypeptide A1) (eg, irinotecan metabolism), gene analysis, common variants (eg, *28, *36, *37)~~
   h) ~~CPT 81355, VKORC1 (vitamin K epoxide reductase complex, subunit 1) (eg, warfarin metabolism), gene analysis, common variants (eg, -1639/3673)~~

i) ~~CPT 81417, re-evaluation of whole exome sequencing~~
j) ~~CPT 81425-81427, Genome sequence analysis~~
k) ~~CPT 81470, 81471, X-linked intellectual disability (XLID) genomic sequence panels~~
l) ~~CPT 81504, Oncology (tissue of origin), microarray gene expression profiling of > 2000 genes, utilizing formalin-fixed paraffin-embedded tissue, algorithm reported as tissue similarity scores~~

3) 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)
      CFTR, cystic fibrosis transmembrane conductance regulator tests. CPT 81220, 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) Carrier testing for cystic fibrosis
      i) CFTR gene analysis of a panel containing at least the mutations recommended by the American College of Medical Genetics* (CPT 81220) is covered once in a lifetime.
   d) 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.
   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) CPT 81221, SERPINA1 (serpin peptidase inhibitor, clade A, alpha-1 antiproteinase, antitrypsin, member 1) (eg, alpha-1-antitrypsin deficiency), gene analysis, common variants (eg, *S and *Z): The alpha-1-antitrypsin protein level should be the first line test for a suspected diagnosis of AAT deficiency in symptomatic individuals with unexplained liver disease or obstructive lung disease that is not asthma or in a middle age individual with unexplained dyspnea. Genetic testing of the anpha-1 phenotype test is appropriate if the protein test is abnormal or borderline. The genetic test is appropriate for siblings of people with AAT deficiency regardless of the AAT protein test results.
l) CPT 81415-81416, exome testing: A genetic counseling/geneticist consultation is required prior to ordering test
m) CPT 81430-81431, Hearing loss (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 81412 Ashkenazi Jewish carrier testing panel: panel testing is only covered when the panel would replace and would be similar or lower cost than individual gene testing including CF carrier testing.

* American College of Medical Genetics Standards and Guidelines for Clinical Genetics Laboratories. 2008 Edition, Revised 3/2011 and found at https://www.acmg.net/StaticContent/SGs/CFTR%20Mutation%20Testing.pdf

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

The following treatments are prioritized on Line 660, CONDITIONS FOR WHICH CERTAIN INTERVENTIONS HAVE NO CLINICALLY IMPORTANT BENEFIT OR HAVE HARMS THAT OUTWEIGH BENEFITS; UNPROVEN INTERVENTIONS for the conditions listed here:

Procedure Code	Intervention	Rationale	Last Review
81225-81227, 81230-81231	Cytochrome P450 gene analysis	Insufficient evidence of effectiveness	December, 2011 November, 2017
81232, 81246	5-fluorouracil/5-FU and capecitabine drug metabolism	Insufficient evidence of effectiveness	November, 2017
81283	IFNL3 (interferon, lambda 3) (eg, drug response), gene analysis, rs12979860 variant	Insufficient evidence of effectiveness	November, 2017
81287	MGMT (O-6-methylguanine-DNA methyltransferase) (eg, glioblastoma multiforme), methylation analysis	Insufficient evidence of effectiveness	January, 2014
81291	MTHFR (5,10-methylenetetrahydrofolate reductase) gene analysis, common variants	Insufficient evidence of effectiveness	December, 2011
81328	SLCO1B1 (solute carrier organic anion transporter family, member 1B1) gene analysis, common variant(s)	Insufficient evidence of effectiveness	November, 2017
81330	SMPD1(sphingomyelin phosphodiesterase 1, acid lysosomal) gene analysis, common variants	Insufficient evidence of effectiveness	December, 2011
81335	TPMT (thiopurine S-methyltransferase) (eg, drug metabolism), gene analysis	Insufficient evidence of effectiveness	November, 2017
81350	UGT1A1 (UDP glucuronosyl-transferase 1 family, polypeptide A1) (eg, irinotecan metabolism), gene analysis, common variants	Insufficient evidence of effectiveness	December, 2011
81355	VKORC1 (vitamin K epoxide reductase complex, subunit 1) (eg, warfarin metabolism), gene analysis, common variants	Insufficient evidence of effectiveness	December, 2011
81417	re-evaluation of whole exome sequencing	Insufficient evidence of effectiveness	December, 2011
81425-81427	Genome sequence analysis	Insufficient evidence of effectiveness	November, 2014
81470, 81471	X-linked intellectual disability (XLID) genomic sequence panels	Insufficient evidence of effectiveness	November, 2014
81504	Oncology (tissue of origin), microarray gene expression profiling of > 2000 genes, utilizing formalin-fixed paraffin-embedded tissue, algorithm reported as tissue similarity scores	Insufficient evidence of effectiveness	January, 2014

DIAGNOSTIC GUIDELINE D17, PRENATAL GENETIC TESTING

The following types of prenatal genetic testing and genetic counseling are covered for pregnant women:

1. Genetic counseling (CPT 96040, HPCPS S0265) for high risk women who have family history of inheritable disorder or carrier state, ultrasound abnormality, previous pregnancy with aneuploidy, or elevated risk of neural tube defect.
2. Genetic counseling (CPT 96040, HPCPS S0265) prior to consideration of chorionic villus sampling (CVS), amniocentesis, microarray testing, Fragile X, and spinal muscular atrophy screening
3. Validated questionnaire to assess genetic risk in all pregnant women
4. Screening high risk ethnic groups for hemoglobinopathies (CPT 83020, 83021)
5. Screening for aneuploidy with any of five screening strategies [first trimester (nuchal translucency, beta-HCG and PAPP-A), integrated, serum integrated, stepwise sequential, and contingency] (CPT 76813, 76814, 81508-81511)
6. Cell free fetal DNA testing (CPT 81420, 81507) for evaluation of aneuploidy in women who have an elevated risk of a fetus with aneuploidy (maternal age >34, family history or elevated risk based on screening).
7. Ultrasound for structural anomalies between 18 and 20 weeks gestation (CPT 76811, 76812)
8. CVS or amniocentesis (CPT 59000, 59015,82106, 88235, 88267, 88269, 88280, 88285) for a positive aneuploidy screen, maternal age >34, fetal structural anomalies, family history of inheritable chromosomal disorder or elevated risk of neural tube defect.
9. Array CGH (CPT 81228, 81229) when major fetal congenital anomalies are apparent on imaging, or with normal imaging when array CGH would replace karyotyping performed with CVS or amniocentesis in #8 above.
10. FISH testing (CPT 88271, 88275) only if karyotyping is not possible due a need for rapid turnaround for reasons of reproductive decision-making (i.e. at 22w4d gestation or beyond)
11. Screening for Tay-Sachs carrier status (CPT 81255) in high risk populations. First step is hex A, and then additional DNA analysis in individuals with ambiguous Hex A test results, suspected variant form of TSD or suspected pseudodeficiency of Hex A
12. Screening for cystic fibrosis carrier status once in a lifetime (CPT 81220-81224)
13. Screening for fragile X status (CPT 81243, 81244) in patients with a personal or family history of
    a. fragile X tremor/ataxia syndrome
    b. premature ovarian failure
    c. unexplained early onset intellectual disability
    d. fragile X intellectual disability
    e. unexplained autism through the pregnant woman's maternal line
14. Screening for spinal muscular atrophy (CPT 81401) once in a lifetime
15. Screening those with Ashkenazi Jewish heritage 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.
16. Expanded carrier screening only for those genetic conditions identified above

The following genetic screening tests are not covered:

1. Serum triple screen
2. Screening for thrombophilia in the general population or for recurrent pregnancy loss
3. Expanded carrier screening which includes results for conditions not explicitly recommended for coverage

The development of this guideline note was informed by a HERC coverage guidance. See http://www.oregon.gov/oha/herc/Pages/blog-prenatal-genetic.aspx

Section 5.0

New Codes

2018 CPT Codes
Straightforward

code	long_code_description	Recommended Placement	Comments
00731	Anesthesia for upper gastrointestinal endoscopic procedures, endoscope introduced proximal to duodenum; not otherwise specified	Ancillary Procedures File	Anesthesia generally treated as Ancillary (covered if primary procedure is covered) Similar CPT code 00740 (Anesthesia for upper gastrointestinal endoscopic procedures, endoscope introduced proximal to duodenum) was Ancillary, now is being replaced by more specific codes
00732	Anesthesia for upper gastrointestinal endoscopic procedures, endoscope introduced proximal to duodenum; endoscopic retrograde cholangiopancreatography (ERCP)	Ancillary Procedures File	See 00731
00811	Anesthesia for lower intestinal endoscopic procedures, endoscope introduced distal to duodenum; not otherwise specified	Ancillary Procedures File	Similar CPT code 00810 (Anesthesia for lower intestinal endoscopic procedures, endoscope introduced distal to duodenum) was Ancillary, now is being replaced by more specific codes
00812	Anesthesia for lower intestinal endoscopic procedures, endoscope introduced distal to duodenum; screening colonoscopy	Ancillary Procedures File	See 00811
00813	Anesthesia for combined upper and lower gastrointestinal endoscopic procedures, endoscope introduced both proximal to and	Ancillary Procedures File	See 00811
15730	Midface flap (ie, zygomaticofacial flap) with preservation of vascular pedicle(s)	Ancillary Procedures File	Graphs and flaps and pedicles used for multiple procedures added to the Ancillary List in September, 2017

code	long_code_description	Recommended Placement	Comments
15733	Muscle, myocutaneous, or fasciocutaneous flap; head and neck with named vascular pedicle (ie, buccinators, genioglossus, temporalis, masseter, sternocleidomastoid, levator scapulae)	Ancillary Procedures File	Replaces 15732 (Muscle, myocutaneous, or fasciocutaneous flap; head and neck (eg, temporalis, masseter muscle, sternocleidomastoid, levator scapulae)) which was on lines 47,204,212,234,280,292,305,384. The new code includes additional muscles (buccinators, genioglossus). 15732 was moved to the Ancillary Procedures File in September, 2017
31241	Nasal/sinus endoscopy, surgical; with ligation of sphenopalatine artery	469 CHRONIC SINUSITIS 509 NASAL POLYPS, OTHER DISORDERS OF NASAL CAVITY AND SINUSES	Current nasal/sinus endoscopy codes (31254, etc.) are on lines 469,509
31253	Nasal/sinus endoscopy, surgical with ethmoidectomy; total (anterior and posterior), including frontal sinus exploration, with removal of tissue from frontal sinus, when performed	469 CHRONIC SINUSITIS 509 NASAL POLYPS, OTHER DISORDERS OF NASAL CAVITY AND SINUSES	Current nasal/sinus endoscopy codes (31254, etc.) are on lines 469,509
31257	Nasal/sinus endoscopy, surgical with ethmoidectomy; total (anterior and posterior), including sphenoidotomy	469 CHRONIC SINUSITIS 509 NASAL POLYPS, OTHER DISORDERS OF NASAL CAVITY AND SINUSES	Current nasal/sinus endoscopy codes (31254, etc.) are on lines 469,509
31259	Nasal/sinus endoscopy, surgical with ethmoidectomy; total (anterior and posterior), including sphenoidotomy, with removal of tissue from the sphenoid sinus	469 CHRONIC SINUSITIS 509 NASAL POLYPS, OTHER DISORDERS OF NASAL CAVITY AND SINUSES	Current nasal/sinus endoscopy codes (31254, etc.) are on lines 469,509
31298	Nasal/sinus endoscopy, surgical; with dilation of frontal and sphenoid sinus ostia (eg, balloon dilation)	469 CHRONIC SINUSITIS 509 NASAL POLYPS, OTHER DISORDERS OF NASAL CAVITY AND SINUSES	Current nasal/sinus endoscopy codes (31254, etc.) are on lines 469,509

code	long_code_description	Recommended Placement	Comments
34701	Endovascular repair of infrarenal aorta by deployment of an aorto-aortic tube endograft including pre-procedure sizing and device selection, all nonselective catheterization(s), all associated radiological supervision and interpretation, all endograft ex	289 DISSECTING OR RUPTURED AORTIC ANEURYSM 330 NON-DISSECTING ANEURYSM WITHOUT RUPTURE	Endovascular aortic repair codes have been overhauled. 8 previous codes deleted and 16 new codes added. Current endovascular repair of aorta CPT codes are on lines 289,330 Similar code 34800 (Endovascular repair of infrarenal abdominal aortic aneurysm or dissection; using aorto-aortic tube prosthesis) deleted
34702	Endovascular repair of infrarenal aorta by deployment of an aorto-aortic tube endograft including pre-procedure sizing and device selection, all nonselective catheterization(s), all associated radiological supervision and	289 DISSECTING OR RUPTURED AORTIC ANEURYSM 330 NON-DISSECTING ANEURYSM WITHOUT RUPTURE	See 34701
34703	Endovascular repair of infrarenal aorta and/or iliac artery(ies) by deployment of an aorto-uni-iliac endograft including pre-procedure sizing and device selection, all nonselective catheterization(s), all associated radiological	289 DISSECTING OR RUPTURED AORTIC ANEURYSM 330 NON-DISSECTING ANEURYSM WITHOUT RUPTURE	Iliac artery aneurysm is on line 330
34704	Endovascular repair of infrarenal aorta and/or iliac artery(ies) by deployment of an aorto-uni-iliac endograft including pre-procedure sizing and device selection, all nonselective catheterization(s), all associated radiological	289 DISSECTING OR RUPTURED AORTIC ANEURYSM 330 NON-DISSECTING ANEURYSM WITHOUT RUPTURE	Iliac artery aneurysm is on line 330. Aortic aneurysms are on lines 289 and 330
34705	Endovascular repair of infrarenal aorta and/or iliac artery(ies) by deployment of an aorto-bi-iliac endograft including pre-procedure sizing and device selection, all nonselective catheterization(s), all associated radiological	289 DISSECTING OR RUPTURED AORTIC ANEURYSM 330 NON-DISSECTING ANEURYSM WITHOUT RUPTURE	See 34704
34706	Endovascular repair of infrarenal aorta and/or iliac artery(ies) by deployment of an aorto-bi-iliac endograft including pre-procedure sizing and device selection, all nonselective catheterization(s), all associated radiological	289 DISSECTING OR RUPTURED AORTIC ANEURYSM 330 NON-DISSECTING ANEURYSM WITHOUT RUPTURE	See 34704

code	long_code_description	Recommended Placement	Comments
34707	Endovascular repair of iliac artery by deployment of an ilio-iliac tube endograft including pre-procedure sizing and device selection, all nonselective catheterization(s), all associated radiological supervision and	330 NON-DISSECTING ANEURYSM WITHOUT RUPTURE	Iliac artery aneursm (I72.3) is on line 330
34708	Endovascular repair of iliac artery by deployment of an ilio-iliac tube endograft including pre-procedure sizing and device selection, all nonselective catheterization(s), all associated radiological supervision and	330 NON-DISSECTING ANEURYSM WITHOUT RUPTURE	Iliac artery aneursm (I72.3) is on line 330
34709	Placement of extension prosthesis(es) distal to the common iliac artery(ies) or proximal to the renal artery(ies) for endovascular repair of infrarenal abdominal aortic or iliac aneurysm, false aneurysm, dissection, penetrating ulcer,	289 DISSECTING OR RUPTURED AORTIC ANEURYSM 330 NON-DISSECTING ANEURYSM WITHOUT RUPTURE	Iliac artery aneurysm is on line 330. Aortic aneurysms are on lines 289 and 330
34710	Delayed placement of distal or proximal extension prosthesis for endovascular repair of infrarenal abdominal aortic or iliac aneurysm, false aneurysm, dissection, endoleak, or endograft migration, including pre-procedure	289 DISSECTING OR RUPTURED AORTIC ANEURYSM 330 NON-DISSECTING ANEURYSM WITHOUT RUPTURE	Iliac artery aneurysm is on line 330. Aortic aneurysms are on lines 289 and 330
34711	Delayed placement of distal or proximal extension prosthesis for endovascular repair of infrarenal abdominal aortic or iliac aneurysm, false aneurysm, dissection, endoleak, or endograft migration, including pre-procedure	289 DISSECTING OR RUPTURED AORTIC ANEURYSM 330 NON-DISSECTING ANEURYSM WITHOUT RUPTURE	Iliac artery aneurysm is on line 330. Aortic aneurysms are on lines 289 and 330
34712	Transcatheter delivery of enhanced fixation device(s) to the endograft (eg, anchor, screw, tack) and all associated radiological supervision	Ancillary Procedure File	Could be used for a variety of endografts
34713	Percutaneous access and closure of femoral artery for delivery of endograft through a large sheath (12 French or larger), including ultrasound guidance, when performed, unilateral (List separately in addition to code for	330 NON-DISSECTING ANEURYSM WITHOUT RUPTURE	Similar code 34812 (Open femoral artery exposure for delivery of endovascular prosthesis, by groin incision, unilateral) is on line 330

code	long_code_description	Recommended Placement	Comments
34714	Open femoral artery exposure with creation of conduit for delivery of endovascular prosthesis or for establishment of cardiopulmonary bypass, by groin incision, unilateral (List separately in addition to code for primary procedure)	Ancillary Procedure File	May be used for cardiopulmonary bypass for a variety of cardiac and pulmonary surgeries. Cardiopulmonary bypass is noted as a part of a procedure on lines 48,49,51,54,73,81,84,86,90,93, 109,110,123,132,138,142,147,180,190,192,193,204, 218,228,245,258,262,268,281,286, 289,290,330,352, 362,371,377,428
34715	Open axillary/subclavian artery exposure for delivery of endovascular prosthesis by infraclavicular or supraclavicular incision, unilateral (List separately in addition to code for	330 NON-DISSECTING ANEURYSM WITHOUT RUPTURE	Similar code 34834 (Open brachial artery exposure to assist in the deployment of aortic or iliac endovascular prosthesis by arm incision, unilateral) is on line 330
34716	Open axillary/subclavian artery exposure with creation of conduit for delivery of endovascular prosthesis or for establishment of cardiopulmonary bypass, by infraclavicular or supraclavicular incision, unilateral (List	Ancillary Procedure File	May be used for cardiopulmonary bypass for a variety of cardiac and pulmonary surgeries
38222	Diagnostic bone marrow; biopsy(ies) and aspiration(s)	Diagnostic Procedures File	Similar code 38220 (Bone marrow; aspiration only) is Diagnostic
38573	Laparoscopy, surgical; with bilateral total pelvic lymphadenectomy and peri-aortic lymph node sampling, peritoneal washings, peritoneal biopsy(ies), omentectomy, and diaphragmatic washings, including diaphragmatic and other serosal biopsy(ies), when perf	116 CANCER OF TESTIS 137 CANCER OF CERVIX 213 CANCER OF UTERUS 243 CANCER OF OVARY 275 CANCER OF BLADDER AND URETER 291 CANCER OF VAGINA, VULVA, AND OTHER FEMALE GENITAL ORGANS 334 CANCER OF PROSTATE GLAND	Similar code 38572 (Laparoscopy, surgical; with bilateral total pelvic lymphadenectomy and peri-aortic lymph node sampling (biopsy), single or multiple) is on lines 116,137,213,243,275,291,334

code	long_code_description	Recommended Placement	Comments
43286	Esophagectomy, total or near total, with laparoscopic mobilization of the abdominal and mediastinal esophagus and proximal gastrectomy, with laparoscopic pyloric drainage procedure if performed, with open cervical pharyngogastrostomy or esophagogastrosto	60 ULCERS, GASTRITIS, DUODENITIS, AND GI HEMORRHAGE 68 CONGENITAL ANOMALIES OF UPPER ALIMENTARY TRACT, EXCLUDING TONGUE 319 CANCER OF ESOPHAGUS; BARRETT'S ESOPHAGUS WITH DYSPLASIA	Similar codes 43107-43108 (Total or near total esophagectomy, without thoracotomy; with pharyngogastrostomy or cervical esophagogastrostomy, with or without pyloroplasty (transhiatal)) are on lines 60,319 and 43112-43113 (Total or near total esophagectomy, with thoracotomy; with pharyngogastrostomy or cervical esophagogastrostomy, with or without pyloroplasty) are on lines 60,68,319
43287	Esophagectomy, distal two-thirds, with laparoscopic mobilization of the abdominal and lower mediastinal esophagus and proximal gastrectomy, with laparoscopic pyloric drainage procedure if performed, with separate thoracoscopic mobilization of the middle	60 ULCERS, GASTRITIS, DUODENITIS, AND GI HEMORRHAGE 68 CONGENITAL ANOMALIES OF UPPER ALIMENTARY TRACT, EXCLUDING TONGUE 319 CANCER OF ESOPHAGUS; BARRETT'S ESOPHAGUS WITH DYSPLASIA	See 43286
43288	Esophagectomy, total or near total, with thoracoscopic mobilization of the upper, middle, and lower mediastinal esophagus, with separate laparoscopic proximal gastrectomy, with laparoscopic pyloric drainage procedure if performed, with open cervical phar	60 ULCERS, GASTRITIS, DUODENITIS, AND GI HEMORRHAGE 68 CONGENITAL ANOMALIES OF UPPER ALIMENTARY TRACT, EXCLUDING TONGUE 319 CANCER OF ESOPHAGUS; BARRETT'S ESOPHAGUS WITH DYSPLASIA	See 43286

code	long_code_description	Recommended Placement	Comments
58575	Laparoscopy, surgical, total hysterectomy for resection of malignancy (tumor debulking), with omentectomy including salpingo-oophorectomy, unilateral or bilateral, when performed	137 CANCER OF CERVIX 213 CANCER OF UTERUS 243 CANCER OF OVARY 291 CANCER OF VAGINA, VULVA, AND OTHER FEMALE GENITAL ORGANS	New type of code. Could be used for ovarian, uterine, cervical, fallopian tube cancer
71045	Radiologic examination, chest; single view	Diagnostic Procedures File	CPT is consolidating many types of chest xrays into a few codes. Older codes were all diagnostic
71046	Radiologic examination, chest; 2 views	Diagnostic Procedures File	
71047	Radiologic examination, chest; 3 views	Diagnostic Procedures File	
71048	Radiologic examination, chest; 4 or more	Diagnostic Procedures File	
74018	Radiologic examination, abdomen; 1 view	Diagnostic Procedures File	CPT is consolidating many types of abdominal xrays into a few codes. Older codes were all diagnostic
74019	Radiologic examination, abdomen; 2 views	Diagnostic Procedures File	
74021	Radiologic examination, abdomen; 3 or more	Diagnostic Procedures File	
86794	Antibody; Zika virus, IgM	Diagnostic Procedures File	
87634	Infectious agent detection by nucleic acid (DNA or RNA); respiratory syncytial virus,	Diagnostic Procedures File	
87662	Infectious agent detection by nucleic acid (DNA or RNA); Zika virus, amplified probe	Diagnostic Procedures File	
90587	Dengue vaccine, quadrivalent, live, 3 dose schedule, for subcutaneous use	Excluded	Travel vaccine. Cannot be on any line on the Prioritized List
90682	Influenza virus vaccine, quadrivalent (RIV4), derived from recombinant DNA, hemagglutinin (HA) protein only, preservative and antibiotic	3 PREVENTION SERVICES WITH EVIDENCE OF EFFECTIVENESS	"High dose" older adult formulation of flu vaccine
90750	Zoster (shingles) vaccine (HZV), recombinant, subunit, adjuvanted, for intramuscular use	3 PREVENTION SERVICES WITH EVIDENCE OF EFFECTIVENESS	Live zoster vaccine is on line 3.
90756	Influenza virus vaccine, quadrivalent (ccIIV4), derived from cell cultures, subunit, antibiotic free, 0.5 mL dosage, for intramuscular use	3 PREVENTION SERVICES WITH EVIDENCE OF EFFECTIVENESS	

code	long_code_description	Recommended Placement	Comments
93793	Anticoagulant management for a patient taking warfarin, must include review and interpretation of a new home, office, or lab international normalized ratio (INR) test result, patient instructions, dosage adjustment (as needed), and scheduling of addition	All lines which currently contain 99363/99364	Replacing CPT 99363 and 99364 (Anticoagulant management for an outpatient taking warfarin, physician review and interpretation of International Normalized Ratio (INR) testing, patient instructions, dosage adjustment (as needed), and ordering of additional tests; first 90 days/after 90 days) which were on 600 lines (approx). Appears that the first 90 days and later differentiation is being eliminated
94617	Exercise test for bronchospasm, including pre- and post-spirometry, electrocardiographic recording(s), and pulse oximetry	Diagnostic Procedures File	94070 (Bronchospasm provocation evaluation, multiple spirometric determinations as in 94010, with administered agents (eg, antigen[s], cold air, methacholine)) is Diagnostic
94618	Pulmonary stress testing (eg, 6-minute walk test), including measurement of heart rate, oximetry, and oxygen titration, when performed	Diagnostic Procedures File	Replacing 94620 (Pulmonary stress testing; simple (eg, 6-minute walk test, prolonged exercise test for bronchospasm with pre- and post-spirometry and oximetry)) which was diagnostic
95249	Ambulatory continuous glucose monitoring of interstitial tissue fluid via a subcutaneous sensor for a minimum of 72 hours; patient-provided equipment, sensor placement, hook-up, calibration of monitor, patient training, and printout of recording	8 TYPE 1 DIABETES MELLITUS	95250 and 95251 (Ambulatory continuous glucose monitoring of interstitial tissue fluid via a subcutaneous sensor for a minimum of 72 hours; sensor placement, hook-up, calibration of monitor, patient training, removal of sensor, and printout of recording) on line 8

code	long_code_description	Recommended Placement	Comments
97127	Therapeutic interventions that focus on cognitive function (eg, attention, memory, reasoning, executive function, problem solving, and/or pragmatic functioning) and compensatory strategies to manage the performance of an activity (eg, managing time or sc	96 SEVERE/MODERATE HEAD INJURY: HEMATOMA/EDEMA WITH PERSISTENT SYMPTOMS 182 INTRACEREBRAL HEMORRHAGE 200 SUBARACHNOID AND INTRACEREBRAL HEMORRHAGE/HEMATOMA; CEREBRAL ANEURYSM; COMPRESSION OF BRAIN 206 CHRONIC ORGANIC MENTAL DISORDERS INCLUDING DEMENTIAS 290 COMPLICATIONS OF A PROCEDURE ALWAYS REQUIRING TREATMENT 322 STROKE 350 NEUROLOGICAL DYSFUNCTION IN COMMUNICATION CAUSED BY CHRONIC CONDITIONS 382 DYSFUNCTION RESULTING IN LOSS OF ABILITY TO MAXIMIZE LEVEL OF INDEPENDENCE IN SELF-DIRECTED CARE CAUSED BY CHRONIC CONDITIONS THAT CAUSE NEUROLOGICAL DYSFUNCTION	Replacing code 97532 (Development of cognitive skills to improve attention, memory, problem solving (includes compensatory training), direct (one-on-one) patient contact, each 15 minutes) which is on lines 96,182,200,206,290,322,350,382

code	long_code_description	Recommended Placement	Comments
97763	Orthotic(s)/prosthetic(s) management and/or training, upper extremity(ies), lower extremity(ies), and/or trunk, subsequent orthotic(s)/prosthetic(s) encounter, each 15 minutes	46,57,68,71,72,81,91,92,131,132,136, 150, 153,160,178,183,184,196,197,201,208,257,272,285, 292,301,309,317,341,345,355,356,359,361,376,377, 400,417,421,422,430,441,461,476,484,553,556,569, 586,605	97760 (Orthotic(s) management and training (including assessment and fitting when not otherwise reported), upper extremity(s), lower extremity(s) and/or trunk, each 15 minutes) is on lines 46,57,68,71,72,81,91,92,131,132,136, 150, 153,160,178,183,184,196,197,201,208,257,272,285, 292,301,309,317,341,345,355,356,359,361,376,377, 400,417,421,422,430,441,461,476,484,553,556,569, 586,605 97661 (Prosthetic(s) training, upper and/or lower extremity(ies), initial prosthetic(s) encounter, each 15 minutes) is on nearly all the above lines
99483	Assessment of and care planning for a patient with cognitive impairment, requiring an independent historian, in the office or other outpatient, home or domiciliary or rest home, with all of the following required elements: Cognition-focused evaluation in	Diagnostic Procedures File	Replaces HCPCS G0505 (Cognition and functional assessment using standardized instruments with development of recorded care plan for the patient with cognitive impairment, history obtained from patient and/or caregiver, in office or other outpatient setting or home or domicilia) which was Diagnostic
99484	Care management services for behavioral health conditions, at least 20 minutes of clinical staff time, directed by a physician or other qualified health care professional, per calendar month, with the following required elements: initial assessment or fo	Ancillary Procedures File	Replaces HCPCS G0507 (Care management services for behavioral health conditions, at least 20 minutes of clinical staff time, directed by a physician or other qualified health care professional, per calendar month, with the following required elements: initial assessment or fol) which was Ancillary

code	long_code_description	Recommended Placement	Comments
99492	Initial psychiatric collaborative care management, first 70 minutes in the first calendar month of behavioral health care manager activities, in consultation with a psychiatric consultant, and directed by the treating physician or other qualified health	Ancillary Procedures File	Replaces HCPCS G0503 (Subsequent psychiatric collaborative care management, first 60 minutes in a subsequent month of behavioral health care manager activities, in consultation with a psychiatric consultant, and directed by the treating physician or other qualified health care) which was ancillary. HSD mental health division staff agree with Ancillary
99493	Subsequent psychiatric collaborative care management, first 60 minutes in a subsequent month of behavioral health care manager activities, in consultation with a psychiatric consultant, and directed by the treating	Ancillary Procedures File	See 99492
99494	Initial or subsequent psychiatric collaborative care management, each additional 30 minutes in a calendar month of behavioral health care manager activities, in consultation with a psychiatric consultant, and directed by the	Ancillary Procedures File	See 99492

2018 CPT Code Review Issues

1) Intraoperative radiation therapy for breast cancer
    a. Code: **19294** Preparation of tumor cavity, with placement of a radiation therapy applicator for intraoperative radiation therapy (IORT) concurrent with partial mastectomy (List separately in addition to code for primary procedure)
    b. Code placement: breast cancer and partial mastectomy CPT codes are on line 191 CANCER OF BREAST; AT HIGH RISK OF BREAST CANCER
    c. **NCCN 2017**: does not include IORT in their guidelines for treatment of breast cancer
    d. Evidence:
        i. **Esposito 2015,** review of TARGIT-A and ELIOT trials
            1. TARGIT-A: 3451 patients, RCT of IORT vs post-operative whole breast irradiation (EBRT)
            2. ELIOT: 1305 patients, RCT of IORT vs EBRT
            3. Results: The TARGIT-A and ELIOT trials have demonstrated that IORT is associated with a low rate of local recurrence, although higher than that after EBRT (TARGIT-A: 3.3 versus 1.3 per cent respectively, $P = 0.042$; ELIOT: 4.4 versus 0.4 per cent, $P < 0.001$). However, the local recurrence rate for IORT fell within the predefined 2.5 per cent non-inferiority margin in TARGIT-A, and the 7.5 per cent equivalence margin in ELIOT.
            4. Conclusion: Longer follow-up data from existing trials, optimization of patient criteria and cost-effectiveness analyses are needed. Based on the current evidence, IORT can be offered as an alternative to EBRT to selected patients within agreed protocols, and outcomes should be monitored within national registries.
        ii. **Picot 2015,** health technology assessment and economic review of IORT for breast cancer
            1. N=1 RCT (TARGIT-A trial)
            2. The review found that local recurrence was slightly higher following INTRABEAM IORT than whole-breast external beam radiotherapy (WB-EBRT), but the difference did not exceed the 2.5% non-inferiority margin providing INTRABEAM was given at the same time as breast conserving surgery (BCS). Overall survival was similar with both treatments.
            3. Statistically significant differences in complications were found for the occurrence of wound seroma requiring more than three aspirations (more frequent in the INTRABEAM group) and for a Radiation Therapy Oncology Group toxicity score of grade 3 or 4 (less frequent in the INTRABEAM group).
            4. Cost-effectiveness base-case analysis indicates that INTRABEAM is less expensive but also less effective than WB-EBRT because it is associated with lower total costs but fewer total quality-adjusted life-years gained. However, sensitivity analyses identified four model parameters that can cause a switch in the treatment option that is considered cost-effective.
            5. Conclusions and implications: A significant investment in INTRABEAM equipment and staff training (clinical and non-clinical) would be required to make this technology available across the NHS. Longer-term

follow-up data from the TARGIT-A trial and analysis of registry data are required as results are currently based on a small number of events and economic modelling results are uncertain

e. Other policies:
    i. Aetna: considers IORT for breast cancer experimental
    ii. Cigna 2016: considers IORT for breast cancer experimental
    iii. Anthem 2017:
        1. External beam intraoperative partial breast irradiation (electron or low-energy x-ray radiotherapy) is considered **medically necessary** as an alternative to whole breast irradiation in the treatment of early stage breast cancer when **all** of the following criteria are met:
            a. Individual is 50 years of age or older; **and**
            b. Clinically node negative on either preoperative physical examination (that is, non-palpable node[s]), **or** medical imaging if performed (for example, mammography, magnetic resonance imaging [MRI], or ultrasound); **and**
            c. Tumor is **either**:
                i. Invasive ductal carcinoma measuring less than or equal to 2 centimeters (T1 disease) with negative margin widths of greater than or equal to 2 millimeters, no lymphovascular space invasion, estrogen-receptor positive (ER+), and BRCA negative; **or**
                ii. Low or intermediate nuclear grade, screen-detected ductal carcinoma in situ measuring less than or equal to 2.5 centimeters with negative margin widths of greater than or equal to 3 millimeters.

f. Expert input: Dr. Jeannie Louie, Providence oncology
    i. I find the data for breast intra-operative radiation treatments (IORT) not very straightforward as some of the patients in the trials received external beam radiation treatments as well as IORT. The main data supporting IORT comes from the TARGIT-A randomized trial which was updated in a report in Lancet 2014. Although the title of the paper states that five year results are available, the median follow-up time is significantly less for most of the patients enrolled – 3,451 patients had a median follow-up of 29 months, 2,020 with a follow-up of 4 years and 1,222 with a follow-up of five years. The total number of patients was 3,451. Local recurrence was higher in the IORT group – 3.3% versus 1.3% which was significant. Local recurrence rates were higher when IORT was delivered after lumpectomy (reopening the wound) as compared to IORT delivery at the time of lumpectomy. About 15% of patients required external beam radiation when adverse pathologic factors were identified at the time of lumpectomy. Surprisingly, the 5 year rate of ipsilateral breast recurrence in the post-pathology stratum (well-selected, favorable patients treated with IORT alone) was higher than in the pre-pathology stratum, in which about 15-20% of patients received whole breast radiation. The absolute excess in local failure

was 3.7% in the post-pathology stratum and 1% for patients in the pre-pathology stratum as compared to standard whole breast radiation therapy. This suggests that the TARGIT dose (20Gy at the surface of the applicator – with 50 keV x-rays this is about 5Gy at 1cm from the surface of the applicator) is perhaps too low to be efficacious without whole breast radiation, even in low risk patients. I know OHSU has used this. But I would only use in a clinical trial setting.

g. HERC staff summary: IORT for breast cancer has been studied in two trials to date, with follow up less than the usual time to recurrence for these types of cancers. This treatment appears promising, but still experimental. It is not included in the NCCN breast cancer therapy guidelines, nor covered by most major insurers, nor recommended by experts.
h. HERC staff recommendation:
    i. Add **19294** Preparation of tumor cavity, with placement of a radiation therapy applicator for intraoperative radiation therapy (IORT) concurrent with partial mastectomy (List separately in addition to code for primary procedure) to line 660 CONDITIONS FOR WHICH CERTAIN TREATMENTS HAVE NO CLINICALLY IMPORTANT BENEFIT OR HAVE HARMS THAT OUTWEIGH BENEFITS; UNPROVEN TREATMENTS with an entry for GN173 as shown below

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

The following treatments are prioritized on Line 660, CONDITIONS FOR WHICH CERTAIN TREATMENTS HAVE NO CLINICALLY IMPORTANT BENEFIT OR HAVE HARMS THAT OUTWEIGH BENEFITS; UNPROVEN TREATMENTS for the conditions listed here:

CPT/HCPCS code	INTERVENTION	Rationale	Date of last Review
19294	Intraoperative radiation therapy (IORT) concurrent with partial mastectomy	Unproven treatment	November, 2017

Review

Intraoperative radiotherapy in early breast cancer

E. Esposito[1,3], B. Anninga[1], S. Harris[2], I. Capasso[3], M. D'Aiuto[3], M. Rinaldo[3] and M. Douek[1]

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Background: **Intraoperative radiotherapy (IORT) constitutes a paradigm shift from the conventional 3–5 weeks of whole-breast external beam radiotherapy (EBRT). IORT enables delivery of radiation at the time of excision of the breast tumour, targeting the area at highest risk of recurrence, while minimizing excessive radiation exposure to healthy breast tissue. The rationale for IORT is based on the observation that over 90 per cent of local recurrences after breast-conserving surgery occur at or near the original operation site.**

Methods: **This article reviews trials of IORT delivered with different techniques and devices.**

Results: **IORT is a very attractive option for delivering radiotherapy, reducing the traditional fractionated treatment to a single fraction administered at the time of surgery. IORT has been shown to be associated with reduced toxicity and has several potential benefits over EBRT. Only two randomized clinical trials have been published to date. The TARGIT-A and ELIOT trials have demonstrated that IORT is associated with a low rate of local recurrence, although higher than that after EBRT (TARGIT-A: 3·3 *versus* 1·3 per cent respectively, $P = 0·042$; ELIOT: 4·4 *versus* 0·4 per cent, $P < 0·001$). However, the local recurrence rate for IORT fell within the predefined 2·5 per cent non-inferiority margin in TARGIT-A, and the 7·5 per cent equivalence margin in ELIOT.**

Conclusion: **Longer follow-up data from existing trials, optimization of patient criteria and cost-effectiveness analyses are needed. Based on the current evidence, IORT can be offered as an alternative to EBRT to selected patients within agreed protocols, and outcomes should be monitored within national registries.**

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Introduction

Adjuvant whole-breast external beam radiotherapy (EBRT) following breast-conserving surgery (BCS) has been shown to reduce local recurrence and improve survival[1–3]. It is now recognized worldwide as the standard of care for the treatment of early breast cancer along with BCS. The local recurrence rate (LRR) after BCS and conventional radiotherapy (RT) is estimated to be under 1 per cent per year, and varies between 4 and 7 per cent at 5 years[4,5]. The additional administration of an external radiation boost of 10–16 Gy to the tumour bed can further reduce the LRR by 40 per cent[6]. The landmark UK Standardization of Breast Radiotherapy (START) A and START-B studies found that the conventional schedule of 50 Gy in 25 fractions could be safely reduced to 41·6 Gy in 13 fractions and 40 Gy in 15 fractions respectively over 3 weeks[7–10]. Despite these data, in many countries women are still required to attend postoperative RT for 5 weeks consecutively. Athas and colleagues[11] suggested that up to 30 per cent of patients who undergo BCS for early breast cancer do not receive postoperative breast irradiation because they live a substantial distance away from a RT centre, or have significant co-morbidities or serious difficulties preventing them from attending daily treatment, especially the elderly. Because of this, in some countries patients decline RT or even opt for mastectomy to avoid radiotherapy[12–14].

In recent years there has been an expansion of oncoplastic breast surgery, with the accompanying challenge of accurate delivery of RT to the tumour bed. While rearranging the breast tissue, the position of the tumour bed is shifted and breast scars are often remote from the operation site. Complications following oncoplastic breast surgery may also delay adjuvant RT. A delay of over 8 weeks from

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Abstract

The INTRABEAM® Photon Radiotherapy System for the adjuvant treatment of early breast cancer: a systematic review and economic evaluation

Jo Picot,* Vicky Copley, Jill L Colquitt, Neelam Kalita, Debbie Hartwell and Jackie Bryant

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Background: Initial treatment for early breast cancer is usually either breast-conserving surgery (BCS) or mastectomy. After BCS, whole-breast external beam radiotherapy (WB-EBRT) is the standard of care. A potential alternative to post-operative WB-EBRT is intraoperative radiation therapy delivered by the INTRABEAM® Photon Radiotherapy System (Carl Zeiss, Oberkochen, Germany) to the tissue adjacent to the resection cavity at the time of surgery.

Objective: To assess the clinical effectiveness and cost-effectiveness of INTRABEAM for the adjuvant treatment of early breast cancer during surgical removal of the tumour.

Data sources: Electronic bibliographic databases, including MEDLINE, EMBASE and The Cochrane Library, were searched from inception to March 2014 for English-language articles. Bibliographies of articles, systematic reviews, clinical guidelines and the manufacturer's submission were also searched. The advisory group was contacted to identify additional evidence.

Methods: Systematic reviews of clinical effectiveness, health-related quality of life and cost-effectiveness were conducted. Two reviewers independently screened titles and abstracts for eligibility. Inclusion criteria were applied to full texts of retrieved papers by one reviewer and checked by a second reviewer. Data extraction and quality assessment were undertaken by one reviewer and checked by a second reviewer, and differences in opinion were resolved through discussion at each stage. Clinical effectiveness studies were included if they were carried out in patients with early operable breast cancer. The intervention was the INTRABEAM system, which was compared with WB-EBRT, and study designs were randomised controlled trials (RCTs). Controlled clinical trials could be considered if data from available RCTs were incomplete (e.g. absence of data on outcomes of interest). A cost–utility decision-analytic model was developed to estimate the costs, benefits and cost-effectiveness of INTRABEAM compared with WB-EBRT for early operable breast cancer.

Results: One non-inferiority RCT, TARGeted Intraoperative radioTherapy Alone (TARGIT-A), met the inclusion criteria for the review. The review found that local recurrence was slightly higher following INTRABEAM than WB-EBRT, but the difference did not exceed the 2.5% non-inferiority margin providing INTRABEAM was given at the same time as BCS. Overall survival was similar with both treatments. Statistically significant differences in complications were found for the occurrence of wound seroma requiring more than three aspirations (more frequent in the INTRABEAM group) and for a Radiation Therapy Oncology Group toxicity score of grade 3 or 4 (less frequent in the INTRABEAM group). Cost-effectiveness base-case analysis indicates that INTRABEAM is less expensive but also less effective than WB-EBRT because it is associated with lower total costs but fewer total quality-adjusted life-years

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2018 CPT Code Issues

1) Bone marrow aspirate for spinal fusion
    a. Code: **20939** Bone marrow aspiration for bone grafting, spine surgery only, through separate skin or fascial incision
    b. Background: Iliac crest bone harvest has been considered the "gold standard" at producing successful arthrodesis of the lumbar spine but is also associated with many donor-site morbidities. There has been investigative work on using many alternative types of materials to aid fusion, including bone marrow or stem cells.
    c. Similar codes:
        i. Previously, 38220 (Bone marrow; aspiration only) was the only code available for this procedure. This code is diagnostic.
        ii. 20937 (Autograft for spine surgery only (includes harvesting the graft); morselized (through separate skin or fascial incision)) is on lines 51,154,205,259,351,366,406,482, 532, 561
    a. Evidence
        iii. **Khashan 2013**, systematic review of alternative fusion materials for spinal surgery
            1. KQ1: Does the use of bone marrow aspirate (BMA) combined with synthetic or allograft extenders contribute to thoracolumbar fusion rates that are comparable with the rates achieved by the use of iliac crest graft?
                a. 4 level II, III studies used iliac crest bone graft as control. The results of these studies were inconsistent, and the overall body of evidence was found insufficient.
            2. KQ2: Are these fusion rates comparable with those of local bone graft (LBG)?
                a. Three, level II, III studies were identified for KQ2. Comparable fusion rates were demonstrated between LBG and BMA combined with calcium phosphate or collagen carrier. The overall body of evidence was found to be weak.
            3. KQ3: Does the addition of MSCs or BMA to iliac crest bone graft or LBG contribute to better throracolumbar fusion rates?
                a. For KQ3, one level III study was found. No significant difference was found in the fusion rates.
            4. KQ4: Are the cervical spine fusion outcomes achieved by the use of SCM or BMA with synthetic or allograft scaffolds comparable with the iliac crest bone graft or LBG outcomes?
                a. No studies met the criteria for KQ4
            5. KQ5: Was there any difference in terms of fusion rates, when MSCs were compared with BMA?
                b. No studies met the criteria for KQ5
            6. Conclusion. The currently available evidence is insufficient to support the use of MSCs or BMA combined with synthetic or allograft materials as a substitute or supplementary graft to autologous bone graft.

b. Other policies:
    iv. Aetna considers bone marrow aspiration for spinal fusion experimental
    v. Cigna does not appear to cover bone marrow aspiration for spinal fusion
    vi. Anthem covers bone marrow aspiration for spinal fusion when used with particular substrates
d. HERC staff summary: bone marrow aspirate for spinal fusion appears to be experimental. Alternative fusion techniques, such as use of iliac crest bone, are available and have good reported outcomes.
e. HERC staff recommendations:
    i. Add **20939** Bone marrow aspiration for bone grafting, spine surgery only, through separate skin or fascial incision to line 660 CONDITIONS FOR WHICH CERTAIN TREATMENTS HAVE NO CLINICALLY IMPORTANT BENEFIT OR HAVE HARMS THAT OUTWEIGH BENEFITS; UNPROVEN TREATMENTS with an entry for GN173 as shown below

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

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CPT/HCPCS code	**INTERVENTION**	**Rationale**	**Date of last Review**
20939	Bone marrow aspiration for bone grafting, spine surgery	Unproven treatment	November, 2017

Spine

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LITERATURE REVIEW

Cell Based Therapies as Compared to Autologous Bone Grafts for Spinal Arthrodesis

Morsi Khashan, MD,* Shinichi Inoue, MD,† and Sigurd H. Berven, MD*

Study Design. Systematic review.

Objective. To compare the clinical outcome of cell based grafts combined with bone extenders to autologous bone grafts.

Summary of Background Data. Alternative graft options that combine mesenchymal stem cells (MSCs) and bone marrow aspirate (BMA) with synthetic or allograft scaffolds have been recently used in several animal and clinical studies.

Methods. This systematic review of the literature addresses the following key questions (KQs): (1) Does the use of MSCs or BMA combined with synthetic or allograft extenders contribute to thoracolumbar fusion rates that are comparable with the rates achieved by the use of iliac crest graft? (2) Are these fusion rates comparable with those of local bone graft (LBG)? (3) Does the addition of MSCs or BMA to iliac crest bone graft or LBG contribute to better throracolumbar fusion rates? (4) Are the cervical spine fusion outcomes achieved by the use of SCM or BMA with synthetic or allograft scaffolds comparable with the iliac crest bone graft or LBG outcomes? (5) Was there any difference in terms of fusion rates, when MSCs were compared with BMA?

Results. For KQ1, 4 level II, III studies used iliac crest bone graft as control. The results of these studies were inconsistent, and the overall body of evidence was found insufficient. Three, level II, III studies were identified for KQ2. Comparable fusion rates were demonstrated between LBG and BMA combined with calcium phosphate or collagen carrier. The overall body of evidence was found weak. For KQ3, one level III study was found. No significant difference was found in the fusion rates. No studies met the criteria for KQ4, 5.

Conclusion. The currently available evidence is insufficient to support the use of MSCs or BMA combined with synthetic or allograft materials as a substitute or supplementary graft to autologous bone graft.

Key words: bone marrow aspirate, mesenchymal stem cells, bone scaffolds, bone extenders, fusion, iliac bone graft, local bone graft, thoracolumbar, lumbar, osteocondcution, osteogenesis.

Level of Evidence: 2

Spine 2013;38:1885–1891

Fusion procedures are widely used to treat various spinal disorders, and their number has been increasing steadily in the past decades.[1,2] For a successful fusion, graft materials with specific characteristic are needed. The optimal graft should contribute to osteogenesis, osteoconduction, osteoinduction, and structural integrity. It should also result in low complication rates.

Autologous iliac crest bone graft (ICBG) has been long considered the "gold standard" graft material.[2,3] It comprises all the properties mentioned earlier but unfortunately, it is associated with a substantial complication rate, reported to occur in up to 39% of the cases.[4] The main complications are pseudarthrosis and donor site morbidity.[5,6] Local bone graft (LBG) is another widely used graft for augmentation of instrumented spinal arthrodesis with good fusion rates[7,8] Yet, it does not provide mechanical integrity, and its availability is limited. The challenges of autologous bone use have motived extensive investigation seeking alternative graft options.

One of these alternatives is cellular based graft, which lacks osteoconduction ability and is used in combination with biological scaffolds (allografts and autografts) as well as with synthetic carriers. Bone marrow aspirate (BMA) contains different cell populations including osteoprogenitors and hematoprogenitors.[9] It is easily obtained in the supine position, from the posterior iliac bone, although vertebral bodies have been also used as bone marrow aspiration donors.[10] Mesenchymal stem cells (MSCs), can be isolated from various tissues and can differentiate into the osteogenic lineage to promote bone fusion.[11–13] In spinal surgery, the use of MSCs has been studied mainly *in vitro* and in animal models.

Bone extenders include osteoconductive cortical allografts, which have minimal osteoinductive properties due to the removal of these factors during processing.[14] Allograft has been shown to be inferior to autograft for spinal fusion.[14] Demineralized bone matrices (DBMs) lack the mineralized

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2018 CPT Code Issues

1) Cryoablation for pulmonary tumors
    a. Code: **32994** Ablation therapy for reduction or eradication of 1 or more pulmonary tumor(s) including pleura or chest wall when involved by tumor extension, percutaneous, including imaging guidance when performed, unilateral; cryoablation
    b. Background: Cryoablation is the use of cold to destroy tumor tissue. This technique may be done with a radiology-guided probe as an alternative to open surgery or when open surgery is not an option.
    c. Similar codes: 32998 (Ablation therapy for reduction or eradication of 1 or more pulmonary tumor(s) including pleura or chest wall when involved by tumor extension, percutaneous, radiofrequency, unilateral) is SNRC
    d. Evidence
        i. **Lee 2011**, systematic review of cryotherapy for treatment of lung malignancies
            1. N=16 studies, many non-controlled
            2. Overall success rates for significant recanalization of the obstruction were approximately 80%, although they varied, depending on disease status in the patient population. Complications from the procedure developed in 0-11.1% of cases, most of which were minor and controlled by conservative management.
            3. Conclusions: Endoscopic cryotherapy was found to be a safe and useful procedure in the management of endobronchial tumors although its efficacy and appropriate indications have yet to be determined in well-designed controlled studies
    e. Other policies
        i. **NICE 2005**: Cyrotherapy is covered for palliative treatment of endobronchial obstruction from inoperable lung tumors. Cryotherapy is not mentioned in the NICE guidance on curative treatment of lung cancer
            1. Efficacy: The main aim of the procedure in the studies was palliation of symptoms such as cough, dyspnoea and haemoptysis. In one case series of 521 patients, 86% (448/521) had improvement in one or more symptoms and quality of life scores were significantly improved. Dyspnoea improved in 59% (300/507) of patients. In two further studies, dyspnoea improved in 71% (12/17) and 81% (87/107) of patients.
            2. Safety: A large case series study reported in-hospital mortality of 1% (7/521), which was due to respiratory failure. This study also reported that 3% (16/521) of patients developed respiratory distress after the procedure
    f. Expert input from Providence thoracic surgery team:
        i. Available evidence supports use of this technology with the purpose of symptom palliation secondary to presence of endobronchial obstructing lesions.
        ii. Appropriate use:
            1. Tumor type: primary lung cancer or other metastatic malignancy to the large airway;

2. Presence of endobronchial lesion with associated (at least lobar) parenchymal atelectasis;
3. Hemoptysis secondary to the endobronchial location of the lesion;

iii. Not appropriate use:
1. Distal endobronchial lesions without evidence of lobar atelectasis and without symptoms;
2. Parenchymal, pleural or chest wall tumors;

iv. Alternative therapies: Alternative treatment options to cryotherapy are bronchoscopic resection or debulking, use of laser with bronchoscopic guidance, brachytherapy, photodynamic therapy, and external radiation. Some of these are associated with high cost of pharmaceutical agent (photodynamic therapy) or availability of highly specialized equipment (brachytherapy). Use of laser is associated with airway fire and the need to ensure that participating personnel has appropriate protective gear. External radiation requires the patient to be able to undergo transport to location where radiation can be administered and symptomatic response is usually delayed.

v. Cryotherapy equipment is easily mobile and the procedure can be performed in a variety of settings: operating room, specialized procedure unit, intensive care unit thus making is a versatile intervention option.

vi. Effectiveness: Cryotherapy does provide rapid symptomatic improvement (within 24h) with symptom improvement seen in 85% of patients.

g. HERC staff recommendations:
i. Add CPT **32994** (Ablation therapy for reduction or eradication of 1 or more pulmonary tumor(s) including pleura or chest wall when involved by tumor extension, percutaneous, including imaging guidance when performed, unilateral; cryoablation) to line 267 CANCER OF LUNG, BRONCHUS, PLEURA, TRACHEA, MEDIASTINUM AND OTHER RESPIRATORY ORGANS
1. Add the following guideline note to line 267

GUIDELINE NOTE XXX CRYOABLATION OF PULMONARY TUMORS

Line 267

Cryoablation of pulmonary tumors is included on this line only for palliative treatment of an inoperable lung tumor with one of the following:

1) Symptomatic proximal endobronchial obstruction, OR
2) Presence of endobronchial lesion with associated lobar or greater parenchymal atelectasis, OR
3) Hemoptysis from endobronchial location of the tumor.

ORIGINAL ARTICLE
DOI: 10.3904/kjim.2011.26.2.137

Endoscopic Cryotherapy of Lung and Bronchial Tumors: A Systematic Review

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Background/Aims: We made a systematic review and evaluation of endoscopic cryotherapy of endobronchial tumors, investigating safety and efficacy.
Methods: Qualified studies regarding endoscopic cryotherapy of lung tumors were systemically evaluated using available databases according to predefined criteria.
Results: In total, 16 publications were included in the final assessment. A narrative synthesis was performed because a formal meta-analysis was not viable due to the lack of controlled studies and study heterogeneity. Overall success rates for significant recanalization of the obstruction were approximately 80%, although they varied, depending on disease status in the patient population. Complications from the procedure developed in 0-11.1% of cases, most of which were minor and controlled by conservative management. Although limited data were available on comprehensive functional assessment, some studies showed that respiratory symptoms, pulmonary function tests, and performance status were significantly improved.
Conclusions: Endoscopic cryotherapy was found to be a safe and useful procedure in the management of endobronchial tumors although its efficacy and appropriate indications have yet to be determined in well-designed controlled studies. **(Korean J Intern Med 2011;26:137-144)**

Keywords: Cryotherapy; Bronchoscopy; Lung neoplasms; Carcinoma, bronchogenic; Airway obstruction

INTRODUCTION

Despite recent development of therapies and anti-cancer drugs, lung cancer does not yet respond well to treatments and continues to have a poor prognosis. Accordingly, it is ranked first in the world in terms of mortality among malignant tumors [1-3].

Two-thirds of all lung cancers are already in a stage where surgery is difficult by the time of diagnosis, and conservative treatments play an important role. In approximately 30% of lung cancer patients, central airway obstruction is accompanied by symptoms such as dyspnea and hemoptysis. Local treatment for these symptoms plays an important role in alleviating patient symptoms and improving their quality of life [4]. In progressive lung cancers, accompanied by central airway obstruction, various interventional methods for improving airway obstruction have been tried, including Nd:YAG laser

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therapy, electrocautery, brachytherapy, photodynamic therapy and cryotherapy [4,5]. Nd:YAG laser therapy, which has been widely used, and electrocauterization are effective and instantly open up the airway, but are more likely to result in such complications as airway perforation [5]. Also, photodynamic therapy is effective on small tumors, but is expensive, and may result in complications, including hemorrhage or secondary skin burns [5-7].

Cryotherapy uses flexible or rigid bronchoscopy to quickly freeze cells to -70°C, destroying them. Although it has a relatively long history, it has been used less than other treatment methods [5,8]. This is believed to be attributed to the fact that its effect is more delayed and its indication narrower than the more popular Nd:YAG laser therapy. Several case studies have shown that endoscopic cryotherapy is fairly effective and safe, but its objective efficacy has not been proven through large-scale controlled studies [9,10]. However, based on available research reports, endoscopic cryotherapy has a number of advantages: it is less expensive, and less likely to result in complications, such as perforation or hemorrhage. If it is used for appropriate indications, it is expected to establish itself as a useful interventional treatment method.

In this study, we systematically analyzed and evaluated research data on endoscopic cryotherapy, and discuss reference materials useful in the treatment of airway obstruction caused by tumors.

METHODS

Literature search strategy

The strategy to review the literature for 'endoscopic cryotherapy performed on lung and bronchial tumors' focused on studies that used the bronchoscope, and included studies that conducted a comparative analysis of laser therapy, electrocauterization, brachytherapy, stent insertion, and photodynamic therapy. After analysis, operation-related factors, such as safety, response, relapse, survival, and patient condition improvement factors, such as symptom improvement, pulmonary function, performance, quality of life, degree of bronchial obstruction, and oxygen saturation, were selected as major results.

Regarding 'endoscopic cryotherapy for lung and bronchial tumors,' eight domestic databases including KoreaMed and foreign databases like Ovid-Medline, EMBASE, CINAHL, and the Cochrane Library were used. The search strategy integrated 'lung neoplasm, bronchogenic carcinoma, bronchial neoplasm and tracheal neoplasia' and 'cryotherapy, cryosurgery, cryoablation, cryocoagulation, cryodestruction and cryoextraction.' In total, 664 documents in Korean and English were identified initially. Publications that were review articles, editorials, non-human experiments, preclinical studies, and documents containing abstracts only were excluded. In total, 648 documents, including 210 overlapping documents, were excluded, leaving 16 documents in the final evaluation. Each step, from literature review through application of selection criteria to data extraction, was carried out independently by a subcommittee and two evaluators. Scottish Intercollegiate Guidelines Network (SIGN) methodology was used to evaluate the quality of the literature, and levels of evidence and grades of recommendation were selected accordingly [11].

Study inclusion criteria

- Studies on lung and bronchial tumor patients.
- Studies on cryotherapy using bronchoscopy.
- Studies in which more than one appropriate medical outcome was reported.

Study exclusion criteria

- Non-human and pre-clinical studies.
- Studies that were not original articles (non-systematic reviews, editorials, letters, opinion pieces).
- Studies not published in Korean or English.
- Cases where the effects of other therapies were mixed with that of cryotherapy.
- Studies that published abstracts only.

Effectiveness assessment of cryotherapy

The effectiveness of endoscopic cryotherapy for lung and bronchial tumors was evaluated on the basis of discussions of the subcommittee in terms of operation-related factors and influences on the results of medical treatment. Operation-related factors included response, relapse, survival, and success rate, whereas influences on the results of medical treatment included improvement in clinical symptoms, pulmonary function, performance, quality of life, degree of bronchial obstruction, and the increase in oxygen saturation.

RESULTS

Literature search results

In total, one domestic report and 15 foreign reports were

Table 1. General characteristics of studies selected for evaluation

Serial no.	Year	Author	No. of patients	Age (mean or range)	Population	Study type
1	2008	Jung et al. [13]	4	40-64	Advanced lung cancer: stage IIIb, 1; stage IV, 3	Case study
2	2007	Beeson [14]	645	68.3	Inoperable lung cancer due to advanced stage, poor lung function or poor performance status	Case study
3	2006	Berotoletti et al. [15]	18	47	Typical carcinoid tumor	Case study
4	2006	Zoganas et al. [12]	163	67.9	Inoperable lung cancer due to advanced stage or poor general conditions	Comparison observation
5	2005	Asimakopoulos et al. [9]	329	68	Inoperable lung cancer due to advanced stage, poor lung function or poor performance status	Case study
6	2004	Hetzel et al. [16]	60	19-81	Endobronchial tumors: lung cancer; 56, benign tumors, 3; malignant lymphoma 1	Case study
7	2004	Maiwand et al. [17]	521	67.9	Inoperable lung cancer due to advanced stage or patients' general conditions	Case study
8	2001	Deygas et al. [18]	35	61	Early superficial bronchogenic carcinoma that cannot be operated due to comorbidities	Case study
9	2001	Noppen et al. [19]	15	63.5	Advanced lung cancer, 9; lung carcinoma *in situ*, 4; hemangioma, 1; melanoma, 1	Case study
10	1999	Maiwand [10]	153	68.8	Inoperable lung cancer due to advanced stage, site of the tumor, poor lung function or poor general health	Case study
11	1996	Mathur et al. [20]	20	62	Inoperable endobronchial tumors: primary lung cancer, 17; metastatic lung cancer, 3	Case study
12	1993	Marasso et al. [21]	234	62	Lung tumors of various status: malignant tumors, 190; benign tumors, 44	Case study
13	1990	Walsh et al. [22]	33	75	Inoperable lung cancer due to advanced stage or poor general conditions	Case study
14	1986	Homasson et al. [23]	22	39-88	Inoperable lung cancer due to advanced stage or poor general conditions	Case study
15	1986	Maiwand [24]	75	63	Advanced lung cancer: previous surgery, 26; previous radiotherapy, 16; cryotherapy as primary therapy, 33	Case study
16	1981	Sanderson et al. [25]	28	63	Inoperable lung cancer due to advanced stage or poor general conditions	Case study

used for the evaluation. The safety and effectiveness of endoscopic cryotherapy for the lung and bronchus were discussed in all 16 documents. Of the 16 selected reports, one was a comparison observation study with evidence level 2 [12], and the remaining 15 were case studies [9,10,13-25]. General characteristics of the studies are presented in Table 1.

Clinical data and outcomes

Safety

The safety of endoscopic cryotherapy for lung and bronchial tumors was evaluated on the basis of one comparison observation study, and 15 case studies with regard to deaths and complications within 30 days. Except for the small-scale study involving four subjects, complications, such as hemorrhage, mediastinal emphysema, atrial fibrillation, and dyspnea, occurred

Table 2. Complications of endoscopic cryotherapy

Year	Author	Occurrence	Complications	Treatment
2008	Jung et al. [13]	2/4	Mediastinal emphysema, hemoptysis	Controlled by conservative management
2007	Beeson [14]		Hemorrhage	Controlled by conservative management
2006	Berotoletti et al. [15]	2/18	Hemorrhage, subcutaneous emphysema	Controlled by conservative management
2005	Asimakopoulos et al. [9]	35/329	Hemorrhage, atrial fibrillation, dyspnea	Controlled by conservative management
2004	Hetzel et al. [16]	10/60	Hemorrhage	Controlled by hemostasis with plasma beamer
2004	Maiwand et al. [17]	49/521	Hemoptysis, atrial fibrillation, dyspnea	Transient and not serious complications
2001	Deygas et al. [18]	0/35		
2001	Noppen et al. [19]	0/12		
1999	Maiwand [10]	11/153	Hemorrhage, pneumothorax, anesthesia complication	Controlled by conservative management
1990	Walsh et al. [22]	0/33		
1986	Homasson et al. [23]	2/27	Light fever	Transient
1986	Maiwand [24]	0/75		

Table 3. 30-day mortality after endoscopic cryotherapy

Year	Author	Occurrence (%)
2005	Asimakopoulos et al. [9]	9/32 (2.4)
2004	Maiwand et al. [17]	7/512 (1.2)
1999	Maiwand [10]	0/153 (0.0)
1986	Homasson et al. [23]	1/27 (3.7)
1981	Sanderson et al. [25]	2/28 (7.1)

in 11.1% of all cases in 10 of the 16 studies. Most of the complications were controlled with simple conservative treatments (Table 2). In five of the 16 studies, mortality occurred in 7.1% of cases within 30 days of the operation. Causes of death were hemoptysis and respiratory failure. However, it was considered that most of the mortality was more likely to be associated with disease progression rather than a direct consequence of the procedures (Table 3).

Response rate

The case study by Hetzel et al. [16] evaluated the response rate of endobronchial tumors accompanied by a high level of stenosis after cryotherapy; the complete response rate was 61% (37/60), the partial response rate was 22% (13/60), and the total response rate was 83%. Deygas et al. [18] performed cryotherapy in treating 35 early superficial bronchogenic carcinoma patients who were inoperable due to comorbidities. The process was repeated 10-15 days later. They also followed 22 of the 35 patients; as a result, the complete response rate after 1 year was 91% (32/35). Homasson et al. [23] performed three cycles of -80°C cryotherapy in 27 lung cancers including patients who underwent preoperative radiation treatment (n = 5), chemotherapy (n = 3), and chemoradiation therapy (n = 3). The procedure was repeated 4-6 days layer and the response rate was evaluated. The results showed that the response rate of malignant tumors was 61.9% (13/21), and that of benign tumors was 100% (5/5). In the case study by Jung et al. [13], endoscopic cryotherapy was performed on one stage IIIb, and three stage IV lung cancer patients, with a success rate of 75% (3/4). Noppen et al. [19] performed 3 × 20-s cycles of -80°C cryotherapy in five invasive lung cancer patients, four carcinoma *in situ* (CIS) patients, two metastatic cancer patients, and one hemangioma patient. The process was repeated 1-2 weeks later, and the success rate was evaluated. Results showed the success rate to be 80% (4/5) in lung cancer, and zero in metastatic lung cancer. In all cases where the operation needed to be repeated, the second operation was a success. In the case study by Beeson [14] -70°C cryotherapy was performed on 645 patients who were inoperable for various reasons. They reported that the tumor in the bronchus was reduced, and the airway was opened in most cases. Walsh et al. [22] performed three cycles of -70°C cryotherapy for 33 inoperable patients, and evaluated the degree of bronchial obstruction. The degree of bronchial

obstruction improved in 77% (20/26) of the patients, and, radiologically, atelectasis improved in 24% (7/24) of the patients.

Relapse rate

Hetzel et al. [16] reported a relapse rate of 24.6% (14/57) 10-24 weeks after cryotherapy in endobronchial tumors with obstruction. Deygas et al. [18] performed two successive sessions of cryotherapy for 35 superficial endobronchial tumors, and the relapse rate was 28% (10/35) after 13-45 months. According to the case study by Berotoletti et al. [15], three cycles of -70°C cryotherapy was performed for 18 typical carcinoid tumor patients. They were followed up for 44.5 months, and there was no relapse. However, after 7 years, two of the patients had relapsed (11.1%).

Survival rate

In the case study by Beeson [14], -70°C cryotherapy was performed on 645 patients who were inoperable. Among them, squamous cell carcinoma patients accounted for 68.3%, adenocarcinoma 15.2%, large cell carcinoma 2.6%, undifferentiated carcinoma 5.2%, and small cell carcinoma 8.7%. Patients in stage II accounted for 6.7%, stage IIIa 21.0%, IIIb 23.9%, and stage IV 48.4%. This case study did not present comprehensive data on survival rates, but suggested the possibility of an increase in the survival rate due to the procedure. In the case study by Zoganas et al. [12], cryotherapy was performed for inoperable cancer patients, and the survival rate was analyzed 2 years later. The result showed that the survival rate was 19.3% in the group to which only cryotherapy was performed, and 25% in the group to which anticancer treatment was performed concurrently, but the difference was not statistically significant (p = 0.388).

In the case study by Asimakopoulos et al. [9], cryotherapy was performed more than twice for advanced lung cancer patients. This group survived for 15 months, on average, whereas the other group for whom cryotherapy was performed only once survived for 8.3 months, on average. In the case study by Hetzel et al. [16], cryotherapy was performed on patients with protruding tumors accompanied with a high level of stenosis, and their survival rate after 36 weeks was 52.6% (30/57). Maiwand and Asimakopoulos [17] performed two sessions of cryotherapy for 521 cancer patients who were inoperable, and observed them for 18 months (4 to 84 months). Average survival was 8.2 months, and according to the stage, the average survival period of the patients was 15.1 months in stage IIb, 8.5 months in stage IIIa, 9.0 months in stage IIIb, and 6.6 months in stage IV. Also, the 1-year survival rate was 38.4%, while the 2-year survival rate was 15.9%. Deygas et al. [18] followed up 22 of 35 early superficial cancer patients, and the 2-year survival rate was 62.5% (20/32), and after 48-89 months the survival rate was 50% (11/22). Six of the 19 died from other causes, six died of a relapse in the same location, and the remaining seven died of metastasis in other locations. Maiwand [24] performed two cycles of -70°C cryotherapy on 75 lung cancer patients with endobronchial tumors, who had undergone pneumonectomy (n = 18), preoperative radiation treatment (n = 16), and pneumonectomy and radiation treatment (n = 8), repeated for 2, 4, and 8 weeks, and followed them for 12 months. Results showed that the survival period of 19 patients was less than 1 month, 35 patients survived for 1-5 months, six patients survived for 6-11 months, and the remaining 16 patients survived for 12 months or longer.

Improvement in clinical symptoms and pulmonary function

In most studies, the procedure was performed for advanced lung and bronchial cancer patients who were inoperable. Following the procedure, symptoms, such as dyspnea, cough, hemoptysis, and stridor, showed statistically significant improvements. This was also the case for pulmonary function; forced expiratory volume at 1 second (FEV_1), forced vital capacity (FVC), and maximal flow rates showed statistically significant improvements after cryotherapy. The results of the studies are summarized in Table 4. Walsh et al. [22] reported that oxygen saturation (SaO_2) improved in 77% (20/26) of patients.

Improvement in performance and quality of life

In the study by Maiwand and Asimakopoulos [17], performance status and quality of life were assessed before and after cryotherapy in 521 inoperable cancer patients. Results showed that the Karnofsky score improved significantly, from 60 to 75, and the WHO score was reduced significantly, from 3.04 to 2.20. Walsh et al. [22] reported that in 33 inoperable patients, the performance of 27% (6/22) improved in the 6-minutes walking test. In the case study by Asimakopoulos et al. [9], cryotherapy was performed twice or more for Group A of advanced cancer patients, and once for Group B. The Karnofsky scores of

Table 4. Improvement in clinical symptoms and pulmonary function

Year	Author	Operation method	Improvement of clinical symptoms	Improvement of the pulmonary function
2008	Jung et al. [13]	-89°C freezing for 5-20 sec, and thawing repeated	Cases 1 and 2: dyspnea and atelectasis improved; Case 3: dyspnea improved	Not mentioned
2007	Beeson [14]	-70°C		FEV_1 and FVC improved
2006	Zoganas et al. [12]	Not mentioned	Single: 65%; Concurrent[a]: 80%	Not mentioned
2005	Asimakopoulos et al. [9]	3-min, -70°C 2 times or more (Group A), once (Group B)	Dyspnea improvement rate: Group A, 36.6%; Group B, 10.8% Coughing improvement rate: Group A, 41.9%; Group B, 11.4% Hemoptysis improvement rate: Group A, 35%; Group B, 6%	Group A: significant improvement of FVC Group B: no significant improvement of FVC or FEV_1
2004	Maiwand et al. [17]	3-min, -70°C 2.4 times on average, repeated 2 wk later	Cough, 69%; dyspnea, 59.2%; hemoptysis, 76.4%; chest pain, 42%	Significant improvement of FEV_1 (1.39 → 1.51 L) and FVC (1.93 → 2.13 L)
1990	Walsh et al. [22]	3-min, -70°C 3 times, repeated 2-4 wk later	Subjective improvement, 23/33 (70%); dyspnea score, 10/27 (37%); hemoptysis, 6/9 (67%); stridor, 4/7 (56%)	Improvement rates: FEV_1, 7/29 (24%); FVC, 7/29 (24%); MEF, 6/29 (21%); MIF, 3/11 (27%)
1986	Homasson et al. [23]	1-min, -80°C 3 times, repeated 4-6 days later	Favorable, 17: atelectasis improved (15), hemoptysis improved (2); no benefit, 9: technical failure (5), no reaction (3), death before treatment (1)	Not mentioned
1986	Maiwand [24]	150 sec, -70°C 2 times, repeated 2, 4, and 8 wk later	Symptom improvement: stridor, 20/33 (61%); dyspnea, 23/31 (74%); hemoptysis, 11/11 (100%)	Not mentioned
1981	Sanderson et al. [25]	2-min, -160°C 3 times, performed 1-8 times	Favorable, 15/28 (53.6%): tumors reduced (8), hemorrhage reduced (4), airway opened (3); no benefit, 13/28 (46.4%)	Not mentioned

FEV_1, forced expiratory volume at 1 sec; FVC, forced vital capacity; MEF, maximal expiratory flow rate; MIF, maximal inspiratory flow rate.
[a] Concurrent treatment: concurrent with radiotherapy, brachytherapy or chemotherapy.

Group A were 67.7, 72.2, and 74.6 before cryotherapy, after the first cryotherapy and after the second cryotherapy, respectively, whereas the Karnofsky scores in Group B was 67.5, 74.6, and 73.6, respectively. Both groups showed statistically significant improvements.

DISCUSSION

We have discussed the available safety and efficacy data of cryotherapy in the treatment of the endobronchial tumors, although detailed and comprehensive analysis was not possible due to the variability of methodologies and lack of standardization of the procedures. According to this study, endoscopic cryotherapy generally showed high treatment efficiency in approximately 80% of cases, although there was variation depending on operation methods or target patient groups. It was also effective in improving quality of life, improving symptoms, like dyspnea, and improving pulmonary function. In lung tumors, airway obstruction is one of the symptoms seen in patients, but it has an important influence on quality of life, so appropriate treatment is required on many occasions, and although it may be difficult to expect that

such local treatment will ultimately improve the survival rate, it will play an important role in patient management and conservative treatment. Laser therapy has been the preferred treatment for airway obstruction due to tumors. This is perhaps because laser therapy can instantly and powerfully open up even severe obstructions [26-28]. Laser therapy is known to result in more complications, including hemorrhage and perforation. Cryotherapy can be said to be superior in terms of safety [5]. Photodynamic therapy is also a useful local treatment method for various purposes, including curative treatment of an early cancer in the airway or alleviation of airway obstruction, but it is relatively expensive, and pre-and post-operation management is cumbersome [29]. Other endobronchial local treatment methods, including brachytherapy and electric cauterization, are used, and these methods have their own strengths and weaknesses. Accordingly, several factors, such as the status of the patient's disease, experience of the practitioner, and financial considerations, must be taken into account when any of these methods are selected.

As described previously, endoscopic cryotherapy may still be less researched and used than other treatment methods, including laser therapy. Because cryotherapy does not affect the cartilage or collagen in the bronchus, there is almost no risk of perforation, and, in this sense, it is safer than other methods, but it has less destructive power and its effect is delayed. Thus, its efficacy may be considered to be limited in cases with severe airway obstruction due to a large and extensive tumor [5]. As the spectrum of cryotherapy is about 5 mm, it is limited, and though it is possible to overcome this with repetition, there are other limitations. As laser therapy is more effective in opening up severe obstructions, it may be inappropriate to select cryotherapy as an initial treatment in such a case. It is recommended to perform laser therapy or cauterization first, and then cryotherapy as an additional treatment for the remaining tumor. It can also be a useful treatment method in removing early tumors limited to the airway [5]. As reports on the supplementary efficacy and synergistic effect of using cryotherapy together with anticancer chemotherapy or radiation treatment are published, the possibility of using it as part of concurrent treatments is also suggested [30,31].

Limitations of the analysis in this study relate to cryotherapy not being standardized; individual studies differed in research methods and frequencies, and the characteristics of patient groups varied. Thus, comprehensive statistical analysis was difficult. Accordingly, comprehensive statistical analysis was avoided in the results section, and we focused on describing the characteristics and results of each study. Additionally, both rigid and flexible bronchoscopy can be used for cryotherapy; depending on the choice, efficacy can vary. Because there are many different types of probe, there are slight differences in the mechanism of action and efficacy. Thus, there are limitations in comprehensively analyzing multiple studies [5].

In conclusion, endoscopic cryotherapy performed for endobronchial tumors is a safe and effective treatment method that will improve the symptoms, pulmonary function, and performance in patients with endobronchial obstruction, especially in inoperable cases. Given the lack of well-designed studies comparing it with other treatment methods, it must be objectively compared with other treatment methods and more cases need to be analyzed in future studies.

Conflict of interest

No potential conflict of interest relevant to this article was reported.

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NICE guidance

Cryotherapy for malignant endobronchial obstruction

Interventional procedures guidance
Published: 23 November 2005
nice.org.uk/guidance/ipg142

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

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

1 Guidance

1.1 Current evidence on the safety and efficacy of cryotherapy for malignant endobronchial obstruction appears adequate to support the use of this procedure provided that the normal arrangements are in place for consent, audit and clinical governance.

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1.2 Clinicians should ensure that patients fully understand that this is one of a variety of treatment options available. In addition, use of the Institute's information for the public is recommended.

2 The procedure

2.1 Indications

2.1.1 Lung cancer is often at an advanced stage when it is diagnosed, with low survival rates. Patients can develop endobronchial lesions that obstruct the major airways, causing symptoms such as dyspnoea, cough, haemoptysis and postobstructive pneumonia. Bronchial obstruction may lead to gradual asphyxiation.

2.1.2 The aim of treatment in patients with malignant endobronchial obstruction is mainly palliative. Current treatment options include a variety of endobronchial therapies such as bronchoscopic resection, brachytherapy, laser ablation, photodynamic therapy and stenting. Externalbeam radiotherapy and chemotherapy may also be used for palliative treatment.

2.2 Outline of the procedure

2.2.1 General anaesthesia is usually used. A cryoprobe is inserted through a bronchoscope to reach the tumour; the probe diameter selected depends on the size and position of the tumour. After a period of freezing, the tumour is allowed to thaw until the probe separates from the tissue. The freeze/thaw cycle may be repeated two to three times in the same place. The probe is then moved to an adjacent area and the process is repeated until the whole tumour has been treated. Any resulting necrotic tumour material is then removed with forceps or using the cryoprobe. Further necrotic material may be expectorated during the following 24–48 hours. The procedure can be repeated if necessary.

2.2.2 Cryotherapy does not provide immediate relief of bronchial obstruction and is therefore not suitable for the emergency treatment of acute respiratory distress.

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2.3 Efficacy

2.3.1 The main aim of the procedure in the studies was palliation of symptoms such as cough, dyspnoea and haemoptysis. In one case series of 521 patients, 86% (448/521) had improvement in one or more symptoms and quality of life scores were significantly improved. Dyspnoea improved in 59% (300/507) of patients. In two further studies, dyspnoea improved in 71% (12/17) and 81% (87/107) of patients. For more details, refer to the Sources of evidence.

2.3.2 The Specialist Advisors did not express any major concerns about the efficacy of this procedure.

2.4 Safety

2.4.1 A large case series study reported in-hospital mortality of 1% (7/521), which was due to respiratory failure. This study also reported that 3% (16/521) of patients developed respiratory distress after the procedure.

2.4.2 A case series study of 27 patients reported one death due to myocardial ischaemia. Another study of 22 patients reported one cardiopulmonary arrest during the procedure. Two studies reported changes to the heart rhythm in 2% (12/521) and 11% (3/27) of patients. For more details, refer to the Sources of evidence.

2.4.3 The Specialist Advisors listed haemorrhage, fistula formation, cardiac arrhythmias, respiratory distress and infection as potential adverse effects.

3 Further information

3.1 The Institute has issued guidance on the diagnosis and treatment of lung cancer. The Institute has also issued Interventional Procedures guidance on the use of photodynamic therapy for advanced bronchial carcinoma and photodynamic therapy for localised inoperable endobronchial cancer.

Andrew Dillon
Chief Executive
November 2005

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Sources of evidence

The evidence considered by the Interventional Procedures Advisory Committee is described in the following document.

'Interventional procedures overview of cryotherapy for malignant endobronchial obstruction', February 2005.

Information for the public

NICE has produced information describing its guidance on this procedure for patients, carers and those with a wider interest in healthcare. It explains the nature of the procedure and the decision made, and has been written with patient consent in mind.

4 About this guidance

NICE interventional procedure guidance makes recommendations on the safety and efficacy of the procedure. It does not cover whether or not the NHS should fund a procedure. Funding decisions are taken by local NHS bodies after considering the clinical effectiveness of the procedure and whether it represents value for money for the NHS. It is for healthcare professionals and people using the NHS in England, Wales, Scotland and Northern Ireland, and is endorsed by Healthcare Improvement Scotland for implementation by NHSScotland.

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

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

Changes since publication

22 January 2012: minor maintenance.

Your responsibility

This guidance represents the views of NICE and was arrived at after careful consideration of the available evidence. Healthcare professionals are expected to take it fully into account when exercising their clinical judgement. This guidance does not, however, override the individual

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responsibility of healthcare professionals to make appropriate decisions in the circumstances of the individual patient, in consultation with the patient and/or guardian or carer.

Implementation of this guidance is the responsibility of local commissioners and/or providers. Commissioners and providers are reminded that it is their responsibility to implement the guidance, in their local context, in light of their duties to avoid unlawful discrimination and to have regard to promoting equality of opportunity. Nothing in this guidance should be interpreted in a way which would be inconsistent with compliance with those duties.

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This guidance has been endorsed by Healthcare Improvement Scotland.

2018 CPT Code Issues

1) Total artificial heart
    a. Codes
        i. **33927** Implantation of a total replacement heart system (artificial heart) with recipient cardiectomy
        ii. **33928** Removal and replacement of total replacement heart system (artificial heart)
        iii. **33929** Removal of a total replacement heart system (artificial heart) for heart transplantation (List separately in addition to code for primary procedure)
    b. Background: Similar to a heart transplant, the total artificial heart (TAH) replaces both failing heart ventricles and the four heart valves, in patients with end-stage biventricular heart failure. The native heart is removed and replaced by the artificial heart. Currently, there are 2 FDA approved total artificial hearts on the market. The indications for total artificial heart are bridge to transplant and treatment of biventricular heart failure in patients not eligible for heart transplant.
    c. Evidence
        i. **Cook 2015**: review of artificial hearts
            1. The original safety and efficacy trial for the SynCardia TAH involved patients dying of biventricular heart failure receiving a TAH as a bridge to heart transplantation; patients were included who had class IV heart failure and hemodynamic insufficiency (hypotension, elevated CVP, on multiple vasoactive medications, IABP, or cardiopulmonary bypass). Patients were only chosen who were deemed to be poor LVAD candidates. 79% of patients were successfully bridged to transplant.
            2. To date, there have been no head-to-head randomized control trials comparing the efficacy of TAH with LVADs. One retrospective study published in 2001 compared the CardioWest TAH with Novacor and Thoratec LVADs; patients were effectively bridged to transplantation at a rate of 75%, 57%, 38%, respectively.
            3. The major complications of TAH implantation include strokes, infection, bleeding, thrombosis, renal failure, and chronic anemia.
    d. Other policies
        i. NICE is currently reviewing total artificial hearts
        ii. Aetna covers total artificial hearts as a bridge to cardiac transplant for transplant-eligible patients at imminent risk of death
    e. Expert input:
        i. Dr. Howard Song, Director of the OHSU heart transplant program: “The TAH is not performed at any Oregon Hospital. We have decided to not go in that direction because of its high morbidity. I do not think it is necessary for you to entertain coverage.”
    f. HERC staff summary: Total artificial hearts may be promising as a bridge to transplant in patients at imminent risk of death; however, this technology is not well studied compared to LVADs and other more conventional therapy. NICE is currently reviewing the technology; coverage of total artificial hearts should be reconsidered once the NICE review is published.

g. HERC staff recommendation:
    i. Add CPT codes for total artificial hearts to line 660 CONDITIONS FOR WHICH CERTAIN TREATMENTS HAVE NO CLINICALLY IMPORTANT BENEFIT OR HAVE HARMS THAT OUTWEIGH BENEFITS; UNPROVEN TREATMENTS with an entry for GN173 as shown below
        1. **33927** Implantation of a total replacement heart system (artificial heart) with recipient cardiectomy
        2. **33928** Removal and replacement of total replacement heart system (artificial heart)
        3. **33929** Removal of a total replacement heart system (artificial heart) for heart transplantation (List separately in addition to code for primary procedure)

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

The following treatments are prioritized on Line 660, CONDITIONS FOR WHICH CERTAIN TREATMENTS HAVE NO CLINICALLY IMPORTANT BENEFIT OR HAVE HARMS THAT OUTWEIGH BENEFITS; UNPROVEN TREATMENTS for the conditions listed here:

CPT/HCPCS code	**INTERVENTION**	**Rationale**	**Date of last Review**
33827-33929	Total artificial heart	Unproven treatment	November, 2017

Review Article on Left Ventricular Assist Devices

The total artificial heart

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Abstract: The total artificial heart (TAH) is a form of mechanical circulatory support in which the patient's native ventricles and valves are explanted and replaced by a pneumatically powered artificial heart. Currently, the TAH is approved for use in end-stage biventricular heart failure as a bridge to heart transplantation. However, with an increasing global burden of cardiovascular disease and congestive heart failure, the number of patients with end-stage heart failure awaiting heart transplantation now far exceeds the number of available hearts. As a result, the use of mechanical circulatory support, including the TAH and left ventricular assist device (LVAD), is growing exponentially. The LVAD is already widely used as destination therapy, and destination therapy for the TAH is under investigation. While most patients requiring mechanical circulatory support are effectively treated with LVADs, there is a subset of patients with concurrent right ventricular failure or major structural barriers to LVAD placement in whom TAH may be more appropriate. The history, indications, surgical implantation, post device management, outcomes, complications, and future direction of the TAH are discussed in this review.

Keywords: Total artificial heart (TAH)

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Mechanical circulatory support, including the total artificial heart (TAH) and its more widely used counterpart the left ventricular assist device (LVAD), has a vital and expanding role in the care of patients with end-stage heart failure. Worldwide, the prevalence of heart failure is increasing. The Global Burden of Disease Study 2013 demonstrated that the number of cardiovascular deaths has increased with the aging population and accounts for approximately one-third of all deaths (1). Although considered to be the gold standard for the treatment of end stage heart failure, heart transplantation is only able to meet a small subset of the clinical need. The number of heart transplants performed worldwide has remained fixed at 4,000 to 4,500 per year for the last decade (2). Advances in durable mechanical circulatory support have thus seen an exponential growth in use (3). In 2013, the number of durable device implants [2,744] exceeded the number of heart transplants [2,614] in North America. Roughly forty percent of patients receiving heart transplantation are bridged with mechanical circulatory support (2). The vast majority of patients with end stage heart failure can be adequately treated with isolated LVAD support. However, there is a small subset of patients with profound biventricular dysfunction or other severe structural abnormalities that is at high risk for poor outcomes following LVAD implantation. The TAH is an important therapeutic option for such patients (4). This review paper will focus on the history, indications, surgical implantation, post device management, outcomes, complications, and future direction of the TAH.

History of the TAH

The development of TAHs was preceded by decades of

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research, experimentation, and collaboration conducted at various institutions around the world.

Much of the developmental work leading to the modern TAH was performed by Willem Kolf and his trainees. In 1957, Dr. Kolff and Tetsuzo Akutsu performed their first successful animal TAH implant in a dog supporting circulation for 90 min (5).

In 1967, the first human heart transplant was performed in South Africa by Christiaan Barnard (6). However, early experience with poor post-transplant survival would soon dampen enthusiasm. A similar experience would be repeated with the artificial heart.

In 1969, Denton Cooley and Domingo Liotta performed the first human TAH implant using the Liotta Heart (an experimental device designed by Dr. Liotta, a former trainee of Dr. Kolff) (7). The patient was a 47-year-old man with ischemic cardiomyopathy who was unable to come off cardiopulmonary bypass following remodeling ventriculoplasty. The TAH successfully provided hemodynamic support, but the patient quickly developed hemolysis and progressive renal failure. The patient was bridged to transplantation after 64 h of support but unfortunately died 32 h later from pseudomonal sepsis. The ground breaking event was filled with controversy regarding improper consent and experimentation (8).

The following decade was notable for advances in immune suppression and improved outcomes for heart transplantation. Following the introduction of cyclosporine, Norman Shumway and the Stanford group reported an improvement in 1 year survival from 63% in 1980 to 83% in 1985 (9). It would take longer for similar success with the TAH.

In 1981, Dr. Cooley performed the second human TAH implant (the Akutsu III, developed by Dr. Akutsu) in a 36-year-old man with post cardiotomy shock following coronary bypass surgery (10). The postoperative course was notable for renal failure and severe hypoxia secondary to left pulmonary venous obstruction and required veno-venous extracorporeal membrane oxygenation. The patient was bridged to transplantation after 55 h of support, but unfortunately died 1 week later from overwhelming sepsis.

Due to the poor outcomes, it was felt that further human TAH implants should be restricted to patients who were not candidates for transplantation and had no other alternatives. In 1982, William DeVries performed the well-publicized permanent (now referred to as destination therapy) TAH implant of an artificial heart (the Jarvik 7, designed by Robert Jarvik, another Kolff trainee) into Dr. Barney Clark (11). Dr. Clark was a 61-year-old man with non-ischemic cardiomyopathy, refractory ventricular arrhythmias and multiorgan dysfunction that precluded consideration for transplant. He was hemodynamically supported for 112 days. His postoperative course was difficult and notable for respiratory failure requiring tracheostomy and resection of pulmonary blebs, fracture of the prosthetic mitral valve strut requiring replacement of the artificial left ventricle, fevers, stroke, seizures, delirium, renal failure, and bleeding related to anticoagulation. He ultimately succumbed to pseudomembranous colitis. Despite his willingness to volunteer for the benefit of science, the public spectacle of his story provoked discussions of Frankenstein and the ethics of extreme human experimentation.

As transplant outcomes continued to improve, further TAH implants as destination therapy was abandoned and attention refocused on bridging patients to transplantation. The majority of this focused on development of LVADs, however work on the TAH continued for the subset in whom LVADs were not adequate.

In 1985, Copeland successfully implanted the Jarvik 7 TAH as a bridge to transplantation (12). The recipient was a 25-year-old man with non-ischemic cardiomyopathy listed for transplantation but deteriorating with refractory ventricular tachycardia. With device support, he had marked hemodynamic improvement, but developed a stroke after 7 days of support. He had neurologic improvement and underwent transplantation 2 days later. Findings at the time of his surgery were notable for fibrinous deposits in the mechanical valve housings of the device. He subsequently had full neurologic recovery and did well with his transplant. He died 5.5 years later from lymphoma (13).

As success with the TAH as a bridge to transplant accumulated a trial of the CardioWest TAH (developed from the Jarvik 70 and now marketed as the Syncardia TAH) was started in 1993 and completed in 2002 (14). Eighty-one patients were implanted under the trial protocol with 79% survival to transplantation and an overall 1 year survival of 70%.

Development of the portable Freedom driver (both CE Mark and FDA approved) has enabled discharge of artificial heart patients while they awaited transplant (see *Figure 1*). With increased clinical success, there has been increased utilization and to date there has been more than 1,400 Syncardia/CardioWest TAH implants (15). In contrast, there have been more than 20,000 Heartmate II LVAD implants (16).

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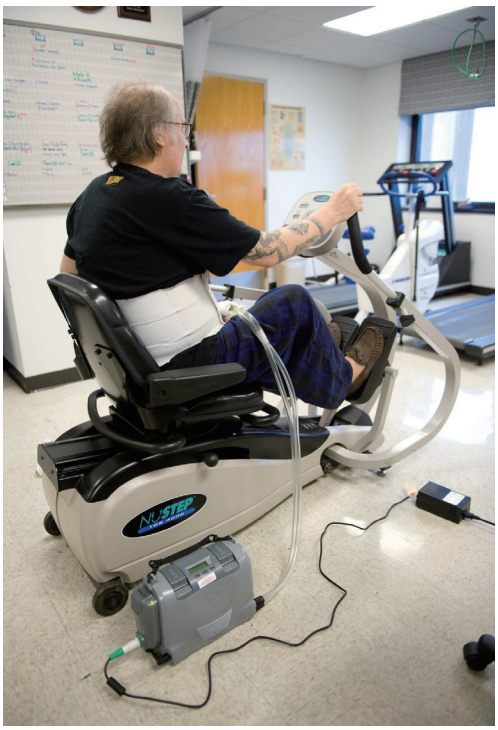

Figure 1 Syncardia Freedom Driver: compact external pneumatic pump which enables patients to be discharged from the hospital.

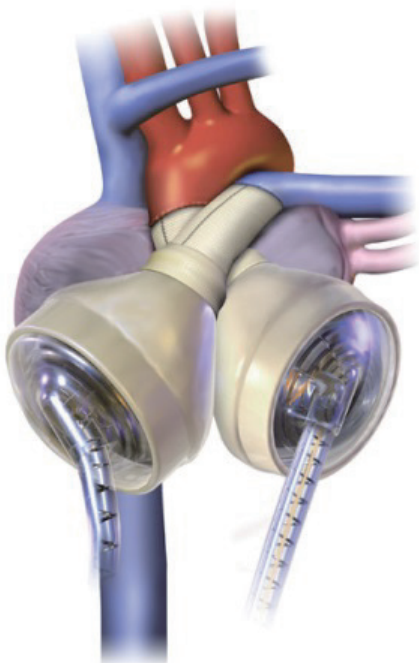

Figure 2 Syncardia CardioWest-t Total Artificial Heart: orthotopic artificial heart which replaces the ventricles and valves of the native heart. Used with permission from Syncardia Systems, Inc., Communications Department.

Patient selection

Compared with LVADs, the TAH is implanted in a much smaller subset of patients. The Syncardia TAH (SynCardia Systems, Inc., Tucson, AZ) is the only commercially available TAH in the United States approved by the Food and Drug Administration (FDA) (17) (see *Figure 2*).

The pivotal clinical trial published in 2004, included patients with irreversible biventricular cardiac failure (14). The device is indicated in patients who are eligible for transplantation with New York Heart Association Class IV symptoms with the appropriate chest size (BSA 1.7-2.5 m^2 or >10 cm between the 10^{th} thoracic vertebrae and the sternum) who have hemodynamic insufficiency requiring cardioactive medications (vasopressors and inotropes) or mechanical support.

Importantly, patients were only considered if they were deemed to not be LVAD candidates. These patients were unable to wean from cardiopulmonary bypass, had central venous pressures greater than 18 mmHg, RV ejection fractions less than 20%, ventricular tachycardia, aortic prostheses, or RV damage at time of sternotomy. Thus, based on the original clinical trials, TAH's primary role is in patients dying from biventricular failure who are not LVAD candidates as a salvage therapy to bridge to heart transplantation.

As experience with TAH advances, growing evidence supports its use in patients with biventricular heart failure. Patients with concurrent right ventricular failure in addition to left ventricular failure have poorer outcomes with LVADs than patients with isolated left ventricular failure (18,19). In these patients, biventricular support is indicated. While the orthotopic TAH provides definitive biventricular support, paracorporeal BiVADs provide an alternative MCS strategy for biventricular dysfunction. This includes temporary and durable RVADs in conjunction with an LVAD. Initial biventricular mechanical support for critically ill patients usually provides higher cardiac output at lower doses of inotropes which can help resuscitate end organ malperfusion. While no head-to-head prospective randomized controlled trials have compared these two types of mechanical circulatory support, one small retrospective study showed no difference in mortality for patients implanted with a TAH compared with BiVADs (20). Conversely, although the number of implants remains too small to draw conclusions, analysis of the INTERMACS registry has suggested improved short term survival of patients implanted with a TAH compared to BiVADs (3).

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Identifying patients with biventricular heart failure who would require biventricular support is challenging. A number of risk scores have been devised to identify these patients pre-operatively. For example, Drakos *et al.* statistically analyzed retrospective outcomes data for patients who underwent LVAD placement to determine pre-implant characteristics which were predictive of RV failure post-implant (21). Their scoring system includes six categories: destination therapy as device indication, use of intra-aortic balloon pump, elevated pulmonary vascular resistance, inotrope dependency, obesity, and use of ACE inhibitor or ARB. Higher scores equate to higher rates of RV dysfunction and higher mortality post-operatively. Another scoring system which does not use direct hemodynamic measurements includes vasopressor requirements, elevated aspartate aminotransferase, elevated bilirubin, and elevated creatinine to predict RV dysfunction (22).

The TAH is also indicated in end stage heart failure patients with anatomical or other clinical conditions that are not well treated with LVADS. This includes patients with small/non dilated ventricles (4) (hypertrophic, infiltrative, and other restrictive cardiomyopathies) and patients requiring significant concomitant repair [e.g., post-infarct ventricular septal defects, aortic root/ascending aortic aneurysms, congenital heart disease (23), massive LV thrombus].

Surgical implantation

The CardioWest TAH (SynCardia Systems, Inc., Tucson, AZ) is currently the only commercially available TAH in the United States approved by the FDA as a bridge to heart transplantation (13).

The TAH is nearly identical to the is device descended from its predecessor the Jarvik-7 (Symbion, Inc., Salt Lake City) which was first implanted in 1982. In 1988, Dr. DeVries published in JAMA a detailed description of the surgical technique for implanting the Jarvik-7 (24). The pneumatically powered device weighed 480 g and was 10 cm × 10 cm × 15 cm in volume. Since that time, substantial surgical experience has accumulated at numerous centers across the country. More than 1,400 SynCardia TAH's have been implanted into patients (15).

The CardioWest TAH consists of two polyurethane ventricles each with a stroke volume of 70 mL and occupies a volume of 400 cc within the chest (25). Given the size of the device, an anterior-posterior chest diameter of at least 10 cm is required by computed tomography (CT) from the anterior border of T10 vertebra to the posterior table of the sternum (24). Each chamber contains 2 mechanical single leaflet tilting disc valves [SynHall (formerly Medtronic Hall), 27 mm inflow, 25 mm outflow] to regulate direction of flow. The two ventricles are pneumatically actuated via drive lines that percutaneously attach to an external pump.

Prior to implantation, the Dacron aortic and pulmonary grafts are sealed using CoSeal Surgical Sealant (Baxter Healthcare Co., Freemont, CA) (25). The grafts and artificial ventricles are soaked in rifampin. A standard median sternotomy is performed. Two small incisions are made in the left upper abdomen and intramuscular tunnels are created through the left rectus muscle for the TAH drivelines. The drivelines are kept away from the midline to avoid injury and loss of pneumatic pressure during redo sternotomy. The patient is started on cardiopulmonary bypass. Mediastinal dissection and mobilization of the great vessels is minimized to maintain dissection planes for subsequent transplantation. The superior vena cava and inferior vena cava are cannulated via the right atrium. The aorta is cross clamped. The pulmonary artery and aorta are divided and separated at the level of the valvular commissures. The left and right ventricles are excised leaving a 1 cm rim of ventricular muscle around the mitral and tricuspid annulus. The mitral and tricuspid valve leaflets are excised. The coronary sinus is overseen. The atrial septum is inspected for a patent foramen ovale, which is closed if found. The TAH atrial quick connects are sutured to the respective valve annulus. Some institutions will reinforce this suture line with a strip of felt. The aortic and pulmonary artery graft quick connects are trimmed and sutured to the respective vessels. It is important that these are carefully cut to size to avoid both stretching and kinking. The pulmonary artery graft is longer than the aortic graft in order to reach over the aortic graft and connect to the artificial right ventricle (24).

At re-entry for transplantation, we have noted an intense inflammatory thickening of the pericardium that increases the difficulty of the mediastinal dissection (25). Polytetrafluoroethylene membrane (PTFE) (Preclude Pericardial Membrane, formerly called the Gore-Tex Surgical Membrane; W.L. Gore & Associates, Flagstaff, AZ) is used to fully reconstruct the pericardium. This maintains avascular tissue planes and dramatically simplifies re-entry for transplantation. Other centers have found wrapping the aortic anastomosis with a sterile tourniquet band to be helpful.

In contrast to the normal oblong cardiac silhouette, the TAH has an overall spherical configuration (25).

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While PTFE lining of the pericardium facilitates re-entry, contracture of the pericardium about the TAH can limit the space available for transplantation and require maneuvers to open the pericardium/pleura. A saline implant (Mentor smooth round, Mentor Worldwide LLC, Santa Barbara) placed at the former cardiac apex and inflated to 150-200 mL will adequately maintain this space and make such maneuvers unnecessary.

The drivelines are passed through the intramuscular tunnels in the left rectus with the Penrose drains (25). The TAH ventricles are attached to their respective atrial and arterial graft quick connects. An aortic root vent is placed and low pressure/low rate pumping (LV drive pressure 40 mmHg, rate 40 bpm, 40% systole, RV drive pressure 0 mmHg) of the left ventricle is started. Routine de-airing maneuvers are done and the aortic cross clamp is removed. De-airing is confirmed by transesophageal echocardiography (TEE). The patient is often readily weaned off cardiopulmonary bypass as TAH support is increased. Usual post bypass TAH parameters are left drive pressure 180-200 mmHg, right drive pressure 30-60 mmHg, HR 100-120 bpm, and 50% systole. Vacuum is usually not initiated until the chest is closed or sealed.

The decision on whether to close the chest immediately is made based on the bleeding risk (25). If coagulopathy is present, there is a low threshold for packing the mediastinum and delayed sternal closure. Compression of the TAH during chest closure can translate to compression of the left sided pulmonary veins, the inferior vena cava and the left bronchus. TEE is used at the end of the case to evaluate for adequate right and left atrial venous return. Should compression be identified it can generally be relieved by tethering the TAH anteriorly to the left costal margin.

Anticoagulation

Long term anticoagulation is routinely used in TAH patients to avoid thromboembolic complications. The initial safety and efficacy trial for the SynCardia TAH as bridge to transplantation reported strokes in 12% of patients and peripheral thrombotic events in 14% patients followed from enrollment to 30 days post-heart transplantation (11).

While the approach to anticoagulation in patients with TAH varies by institution, a multi-targeted antithrombotic approach including anticoagulants, antiplatelet, and rheologic agents are used.

This strategy was first introduced by Szefener at La Pitié Hospital (26). During 1,930 days of TAH support with either Jarvik-7 or CardioWest TAH-t, Szefener did not observe any strokes in patients who were treated with a combination of aspirin, dipyridamole, heparin, and pentoxifylline. Copeland and his colleagues published similar findings on thrombosis and bleeding outcomes on 99 patients with TAH who were treated with aspirin, unfractionated heparin or warfarin, dipyridamole and pentoxifylline (27). Strokes were observed at a rate of 2%. GI bleeding was observed in 4% of patients, intracranial bleeding at 2%, and late thoracic bleeding in 2%.

Anticoagulation begins post-operatively once homeostasis is achieved (28). Heparin is commonly used. As thrombocytopenia is common in critically ill patients requiring a TAH (particularly in patients with prior temporary MCS or CRRT), there is frequently a concern for heparin induced thrombocytopenia. We routinely use bivalirudin, a direct thrombin inhibitor, as our initial anticoagulation strategy. An aPTT goal of 50-70 is targeted. Once the patient is stable and tolerating oral intake well, they are bridged to warfarin anticoagulation with a target INR of 2-3. The antiplatelet medications aspirin 81 mg daily and dipyridamole 50 mg every 8 h are both started to maintain suppressed platelet function. Platelet function tests (e.g., light transmittance aggregometry) and the thromboelastogram (TEG) can be used to help titrate appropriate anticoagulation and platelet suppression.

The presence of four single leaflet mechanical valves in the TAH creates a constant amount of hemolysis (29). Similar to LVADs, the LDH, plasma free hemoglobin, and haptoglobin are monitored to assess the degree of hemolysis. Pentoxifylline is a rheologic agent that decreases blood viscosity, platelet adhesion, and increases red blood cell deformity and appears to improve the underlying hemolysis (28). Typical doses are 400 mg every 8 h.

The introduction of novel oral anticoagulants holds promise for improving the management of thromboembolic and bleeding complications in TAH patients.

Outcomes

The original safety and efficacy trial for the SynCardia TAH was responsible for first establishing the TAH as a relevant and effective intervention for bridging patients dying of biventricular heart failure to heart transplantation (14). As discussed earlier, patients were included who had class IV heart failure and hemodynamic insufficiency (hypotension, elevated CVP, on multiple vasoactive medications, IABP, or cardiopulmonary bypass). Patients were only chosen who were deemed to be poor LVAD candidates. Patients were

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effectively bridged to transplantation in an impressive 79% of patients.

To date, there have been no head-to-head randomized control trials comparing the efficacy of TAH with LVADs. One retrospective study published in 2001 compared the CardioWest TAH with Novacor and Thoratec LVADs; patients were effectively bridged to transplantation at a rate of 75%, 57%, 38%, respectively (19). Strokes were reported at a rate of 0.03 events per patient-month in CardioWest, 0.28 events per patient-month in Novacor LVAD, and 0.08 events per patient-month in Thoratec LVAD. In this study, it was observed that the patients who had poor outcomes in the LVAD groups were more likely to have concurrent right ventricular failure. The authors concluded that CardioWest be considered first-line in unstable patients who met device size parameters.

Another larger retrospective study of 383 patients published in the Journal of Heart and Lung Transplantation in 2012 selected patients from a multicenter French database and attempted to determine whether type of device, bi-ventricular assist devices or TAH, impacted rates of successful bridging to transplantation (20). This study found no statistically significant difference in rates of successful bridging to transplantation between patients treated with extracorporeal bi-ventricular assist devices, paracorporeal bi-ventricular assist devices, and CardioWest TAH . There was, however, a striking difference in the rates of stroke. Compared with the strokes reported in 61% and 57% in implantable and paracorporeal biventricular devices, respectively, strokes were reported in 16% of patients bridged with CardioWest TAH with a P value <0.001.

Our single center outcomes data was published in 2014. From April 2006 through July 2012 at Virginia Commonwealth University Medical Center, 66 patients were implanted with a TAH (25). Patients were supported for a median duration of 87.5 days. At the time of publication, 76% were successfully bridged to transplantation, 15% were discharged home on a portable Freedom Driver as part of a clinical trial, 11% remained on the device awaiting transplantation, and 14% died on the device.

Complications

As experience has grown with the TAHs, rates for the common complications have been established. The major complications of TAH implantation include strokes, infection, bleeding, thrombosis (discussed previously), renal failure, and chronic anemia. One center published outcomes data on 101 patients bridged with the TAH supported for an average of 87 days of support (30). Strokes were reported in 7.9% of patients, 63.4% developed an infection requiring treatment, and bleeding occurred in 42.6% of patients.

The lungs and the urinary tract system were the most common sites of infection. However, mediastinitis occurred in 3% of patients, two of whom died. There was one case of methicillin resistant staphylococcus aureus (MRSA) endocarditis complicated by multiple strokes and death.

Bleeding complications varied in severity. High rates of mediastinal bleeding requiring mediastinal exploration were observed in 24.7% of patients, 44% of whom died within one month. Approximately 4% developed gastrointestinal bleeding. Fifty-eight percent had no bleeding complications.

Renal dysfunction

Post-surgical oliguric renal failure is a frequent complication following TAH implantation. Severe renal dysfunction resulting in a rise in creatinine above 5 mg/dL or requiring dialysis is seen in up to 12% of patients post-operatively (31). One study found 15% of patients required renal replacement therapy who had no previous renal failure (32). Following the removal of the ventricles, B-type natriuretic peptide (BNP) levels drop precipitously (33,34). It has been postulated that interruption of this hormonal compensatory mechanism may precipitate renal failure (33,34). Patients who do develop oliguric renal failure have a prompt and robust increase in urine output following nesiritide infusion without worsening in hemodynamics (33,34). One small study looked at routinely administering low dose nesiritide (0.05 mcg/kg/min) to all patients undergoing TAH implantation at the time of ventriculectomy and demonstrated maintenance of urine output and GFR (34). While nesiritide administration appears to be beneficial in maintaining short term renal function and management of volume status, whether this results in a durable response compared with the natural history of renal recovery without the addition of nesiritide remains to be proven.

Longterm complications

While currently being investigated for use as destination therapy, the TAH is currently only approved for bridge to transplantation. As a result, data is lacking regarding long-term complications. As of 2011, 47 patients had been supported with a SynCardia TAH for greater than one year worldwide (35). The mean support time was 554 days.

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Device failure occurred in 10% of patients. Systemic infections were observed in 53% of patients, driveline infections in 27% of patients, thromboembolic events in 19% of patients, and hemorrhagic events in 14% of patients.

Chronic anemia

Severe anemia occurs following TAH implantation that is multifactorial in etiology. Levinson *et al.* demonstrated that hemolysis, similar to that seen following LVAD placement, occurs in patients following TAH implantation (36). The degree of anemia seen following TAH implantation is generally more severe than following LVAD placement. Mankad *et al.* published a study comparing anemia in 36 patients who underwent TAH implantation and 14 patients who underwent LVAD placement (29). Baseline hematocrits were similar between the two groups, and both groups experienced significant drops in hematocrit following device implantation. The anemia following TAH implantation, however, was statistically lower at 2, 4, 6 and 8 weeks following device implantation ($P<0.001$ for each). The researchers proposed multiple contributory mechanisms to the anemia. Evidence of severe hemolysis, like that which occurs in LVAD patients, was similarly found in TAH patients. Ninety-six percent of TAH patients had undetectable haptoglobin levels and elevated LDH (mean 1,128), and 40% of samples had detectable plasma free hemoglobin. They attributed this hemolysis to shear stress of multiple mechanical parts including the four mechanical valves and pneumatically powered diaphragms. Additionally, they proposed inflammation induced anemia to be playing a role as evidenced by elevated C-reactive protein which may be related to device materials. There was also evidence of inadequate hematopoiesis as demonstrated by a reduced reticulocyte production index. They hypothesized that this may also be mediated by inflammation. Interestingly, post-heart transplantation, the difference in hematocrit between LVAD and TAH disappeared, and by three months post heart transplantation hematocrit returned to baseline in both groups. Despite the severe anemia that occur post-TAH implantation, patients required a median of only 2.5 units of blood outside the post-operative period.

Future of the TAH

The TAH has an established role in the care of patients with biventricular heart failure as a bridge to transplantation. As discussed previously, the number of patients transplanted each year is outpaced by the number of patients waiting for heart transplant. On the frontier for TAH therapy is the expanded use to patients who are not candidates for heart transplantation. This type of application is referred to as destination therapy. On December 18, 2014, the FDA approved clinical study to evaluate safety and efficacy for the CardioWest TAH as destination therapy in 19 patients (37). Already in clinical use are portable "Freedom Drivers" which enable patients to be mobile and discharged from the hospital following device implantation (38). If approved for destination therapy, this would revolutionize the care of patients with end stage heart disease who are not transplant candidates.

Traditional chest wall size constraints of the TAH as discussed previously are being challenged by new technology. SynCardia has a designed a 50 cc version of its 70 cc predecessor which fits smaller patients with body surface areas down to 1.2 m^2 (39). The FDA approved the smaller SynCardia TAH for use as a Humanitarium Use Device for adult patients at risk of imminent death due to cardiogenic shock and pediatric patients with congenital heart disease.

In addition to the well-established role in adult patients, there is an increased interest in use of the TAH in the pediatric patient population (23). This role may expand as smaller devices become available.

Other TAH devices

While this review has focused on the SynCardia TAH as it is the only commercially available TAH that is FDA approved, there are a few other notable devices that are currently under investigation. The AbioCor TAH is the first entirely implantable TAH with an internal battery that is charged transcutaneously (40). The results of the initial human trials were published in 2004. In total, seven patients underwent implantation, two of whom survived to hospital discharge. Two patients died early (one from intraoperative bleeding and another believed to be a reaction to aprotinin), and the other three patients died of a variety of complications including two from stroke which were felt to be related to thrombus formation on atrial struts. The overall 30-day survival was 71% and 43% at 60 days. This device is not currently in clinical use.

The BiVACOR TAH/BiVAD is a continuous flow magnetically powered designed to have the ability to either assist a failing heart or entirely assume the work of the heart. This is under development at the Texas Heart Institute (41). Cleveland Clinic has also developed a

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continuous flow TAH which has undergone animal testing in calves and human fit modeling (42,43).

Conclusions

The TAH is an important and effective intervention for patients who are dying of biventricular heart failure. Its role in destination therapy is on the horizon. As technology advances with the availability of the freedom driver, patients who have received a TAH are afforded more mobility and better quality of life.

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None.

Footnote

Conflicts of Interest: Shah: Research Grants from Thoratec Corp; Tang: Principal Investigator for Syncardia Systems, HeartWare Corp and Sunshine Heart; Kasirajan: Principal Investigator for Thoratec Corp and Syncardia Systems.

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2018 CPT Code Issues

1) Ablation of varicose veins with foam sclerosant or cyanoacrylate
    a. Codes:
        i. CPT **36465** Injection of non-compounded foam sclerosant with ultrasound compression maneuvers to guide dispersion of the injectate, inclusive of all imaging guidance and monitoring; single incompetent extremity truncal vein (eg, great saphenous vein, accessory saphenous vein)
        ii. CPT **36466** …multiple incompetent truncal veins
        iii. CPT **36482** Endovenous ablation therapy of incompetent vein, extremity, by transcatheter delivery of a chemical adhesive (eg, cyanoacrylate) remote from the access site, inclusive of all imaging guidance and monitoring, percutaneous; first vein treated
        iv. CPT **36483** …subsequent vein(s) treated
    b. Similar codes
        i. 36470 (Injection of sclerosing solution; single vein) is on lines 379, 514, 517, 545, 637
        ii. 36475 (Endovenous ablation therapy of incompetent vein, extremity, inclusive of all imaging guidance and monitoring, percutaneous, radiofrequency; first vein treated) is on lines 379,514,517,637
        iii. 36478 (Endovenous ablation therapy of incompetent vein, extremity, inclusive of all imaging guidance and monitoring, percutaneous, laser; first vein treated) is on lines 379,514,517,637
    c. Background: Varicose veins may require no treatment, or may be treated conservatively with compression stockings and leg elevation. If pain or skin ulceration continue after a trial of conservative therapy, the treatment of varicose veins in the lower legs includes injection/compression sclerotherapy and surgical stripping or ligation or a combination of these approaches depending upon the severity of the condition. Newer technology includes foam sclerotherapy, in use for >10 yrs, as use of cyanoacrylate for vein ablation, which has just begun to be marketed.
    d. Evidence

        Foam sclerotherapy

        i. **Washington HTA 2017,** review of selected interventions for varicose veins compared with surgery (vein ligation with or without stripping). https://www.hca.wa.gov/about-hca/health-technology-assessment/varicose-veins
            1. The interventions of interest are endovascular laser ablation (EVLA), endovascular radiofrequency ablation (RFA), sclerotherapy (i.e., liquid or foam chemical ablation), ambulatory phlebectomy (i.e., stab phlebectomy or microphlebectomy).
            2. Overall, moderate-quality evidence for Key Question #1 suggests that EVLA is similar to or better than conventional surgery in the treatment of varicose veins for many clinical and patient-centered outcomes.
            3. A low-quality body of evidence suggests that the effectiveness of RFA is similar to or better than surgery for many outcomes, most notably, RFA

may be associated with less postoperative pain than conventional surgery.

4. Similarly, a low-quality body of evidence suggests similarities in many clinical and patient-centered outcomes between sclerotherapy and conventional surgery; however, it is difficult to draw conclusions on comparative effectiveness due to a lack of sufficient or consistent data on several outcomes.
5. The overall quality of evidence for Key Question #2 is moderate and suggests that EVLA, RFA, and sclerotherapy are relatively safe compared with surgery—few significant differences were reported. Rates of serious complications are low and similar when compared with surgery. However, results from 2 large observational studies suggest that the risk of DVT after procedures such as EVLA and RFA may need further investigation. More common complications included bruising, phlebitis, hematoma, and infection.
6. The 2 U.S.-based cost analyses identified through the recent literature search found that the minimally invasive varicose vein treatments were associated with lower costs than surgery.

ii. **Paravatsu 2016**, Cochrane review of methods for treatment of varicose veins

1. Compared the effectiveness of endovenous laser ablation (EVLA), radiofrequency ablation (RFA) and ultrasound-guided foam sclerotherapy (UGFS) versus conventional surgery for repair of short (or small) saphenous vein (SSV) varices
    a. N=1 study for UGFS vs surgery
        i. N=42 (21 in each group)
    b. Quality of evidence low for UGFS vs surgery (only one trial offered UGFS and several participants were missing from the analysis) and a limitation in design (the study was inadequately powered for SSV participants alone).
    c. For the UGFS versus surgery comparison, there were insufficient data to detect clear differences between the two treatment groups for the two outcomes recanalisation or persistence of reflux at six weeks (OR 0.34, 95% CI 0.06 to 2.10; 33 participants, 1 study, low quality evidence), and recurrence of reflux at one year (OR 1.19, 95% CI 0.29 to 4.92; 31 participants, 1 study, low-quality evidence).
    d. **Authors' conclusions:** For the UGFS versus conventional surgery comparison, the quality of evidence is assessed to be low; consequently, the effectiveness of UGFS compared with conventional surgery in the treatment of SSV varices is uncertain.

iii. **Boersma 2016,** review and meta-analysis on treatment of small saphenous vein varicosities (SSV)

1. Compared surgery, endovenous laser ablation (EVLA), radiofrequency ablation (RFA), ultrasound-guided foam sclerotherapy (UGFS), steam ablation, and mechanochemical endovenous ablation (MOCA).
    a. N=6 studies for UGFS
2. The pooled anatomical success rate was 58.0% (95% CI 40.9% to 75.0%) for surgery in 798 SSVs, and 63.6% (95% CI 47.1% to 80.1%) for UGFS in 494 SSVs.
3. Neurologic complications were most frequently reported after surgery (mean 19.6%) and thermal ablation (EVLA: mean 4.8%; RFA: mean 9.7%). Deep venous thrombosis was a rare complication (0% to 1.2%).
4. **Conclusion:** Endovenous thermal ablation (EVLA/RFA) should be preferred to surgery and foam sclerotherapy in the treatment of SSV incompetence.

iv. **Marsden 2015,** economic analysis of cost-effectiveness of various interventions for treatment of varicose veins
1. Compared the cost-effectiveness of surgery, endothermal ablation (ETA), ultrasound-guided foam sclerotherapy (UGFS), and compression stockings (CS).
2. Results: All interventional treatments were found to be cost-effective compared with CS at a cost-effectiveness threshold of £20,000 per QALY gained. ETA was found to be the most cost-effective strategy overall, with an incremental cost-effectiveness ratio of £3,161 per QALY gained compared with UGFS. Surgery and CS were dominated by ETA.
3. Conclusions: Interventional treatment for VV is cost-effective in the UK NHS. Specifically, based on current data, ETA is the most cost-effective treatment in people for whom it is suitable

<u>Cyanoacrylate</u>

i. **Morrison 2015**, RCT of cyanoacrylate embolization (CAE) and radiofrequency ablation (RFA) for treatment of incompetent saphenous veins (GSV)
a. N=222 subjects (N=108 CAE, 114 RFA)
b. Results: By use of the predictive method for imputing missing data, 3-month closure rates were 99% for CAE and 96% for RFA. All primary end point analyses, which used various methods to account for the missing data rate (14%), showed evidence to support the study's noninferiority hypothesis (all P < .01); some of these analyses supported a trend toward superiority (P [.07 in the predictive model). Pain experienced during the procedure was mild and similar between treatment groups (2.2 and 2.4 for CAE and RFA, respectively, on a 10-point scale; P [.11). At day 3, less ecchymosis in the treated region was present after CAE compared with RFA (P < .01). Other adverse events occurred at a similar rate between groups and were generally mild and well tolerated.
c. Conclusions: CAE was proven to be noninferior to RFA for the treatment of incompetent GSVs at month 3 after the procedure. Both

treatment methods showed good safety profiles. CAE does not require tumescent anesthesia and is associated with less postprocedure ecchymosis.

ii. Several case series identified

a. Gibson and Ferris 2017, N=50, full text not available

b. Tenkin 2016

i. N=62

ii. Conclusions: Endovenous ablation of incompetent great saphenous vein with cyanoacrylate based glue is feasible. Operation time is short, and tumescent anesthesia is unnecessary as postprocedure compression stockings. Lack of significant side effects and a yearly success rate of 100% are benefits of the system.

e. Expert groups

i. The American College of Phlebology Guidelines Committee 2017

1. Consensus opinion that patients with symptomatic incompetence of the accessory great saphenous veins (anterior and posterior accessory saphenous veins) be treated with endovenous thermal ablation (laser or radiofrequency) or ultrasound-guided foam sclerotherapy to eliminate symptomatology (Recommendation Grade 1C).
2. Full text not available

f. Other policies

i. **NICE 2013**: interventional therapy for varicose veins that is recommended includes endothermal ablation. If endothermal ablation is unsuitable, offer ultrasound-guided foam sclerotherapy.
https://www.nice.org.uk/guidance/cg168

1. No mention is made of cyanoacrylate as an option for ablation

ii. Most major insurers cover foam sclerotherapy; most do not cover cyanoacrylate ablation

g. HERC staff summary:

i. Foam sclerotherapy is recommended by expert groups such as the American College of Phlebology and NICE, and has been found to be cost effective by a NICE economic evaluation. The WHTA report found low-quality evidence suggesting similarities in many clinical and patient-centered outcomes between sclerotherapy and conventional surgery. However, foam sclerotherapy appears to be inferior to endothermal ablation therapies (radiofrequency ablation and laser ablation) for treatment of varicose veins in meta-analyses. Based on the available evidence, it appears that foam sclerotherapy is likely as effective as other non-invasive therapies for varicose veins, or possibly slightly less effective than RFA and laser ablation.

1. Note: surgery, radiofrequency ablation, laser ablation and mechanochemical ablation are all currently included for treatment of varicose veins on the Prioritized List

ii. Vein ablation with cyanoacrylate appears to be experimental, based on the small number of studies identified, lack of inclusion in major reviews, and lack of recommendations for use by major expert groups.

h. HERC staff recommendations:
   i. Add CPT **36465** Injection of non-compounded foam sclerosant with ultrasound compression maneuvers to guide dispersion of the injectate, inclusive of all imaging guidance and monitoring; single incompetent extremity truncal vein (eg, great saphenous vein, accessory saphenous vein) and CPT **36466** (multiple incompetent truncal veins) to lines
      1. 379 CHRONIC ULCER OF SKIN
      2. 514 PHLEBITIS AND THROMBOPHLEBITIS, SUPERFICIAL
      3. 517 POSTTHROMBOTIC SYNDROME
      4. 637 VARICOSE VEINS OF LOWER EXTREMITIES WITHOUT ULCER OR OTHER MAJOR COMPLICATION
   ii. Add CPT **36482** (Endovenous ablation therapy of incompetent vein, extremity, by transcatheter delivery of a chemical adhesive (eg, cyanoacrylate) remote from the access site, inclusive of all imaging guidance and monitoring, percutaneous; first vein treated) and CPT **36483** (subsequent vein(s) treated) to line 660 CONDITIONS FOR WHICH CERTAIN TREATMENTS HAVE NO CLINICALLY IMPORTANT BENEFIT OR HAVE HARMS THAT OUTWEIGH BENEFITS; UNPROVEN TREATMENTS with an entry for GN173 as shown below

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

The following treatments are prioritized on Line 660, CONDITIONS FOR WHICH CERTAIN TREATMENTS HAVE NO CLINICALLY IMPORTANT BENEFIT OR HAVE HARMS THAT OUTWEIGH BENEFITS; UNPROVEN TREATMENTS for the conditions listed here:

CPT/HCPCS code	INTERVENTION	Rationale	Date of last Review
36482-36483	Endovenous ablation therapy of incompetent vein, extremity, by transcatheter delivery of a chemical adhesive (eg, cyanoacrylate)	Unproven treatment	November, 2017

[Intervention Review]

Endovenous ablation therapy (laser or radiofrequency) or foam sclerotherapy versus conventional surgical repair for short saphenous varicose veins

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ABSTRACT

Background

Short (or small) saphenous vein (SSV) varices occur as a result of an incompetent sapheno-popliteal junction, where the SSV joins the popliteal vein, resulting in reflux in the SSV; they account for about 15% of varicose veins. Untreated varicose veins may sometimes lead to ulceration of the leg, which is difficult to manage. Traditionally, treatment was restricted to surgery or conservative management. Since the 1990s, however, a number of minimally invasive techniques have been developed; these do not normally require a general anaesthetic, are day-case procedures with a quicker return to normal activities and avoid the risk of wound infection which may occur following surgery. Nerve injury remains a risk with thermal ablation, but in cases where it does occur, the injury tends to be transient.

Objectives

To compare the effectiveness of endovenous laser ablation (EVLA), radiofrequency ablation (RFA) and ultrasound-guided foam sclerotherapy (UGFS) versus conventional surgery in the treatment of SSV varices.

Search methods

The Cochrane Vascular Information Specialist searched the Specialised Register (last searched 17 March 2016) and the Cochrane Central Register of Controlled Trials (CENTRAL; 2016, Issue 2). We searched clinical trials databases for details of ongoing or unpublished studies.

Selection criteria

We considered all randomised controlled trials (RCTs) comparing EVLA, endovenous RFA or UGFS with conventional surgery in the treatment of SSV varices for inclusion.

Data collection and analysis

We independently reviewed, assessed and selected trials that met the inclusion criteria; any disagreements were resolved by discussion. We extracted data and used the Cochrane's tool for assessing risk of bias. When the data permitted, we performed either fixed-effect meta-analyses with odds ratios (ORs) and 95% confidence intervals (CIs) or random-effects meta-analyses where there was moderate to significant heterogeneity.

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Main results

We identified three RCTs, all of which compared EVLA with surgery; one also compared UGFS with surgery. There were no trials comparing RFA with surgery. The EVLA versus surgery comparison included 311 participants: 185 received EVLA and 126 received surgery. In the UGFS comparison, each treatment group contained 21 people. For several outcomes in the EVLA comparison, only a single study provided relevant data; as a result, the current review is limited in its ability to demonstrate meaningful results for some planned outcomes. The quality of evidence according to GRADE was moderate to low for the outcome measures in the EVLA versus surgery comparison, but low for the UGFS versus surgery comparison. Reasons for downgrading in the EVLA versus surgery comparison were risk of bias (for some outcomes, the outcome assessors were not blinded; and in one study the EVLA-surgery allocation of 2:1 did not appear to be prespecified); imprecision (data were only available from a single small study and the CIs were relatively wide); indirectness (one trial reported results at six months rather than one year and was inadequately powered for SSV varices-only analysis). Reasons for downgrading in the UGFS versus surgery comparison were imprecision (only one trial offered UGFS and several participants were missing from the analysis) and a limitation in design (the study was inadequately powered for SSV participants alone).

For the EVLA versus surgery comparison, recanalisation or persistence of reflux at six weeks occurred less frequently in the EVLA group than in the surgery group (OR 0.07, 95% CI 0.02 to 0.22; I^2 = 51%; 289 participants, 3 studies, moderate-quality evidence). Recurrence of reflux at one year was also less frequent in the EVLA group than in the surgery group (OR 0.24, 95% CI 0.07 to 0.77; I^2 = 0%; 119 participants, 2 studies, low-quality evidence). For the outcome clinical evidence of recurrence (i.e. presence of new visible varicose veins) at one year, there was no difference between the two treatment groups (OR 0.54, 95% CI 0.17 to 1.75; 99 participants, 1 study, low-quality evidence). Four participants each in the EVLA and surgery groups required reintervention due to technical failure (99 participants, 1 study, moderate-quality evidence). There was no difference between the two treatment groups for disease-specific quality of life (QoL) (Aberdeen Varicose Veins Questionnaire) either at six weeks (mean difference (MD) 0.15, 95% CI -1.65 to 1.95; I^2 = 0%; 265 participants, 2 studies, moderate-quality evidence), or at one year (MD -1.08, 95% CI -3.39 to 1.23; 99 participants, 1 study, low-quality evidence). Main complications reported at six weeks were sural nerve injury, wound infection and deep venous thrombosis (DVT) (one DVT case in each treatment group; EVLA: 1/161, 0.6%; surgery 1/104, 1%; 265 participants, 2 studies, moderate-quality evidence).

For the UGFS versus surgery comparison, there were insufficient data to detect clear differences between the two treatment groups for the two outcomes recanalisation or persistence of reflux at six weeks (OR 0.34, 95% CI 0.06 to 2.10; 33 participants, 1 study, low-quality evidence), and recurrence of reflux at one year (OR 1.19, 95% CI 0.29 to 4.92; 31 participants, 1 study, low-quality evidence). No other outcomes could be reported for this comparison because the study data were not stratified according to saphenous vein.

Authors' conclusions

Moderate- to low-quality evidence exists to suggest that recanalisation or persistence of reflux at six weeks and recurrence of reflux at one year are less frequent when EVLA is performed, compared with conventional surgery. For the UGFS versus conventional surgery comparison, the quality of evidence is assessed to be low; consequently, the effectiveness of UGFS compared with conventional surgery in the treatment of SSV varices is uncertain. Further RCTs for all comparisons are required with longer follow-up (at least five years). In addition, measurement of outcomes such as recurrence of reflux, time taken to return to work, duration of procedure, pain, etc., and choice of time points during follow-up should be standardised such that future trials evaluating newer technologies can be compared efficiently.

PLAIN LANGUAGE SUMMARY

Endovenous ablation therapy (laser or radiofrequency) or foam sclerotherapy versus open surgery for the treatment of short saphenous varicose veins

Background

Varicose veins (varices) are enlarged veins occurring below the skin's surface, usually in the legs. One-third of the UK population may be affected. They can be painful and itchy, the surrounding skin may change colour, and occasionally they may bleed; in some people, untreated varicose veins may lead to ulceration. Varicose veins occur due to leaky valves within the veins. Traditionally, they were treated with surgery to remove the veins. Newer techniques require neither vein removal, nor a general anaesthetic; they may involve less pain after the procedure and have a lower risk of complications, resulting in quicker recovery and return to normal activities. Endovenous laser ablation (EVLA) and radiofrequency ablation (RFA) are methods that seal the main leaking vein. They are performed using a

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Treatment Modalities for Small Saphenous Vein Insufficiency: Systematic Review and Meta-analysis

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Abstract

Purpose: To investigate and compare the anatomical success rates and complications of the treatment modalities for small saphenous vein (SSV) incompetence. **Methods:** A systematic literature search was performed in PubMed, EMBASE, and the Cochrane Library on the following therapies for incompetence of SSVs: surgery, endovenous laser ablation (EVLA), radiofrequency ablation (RFA), ultrasound-guided foam sclerotherapy (UGFS), steam ablation, and mechanochemical endovenous ablation (MOCA). The search found 49 articles (5 randomized controlled trials, 44 cohort studies) reporting on the different treatment modalities: surgery (n=9), EVLA (n=28), RFA (n=9), UGFS (n=6), and MOCA (n=1). A random-effects model was used to estimate the primary outcome of anatomical success, which was defined as closure of the treated vein on follow-up duplex ultrasound imaging. The estimate is reported with the 95% confidence interval (CI). Secondary outcomes were technical success and major complications [paresthesia and deep vein thrombosis (DVT)], given as the weighted means. **Results:** The pooled anatomical success rate was 58.0% (95% CI 40.9% to 75.0%) for surgery in 798 SSVs, 98.5% (95% CI 97.7% to 99.2%) for EVLA in 2950 SSVs, 97.1% (95% CI 94.3% to 99.9%) for RFA in 386 SSVs, and 63.6% (95% CI 47.1% to 80.1%) for UGFS in 494 SSVs. One study reported results of MOCA, with an anatomical success rate of 94%. Neurologic complications were most frequently reported after surgery (mean 19.6%) and thermal ablation (EVLA: mean 4.8%; RFA: mean 9.7%). Deep venous thrombosis was a rare complication (0% to 1.2%). **Conclusion:** Endovenous thermal ablation (EVLA/RFA) should be preferred to surgery and foam sclerotherapy in the treatment of SSV incompetence. Although data on nonthermal techniques in SSV are still sparse, the potential benefits, especially the reduced risk of nerve injury, might be of considerable clinical importance.

Keywords

endovenous laser ablation, foam sclerotherapy, incompetent vein, mechanochemical ablation, meta-analysis, pharmacomechanical ablation, radiofrequency ablation, reflux, small saphenous vein, varicose vein, venous insufficiency

Introduction

Chronic venous insufficiency (CVI) of the lower limbs is a common disorder: the Bonn Vein Study demonstrated a prevalence of superficial vein reflux of 21% in the adult population, which increased linearly with age.[1] Some clinical signs of CVI are present in ~10% of all adults.[2] CVI has been associated with decreased general and disease-specific quality of life.[3,4] Although superficial venous disease has frequently been associated with great saphenous vein (GSV) incompetence, small saphenous vein (SSV) reflux is responsible for ~15% of all varicose vein disease.[5] In addition, saphenopopliteal and SSV incompetence may result in complaints of equal severity compared with GSV incompetence.[5]

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For more than a century, surgical high ligation with or without stripping or compression therapy was the only treatment option of truncal venous incompetence.[6] In contrast with the surgical treatment of GSV incompetence, there was no uniformity in the surgical treatment of SSVs among vascular surgeons. SSV surgery is considered more challenging and is associated with higher recurrence and complication rates.[7] The close anatomical location of the sural nerve to the SSV poses increased risks of nerve injury. Owing to anatomical variations, the proximal SSV/saphenopopliteal junction (SPJ) is not adequately identified in 22% of patients, even after preoperative ultrasound localization.[8] There is a higher rate of recurrence in limited surgical exploration, whereas the risk of complications increases with the extent of exploration.[9]

The treatment of varicose veins has been revolutionized in recent decades by the introduction of minimally invasive endovenous ablation techniques. Many clinical studies of endothermal ablation in the GSV have shown excellent results; however, less is known about the optimal therapy for SSV incompetence.[10]

This systematic review and meta-analysis summarizes and compares the outcomes and major complications of the available treatment modalities for incompetent SSVs, including surgery, endovenous laser ablation (EVLA), radiofrequency ablation (RFA), ultrasound-guided foam sclerotherapy (UGFS), steam ablation, and the more recently introduced mechanochemical ablation (MOCA).

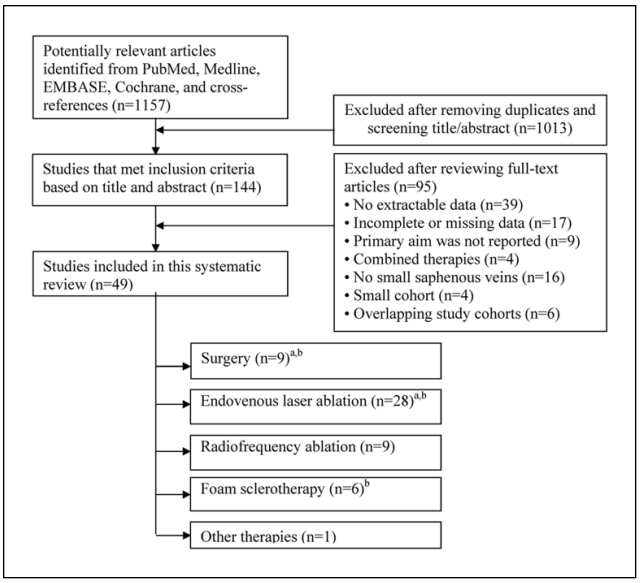

Figure 1. Flowchart of the search strategy.
[a] Two studies described surgery vs endovenous laser ablation.
[b] One study described surgery vs endovenous laser ablation vs foam sclerotherapy.

Methods

Search Strategy

A structured literature search was performed using the guidelines outlined in the Cochrane Handbook for Systematic Interventions (version 5.1.0) and the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA).[11,12] Three different biomedical bibliographic databases (PubMed, EMBASE, and the Cochrane Library) were used to perform a systematic search for all English-language literature. Search terms were all differently spelled text words or abbreviations on ("vein incompetence," "varicose vein," "small saphenous vein," "venous reflux") *and* ("stripping," "saphenopopliteal ligation," "saphenopopliteal disconnection," "endovenous laser," "endovenous ablation," "foam sclerotherapy," "radiofrequency ablation," "mechanochemical ablation," "steam," "VNUS," "ClariVein," "Sapheon," "cyanoacrylate glue") *and* ("outcome," "results," "success rate," "failure rate," "complications," "obliteration," "occlusion," "recurrence," "recanalization," "reflux," "pain," "return to normal activities or work," "hematoma," "paresthesia," "nerve injury," "wound infection," "deep vein thrombosis," "thromboembolism") in the title, abstract, and medical subject heading (MeSH). The new subspecialty journal, the *Journal of Vascular Surgery: Venous and Lymphatic Disorders*, which is not currently indexed in the databases, was also searched. The latest search was performed on July 1, 2015.

Selection Criteria and Selection

Studies were included if they involved patients treated for SSV incompetence with surgical stripping, SPJ ligation/disconnection, EVLA, RFA, foam sclerotherapy, MOCA, steam ablation, or cyanoacrylate glue ablation and if they provided the primary outcome. Exclusion criteria were unavailable full text (in 5 different Dutch university medical libraries), case reports, studies with ≤5 treated legs, studies on GSV incompetence, and recurrent SSV incompetence. Studies describing mixed cohorts with vein incompetence were included only if the data for patients with SSV incompetence could be specifically extracted from the results. If more than one study reported the same patient cohort, only the most recent and complete manuscript was included in this review. Finally, the same criteria were used to screen all cross-references for potentially relevant studies not identified by the initial literature search.

Two independent reviewers (D.B., V.N.N.K.) selected the articles according to these criteria with differences resolved by consensus. Of the 1157 abstracts (Figure 1) initially scanned, 1013 were excluded for the following reasons: not written in English, review articles, case reports, solely concerning GSVs, duplicate studies, and other study

aim or subject (ie, hemodynamic assessment, different analgesics, skin condition, anomalies). Of the 144 full text articles analyzed, 95 articles were excluded, leaving 49 studies appropriate for this systematic review (Figure 1).

Data Extraction and Quality Assessment

Two authors (D.B., V.N.N.K.) extracted the following data from the studies on patients undergoing SSV therapy using a standardized extraction form: year of publication, authors, study design, study period, sample size (legs treated), treatment modality, type of anesthesia, procedure details, additional therapy, follow-up period, definition of outcome, anatomical/technical success, and major complications. The same authors assessed the methodological quality of the articles using the Cochrane collaboration checklist and MINORS (methodological index for non-randomized studies) quality score.[13] The Oxford Centre for Evidence-Based Medicine levels of evidence was noted for each included study.[14] Disagreement was resolved by discussion and consensus.

Outcome Measures and Definition

The primary outcome was anatomical success, defined as closure, occlusion, obliteration, or ablation of the incompetent vein and absence of reflux on duplex ultrasound imaging.[15,16] In some studies, failure was described instead, using terms such as recurrence, reflux, recanalization, patent, or open. Failure rates were deducted from 100% to standardize the primary outcome.

Secondary outcomes were initial technical success and major complications. Technical success, defined as the absence of technical failure, was the ability to complete the procedure as planned and the absence of recurrent reflux in target veins as demonstrated with duplex scanning.[15] Two major complications were scored: deep venous thrombosis (DVT) and nerve injury. The latter was reported differently throughout the manuscripts as (sural) nerve injury, numbness, or paresthesia. The different terms describing persisting or transient nerve injury were pooled and defined as paresthesia in this review. Other (minor) complications (eg, superficial phlebitis, hematoma, superficial infection, and skin staining), postinterventional pain, clinical success, and satisfaction were poorly described and were excluded from analyses.

Data Analysis

Raw data were pooled into a database according to the treatment modality, and outcomes were separately described. For follow-up, the mean duration of follow-up per study was used. The secondary outcomes of technical success and major complications were calculated for each treatment modality and were corrected for the number of treated legs for each treatment modality (weighted means).

A meta-analysis was performed for the primary outcome of anatomical success (loss to follow-up was not considered). To provide a reliable outcome and to gain sufficient homogeneity of the pooled data, only studies with MINORS scores of at least 8 and a minimum follow-up of 6 months were used for the pooled analyses. Rates were pooled using a random-effects model that produced incidence estimates with 95% confidence intervals (CIs). The presence of heterogeneity among the studies was determined by applying a chi-square heterogeneity test and constructing forest plots. The I^2 index was calculated. Differences between treatments were assessed using the Mann-Whitney U test. All probability values were 2-tailed, and $p<0.05$ was the threshold of significance. Data were analyzed using SPSS statistical software (version 21.0; IBM Corporation, Somers, NY, USA) and the open access MetaAnalyst software (version 3.1; http://metaanalyst.software.informer.com).

Results

Study Characteristics

Data from the included studies were pooled and divided over the different treatment modalities: surgery (n=9), EVLA (n=28), RFA (n=9), foam sclerotherapy (n=6), and other therapies (n=1). Two studies[17,19] described 2 patient cohorts (surgery and EVLA) and another study[18] reported 3 patient cohorts (surgery, EVLA, and foam sclerotherapy).[18] No data meeting inclusion criteria were available on steam ablation or cyanoacrylate glue embolization in the SSVs. All of the included studies used duplex imaging to evaluate patients and all were of moderate to good quality according to the MINORS scoring scale (Supplemental Tables 1 and 2; supplementary material available at http://jet.sagepub.com/content/by/supplemental-data).

Treatment Modalities

Nine articles[8,17–24] described surgical treatment of 798 SSVs (Table 1). One study included 679 legs, of which only 52 underwent follow-up with duplex imaging.[24] Only these 52 legs were included in the analysis of anatomical and technical success. Uniformity was lacking among the chosen surgical procedures, which included ligation and/or disconnection of the SPJ, with or without stripping. The anatomical success rates were 24% to 94% with a mean follow-up of 17.3 months. Two studies randomized between surgery and EVLA; both showed inferior anatomical success rates for surgery.[17,19] One study randomized between surgery, EVLA, and foam and showed inferior anatomical success rates compared with EVLA but comparable results

Table 1. General Characteristics and Results of Surgery for Small Saphenous Vein Incompetence.

First Author, Year, Country	Design, Period	Level of Evidence[a]	MINORS	Sample Size, Legs	Anesthesia	Additional Therapy	Follow-up, mo	Definition of Outcome	Anatomical/ Technical Success, %	DVT/ Paresthesia, %
Nandhra, 2015[17] UK	RCT, 2005–2010	1b	22	53	GA	Phlebectomy, stripping	24	Recurrence	66/100	NR/6.8[d]
Brittenden, 2015[18] UK	RCT, 2008–2012	1b	23	37	GA, RA	Phlebectomy	6	Recurrence	56/NR	0/NR
Roopram, 2013[19] Netherlands	RCT, NR	1b	22	57	GA, SA	NR	1.5	Occlusion	67/NR	0/31.0
Ikponmwosa, 2010[20] UK	P, NR	2b	11	90	GA	NR	2	Recurrence	62/97	0/9
O'Hare, 2008[21] UK	P, 2002–2005	2b	13	234	GA, SA	NR	12	Recurrence	40/NR	0/23
Allegra, 2007[22] Italy	P, 1989–2001	2b	13	132	GA + TA	NR	60	Recurrence	70/NR	NR/NR
Dumas, 2007[23] Netherlands	RCT, 2001–2004	1b	18	84	GA, SA	Sclerotherapy/surgery GSV	3.8	Recurrence	24/NR	2/27
Whiteley, 2006[24] UK	NR, NR	NR	7	52[b]	GA	Surgery GSV and/or perforators	NR	Recurrence	94[c]/100	2/11[e]
Rashid, 2002[8] UK	R, 1998–2001	2b	10	59	GA	Surgery GSV	1.5	Recurrence	39/59	3/NR

Abbreviations: DVT, deep vein thrombosis; GA, general anesthesia; GSV, great saphenous vein; MINORS, methodological index for non-randomized studies; NR, not reported; P, prospective; R, retrospective; RA, regional anesthesia; RCT, randomized controlled trial; SA, spinal anesthesia; TA, tumescent anesthesia.

[a]Level of evidence: 1b, individual randomized controlled trial; 2b, individual cohort study.

[b]Only 52 of 679 legs underwent follow-up duplex sonography.

[c]Minor revascularization of treated track in 3 of 52 legs.

[d]Paresthesia occurred in 26% at 6 weeks and persisted in 7% at 24 months.

[e]Percentage of the total 679 legs after small saphenous vein surgery.

Table 2. General Characteristics and Results of Endovenous Laser Ablation for Small Saphenous Vein Incompetence.

First Author, Year, Country	Design, Period	Level of Evidence[a]	MINORS	Sample Size, Legs	Anesthesia	Additional Therapy	Follow-up, mo	Definition of Outcome	Anatomical/ Technical Success, %	DVT/ Paresthesia, %
Nandhra, 2015[17] UK	RCT, 2005–2010	1b	22	53	TA	Phlebectomy, stripping, sclerotherapy	24	Recurrence	81/100	NR/2.4
Brittenden, 2015[18] UK	RCT, 2008–2012	1b	23	14	LA, TA	Phlebectomy, foam	6	Recurrence	100/NR	0/NR
Aktas, 2015[25] Turkey	P, 2013–2014	2b	14	52	TA	Retreatment EVLA	12	Recurrence	100/NR	0/NR
Park, 2014[26] Korea	R, 2011–2013	2b	10	103	TA	Sclerotherapy	12	Recurrence	98/100	0/NR
Spreafico, 2014[27] Italy	P, 2008–2012	2b	14	62	TA	Phlebectomy, sclerotherapy	12	Recurrence	100/100	0/NR
Moul, 2014[28] USA	R, 2007–2011	2b	10	105	TA	Phlebectomy, sclerotherapy	24	Occlusion	100/100	0/0
Murli, 2013[29] Malaysia	R, 2010–2011	2b	13	57	GA, SA	Phlebectomy, sclerotherapy	24	Recurrence	98/NR	NR/NR
Von Hodenberg, 2013[30] Germany	P, 2008–2009	2b	13	41	TA	Sclerotherapy	12	Occlusion	100/100	0/0
Roopram, 2013[19] Netherlands	RCT, NR	1b	22	118	TA	NR	1.5	Occlusion	91/NR	0.9/6.7
Ozkan, 2012[31] Turkey	P, NR	2b	11	28	TA	Retreatment EVLA, sclerotherapy	6	Recurrence	96/100	0/0
Doganci, 2011[32] Turkey	RCT, 2009–2010	1b	19	68	TA	None	6	Recurrence	100/100	0/10.3
Desmyttere, 2010[33] France	P, 2003–2006	2b	12	147	TA	Phlebectomy	36	Occlusion	97/100	NR/40
Janne d'Othee, 2010[34] USA	R, NR	2b	12	67	TA	Sclerotherapy	8	Recurrence	99/100	0/3
Ravi, 2009[35] USA	R, 2002–2009	2b	11	269	LA	Phlebectomy, sclerotherapy	0.5	Occlusion	93/NR	0/NR
Huisman, 2009[36] Netherlands	P, 2006–2008	2b	12	169	GA, TA	Phlebectomy, sclerotherapy	3	Occlusion	98/NR	0/1.3
Konthothanassis, 2009[37] Italy, France	NR, 2003–2007	NR	9	229	TA	Phlebectomy, sclerotherapy, surgery perforators	36	Recurrence	99/100	1.3/2.2
Nwaejike, 2009[38] UK	P, 2004–2009	2b	13	66	LA	Phlebectomy, sclerotherapy	1.5	Occlusion	100/100	0/0
Myers, 2009[39] Australia	P, 2002–2007	2b	12	96	TA	Sclerotherapy	48	Occlusion	95/99	2.1/1
Pannier, 2009[40] Latvia, Netherlands	P, 2006–2007	2b	12	26	TA	Phlebectomy	11	Occlusion	100/100	0/9.5
Hamel, 2009[41] France, Switzerland	R, NR	2b	8	309	TA	Phlebectomy, sclerotherapy	6	Occlusion	100/99	0.3/1
Elmore, 2008[42] USA	R, 2001–2006	2b	9	32	TA	Sclerotherapy	15	Occlusion	96/NR	0/9.4
Trip-Hoving, 2008[43] Netherlands	R, 2007	2b	12	52	TA	NR	6	Occlusion	100/100	2/6
Jung, 2008[44] Korea	R, 2003–2006	2b	10	41	TA	Phlebectomy, sclerotherapy	3	Occlusion	93/NR	0/12
Park, 2008[45] Korea	P, 2003–2006	2b	12	390	TA	Phlebectomy, sclerotherapy	9	Occlusion	94/100	0/2
Gibson, 2007[46] USA	P, NR	2b	12	210	TA	EVLA GSV, phlebectomy, sclerotherapy, perforator surgery	4	Occlusion	96/100	5.7/1.6
Theivacumar, 2007[47] UK	P, 2004–2006	2b	10	68	TA	Sclerotherapy	6	Occlusion	100/100	0/4
Perkowski, 2004[48] USA	NR, 2002–2003	NR	9	37	TA	Phlebectomy	12	Occlusion	100/100	0/0
Proebstle, 2003[49] Germany	P, NR	2b	11	41	TA	None	6	Recurrence	100/95	3/11

Abbreviations: DVT, deep vein thrombosis; EVLA, endovenous laser ablation; GA, general anesthesia; GSV, great saphenous vein; LA, local anesthesia; MINORS, methodological index for non-randomized studies; NR, not reported; P, prospective; R, retrospective; RA, regional anesthesia; RCT, randomized controlled trial; SA, spinal anesthesia; TA, tumescent anesthesia.

[a] Level of evidence: 1b, individual randomized controlled trial; 2b, individual cohort study.

with foam sclerotherapy.[18] Allegra et al[22] reported long-term anatomical success in 70% of 132 SSVs after 5 years of follow-up. Paresthesia occurred in up to 31% (mean 19.6%) and DVT in 0.7%. Data were inconclusive to show superiority of any one of the surgical treatment modalities.

EVLA in 2950 SSVs was described in 28 reports[17–19,25–49] (Table 2), which were mostly individual cohort studies. Two randomized controlled trials (RCTs) randomized between EVLA and surgery[17,19] and one study between EVLA, surgery, and foam.[18] Another study randomized patients between cannulation of the SSV at the malleolar level vs cannulation at the midcalf level.[32] Studies were heterogeneous regarding energy delivery. Wavelengths differed between and even within the 28 studies: 810 nm (n=14), 940 nm (n=3), 980 nm (n=8), 1320 nm (n=1), and 1470 nm (n=7). One study did not clearly describe the wavelength of the laser. Moreover, pulsed and continuous modes were both used, with no uniform amount of force discernable (range 15–300 J/cm). Mean follow-up was 12.5 months (range 0.5–48) for all studies. In almost all studies, patients underwent additional therapies. Mean technical success was almost 100% (range 95%–100%). DVT was seen in 0.8% of all patients, and postprocedural paresthesia was described in 4.8%.

Nine articles[50–58] reported the results of RFA in 386 legs (Table 3). Three studies included only patients with SSV incompetence.[52,53,57] The studies reported an initial technical success rate of 100%. The anatomical success after a mean follow-up of 14.3 months ranged from 82% to 100%. Five studies reported results of the ClosureFast device (VNUS, San Jose, CA, USA/Covidien, Mansfield, MA, USA).[54–57] One study analyzed the use of a double heat cycle during RFA with the ClosureFast device.[50] One study used the ClosurePlus catheter in the initial stages of the study but changed to ClosureFast in the latter stages.[52] Studies by Doerler et al[51] and Boon et al[58] used the bipolar Celon device (Olympus, Hamburg, Germany). Complications were poorly reported: 5 studies described a mean DVT rate of 1.2%, ranging from 0% to 8%. Paresthesia was seen in 9.7% (mean). Park et al[52] described paresthesia in 26% of patients; RFA in some patients in this cohort was performed by proximal ligation and retrograde ablation.[52]

Six articles[18,59–63] reported the results of UGFS in 494 SSVs (Table 4). The Tessari method was mostly used to produce foam. A 1:4 liquid-to-air ratio was used in 2 studies,[59,60] and the remaining 4 groups used a 1:3 ratio.[18,61–63] Two research groups used 1% or 3% concentrations of polidocanol.[59,62] Sodium tetradecyl sulfate (1% or 3%) was used in 3 studies.[18,60,61] One study described treatment of foam sclerotherapy with polidocanol (1%) and with sodium tetradecyl sulfate (1% or 3%).[63] The mean anatomical success rate ranged from 20% to 96%. Five studies allowed retreatment with foam sclerotherapy. Only 2 studies described postprocedural complications. DVT was noted in just 1 patient. Major complications after SSV treatment were not recorded in the remaining 4 studies.

One study[62] described the result of MOCA in patients with SSV incompetence. In this recent prospective study, 50 patients were treated with the ClariVein catheter (Vascular Insights, Madison, CT, USA) along with polidocanol under local anesthesia. Initial technical success was 100%, and a 94% anatomical success rate was determined after a follow-up of 12 months. The absence of major complications, for example, DVT and especially nerve injury, could be considered an important finding. The MINORS quality score was 13.

A summary of the treatment of small saphenous vein incompetence is given in Table 5.

Pooled Data

The pooled anatomical success rates of 98.5% in EVLA (95% CI 97.7% to 99.2%) and 97.1% (95% CI 94.3% to 99.9%) in RFA were significantly higher ($p<0.001$) than for surgery (58.0% 95% CI 40.9% to 75.0%) and UGFS (63.6%, 95% CI 47.1% to 80.1%). The pooled data of EVLA and RFA were associated with moderate heterogeneity (I^2=54% and I^2=50%, respectively). Pooled data for surgery and UGFS showed considerable heterogeneity (I^2=92% and I^2=94%, respectively; Figure 2).

Discussion

There is abundant literature on the treatment of GSV incompetence; however, large comparative trials for the treatment of SSV are lacking so far. Only 3 RCTs, randomizing between different treatment modalities were included in this review[17–19]; nonetheless, the meta-analysis showed that EVLA and RFA techniques to treat SSV incompetence will lead to higher anatomical success rates compared with surgery and UGFS.

The available SSV literature remains heterogeneous regarding techniques and treatment protocols. In the manuscripts regarding UGFS, different types and concentrations of sclerosant as well as liquid-to-air ratios were described.[65,66] In the EVLA studies, 5 different laser wavelengths were used, and in some studies, subgroups of patients were treated with different wavelengths.[34,37,41] Although anatomical success of the various laser wavelengths seems similar, there may be differences in adverse effects.[67,68] Another important drawback is the mixture of additional treatments as well as renewed SSV treatments during the primary procedure or as a staged procedure (ie, phlebectomy and sclerotherapy after EVLA, repeated UGFS after initial foam sclerotherapy, etc). To be able to adequately extract and compare data, the terms "anatomical" and "technical success" were used to reduce bias and to draw conclusions.[10,15,16]

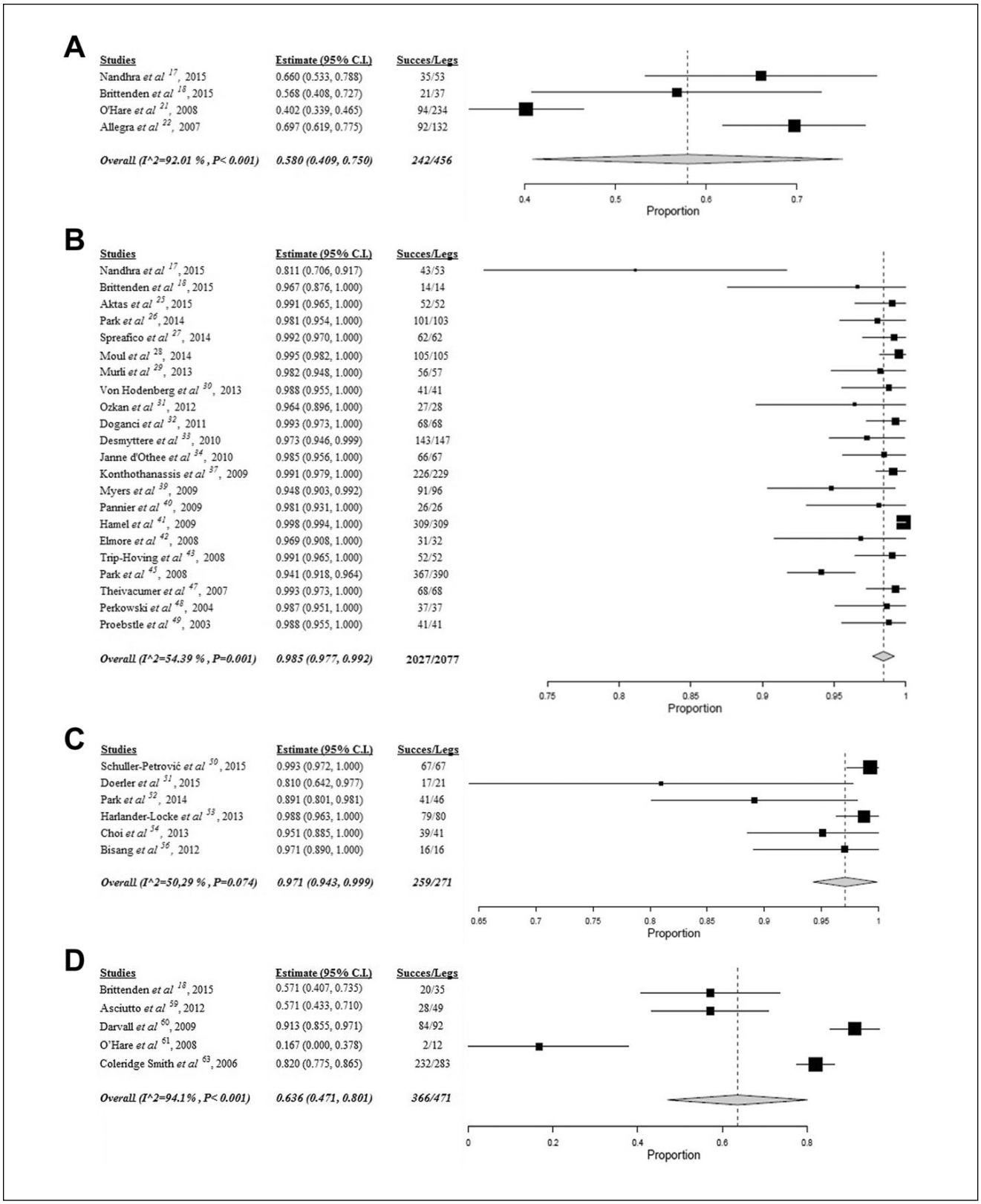

Figure 2. Forest plots of pooled data on anatomical success: (A) surgery, (B) endovenous laser ablation, (C) radiofrequency ablation, and (D) ultrasound-guided foam sclerotherapy. The solid squares denote the mean difference, the horizontal lines represent the 95% confidence intervals (CIs), and the diamonds denote the weighted mean differences.

Table 3. General Characteristics and Results of Radiofrequency Ablation for Small Saphenous Vein Incompetence.

First Author, Year, Country	Design, Period	Level of Evidence[a]	MINORS	Sample Size, Legs	Anesthesia	Additional Therapy	Follow-up, mo	Definition of Outcome	Anatomical/ Technical Success, %	DVT/ Paresthesia, %
Schuller-Petrović, 2015[50] Slovenia, Austria	R, 2007–2011	2b	9	67	TA	Phlebectomy, sclerotherapy	36	Recurrence	100/100	NR/NR
Doerler, 2015[51] Germany	R, 2009–2011	2b	10	21	TA	NR	22	Occlusion	82/NR	NR/9.5
Park, 2014[52] Korea	NR, 2007–2012	NR	10	46	TA	High ligation	27	Recurrence	89/NR	0/26.1
Harlander-Locke, 2013[53] USA	NR, 2008–2012	NR	10	80	GA, LA	Phlebectomy	6	Occlusion	99/NR	0/NR
Choi, 2013[54] Korea	R, 2009–2011	2b	12	41	GA, SA, TA	Phlebectomy	14	Occlusion	95/100	NR/NR
Gabriel, 2012[55] USA	R, 2005–2011	2b	12	12	NR	None	0.1	Occlusion	100/100	0/0
Bisang, 2012[56] Switzerland	R, 2007–2009	2b	10	16	TA	NR	12	Occlusion	100/100	0/NR
Monahan, 2012[57] USA	R, 2007–2008	2b	12	27	TA	Phlebectomy/RFA GSV	3	Occlusion	96/100	8/NR
Boon, 2010[58] Netherlands	P, 2007–2009	2b	11	76	SA or GA ± TA	Phlebectomy, crossectomy, sclerotherapy	0.7	Occlusion	100/100	NR/1.3

Abbreviations: DVT, deep vein thrombosis; GA, general anesthesia; GSV, great saphenous vein; LA, local anesthesia; MINORS, methodological index for non-randomized studies; NR, not reported; P, prospective; R, retrospective; RA, regional anesthesia; RFA, radiofrequency ablation; SA, spinal anesthesia; TA, tumescent anesthesia.
[a]Level of evidence: 2b, individual cohort study.

Table 4. General Characteristics and Results of Foam Sclerotherapy for Small Saphenous Vein Incompetence.

First Author, Year, Country	Design, Period	Level of Evidence[a]	MINORS	Sample Size, Legs	Anesthesia	Additional Therapy	Follow-up, mo	Definition of Outcome	Anatomical/ Technical Success, %	DVT/ Paresthesia, %
Brittenden, 2015[18] UK	RCT, 2008–2012	1b	23	35	NR	Retreatment UGFS	6	Recurrence	57/NR	NR/NR
Asciutto, 2012[59] Sweden	P, 2006–2010	2b	13	49	LA	Retreatment UGFS	12	Occlusion	58/100	NR/NR
Darvall, 2009[60] UK	P, 2004–2007	2b	14	92	NR	GSV sclerotherapy	12	Occlusion	91/100	1/0
O'Hare, 2008[61] UK	NR, 2005–2007	NR	10	12	NR	Retreatment UGFS	6	Occlusion	20/NR	0/NR
Darke, 2006[62] UK	NR, NR	NR	11	23	NR	Retreatment UGFS	1.5	Occlusion	96/100	NR/NR
Coleridge Smith, 2006[63] UK	NR, NR	NR	10	283	NR	Retreatment UGFS	11	Occlusion	82/100	NR/NR

Abbreviations: DVT, deep vein thrombosis; GSV, great saphenous vein; LA, local anesthesia; MINORS, methodological index for non-randomized studies; NR, not reported; P, prospective; RCT, randomized controlled trial; UGFS, ultrasound-guided foam sclerotherapy.
[a]Level of evidence: 1b, individual randomized controlled trial; 2b, individual cohort study.

Table 5. Summary for Treatment of Small Saphenous Vein Incompetence.

Treatment	No. of Studies	Mean Follow-up, mo	No. of Treated Legs	Mean Technical Success, %	Mean Complication Rates, %	
					DVT	Paresthesia
Surgery[8,17–24]	9	17.3	798	89.4 (n=4)	0.7 (n=7)	19.6 (n=9)
Endovenous laser ablation[17–19,25–49]	28	12.5	2950	99.7 (n= 20)	0.8 (n=24)	4.8 (n=22)
Radiofrequency ablation[50–58]	9	14.3	386	100 (n=6)	1.2 (n=5)	9.7 (n=3)
Foam sclerotherapy[18,59–63]	6	10.4	494	100 (n=4)	0.9 (n=2)	0 (n=1)
Other therapies[64]	1	12	50	100 (n=1)	0 (n=1)	0 (n=1)

Abbreviation: DVT, deep vein thrombosis; n, number of studies on which the percentage is based.

Follow-up can be considered the major drawback in SSV research of most of the included studies. Within the current meta-analysis, the pooled data included only studies with follow-up periods >6 months to provide a homogenous and reliable outcome. Moreover, approximately two-thirds of the included studies had substantial loss to follow-up or failed to report on loss to follow-up, thereby inducing potential bias regarding the calculation of success rates during follow-up.

A considerable part of the studies included in the present review were of moderate methodological quality. Statistical power calculations were not performed in any of the prospective cohort studies. Another drawback of the available studies was the study design: almost half of the studies were retrospective analyses or the design was not reported. The interpretation of this systematic review might have been hampered by publication bias. In addition, selective reporting can never be excluded.

A possible explanation for the low anatomical success of the surgical results may be due to more complex anatomy and anatomical variations of the proximal SSV and the SPJ.[9] Rashid et al[8] showed that even despite preoperative duplex identification, SPJ ligation was technically successful in only 59% of patients; moreover, one-third of these patients showed superficial venous residual flow.[8]

The risk of neurological damage is a clinically important downside of surgical treatment and thermal ablation. Paresthesia is seen in 19.6% of patients after surgery vs 9.7% after RFA and 4.8% after EVLA. An important advantage of nonthermal techniques is that no paresthesia was described. The incidence of paresthesia may be underreported due to mild or transient complaints and because no specific neurologic examination was performed routinely. Even in cases with recurrent varicosis after SPJ disconnection, EVLA remains a good option in terms of technical success and low occurrence of paresthesia.[69] DVT occurred rarely (0% to 1.2%) but remains a dreaded complication after venous intervention. DVT rates seem comparable after both surgical and endovenous therapy.

Patient-reported outcome measures could not be reviewed due to the variety in the reporting results or missing data. As recently reported by Brittenden et al,[70] clinical outcome and patient-reported disease-specific quality of life scores were similar after EVLA or surgery (of both GSV and SSV), despite the expected differences in anatomical success. Similar results were shown in a recent RCT; EVLA of the SSV was associated with a superior success rate, fewer complications, and earlier return to work compared with surgery, but no significant differences in quality of life measures were found.[19] A recently started RCT comparing nonthermal ablation (MOCA) and endothermal ablation (RFA) in SSVs might give further information on patient-reported clinical success.[71]

To date, innovative nonthermal techniques are very limited; only 1 study covered new treatments and included MOCA. Although a single study limits the ability to draw firm conclusions, this new technique shows excellent 1-year results and some important advantages: no paresthesia, less postoperative pain compared with RFA and EVLA, and earlier return to work.[72,73] No data on cyanoacrylate glue ablation in SSV is available; nevertheless, this tumescentless and nonthermal technique should be considered promising due to the results in GSVs and the reduced risk of nerve injury.[74] Innovation for surgery and even for UGFS seems to have reached a plateau, but the techniques for EVLA and RFA are updated continuously. Therefore, it might be expected that future results will evolve even more favorably for the endovenous techniques.

Conclusion

Endovenous thermal ablation (both EVLA and RFA) should be preferred to surgery and foam sclerotherapy in the treatment of SSV incompetence. Surgical treatment and UGFS should be reserved for patients in whom thermal ablation is technically not possible (eg, extreme tortuosity, intraluminal thrombus, or short segment neovascularization). Although the evidence on nonthermal techniques in the treatment of SSV incompetence is still sparse, the potential benefits, especially the reduced risk of nerve injury, might be of considerable clinical importance.

Declaration of Conflicting Interests

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A Cost-effectiveness Analysis of Surgery, Endothermal Ablation, Ultrasound-guided Foam Sclerotherapy and Compression Stockings for Symptomatic Varicose Veins

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WHAT THIS PAPER ADDS

This cost-effectiveness analysis directly informed the recommendations made by NICE clinical guideline CG168, which was commissioned to reduce the uncertainty around the clinical and cost-effectiveness of these treatments. The analysis shows that interventional treatment for varicose veins is a cost-effective use of NHS resources.

Objective: The aim was to investigate the cost-effectiveness of interventional treatment for varicose veins (VV) in the UK NHS, and to inform the national clinical guideline on VV, published by the National Institute of Health and Care Excellence.

Design: An economic analysis was constructed to compare the cost-effectiveness of surgery, endothermal ablation (ETA), ultrasound-guided foam sclerotherapy (UGFS), and compression stockings (CS). The analysis was based on a Markov decision model, which was developed in consultation with members of the NICE guideline development group (GDG).

Methods: The model had a 5-year time horizon, and took the perspective of the UK National Health Service. Clinical inputs were based on a network meta-analysis (NMA), informed by a systematic review of the clinical literature. Outcomes were expressed as costs and quality-adjusted life years (QALYs).

Results: All interventional treatments were found to be cost-effective compared with CS at a cost-effectiveness threshold of £20,000 per QALY gained. ETA was found to be the most cost-effective strategy overall, with an incremental cost-effectiveness ratio of £3,161 per QALY gained compared with UGFS. Surgery and CS were dominated by ETA.

Conclusions: Interventional treatment for VV is cost-effective in the UK NHS. Specifically, based on current data, ETA is the most cost-effective treatment in people for whom it is suitable. The results of this research were used to inform recommendations within the NICE guideline on VV.

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INTRODUCTION

Visible varicose veins (VV) in the lower limbs are estimated to affect at least a third of the UK population.[1] Although in some people these veins remain asymptomatic, in others they cause symptoms such as pain, aching, or itching and can have a significant negative effect on health-related quality of life (HRQL). Symptoms may become more severe with time or complications may develop, including bleeding, thrombophlebitis, skin damage, and ulceration. One study showed that 28.6% of those who had visible VV without oedema or other complications progressed to more severe venous disease after 6.6 years.[2] A number of treatments for VV have been shown to increase HRQL[3] and are thought to slow progression of the disease. Such treatments range from compression stockings (CS), to minimally invasive (endovenous) interventional procedures (principally ultrasound-guided foam sclerotherapy, UGFS, and

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endothermal ablation, ETA), to surgery. In 2011/2012, 32,704 VV procedures were carried out in the UK NHS,[4] yet national figures suggest that the number of VV procedures undertaken in the UK is decreasing each year. In addition, the UK NHS lags significantly behind its European counterparts in terms of numbers of procedures per population; a fourfold difference can be seen between the number of procedures per million population in the UK compared with Germany.[5] Clearly there is great disparity in the way VV are treated across Europe.

Recommendations for referral were published by NICE in 2001,[6] yet the recommendations have not widely been adhered to. This has led to a "postcode lottery", and precipitated a clinical guideline on the diagnosis and management of VV, which was commissioned by the NICE.[7,8] The aim was to provide guidance on the diagnosis and management of VV in order to improve patient care and minimize regional variation across the UK. The guideline was developed through work with a multi-disciplinary Guideline Development Group (GDG), and followed the procedures set out in the guidelines manual.[9] The cost—utility analysis (CUA) outlined in this paper was developed as part of the VV guideline. Cost-effectiveness analysis is integral to the guideline process, as it allows the interventions that offer the greatest value for money to be prioritized, where clinically appropriate. Such prioritization is necessary when faced with budget constraints, as spending in one area of healthcare displaces spending elsewhere. The relevance of cost-effectiveness analysis and the implications for the treatment of VV have been discussed elsewhere.[10]

METHODS

An overview of the methods for this economic evaluation are presented here; full details can be found in Appendix L to the full guideline.[7]

An economic analysis was conducted to compare the cost-effectiveness of surgery (stripping and ligation), ETA (radiofrequency ablation, RFA, and endovenous laser ablation, EVLA, considered together), UGFS, and CS, as these were the treatments considered in the guideline. Note that the decision to consider RFA and EVLA together was made by the GDG, as the basic principle of ultrasound-guided endovenous thermal ablation is shared between the techniques and the results are very similar. For a discussion on the potential differences in costs between RFA and EVLA please refer to Appendix L of the full guideline.[7] The model considered adults with primary unilateral great saphenous vein (GSV) incompetence (chosen for being a common presentation of VV), who were potentially suitable for treatment by any of the four treatment options.

A Markov model was developed (Fig. 1). All patients were assumed to have a first treatment episode, which comprised an initial treatment and top-up treatment where necessary. Following this, the treatment episode was considered to be complete. Patients could experience clinical recurrence of VV (defined as development of symptoms of VV in a treated limb), the probability of which differed by

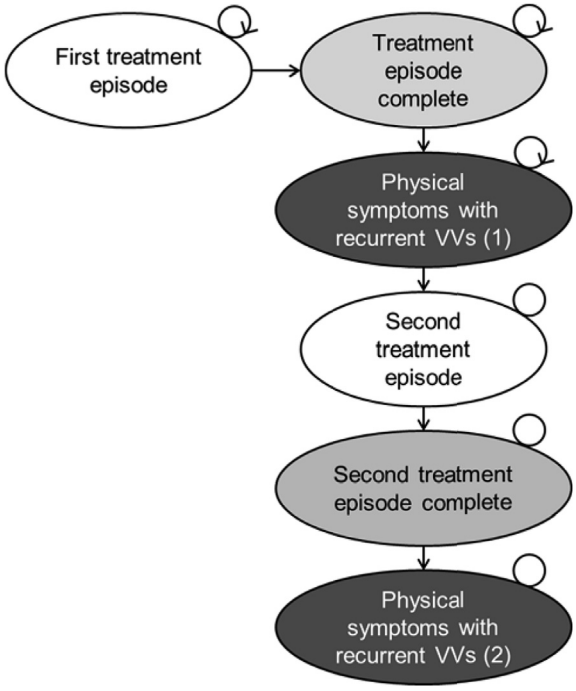

Figure 1. Model diagram. Schematic diagram of the Markov model designed to compare the cost-effectiveness of treatments for VV. The arrows denote possible transitions between states. All patients enter the model through the "First treatment episode" state. The state "Dead" was included in the model but is not shown in this diagram.

treatment option. A proportion of recurrent patients were assumed to undergo a second treatment episode (6 months after the onset of the recurrence), after which they could experience recurrence for a second time, but would not receive further treatment.

CS was modelled separately to the other three treatments, as the outcomes of completed treatment and clinical recurrence are not clinically meaningful when considering this management technique. Inputs were based on clinical evidence identified in the systematic review undertaken for the guideline, supplemented by additional data sources as required. The model cohort was assumed to be 65% female and have a starting age of 50, which was the approximate mean of all the patients from the included trials (all-cause mortality rates are age and gender specific but are unrelated to health state or treatment strategy). The model was built probabilistically to take account of the uncertainty surrounding each input parameter. Various deterministic sensitivity analyses were also undertaken to test the robustness of the model to different assumptions and data sources (deterministic sensitivity analysis involves varying the inputs of the model, in order to investigate the effect they have on the results). The model was built with a 1-month cycle length (chosen as this was deemed to be the minimum clinically meaningful time interval to detect differences between interventions), over a time horizon of 5 years in the base case. A time horizon of 5 years was chosen as clinical data were only available for a follow-up of 3 years, and the GDG did not feel

Table 1. Overview of parameters and parameter distributions used in the model.

Parameter description	Point estimate	Probability distribution	Distribution parameters	Source
Utility weights				
Primary VV	0.764	Beta	$\alpha = 37600$, $\beta = 12800$	PROMs[3]
Change in utility (from baseline) post treatment	+0.091	Lognormal	$\mu = -2.397$, $\sigma = 0.0007$	PROMs[3]
Change in utility (from baseline) due to recurrent VV	−0.093	Lognormal	$\mu = -2.206$, $\sigma = 0.0128$	Beresford et al.[13]
Conservative care (relative to surgery at 1 year)	−0.101	Normal	$\mu = 0.101$, $\sigma = 0.0198$	Michaels et al.[15]
Transition probabilities				
Probability of requiring top-up treatment (within 2 months post treatment)				
Surgery	5%	Deterministic SA only		GDG estimate
Endothermal	5%	Deterministic SA only		GDG estimate
Foam Sclerotherapy	20%	Deterministic SA only		GDG estimate
Conservative care	NA			
Probability of recurrence (per month)				
Surgery	0.0083 (SD 0.0031)	Point estimate and uncertainty from NMA		
Endothermal	0.0058 (SD 0.0134)	Point estimate and uncertainty from NMA		
Ultrasound-guided foam sclerotherapy	0.0091 (SD 0.0037)	Point estimate and uncertainty from NMA		
Conservative care	NA			
Cost (£)				
Surgery	£908	Gamma	See Appendix L to the full guideline — only NHS reference cost components modelled probabilistically	See Appendix L to the full guideline for full breakdown of costs and sources
Endothermal	£624	Gamma		
Ultrasound-guided foam sclerotherapy	£315	Gamma		
Conservative care[a]	£234	Deterministic SA only		
Additional cost associated with retreatment	£417	Gamma	See Appendix L to the full guideline — only NHS reference cost components modelled probabilistically	See Appendix L to the full guideline for full breakdown of costs and sources

GDG = guideline development group; NMA = network meta-analysis; PROMs = patient-reported outcome measures; SA = sensitivity analysis; SD = standard deviation.

[a] This is an annual cost (first year incurs an additional £15).

that basing long-term extrapolation on arbitrary assumptions in the absence of data was appropriate.

Probabilities

Clinical recurrence (network meta-analysis). A network meta-analysis[11] was conducted to calculate treatment-specific probabilities of clinical recurrence. In order to account for the different follow-up times of the various trials, an underlying Poisson process with a constant event rate was assumed for each trial arm, and a complementary log—log (cloglog) link function used to model the event rate. A key assumption employed here is a constant hazard of recurrence — this was deemed to be a reasonable simplifying assumption as the time horizon of the model is relatively short.

Surgery was chosen as the baseline comparator as it featured in all the trials. The baseline hazard was estimated on the cloglog scale through a meta-analysis of the surgery arms of the included trials. The resulting predictive distribution for the baseline hazard was combined with treatment-specific hazard ratios resulting from the network meta-analysis to calculate the probability of clinical recurrence for each treatment. The codes for both the baseline and relative effects models were adapted from that provided on the NICE Decision Support Unit (DSU) website,[12] and run in WinBUGS 1.4. The baseline and relative effects models were run for a sample of 50,000 iterations after an initial 'burn in' of 50,000 iterations. Convergence was checked through examination of trace and history plots.

Top-up treatment and re-treatment. The model assumed that all top-up treatments were UGFS; this assumption does not impact recurrence rates, it only impacted costs, which were thoroughly explored through sensitivity analyses. The purpose here was to include a cost of top-up treatment to capture the increased cost if some procedures require more top-ups than others. The choice of top-up treatment was therefore not of primary relevance.

Not all patients were expected to be retreated after experiencing clinical recurrence; the GDG estimated that 75% of patients would receive further interventional treatment, and it was assumed that the remaining 25%

would receive CS. The proportion of patients undergoing each modality of re-treatment was assumed to be independent of the modality of their initial treatment (Table 1).

Utilities

In CUA, measures of health benefit are valued in terms of quality adjusted life years (QALYs). A QALY is a measure of a person's length of life weighted by a valuation of their HRQL over that period. The weight used is called a utility value, which is a measurement of the preference for a particular health state, with a score usually ranging from 0 (death) to 1 (perfect health). Utility inputs for the model were taken from the patient-reported outcome measures (PROMs),[3] and are documented in Table 1. The baseline value was used in the model to represent the utility of a patient with primary VV, that is when a patient first receives treatment. The health gain after treatment was used to model the increase in utility associated with treatment.

The HRQL associated with recurrent VV was taken from Beresford et al.,[13] and the SF-36 data provided in the paper were mapped to EQ-5D utility scores, using an established equation developed by Ara and Brazier.[14]

As mentioned previously, CS was modelled separately to the main analysis. The difference in utility between patients undergoing surgery and CS was used to calculate the difference in QALYs over time between these two treatments. The difference in utility between these two treatments was taken from Michaels et al.[15] (Table 2) as this was the only paper found to report such data. For the probabilistic analysis the difference between utility following CS and surgery was modelled using a Normal distribution to allow positive and negative differences.

Costs and resource use

Costs were expressed in 2013 UK pounds and were considered from a UK NHS and personal social services perspective. Costs and QALYs were both discounted at 3.5% per annum, in accordance with the NICE reference case.

NHS reference costs do not distinguish between the various treatments for VV, so the GDG decided on a bottom-up costing approach. Resource use was estimated by the clinical members of the GDG, and where possible unit costs for these resources were collected from nationally available lists, such as the NHS reference costs or the PSSRU. Only NHS reference cost components were modelled probabilistically, and this was done using a Gamma distribution. A summary of the costs used in the model is presented in Table 1; the breakdown of the costs is presented in Appendix L of the full guideline. Costs were subject to extensive deterministic sensitivity analyses.

Calculating cost-effectiveness

Incremental cost-effectiveness ratios (ICERs) are commonly used in cost-effectiveness analysis. ICERs are calculated by dividing the difference in costs between two alternatives by the difference in QALYs. Then, if the resulting ICER falls below a given cost per QALY threshold, the more clinically effective treatment is considered to be cost effective. The cost per QALY threshold suggested by NICE is £20,000 per QALY gained.[16]

For a given cost-effectiveness threshold, cost-effectiveness can also be expressed in term of net monetary benefit (NMB). This is calculated by multiplying the total QALYs for a comparator by the threshold cost per QALY value (£20,000 in this case) and then subtracting the total costs (formula below).

$$\text{NMB} = \text{MeanQALYs} \times £20{,}000 - \text{MeanCosts}$$

The most cost-effective strategy is that with the highest NMB. Both methods of determining cost effectiveness will identify the same optimal strategy.

RESULTS

Network meta-analysis

Eight studies were identified from the clinical effectiveness review that included clinical recurrence as an outcome.[17–24] The network of included trials is shown in Fig. 2, with the number of trials included for each pair-wise comparison noted in parentheses. Full details of the included data are provided in Appendix L of the full guideline.

The final treatment-specific probability estimates can be seen in Table 1. The table indicates that ETA was associated with the lowest probability of clinical recurrence per month. These estimates were used to parameterize treatment effects in the decision model.

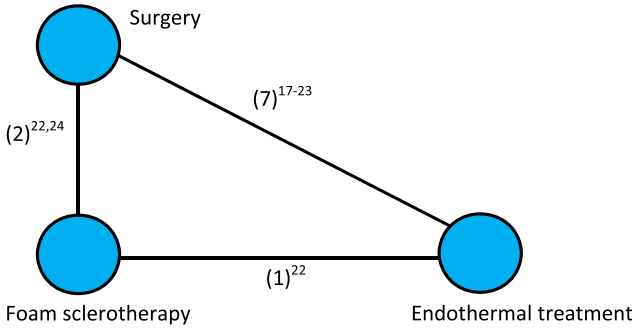

Figure 2. Network of trials compared in the network meta-analysis.

Table 2. EQ-5D data for conservative care.

Study	Relevant comparators	Utility values				
		Baseline	3 months	6 months	12 months	24 months
Michaels et al.[15] (Group 3 only: severe VV)	Surgery	0.76 (0.19)	NR	0.89 (0.13)	0.87 (0.14)	0.84 (0.21)
	Conservative care	0.77 (0.18)	NR	0.80 (0.17)	0.78 (0.18)	0.85 (0.17)

Economic model

CS and surgery dominated in the base case, as they provided fewer QALYs at increased cost compared with ETA (Table 3 and Fig. 3). ICERs are not applicable for the dominated strategies; therefore, only one ICER was calculated, comparing UGFS with ETA. Net monetary benefit (NMB) is calculated for all strategies.

ETA produced the greatest QALY gain, and was therefore the most clinically effective treatment, yet it came at an additional cost compared to UGFS, of £151 (note that this includes the downstream costs of top-up treatments and clinical recurrence, as well as the cost of the initial procedure). Using the mean costs and QALYs generated by the probabilistic sensitivity analysis, the ICER of the ETA to FS was £3,161. This is below the NICE threshold of £20,000 per QALY gained, and therefore ETA was found to be the cost-effective strategy.

In this analysis, an area of particular uncertainty is the costs. Yet, sensitivity analyses revealed that the model is robust to changes in relative costs. If the costs of surgery, UGFS, and conservative care remain as specified in the base case, ETA remains cost-effective even with increases in cost of up to £681. A wide range of further sensitivity analyses was undertaken in which key assumptions and parameters were varied. Baseline recurrence rate, utility values, time horizon, top-up rates, and modality of retreatment were among the inputs subject to such variation. An analysis was also conducted to investigate the impact of conducting ETA without concurrent phlebectomies. None of the sensitivity analyses changed the optimum result. This shows that although uncertainty surrounds model inputs and assumptions, variation within reasonable ranges does not change the results. Probabilistic analysis revealed that ETA had a probability of being cost-effective of 71% (at the threshold of £20,000 per QALY gained), followed by UGFS, which had a probability of being the most cost-effective option of 23%. The probability of each treatment being cost-effective at different threshold values is shown in Fig. 4. Full details of all sensitivity analyses and associated results are provided in Appendix L of the full guideline.

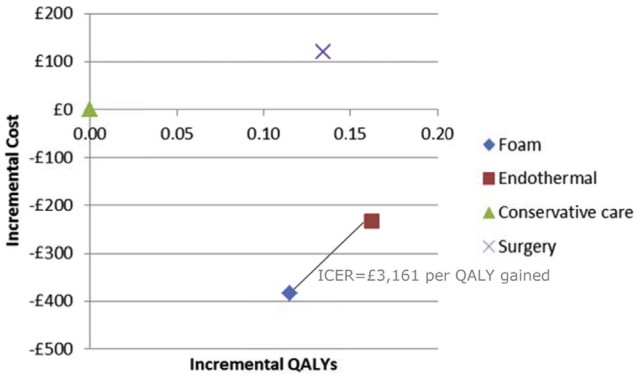

Figure 3. Cost-effectiveness plane showing incremental cost and QALYs per patient expected with each strategy (base case, probabilistic analysis).

DISCUSSION

The most important finding of this study is that all interventional treatments (surgery, ETA, and UGFS) for VV are cost-effective compared with compression therapy. The study also found that ETA is cost-effective compared with surgery and UGFS.

However, the findings of this study need to be carefully interpreted in the context of clinical practice. The model is based upon the treatment of unilateral GSV VV, which, although arguably the most common, are only one of many different presentations (bilateral, recurrent, small saphenous vein either alone or in combination with GSV). The model also assumes that the patient can be treated by all four modalities, which may rarely be the case.

In addition, the quantity and quality of data available for the NMA were limited, particularly for UGFS, for which only two trials were included. Of note, some concern was expressed by members of the GDG that the foam technique used in these trials was inadequate (1 trial used 3% polidocanol, 2 mL of solution mixed with 8 mL of air,[22] and the other used 3% polidocanol in a sclerosant to air ratio of 1:4[24]). Therefore, although the data comparing surgery with ETA is considered to be reasonably robust, there are residual concerns over the data for UGFS. Interestingly, results from one recent study[25] suggest little difference in quality of life outcomes between surgery, ETA, and UGFS over a 1-year period, despite differences in clinical outcomes. Clearly additional research is required in this area, a finding echoed by a recent HTA-funded systematic review.[26] Finally, there are as yet very limited data available on the long-term durability of ETA or UGFS, which makes predicting outcomes beyond a few years problematic. Clearly further long-term cohort and controlled studies are required.

This study reinforces the findings of Gohel et al.,[27] who found, based on a UK CUA, that RFA or EVLA performed as an outpatient procedure, or surgery performed as a day case procedure, are likely to be cost-effective treatments. The analysis presented here goes beyond that carried out by Gohel et al., by combining all available evidence in a network meta-analysis, and by including additional details such as the ongoing potential for recurrence of varicosities.

Table 3. Mean base case results (probabilistic).

Treatment	Mean per patient		Cost-effectiveness at a threshold of £20,000 per QALY gained		
	QALYs	Cost	NMB	Rank	Probability of being cost effective
Conservative care	3.55	£1 102	£69 965	4	4%
Surgery	3.69	£1 222	£72 554	3	3%
UGFS	3.67	£718	£72 681	2	23%
ETA	3.72	£869	£73 484	1	71%

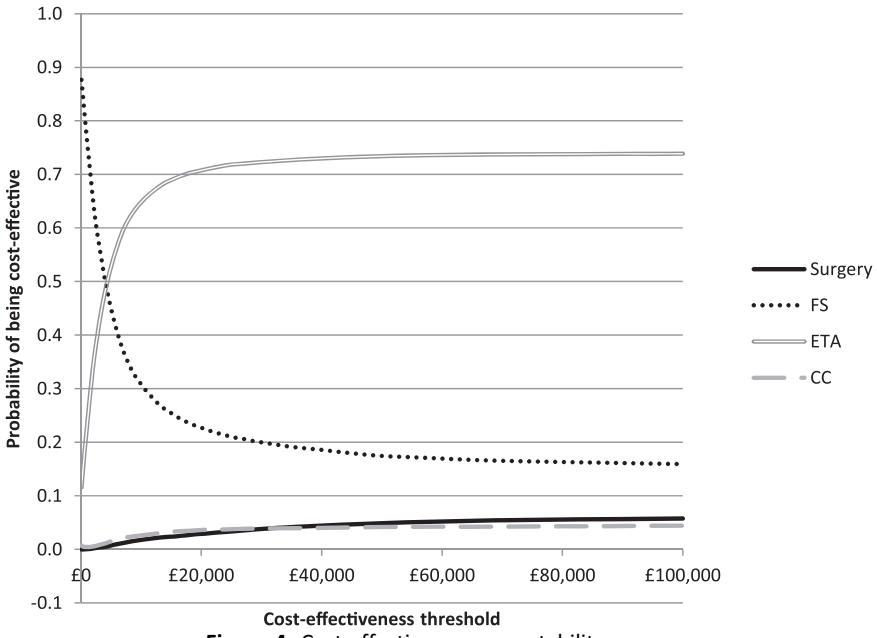

Figure 4. Cost-effectiveness acceptability curve.

A further recent UK CUA[26] found FS to be cost-effective compared with surgery, EVLA, and RFA. This study differed from the model presented here, as the analysis focused on technical (as opposed to clinical) recurrence, which included outcomes such as reflux, recanalization and incomplete obliteration of the vein all analysed together in an NMA. Using this method, little clinical difference was found between the strategies, and the model was therefore largely driven by the cost of the treatments. FS was the cheapest treatment; therefore, this was the cost-effective option in the base case. The GDG discussed this analysis at length, and raised concerns about the use of technical recurrence as a key clinical outcome (as, for example, recurrent reflux may not lead to recurrent symptoms), and about the cost figures used. Specifically, the GDG did not agree that EVLA and RFA would be more costly than surgery.

Several partial, pairwise, UK economic evaluations have also been published, where costs have been collected alongside randomized trials.[28–30] Bountouroglou et al.[29] found that foam sclerotherapy conducted under local anaesthetic costs £672.97, whereas surgery under general anaesthetic costs £1,120.64; Subramonia and Lees[30] found endothermal treatment to be more costly than surgery (£1,275.90 compared with £559.13), although the technique that was used for endothermal ablation in this trial is now considered out of date; Lattimer[28] found that foam sclerotherapy was substantially less costly than endothermal treatment (£230.24 vs. £724.72). These studies are of limited value when attempting to assess which out of all the available treatments are cost-effective, as they provide only pairwise comparisons, have relatively short follow up times, and generally don't account for recurrence or HRQL.

Throughout this analysis ETA and UGFS were assumed to take place in an outpatient setting (under local anaesthetic), and surgery as a day case procedure (under general anaesthetic). The analysis has not considered different settings of treatment, for example ETA as a day case procedure. Nevertheless, sensitivity analysis did show that the optimal strategy was fairly robust to increases in the cost of ETA and so if ETA under local anaesthetic was not considered suitable for a patient, endothermal treatment under general anaesthetic may represent a cost-effective alternative.

The results of this CUA were used to inform guideline development; therefore, ETA is the recommended strategy for treatment of truncal VV in the UK NHS, providing it is clinically and anatomically suitable for the patient. By logical extension the GDG expect that these results will hold for the treatment of the small saphenous vein,[31,32] for recurrent varicose veins, and also for bilateral treatment, again providing that ETA is deemed suitable for the patient in question. It is acknowledged within the guideline that ETA may not be suitable for all patients. If ETA is not suitable, then UGFS is considered to be the cost-effective option. If UGFS is not suitable either, surgery is the optimal strategy provided the patient is suitable and willing to be operated on.

The clinical data employed in the analysis above has been collected from around the world, yet the cost data is specific to the UK. The implication of this is that where other healthcare systems (either state or privately funded) face similar costs, and treatments can be expected to have a similar impact on quality of life, the conclusions may generalize. Indeed sensitivity analyses have shown that our conclusions are robust to substantial changes in relative costs, indicating that interventional treatment for VV may be cost-effective in various other scenarios or settings. The cost-effectiveness acceptability curve (Fig. 4) shows how the

probability of each intervention being cost-effective at different values of the cost-effectiveness threshold, which may be faced in other countries.

CONCLUSION

The model found that all interventional treatments (surgery, ETA, and UGFS) for VV are cost-effective compared with compression therapy. Based on currently available data, it is likely that endothermal treatment is the most cost-effective strategy for people in whom all treatments are suitable. When ETA is not deemed suitable for a patient, UGFS is likely to be the optimal strategy. Surgery represents the optimal choice if neither ETA nor UGFS is thought suitable.

The guideline recommends offering treatment in accordance with these findings for people with symptomatic VV. This guidance will most likely increase the number of referrals to vascular specialists, as it challenges the traditional practice of providing conservative care as a "low cost" alternative to interventional treatment. NICE estimates that much of the costs arising from the increase in referrals will be offset by a decrease in the number of expensive surgical procedures in favour of the cost-effective alternative,[33] ETA.

CONFLICT OF INTEREST

Prof. Bradbury reports grants from BTG plc, outside the submitted work; an honorarium of Euro 1000 from the European Venous Forum who have also covered travel and accommodation expenses to speak and teach on their Hands-On Workshop in Cyprus in November 2012, Stockholm in November 2013, and Tiblisi in March 2014. Also, travel and accommodation expenses to attend the Union Internationale de Phlebologie in Boston in September 2013 form STD Pharmaceuticals who make Fibrovein, which is used for foam sclerotherapy. Prof. Davies reports grants from Vascular insights, grants from Urgo Laboratoire, grants from First Kind, grants from Acergy, grants from Royal College of Surgeons, grants from NIHR, grants from BHF, outside the submitted work.

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Randomized trial comparing cyanoacrylate embolization and radiofrequency ablation for incompetent great saphenous veins (VeClose)

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Background: **Whereas thermal ablation of incompetent saphenous veins is highly effective, all heat-based ablation techniques require the use of perivenous subfascial tumescent anesthesia, involving multiple needle punctures along the course of the target vein. Preliminary evidence suggests that cyanoacrylate embolization (CAE) may be effective in the treatment of incompetent great saphenous veins (GSVs). We report herein early results of a randomized trial of CAE vs radiofrequency ablation (RFA) for the treatment of symptomatic incompetent GSVs.**

Methods: **Two hundred twenty-two subjects with symptomatic GSV incompetence were randomly assigned to receive either CAE (n = 108) with the VenaSeal Sapheon Closure System (Sapheon, Inc, Morrisville, NC) or RFA (n = 114) with the ClosureFast system (Covidien, Mansfield, Mass). After discharge, subjects returned to the clinic on day 3 and again at months 1 and 3. The study's primary end point was closure of the target vein at month 3 as assessed by duplex ultrasound and adjudicated by an independent vascular ultrasound core laboratory. Statistical testing focused on showing noninferiority with a 10% delta conditionally followed by superiority testing. No adjunctive procedures were allowed until after the month 3 visit, and missing month 3 data were imputed by various methods. Secondary end points included patient-reported pain during vein treatment and extent of ecchymosis at day 3. Additional assessments included general and disease-specific quality of life surveys and adverse event rates.**

Results: **All subjects received the assigned intervention. By use of the predictive method for imputing missing data, 3-month closure rates were 99% for CAE and 96% for RFA. All primary end point analyses, which used various methods to account for the missing data rate (14%), showed evidence to support the study's noninferiority hypothesis (all $P < .01$); some of these analyses supported a trend toward superiority ($P = .07$ in the predictive model). Pain experienced during the procedure was mild and similar between treatment groups (2.2 and 2.4 for CAE and RFA, respectively, on a 10-point scale; $P = .11$). At day 3, less ecchymosis in the treated region was present after CAE compared with RFA ($P < .01$). Other adverse events occurred at a similar rate between groups and were generally mild and well tolerated.**

Conclusions: **CAE was proven to be noninferior to RFA for the treatment of incompetent GSVs at month 3 after the procedure. Both treatment methods showed good safety profiles. CAE does not require tumescent anesthesia and is associated with less postprocedure ecchymosis. (J Vasc Surg 2015;61:985-94.)**

From the Morrison Vein Institute, Scottsdale[a]; the Lake Washington Vascular, Bellevue[b]; the Sentara Vascular Specialists, Virginia Beach[c]; the Cosmetic Laser Dermatology, San Diego[d]; the Vein Clinics of America, Oakbrook[e]; the Maryland Laser, Skin, and Vein Institute, Hunt Valley[f]; the Wild Iris Consulting LLC, Palo Alto[g]; and the Inovia Vein Specialty Center, Bend.[h]

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Chronic venous disorders (CVDs) are progressive medical conditions that afflict approximately 30 million adults in the United States or approximately 35% of screened adults in the United States [1] and the United Kingdom.[2] In the most common manifestation of CVD, the valves in the great saphenous vein (GSV) and other superficial veins transporting blood from the legs toward the heart are dysfunctional, leading to venous dilation and stasis, causing symptoms and physical findings such as fatigue, swelling, pain, chronic skin changes, spontaneous hemorrhage, and leg ulcers. As CVD progresses, symptoms can be burdensome and profoundly affect quality of life. In the United States, time away from work due to CVD exceeds work time lost from peripheral artery disease.[3] Nonetheless, only a small fraction of those with CVD seek treatment.[4]

Treatment of CVD and saphenous insufficiency has undergone a substantial shift in the past decade. Previously, surgical treatment (ligation and stripping) was the primary treatment choice, in most cases requiring a general or regional anesthetic in an operating room. Complications from surgical treatments include hematoma,

paresthesia, disfigurement from scarring, and a high recurrence rate.[5-7]

Endovenous thermal ablation (EVTA) by radiofrequency ablation (RFA) or laser ablation has been shown to be a safe and effective treatment of CVD with high long-term target vein closure rates.[8] Both techniques have gained broad acceptance in many countries and by multiple specialties. One disadvantage of these techniques is the requirement for use of tumescent anesthesia (TA), which provides necessary local anesthesia, protects surrounding structures from potential thermal injury generated through the RF catheter and laser fibers, and reduces the caliber of the target vein to evacuate as much blood as possible to enhance vein wall thermal injury. TA not only requires additional time during a procedure but may also be associated with adverse events, such as pain, hematoma, and ecchymosis.[7-9] New treatments that circumvent the need for TA are desirable, provided treatment efficacy remains high.

Cyanoacrylate embolization (CAE) for varicose veins (VenaSeal; Sapheon, Inc, Morrisville, NC) has recently been approved for treatment of the incompetent GSV in the European Union, Hong Kong, and Canada. Cyanoacrylate adhesive (CA) has a long history of medical use, most notably in the embolic treatment of intracranial arteriovenous malformations.[10] Recently, a modified CA has been developed with the following desirable properties: (1) rapid polymerization on contact with blood and tissue, (2) flexibility sufficient to tolerate dynamic movement in the legs without generation of symptoms or being perceptible by the patient, and (3) high viscosity to eliminate the risk of embolization to the deep veins or pulmonary circulation.

Two prospective clinical trials provided early evidence of CAE's safety and effectiveness. In the first trial, 38 subjects at a single center with symptomatic GSV reflux treated with CAE had a 92% 12-month target vein closure rate.[11] In a second study (the European Sapheon Closure System Observational ProspectivE [eSCOPE]), 70 subjects treated at seven sites in Europe had a 93% 12-month closure rate.[12] In neither of these studies did subjects receive perivenous TA or require postprocedure compression stockings. Subjects in both studies demonstrated clinically and statistically significant improvements in symptoms and health-related quality of life.

We report initial results of VeClose in a prospective, multicenter randomized clinical trial comparing CAE with RFA for the treatment of the incompetent GSV. Because RFA with ClosureFast has been shown to cause less ecchymosis and pain in the postoperative follow-up period compared with laser ablation,[13] we chose RFA as the comparator for this pivotal trial of the effectiveness and safety of CAE. The goal of the study was to show statistical noninferiority of CAE efficacy compared with RFA.

METHODS

Study design. VeClose is a multicenter, prospective randomized controlled trial conducted under investigational device exemption from the U.S. Food and Drug Administration at 10 participating sites in the United States. The goal of the study was to show statistical noninferiority of CAE efficacy compared with RFA. Subjects were enrolled between March and September 2013. All sites obtained central Institutional Review Board approval before enrollment. The study underwent rigorous remote and on-site monitoring as well as 100% source verification.

Study subjects. The study enrolled adults aged 21 to 70 years with symptomatic moderate to severe varicosities (Clinical, Etiology, Anatomy, and Pathophysiology [CEAP] clinical classification of symptomatic C2-C4b) and incompetence of the GSV, with reflux time of at least 0.5 second assessed in the standing position. Subjects were excluded if they had hemodynamically significant reflux of the small saphenous vein or anterior accessory GSV, prior treatment of the target GSV, symptomatic peripheral arterial disease, a history of deep venous thrombosis or pulmonary embolism, or aneurysm of the target GSV >12 mm in diameter (additional eligibility criteria are shown in Table I).

After eligibility was confirmed and informed consent was obtained, subjects underwent baseline examination, including a brief, focused physical examination, completion of CEAP and Venous Clinical Severity Score (VCSS) assessments,[14] and duplex ultrasound of both legs. In addition, subjects completed the EQ-5D quality of life survey[15] and the Aberdeen Varicose Vein Questionnaire (AVVQ).[16] Subjects were then randomized (1:1) to CAE performed with VenaSeal Sapheon Closure System (VSCS; Sapheon, Inc, Morrisville, NC) or RFA performed with ClosureFast (Covidien, Mansfield, Mass). Randomization was stratified by study site and used random block sizes of 4 or 6; assignments were obtained with an interactive voice response system linked to a web-based database. The first two subjects at each site were not randomized but rather treated with CAE (ie, roll-in cases) to ensure familiarity with the CAE procedure. All operators were experienced with EVTA procedures and were currently using RFA. Because study outcomes in roll-in subjects (n = 20) did not differ from the randomized cohort (n = 222), this report excludes discussion of roll-in cases.

Devices and procedures. VSCS consists of a delivery system and proprietary CA. Endovenous embolization of the GSV with VSCS was performed as previously described.[11] Briefly, with high-resolution ultrasound guidance, a 5F introducer sheath/catheter was advanced to the saphenofemoral junction (SFJ) and positioned 5.0 cm caudal to the SFJ. With proximal GSV compression by the ultrasound probe, two injections of approximately 0.10 mL CA were given 1 cm apart at this location, followed by a 3-minute period of local compression, and then repeated injections and 30-second ultrasound probe and hand compression sequences until the entire length of the target vein segment was treated. The sheath/catheter was removed and compression applied to the catheter entry site until hemostasis was achieved. A single small bandage was applied, and venous occlusion was confirmed by duplex ultrasound.

RFA of the target vein was performed with ClosureFast according to the manufacturer's instructions for use.

Table I. Study eligibility criteria

Inclusion criteria
1. Age ≥21 years and ≤70 years at the time of screening
2. Reflux in the GSV >0.5 second
3. One or more of the following symptoms related to the target vein: aching, throbbing, heaviness, fatigue, pruritus, night cramps, restlessness, generalized pain or discomfort, swelling
4. GSV diameter while standing of 3-12 mm throughout the target vein as measured by duplex ultrasound
5. CEAP classification of C2 (if symptomatic)-C4b
6. Ability to walk unassisted
7. Ability to attend follow-up visits
8. Ability to understand the requirements of the study and to provide informed consent
Exclusion criteria
1. Life expectancy <1 year
2. Active treatment for malignant disease other than nonmelanoma skin cancer
3. Symptomatic peripheral arterial disease with ABI <0.89
4. Daily use of narcotic or nonsteroidal anti-inflammatory pain medications to control pain associated with GSV reflux
5. Current, regular use of systemic anticoagulation (eg, warfarin, heparin)
6. Previous or suspected deep venous thrombosis or pulmonary embolus
7. Previous superficial thrombophlebitis in the target GSV
8. Previous treatment of venous disease in target limb, other than spider vein treatment
9. Known hypercoagulable disorder
10. Conditions that prevent vein treatment with either RFA or VSCS
11. Immobilization or inability to ambulate
12. Pregnant before enrollment
13. Tortuous GSV, which, in the opinion of the investigator, will limit catheter placement or require more than one primary access site
14. Aneurysm of the target vein with local vein diameter >12 mm
15. Significant, incompetent, ipsilateral small saphenous veins, intersaphenous veins, or anterior accessory GSVs
16. Known sensitivity to cyanoacrylate adhesives
17. Current participation in another clinical study involving an investigational agent or treatment or within the 30 days before enrollment
18. Patients who require bilateral treatment during the next 3 months
19. Patients who require additional ipsilateral treatments on the same leg within 3 months following treatment

ABI, Ankle-brachial index; *CEAP*, clinical, etiology, anatomy, and pathophysiology classification; *GSV*, great saphenous vein; *RFA*, radiofrequency ablation; *VSCS*, VenaSeal Sapheon Closure System.

Perivenous TA was delivered to the saphenous compartment surrounding the vein, and the dosage was recorded. Use of reprocessed catheters was not allowed. Double cycles of RF were employed at the first treatment zone near the SFJ in all subjects.

All procedures took place in an outpatient setting at the investigator's clinic with use of standard sterile technique. Immediately after venous access, subjects rated their pain on venous access on a numeric rating scale of 0 to 10 (0, no pain; 10, worst imaginable pain). When the procedure was completed, subjects used the same scale to rate intraoperative pain experienced during the procedure itself, including during TA but excluding pain felt during venous access. Subjects were discharged from the clinic on completion of the procedure. Consistent with the ClosureFast instructions for use, postprocedure compression stockings were used in both groups for 3 days continuously and an additional 4 days during waking hours. Subjects were instructed to avoid strenuous activities for 1 to 2 days.

Postoperative study visits. Subjects returned to the clinic at day 3 for a brief clinical assessment, including the subject's reporting of pain medications taken within 24 hours, the subject's rating of pain experienced in the index leg, and the investigator's assessment of the presence of ecchymosis, rated on a previously used 0- to 5-point graded scale (0, none; 1, involving <25% of the treatment area; 2, 25%-50%; 3, 50%-75%; 4, 75%-100%; 5, extension above or below the treatment segment).[13] Subjects also returned at month 1 and month 3 for clinical assessment (including CEAP score [month 3 only] and VCSS), quality of life evaluation (AVVQ and EQ-5D), and duplex ultrasound examination of the treated limb. The allowed 3-month window was ±4 weeks. No subject underwent ipsilateral adjunctive varicose vein treatments until the 3-month visit was complete to evaluate index device/procedure efficacy without the potential for confounding by additional therapies. Trial follow-up continues to 36 months after index treatment.

Adverse events were monitored at each study visit by querying subjects using a list of expected adverse events with RFA and CAE procedures. Investigators rated event severity as well as the relationship of the adverse events to the device and the procedure. Safety was reviewed by an independent data safety and monitoring board.

End points and statistical methods. The study's primary end point was complete closure of the target GSV, defined as Doppler ultrasound examination (including color flow, compression, and pulsed Doppler) showing closure along the entire treated target vein segment with no discrete segments of patency exceeding 5 cm at the month 3 visit. Closure was confirmed by an independent vascular ultrasound core laboratory (VasCore, Boston, Mass). Incomplete closure seen with any of these methods counted against the primary end point. The primary end

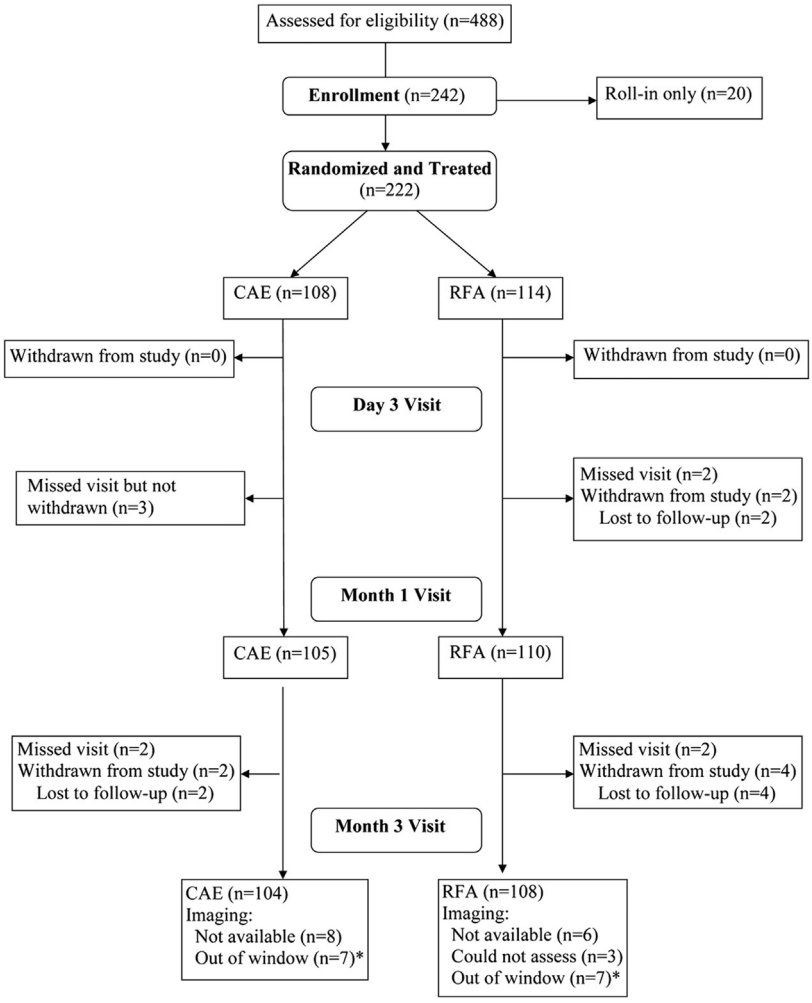

Fig 1. Study disposition. *CAE*, Cyanoacrylate embolization; *RFA*, radiofrequency ablation. *All out-of-window scans showed complete occlusion of the target vein.

point was analyzed by an intent-to-treat approach with the following prespecified methods to impute missing data: last observation carry forward, pessimistic and optimistic models, and Bayesian predictive models. Predictive models, used for missing RFA observations only, took into account the following in-study factors predictive of incomplete occlusion: male gender, decreased body mass index, and number of tributaries >3 mm in diameter. The study was interpreted as a primary end point success if the proportion of subjects with complete closure with CAE was statistically noninferior to that with RFA, with a 10% noninferiority margin. Proportions were compared by χ^2 tests for two independent binomial event rates, and confidence limits were calculated by the method of Miettinen and Nurminen.[17] Noninferiority was concluded when the P value was $< .05$ and the lower confidence interval for the difference in success rates exceeded -10%. If noninferiority was demonstrated, superiority was then tested by similar methods.

The study's two secondary end points were subject-rated pain experienced during the procedure (ie, pain experienced after vein access but before all treatment/access catheters were removed) and investigator-rated ecchymosis at day 3. Treatment differences for the former were compared by a two-tailed t-test, the latter by a Wilcoxon test. Changes from baseline in VCSS, AVVQ, and EQ-5D were compared between groups by repeated-measures analysis of variance and a Wilcoxon test for CEAP category at month 3. The rates of adverse events were compared by Fisher exact test. All analyses were performed with R, an open-source statistical package.[18]

RESULTS

Subject characteristics and disposition. Of 488 patients screened at 10 sites between March and September 2013, 242 met enrollment criteria and were enrolled (Fig 1). The first two subjects at each site (20 total) were treated with CAE in the roll-in phase; 222 subjects were

Table II. Demographic and baseline characteristics of VeClose study subjects

Characteristic	*VSCS (n = 108)*	*RFA (n = 114)*	P *value*
Female[a]	83 (77)	93 (82)	.48
Hispanic[a]	4 (4)	8 (7)	.43
Nonwhite[a]	6 (6)	8 (7)	.32
Target leg[a]			
Right	47 (44)	56 (49)	.48
Left	51 (57)	58 (51)	
Age, mean (range)[b]	49.0 (26.6-70.6)	50.5 (25.6-70.1)	.34
Body mass index, mean (range)[b]	27.0 (17.4-44.5)	27.0 (17.0-46.7)	.95
Primary symptom[a]			
Pain	33 (31)	24 (21)	.65
Aching	32 (30)	39 (34)	
Swelling	17 (16)	18 (16)	
Heaviness	14 (13)	16 (14)	
Burning	5 (5)	3 (3)	
Itching	2 (2)	5 (4)	
Other	4 (4)	7 (6)	
Smoking[a]			
Current	16 (15)	5 (4)	.02
Former	25 (23)	35 (31)	
Never	66 (61)	74 (65)	
GSV diameter, mean (range), mm[b]			
Mid GSV	4.9 (0-9)	5.1 (2.4-11)	.28
Proximal GSV	6.3 (3-12)	6.6 (2.8-12)	.15
CEAP category[a]			
C2 (varicose veins)	61 (57)	64 (56)	.96
C3 (edema)	32 (30)	36 (32)	
C4a (pigmentation/eczema)	13 (12)	12 (11)	
C4b (lipodermatosclerosis and atrophie blanche)	2 (2)	2 (2)	
VCSS, mean (SD)[b]	5.5 (2.6)	5.6 (2.6)	.99
AVVQ, mean (SD)[b]	18.9 (9.0)	19.4 (9.9)	.72
EQ-5D TTO, mean (SD)[b]	0.935 (0.113)	0.918 (0.116)	.29

AVVQ, Aberdeen Varicose Vein Questionnaire; *CEAP,* clinical, etiology, anatomy, and pathophysiology classification; *GSV,* great saphenous vein; *RFA,* radiofrequency ablation; *SD,* standard deviation; *TTO,* time trade-off; *VCSS,* Venous Clinical Severity Score; *VSCS,* VenaSeal Sapheon Closure System.
Data are presented as number (%) unless otherwise indicated.
[a]Binary or ordinal outcomes tested by χ^2 tests.
[b]Continuous outcomes tested by unpaired *t*-tests.

Table III. Procedure characteristics

Characteristic	*VSCS (n = 108)*	*RFA (n = 114)*	P *value*[a]
Treatment zone maximum diameter, mm	5.9 (2-12)	6.2 (1.5-11)	.19
GSV treatment length, cm	32.8 (8-61)	35.1 (6.5-84.5)	.17
Tumescent anesthesia amount, mL	—	272 (50-550)	—
Stump length, cm	22.5 (0-83)	18.9 (0-330)	.38
CA delivered, mL	1.2 (0.4-2.3)	—	—
Procedure duration, minutes	24 (11-40)	19 (5-46)	<.01
Volume lidocaine, mL	1.6 (0.2-6)	2.7 (0.2-10)	.1

CA, Cyanoacrylate adhesive; *GSV,* great saphenous vein; *RFA,* radiofrequency ablation; *VSCS,* VenaSeal Sapheon Closure System.
Data are presented as mean (range).
[a]*P* values derived from unpaired *t*-test or Wilcoxon test.

randomly assigned to either CAE or RFA. All subjects returned for the day 3 visit, and subsequently a small and similar number of subjects in each group were lost to follow-up or voluntarily withdrew. The majority of subjects were women (79%) and white (94%) (Table II). Most (87%) subjects had CEAP clinical class 2 and 3 venous disease. There was a slight predominance of current and former smokers in the CAE groups ($P = .02$). The predominant symptoms were leg pain and aching. Risk factors for varicose veins were common and similar between groups. VCSS and AVVQ scores were consistent with mild to moderate venous reflux disease. Baseline characteristics were similar between treatment groups.

Procedure characteristics. All subjects received the assigned intervention. The average maximum diameter of the GSV in the treatment zone was 6 mm (Table III).

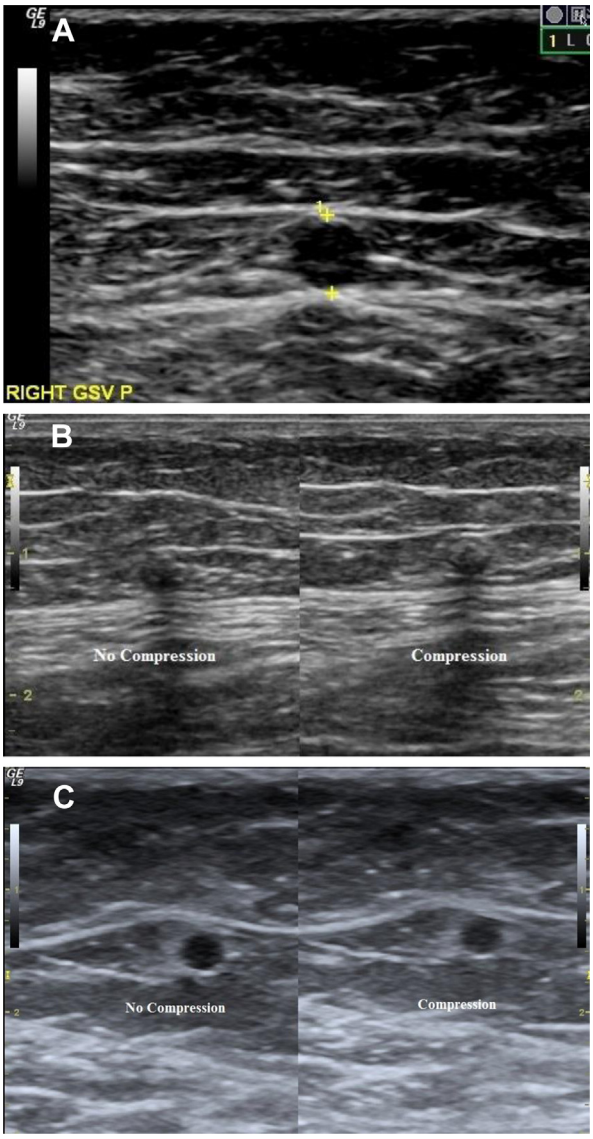

Fig 2. Ultrasound images of incompetent great saphenous vein (*GSV*) **(A)** before treatment and **(B)** after treatment with cyanoacrylate embolization (CAE) and **(C)** after treatment with radiofrequency ablation (RFA).

The treatment zone had a mean (range) of 1.4 (0-12) tributaries >3 mm in diameter. Mean procedure time was 5 minutes longer for CAE vs RFA (24 vs 19 minutes; $P <$ .01). At the end of the procedure, one subject each in the CAE and RFA groups had residual flow along the treated segment. Five (4%) technical deviations occurred during RFA treatment, requiring use of an additional separate hydrophilic guidewire (Cook HiWire, Bloomington, Ind) in four cases to assist in proximal positioning of the RFA catheter. No technical deviations occurred during CAE treatment. Fig 2 shows an ultrasound image of the GSV before (*A*) and after (*B* and *C*) the CAE and RFA procedure.

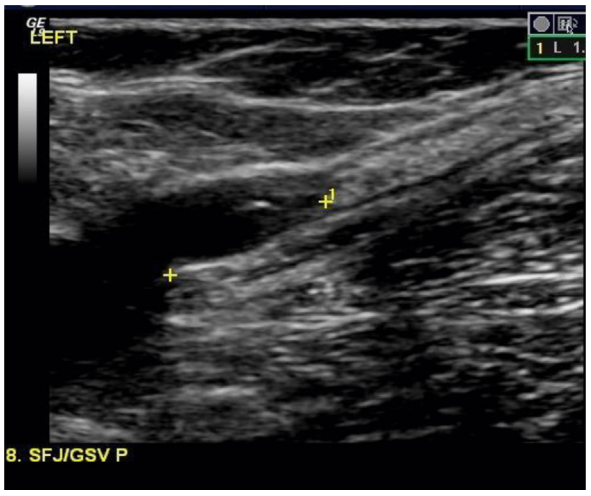

Fig 3. Complete closure of cyanoacrylate embolization (CAE)-treated incompetent great saphenous vein (*GSV*) with stump length calipers.

Venous closure. On day 3, 100% of GSVs were closed in both groups (Fig 3). At month 1, patency of the treated vein segment on duplex ultrasound was identified in 15 GSVs treated with RFA and 0 GSVs treated with CAE, with closure rates of 86% and 100%, respectively ($P <$ .01 for both noninferiority and superiority). Of the 222 randomized subjects, a 3-month visit was done in 212 (96%), of which 7 (3%) were out of window. Month 3 Doppler ultrasound images, used for the core laboratory's assessments, were available in 194 of 222 subjects. Ultrasound images were missing or uninterpretable in 15 CAE and 16 RFA cases (total missing rate of 14%; Fisher exact, $P =$ 1.0). Missing images were due to early withdrawal (n = 8 and 6 in the CAE and RFA groups, respectively), uninterpretable images (3 RFA cases), and images beyond the allowed 3-month study window (n = 7 and 7 in the CAE and RFA groups). All out-of-window images showed complete occlusion. For available images, there was 100% agreement between site investigator and core laboratory readings of target vein closure.

Among available images, the GSV was patent in five RFA-treated subjects and one CAE-treated subject. Taking into account the 31 missing images using several prespecified imputation methods (Table IV), statistical noninferiority was demonstrated with P values $<$ .01 in all models. In three of the five missing data imputation methods, there was a trend toward statistical superiority for CAE ($P =$ .06, .06, and .07). With use of the predictive model for missing data interpretation, closure rates were 99% and 96% in the CAE and RFA groups, respectively.

Pain and ecchymosis. Mean pain ratings during venous access were similar between the two groups (1.6 for CAE vs 2.0 for RFA; $P =$ .13); mean intraprocedural pain ratings were also low and similar in both groups (2.2 vs 2.4; $P =$ .11). There was no difference between treatment groups in pain experienced in the 24 hours

Table IV. Primary end point analyses under various models for imputing missing data

Model	*Description*	*Closure rate*				
		VSCS (n = 108)	*RFA (n = 114)*	*Rate difference (95% CI)*	P *NI*	P *Sup*
Last observation carry forward	Most recent ultrasound observation used to impute missing value	107 (99%)	109 (96%)	3.5% (−0.7% to 8%)	<.01	.06
Optimistic	Assume missing values are successes	107 (99%)	109 (96%)	3.5% (−0.7% to 8%)	<.01	.06
Pessimistic	Assume missing values are failures	92 (85%)	93 (82%)	3.6 (−6.2 to 13)	<.01	.24
Alternative pessimistic	Assume missing values are failures but late month 3 evaluations are successes	99 (92%)	100 (88%)	3.9 (−4.0 to 12)	<.01	.17
Predictive	Estimate distribution of successes taking into account gender, body mass index, and number of tributaries ≥3 mm	99%[a]	96%	4%	<.01	.07

CI, Confidence interval; P_{NI}, *P* value for noninferiority; P_{Sup}, *P* value for superiority; *RFA,* radiofrequency ablation; *VSCS,* VenaSeal Sapheon Closure System.
[a]Number not reported as predictive values are distributions, not fixed values.

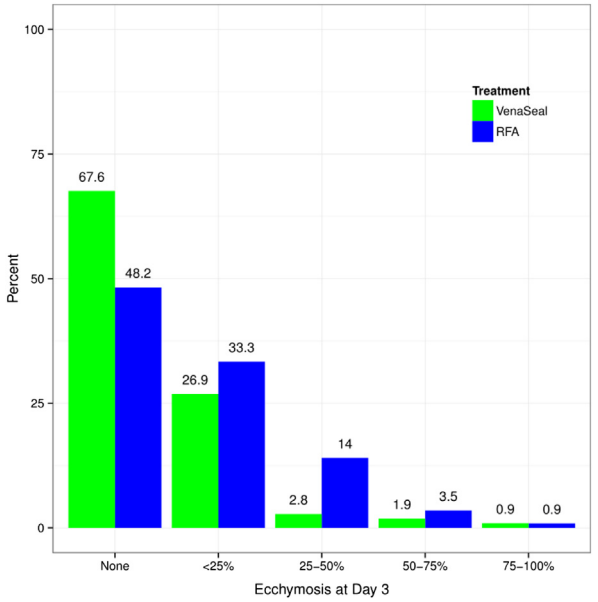

Fig 4. Ecchymosis assessed by investigators with a 5-point scale on day 3 by treatment group. Subjects treated with cyanoacrylate embolization (CAE) had less ecchymosis at day 3 compared with radiofrequency ablation (*RFA*) ($P < .01$, Wilcoxon test).

before the day 3 visit (0.93 in each group; $P = .36$). Ecchymosis severity at day 3 was lower in the CAE group ($P < .01$; Fig 4), and ecchymosis at day 3 was absent in significantly more subjects after CAE than after RFA (68% of CAE subjects vs 48% of RFA subjects; $P < .01$).

Clinical measures. Additional measures of clinical severity of CVD showed marked, sustained, and equal reductions in both groups over time (Table V). By month 3, VCSS had improved approximately 3.5 points from baseline ($P < .01$), with no differences between treatment groups. Similarly, by month 3, AVVQ score improved by approximately 8 points ($P < .01$), and EQ-5D time trade-off utility index had improved by approximately 0.03 unit ($P = .01$), with no differences between treatment groups. At baseline, no subject was CEAP 0/1; by month 3, 26% and 33% of subjects in the CAE and RFA groups were CEAP 0/1. CEAP improved by approximately 0.5 point per group ($P < .01$), with no difference between groups.

Table V. Follow-up clinical assessments

	VenaSeal (n = 108)	*RFA (n = 114)*	P *value*[a]
VCSS			
Baseline	5.5 (2.6), 108	5.6 (2.6), 114	.60
Day 3	4.9 (1.3), 108	5.0 (1.9), 114	
Month 1	2.3 (1.7), 105	2.6 (2.0), 110	
Month 3	1.9 (1.6), 104	2.0 (2.0), 108	
AVVQ			
Baseline	18.9 (9.0), 107	19.4 (9.9), 111	.53
Month 1	11.9 (7.1), 102	12.6 (8.3), 109	
Month 3	11.6 (7.5), 104	10.7 (8.6), 108	
EQ-5D TTO			
Baseline	0.935 (0.113), 108	0.918 (0.116), 114	.34
Month 1	0.965 (0.113), 105	0.961 (0.106), 110	
Month 3	0.965 (0.095), 104	0.965 (0.083), 108	

AVVQ, Aberdeen Varicose Vein Questionnaire; *RFA,* radiofrequency ablation; *TTO,* time trade-off; *VCSS,* Venous Clinical Severity Score.
Values are given as mean (standard deviation), number.
[a]*P* values are derived from repeated-measures analysis of variance.

Safety. No subject withdrew because of an adverse event and no subject developed deep venous thrombosis or pulmonary embolism. Four mild adverse events occurred during the RFA procedure and one occurred after the CAE procedure (RFA: lightheadedness [1], nausea [1], and vasovagal symptoms [2]; CAE: lightheadedness after the procedure). As of the month 3 visit, 78 adverse events had occurred in 63 subjects (34 CAE subjects and 29 RFA subjects; Table VI; $P = .37$ for difference in number of adverse events per subject between treatment groups). The type and rate of expected predefined adverse events were similar between treatments, except that post-treatment phlebitis (in the treated segment or nontreated tributary) was somewhat more common after CAE (20 vs 15 events; $P = .36$). Most cases of phlebitis in both groups were mild, transient, and

Table VI. Adverse events

	VenaSeal, No. (%)	*RFA, No. (%)*	P *value*[a]
No. of adverse events per subject			
0	74 (69)	85 (75)	.37
1	28 (26)	22 (19)	
2	6 (6)	6 (5)	
3	0 (0.0)	0 (0.0)	
4	0 (0.0)	1 (1)	
Event severity			
Mild	26 (24)	30 (26)	.35[c]
Moderate	12 (11)	7 (6)	
Severe	2 (2)	1 (1)	
Procedure-related adverse events[b]	27 (25)	31 (27)	.76
Device-related adverse events[b]	13 (12)	7 (6)	.16
Reported adverse events			
Phlebitis, any zone	22 (20)	16 (14)	.36
Phlebitis in treatment zone	11 (10)	10 (9)	.82
Phlebitis not in treatment zone	8 (7)	4 (4)	.24
Phlebitis in both treatment zone and nontreatment zone	1 (1)	1 (1)	1.0
Paresthesia in treatment zone	3 (3)	3 (3)	1.0
Stocking irritation	2 (2)	3 (3)	1.0
Access site infection	1 (1)	1 (1)	1.0
Superficial thrombophlebitis	4 (4)	3. (3)	.72
Access site burn	0 (0)	1 (1)	1.0
Paresthesia not in treatment zone	0 (0)	1 (1)	1.0
Other adverse events[d]	10 (9)	11 (10)	1.0

RFA, Radiofrequency ablation.
Percentages represent number of events divided by number treated.
[a]*P* values derived from χ^2 test, Wilcoxon test, or Fisher exact test.
[b]Judged by investigator to be probably or definitely related.
[c]Cochrane-Armitage trend test.
[d]Adverse events not related to varicose veins or the treatment area.

successfully treated with over-the-counter nonsteroidal anti-inflammatory medication (ibuprofen). Three adverse events were rated severe (one case each of breast cancer, kidney stones, and symptomatic orthostatic hypotension), none of which was deemed related to either the index device or procedure. No device- or procedure-related serious adverse events occurred in either group, and no postprocedural thrombus extensions into the common femoral vein were identified by duplex ultrasound in any patient.

In both treatment groups, the number of adverse events that investigators attributed to the study device was small (Table VI). Events rated as probably or definitely related to CAE devices included moderate access site infection (1), mild paresthesia in the treatment zone (1), moderate paresthesia in the treatment zone (1), mild phlebitis in the treatment zone (6), moderate phlebitis not in the treatment zone (1), and mild superficial vein thrombophlebitis (3). Events rated as probably or definitely related to RFA study devices included mild access site burn (1), mild paresthesia in the treatment zone (2), mild phlebitis in the treatment zone (2), moderate phlebitis in the treatment zone (1), and mild phlebitis not in the treatment zone (1).

DISCUSSION

Results from this study confirm that CAE is safe and highly effective for the treatment of CVD. The study showed that occlusion of the target vein at 3 months by CAE was at least as effective as RFA. Short-term (3-month) probability of complete closure of the target GSV with CAE in this study was high (99%) and similar to that observed in a prior single-arm CAE study (95% in a small feasibility study[19]) and in a prospective CAE multicenter European study (96%).[12] High long-term GSV closure rates with RFA (93% at 3 years) have been reported,[20] although a meta-analysis reported somewhat lower long-term success rates (84% at 3 years[8]). The reports in this meta-analysis included the use of an earlier generation RF system (VNUS Closure; VNUS Medical Technologies, San Jose, Calif), which may be the reason for lower success rates than are seen with newer RF equipment. In addition, methods to assess complete occlusion varied slightly across studies. Closure rate associated with RFA may have been lower in this study because of the critical ultrasound evaluation performed at each study center. Long-term follow-up from the current study may provide the best estimate of differences in venous closure rates between CAE and RFA.

In previous reports of CAE treatment of GSV, incomplete occlusion and recanalization appeared to be caused by continued flow of blood from GSV tributaries into the treated GSV, resulting in areas of failed closure. In the present study, high closure rates (especially in the CAE treatment group) were seen despite use of a stricter definition of vein closure (only 5 cm of patency allowed vs 10 cm used in some other studies[13]) and in the absence of adjunctive treatments at the time of index treatment.

Our findings suggest that adjunctive treatments may be withheld at the time of the index procedure when highly effective GSV closure methods are used, such as RFA or CAE, and delivered later, if required, as has been previously suggested.[21,22]

Both CAE and RFA were associated with low pain scores. Moreover, presumably because it does not require TA, CAE treatment resulted in less ecchymosis over the treated segment at day 3 compared with subjects treated with RFA. In addition, in controlled studies comparing RFA with ClosureFast to laser ablation, pain and ecchymosis measurements were also somewhat dissimilar to those in our studies.[13,23] In these studies, pain was not rated immediately after the procedure, as was done in our study. These differences make comparisons of some aspects of our study with previous studies difficult.

The severity and impact of venous disease on quality of life were measured with several end points in this study. Both CAE-treated and RFA-treated subjects improved significantly over time. VCSS scores of 1.5 points at 3 months, with significant improvements from baseline, are similar to those seen in previous CAE clinical trials.[12,19] Likewise, subjects' improvements in AVVQ and EQ-5D were similar to those previously reported with CAE treatment.[19] Although CEAP class improved significantly in both treatment groups, the importance of this finding is unclear.

Adverse events were similar between groups. No severe procedure- or device-related adverse events occurred in either group. Device-related adverse events with CAE were mostly cases of phlebitis of the treated GSV and, although not statistically significant, occurred somewhat more commonly than in RFA-treated subjects (20 vs 15 cases; $P = .36$). The difference might reflect the mechanism of action of the adhesive. Most cases of phlebitis in both groups were mild, transient, and successfully treated with over-the-counter nonsteroidal anti-inflammatory medication (ibuprofen). Slight technical deviations (use of additional guidewire), although minor, were experienced during only the RFA procedures.

The current study has several novel features compared with other clinical trials of treatments for CVD. A randomized active control group (RFA) allowed the observed closure rate for CAE to be compared in the same operator/investigator group. This study was tightly controlled, monitored, and 100% source verified, yielding high-quality data. The investigators' ultrasound results were confirmed by an independent vascular ultrasound core laboratory. The study's primary end point (occlusion of the target GSV) was objective and easily judged, with full agreement between investigator and core laboratory readings. Moreover, the study's primary ultrasonographic end point was more strictly defined than that used in some other studies of EVTA.[24] Given the high target vein occlusion rate in both groups, the observed improvements in CVD-associated symptoms (as assessed by VCSS and AVVQ) and general quality of life (as assessed with EQ-5D) were expected, with no significant difference between treatment groups found. Finally, the multicenter, multioperator performance of the study increases study validity by reporting the combined experience of multiple physician participants, removing the bias of a single-center/operator study. Study follow-up will continue to 3 years, allowing documentation of longer term index vein success rates as well as the likelihood of recanalization or CVD progression.

Although this study has some limitations, the results are significant even though data were missing in a small number of subjects. However, all methods used to impute missing data (including pessimistic models) provided strong evidence of noninferiority. The assessment of vein closure could not be blinded to treatment because the ultrasonographic appearance of the implanted cyanoacrylate is unique and different from that observed after RFA treatment. There was complete agreement, however, between site investigators and the core laboratory for all vein closure assessments. To reduce bias between groups, post-treatment stockings were worn by both CAE and RFA subjects because the RFA instructions for use require compression. Saphenous occlusion rates were high in prior studies of CAE without use of compression. Finally, adjunctive treatments were withheld until after the month 3 visit to prevent confounding variables in the primary occlusion analysis.

The advantages of CAE for the treatment of incompetent truncal veins are, first, because CAE does not require the use of TA, the patient avoids its associated burden; and second, CAE may also allow elimination of postprocedure compression stockings, for which compliance is known to be poor.[25,26]

CONCLUSIONS

In the current study, CAE was shown to be noninferior to RFA for the occlusion of symptomatic incompetent GSVs at 3 months. CAE does not require TA, which resulted in reduced side effects such as ecchymosis compared with RFA. The rate of postoperative phlebitis was slightly higher for CAE but not statistically significant compared with RFA.

The authors acknowledge Monte Madsen and the Sapheon Clinical Affairs team for their efforts in overseeing execution of the VeClose clinical trial, as well as the patients and study site personnel who participated. The authors also acknowledge Elizabeth Field, PhD, of Field Advantage Medical Communications and Kate Giovino for editorial assistance.

AUTHOR CONTRIBUTIONS

Conception and design: NM, DC
Analysis and interpretation: NM, DC, KG
Data collection: NM, DC, KG, SM, MG, TK, RW, AJ
Writing the article: NM, DC, KG
Critical revision of the article: NM, DC, KG
Final approval of the article: NM, KG, DC
Statistical analysis: DC
Obtained funding: Not applicable
Overall responsibility: NM

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Nonthermal, Nontumescent Endovenous Treatment of Varicose Veins

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Background: Endothermal treatment of the great saphenous vein has become the first line of treatment for superficial venous reflux. A new technique for venous insufficiency is non-thermal ablation with vein sealing system which comprises the endovenous delivery of cyanoacrylate tissue adhesive to the vein causing fibrosis.

Methods: This is a single-center prospective study of treatment of great saphenous vein incompetence in 62 patients with vein sealing system (Biolas VariClose® FG Group, Turkey). All cases were implemented under local anesthesia. Tumescent anesthesia was not required. Patients were not given any nonsteroidal anti-inflammatory drug postoperatively; advised to wear elastic bandages for 1 day; and compression stockings were not offered.

Results: Treatment success was defined as complete occlusion of treated vein or recanalized segment shorter than 5 cm. Subtotal recanalization was defined as great saphenous vein flow containing 5−10 cm segment of treated vein. A recanalized great saphenous vein or treatment failure was defined as an open part of the treated vein segment more than 10 cm in length. At 1 week and 1 month control, duplex scans showed total occlusion for all patients (100%), total occlusion for 58 patients (93.5%), and subtotal occlusion for 4 patients (6.5%) at third month. At the end of 6 months, total occlusion 56 patients (90.3%) and subtotal occlusion for 2 patients (3.2%). For 4 (6.5%) patients, no occlusion was observed, and the diameter was >11 mm. Embolization of great saphenous vein with cyanoacrylate has been performed since the beginning of this decade. Combined chemical and physical mechanism of action results in permanent vein closure. In a recently published study, a 24-month occlusion rate of 92% was demonstrated. The most commonly reported complications of cyanoacrylate use for the treatment of varicose vein disease, so far, include ecchymosis and phlebitis. Almeida et al. reported that phlebitis is the most frequent side effect at a rate of 16%. In our study, phlebitis rate was not as high as reported. It may be caused due to shorter time of follow-up in the hospital.

Conclusion: Endovenous ablation of incompetent great saphenous vein with cyanoacrylate-based glue is feasible. Operation time is short, and tumescent anesthesia is unnecessary as postprocedure compression stockings. Lack of significant side effects and an yearly success rate of 100% are benefits of the system.

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2018 CPT Code Issues

1) Absorbable perirectal spacer
    a. Code: CPT **55874** Transperineal placement of biodegradable material, peri-prostatic, single or multiple injection(s), including image guidance, when performed
    b. Background: An absorbable perirectal spacer is composed of biodegradable material that temporarily positions the anterior rectal wall away from the prostate during radiotherapy for prostate cancer with the intent to reduce the radiation dose delivered to the anterior rectum. The absorbable spacer maintains space for the entire course of prostate radiotherapy treatment and is completely absorbed by the patient's body over time. Currently, this is commercially available as the SpaceOAR System.
    c. **CMS NCD** (updated July 2017): perirectal spacers are not reasonable and necessary for treatment of illness in the Medicare population
        i. In summary, there is only one single-blinded randomized control trial of patients in which the spacer (SpaceOAR® system) has been implanted prior to receiving image-guided IMRT. Reports at 15 months and three years are available. The participants in the three-year study were volunteers agreeing to continue being assessed. There has been some evidence of reduced rectal toxicity in spacer patients. However, as noted above, there is a second peak for radiation toxicity at 4.5 years. Other studies are available without controls and with other radiation delivery methods. The studies generally show the procedure to be safe but Habl et al. (2016) stopped using the spacer gel due to the development of rectal fistulae in two patients. Coverage by other payers seems to be sparse, if at all. Although the device would seem to have promise, currently there is insufficient evidence to conclude that the it is reasonable and necessary for the treatment of illness (SSA § 1862 (a)(1)(A) in the Medicare population.
    d. HERC staff recommendation:
        i. Add CPT **55874** (Transperineal placement of biodegradable material, peri-prostatic, single or multiple injection(s), including image guidance, when performed) to line 660 CONDITIONS FOR WHICH CERTAIN TREATMENTS HAVE NO CLINICALLY IMPORTANT BENEFIT OR HAVE HARMS THAT OUTWEIGH BENEFITS; UNPROVEN TREATMENTS with an entry for GN173 as shown below

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

The following treatments are prioritized on Line 660, CONDITIONS FOR WHICH CERTAIN TREATMENTS HAVE NO CLINICALLY IMPORTANT BENEFIT OR HAVE HARMS THAT OUTWEIGH BENEFITS; UNPROVEN TREATMENTS for the conditions listed here:

CPT/HCPCS code	INTERVENTION	Rationale	Date of last Review
55874	Absorbable perirectal spacer for use during prostate cancer radiation therapy	Unproven treatment	November, 2017

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RECONSIDERATION REQUESTS

Transperineal placement of biodegradable material, peri-prostatic (via needle), single or multiple, includes image guidance; report supply of material separately- CPT code 0438T

December 2016 Response to Reconsideration

National Government Services has completed a review of your request to reconsider and revise our local coverage determination (LCD) for Category III CPT® Codes (LCD ID Number L33392) specifically regarding coverage for CPT code 0438T [Transperineal placement of biodegradable material, peri-prostatic (via needle), single or multiple, includes image guidance; report supply of material separately] **(**effective July 1, 2016), for the SpaceOAR® system. Thank you for the many references regarding spacers in patients receiving radiation therapy (RT) for prostate cancer (PC). The initial cadaver study (Susil, 2010)[1] as well as a recent trial (Mariados, 2015 and Pieczonka, 2016)[2,3] were included. Only the specific papers discussed here will be listed in this letter but the entire list (minus the abstracts and case reports) will be published with the local coverage determination (LCD).

Mariados et al. (2015)[2] reported on a prospective, randomized, controlled, multicenter trial with 222 patients with stage T1 or T2 prostate cancer. Computed tomography (CT) and magnetic resonance imaging (MRI) scans were performed for treatment planning, followed by placement of fiducial markers. Patients were then randomized 2:1 to receive a polyethylene glycol (PEG) prostate-rectal absorbable spacer (SpaceOAR® system) injection or no injection. The planning CTs and MRIs were repeated prior to image-guided intensity modulated radiation therapy (79.2 GY in 1.8-Gy fractions). A primary end-point of a ≥25% reduction in the rectal volume (rV70) was achieved in 97.3% of the spacer patients. The primary safety endpoint was the proportion of patients experiencing grade 1 or greater rectal or procedural adverse events (AEs) in the first six months. The treatment group had a reduction in pain during RT (spacer 2.7% and control 11.8%, $p = 0.022$) but overall there were no statistically significant differences in acute AEs between the treatment (34.2%) and control (31.5%) groups. There were also no differences between groups in urinary toxicity. Late rectal toxicity (3 – 15 months) was seen in 2.0% of the spacer patients and 7.0% of the controls which was statistically significant ($p = 0.044$). No differences were found in bowel and urinary quality-of-life (QOL) at three months and both groups had 5- and 10-point bowel QOL declines at 6, 12, and 15 months. There was a statistically significant difference ($p = 0.003$) in urinary QOL at six months between groups favoring the treatment group, but there was no difference at 15 months.

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Pieczonka et al. (2016)[3] also reported on the same group immediately above. Insertion of the spacer was described as "very easy" in 98.7% and successful in 99.3%. It was noted that the mean perirectal space was 12.6 mm after implant and 10.9 mm at 12.4 weeks, with absorption at 12 months.

Song et al. (2013)[4] conducted a prospective pilot clinical trial with 52 patients at four institutions. Spacer hydrogel was injected after CT and MRI planning scans with repeat scans after the injection. IMRT plans were composed using each set of CT and MRI scans. A prostate-rectal separation of $\geq$ 7.5 mm was achieved in 95.8% of the patients. A decreased rectal V70 $\geq$ 25% occurred in 95.7%. No significant differences were found in prostate, planning treatment volume (PTV), rectal, and bladder volumes. Four of the 52 patients were not successfully injected and a separate publication was planned detailing these occurrences. Acute toxicity was not addressed in this report. The author concluded statistically significant rectal dose reductions across the entire dose range occurred in > 90% of the patients.

Uhl et al. (2014)[5] reported on the 12-month toxicity of 52 patients who received IMRT (78 Gy) for localized prostate cancer along with a prostate-rectal PEG spacer. Injection was not successful in four and in the rectal wall in one patient, leaving 47 patients in the study. In addition to toxicity data at 3, 6, and 12 months, proctoscopy was performed at 12 months. Grade 1 acute rectal toxicity was noted in 19 (39.6%) and grade 2 in 6 (12.5%). No patients had grade 3 or 4 acute toxicity. Late grade 1 toxicity was experienced by 2 (4.3%), but none had grades 2, 3, or 4 toxicity. Grades 1, 2, and 3 genitourinary (GU) toxicity occurred in 20 (41.7%), 17 (35.4%), and 1 (2.1%), respectively. Forty-five of the 47 patients had proctoscopy at 12 months after IMRT treatment. Using the Vienna Rectoscopy Scale (VRS), 32 (71%) had a score of zero. Grade 2 congested mucosa was noted in 1 (3%) and telangiectasae were found in 28%: grade 1 - 13%, grade 2 – 13%, and grade 3 – 2%. Ulceration, stricture, or necrosis were not found.

Hatiboglu et al. (2012)[6] reported on 29 of the patients in the study immediately above. The method of selecting the 29 out of 52 patients is not described, and the study is described as prospective, single-arm, open-label performed at four institutions. Safety evaluation and performance of the spacer were the main objectives. Scans (CT and MRI) were performed prior to and after spacer injection and after IMRT at 3 and 6 months. An independent reviewer measured the distance between the prostate and rectum. " Functional" (7.5 mm space after spacer injection) and "clinical success" ($\geq$ 25% reduction in rectal V70) occurred in 28/29 (96.6%)

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and 26/27 (96.3%) of patients. Two patients were excluded due to technical difficulties loading their data for review.

Whalley et al. (2016)[7] studied 30 patients with T1-T3 prostate cancer for whom dose-escalated radiation therapy was considered appropriate and who were enrolled in a Phase I/II trial. A contemporary control group of 110 patients receiving the same dose was identified for comparison. Primary endpoints were comparison of the rectal volume receiving 30 – 82 Gy and post-operative toxicity. Secondary end-points were acute and late toxicity. Hydrogel (spacer) was successfully injected into 29 patients with injection into the rectal lumen in one. Mean difference of rectal - prostate separation was 10.5 mm. Toxicity related to the injection occurred in five but resolved within a week. Acute radiation gastrointestinal (GI) toxicity occurred in 13 (43%), which was primarily increased stool frequency. It was noted that stool softeners had been prescribed. Two patients had grade 1 rectal bleeding. There was no $\geq$ 2 stage acute gastrointestinal toxicity. Late grade 1 GI toxicity of increased stool frequency occurred in five (16.6%) spacer patients. One patient received laser coagulation at 13 months and at 18 months the bleeding had not recurred. In the control group, acute grade 1 toxicity occurred in 56 (50.6%) and grade 2 in five (4.5%). Late grade 1 GI toxicity in the control patients was noted in 46 (41.8%) occurring at a median of 11.5 months after radiation with a range of 6 – 43 months. Symptoms were increased stool frequency and rectal bleeding not requiring intervention. Late grade 2 toxicity was seen in four (3.6%) patients and occurred at a median of 20 months. There was no grade 3 toxicity in either group. Late grade 1 toxicity was reduced in the spacer group compared to the control ($p = 0.04$) but there was no difference in late grade 2 toxicity. Median follow-up in this study was greater than two years. The authors noted that GI toxicity occurs at a median of 17 months with peaks at 1.5 and 4.5 years [Zelefsky et al. (2008)[8] and Odrazka et al. (2010)[9]].

Some of the literature provided endorsed that the injection of the PEG spacer is usually safe and without untoward events once the physician becomes familiar with the procedure. Habl et al. (2016)[10] stopped using the spacer gel due to the development of rectal fistulae in two patients and the fistulae were presumed to be due to the gradual accumulation of gel within the anterior rectal wall.

Other references provided described materials used to increase the distance between the prostate and rectum during radiation therapy for prostate cancer. Hyaluronic acid, human collagen, interstitial balloons, as well as synthetic polyethylene glycols have been used. The

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CPT code 0438T could be used for any of these substances and discussion here has only been related to the request for PEG coverage.

In summary, reports of use of the PEG spacer (SpaceOAR® system) in patients receiving radiation therapy noted it is usually easily injected but there are limited reports of safety issues. Several studies indicated that decreased radiation to the rectum occurs and acute GI toxicity is usually grade 1 and less than that in controls. However, there are few studies with controls. Also significant is that the results show variable findings for acute GI grade 2 toxicity as well as for late toxicity. Patient follow-up in the one randomized controlled trial was only 15 months. Late GI toxicity has been shown to have a median of 17 months with peaks at 1.5 and 4.5 years after the radiation therapy. Although the device seems promising, there is insufficient evidence at this point to show it would be reasonable and necessary for the treatment of illness (SSA § 1862 (a)(1)(A) in the Medicare population. Therefore, the non-coverage status will remain.

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[10] Habl G, Uhl M, Katayama S, et al. Acute toxicity and quality of life in patients with prostate cancer treated with protons or carbon ions in a prospective randomized phase II study – the IPI trial. *Int J Radiat Oncol*. 2016;95(1):435-443. controlled trial. *Urology Practice,* March 2016;3:141-146.

July 2017 Response to Reconsideration

National Government Services has completed a review of your request to reconsider and revise our local coverage determination (LCD) for Category III CPT® Codes (LCD ID Number L33392) specifically regarding coverage for CPT code 0438T [Transperineal placement of biodegradable material, peri-prostatic (via needle), single or multiple, includes image guidance; report supply of material separately] **(**effective July 1, 2016), for the SpaceOAR® system. Thank you for the recently published reference (Hamstra et al., 2017)[1] Please note that the full text article from Whalley et al. (2016)[2] was reviewed in a previous reconsideration request. A summary will be included in this letter. In addition, abstracts are not acceptable for our use in LCD reconsideration requests.

Hamstra et al. (2017)[1] reported on the population enrolled in the studies reported by Mariados et al, (2015)[3] and Pieczonka et al. (2016)[4]. The trial was a prospective, randomized, controlled, multicenter trial with 222 patients with stage T1 or T2 prostate cancer. Patients were blinded to randomization but the physicians were not. An independent Clinical Events Committee (CEC) was blinded to randomization and reviewed rectal and urinary adverse events using the National Cancer Institute's Common Terminology Criteria for Adverse Events (CTCAE). Computed tomography (CT) and magnetic resonance imaging (MRI) scans were performed for treatment planning, followed by placement of fiducial markers. Patients were then randomized 2:1 to receive a polyethylene glycol (PEG) prostate-rectal absorbable spacer (SpaceOAR® system) injection or no injection. The planning CTs and MRIs were repeated prior to image-guided intensity modulated radiation therapy (79.2 GY in 1.8-Gy fractions). A primary end-point of a ≥25% reduction in the rectal volume (rV70) was achieved in 97.3% of the spacer patients. The primary safety endpoint was the proportion of patients experiencing grade 1 or greater rectal toxicity or procedural adverse events (AEs) in the first six months. The treatment group had a reduction in pain during RT (spacer 2.7% and control 11.8%, p = 0.022) butoverall

there were no statistically significant differences in acute AEs between the treatment (34.2%) and control (31.5%) groups. There were also no differences between groups in urinary toxicity. Late rectal toxicity (3 – 15 months) was seen in 2.0% of the spacer patients and 7.0% of the controls which was statistically significant (p = 0.044). No differences were found in bowel and urinary quality-of-life (QOL) at three months and both groups had 5- and 10-point bowel QOL declines at 6, 12, and 15 months. There was a statistically significant difference (p = 0.003) in urinary QOL at six months between groups favoring the treatment group, but there was no difference at 15 months.

Hamstra et al. (2017)[1] studied the extended three-year follow-up data of the above subjects. Patient participation was voluntary and included 63% of both spacer (n=94) and control (n=46) patients. A comparison of the group volunteer members was not presented, except that there was no difference between groups regarding participation. A median follow-up of 37 months (range 26-46) occurred for the controls and 37.1 (range 32-47) months for the spacer subjects. Data showed the spacer group had a smaller volume of rectal radiation for all volumes from V50 to V80 (p< .0001). Relative reductions were 54% for V50, 79% for V70, and 96% for V80. Grade $\geq$1 rectal toxicity at three years was decreased by 75% in the spacer patients (spacer 2%, 95% CI 1%- 6%) and (control 9%, 95% CI 4% - 20%), p<.03. No grade $\geq$2 rectal toxicity was seen in the spacer patients with 6% in the control group and one case of grade 3. It was noted that the toxicity in the control group was less than usually reported and no explanation was available. There were no differences in grades 1 or 2 urinary toxicities between the groups at three years with the exception of urinary incontinence in 15% of the controls and 4% in the spacer group (p = .046).

The Expanded Prostate Cancer Index Bowel Composite (EPIC)[5] quality of life (QOL) and minimally important difference (MID)[6] tools were used to assess patient opinions of treatment. Bowel QOL declined in both groups in the first three months with return to baseline at six months. At three years the spacer group was near or greater than baseline, but the control group had decreased (p=.002). Differences were at the 5 point level of MID but not at the 10 point level. A correlation between an increasing rectal V50 to V80 and a decline in bowel QOL was found. Urinary QOL also declined in both groups in the first three months with return to baseline at six months. At three years, there was a statistical difference between the two groups favoring the spacer group, but it did not meet the MID level. However, it was also stated that there was a statistically significant difference between the groups regarding urinary frequency favoring the spacer arm (5%) versus the controls (18%) p = .05. No differences were found in the sexual QOL or vitality/hormonal QOL.

Whalley et al. (2016)[2] studied 30 patients with T1-T3 prostate cancer for whom dose-escalated radiation therapy was considered appropriate and who were enrolled in a Phase I/II trial. A contemporary control group of 110 patients receiving the same dose was identified for comparison. Primary endpoints were comparison of the rectal volume receiving 30 – 82 Gy and post-operative toxicity. Secondary end-points were acute and late toxicity. Hydrogel (spacer) was successfully injected into 29 patients with injection into the rectal lumen in one. Mean difference of rectal - prostate separation was 10.5 mm. Toxicity related to the injection occurred

in five but resolved within a week. Acute radiation gastrointestinal (GI) toxicity occurred in 13 (43%), which was primarily increased stool frequency. It was noted that stool softeners had been prescribed. Two patients had grade 1 rectal bleeding. There was no ≥ 2 stage acute gastrointestinal toxicity. Late grade 1 GI toxicity of increased stool frequency occurred in five (16.6%) spacer patients. One patient received laser coagulation at 13 months and at 18 months the bleeding had not recurred. In the control group, acute grade 1 toxicity occurred in 56 (50.6%) and grade 2 in five (4.5%). Late grade 1 GI toxicity in the control patients was noted in 46 (41.8%) occurring at a median of 11.5 months after radiation with a range of 6 – 43 months. Symptoms were increased stool frequency and rectal bleeding not requiring intervention. Late grade 2 toxicity was seen in four (3.6%) patients and occurred at a median of 20 months. There was no grade 3 toxicity in either group. Late grade 1 toxicity was reduced in the spacer group compared to the control ($p = 0.04$) but there was no difference in late grade 2 toxicity. Median follow-up in this study was greater than two years. The authors noted that GI toxicity occurs at a median of 17 months with peaks at 1.5 and 4.5 years [Zelefsky et al. (2008)[7] and Odrazka et al. (2010)[8]].

In summary, there is only one single-blinded randomized control trial of patients in which the spacer (SpaceOAR® system) has been implanted prior to receiving image-guided IMRT. Reports at 15 months and three years are available. The participants in the three-year study were volunteers agreeing to continue being assessed. There has been some evidence of reduced rectal toxicity in spacer patients. However, as noted above, there is a second peak for radiation toxicity at 4.5 years. Other studies are available without controls and with other radiation delivery methods. The studies generally show the procedure to be safe but Habl et al. (2016)[9] stopped using the spacer gel due to the development of rectal fistulae in two patients. Coverage by other payers seems to be sparse, if at all. Although the device would seem to have promise, currently there is insufficient evidence to conclude that the it is reasonable and necessary for the treatment of illness (SSA § 1862 (a)(1)(A) in the Medicare population. We will be happy to review additional literature as it develops. The device will be presented as a draft LCD so there will be an opportunity for public and Contractor Advisory Committee (CAC) comments during the next CAC cycle.

[1] Hamstra d, Mariados N, Sylvester J et al. Continued benefit to rectal separation for prostate radiation therapy: final results of a phase III trial. *Int J Radiat Oncol Biol Phys.*2017;97(5):976-985,

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[3] Mariados N, Sylvester J, Shah D, et al. Hydrogel spacer prospective multicenter randomized controlled pivotal trial: dosimetric and clinical effects of perirectal spacer application in men undergoing prostate image guided intensity modulated radiation therapy. *Int J Radiat Oncol Biol Phys.* 2015;92(5):971-977.

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controlled trial. *Urology Practice,* March 2016;3:141-146.

[5] Wei JT, Dunn RL, Litwin MS et al. Development and validation of the expanded prostate cancer index composite (EPIC) for comprenesive ssessment of health-related quality of life in men with prostate cancer. *Urology.* 2000;56:899-905.

[6] Skolarus TA, Dunn RL, Sandra MG et al. Minimally important difference for the expanded prostate cancer index composite short form. *Urology.* 2015;85(1):101-105.

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[8] Odraska K, Dolezel M, Vanasek J et al. Time course of late rectal toxicity after radiation therapy for prostate cancer. *Prostate Cancer and Prostatic Diseases.* 2010;13:138-143.

[9] Habl G, Uhl M, Katayama S, et al. Acute toxicity and quality of life in patients with prostate cancer treated with protons or carbon ions in a prospective randomized phase II study – the IPI trial. *Int J Radiat Oncol*. 2016;95(1):435-443.

2018 CPT Code Review Issues

1) Nerve repair with nerve allografts
    a. Codes:
        i. CPT **64912** Nerve repair; with nerve allograft, each nerve, first strand
        ii. CPT **64913** each additional strand
    b. Background: Transplantation of a cadaver donor nerve (or nerve segment) into a recipient for the repair and closure of a nerve gap resulting from a peripheral nerve injury. Nerve allograft transplantation from cadavers offers an alternative without the morbidities associated with nerve autografts, but these grafts are rapidly rejected unless appropriate immunosuppression is achieved. There is a newer technology were the nerve allograft is processed to remove cellular components, and then acts as a substrate for the host to rebuild the nerve pathway. Such decellular nerve allografts do not require immunosuppression. Alternative therapies include nerve autograft (transplantation of nerve from elsewhere in the patient's own body), and synthetic nerve conduits for nerve regrowth. Nerve autograft is considered standard of care.
    c. Evidence
        i. Only animal studies and small case series identified
    d. Expert input
        i. orthopedic hand surgeon in southern Oregon: "Nerve allografts are becoming increasing popular. They are pretty much accepted as a good option for sensory nerve repair, but are controversial for mixed motor/sensory nerves. There is a large, multicenter trial --RANGER--sponsored by Axogen with ongoing data collection. I've used the allografts a number of times for sensory nerves with acceptable results. I continue to use autograft for mixed motor/sensory or any critical sensory area (eg ulnar digital to thumb, radial digital to index/long)"
            1. Note: the RANGER study is examining processed nerve tissue allograft. Study completion is expected in December 2020.
    e. Other policies:
        i. Decellular nerve allografts are currently under review by NICE
        ii. It is unclear whether major insurers cover nerve allograft
    f. HERC staff summary: Nerve allografts appear to be an experimental therapy. Standard nerve autografts are covered for nerve injuries on the Prioritized List. NICE is currently reviewing decellular nerve allografts; this topic should be revisited when the NICE review is completed and the results of the RANGER trial are published.
    g. HERC staff recommendation:
        i. Add CPT **64912**-**64913** (Nerve repair; with nerve allograft, each nerve) to line 660 CONDITIONS FOR WHICH CERTAIN TREATMENTS HAVE NO CLINICALLY IMPORTANT BENEFIT OR HAVE HARMS THAT OUTWEIGH BENEFITS; UNPROVEN TREATMENTS with an entry for GN173 as shown below

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

The following treatments are prioritized on Line 660, CONDITIONS FOR WHICH CERTAIN TREATMENTS HAVE NO CLINICALLY IMPORTANT BENEFIT OR HAVE HARMS THAT OUTWEIGH BENEFITS; UNPROVEN TREATMENTS for the conditions listed here:

CPT/HCPCS code	INTERVENTION	Rationale	Date of last Review
64912-64913	Nerve repair; with nerve allograft	Unproven treatment	November, 2017

2018 CPT Code Issues
Oncology Tests

1) IDH1/2 tumor markers for glioma
    a. Codes:
        i. CPT **81120** IDH1 (isocitrate dehydrogenase 1 [NADP+], soluble) (eg, glioma), common variants (eg, R132H, R132C)
        ii. CPT **81121** IDH2 (isocitrate dehydrogenase 2 [NADP+], mitochondrial) (eg, glioma), common variants (eg, R140W, R172M)
    b. Background: IDH1 and 2 are tumor markers commonly used by neuropathologists to facilitate characterizations of gliomas and used by neuro-oncologists to guide treatment decisions
    c. **NCCN 2017**, treatment of CNS malignancies
        i. Can help identify a glioblastoma as being a secondary glioblastoma (one that has transformed from a lower grade glioma and generally does not behave as aggressively as a primary glioblastoma). IDH1 and 2 mutations are associated with a favorable prognosis and are important in stratification for clinical trials. IDH1 or 2 mutations are associated with survival benefit for patients treatment with radiation or alkylator chemotherapy.
    d. HERC staff recommendation
        i. Add CPT **81120** IDH1 (isocitrate dehydrogenase 1 [NADP+], soluble) (eg, glioma), common variants (eg, R132H, R132C) and CPT **81121** IDH2 (isocitrate dehydrogenase 2 [NADP+], mitochondrial) (eg, glioma), common variants (eg, R140W, R172M) to the Diagnostic Procedures File

2) ASXL gene analysis for myelodysplastic syndrome
    a. Codes
        i. CPT **81175** ASXL1 (additional sex combs like 1, transcriptional regulator) (eg, myelodysplastic syndrome, myeloproliferative neoplasms, chronic myelomonocytic leukemia), gene analysis; full gene sequence
        ii. CPT **81176** ASXL1 (additional sex combs like 1, transcriptional regulator) (eg, myelodysplastic syndrome, myeloproliferative neoplasms, chronic myelomonocytic leukemia), gene analysis; targeted sequence analysis (eg, exon 12)
    b. **NCCN 2018**, treatment of myelodysplastic syndromes
        i. ASXL are tumor markers that can help refine the prognosis of MDS in patients risk stratified by the IPSS or IPSS-R and may be helpful in patients predicted to have intermediate risk. ASXL1 is independently associated with a poorer prognosis in MDS and CMML.
    c. HERC staff recommendation
        i. Add CPT **81175** ASXL1 (additional sex combs like 1, transcriptional regulator) (eg, myelodysplastic syndrome, myeloproliferative neoplasms, chronic myelomonocytic leukemia), gene analysis; full gene sequence and CPT **81176** ASXL1 (additional sex combs like 1, transcriptional regulator) (eg,

myelodysplastic syndrome, myeloproliferative neoplasms, chronic myelomonocytic leukemia), gene analysis; targeted sequence analysis (eg, exon 12) to the Diagnostic Procedures File

3) RUNX1 in acute myeloid leukemia
    a. Code: CPT **81334** RUNX1 (runt related transcription factor 1) (eg, acute myeloid leukemia, familial platelet disorder with associated myeloid malignancy), gene analysis, targeted sequence analysis (eg, exons 3-8)
    b. **NCCN 2017**, treatment of myelodysplastic syndromes
        i. Acute myeloid leukemia (AML) with a RUNX1 mutation has a poorer prognosis. Studies have been conducted that indicated that a RUNX1 mutation is a predictor of relapse after chemotherapy.
    c. HERC staff recommendation
        i. Add CPT **81334** RUNX1 (runt related transcription factor 1) (eg, acute myeloid leukemia, familial platelet disorder with associated myeloid malignancy), gene analysis, targeted sequence analysis (eg, exons 3-8)to the Diagnostic Procedures File

2018 CPT Code Issues

1) Gene expression profiling for breast and prostate cancer
    a. Codes:
        i. CPT **81520** Oncology (breast), mRNA gene expression profiling by hybrid capture of 58 genes (50 content and 8 housekeeping), utilizing formalin-fixed paraffin-embedded tissue, algorithm reported as a recurrence risk score
            1. Likely to be used for PAM50 test, not previously reviewed
        ii. CPT **81521** Oncology (breast), mRNA, microarray gene expression profiling of 70 content genes and 465 housekeeping genes, utilizing fresh frozen or formalin-fixed paraffin-embedded tissue, algorithm reported as index related to risk of distant metastasis
            1. Likely to be used for Mammaprint, called out for non-coverage in GN148
        iii. CPT **81541** Oncology (prostate), mRNA gene expression profiling by real-time RT-PCR of 46 genes (31 content and 15 housekeeping), utilizing formalin-fixed paraffin-embedded tissue, algorithm reported as a disease-specific mortality risk score
            1. Likely to be used for Prolaris, called out for non-coverage in GN148
    b. Current guideline regarding these tests, based on the previous HTAS review of this topic:

GUIDELINE NOTE 148, BIOMARKER TESTS OF CANCER TISSUE

Lines 161,188,195,234,267,275,334

The use of multiple molecular testing to select targeted cancer therapy (CPT 81504) is included on the Services recommended for non-coverage table.

For breast cancer, Oncotype Dx testing (CPT 81519, HCPCS S3854) is included on Line 195 only for early stage breast cancer when used to guide adjuvant chemotherapy treatment decisions for women who are lymph node negative. Oncotype Dx is not included on this line for lymph node-positive breast cancer. Mammaprint, ImmunoHistoChemistry 4 (IHC4), and Mammostrat for breast cancer are included on the Services recommended for noncoverage table.

For melanoma, BRAF gene mutation testing (CPT 81210) is included on Line 234.

For lung cancer, epidermal growth factor receptor (EGFR) gene mutation testing (CPT 81235) is included on Line 267 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 161. BRAF (CPT 81210) and Oncotype DX are not included on this line. Microsatellite instability (MSI) is included on the Services recommended for noncoverage table.

For bladder cancer, Urovysion testing is included on Services recommended for noncoverage table.

For prostate cancer, Oncotype DX is not included on Line 334 and Prolaris is included on the Services recommended for noncoverage table.

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

c. Background: Various types of gene analysis on tumor tissue with subsequent algorithmic analysis can predict aggressiveness of disease and may help in clinical management of breast or prostate cancer
d. HTAS review: both gene analysis of breast cancer and prostate cancer are currently under review at HTAS, as an update to the previous coverage guidance on this topic. The prostate cancer review is expected to be completed by late November and the breast cancer review by spring of 2018.
e. HERC staff recommendation:
    i. Create a new section to GN173 excluding new health technologies currently under review until the review can be completed and HERC can make a final decision on prioritization of the technology
        1. **CPT 81520**
    ii. Two of the three tests were previously reviewed and recommended for non-coverage; therefore, placement on GN173 is appropriate unless and until HTAS changes their coverage recommendation
        1. **CPT 81521 and 81541**

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

The following treatments are prioritized on Line 660, CONDITIONS FOR WHICH CERTAIN INTERVENTIONS HAVE NO CLINICALLY IMPORTANT BENEFIT OR HAVE HARMS THAT OUTWEIGH BENEFITS; UNPROVEN INTERVENTIONS for the conditions listed here:

CPT/HCPCS code	INTERVENTION	Rationale	Date of last Review
81521	Oncology (breast), mRNA, microarray gene expression profiling of 70 content genes and 465 housekeeping genes	Unproven intervention	August, 2015
81541	Oncology (prostate), mRNA gene expression profiling by real-time RT-PCR of 46 genes (31 content and 15 housekeeping)	Unproven intervention	August, 2015
NEW HEALTH TECHNOLOGIES CURRENTLY UNDER REVIEW			
81520	Gene expression profiling algorithm for breast cancer mRNA gene expression profiling by hybrid capture of 58 genes (50 content and 8 housekeeping),	Under review by HTAS	N/A

2018 CPT Code Review Issues

1) Prostate promoter methylation profiling
    a. Code: CPT **81551** Oncology (prostate), promoter methylation profiling by real-time PCR of 3 genes (GSTP1, APC, RASSF1), utilizing formalin-fixed paraffin-embedded tissue, algorithm reported as a likelihood of prostate cancer detection on repeat biopsy
    b. Background: Silencing of tumor suppressor genes through DNA methylation is a key process in the onset and progression of cancer. Testing prostate biopsy samples for the presents of DNA methylation has been proposed as a predictive test to determine which patients are at high or low risk of having prostate cancer found on future biopsies
    c. Evidence:
        i. **Van Neste 2016**, cohort study
            1. N=803 patients
            2. The NPV of finding low levels of DNA-methylation in the combined cohort was 89.2% for all cancers. The positive predictive value (PPV) of the epigenetic assay performed on the index biopsies was 28.2% for detecting any cancer upon repeat biopsy.
            3. Conclusions: The risk score, comprising DNA-methylation intensity and traditional clinical risk factors, improved the identification of men with high-grade cancer, with a maximum avoidance of unnecessary repeat biopsies. This risk score resulted in better patient risk stratification and significantly outperformed current risk prediction models such as PCPTRC and PSA. The risk score could help to identify patients with histopathologically negative biopsies harboring high-grade prostate cancer.
            4. Study authors were employees of the company marketing the EpiScore test
        ii. **Van Neste 2017**, cohort study
            1. N=102 patients
            2. EpiScore was significantly higher for subjects with high-grade biopsies and higher NCCN risk categories (both $P < 0.001$). In patients diagnosed with GS ≥ 7, increased levels of DNA-methylation were present, not only in the high-grade biopsy cores, but also in other cores with no or low-grade disease ($P < 0.001$). By combining EpiScore with traditional clinical risk factors into a logistic regression model, the prediction of high GS reached an AUC of 0.82 (95%CI: 0.73-0.91) with EpiScore, DRE, and atypical histological findings as most important contributors.
            3. Conclusions: In men diagnosed with PCa, DNA-methylation profiling can detect under-sampled high-risk PCa in prostate biopsy specimens through a field effect. Predictive accuracy increased when EpiScore was combined with other clinical risk factors. These results suggest that EpiScore could aid in the detection of occult highgrade disease at the time of diagnosis, thereby improving the selection of candidates for Active Surveillance.
            4. Study authors were employees of the company marketing the EpiScore test

iii. Expert guidelines
    1. EpiScore is not mentioned in **NCCN 2017** Early Detection of Prostate Cancer

iv. HERC staff summary: EpiScore appears to be an experimental test at this time based on limited research and lack of inclusion in NCCN guidelines

v. HERC staff recommendation:
    1. Add CPT **81551** Oncology (prostate), promoter methylation profiling by real-time PCR of 3 genes (GSTP1, APC, RASSF1), utilizing formalin-fixed paraffin-embedded tissue, algorithm reported as a likelihood of prostate cancer detection on repeat biopsy to line 660 CONDITIONS FOR WHICH CERTAIN TREATMENTS HAVE NO CLINICALLY IMPORTANT BENEFIT OR HAVE HARMS THAT OUTWEIGH BENEFITS; UNPROVEN TREATMENTS with an entry for GN173 as shown below

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

The following treatments are prioritized on Line 660, CONDITIONS FOR WHICH CERTAIN INTERVENTIONS HAVE NO CLINICALLY IMPORTANT BENEFIT OR HAVE HARMS THAT OUTWEIGH BENEFITS; UNPROVEN INTERVENTIONS for the conditions listed here:

CPT/HCPCS code	INTERVENTION	Rationale	Date of last Review
81551	Oncology (prostate), promoter methylation profiling by real-time PCR of 3 genes (GSTP1, APC, RASSF1)	Unproven intervention	November, 2017

Risk Score Predicts High-Grade Prostate Cancer in DNA-Methylation Positive, Histopathologically Negative Biopsies

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BACKGROUND. Prostate cancer (PCa) diagnosis is challenging because efforts for effective, timely treatment of men with significant cancer typically result in over-diagnosis and repeat biopsies. The presence or absence of epigenetic aberrations, more specifically DNA-methylation of *GSTP1*, *RASSF1*, and *APC* in histopathologically negative prostate core biopsies has resulted in an increased negative predictive value (NPV) of ∼90% and thus could lead to a reduction of unnecessary repeat biopsies. Here, it is investigated whether, in methylation-positive men, DNA-methylation intensities could help to identify those men harboring high-grade (Gleason score ≥7) PCa, resulting in an improved positive predictive value.

METHODS. Two cohorts, consisting of men with histopathologically negative index biopsies, followed by a positive or negative repeat biopsy, were combined. EpiScore, a methylation intensity algorithm was developed in methylation-positive men, using area under the curve of the receiver operating characteristic as metric for performance. Next, a risk score was developed combining EpiScore with traditional clinical risk factors to further improve the identification of high-grade (Gleason Score ≥7) cancer.

RESULTS. Compared to other risk factors, detection of DNA-methylation in histopathologically negative biopsies was the most significant and important predictor of high-grade cancer, resulting in a NPV of 96%. In methylation-positive men, EpiScore was significantly higher for those with high-grade cancer detected upon repeat biopsy, compared to those with either no or low-grade cancer. The risk score resulted in further improvement of patient risk stratification and was a significantly better predictor compared to currently used metrics as PSA and the prostate cancer prevention trial (PCPT) risk calculator (RC). A decision curve

Grant sponsor: MDxHealth.

Leander Van Neste and Alan W. Partin contributed equally to this work.

Conflicts of interest: LVN and WVC are employees of or consulting for MDxHealth and may have corporate stock or stock options.

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analysis indicated strong clinical utility for the risk score as decision-making tool for repeat biopsy.

CONCLUSIONS. Low DNA-methylation levels in PCa-negative biopsies led to a NPV of 96% for high-grade cancer. The risk score, comprising DNA-methylation intensity and traditional clinical risk factors, improved the identification of men with high-grade cancer, with a maximum avoidance of unnecessary repeat biopsies. This risk score resulted in better patient risk stratification and significantly outperformed current risk prediction models such as PCPTRC and PSA. The risk score could help to identify patients with histopathologically negative biopsies harboring high-grade PCa. *Prostate 76:1078–1087, 2016.* © 2016 The Authors. *The Prostate* Published by Wiley Periodicals, Inc.

KEY WORDS: **DNA methylation; epigenetics; prostate neoplasms; significant cancer; high-grade; repeat biopsy; logistic regression**

INTRODUCTION

Prostate cancer (PCa) patient management is challenging when trying to achieve high sensitivity, in order not to miss clinically significant cancer, while retaining high specificity, to avoid false positives. Effective, timely treatment of potential aggressive PCa can be achieved through early detection by adequate screening, for example, by means of prostate-specific antigen (PSA) [1,2]. However, these same first-line diagnostic techniques quite often result in over-diagnosis and over-treatment of patients with indolent disease and unnecessary biopsies [3–6]. In the US alone, over one million biopsies are performed each year, with ~25% of these resulting in a PCa diagnosis [7]. Furthermore, only a fraction of these would be considered at high risk for harboring clinically significant, aggressive PCa [8].

No single biomarker has proven to be efficient enough to be used as the sole diagnostic or prognostic tool. While serum PSA is easy to assess, there is no optimal cut point simultaneously resulting in high sensitivity and specificity as high-grade tumors can be missed even when applying low PSA cutoffs [1,9]. Histopathological examination of prostate biopsies, the diagnostic gold standard, suffers from a sampling bias, due to a limited amount of the prostate tissue being examined [10–12]. When, over time, risk factors persist and the risk for missed PCa is considered too high, those men will undergo one or more repeat biopsies. However, because the high false positive rate [9], these (repeat) biopsies can be an unnecessary patient burden and healthcare cost, and can also lead to complications [13,14].

Epigenetic profiling by determining the DNA-methylation status of *GSTP1*, *APC*, and *RASSF1* has been validated in two large, independent cohorts to be able to increase the negative predictive value (NPV) for men with PCa-negative biopsy tissue. When no methylation of either one of these three markers is detected in any of the residual tissues from previously cancer-negative prostate biopsy cores, this biomarker panel has been shown to result in an NPV of 88–90% for all PCa [15,16]. This is a significant increase over the gold standard histopathological evaluation of these same biopsies and could result in a decrease in unnecessary repeat biopsies [17].

Due to the high rate of unnecessary (repeat) biopsies, attention has shifted towards identifying men with significant PCa, often characterized as the presence of Gleason pattern four or five, non-organ-confined disease and larger tumor volume [18]. In addition, patients with insignificant or low-risk disease under active surveillance, are at risk for disease reclassification, upgrading and upstaging, warranting faster radical treatment for these men [19–22]. A large, contemporary study in over 34,000 men found that Gleason score (GS) upgrading in GS6 patients is still very frequent when comparing the clinical and pathological scores [23,24].

In current clinical practice, multimodal approaches are used, with experts integrating several information sources to determine the best course of action for each patient. This entails both classical clinical risk factors, such as digital rectal examination (DRE) and histopathological examination of biopsy tissue, and traditional biomarkers, such as PSA. More recently, better molecular biomarkers with higher specificity for PCa have been introduced into clinical practice to improve patient management, in particular DNA-methylation profiling of *GSTP1*, *RASSF1*, and *APC* [25,26]. The goal of this study is to evaluate the performance of an existing DNA-methylation assay [15,16], to predict men at risk of harboring high-grade cancer. Interestingly, the three genes involved in this assay have all been associated with PCa prognosis and might therefore also be predictive of PCa aggressiveness [27,28]. Therefore, two main objectives were set; first, absence or low levels of DNA-methylation of the genes in the assay should reach a high NPV for high-grade cancer, and second, assay-positive patients should be further accurately stratified according to the risk of harboring high-grade cancer.

MATERIALS AND METHODS

Two previously published cohorts, of which all patients had two consecutive biopsies within 24–30 months, were combined into one set of 803 patients [15,16]. Each center received institutional review board approval, exemption, or waiver to use archived clinical samples for research purposes (Western General Hospital, Edinburgh, UK; University Hospital of Liège, Belgium; Institut de Pathologie et Génétique, Belgium; Cleveland Clinic, USA; Eastern Virginia Medical School, USA; Lahey Hospital and Medical Center, USA; Johns Hopkins University, USA; University of California Los Angeles, USA). Because this is a non-interventional, retrospective, subject-anonymized study, written patient consent was not required by the ethics committees. All men had a negative index biopsy followed by either a positive (179 men) or negative (624 men) repeat biopsy. The cohorts were joined and annotation was harmonized for histopathology of the first, PCa-negative biopsy, that is, benign, high-grade prostatic intraepithelial neoplasia (HGPIN) or atypia, and DRE, that is, normal or abnormal.

The DNA-methylation profile based on *GSTP1*, *RASSF1*, and *APC* was measured using quantitative real-time PCR as described before [15,16]. Besides the final assay result per patient (methylation positive or negative), the methylation intensity of each individual marker in each core of the index biopsy was evaluated.

Patients were classified according to the histopathological outcome of the repeat biopsy. Men with high-grade PCa (GS $\geq$7) detected upon repeat biopsy (n = 67) were considered high-risk patients, while men with GS $\leq$6 disease (n = 106) potentially/likely have indolent PCa. Six PCa patients (3.4%) were not classified due to incomplete Gleason scoring. Men without PCa detected, after repeat biopsy, are considered control patients, although cancer could be missed due to biopsy sampling error.

Patients are also stratified according to their overall methylation status (positive or negative) as determined in MATLOC and DOCUMENT [15,16]. Only 36.2% of all control patients are methylation positive, compared to almost the double (64.8%) for men with cancer detected upon repeat biopsy. A risk score was developed to improve stratification of methylation-positive patients according to their risk of harboring occult, high-grade cancer. In addition to the epigenetic profiling, the contribution of standard risk factors, that is, histopathology of the negative index biopsy, digital rectal examination, PSA, and age were considered. Clinical risk was also examined by the risk calculator (RC) of the prostate cancer prevention trial (PCPT) [29]. Logistic regression models were optimized and the final selection was based on the overall predictive accuracy as measured by the area under the curve (AUC) of the receiver operating characteristic (ROC) and DeLong confidence intervals.

All statistical analyses were performed in R [30]. Continuous variables are compared with either Welch's *t*-test or the Mann–Whitney–Wilcoxon test for two samples, and ANOVA or Kruskal–Wallis test for more samples. The χ^2 or Fisher's exact test was applied to assess the significance of frequency distributions and a binomial test was applied when comparing proportions. *P*-values were corrected using the false discovery rate for multiple hypothesis testing, resulting in a *q*-value [31]. Calculations that are dependent on prevalence all made used of the overall cancer detection rate upon repeat biopsy observed in MATLOC, that is, 18%. Finally, clinical utility was determined used a decision curve analysis (DCA), and executed with the available R package [32].

RESULTS

Combined Cohort Description

A total of 7,899 prostate core biopsies from 803 patients in the unified cohort were epigenetically profiled. The most important clinical and demographic characteristics are shown in Table I. Each individual patient typically had 10 evaluable cores and the repeat biopsy often took place within 1 year of the index biopsy. The NPV of finding low levels of DNA-methylation in the combined cohort was 89.2% for all cancers. The positive predictive value (PPV) of the epigenetic assay performed on the index biopsies was 28.2% for detecting any cancer upon repeat biopsy. Of note, none of these cancers were identified at the time of the index biopsy, and based on the cancer detection rate after repeat biopsy, the epigenetic assay had a significantly increased PPV ($P < 0.001$) compared to current clinical practice. Of the traditional clinical risk factors, only histopathology was significantly different between the distinct groups, however, this did not allow a straightforward separation between controls, patients with low-grade cancer and men with high-grade cancer.

Limiting Delayed Diagnosis of High-Grade Cancer

While no tumors were found at time of the index biopsy, both high- and low-grade disease were found during repeat biopsy. Here, 106 out of 173 men with PCa had GS6 disease, thus 38.7% of all cancers identified at repeat biopsy were considered clinically

TABLE I. Main Clinical and Demographic Characteristics of the Combined MATLOC and DOCUMENT Cohorts

	Group			
	Controls	GS ≤6	GS ≥7	*P*
n	624	106	67	
PSA (ng/ml)				
Mean/median	6.85/5.6	7.19/5.0	8.26/6.0	0.117
DRE				
% Abnormal	31.3%	29.8%	38.8%	0.520
Histopathology				
%HGPIN	22.8%	33.0%	19.4%	<0.001
%Atypia	6.7%	17.9%	13.4%	
Age				
Mean/median	62.5/62.0	63.3/64.0	65.6/66.0	<0.001
Evaluable cores				
Mean/median	9.9/10	9.6/10	9.4/10	0.265
Time between biopsies (months)				
Mean/median	12.5/9.2	9.8/8.5	12.0/11.1	0.178

significant, based on the clinical grade. High-grade cancer is found in merely 7.0% (18% of men will have PCa detected upon repeat biopsy, of which 38.7% will have high-grade [GS ≥7] disease) of men undergoing repeat biopsy. Because frequent upgrading of GS6 patients, the NPV of high-grade cancer cannot easily be determined based on clinical GS. When including all patients with clinical GS6 as control, a lower boundary for the NPV for high-grade cancer of 95.7% was obtained. When GS6 patients were omitted from the calculations, the NPV was 95.9% for high-grade cancer.

Stratifying Methylation-Positive Men for High-Grade PCa Risk

From the entire cohort, a subset consisting of the 43 men with high-grade PCa and the 226 men without PCa detected in a repeat biopsy was taken, however, all of which had a DNA-methylation positive index biopsy. This subset was used to evaluate whether men with high-grade PCa can be identified by determining DNA-methylation intensities in their PCa-negative index biopsies. GS6 patients were not included due to the high reclassification risk of under-graded disease. Several methylation parameters were evaluated, that is, the relative number of methylation positive cores, the relative number of methylation events, and the number of distinct, methylated genes. These methylation-based metrics were compared with traditional risk factors in their ability to identify men with high-grade PCa, but with histopathologically cancer-negative biopsies (Table II). DNA-methylation metrics and age at the time of the index biopsy were significantly higher in the men with high-grade PCa upon repeat biopsy. Pathology, PSA and DRE did not perform better than random (all $P > 0.05$; Table II).

EpiScore: Measuring Epigenetic Risk Via DNA-Methylation Intensity

Because the level of DNA methylation was the most significant and strongest predictor (Table II) of a methylation-positive man having high-grade cancer detected upon repeat biopsy, a general epigenetic risk score was developed based on methylation intensities of the three genes in individual cores. Per core, the methylation intensity of each gene was divided by a normalization factor, optimally weighing each gene's contribution. These normalized intensities were added per core and subsequently averaged over all evaluable cores per patient, to obtain one final epigenetic score. This EpiScore summarizes all available methylation signals that can help in identifying men with high-grade PCa detected upon repeat biopsy, that is, methylation intensity, number of methylated cores, and number of methylated genes.

A saturation parameter was applied to avoid overweighing a limited number of patients with very high methylation signals. Gene weights and the saturation

TABLE II. Univariate Analysis of All Available Traditional and Molecular Risk Factors

Risk factor	AUC	95%CI	*P*-value
PSA (continuous or log-transformed)	0.574	0.481–0.667	0.151
PSA (three categories: <4, ≥4 and <10, >10)	0.550	0.476–0.625	0.157
PSA (two categories:<10, ≥10)	0.493	0.432–0.554	1.000
PSA (continuous when ≥4, otherwise 0)	0.569	0.474–0.664	0.179
PSA (continuous when ≥10, otherwise 0)	0.497	0.433–0.561	0.924
DRE	0.529	0.432–0.626	0.549
Pathology	0.486	0.400–0.572	0.152
Pathology (only presence of atypia)	0.532	0.477–0.587	0.228
Age	0.632	0.544–0.720	0.006
#Cores methylated	0.635	0.541–0.730	0.005
#Methylation events	0.661	0.572–0.751	0.001
#Distinct genes methylated	0.596	0.522–0.671	0.002

Performance of the risk factor was measured as the AUC of the ROC and as the significance when comparing the controls to the GS ≥7 patients (Fisher's exact test for categorical variables and a Mann–Whitney–Wilcoxon test for numerical variables).

parameters were exhaustively optimized to reach a maximal AUC of 0.742 (Fig. 1). In addition to the AUC, the mean EpiScore for the control group was compared to that in the group of men with high-grade PCa during the optimization process, to assure robustness of the algorithm, and only models with $q < 0.001$ were retained. In the final model, EpiScore was significantly higher for those men with high-grade PCa detected upon repeat biopsy compared to those with a non-cancer diagnosis ($P < 0.001$; Fig. 2).

EpiScore and Potentially Indolent Cancer

As an additional test of robustness of the algorithm, EpiScore was calculated for methylation-positive men with likely indolent disease (GS $\leq$6), detected at time of repeat biopsy. This confirmed the original hypothesis concerning these men, with intermediate EpiScores compared to the other two groups (Fig. 2). Indeed, overall there were significant differences between the three groups ($P < 0.001$). A more detailed analysis of the differences indicated significantly higher EpiScores for those men with high-grade disease versus the control group ($P < 0.001$) and the men with GS6 PCa detected upon repeat biopsy ($P < 0.001$), while the increase of EpiScore for GS6 patients versus the control patients was not significant ($P = 0.184$).

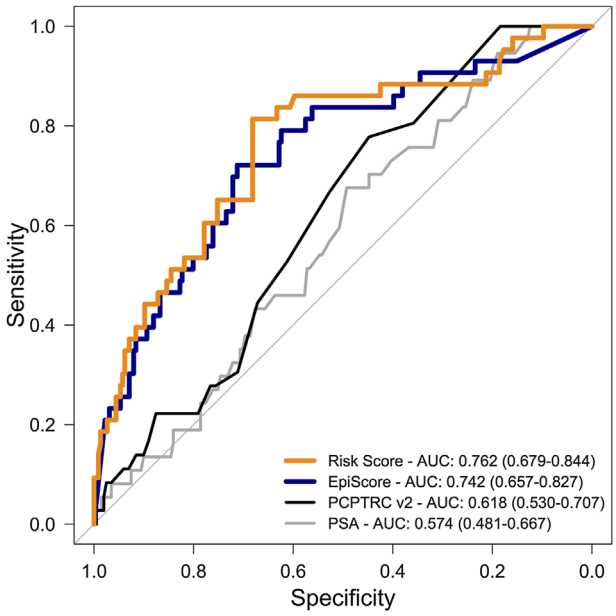

Fig. 1. ROC of EpiScore and the risk score in methylation positive men with either a negative repeat biopsy (controls) or GS $\geq$7 repeat biopsy (cases). PSA and PCPTRC v2 are also depicted, serving as current references for clinical practice. AUC and 95% confidence interval (CI) are shown in the legend.

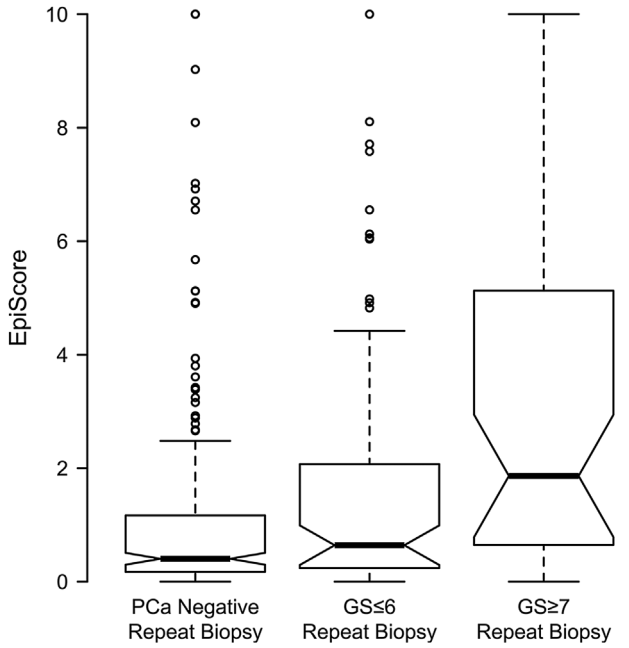

Fig. 2. Box-and-whisker plot of EpiScore in methylation-positive men, that is, for control patients with a negative repeat biopsy, for the group of men with potentially insignificant cancer detected upon repeat biopsy (GS $\leq$6) and for those men with significant cancer (GS $\geq$7) detected upon repeat biopsy.

Holistic, Multimodal Risk Score for Clinically High-Grade Cancer

It was evaluated whether the EpiScore logic could be improved further by adding classical risk factors to the algorithm. First a logistic regression model was built, including EpiScore, age, PSA, DRE, and histopathology of the PCa-negative index biopsy. When the logarithm (base 10) of PSA was used instead of the actual PSA value (in ng/ml), the relevance of PSA in the model increased, most likely due to the restricted weight of very high PSA values. EpiScore was the only significant factor in this model with an odds ratio (OR) of 9.80 (95%CI: 2.12–45.23) (Fig. 3). PSA was borderline significant and a positive trend was observed for the presence of atypia and age at time of the index biopsy (all $P > 0.05$). HGPIN was the only risk factor that inversely correlated with the detection of high-grade PCa upon repeat biopsy (OR < 1).

A stepwise forward selection procedure was implemented. When combining two risk factors, pathology of the cancer-negative index biopsy was added to the EpiScore and, next, age was selected as third factor. Adding more factors did not further improve the model, however, missing data for PSA (not available for 11.5% of patients) and DRE (not available for 23.4% of patients) could lead to an underestimation of their effects. In this final logistic regression model

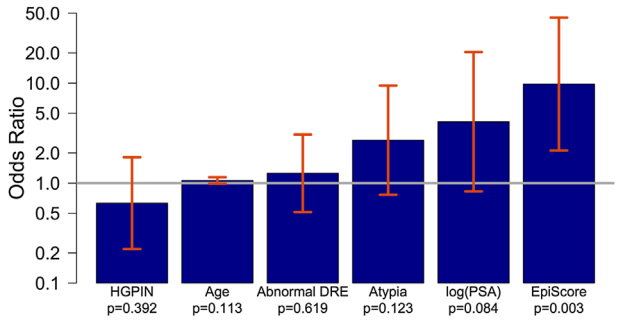

Fig. 3. Odds ratios (OR) of a logistic regression model containing EpiScore and classical risk factors. A horizontal line is drawn at OR = 1 above which the risk factors have a positive contribution.

containing EpiScore, age and histopathology, the trends for these risk factors remained unchanged relative to those depicted in Figure 3. However, now age was a significant contributor ($P = 0.010$) and the OR for EpiScore increased to 14.12 and appeared more robust (95%CI: 12.59–15.84; $P < 0.001$). The final model, based on EpiScore, histopathology of the first, cancer negative biopsy and age, reached an AUC of 0.762 (Fig. 1).

To further evaluate the role of missing clinical data, the risk score was generated using all available risk factors for each individual patient. The risk score was calculated based on EpiScore, pathology, age, DRE and PSA, however, models were also optimized for all combinations of missing data, that is, most often DRE and PSA in this cohort. With this strategy an AUC of 0.77 (95%CI: 0.69–0.84) was obtained, which was not significantly higher than the model only including EpiScore, pathology and age ($P = 0.688$).

Clinical risk was also calculated by means of the PCPTRC version 2. Due to the small, and sometimes counterintuitive, effect of DRE in this cohort, PCPT risk for high-grade cancer was calculated with and without DRE, but always including PSA, age and race. Because of missing values, the cohort was limited to those men with a valid PCPT risk score, since PSA is a necessary parameter for this algorithm. While EpiScore alone reached an AUC of 0.714 in this subset of the cohort, the PCPT risk was far less predictive, with an AUC of 0.618, regardless of DRE inclusion. Combining EpiScore with the risk predicted by the PCPT risk calculator increased the AUC to 0.742 (without DRE; or 0.741 with DRE). Relative to EpiScore, the single most significant parameter in the model, the addition of the PCPTRC traditional clinical risk represents an increase of 3.9% for the AUC, compared to 2.7% (increase from 0.742 to 0.762) with the addition of clinical risk as specifically optimized in this cohort. The risk score resulted in a significantly higher AUC compared to currently used risk stratification algorithms, that is, PSA ($P = 0.004$) and PCPTRC ($P = 0.029$).

Clinical Utility

A DCA was executed to determine the clinical utility of the risk score and to obtain an accurate assessment of the net benefit, in terms of high-grade PCa detected corrected for performing unnecessary repeat biopsies, and net avoidance rate, that is, the reduction in repeat biopsies corrected for missing high-grade cancers. Test harm, that is, the fact that a larger number of men needs to be tested in order to identify a subset of men with high-grade PCa, was not included in the DCA, since no additional testing would be required. PSA and DRE (included in PCPTRC) were obtained at the time of the first biopsy, and EpiScore was calculated as the DNA-methylation intensity observed in the previous, cancer-negative biopsy. Hence, all information was already available at the time when a repeat biopsy was considered, with no additional testing required.

Compared to PSA and PCPTRC, the risk score clearly had the highest net benefit in terms of identifying men with high-grade PCa (Fig. 4A). Taking into account the 7.0% prevalence of high-grade PCa in the general repeat biopsy population, and 16.0% for those men with a methylation-positive prior biopsy, the risk score proved to have a large net benefit, even for those men who are very risk averse, that is, at low probability thresholds. The net benefit of the risk score was larger compared to a biopsy strategy where all men receive a repeat biopsy, as soon the accepted risk was $\geq$3%, that is, starting well below the overall risk of having high-grade PCa detected in either the general or the methylation-positive population repeat biopsy population. The risk score showed the largest net benefit over the entire range of clinically applicable and acceptable probability thresholds that high-grade PCa will be found upon repeat biopsy.

Importantly, the risk score also resulted in the largest reduction of unnecessary repeat biopsies compared to PSA and PCPTRC. If a risk, or the probability threshold below which an intervention is not considered desirable, of having high-grade PCa detected upon repeat biopsy of 15% is considered, that is, similar to the overall prevalence of high-grade cancer in the methylation-positive population, then the risk score resulted in a 3.3- and 5.0-fold net reduction in repeat biopsies compared to PCPTRC and PSA, respectively. This net reduction is the unnecessary repeat biopsy part of interventions avoided and hence does not come at the cost of additional high-grade PCa missed. In summary, in methylation-positive men, and applying the same probability

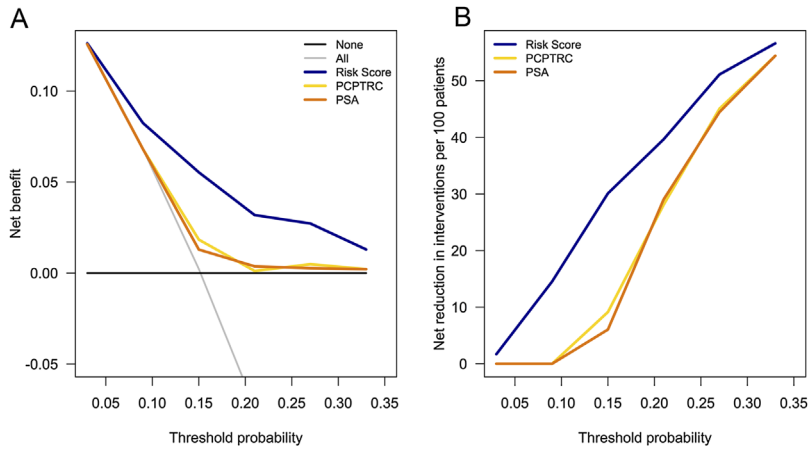

Fig. 4. DCA illustrating the overall clinical utility of the risk score compared to PCPTRC and PSA. Clinical utility of the risk score is demonstrated by the overall net benefit in detecting high-grade PCa corrected for unnecessary biopsies (**A**) and the net reduction in interventions corrected for missed high-grade cancers (**B**).

threshold of 15%, an additional 30 unnecessary repeat biopsies per 100 patients would be avoided with the risk score, compared to only nine and six for the PCPTRC and PSA, respectively.

DISCUSSION

PCa screening and diagnosis debates center around two goals that are often hard to reconcile. First, all men with high-grade cancer should be identified as early as possible, as these patients usually require radical treatment. Second, men with low-grade PCa should not be over-treated, especially because the treatment could cause more harm than benefit [14]. The absence of DNA-methylation of *GSTP1*, *APC*, or *RASSF1* in PCa-negative, residual biopsy tissue resulted in a NPV of 96% for high-grade cancer, successfully addressing the over-treatment issue.

To better stratify methylation-positive patients for the risk of harboring high-grade cancer missed by biopsy, a novel algorithm was developed. EpiScore weighs the DNA-methylation intensities of *GSTP1*, *RASSF1*, and *APC* across a patient's biopsy cores, with significantly higher intensities observed in men with high-grade PCa detected upon repeat biopsy. EpiScore successfully identified men with high-grade PCa that was missed by a prior biopsy, and stratified men who are likely in higher need of a repeat biopsy, due to an increased risk of occult, high-grade cancer.

An important aspect of current and future clinical research is a multimodal approach, integrating several information sources to obtain the best possible, most objective assessment for each individual patient. Therefore, known, traditional risk factors were combined with EpiScore into one holistic model, albeit with the epigenetic component of this risk score being the most significant and important risk factor. The risk score consists of EpiScore, histopathology of the cancer-negative index biopsy (atypia, HGPIN, or benign) and a patient's age at time of the index biopsy. In this cohort the risk score resulted in an improved patient segregation, with a higher AUC than EpiScore alone. While the cohort was sufficiently complete for all risk factors, at least to get an idea about the potential contribution to the risk score, the missing data for PSA and DRE might have led to over- or under-interpretation of the actual effect for these two factors. When available, the addition of PSA or DRE to the risk score led to a minor, non-significant increase of the overall model's performance. However, in particular for DRE, inter-observer variability could have an unexpected impact. When the risk score was defined as the combination of EpiScore and the clinical risk as predicted by the PCPT risk calculator, EpiScore remained the most predictive and significant factor, however, a small benefit was again observed by adding clinical risk to the molecular, epigenetic risk. Finally, the risk score significantly outperformed currently used risk prediction models such as the PCPTRC and PSA. In summary, this risk score combines clinical risk factors with EpiScore, resulting in an improved risk stratification of high-grade PCa in histopathologically negative biopsies.

Unfortunately, due to the lack of sufficient long-term follow-up data, for example, pathological grades were not available, and more extensive clinical information, men with high-grade cancer were defined as those with PCa-positive, GS $\geq$7 repeat biopsies. In addition, data on Gleason patterns were also not recorded, so a more detailed analysis of Gleason 3 + 4

versus 4 + 3 patients was not possible. While more accurate risk classification tools exits, such as the guidelines from the National Comprehensive Cancer Network, most of these are dependent, at least to some extent, on the clinical GS used here [33]. Men with GS6 cancer were not included in the cohort for the development of the risk score, because risk for men with clinical GS6 is harder to predict. This also reflects a clinical reality, since upgrading of clinical GS6 patients occurs frequently [23]. Inter-observer variability could also play a role, since centralized pathology review occurred only within the DOCUMENT sub-cohort.

While it can be debated whether GS6 patients should be detected by screening, such a statement would only hold value when knowing the true pathological GS. In addition, if disease progresses over time, it would be more efficient to have such patients monitored closely or predict who is at increased risk for disease progression. For these two reasons, men with clinical GS6 disease would still benefit from being identified, however with lower priority compared to men likely harboring high-grade cancer.

While unique, optimal solutions were found for the weighing factors in both EpiScore and the risk score, closely related algorithms resulted in a similar performance in terms of AUC. Therefore, cohorts for validation studies would benefit from enrichment for men with high-grade PCa detected upon repeat biopsy, making the risk score more robust. In addition, future studies would also benefit from including long-term follow-up, that is, radical prostatectomy results and pathological GS. The same or a similar algorithm could also be validated as an identification tool for those patients diagnosed with GS6 that are at risk of being under-graded. It remains to be evaluated whether these epigenetic-based algorithms or the applied molecular methodology could also help triage such patients in active surveillance programs and separate those who are likely under-graded or likely to progress, from those with stable, low-grade disease.

Finally, besides the clinical performance, the clinical utility of the risk score was investigated. A DCA was executed, evaluating clinically acceptable probability thresholds above which a repeat biopsy is warranted. Because this probability threshold is personal, it is important to note that the risk score resulted in a net benefit, and the largest benefit compared to PCPTRC and PSA, across the entire range of clinically relevant probability thresholds. In addition, the risk score also resulted in the largest reduction of unnecessary repeat biopsies, again over the entire range of clinically relevant probability thresholds. This demonstrates the large clinical utility of the risk score for men with a PCa-negative, methylation-positive index biopsy.

CONCLUSIONS

Clinical practice is shifting towards more complex integrations of several risk factors, rather than relying on an individual (bio) marker. Here, a risk score was developed that combines EpiScore and known clinical risk factors into one algorithm, identifying men at risk of harboring high-grade PCa, despite a negative biopsy result. EpiScore is an epigenetic profiling algorithm based on the DNA-methylation intensities of *GSTP1*, *RASSF1*, and *APC* and was the most significant and best performing risk factor to identify men with occult, high-grade PCa based on residual tissue of a prior biopsy negative for PCa. A DCA indicated that the risk score was associated with the largest net benefit and the largest avoidance of unnecessary repeat biopsies, compared to two commonly used methods for decision-making, that is, the PCPTRC and PSA, demonstrating clinical utility.

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ORIGINAL ARTICLE

WILEY The Prostate

Epigenetic risk score improves prostate cancer risk assessment

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Background: Early detection of aggressive prostate cancer (PCa) remains crucial for effective treatment of patients. However, PCa screening remains controversial due to a high rate of overdiagnosis and overtreatment. To better reconcile both objectives, more effective methods for assessing disease severity at the time of diagnosis are needed.

Methods: The relationship between DNA-methylation and high-grade PCa was examined in a cohort of 102 prospectively enrolled men who received standard 12-core prostate biopsies. EpiScore, an algorithm that quantifies the relative DNA methylation intensities of *GSTP1*, *RASSF1*, and *APC* in prostate biopsy tissue, was evaluated as a method to compensate for biopsy under-sampling and improve risk stratification at the time of diagnosis.

Results: DNA-methylation intensities of *GSTP1*, *RASSF1*, and *APC* were higher in biopsy cores from men diagnosed with GS ≥ 7 cancer compared to men with diagnosed GS 6 disease. This was confirmed by EpiScore, which was significantly higher for subjects with high-grade biopsies and higher NCCN risk categories (both $P < 0.001$). In patients diagnosed with GS ≥ 7, increased levels of DNA-methylation were present, not only in the high-grade biopsy cores, but also in other cores with no or low-grade disease ($P < 0.001$). By combining EpiScore with traditional clinical risk factors into a logistic regression model, the prediction of high GS reached an AUC of 0.82 (95%CI: 0.73-0.91) with EpiScore, DRE, and atypical histological findings as most important contributors.

Conclusions: In men diagnosed with PCa, DNA-methylation profiling can detect under-sampled high-risk PCa in prostate biopsy specimens through a field effect. Predictive accuracy increased when EpiScore was combined with other clinical risk factors. These results suggest that EpiScore could aid in the detection of occult high-grade disease at the time of diagnosis, thereby improving the selection of candidates for Active Surveillance.

KEYWORDS
epigenetic, Gleason grade, logistic regression model, prognosis, prostate cancer, risk score

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2018 CPT Code Review Issues

1) Serum allergy testing
    a. Code: **86008** Allergen specific IgE; quantitative or semiquantitative, recombinant or purified component, each
        i. Similar serum allergy test codes are diagnostic. These codes have never been reviewed to current HERC staff knowledge.
            1. 86001 Allergen specific IgG quantitative or semiquantitative, each allergen
            2. 86003 Allergen specific IgE; quantitative or semiquantitative, crude allergen extract, each
            3. 86005 Allergen specific IgE; qualitative, multiallergen screen (eg, disk, sponge, card)
        ii. Non-serum allergy testing (i.e. skin testing) is on lines 9,124,223,313,530,531,550,559,566
            1. 95018 Allergy testing, any combination of percutaneous (scratch, puncture, prick) and intracutaneous (intradermal), sequential and incremental, with drugs or biologicals, immediate type reaction, including test interpretation and report, specify number of tests
            2. 95024-95028 Intracutaneous (intradermal) test, various types
            3. 95044 Patch or application test(s) (specify number of tests)
        iii. Lines containing food allergy diagnoses
            1. ICD-10 T78.0 (Anaphylactic reaction due to food products) is on line 124 ANAPHYLACTIC SHOCK; EDEMA OF LARYNX AND THE 4 DYSFUNCTION LINES
            2. ICD-10 T78.1XX (Other adverse food reactions, not elsewhere classified) is on line 543 SYMPTOMATIC URTICARIA
            3. ICD-10 J30.5 (Allergic rhinitis due to food) is on line 559 ALLERGIC RHINITIS AND CONJUNCTIVITIS, CHRONIC RHINITIS
            4. ICD10 L27.2 (Dermatitis due to ingested food) is on line 566 DERMATITIS DUE TO SUBSTANCES TAKEN INTERNALLY
            5. ICD-10 K52.2 (Food protein-induced enterocolitis syndrome) is on line 550 OTHER NONINFECTIOUS GASTROENTERITIS AND COLITIS
            6. ICD-10 K90.0 (Celiac disease) is on line 228 INTESTINAL MALABSORPTION
                a. Note: celiac disease is diagnosed by intestinal biopsy
            7. ICd-10 K90.41 (Non-celiac gluten sensitivity) is on line 658 GASTROINTESTINAL CONDITIONS WITH NO OR MINIMALLY EFFECTIVE TREATMENTS OR NO TREATMENT NECESSARY
    b. Background: Allergy testing can be conducted in several ways. The most common type of testing involves the suspected allergen(s) applied to the skin through a pin prick or scratch. If the patient is allergic to that substance, then the area becomes red and swells or otherwise shows a reaction. If a patient cannot have skin testing for some reason (severe skin disease, high risk of anaphylaxis, etc.), there are blood tests to test

for allergen specific immune substances. These are generally IgE tests, which is the immunoglobulin related to allergy issues.

c. Other policies:
    i. Aetna 2017:
        1. In vitro IgG antibody tests are considered experimental
        2. In Vitro IgE Antibody Tests (RAST, MAST, FAST, ELISA, ImmunoCAP) are considered medically necessary for 1) patients receiving skin test suppressive medication therapy that cannot be temporarily discontinued (eg, antihistamines or beta blockers); 2) presence of widespread skin disease (eg, dermatographism, ichthyosis, intensive dermatitis or generalized eczema); 3) uncooperative patients (eg, small children, individuals with mental or physical impairments); 4) when clinical history suggests an unusually greater risk of anaphylaxis from skin testing; 5) evaluating cross-reactivity between insect venoms; *or* 6) as an adjunctive laboratory test for disease activity of allergic bronchopulmonary aspergillosis or certain parasitic diseases ; *and* testing is performed for any of the following indications: Allergic broncho-pulmonary aspergillosis (ABPA) and certain parasitic diseases; *or* Food allergy; *or* Hymenoptera venom allergy (stinging insects); *or* Inhalant allergy; *or* Specific drugs.
    ii. Wellmark 2017:
        1. The use of in vitro (blood) (86003) allergy testing for IgE should be limited to individuals where skin testing is not possible.
        2. Any IgG in-vitro assay used for evaluation is investigational

d. Expert society recommendations:
    i. **American Academy of Allergy, Asthma & Immunology, 2014**, Choosing Wisely:
        1. Don't perform unproven diagnostic tests, such as immunoglobulin G (IgG) testing or an indiscriminate battery of immunoglobulin E (IgE) tests, in the evaluation of allergy
        2. Don't perform food IgE testing without a history consistent with potential IgE-mediated food allergy. False or clinically irrelevant positive allergy tests for foods are frequent. Indiscriminate screening results in inappropriate avoidance of foods and wastes healthcare resources. IgE testing for specific foods must be driven by a history of signs or symptoms consistent with an IgE-mediated reaction after eating a particular food. Ordering IgE testing in individuals who do not have a history consistent with or suggestive for food allergy based on history frequently reveals positive tests that are unlikely to be clinically relevant. Testing, when done, should be limited to suspected foods. The diagnostic utility of IgE testing for specific foods is optimal when a history compatible with or suggestive for the diagnosis of food allergy is present. In the absence of a compatible or suggestive history, the pre-test probability for a diagnosis of food allergy is low and a positive skin or in vitro IgE test does not establish a diagnosis of food allergy. Skin

testing or serum testing for specific-IgE to food antigens has excellent sensitivity and high negative predictive value, but has low specificity and low positive predictive value. Considering that 50 to 90 percent of presumed cases of food allergy do not reflect IgE-mediated (allergic) pathogenesis and may instead reflect food intolerance or symptoms not causally associated with food consumption, ordering panels of food tests leads to many incorrectly identified food allergies and inappropriate recommendations to avoid foods that are positive on testing.

e. NICE 2017

i. Includes serum IgE testing for patients undergoing evaluation for food allergies

f. **Sicherer 2012**, American Academy of Pediatrics summary of recommendations for serum allergy testing

1. Tests measuring immunoglobulin G (IgG) antibodies for diagnosis are not recommended.
2. Screening panels of food allergens without previous consideration of the history is not recommended, because sensitization without clinical allergy is common
3. Intradermal tests are not recommended, because they are too sensitive and carry risk of a severe allergic reaction.

g. Utilization

1 year—7/1/16-6/30/17; paid claims only. 86005 had minimal billing (<$2000) during this period

Claim Indicator	Sum of Allowed Quantity	Procedure Code	Sum of Billed Quantity	Sum of Allowed Amount	Sum of Billed Amount	FFS/Managed Care Paid Amount
CCOs	840.00	86001 –IGG	12,318	$3,867.92	$82,460.25	$15,287.14
CCOs	57,528.00	86003 –IgE crude	107,722	$209,241.68	$2,224,311.30	$515,602.95
FFS	6.00	86001 - IGG	23	$29.97	$911.66	$29.97
FFS	3,767.00	86003 – IgE Crude	6,827	$18,388.62	$130,018.35	$11397.02

e. Major diagnoses paired with serum allergy testing in claims data review

a. 86001: R53.83 (other fatigue), Z13.0 (Encounter for screening for diseases of the blood and blood-forming organs and certain disorders involving the immune mechanism), T78.40XA (Allergy, unspecified, initial encounter), K58 (Irritable bowel syndrome)

b. 86003: J30.9 (Allergic rhinitis, unspecified), L50.9 (Urticaria, unspecified), Z91.018 (Allergy to other foods), J45.909 (Unspecified asthma, uncomplicated), T78.40XA (Allergy, unspecified, initial encounter)

f. HERC staff summary: Serum IgG testing is included in Choosing Wisely as a non-recommended test by the AAAAI and is not recommended by the AAP. Serum IgE

testing appears to be useful when done in appropriate clinical settings for confirmation of allergies causing asthma, allergic rhinitis, and similar conditions, and for food allergies. Serum IgE testing is not appropriate when done as a screening panel and is listed as a non-recommended test in this setting in the AAAAI Choosing Wisely due to the high risk of non-clinically relevant positive results.

g. HERC staff recommendations:
    a. Add specific serum IgE testing to the lines with allergic conditions that also contain skin allergen testing. Additionally, add to lines with food allergies. These tests should be used to confirm clinical suspicion of allergies, not for screening. They should be treated like the skin allergy testing CPT codes.
        i. Codes:
            1. 86003 Allergen specific IgE; quantitative or semiquantitative, crude allergen extract, each
            2. 86008 Allergen specific IgE; quantitative or semiquantitative, recombinant or purified component, each
        ii. Lines:
            1. 9 ASTHMA
            2. 124 ANAPHYLACTIC SHOCK; EDEMA OF LARYNX
            3. 223 OCCUPATIONAL LUNG DISEASES
            4. 313 DISORDERS INVOLVING THE IMMUNE SYSTEM
            5. 530 ATOPIC DERMATITIS
            6. 531 CONTACT DERMATITIS AND OTHER ECZEMA
            7. 543 SYMPTOMATIC URTICARIA
            8. 550 OTHER NONINFECTIOUS GASTROENTERITIS AND COLITIS
            9. 559 ALLERGIC RHINITIS AND CONJUNCTIVITIS, CHRONIC RHINITIS
            10. 566 DERMATITIS DUE TO SUBSTANCES TAKEN INTERNALLY
        iii. Advise HSD to remove 86003 from the Diagnostic Workup File
    b. Add 86001 Allergen specific IgG quantitative or semiquantitative, each allergen and 86006 Allergen specific IgE; qualitative, multiallergen screen (eg, disk, sponge, card) to line 660 CONDITIONS FOR WHICH CERTAIN TREATMENTS HAVE NO CLINICALLY IMPORTANT BENEFIT OR HAVE HARMS THAT OUTWEIGH BENEFITS; UNPROVEN TREATMENTS with an entry for GN173 as shown below
        i. Advise HSD to remove 86001 and 86006 from the Diagnostic Work up File

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

The following treatments are prioritized on Line 660, CONDITIONS FOR WHICH CERTAIN TREATMENTS HAVE NO CLINICALLY IMPORTANT BENEFIT OR HAVE HARMS THAT OUTWEIGH BENEFITS; UNPROVEN TREATMENTS for the conditions listed here:

2018 CPT Code Review Issues

CPT/HCPCS code	INTERVENTION	Rationale	Date of last Review
86001	Allergen specific IgG testing	No clinically important benefit	November, 2017
86006	Allergen specific IgE, multiallergen screen	Harms outweigh benefits	November, 2017

Choosing Wisely®

An initiative of the ABIM Foundation

American Academy of Allergy, Asthma & Immunology

American Academy of Allergy Asthma & Immunology
www.aaaai.org

Five Things Physicians and Patients Should Question

1 Don't perform unproven diagnostic tests, such as immunoglobulin G (IgG) testing or an indiscriminate battery of immunoglobulin E (IgE) tests, in the evaluation of allergy.

Appropriate diagnosis and treatment of allergies requires specific IgE testing (either skin or blood tests) based on the patient's clinical history. The use of other tests or methods to diagnose allergies is unproven and can lead to inappropriate diagnosis and treatment. Appropriate diagnosis and treatment is both cost effective and essential for optimal patient care.

2 Don't order sinus computed tomography (CT) or indiscriminately prescribe antibiotics for uncomplicated acute rhinosinusitis.

Viral infections cause the majority of acute rhinosinusitis and only 0.5 percent to 2 percent progress to bacterial infections. Most acute rhinosinusitis resolves without treatment in two weeks. Uncomplicated acute rhinosinusitis is generally diagnosed clinically and does not require a sinus CT scan or other imaging. Antibiotics are not recommended for patients with uncomplicated acute rhinosinusitis who have mild illness and assurance of follow-up. If a decision is made to treat, amoxicillin should be first-line antibiotic treatment for most acute rhinosinusitis.

3 Don't routinely do diagnostic testing in patients with chronic urticaria.

In the overwhelming majority of patients with chronic urticaria, a definite etiology is not identified. Limited laboratory testing may be warranted to exclude underlying causes. Targeted laboratory testing based on clinical suspicion is appropriate. Routine extensive testing is neither cost effective nor associated with improved clinical outcomes. Skin or serum-specific IgE testing for inhalants or foods is not indicated, unless there is a clear history implicating an allergen as a provoking or perpetuating factor for urticaria.

4 Don't recommend replacement immunoglobulin therapy for recurrent infections unless impaired antibody responses to vaccines are demonstrated.

Immunoglobulin (gammaglobulin) replacement is expensive and does not improve outcomes unless there is impairment of antigen-specific IgG antibody responses to vaccine immunizations or natural infections. Low levels of immunoglobulins (isotypes or subclasses), without impaired antigen-specific IgG antibody responses, do not indicate a need for immunoglobulin replacement therapy. Exceptions include IgG levels <150mg/dl and genetically defined/suspected disorders. Measurement of IgG subclasses is not routinely useful in determining the need for immunoglobulin therapy. Selective IgA deficiency is not an indication for administration of immunoglobulin.

5 Don't diagnose or manage asthma without spirometry.

Clinicians often rely solely upon symptoms when diagnosing and managing asthma, but these symptoms may be misleading and be from alternate causes. Therefore spirometry is essential to confirm the diagnosis in those patients who can perform this procedure. Recent guidelines highlight spirometry's value in stratifying disease severity and monitoring control. History and physical exam alone may over- or under-estimate asthma control. Beyond the increased costs of care, repercussions of misdiagnosing asthma include delaying a correct diagnosis and treatment.

These items are provided solely for informational purposes and are not intended as a substitute for consultation with a medical professional. Patients with any specific questions about the items on this list or their individual situation should consult their physician.

Released April 4, 2012 (Items 1 – 5) and March 3, 2014 (Items 6 – 10)

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Five More Things Physicians and Patients Should Question

6

Don't rely on antihistamines as first-line treatment in severe allergic reactions.

Epinephrine is the first-line treatment for anaphylaxis. Data indicate that antihistamines are overused as the first-line treatment of anaphylaxis. By definition, anaphylaxis has cardiovascular and respiratory manifestations, which require treatment with epinephrine. Overuse of antihistamines, which do not treat cardiovascular or respiratory manifestations of anaphylaxis, can delay the effective first-line treatment with epinephrine.

Epinephrine should be administered as soon as the diagnosis of anaphylaxis is suspected. Antihistamines are second-line supportive therapy for cutaneous non-life-threatening symptoms (hives), but do not replace epinephrine as the first-line treatment for anaphylaxis.

Fatalities during anaphylaxis have been associated with delayed administration of epinephrine.

7

Don't perform food IgE testing without a history consistent with potential IgE-mediated food allergy.

False or clinically irrelevant positive allergy tests for foods are frequent. Indiscriminate screening results in inappropriate avoidance of foods and wastes healthcare resources. IgE testing for specific foods must be driven by a history of signs or symptoms consistent with an IgE-mediated reaction after eating a particular food. Ordering IgE testing in individuals who do not have a history consistent with or suggestive for food allergy based on history frequently reveals positive tests that are unlikely to be clinically relevant. Testing, when done, should be limited to suspected foods.

The diagnostic utility of IgE testing for specific foods is optimal when a history compatible with or suggestive for the diagnosis of food allergy is present. In the absence of a compatible or suggestive history, the pre-test probability for a diagnosis of food allergy is low and a positive skin or in vitro IgE test does not establish a diagnosis of food allergy. Skin testing or serum testing for specific-IgE to food antigens has excellent sensitivity and high negative predictive value, but has low specificity and low positive predictive value.

Considering that 50 to 90 percent of presumed cases of food allergy do not reflect IgE-mediated (allergic) pathogenesis and may instead reflect food intolerance or symptoms not causally associated with food consumption, ordering panels of food tests leads to many incorrectly identified food allergies and inappropriate recommendations to avoid foods that are positive on testing.

8

Don't routinely order low- or iso-osmolar radiocontrast media or pretreat with corticosteroids and antihistamines for patients with a history of seafood allergy, who require radiocontrast media.

Although the exact mechanism for contrast media reactions is unknown, there is no cause and effect connection with seafood allergy. Consequently there is no reason to use more expensive agents or pre-medication before using contrast media in patients with a history of seafood allergy. A prior history of anaphylaxis to contrast media is an indication to use low- or iso-osmolar agents and pretreat with corticosteroids and antihistamines.

Patients with a history of seafood allergy are not at elevated risk for anaphylaxis from iodinated contrast media. Similarly, patients who have had anaphylaxis from contrast media should not be told that they are allergic to seafood.

Patients with a history of seafood allergy who are labeled as being at greater risk for adverse reaction from contrast infusions experience considerable morbidity from unnecessary precautions – including but not limited to denying them indicated roentgenographic procedures and adverse effects from pretreatment with antihistamine and/or corticosteroid medications.

Regardless of whether these patients truly have IgE-mediated allergies to seafood (crustacean), there is no evidence in the medical literature that indicates they are at elevated risk for anaphylaxis from contrast infusion compared with the history-negative general population.

In a random telephone survey of 5,529 households with a census of 14,948 individuals, seafood allergy was reported by 3.3 percent of survey respondents. According to current U.S. population estimates for 2013, this corresponds to 10,395,000 Americans.

The mechanism for anaphylaxis to radio-iodinated contrast media relates to the physiochemical properties of these media and is unrelated to its iodine content. Further, although delayed-type hypersensitivity (allergic contact dermatitis) reactions to iodine have rarely been reported, IgE-mediated reactions to iodine have not, and neither type of reaction would be related to IgE-mediated shellfish allergy nor to contrast media reactions.Patients with a history of prior anaphylaxis to contrast media are at elevated risk for anaphylactic reaction with re-exposure to contrast media.

Patients with asthma or cardiovascular disease, or who are taking beta blockers, are at increased risk for serious anaphylaxis from radiographic contrast media.

9

Don’t routinely avoid influenza vaccination in egg-allergic patients.

Of the vaccines that may contain egg protein (measles, mumps, rabies, influenza and yellow fever), measles, mumps and rabies vaccines have at most negligible egg protein; consequently no special precautions need to be followed in egg-allergic patients for these vaccines. Studies in egg-allergic patients receiving egg-based inactivated influenza vaccine have not reported reactions; consequently egg-allergic patients should be given either egg-free influenza vaccine or should receive egg-based influenza vaccine with a 30-minute post-vaccine observation period. Egg-allergic patients receiving the yellow fever vaccine should be skin tested with the vaccine and receive the vaccine with a 30-minute observation period if the skin test is negative. If positive, the vaccine may be given in graded doses with appropriate medical observation.

Egg protein is present in influenza and yellow fever vaccines and in theory could cause reactions in egg-allergic patients. However, in 27 published studies collectively 4,172 patients with egg allergy received 4,729 doses of egg-based inactivated influenza vaccine (IIV) with no cases of anaphylaxis, including 513 with severe egg allergy who uneventfully received 597 doses. The CDC’s Advisory Committee on Immunization Practices recommends that egg-allergic persons receive IIV as a single dose without prior vaccine skin testing and be observed for 30 minutes afterwards for any possible allergic reaction. If the reaction to the ingestion of eggs was hives only, the vaccine can be administered in a primary care setting, whereas if the reaction to the ingestion of eggs was more severe, the vaccine should be administered in an allergist/immunologist’s office. Two new IIVs not grown in eggs have been approved for patients 18 years and older: Flucelvax, prepared from virus propagated in cell culture, and Flublok, recombinant hemagglutinin proteins produced in an insect cell line. For egg-allergic patients 18 years of age and older, either egg-based IIV can be used with the precautions above or egg-free IIV can be used.

Measles and mumps vaccines (and Purified Chick Embryo Cell [PCEC] rabies vaccine) are grown in chick embryo fibroblast cultures and contain negligible or no egg protein. Thus, MMR and PCEC rabies vaccine can be administered to egg-allergic recipients in the usual manner.

Per the Yellow Fever vaccine package insert, egg-allergic recipients should be skin tested with the vaccine prior to administration. If negative, the vaccine can be given in the usual manner, but the patient should be observed for 30 minutes afterward. If the vaccine skin test is positive, the vaccine can be given in graded doses under appropriate medical observation.

10

Don’t overuse non-beta lactam antibiotics in patients with a history of penicillin allergy, without an appropriate evaluation.

While about 10 percent of the population reports a history of penicillin allergy, studies show that 90 percent on more of these patients are not allergic to penicillins and are able to take these antibiotics safely. The main reason for this observation is that penicillin allergy is often misdiagnosed and when present wanes over time in most (but not all) individuals. Patients labeled penicillin-allergic are more likely to be treated with alternative antibiotics (such as vancomycin and quinolones), have higher medical costs, experience longer hospital stays, and are more likely to develop complications such as infections with vancomycin-resistant enterococcus (VRE) and Clostridium difficile.

Evaluation for specific IgE to penicillin can be carried out by skin testing. Ideally, penicillin skin testing should be performed with both major and minor determinants. The negative predictive value of penicillin skin testing for immediate reactions approaches 100 percent, whereas the positive predictive value is between 40 and 100 percent. The usefulness of in vitro tests for penicillin-specific IgE is limited by their uncertain predictive value. They are not suitable substitutes for penicillin skin testing.

By identifying the overwhelming majority of individuals who can safely receive penicillin and penicillin-like drugs, we can improve the appropriateness of antibiotic therapy and clinical care outcomes.

How This List Was Created

The American Academy of Allergy, Asthma & Immunology (AAAAI) Executive Committee created a task force to lead work on Choosing Wisely consisting of board members, the AAAAI President and Secretary/Treasurer and AAAAI participants in the Joint Task Force on Practice Parameters. Through multiple society publications and notifications, AAAAI members were invited to offer feedback and recommend elements to be included in the list. A targeted email was also sent to an extended group of AAAAI leadership inviting them to participate.

The work group reviewed the submissions to ensure the best science in the specialty was included. Based on this additional members were recruited for their expertise. Suggested elements were considered for appropriateness, relevance to the core of the specialty, potential overuse of resources and opportunities to improve patient care. They were further refined to maximize impact and eliminate overlap, and then ranked in order of potential importance both for the specialty and for the public. Finally, the work group chose its top five recommendations which were then approved by the Executive Committee. AAAAI's disclosure and conflict of interest policy can be found at www.aaaai.org.

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1

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Guidance for the Clinician in Rendering Pediatric Care

CLINICAL REPORT

Allergy Testing in Childhood: Using Allergen-Specific IgE Tests

Scott H. Sicherer, MD, Robert A. Wood, MD, and the SECTION ON ALLERGY AND IMMUNOLOGY

KEY WORDS
allergy, allergy testing, immunoglobulin, IgE, immunotherapy, pediatrics

ABBREVIATIONS
IgE—immunoglobulin E
sIgE—allergen-specific IgE
SPT—skin prick test
IgG—immunoglobulin G

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abstract

FREE

A variety of triggers can induce common pediatric allergic diseases which include asthma, allergic rhinitis, atopic dermatitis, food allergy, and anaphylaxis. Allergy testing serves to confirm an allergic trigger suspected on the basis of history. Tests for allergen-specific immunoglobulin E (IgE) are performed by in vitro assays or skin tests. The tests are excellent for identifying a sensitized state in which allergen-specific IgE is present, and may identify triggers to be eliminated and help guide immunotherapy treatment. However, a positive test result does not always equate with clinical allergy. Newer enzymatic assays based on anti-IgE antibodies have supplanted the radioallergosorbent test (RAST). This clinical report focuses on allergen-specific IgE testing, emphasizing that the medical history and knowledge of disease characteristics are crucial for rational test selection and interpretation. *Pediatrics* 2012;129:193–197

INTRODUCTION

Allergic diseases (allergic rhinitis [hay fever], asthma, atopic dermatitis, and allergic or anaphylactic reactions to foods, drugs, insect venom, or other allergens) often warrant identification of specific allergic triggers for treatment. Most allergic responses are mediated by immunoglobulin E (IgE) antibodies specific for the trigger allergen, which can be detected with in vitro tests or skin testing. This clinical report focuses on using in vitro allergen-specific IgE (sIgE) testing, which is widely available to pediatricians. A full description of the use of tests for diagnosis and management of allergic disease is beyond the scope of this report, but is described in recent guidelines and practice parameters.[1–9]

TESTS AVAILABLE FOR DETECTING sIgE

A number of enzymatic assays that are based on anti-IgE antibodies have supplanted the radioallergosorbent test.[10] Commercial laboratories that are federally licensed under the Clinical Laboratory Improvement Act of 1988 often use automated systems capable of detecting and quantifying sIgE. Laboratory reports may indicate a number of readouts (eg, classes, counts, or units), but quantification of results in units reflecting concentrations of sIgE is becoming more common (eg, kU_A/L). Although the 3 commercial detection systems approved by the Food and Drug Administration have excellent performance characteristics (analytical sensitivity, 0.1 kU_A/L), the

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individual systems appear to detect different populations of IgE antibody or do not measure IgE antibodies with comparable efficiencies. Thus, a result for an allergen in 1 of the 3 test systems may not be equivalent to the same allergen tested in a different system.

The skin prick test (SPT), typically used by allergy specialists, is another means of detecting sIgE antibodies.[11] A number of devices are available for introducing allergen into the surface of the skin with minimal discomfort; a resulting wheal-and-flare response can be measured in 10 to 20 minutes. Saline and histamine controls are placed for comparison. Intradermal skin testing is performed in special circumstances when increased sensitivity is required (eg, after negative SPT for vaccines, venom, penicillin, and some inhalant allergens, such as *Alternaria* organisms and perhaps other outdoor molds).

Both serum sIgE tests and SPT are sensitive and have similar diagnostic properties.[11,12] Advantages of the SPT include immediate results visible to the patient/family and low cost compared with serum sIgE tests. Disadvantages include the need to withhold medications with antihistamine properties and having rash-free skin available for testing. Advantages of the serologic tests include availability and lack of interference from antihistamines or extensive dermatitis. Disadvantages include the need to obtain blood samples, delayed results, and cost. Some discrepancies exist, however; one test or the other may be more sensitive to detect specific allergens, probably because different proteins or IgE binding sites are represented.[2,3,7,9,11,13]

TEST SELECTION AND INTERPRETATION

Tests might be selected to identify triggers from a number of potential common allergens, for confirming a specific trigger when there is suspicion of one, or in less common circumstances, screening for atopy. A positive serum sIgE or skin test denotes a sensitized state. However, detection of sensitization to an allergen is not equivalent to a clinical diagnosis. In fact, many children with positive tests have no clinical illness when exposed to the allergen.[2,3,7,9,11,13] This limitation highlights the need for the clinician to use a detailed medical history and have knowledge of the features of the specific illness when selecting and interpreting tests. For example, there is no need to test for an allergen that is clearly tolerated (eg, egg in a child who eats egg without symptoms) or when exposure is not relevant (eg, testing a pollen to which the child is not geographically exposed). Knowledge of local aerobiology is, therefore, essential. Testing large panels of allergens without consideration of the history, geographic relevance, and disease characteristics may result in many clinically irrelevant positive results, which, if overinterpreted, may lead to costly and socially, emotionally, and/or nutritionally detrimental actions of unnecessary allergen avoidance. Similarly, caution is advised when testing is negative despite a convincing history. Testing for sIgE would also generally not be useful when the disorder has no pathophysiological basis for a relationship to sIgE (eg, behavioral disorders; allergic disorders not related to sIgE, such as allergic contact dermatitis).

Few studies have correlated clinical outcomes to test results.[2,3,4,11] Studies have generally supported the notion that increasingly strong tests correlate with increasing likelihood of clinical reactivity.[2,3,11] Patients should not be told they are allergic based solely on either a skin test or the identification of sIgE. The test characteristics underscore the need to select and interpret tests with consideration of the medical history, which increases diagnostic value by applying previous probability.[4]

A physician interested in screening for atopy (eg, distinguishing recurrent viral infections from allergic rhinitis) might select a small panel of common triggers. Another means to screen for atopy is to use a multiallergen test that contains several common allergens in one test (eg, one test that includes several perennial allergens, such as dust mite, dog dander, and mold). Availability and composition of these tests varies by manufacturer. A positive result will not identify IgE to a specific antigen but can, at less cost than performing many individual tests, identify a child whose symptoms may relate to exposure to a specific allergen and warrant further specific testing or referral. The multiallergen test had excellent predictive value for identifying atopic children compared with SPTs and an allergist's diagnosis.[14,15]

ISSUES SPECIFIC TO RESPIRATORY ALLERGY[1,6,11]

The disorders that respiratory allergy comprises are allergic asthma and seasonal or perennial allergic rhinitis. National asthma guidelines[1] suggest that patients with persistent asthma be evaluated for the role of allergens as contributing factors, with an emphasis on testing for perennial indoor allergens (eg, dust mite, animal dander, cockroach, mold) that might otherwise not be identified as contributing to disease and also suggest testing seasonal or perennial allergens for selected patients with any level of asthma severity as a basis for education about the role of allergens for avoidance and for immunotherapy.

The clinician may be interested in identifying specific indoor (eg, dust mite, animal dander, molds, mice, and cockroach) or outdoor (eg, pollens, molds) triggers. Rational selection and interpretation of specific tests

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requires consideration of the environmental exposures (housing, pets, and geographic floristic patterns), medical history (nature of symptoms, timing in relation to exposures), and disease characteristics (eg, pollen allergy is uncommon in infancy; patients are unlikely to have acute symptoms from dust mite exposure; food allergens do not typically cause chronic respiratory disease). Provocation tests can confirm environmental allergy but are not often undertaken for clinical purposes.

ISSUES SPECIFIC TO FOOD ALLERGY[2,3,4,11]

Food allergy may be suspected when specific symptoms (eg, urticaria, angioedema, cough, wheeze, vomit, and anaphylaxis) occur minutes to hours after the ingestion of a food, and in children diagnosed with certain disorders, such as moderate to severe atopic dermatitis, eosinophilic esophagitis, and other allergic gastrointestinal tract disorders. Testing for sIgE to foods might be considered to identify or confirm triggers, to assist in diagnosis of chronic disorders, or to monitor for allergy resolution. However, they are not considered diagnostic in and of themselves. SPT and serum sIgE provide similar sensitivity and specificity.[12] It is common to have positive test results for tolerated foods; therefore, indiscriminate testing (ie, panels that include foods that are already tolerated) is not advised. Additional means to assist in diagnosis include the medical history and results of medically supervised oral food challenges. Elimination diets, if initiated, should not be maintained in the absence of a convincing previous history of a reaction or a medically supervised oral food challenge. A comprehensive description of the diagnostic and management process is reviewed in recent guidelines.[2–4] Key observations include:

- Screening panels of food allergens without previous consideration of the history is not recommended, because sensitization without clinical allergy is common. For example, ~8% have positive test results for peanut, but ~1% are clinically allergic.[16]
- A negative SPT or serum sIgE test result does not entirely exclude a diagnosis of a food allergy. One test may be positive when the other is negative. SPT using fresh food extracts may increase sensitivity, especially for fruits. Caution is needed when tests are negative when a specific food allergy history is convincing; a medically supervised oral food challenge may be needed.
- Cross-reactivity among proteins may result in a much higher degree of positive sIgE test results among related foods than clinical reactions (eg, >50% of patients with peanut allergy test positive to other legumes, but <5% have clinical symptoms of allergy from ingestion of legumes). Cross-reactivity among homologous proteins of aeroallergens and food allergens may result in positive tests to foods, often without clinical allergy (eg, birch pollen with hazelnut, peanut, soy; grass pollen with wheat, peanut; dust mite with shrimp).
- Strong positive test results correlate with increasing probability of clinical allergy, and particularly high values may indicate a high degree (>95%) of likely allergy; however, there are few studies correlating outcomes to test results, and results vary by age, disease, and other factors.
- sIgE serum concentration or SPT wheal size do not accurately predict the severity of allergic reactions, but do reflect the likelihood of an allergic reaction of variable intensity.
- Testing for total IgE does not identify specific allergies. Atopic individuals often have elevated total IgE, but there is no current evidence to support the interpretation of sIgE in relation to total IgE.
- Tests measuring immunoglobulin G (IgG) antibodies for diagnosis are not recommended.
- Intradermal tests are not recommended, because they are too sensitive and carry risk of a severe allergic reaction.
- Food protein-induced enterocolitis and proctocolitis (eg, cell-mediated food allergic disorders) are not associated with positive IgE tests.

ISSUES SPECIFIC TO OTHER ALLERGIES (DRUG ALLERGY, INSECT VENOM, VACCINES, LATEX)[7-9]

The general caveats regarding sensitization and clinical allergy described previously also apply to allergy tests for substances that may cause acute allergic reactions or anaphylaxis, such as medications, insect venom, vaccines, and latex. The medical history is essential in decision making regarding testing and interpretation, including understanding whether the symptoms are likely to be IgE mediated.

Tests for drug allergy (eg, acute allergic reactions) are generally not standardized, and the sensitivity of serum tests appears poor.[8] IgE tests are not relevant for many drug reactions (maculopapular rashes, Stevens-Johnson syndrome). SPT and intradermal tests for penicillin allergy using recently available reagents have potential utility for IgE-mediated allergies.[8]

Allergy testing for venom allergy should be considered when symptoms of anaphylaxis occur after a sting. When anaphylactic allergy to venom is confirmed by skin testing, immunotherapy

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is indicated and highly effective.[7,9,11] Isolated, localized swelling at a sting site does not identify a risk of anaphylaxis, and testing is not warranted. Generalized urticaria without other symptoms of anaphylaxis in children 16 years and younger usually does not warrant testing, because more severe reactions appear to be unlikely; however, systemic anaphylaxis in any age group and generalized urticaria in adolescents older than 16 years warrant testing. SPT and intradermal testing are considered the standard means of diagnosis, although serum IgE tests for venom or venom components may be performed when skin tests are negative and the history is suggestive.

SPT and intradermal tests can be performed for vaccines suspected of triggering allergic reactions, although care is needed to choose the proper dilution to prevent irritant reactions.[7,17,18] Skin tests are not available for latex; serum tests are available, but the diagnostic utility is not well characterized.[7,11]

TESTS UNDER DEVELOPMENT AND UNPROVEN TESTS

Tests are under development that detect IgE binding to specific proteins in foods (component-resolved diagnosis), with a potential to more accurately identify people likely to react or with more severe allergies; however, further validation of these tests is needed.[2,3,11] Additional tests requiring more validation include basophil activation and atopy patch tests with foods.[2,3,11] These tests are currently primarily research tools, although specific uses have been identified.[8,11]

A number of tests have no evidence to support their use and are not recommended, including: lymphocyte stimulation, facial thermography, gastric juice analysis, hair analysis, applied kinesiology, provocation-neutralization, allergen-specific IgG/IgG4, cytotoxic assay, electrodermal test (VEGA), and mediator release assay.[2,3,11]

SUMMARY

1. Treatment decisions for infants and children with allergy should be made on the basis of history and, when appropriate, identified through directed serum sIgE or SPT testing. Newer in vitro sIgE tests have supplanted radioallergosorbent tests.
2. Allergy tests for sIgE must be selected and interpreted in the context of a clinical presentation; test relevance may vary according to the patient's age, allergen exposure, and performance characteristics of the test.
3. Positive sIgE test results indicate sensitization, but are not equivalent to clinical allergy. Large panels of indiscriminately performed screening tests may, therefore, provide misleading information.
4. Tests for sIgE may be influenced by cross-reactive proteins that may or may not have clinical relevance to disease.
5. Increasingly higher levels of sIgE (higher concentrations on serum tests or SPT wheal size) generally correlate with an increased risk of clinical allergy.
6. sIgE test results typically do not reflect the severity of allergies.
7. Use of a multiallergen serum test can be helpful for screening for atopic disease if there is a clinical suspicion. If positive, allergen-specific testing may be considered.
8. Tests for allergen-specific IgG antibodies are not helpful for diagnosing allergies.
9. Because test limitations often warrant additional evaluation to confirm the role of specific allergens, consultation with a board-certified allergist-immunologist should be considered.

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2018 Code Review Issues

1) Home INR monitoring
    a. Code: **93792** Patient/caregiver training for initiation of home international normalized ratio (INR) monitoring under the direction of a physician or other qualified health care professional, face-to-face, including use and care of the INR monitor, obtaining blood sample
    b. Similar codes are all ancillary:
        i. HCPCS G0248 Demonstration, prior to initiation of home INR monitoring, for patient with either mechanical heart valve(s), chronic atrial fibrillation, or venous thromboembolism who meets Medicare coverage criteria, under the direction of a physician
        ii. HCPCS G0249 Provision of test materials and equipment for home INR monitoring of patient with either mechanical heart valve(s), chronic atrial fibrillation, or venous thromboembolism who meets Medicare coverage criteria
        iii. HCPCS G0250 Physician review, interpretation, and patient management of home INR testing for patient with either mechanical heart valve(s), chronic atrial fibrillation, or venous thromboembolism who meets Medicare coverage criteria
    c. Evidence
        i. **DeSantis 2014**: retrospective cohort study
            1. N= 29,457 patients with home INR monitoring in an independent diagnostic testing facility database
            2. The mean therapeutic INR range for the entire group was 69.7%
            3. Point-of-care patient self-testing at home achieves high-quality warfarin therapy outside of clinical trials and compares favorably with the results achieved in randomized trials or in anticoagulation clinic settings.
    d. Other policies
        i. **CMS 2008**: covers home INR monitoring as long as all of the following are met:
            1. The patient must have been anticoagulated for at least 3 months prior to use of the home INR device; and,
            2. The patient must undergo a face-to-face educational program on anticoagulation management and must have demonstrated the correct use of the device prior to its use in the home; and,
            3. The patient continues to correctly use the device in the context of the management of the anticoagulation therapy following the initiation of home monitoring; and,
            4. Self-testing with the device should not occur more frequently than once a week.
        ii. **NICE 2014**: Recommends home INR monitoring for patients with heart disease or atrial fibrillation who prefer that form of monitoring and the

person or their carer [caregiver] is both physically and cognitively able to self-monitor effectively. https://www.nice.org.uk/guidance/dg14

1. Patients and carers should be trained in the effective use of home PT/INR monitor and clinicians involved in their care should regularly review their ability to self-monitor
2. Equipment for self-monitoring should be regularly checked using reliable quality control procedures, and by testing patients' equipment against a healthcare professional's coagulometer which is checked in line with an external quality assurance scheme. Ensure accurate patient records are kept and shared appropriately.
3. For people who may have difficulty with or who are unable to self-monitor, such as children or people with disabilities, their carers should be considered to help with self-monitoring

iii. HERC staff summary: home INR monitoring appears to have clinical outcomes comparable to in-clinic testing and is supported by CMS and NICE

iv. HERC staff recommendations:

1. Add CPT **93792** (Patient/caregiver training for initiation of home international normalized ratio (INR) monitoring under the direction of a physician or other qualified health care professional, face-to-face, including use and care of the INR monitor, obtaining blood sample) to any line with CPT 99363 and 99364 (Anticoagulant management for an outpatient taking warfarin, physician review and interpretation of International Normalized Ratio (INR) testing, patient instructions, dosage adjustment (as needed), and ordering of additional tests; first 90 days/after 90 days) [note: CPT 99363 and 99364 are being replaced with 93793].
2. Add HCPCS G0248-G0250 to any line with CPT 99363 and 99364
    a. Advise HSD to remove these codes from the Ancillary File

STABLE Results: Warfarin Home Monitoring Achieves Excellent INR Control

Grace DeSantis, PhD; Jackie Hogan-Schlientz, RN, BSN; Gary Liska, BS; Shari Kipp, BS; Ramarion Sallee; Mark Wurster, MD; Kenneth Kupfer, PhD; and Jack Ansell, MD

Objectives: Point-of-care, home international normalized ratio (INR) monitoring (patient self-testing, or PST) provides an opportunity to optimize warfarin therapy as demonstrated in randomized trials. This study sought to determine the quality of warfarin therapy as determined by time in therapeutic INR range (TTR) in patients who perform home monitoring outside of a clinical trial setting.

Study Design: Retrospective analysis.

Methods: The data base of an independent diagnostic testing facility was retrospectively queried over a 2.5-year period (January 2008-June 2011) and patient TTR was analyzed based on frequency of testing, age, gender, indication for therapy, duration of therapy, and critical value occurrence.

Results: A total of 29,457 patients with multiple indications for warfarin therapy comprised the database. The mean TTR for the entire group was 69.7%, with weekly testers achieving a TTR of 74% versus 68.9% for variable testers (testing every 2-4 weeks)(P <.0001). In all categories analyzed (age, indication for anticoagulation, and referral site volume), weekly testers performed significantly better than variable testers. Older individuals had a higher TTR than younger patients. Weekly testers experienced significantly fewer critical values (INR <1.5 or >5.0) than did variable testers.

Conclusions: Point-of-care patient self-testing at home achieves high-quality warfarin therapy outside of clinical trials and compares favorably with the results achieved in randomized trials or in anticoagulation clinic settings.

Am J Manag Care. 2014;20(3):202-209

For author information and disclosures, see end of text.

Approximately 4 million people in the United States receive oral anticoagulation therapy with the vitamin K antagonist (VKA) warfarin,[1] and require frequent international normalized ratio (INR) monitoring to maintain time in the therapeutic range.[2] There are several models of warfarin management designed to maintain the patients' INR within these desired parameters.[3] These include usual care (UC), which means an individual physician manages multiple patients without formal systematic monitoring policies or procedures to focus on dose management; anticoagulation clinic care (AC), which means dose management is overseen by a healthcare provider (usually a nurse or pharmacist) under physician leadership with systematic policies and procedures in place; and patient self-testing (PST) or patient self-management (PSM), which means patients perform their own INR test at home with a portable point-of-care (POC) instrument and receive dose instructions from a healthcare provider (PST) or manage their own dose (PSM). Under UC or AC, test frequency may be irregular, and is often determined by a patient's ability to travel to a lab or clinic to obtain the INR test result, rather than INR testing frequency depending on the pharmacology and metabolism of warfarin.[4]

Clinical evidence has demonstrated that more frequent testing improves warfarin safety and reduces risks for thromboembolic and major bleeding events.[5] The advent of POC INR devices and home monitoring has facilitated more frequent testing, provided greater consistency in testing reagents and instrumentation, and increased patient empowerment. Since 2004, the American College of Chest Physicians (ACCP) has recommended PST as a means of warfarin dose management, and according to the 2012 ACCP guidelines,[6] "for patients who are motivated and can demonstrate competency, PSM is recommended over UC (Grade 2B)." This recommendation is based on the results of numerous clinical trials of PST/PSM compared with both UC and AC care. Recently, Heneghan, et al, and Bloomfield, et al, have performed independent meta-analyses of a number of clinical trials documenting the benefit of PST or PSM.[7,8] Depending on how the analyses are done, each investigative group has shown greater efficacy of PST/PSM with a reduction in thromboembolism risk and/or major bleeding risk. However, there is little evidence to date, outside of randomized clinical trials (RCTs), to assess outcomes for patients who perform PST or PSM.[9] We evaluated the qual-

In this article
Take-Away Points / 203
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National Coverage Determination (NCD) for Home Prothrombin Time/International Normalized Ratio (PT/INR) Monitoring for Anticoagulation Management (190.11)

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Tracking Information

Publication Number	Manual Section Number	Manual Section Title
100-3	190.11	Home Prothrombin Time/International Normalized Ratio (PT/INR) Monitoring for Anticoagulation Management

Version Number	Effective Date of this Version	Implementation Date
2	3/19/2008	8/25/2008

Implementation QR Modifier Date

1/1/1900

Back to Top

Description Information

Benefit Category

Diagnostic Tests (other)

Please Note: This may not be an exhaustive list of all applicable Medicare benefit categories for this item or service.

Item/Service Description

A. General

Use of the International Normalized Ratio (INR) or prothrombin time (PT) - standard measurement for reporting the blood's clotting time - allows physicians to determine the level of anticoagulation in a patient independent of the laboratory reagents used. The INR is the ratio of the patient's PT (extrinsic or tissue-factor coagulation pathway) compared to the mean PT for a group of normal individuals. Maintaining patients within his/her

prescribed therapeutic range minimizes adverse events associated with inadequate or excessive anticoagulation such as serious bleeding or thromboembolic events. Patient self-testing and self-management through the use of a home INR monitor may be used to improve the time in therapeutic rate (TTR) for select groups of patients. Increased TTR leads to improved clinical outcomes and reductions in thromboembolic and hemorrhagic events.

Warfarin (also prescribed under other trade names, e.g., Coumadin®) is a self-administered, oral anticoagulant (blood thinner) medication that affects the vitamin K-dependent clotting factors II, VII, IX and X. It is widely used for various medical conditions, and has a narrow therapeutic index, meaning it is a drug with less than a 2-fold difference between median lethal dose and median effective dose. For this reason, since October 4, 2006, it falls under the category of a Food and Drug Administration (FDA) “black-box” drug whose dosage must be closely monitored to avoid serious complications. A PT/INR monitoring system is a portable testing device that includes a finger-stick and an FDA-cleared meter that measures the time it takes for a person’s blood plasma to clot.

Indications and Limitations of Coverage

B. Nationally Covered Indications

For services furnished on or after March 19, 2008, Medicare will cover for the use of home PT/INR monitoring forchronic, oral anticoagulation management for patients with mechanical heart valves, chronic atrial fibrillation, or venous thromboembolism (inclusive of deep venous thrombosis and pulmonary embolism) on warfarin. The monitor and the home testing must be prescribed by a treating physician as provided at 42 CFR 410.32(a), and all of the following requirements must be met:

1. The patient must have been anticoagulated for at least 3 months prior to use of the home INR device;and,
2. The patient must undergo a face-to-face educational program on anticoagulation management and must have demonstrated the correct use of the device prior to its use in the home; and,
3. The patient continues to correctly use the device in the context of the management of the anticoagulation therapy following the initiation of home monitoring; and,
4. Self-testing with the device should not occur more frequently than once a week.

C. Nationally Non-Covered Indications

N/A

D. Other

1. All other indications for home PT/INR monitoring not indicated as nationally covered above remain at local Medicare contractor discretion.

2. This national coverage determination (NCD) is distinct from, and makes no changes to, the PT clinical laboratory NCD at section 190.17 of Publication 100-03 of the NCD Manual.

(This NCD last reviewed March 2008)

2018 CPT Code Review Issues

1) Photodynamic therapy of premalignant lesions of the skin and adjacent mucosa
    a. Codes:
        i. **96573** Photodynamic therapy by external application of light to destroy premalignant lesions of the skin and adjacent mucosa with application and illumination/activation of photosensitizing drug(s) provided by a physician or other qualified health care professional
        ii. **96574** Debridement of premalignant hyperkeratotic lesion(s) (ie, targeted curettage, abrasion) followed with photodynamic therapy by external application of light to destroy premalignant lesions of the skin and adjacent mucosa with application and illumination/activation of photosensitizing drug(s) provided by a physician or other qualified health care professional, per day
    b. Background: Photodynamic therapy (PDT) is a treatment that uses a drug, called a photosensitizer or photosensitizing agent, and a particular type of light. When photosensitizers are exposed to a specific wavelength of light, they produce a form of oxygen that kills nearby cells. PDT is popularly used in treating acne. It is used clinically to treat a wide range of medical conditions, including wet age-related macular degeneration, psoriasis, atherosclerosis and has shown some efficacy in anti-viral treatments, including herpes. It also treats malignant cancers including head and neck, lung, bladder and particular skin.
    c. The most common precancerous skin lesions are actinic keratoses, Bowen's disease (carcinoma in situ of the skin), and keratoacanthoma
    d. Note: previous iterations of the photodynamic therapy CPT code descriptions specified that adjacent mucosa was the lip
    e. Similar codes:
        i. 96567 (Photodynamic therapy by external application of light to destroy premalignant lesions of the skin and adjacent mucosa with application and illumination/activation of photosensitive drug(s), per day) is on lines 37,93,95,112,113,114,115,116,126,133,135,157,158,161,163,191,200,201,209,211,215,216,218,230,235,238,239,259,260,261,262,263,271,276,286,287,294,314,315,316,329,396,397,399,400,418,433,556,589
            1. Most of the lines above are cancer lines for various cancers of internal organs, not premalignant lesions of the skin or adjacent mucosa (i.e. lip)
            2. Per CPT code book, 96567 is to be used when no qualified health care professional is directly involved in the delivery of the service and 96573 or 96574 is to be billed when a physician/QHCP is involved.
        ii. 96570 (Photodynamic therapy by endoscopic application of light to ablate abnormal tissue via activation of photosensitive drug(s); first 30 minutes (List separately in addition to code for endoscopy or bronchoscopy procedures of lung and gastrointestinal tract)) and 96571 (each add'l 15 minutes) are on the same lines as 96567 and are appropriate to treat non-skin related malignancies of the GI tract and pulmonary system.
    f. Other policies:

   i. Aetna covers photodynamic therapy for non-melanotic premalignant skin lesions, and for cancer of the esophagus, liver, lung, and cholangiocarcinoma only (endoscopic codes)

g. Placement of premalignant skin and mucosal diagnoses:
   i. D04 (Carcinoma in situ of skin): 243 DERMATOLOGICAL PREMALIGNANT LESIONS AND CARCINOMA IN SITU
   ii. D07.4 (Carcinoma in situ of penis): 259 CANCER OF PENIS AND OTHER MALE GENITAL ORGANS
   iii. D23 (keratoacanthoma type diagnoses): 625 BENIGN NEOPLASMS OF SKIN AND OTHER SOFT TISSUES
   iv. L57.0 (Actinic keratosis): 625 BENIGN NEOPLASMS OF SKIN AND OTHER SOFT TISSUES

h. Placement of GI and pulmonary cancer diagnoses:
   i. C15 (cancer of esophagus): 314 CANCER OF ESOPHAGUS; BARRETT'S ESOPHAGUS WITH DYSPLASIA
   ii. C16 (cancer of stomach): 216 CANCER OF STOMACH
   iii. C17/C18 (cancer of intestine/colon): 157 CANCER OF COLON, RECTUM, SMALL INTESTINE AND ANUS
   iv. C22 (cancer of liver): 315 CANCER OF LIVER
   v. C25 (cancer of pancreas): 316 CANCER OF PANCREAS
   vi. C34 (lung cancers):263 CANCER OF LUNG, BRONCHUS, PLEURA, TRACHEA, MEDIASTINUM AND OTHER RESPIRATORY ORGANS

i. <u>HERC staff recommendations</u>:
   i. Add **96573** (Photodynamic therapy by external application of light to destroy premalignant lesions of the skin and adjacent mucosa with application and illumination/activation of photosensitizing drug(s) provided by a physician or other qualified health care professional) and **96574** (Debridement of premalignant hyperkeratotic lesion(s) (ie, targeted curettage, abrasion) followed with photodynamic therapy by external application of light to destroy premalignant lesions of the skin and adjacent mucosa with application and illumination/activation of photosensitizing drug(s) provided by a physician or other qualified health care professional, per day) to lines
      1. 243 DERMATOLOGICAL PREMALIGNANT LESIONS AND CARCINOMA IN SITU
      2. 259 CANCER OF PENIS AND OTHER MALE GENITAL ORGANS
      3. 625 BENIGN NEOPLASMS OF SKIN AND OTHER SOFT TISSUES
   ii. Remove 96567 (Photodynamic therapy by external application of light to destroy premalignant lesions of the skin and adjacent mucosa with application and illumination/activation of photosensitive drug(s), per day) from all current lines except for 259 CANCER OF PENIS AND OTHER MALE GENITAL ORGANS
      1. Add 96567 to lines 243 DERMATOLOGICAL PREMALIGNANT LESIONS AND CARCINOMA IN SITU and 625 BENIGN NEOPLASMS OF SKIN AND OTHER SOFT TISSUES

iii. Add a coding specification to line 259 CANCER OF PENIS AND OTHER MALE GENITAL ORGANS as follows: “CPT 96567, 96573 and 96574 are included on this line only for pairing with ICD-10 D07.4.”

iv. Remove 96570 and 96571 ((Photodynamic therapy by endoscopic application of light to ablate abnormal tissue via activation of photosensitive drug(s); first 30 minutes/each add’l 15 min (List separately in addition to code for endoscopy or bronchoscopy procedures of lung and gastrointestinal tract)) from all current lines except:

1. 157 CANCER OF COLON, RECTUM, SMALL INTESTINE AND ANUS
2. 216 CANCER OF STOMACH
3. 263 CANCER OF LUNG, BRONCHUS, PLEURA, TRACHEA, MEDIASTINUM AND OTHER RESPIRATORY ORGANS
4. 314 CANCER OF ESOPHAGUS; BARRETT'S ESOPHAGUS WITH DYSPLASIA
5. 315 CANCER OF LIVER
6. 316 CANCER OF PANCREAS
7. HERC staff to review evidence for placement on these lines as a future topic

Section 6.0

Previously Discussed Items

Guideline Updates for Lines 500 and 660

Questions:

1) How should lines 500 and 660 and their accompanying guideline notes, as well as Statement of Intent 3 be formatted?
2) Should further SRNC entries be approved for movement to GN172/173?
3) How should Excluded codes be handled?

Question source: HERC staff

Issues:

1) HERC staff have been working with various stakeholders on the implementation of lines 500 and 660. There are several staff recommendations for changing the formatting of these lines and guidelines. Staff review of the newly-approved statement of intent, line descriptions and guideline note titles and formatting required some editing for consistency and to accommodate all services intended to be placed on these lines. These changes are:

1. Change "therapies" and "treatments" to "interventions" throughout to encompass screening interventions, supportive care and diagnostic services as well as treatments. Change the title of Statement of Intent 3 to encompass all interventions for both lines/guideline notes.
2. Update Statement of Intent 3 to include services of unproven/no benefit and for which harms outweigh benefits
3. In Guideline Notes 172-173 (formerly 168-169), change the intervention column to "Intervention Description" and eliminate the "Condition" column. This will allow staff to specify conditions where necessary but not require listing of specific indications, which reduces potential confusion and maintenance challenges.

Additional information for stakeholders about finding these services:
HERC and HSD anticipate questions about the movement of certain services which don't appear on any line. Currently, these are procedure codes (CPT/HCPCS) and are referred to in HERC minutes as "services recommended for noncoverage" or SRNC. They are posted on the Medical Surgical Rules page in Group 1118. Starting January 1, 2018, the HERC will represent these services differently. They will be referred to in minutes as being "placed on line 500" or "placed on line 660" or "attached to Guideline Note 172" or "attached to Guideline Note 173". The codes will not, however, appear in the data files for the lines, but rather in a text table embedded in the guideline notes. Regarding the procedure codes, there is no difference from an automated systems perspective between the current SRNC and new lines 500/660. These services are generally noncovered for all indications, unless otherwise specified in the guideline notes. There will also be at least one drug, Emflaza, which appears on line 500/guideline note 172.

As is currently the case, coverage of these services may be appropriate due to exceptions or the comorbidity rule as specified in contract and rule but are not generally expected to be covered as the HERC has prioritized them below the funding line. They will also continue to appear in Group 1118 on the rules page, though HSD may create a different group for the procedure codes in the future.

The rationales for services, including excerpts from meeting materials and minutes, will continue to appear on the searchable list, with a separate record for each entry (the documents will be adapted from the documents currently used for the Services Recommended for Noncoverage entries).

2) The SRNC file was reviewed and various entries were added to GN173 for services previously recommended as non-covered. Staff put in references to the date of last review when easily found;

DRAFT

many codes had their last review >5 years ago and the reference would take extensive staff time to locate. In these cases, no date or indication for placement were included.

3) Multiple CPT codes on the SRNC are included there because of non-evidence based reasons. For example, sports physicals, autopsies, and similar types of care are not covered due to administrative rules and regulations. Other interventions are not covered because they are considered cosmetic, involve infertility treatment, or involve travel vaccination. These types of services cannot be included on the Prioritized List as they are never covered under any circumstances. However, these codes may change based on administrative rule changes, CMS requirements, etc. HERC staff will work with HSD to make sure these codes are appropriately listed in Group 1118, currently posted at http://www.oregon.gov/oha/HSD/OHP/Pages/Policy-Medical-Surgical.aspx.

DRAFT

HERC staff recommendations:

1) Modify SOI3 as shown below

STATEMENT OF INTENT 3, ~~THERAPIES WITH MARGINAL CLINICAL BENEFIT OR LOW COST-EFFECTIVENESS~~ LOWER-PRIORITY SERVICES

It is the intent of the Commission that therapies that exhibit one or more of the following characteristics generally be given low priority on the Prioritized List:

i. Marginal or clinically unimportant benefit
ii. Unproven/no benefit
iii. Harms outweigh benefits
iv. Very high cost in which the cost does not justify the benefit
v. Significantly greater cost compared to alternate therapies when both have similar benefit
vi. Significant budget impact that could affect the overall Prioritized List funding level

Where possible, the Commission prioritizes pairings of condition and treatment codes to reflect this lower priority, or simply does not pair a procedure code with one or more conditions if it exhibits one of these characteristics. This is, however, impractical in several circumstances:

A) For diagnostic services appropriate for billing with a variety of diagnoses, including diagnoses representing signs and symptoms as well as diagnoses which otherwise appear above the funding line
B) For ancillary services such as prescription drugs, supplies, physician-administered drugs or durable medical equipment and not identified by a CPT or HCPCS code appropriate for placement on the Prioritized List
C) For procedure codes not appropriate for placement in the funded region of the list but which may be billed with many possible diagnoses, some of which are above the funding line while others may be below the funding line

In these circumstances, the HERC identifies the services in Guideline Notes 172 and 173, which are attached to lines 500 and 660 in order to make its intent transparent.

~~As codes for prescription drugs, durable medical equipment & supplies, certain adjunctive procedures and other ancillary services are not typically included on the Prioritized List and are not always billed in conjunction with diagnosis codes, it is more difficult to indicate the importance of these services through the prioritization process. Through evidence reviews conducted by one of its subcommittees, the Pharmacy and Therapeutics Committee, or other reputable sources and based on these reviews, HERC prioritizes such services regarded as having low importance when prescribed for certain conditions on Line 500 or Line 660 and lists the relevant condition/treatment pairings in Guideline Notes 172 or 173.~~

2) Modify the line condition and treatment descriptions for lines 500 and 660 as shown below

Line: 500

Condition: CONDITIONS FOR WHICH CERTAIN INTERVENTIONS ~~TREATMENTS~~ RESULT IN MARGINAL CLINICAL BENEFIT OR LOW COST-EFFECTIVENESS (See Guideline Notes 64,65,172)

Treatment: ~~MEDICAL AND SURGICAL TREATMENT~~ SPECIFIED INTERVENTIONS

Line: 660
Condition: CONDITIONS FOR WHICH CERTAIN INTERVENTIONS ~~TREATMENTS~~ ARE UNPROVEN, HAVE NO CLINICALLY IMPORTANT BENEFIT OR HAVE HARMS THAT OUTWEIGH BENEFITS (See Guideline Notes 64,65,67,173)
Treatment: ~~MEDICAL AND SURGICAL TREATMENT~~ SPECIFIED INTERVENTIONS

3) Modify GN172 and GN173 wording, formatting and entries as shown below
    a. Additional entries are from the former SRNC list
    b. "Condition" column is removed
    c. "Intervention" is changed to "Intervention Description" and may contain condition information
    d. New entries of previous SRNC codes are included
        i. When the date of review was more than 5 yrs ago, no date or reason for exclusion was included.

GUIDELINE NOTE 172, INTERVENTIONS ~~TREATMENTS~~ WITH MARGINAL CLINICAL BENEFIT OR LOW COST-EFFECTIVENESS FOR CERTAIN CONDITIONS

Line 500

The following interventions are prioritized on Line 500 CONDITIONS FOR WHICH CERTAIN INTERVENTIONS ~~TREATMENTS~~ RESULT IN MARGINAL CLINICAL BENEFIT OR LOW COST-EFFECTIVENESS:

Procedure Code	Intervention Description	Rationale	Last Review
N/A	deflazacort (Emflaza)	Marginal benefit/low cost-effectiveness compared to equally effective but much less expensive alternative corticosteroids	September, 2017
61630	Balloon angioplasty, intracranial (eg, atherosclerotic stenosis), percutaneous	Similar or worse outcomes than standard therapies	March 2016
64566	Posterior tibial neurostimulation	Minimally effective, no evidence of long-term effectiveness	December, 2010
69710 *HCPCS L8690-L8693*	Implantation or replacement of electromagnetic bone conduction hearing device in temporal bone *Auditory osseointegrated device*	Less effective than other therapies	June, 2014, Aug. 2015
74263, 81528, 81327	Screening CT Colonography, FIT-DNA (Cologuard), mSEPT9, Chromoscopy	Insufficient evidence for use in population screening	September, 2017

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Procedure Code	Intervention Description	Rationale	Last Review
94669	Mechanical chest wall oscillation	More costly than equally effective therapies	October, 2016
99174, 99177	Photoscreening	More costly than equally effective methods of screening	November, 2015

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

Line 660

The following Interventions are prioritized on Line 660 CONDITIONS FOR WHICH CERTAIN INTERVENTIONS ARE UNPROVEN, HAVE NO CLINICALLY IMPORTANT BENEFIT OR HAVE HARMS THAT OUTWEIGH BENEFITS:

Procedure Code	Intervention Description	Rationale	Last Review
D0422 D0423	Collection and preparation of genetic sample material for laboratory analysis and report Genetic test for susceptibility to diseases – specimen analysis	Insufficient evidence of effectiveness	October, 2015
D9932-D9935	Cleaning and inspection of removable complete or partial denture, maxillary or mandibular	Insufficient evidence of effectiveness	October, 2015
S2300	Arthroscopy, shoulder, surgical; with thermally-induced capsulorrhaphy	More effective treatments are available	September, 2017
S9357	Enzyme replacement therapy (e.g. idursulfase and similar medications) for all inborn error of metabolism conditions except infantile Pompe's disease	No clinically important benefit	August, 2012
15777	Acellular dermal matrix for soft tissue reinforcement (eg, breast, trunk)	Greater harms than other effective therapies	March, 2015
20696-20697	Application of multiplane (pins or wires in more than 1 plane), unilateral, external fixation with stereotactic computer-assisted adjustment (eg, spatial frame)		
20979	Low intensity ultrasound stimulation to aid bone healing, noninvasive (nonoperative)		

DRAFT

Guideline Updates for Lines 500 and 660

Procedure Code	Intervention Description	Rationale	Last Review
20982	Radiofrequency ablation therapy for reduction or eradication of 1 or more bone tumors	No evidence of effectiveness	2004
20983	Cryotherapy ablation therapy for reduction or eradication of 1 or more bone tumors	No evidence of effectiveness	November, 2014
21685	Hyoid myotomy and suspension		
22867-22870	Insertion of interlaminar/ interspinous process stabilization/ distraction device, without fusion, including image guidance when performed, with open decompression, lumbar	Insufficient evidence of effectiveness	November, 2016
27080	Coccygectomy, primary		
27418	Anterior tibial tubercleplasty (eg, Maquet type procedure)	Harms outweigh benefits, more efficacious procedures exist	May, 2011
28890	Extracorporeal shock wave, high energy involving the plantar fascia		
29866-29867	Arthroscopy, knee, surgical; osteochondral autograft(s)/allograft(s) (eg, mosaicplasty)		
29868	Arthroscopy, knee, surgical; meniscal transplantation		
31627	Computer assisted bronchoscopy	Insufficient evidence of effectiveness	December, 2009
31647-31649, 31651	Bronchial valve insertion/removal/replacement	Insufficient evidence of effectiveness	December, 2012
31660-31661	Bronchial thermoplasty	Insufficient evidence of effectiveness	January, 2014
32998	Radiofrequency ablation therapy for reduction or eradication of 1 or more pulmonary tumor(s)		
33140-33141	Transmyocardial laser revascularization, by thoracotomy		
33340	Percutaneous transcatheter closure of the left atrial appendage with endocardial implant	Insufficient evidence of effectiveness	November, 2016
33548	Surgical ventricular restoration procedure, includes prosthetic		

DRAFT

Procedure Code	Intervention Description	Rationale	Last Review
	patch, when performed (eg, ventricular remodeling, SVR, SAVER, Dor procedures)		
36455	Exchange transfusion, blood; other than newborn		
36456	Partial exchange transfusion, blood, plasma or crystalloid necessitating the skill of a physician or other qualified health care professional, newborn	No evidence of effectiveness, evidence of possible harm	November, 2016
41512	Tongue base suspension	No clinically important benefit	January, 2014
41530	Submucosal ablation of the tongue base, radiofrequency		
41821	Operculectomy, excision pericoronal tissue		
43206	Esophagoscopy, flexible, transoral; with optical endomicroscopy	No evidence of effectiveness	December, 2012
43252, 88375	Optical endomicroscopy	Insufficient evidence of effectiveness	December, 2012
43257	Esophagogastroduodenoscopy, flexible, transoral; with delivery of thermal energy to the muscle of lower esophageal sphincter and/or gastric cardia, for treatment of gastroesophageal reflux disease	No evidence of effectiveness	January, 2014
43284	Laproscopy, surgical, esophageal sphincter augmentation procedure, placement of sphincter augmentation device (ie, magnetic band)	Insufficient evidence of effectiveness	November, 2016
43647-43648 43881-43882	Laparoscopy, surgical; implantation or replacement or revision of gastric neurostimulator electrodes, antrum		
43770, 43842-43845, 43886-43888	Gastric restrictive procedures (gastric band, other)	No evidence of effectiveness	October, 2016

DRAFT

Guideline Updates for Lines 500 and 660

Procedure Code	Intervention Description	Rationale	Last Review
45391-45392	Colonoscopy, flexible; with endoscopic ultrasound examination		
46760- 46762	Sphincteroplasty, anal, for incontinence, adult; muscle transplant/implantation artificial sphincter	No evidence of effectiveness	May, 2013
47383	Ablation, 1 or more liver tumor(s), percutaneous, cryoablation	No evidence of effectiveness for both hepatocellular carcinoma and metastatic disease	November, 2013
50380	Renal autotransplantation, reimplantation of kidney		
50592	Radiofrequency ablation, 1 or more renal tumor(s)		
50705	Ureteral embolization or occlusion	Insufficient evidence of effectiveness	November, 2015
52441-52442	Cystourethroscopy, with insertion of permanent adjustable transprostatic implant	No evidence of effectiveness	March, 2015 (CG blog reference)
52647	Laser coagulation of prostate	No evidence of effectiveness	March, 2015 (CG blog reference)
53855	Temporary prostatic stents	Insufficient evidence of effectiveness	October, 2015
53860	Transurethral radiofrequency micro-remodeling of the bladder neck and urethra for stress incontinence	Insufficient evidence of effectiveness	December, 2010
55300	Vasotomy for vasograms, seminal vesiculograms, or epididymogram		
55873	Cryosurgical ablation of the prostate		
58674	Laparoscopy, surgical, ablation of uterine fibroid(s)	Insufficient evidence of effectiveness	November, 2016
61635	Transcather placement of intravascular stent(s), intracranial (eg, atherosclerotic stenosis), including balloon angioplasty, if performed	Results in significantly worse outcomes than medical management	March 2016
61640-61642	Balloon dilation of intracranial vasospasm, percutaneous.	Evidence of harm	March, 2016
61645	Percutaneous arterial transluminal mechanical	No evidence of effectiveness	November, 2015

DRAFT

Procedure Code	Intervention Description	Rationale	Last Review
	thrombectomy and/or infusion for thrombolysis, intracranial		
61650-61651	Endovascular intracranial prolonged administration of pharmacologic agent(s) other than for thrombolysis, arterial	No evidence of effectiveness	November, 2015
62263	Percutaneous lysis of epidural adhesions using solution injection (eg, hypertonic saline, enzyme) or mechanical means		
62290-62292	Discography		
62380	Endoscopic decompression of spinal cord, nerve root(s), including laminotomy, partial facetectomy, foraminotomy, discectomy and/or excision of herniated intervertebral disc	Insufficient evidence of effectiveness	November, 2016
64479-64480	Transforaminal epidural steroid injections, cervical and thoracic spine	Insufficient evidence of benefit	March, 2015 Coverage Guidance Blog
64490-64492	Facet joint injections cervical and thoracic	Insufficient evidence of benefit	March, 2015 Coverage Guidance Blog
64550, 97014, 97032, 0278T, E0720, E0730, G0283	Transcutaneous electrical nerve stimulation (TENS); Scrambler therapy; Cranial electrical stimulation; all similar transcutaneous electrical neurostimulation therapies	No clinically important benefit (CES) or insufficient evidence of effectiveness (all other) for chronic pain; insufficient evidence of effectiveness for all other indications	September, 2017
64617	Chemodenervation of muscle(s); larynx	No evidence of effectiveness	January, 2014
64633-64634	Radiofrequency ablation of the cervical and thoracic spine	Insufficient evidence of benefit	March, 2015 Coverage Guidance Blog
64635-64636	Radiofrequency ablation of the lumbar and sacral spine	Insufficient evidence of benefit	November, 2014 Coverage Guidance Blog

DRAFT

Guideline Updates for Lines 500 and 660

Procedure Code	Intervention Description	Rationale	Last Review
66174-66175	Transluminal dilation of aqueous outflow canal	Insufficient evidence of effectiveness	December, 2010
69720- 69725	Decompression facial nerve		
69740-69745	Suture facial nerve		
69955	Total facial nerve decompression and/or repair		
70554-70555	Functional MRI		
72285, 72295	Discography		
74261- 74262	Computed tomographic (CT) colonography		
75571	CT coronary calcium scoring	Insufficient evidence of benefit, unclear harms of radiation exposure	August 2013 Coverage Guidance Blog
75572	Computed tomography, heart, with contrast material, for evaluation of cardiac structure and morphology	Insufficient evidence of effectiveness	December, 2009
75574	Computed tomography, heart	Insufficient evidence of benefit, unclear harms of radiation exposure	August, 2013 Coverage Guidance Blog
76376- 76377	3D rendering		
77061- 77063	Digital breast tomosynthesis	No evidence of effectiveness	November, 2014
77084	Magnetic resonance (eg, proton) imaging, bone marrow blood supply		
77086	Vertebral fracture assessment using DXA	Insufficient evidence of effectiveness	October, 2015
77767	Remote afterloading high dose rate radionuclide skin surface brachytherapy, includes basic dosimetry	Insufficient evidence of effectiveness	October and November 2015
77768	Skin surface brachytherapy	No evidence of effectiveness	November, 2015
78265-78266	Gastric emptying imaging study	No evidence of effectiveness	November, 2015
78459	Myocardial imaging, positron emission tomography (PET), metabolic evaluation	Insufficient evidence of benefit, unclear harms of radiation exposure	January, 2015 Coverage Guidance Blog
78491-78492	Myocardial imaging, positron emission tomography (PET), perfusion	Insufficient evidence of benefit, unclear	January, 2015

DRAFT

Procedure Code	Intervention Description	Rationale	Last Review
		harms of radiation exposure	Coverage Guidance Blog
81422	Fetal chromosomal microdeletion(s) genomic sequence analysis (eg. DiGeorge syndrome, Cri-du-chat syndrome), circulating cell-free fetal DNA in maternal blood	Insufficient evidence of effectiveness	November, 2016
81490	Autoimmune (rheumatoid arthritis), analysis of 12 biomarkers using immunoassays, utilizing serum, prognostic algorithm	No evidence of effectiveness	November, 2015
81493	Coronary artery disease, mRNA, gene expression profiling	Insufficient evidence of effectiveness	November, 2015
81500	Oncology (ovarian), biochemical assays of two proteins (CA-125 and HE4), utilizing serum, with menopausal status, algorithm reported as a risk score	No evidence of effectiveness	December, 2012
81503	Oncology (ovarian), biochemical assays of five proteins (CA-125, apolipoprotein A1, beta-2 microglobulin, transferrin, and pre-albumin), utilizing serum, algorithm reported as a risk score	No evidence of effectiveness	December, 2012
81504	Biomarker tests for tumor tissue: • Mammaprint, Mammostrat and ImmunoHistoCHemistry 4 (IHC4) for breast cancer • Microsatellite instability (MSI) for colorectal cancer • Urovysion for bladder cancer • Prolaris for prostate cancer • Multiple molecular testing to select targeted cancer therapy	Insufficient evidence of effectiveness. More costly than equally effective therapies for this condition	August, 2015 Coverage Guidance Blog
81506	Endocrinology (type 2 diabetes), biochemical assays of seven analytes (glucose, HbA1c, insulin, hs-CRP, adiponectin, ferritin, interleukin 2-receptor alpha), utilizing serum or plasma, algorithm reporting a risk score	No evidence of effectiveness	December, 2012
81525	Oncology (colon), mRNA, gene expression profiling by real-time	No evidence of effectiveness	November, 2015

DRAFT

Procedure Code	Intervention Description	Rationale	Last Review
	RT-PCR of 12 genes (7 content and 5 housekeeping), utilizing formalin-fixed paraffin-embedded tissue, algorithm reported as a recurrence score		
81535-81536	Oncology (gynecologic), live tumor cell culture and chemotherapeutic response by DAPI stain and morphology, predictive algorithm reported as a drug response score	No evidence of effectiveness	November, 2015
81538	Oncology (lung), mass spectrometric 8-protein signature, including amyloid A, utilizing serum, prognostic and predictive algorithm reported as good versus poor overall survival	No evidence of effectiveness	November, 2015
81539	Oncology (high-grade prostate cancer), biochemical assay of four proteins (Total PSA, Free PSA, Intact PSA, and human kallikrein-2[hk2]), utilizing plasma or serum, prognostic algorithm reported as a probability score	Insufficient evidence of effectiveness	November, 2016
81540	Oncology (tumor of unknown origin), mRNA, gene expression profiling by real-time RT-PCR of 92 genes (87 content and 5 housekeeping) to classify tumor into main cancer type and subtype, utilizing formalin-fixed paraffin-embedded tissue, algorithm reported	No evidence of effectiveness	November, 2015
81545	Oncology (thyroid), gene expression analysis of 142 genes, utilizing fine needle aspirate, algorithm reported as a categorical result	No evidence of effectiveness	November, 2015
82107	Alpha-fetoprotein (AFP); AFP-L3 fraction isoform and total AFP		
82610	Cystatin		
82757	Fructose, semen		
82777	Galectin-3	No evidence of effectiveness	November, 2015

DRAFT

Guideline Updates for Lines 500 and 660

Procedure Code	Intervention Description	Rationale	Last Review
83006	Growth stimulation expressed gene 2 (ST2, Interleukin 1 receptor like-1)	No evidence of effectiveness	November, 2014
83037	Hemoglobin; glycosylated (A1C) by device cleared by FDA for home us3		
83631	Lactoferrin, fecal; quantitative		
83695	Lipoprotein (a)	No evidence of effectiveness	January, 2014
83698	Lipoprotein-associated phospholipase A2 (Lp-PLA2)		
83700-87004	Lipoprotein, blood		
83861	Tear osmolarity		
83951	Oncoprotein; des-gamma-carboxy-prothrombin (DCP)		
83987	pH; exhaled breath condensate	Insufficient evidence of effectiveness	December, 2009
83993	Calprotectin, fecal		
84145	Procalcitonin (PCT)	Insufficient evidence of effectiveness	December, 2009
84431	Thromboxane metabolite(s)	Insufficient evidence of effectiveness	December, 2009
86152-86153	Cell enumeration using immunologic selection and identification in fluid specimen (eg, circulating tumor cells in blood)	No evidence of effectiveness	December, 2012
86305	Human epididymis protein 4 (HE4)	Insufficient evidence of effectiveness	December, 2009
86356	Mononuclear cell antigen, quantitative (eg, flow cytometry		
86386	Nuclear Matrix Protein 22 (NMP22), qualitative	No evidence of effectiveness	December, 2011
87905	Infectious agent enzymatic activity other than virus (eg, sialidase activity in vaginal fluid)		
88738	Hemoglobin (HGB), quantitative, transcutaneous	Insufficient evidence of effectiveness	December, 2009
88740	Hemoglobin, quantitative, transcutaneous, per day; carboxyhemoglobin		
88741	Hemoglobin, quantitative, transcutaneous, per day; methhemoglobin		

DRAFT

Guideline Updates for Lines 500 and 660

Procedure Code	Intervention Description	Rationale	Last Review
90845	Psychoanalysis	No longer utilized in clinical practice	
90869	Therapeutic repetitive transcranial magnetic stimulation (TMS) treatment	No evidence of effectiveness	December, 2012
90880	Hypnotherapy	No clinically important benefit	August, 2015
91040	Esophageal balloon distension study		
91111	Capsule endoscopy, esophagus	No evidence of effectiveness	December, 2012
91112	Gastrointestinal transit and pressure measurement	Insufficient evidence of effectiveness	December, 2012
91117	Colon motility (manometric) study		
91120	Rectal sensation, tone, and compliance test		
92145	Corneal hysteresis determination	No evidence of effectiveness	November, 2014
92354-92355	Fitting of spectacle mounted low vision aid		
92559	Audiometric testing of groups		
92620-92621	Evaluation of central auditory function		
92625	Assessment of tinnitus		
92640	Diagnostic analysis with programming of auditory brainstem implant		
93050	Arterial pressure waveform analysis for assessment of central arterial pressure	Insufficient evidence of effectiveness	November, 2015
93571-93572	Intravascular Doppler velocity and/or pressure derived coronary flow reserve measurement		
93662	Intracardiac echocardiography during therapeutic/diagnostic intervention		
93702	Bioimpedance spectroscopy (BIS)	No evidence of effectiveness	November, 2014
93740	Temperature gradient studies	Insufficient evidence of effectiveness	October, 2015
93890-93893	Transcranial Doppler study of the intracranial arteries		

DRAFT

Guideline Updates for Lines 500 and 660

Procedure Code	Intervention Description	Rationale	Last Review
93895	Quantitative carotid intima media thickness and carotid atheroma evaluation	No evidence of effectiveness	November, 2014
94452-94453	High altitude simulation test (HAST)		
95012	Nitric oxide expired gas determination		
95250-95251	Retrospective (professional) continuous glucose monitoring	Limited evidence of clinical utility	August, 2017
95803	Actigraphy	No clinically important benefit	January, 2009
95928-95929	Central motor evoked potential study		
96020	Neurofunctional testing selection and administration during noninvasive imaging functional brain mapping		
96116	Neurobehavioral status exam (clinical assessment of thinking, reasoning and judgment, eg, acquired knowledge, attention, language, memory, planning and problem solving, and visual spatial abilities)		
96119	Neuropsychological testing (eg, Halstead-Reitan Neuropsychological Battery, Wechsler Memory Scales and Wisconsin Card Sorting Test)	No evidence of effectiveness	January, 2014
96120	Neuropsychological testing (eg, Wisconsin Card Sorting Test)		
96931-96935	Reflectance confocal microscopy for non-melanoma skin lesions	Insufficient evidence of effectiveness	November, 2015
96936	Reflectance confocal microscopy (RCM) for cellular and subcellular imaging of skin.	Insufficient evidence of effectiveness	November, 2016
97022	Application of a modality; whirlpool	Evidence of harm	May, 2016
97024	Application of a modality; diathermy (eg, microwave)	Insufficient evidence of effectiveness	May, 2016
97028	Application of a modality; ultraviolet	Insufficient evidence of effectiveness	May, 2016
97034	Application of a modality; contrast baths	Insufficient evidence of effectiveness	May, 2016

DRAFT

Guideline Updates for Lines 500 and 660

Procedure Code	Intervention Description	Rationale	Last Review
97035	Application of a modality to 1 or more areas; ultrasound		
97036	Application of a modality; Hubbard tank	Evidence of harm	May, 2016
97533	Sensory integrative techniques to enhance sensory processing and promote adaptive responses to environmental demands		
97610	Low frequency, non-contact, non-thermal ultrasound	No clinically important benefit	October, 2013

DRAFT

Code	Code Description	Placement
11920	Tattooing, intradermal introduction of insoluble opaque pigments to correct color defects of skin, including micropigmentation; 6.0 sq cm or less	Excluded (cosmetic)
11921	Tattooing, intradermal introduction of insoluble opaque pigments to correct color defects of skin, including micropigmentation; 6.1 to 20.0 sq cm	Excluded (cosmetic)
11922	Tattooing, intradermal introduction of insoluble opaque pigments to correct color defects of skin, including micropigmentation; each additional 20.0 sq cm, or part thereof (List separately in addition to code for primary procedure)	Excluded (cosmetic)
11980	Subcutaneous hormone pellet implantation (implantation of estradiol and/or testosterone pellets beneath the skin)	
15775	Punch graft for hair transplant; 1 to 15 punch grafts	Excluded (cosmetic)
15776	Punch graft for hair transplant; more than 15 punch grafts	Excluded (cosmetic)
15819	Cervicoplasty	
15820	Blepharoplasty, lower eyelid;	Excluded (cosmetic)
15821	Blepharoplasty, lower eyelid; with extensive herniated fat pad	Excluded (cosmetic)
15824	Rhytidectomy; forehead	Excluded (cosmetic)
15825	Rhytidectomy; neck with platysmal tightening (platysmal flap, P-flap)	Excluded (cosmetic)
15826	Rhytidectomy; glabellar frown lines	Excluded (cosmetic)
15828	Rhytidectomy; cheek, chin, and neck	Excluded (cosmetic)
15829	Rhytidectomy; superficial musculoaponeurotic system (SMAS) flap	Excluded (cosmetic)
15847	Excision, excessive skin and subcutaneous tissue (includes lipectomy), abdomen (eg, abdominoplasty) (includes umbilical transposition and fascial plication) (List separately in addition to code for primary procedure)	Excluded (cosmetic)
30430	Rhinoplasty, secondary; minor revision (small amount of nasal tip work)	Excluded (cosmetic)
38129	Unlisted laparoscopy procedure, spleen	Suspend for review?
44979	Unlisted laparoscopy procedure, appendix	Suspend for review?
52010	Cystourethroscopy, with ejaculatory duct catheterization, with or without irrigation, instillation, or duct radiography, exclusive of radiologic service	Excluded (infertility)
55870	Electroejaculation	Excluded (infertility)
58321	Artificial insemination; intra-cervical	Excluded (infertility)
58322	Artificial insemination; intra-uterine	Excluded (infertility)
58323	Sperm washing for artificial insemination	Excluded (infertility)
58345	Transcervical introduction of fallopian tube catheter for diagnosis and/or re-establishing patency (any method), with or without hysterosalpingography	Excluded (infertility)

Code	Code Description	Placement
58350	Chromotubation of oviduct, including materials	Excluded (infertility)
58672	Laparoscopy, surgical; with fimbrioplasty	Excluded (infertility)
58750	Tubotubal anastomosis	Excluded (infertility)
58752	Tubouterine implantation	Excluded (infertility)
58760	Fimbrioplasty	Excluded (infertility)
58825	Transposition, ovary(s)	Excluded (infertility)
58970	Follicle puncture for oocyte retrieval, any method	Excluded (infertility)
58974	Embryo transfer, intrauterine	Excluded (infertility)
58976	Gamete, zygote, or embryo intrafallopian transfer, any method	Excluded (infertility)
59897	Unlisted fetal invasive procedure, including ultrasound guidance, when performed	Suspend for review?
69090	Ear piercing	Excluded (cosmetic)
81225	CYP2C19 (cytochrome P450, family 2, subfamily C, polypeptide 19) (eg, drug metabolism), gene analysis, common variants (eg, *2, *3, *4, *8, *17)	GAP report
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)	GAP report
81227	CYP2C9 (cytochrome P450, family 2, subfamily C, polypeptide 9) (eg, drug metabolism), gene analysis, common variants (eg, *2, *3, *5, *6)	GAP report
81273	KIT (v-kit Hardy-Zuckerman 4 feline sarcoma viral oncogene homolog) (eg, mastocytosis), gene analysis, D816 variant(s)	
81287	MGMT (O-6-methylguanine-DNA methyltransferase) (eg, glioblastoma multiforme), methylation analysis	GAP report
81291	MTHFR (5,10-methylenetetrahydrofolate reductase) (eg, hereditary hypercoagulability) gene analysis, common variants (eg, 677T, 1298C)	GAP report
81330	SMPD1(sphingomyelin phosphodiesterase 1, acid lysosomal) (eg, Niemann-Pick disease, Type A) gene analysis, common variants (eg, R496L, L302P, fsP330)	GAP report
81350	UGT1A1 (UDP glucuronosyltransferase 1 family, polypeptide A1) (eg, irinotecan metabolism), gene analysis, common variants (eg, *28, *36, *37)	GAP report
81355	VKORC1 (vitamin K epoxide reductase complex, subunit 1) (eg, warfarin metabolism), gene analysis, common variant(s) (eg, -1639G>A, c.173+1000C>T)	GAP report
81417	Exome (eg, unexplained constitutional or heritable disorder or syndrome); re-evaluation of previously obtained exome sequence (eg, updated knowledge or unrelated condition/syndrome)	GAP report

Code	Code Description	Placement
81425	Genome (eg, unexplained constitutional or heritable disorder or syndrome); sequence analysis	GAP report
81426	Genome (eg, unexplained constitutional or heritable disorder or syndrome); sequence analysis, each comparator genome (eg, parents, siblings) (List separately in addition to code for primary procedure)	GAP report
81427	Genome (eg, unexplained constitutional or heritable disorder or syndrome); re-evaluation of previously obtained genome sequence (eg, updated knowledge or unrelated condition/syndrome)	GAP report
81432	Hereditary breast cancer-related disorders (eg, hereditary breast cancer, hereditary ovarian cancer, hereditary endometrial cancer); genomic sequence analysis panel, must include sequencing of at least 10 genes, always including BRCA1, BRCA2, CDH1, MLH1,	under current review
81433	Hereditary breast cancer-related disorders (eg, hereditary breast cancer, hereditary ovarian cancer, hereditary endometrial cancer); duplication/deletion analysis panel, must include analyses for BRCA1, BRCA2, MLH1, MSH2, and STK11	under current review
81470	X-linked intellectual disability (XLID) (eg, syndromic and non-syndromic XLID); genomic sequence analysis panel, must include sequencing of at least 60 genes, including ARX, ATRX, CDKL5, FGD1, FMR1, HUWE1, IL1RAPL, KDM5C, L1CAM, MECP2, MED12, MID1, OCRL,	GAP report
81471	X-linked intellectual disability (XLID) (eg, syndromic and non-syndromic XLID); duplication/deletion gene analysis, must include analysis of at least 60 genes, including ARX, ATRX, CDKL5, FGD1, FMR1, HUWE1, IL1RAPL, KDM5C, L1CAM, MECP2, MED12, MID1, OCRL	GAP report
84830	Ovulation tests, by visual color comparison methods for human luteinizing hormone	Excluded (infertility)
86910	Blood typing, for paternity testing, per individual; ABO, Rh and MN	Excluded (Administrative)
86911	Blood typing, for paternity testing, per individual; each additional antigen system	Excluded (Administrative)
88000	Necropsy (autopsy), gross examination only; without CNS	Excluded (Administrative)
88005	Necropsy (autopsy), gross examination only; with brain	Excluded (Administrative)
88007	Necropsy (autopsy), gross examination only; with brain and spinal cord	Excluded (Administrative)
88012	Necropsy (autopsy), gross examination only; infant with brain	Excluded (Administrative)
88014	Necropsy (autopsy), gross examination only; stillborn or newborn with brain	Excluded (Administrative)
88016	Necropsy (autopsy), gross examination only; macerated stillborn	Excluded (Administrative)
88020	Necropsy (autopsy), gross and microscopic; without CNS	Excluded (Administrative)
88025	Necropsy (autopsy), gross and microscopic; with brain	Excluded (Administrative)

Code	Code Description	Placement
88027	Necropsy (autopsy), gross and microscopic; with brain and spinal cord	Excluded (Administrative)
88028	Necropsy (autopsy), gross and microscopic; infant with brain	Excluded (Administrative)
88029	Necropsy (autopsy), gross and microscopic; stillborn or newborn with brain	Excluded (Administrative)
88036	Necropsy (autopsy), limited, gross and/or microscopic; regional	Excluded (Administrative)
88037	Necropsy (autopsy), limited, gross and/or microscopic; single organ	Excluded (Administrative)
88040	Necropsy (autopsy); forensic examination	Excluded (Administrative)
88045	Necropsy (autopsy); coroner's call	Excluded (Administrative)
88099	Unlisted necropsy (autopsy) procedure	Excluded (Administrative)
88749	Unlisted in vivo (eg, transcutaneous) laboratory service	Suspend for review?
89250	Culture of oocyte(s)/embryo(s), less than 4 days;	Excluded (infertility)
89251	Culture of oocyte(s)/embryo(s), less than 4 days; with co-culture of oocyte(s)/embryos	Excluded (infertility)
89253	Assisted embryo hatching, microtechniques (any method)	Excluded (infertility)
89254	Oocyte identification from follicular fluid	Excluded (infertility)
89255	Preparation of embryo for transfer (any method)	Excluded (infertility)
89257	Sperm identification from aspiration (other than seminal fluid)	Excluded (infertility)
89258	Cryopreservation; embryo(s)	Excluded (infertility)
89259	Cryopreservation; sperm	Excluded (infertility)
89260	Sperm isolation; simple prep (eg, sperm wash and swim-up) for insemination or diagnosis with semen analysis	Excluded (infertility)
89261	Sperm isolation; complex prep (eg, Percoll gradient, albumin gradient) for insemination or diagnosis with semen analysis	Excluded (infertility)
89264	Sperm identification from testis tissue, fresh or cryopreserved	Excluded (infertility)
89268	Insemination of oocytes	Excluded (infertility)
89272	Extended culture of oocyte(s)/embryo(s), 4-7 days	Excluded (infertility)
89280	Assisted oocyte fertilization, microtechnique; less than or equal to 10 oocytes	Excluded (infertility)
89281	Assisted oocyte fertilization, microtechnique; greater than 10 oocytes	Excluded (infertility)
89290	Biopsy, oocyte polar body or embryo blastomere, microtechnique (for pre-implantation genetic diagnosis); less than or equal to 5 embryos	Excluded (infertility)
89291	Biopsy, oocyte polar body or embryo blastomere, microtechnique (for pre-implantation genetic diagnosis); greater than 5 embryos	Excluded (infertility)
89300	Semen analysis; presence and/or motility of sperm including Huhner test (post coital)	Excluded (infertility)
89310	Semen analysis; motility and count (not including Huhner test)	Excluded (infertility)
89320	Semen analysis; volume, count, motility, and differential	Excluded (infertility)

Code	Code Description	Placement
89321	Semen analysis; sperm presence and motility of sperm, if performed	Excluded (infertility)
89322	Semen analysis; volume, count, motility, and differential using strict morphologic criteria (eg, Kruger)	Excluded (infertility)
89325	Sperm antibodies	Excluded (infertility)
89329	Sperm evaluation; hamster penetration test	Excluded (infertility)
89330	Sperm evaluation; cervical mucus penetration test, with or without spinnbarkeit test	Excluded (infertility)
89331	Sperm evaluation, for retrograde ejaculation, urine (sperm concentration, motility, and morphology, as indicated)	Excluded (infertility)
89335	Cryopreservation, reproductive tissue, testicular	Excluded (infertility)
89337	Cryopreservation, mature oocyte(s)	Excluded (infertility)
89342	Storage (per year); embryo(s)	Excluded (infertility)
89343	Storage (per year); sperm/semen	Excluded (infertility)
89344	Storage (per year); reproductive tissue, testicular/ovarian	Excluded (infertility)
89346	Storage (per year); oocyte(s)	Excluded (infertility)
89352	Thawing of cryopreserved; embryo(s)	Excluded (infertility)
89353	Thawing of cryopreserved; sperm/semen, each aliquot	Excluded (infertility)
89354	Thawing of cryopreserved; reproductive tissue, testicular/ovarian	Excluded (infertility)
89356	Thawing of cryopreserved; oocytes, each aliquot	Excluded (infertility)
89398	Unlisted reproductive medicine laboratory procedure	Excluded (infertility)
90625	Cholera vaccine, live, adult dosage, 1 dose schedule, for oral use	Excluded (travel vaccine)
90690	Typhoid vaccine, live, oral	Excluded (travel vaccine)
90691	Typhoid vaccine, Vi capsular polysaccharide (ViCPs), for intramuscular use	Excluded (travel vaccine)
90717	Yellow fever vaccine, live, for subcutaneous use	Excluded (travel vaccine)
90738	Japanese encephalitis virus vaccine, inactivated, for intramuscular use	Excluded (travel vaccine)
90863	Pharmacologic management, including prescription and review of medication, when performed with psychotherapy services (List separately in addition to the code for primary procedure)	excluded (administrative) use not allowed by state law
92596	Ear protector attenuation measurements	excluded (administrative)
97169	Athletic training evaluation, low complexity, requiring these components: A history and physical activity profile with no comorbidities that affect physical activity; An examination of affected body area and other symptomatic or related systems addressin	Excluded (administrative)

Code	Code Description	Placement
97170	Athletic training evaluation, moderate complexity, requiring these components: A medical history and physical activity profile with 1-2 comorbidities that affect physical activity; An examination of affected body area and other symptomatic or related sys	Excluded (administrative)
97171	Athletic training evaluation, high complexity, requiring these components: A medical history and physical activity profile, with 3 or more comorbidities that affect physical activity; A comprehensive examination of body systems using standardized tests a	Excluded (administrative)
97172	Re-evaluation of athletic training established plan of care requiring these components: An assessment of patient's current functional status when there is a documented change; and A revised plan of care using a standardized patient assessment instrument	Excluded (administrative)
97545	Work hardening/conditioning; initial 2 hours	Excluded (administrative)
97546	Work hardening/conditioning; each additional hour (List separately in addition to code for primary procedure)	Excluded (administrative)
99000	Handling and/or conveyance of specimen for transfer from the office to a laboratory	Excluded (administrative)
99001	Handling and/or conveyance of specimen for transfer from the patient in other than an office to a laboratory (distance may be indicated)	Excluded (administrative)
99002	Handling, conveyance, and/or any other service in connection with the implementation of an order involving devices (eg, designing, fitting, packaging, handling, delivery or mailing) when devices such as orthotics, protectives, prosthetics are fabricated	Excluded (administrative)
99024	Postoperative follow-up visit, normally included in the surgical package, to indicate that an evaluation and management service was performed during a postoperative period for a reason(s) related to the original procedure	Excluded (bundled)
99053	Service(s) provided between 10:00 PM and 8:00 AM at 24-hour facility, in addition to basic service	Excluded (administrative)
99056	Service(s) typically provided in the office, provided out of the office at request of patient, in addition to basic service	Excluded (administrative)
99090	Analysis of clinical data stored in computers (eg, ECGs, blood pressures, hematologic data)	Excluded (administrative)
99241	Office consultation for a new or established patient, which requires these 3 key components: A problem focused history; A problem focused examination; and Straightforward medical decision making. Counseling and/or coordination of care with other physicia	Excluded (administrative)

Code	Code Description	Placement
99242	Office consultation for a new or established patient, which requires these 3 key components: An expanded problem focused history; An expanded problem focused examination; and Straightforward medical decision making. Counseling and/or coordination of care	Excluded (administrative)
99243	Office consultation for a new or established patient, which requires these 3 key components: A detailed history; A detailed examination; and Medical decision making of low complexity. Counseling and/or coordination of care with other physicians, other qu	Excluded (administrative)
99244	Office consultation for a new or established patient, which requires these 3 key components: A comprehensive history; A comprehensive examination; and Medical decision making of moderate complexity. Counseling and/or coordination of care with other physi	Excluded (administrative)
99245	Office consultation for a new or established patient, which requires these 3 key components: A comprehensive history; A comprehensive examination; and Medical decision making of high complexity. Counseling and/or coordination of care with other physician	Excluded (administrative)
99251	Inpatient consultation for a new or established patient, which requires these 3 key components: A problem focused history; A problem focused examination; and Straightforward medical decision making. Counseling and/or coordination of care with other physi	Excluded (administrative)
99252	Inpatient consultation for a new or established patient, which requires these 3 key components: An expanded problem focused history; An expanded problem focused examination; and Straightforward medical decision making. Counseling and/or coordination of c	Excluded (administrative)
99253	Inpatient consultation for a new or established patient, which requires these 3 key components: A detailed history; A detailed examination; and Medical decision making of low complexity. Counseling and/or coordination of care with other physicians, other	Excluded (administrative)
99254	Inpatient consultation for a new or established patient, which requires these 3 key components: A comprehensive history; A comprehensive examination; and Medical decision making of moderate complexity. Counseling and/or coordination of care with other ph	Excluded (administrative)

Excluded Codes

Code	Code Description	Placement
99255	Inpatient consultation for a new or established patient, which requires these 3 key components: A comprehensive history; A comprehensive examination; and Medical decision making of high complexity. Counseling and/or coordination of care with other physic	Excluded (administrative)
99450	Basic life and/or disability examination that includes: Measurement of height, weight, and blood pressure; Completion of a medical history following a life insurance pro forma; Collection of blood sample and/or urinalysis complying with "chain of custody	Exclude (Administative)

Issue:
The VBBS approved the placement of 3 HCPCS codes for barium enema for screening for colorectal cancer during the review of the coverage guidance on colorectal cancer screening modalities in September, 2017. HERC has returned these 3 codes to the VBBS for reconsideration for placement. Barium enema is a diagnostic test that is useful in certain clinical situations, but is not a test used for colorectal cancer screening and was not reviewed in the coverage guidance on CRC screening. The barium enema CRC screening HCPCS codes are currently in the Ancillary File.

The following codes are diagnostic and should remain so:
CPT 74270 Radiologic examination, colon; contrast (eg, barium) enema, with or without KUB
CPT 74280 Radiologic examination, colon; air contrast with specific high density barium, with or without glucagon

The following code is ancillary
CPT 74283 Therapeutic enema, contrast or air, for reduction of intussusception or other intraluminal obstruction (eg, meconium ileus)

HERC Staff Recommendations:

1) Add CPT 74283 (Therapeutic enema, contrast or air, for reduction of intussusception or other intraluminal obstruction (eg, meconium ileus)) to line 41 INTUSSCEPTION, VOLVULUS, INTESTINAL OBSTRUCTION, HAZARDOUS FOREIGN BODY IN GI TRACT WITH RISK OF PERFORATION OR OBSTRUCTION
    a. Intussusception and intestinal obstruction are both on line 41.
    b. Advise HSD to remove CPT 74283 from the Ancillary List
2) **Option 1**: Add the following HCPCS codes to line 500 CONDITIONS FOR WHICH CERTAIN INTERVENTIONS RESULT IN MARGINAL CLINICAL BENEFIT OR LOW COST-EFFECTIVENESS and add an entry to GN172 as shown below
    a. G0106 (Colorectal cancer screening; alternative to g0104, screening sigmoidoscopy, barium enema)
    b. G0120 (Colorectal cancer screening; alternative to g0105, screening colonoscopy, barium enema)
    c. G0122 (Colorectal cancer screening; barium enema)
    d. There has been no evidence review of barium enema for CRC screening; therefore it is not known if it is an unproven treatment. However, this test is no longer used for CRC screening nor mentioned in the USPSTF recommendations for CRC screening. Other, more evidence-based and effective screening tools exist.

GUIDELINE NOTE 172, INTERVENTIONS WITH MARGINAL CLINICAL BENEFIT OR LOW COST-EFFECTIVENESS FOR CERTAIN CONDITIONS

The following interventions are prioritized on Line 500 for the conditions listed here:

CPT/HCPCS code	INTERVENTION	Rationale	Date of Last Review/Link to Meeting Minutes
G0106, G0120, G0122	Barium enema as a colorectal cancer screening modality	No longer used as a CRC screening modality	November, 2017

3) **Option 2**: Add the barium enema for CRC screening HCPCS codes to line 660 CONDITIONS FOR WHICH CERTAIN TREATMENTS HAVE NO CLINICALLY IMPORTANT BENEFIT OR HAVE HARMS THAT OUTWEIGH BENEFITS; UNPROVEN TREATMENTS and add an entry to GN173 as shown below
    a. This test is obsolete and not indicated.

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

The following treatments are prioritized on Line 660, CONDITIONS FOR WHICH CERTAIN TREATMENTS HAVE NO CLINICALLY IMPORTANT BENEFIT OR HAVE HARMS THAT OUTWEIGH BENEFITS; UNPROVEN TREATMENTS for the conditions listed here:

CPT/HCPCS code	INTERVENTION	Rationale	Date of last Review
G0106, G0120, G0122	Barium enema as a colorectal cancer screening modality	Not indicated as a CRC screening modality	November, 2017

4) Advise HSD to remove G0106, G0120 and G0122 from the Ancillary File

Nicotine replacement tobacco cessation guideline

Question: Does the tobacco dependence guideline need modification?

Question source: Peter Mahr, MD, local provider

Issue: A local provider was finding difficulty with getting nicotine replacement therapy (specifically patches) covered by a CCO and contacted HERC to determine required coverage. In the follow up to that query, the following questions have arisen:

- Do CCOs need to cover, without any copay or prior authorization, all FDA-approved pharmacotherapies?
    - All types (i.e. the variety of nicotine replacement therapies including gum, lozenges, patches, nasal spray, inhaler, varenicline, buproprion)
    - All brands

The Pharmacy & Therapeutics (P&T) Committee reviewed tobacco cessation medications in 2016. They decided to make 2 of these forms subject to PA: nicotine inhaler and nicotine spray based on the higher cost of these dosage forms.

At the last VbBS meeting, there was concern raised that forcing coverage of all types of NRT did not take into account the variable evidence or cost-effectiveness of some of the forms of nicotine replacement therapy and staff was asked to re-clarify requirements and modify the guideline proposal.

Also, the weblink needs updating.

Cost of various pharmacotherapy (generalized, mostly based on WAC)
See table below

Prioritized List Status

GUIDELINE NOTE 4, Tobacco dependence, including during pregnancy

Lines 1,5

Pharmacotherapy and behavioral counseling are included on this line, alone or in combination, for at least 2 quit attempts per year. A minimum of four counseling sessions of at least 10 minutes each (group or individual, telephonic or in person) are included for each quit attempt. More intensive interventions and group therapy are likely to be the most effective behavioral interventions. During pregnancy, additional intensive behavioral counseling is strongly encouraged. All tobacco cessation interventions during pregnancy are not subject to limits.

Inclusion on this line follows the minimum standard criteria as defined in the Oregon Public Health Division "Standard Tobacco Cessation Coverage" (based on the Patient Protection and Affordable Care Act), available here: https://public.health.oregon.gov/PreventionWellness/TobaccoPrevention/Pages/pubs.aspx. The USPSTF has also made "A" recommendations for screening,

counseling, and treatment of pregnant and nonpregnant adults, included in Guideline Note 106.

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

HERC Staff Summary

The intent of the guideline note would be met if at least one medication within each category is covered fully with no PA or co-pays. For example, if there are two different brands of patches, with significantly different cost, it is reasonable for a CCO to choose to offer a cheaper patch. However, they must also make available all the variety of different options of pharmacotherapy (patches, gum, lozenges, spray, inhaler, varenicline, buproprion).

HERC Staff Recommendations:

1) Update the hyperlink to the public health Standard Tobacco Cessation Coverage document
2) Modify guideline note 4 to clarify coverage of pharmacotherapy as follows:
   GUIDELINE NOTE 4, Tobacco dependence, including during pregnancy

   Lines 1,5

   Pharmacotherapy (including all 7 FDA approved smoking cessation medications) and behavioral counseling are included on this line, alone or in combination, for at least 2 quit attempts per year, without prior authorization.

   Pharmacotherapy includes nicotine replacement therapy (e.g. gum, patches, and lozenges), varenicline, and bupropion. At least one option for each of these listed therapies is included on these lines with no prior authorization requirement for at least two quit attempts per year. Each quit attempt can include concurrent use of either two nicotine replacement dosage forms or one nicotine replacement form plus bupropion SR.

   A minimum of four counseling sessions of at least 10 minutes each (group or individual, telephonic or in person) are included for each quit attempt. More intensive interventions and group therapy are likely to be the most effective behavioral interventions. During pregnancy, additional intensive behavioral counseling is strongly encouraged. All tobacco cessation interventions during pregnancy are not subject to quantity or duration limits.

   Inclusion on this line follows the minimum standard criteria as defined in the Oregon Public Health Division "Standard Tobacco Cessation Coverage" (based on the Patient Protection and Affordable Care Act), available here:

~~https://public.health.oregon.gov/PreventionWellness/TobaccoPrevention/Pages/pubs.aspx.~~
http://www.oregon.gov/oha/PH/PREVENTIONWELLNESS/TOBACCOPREVENTION/Documents/tob_cessation_coverage_standards.pdf. The USPSTF has also made "A" recommendations for screening, counseling, and treatment of pregnant and nonpregnant adults, included in Guideline Note 106.

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

Medication	Form/dose	Times/month	AAAC	Unit	Monthly cost	Notes	Unit costs
Lozenge	POLAcrilex 2 mg	496	0.33099	Each	$ 164.17	Hourly 16hrs/day (max dose)	
Lozenge	Polacrilex 4 mg	496	0.32889	Each	$ 163.13	Hourly 16hrs/day (max dose)	
Gum	POLACRILEX 2 mg	496	0.21845	Each	$ 108.35	Hourly 16hrs/day (max dose)	
Gum	Polacrilex 4 mg	496	0.2555	Each	$ 126.73	Hourly 16hrs/day (max dose)	
Inhaler	Cartridge 10 mg	496	2.22746	cartridge	$ 1,104.82	6 to 16 cartridges/day per packaging; used 16 here	AAAC for 168 cartridges is $374.21
Spray	10ml bottle	124	9.92521	ml	$ 1,230.73	1 dose=2 applications of 0.5; 1 dose=1 mg. There are 10 mg/ml so 10 doses/mL; max 40 doses/day	$99.25 per 10ml bottle
Patch	7 mg/24 h TD24	31	1.58182	Each	$ 49.04		
Patch	14 mg/24h	31	1.62297	Each	$ 50.31		
Patch	21 mg/24h	31	1.60868	Each	$ 49.87		
Bupropion ER	100 MG/tab	60	0.15867	Each	$ 9.52	Oregon AAAC	generic Wellbutrin - Carveout
Buproprion ER	200 MG / tab	60	0.1436	Each	$ 8.62	Oregon AAAC	generic Wellbutrin - Carveout
Buproprion SR	150 MG/TAB-AB1	60	0.0886	Each	$ 5.32	Oregon AAAC	
Buproprion SR	150 mg/tab-AB2	60	0.354	Each	$ 21.24	Oregon AAAC	generic Zyban
Buproprion XL	150 mg/tab	30	0.31061	Each	$ 9.32	Oregon AAAC	generic Wellbutrin - Carveout

Medication	Form/dose	Times/month	AAAC	Unit	Monthly cost	Notes	Unit costs
Buproprion XL	300 mg/tab	30	0.32318	Each	$ 9.70	Oregon AAAC	generic Wellbutrin - Carveout
Varenicline	1mg/tab	60	6.32947	Each	$ 379.77	Oregon AAAC	

FAQS ABOUT AFFORDABLE CARE ACT IMPLEMENTATION (PART XIX)

May 2, 2014

Set out below are additional Frequently Asked Questions (FAQs) regarding implementation of various provisions of the Affordable Care Act. These FAQs have been prepared jointly by the Departments of Labor (DOL), Health and Human Services (HHS), and the Treasury (collectively, the Departments). Like previously issued FAQs (available at http://www.dol.gov/ebsa/healthreform/ and http://www.cms.gov/cciio/resources/fact-sheets-and-faqs/index.html), these FAQs answer questions from stakeholders to help people understand the new law and benefit from it, as intended.

Updated Department of Labor Model Notices

In general, under the Consolidated Omnibus Budget Reconciliation Act (COBRA), an individual who was covered by a group health plan on the day before the occurrence of a qualifying event (such as a termination of employment or a reduction in hours that causes loss of coverage under the plan) may be able to elect COBRA continuation coverage upon that qualifying event.[1] Individuals with such a right are referred to as qualified beneficiaries.

Under COBRA, group health plans must provide covered employees and their families with certain notices explaining their COBRA rights. A group health plan must provide each covered employee and spouse (if any) with a written notice of COBRA rights "at the time of commencement of coverage" under the plan (general notice). A group health plan must also provide qualified beneficiaries with a notice which describes their rights to COBRA continuation coverage and how to make an election (election notice).

General Notice: The general notice must be furnished to each covered employee (and their spouse if covered under the plan) not later than the earlier of: (1) 90 days from the date on which the covered employee or spouse first becomes covered under the plan or, if later, the date on which the plan first becomes subject to the continuation coverage requirements; or (2) the date on which the administrator is required to furnish an election notice to the employee or to his or her spouse or dependent. The general notice is required to include:

- The name of the plan and the name, address, and telephone number of someone whom the employee and spouse can contact for more information on COBRA and the plan;
- A general description of the continuation coverage provided under the plan;
- An explanation of what qualified beneficiaries must do to notify the plan of qualifying events or disabilities;
- An explanation of the importance of keeping the plan administrator informed of addresses of the participants or beneficiaries; and

[1] For more information on COBRA continuation coverage requirements applicable to group health plans, *see* "An Employer's Guide to Group Health Continuation Coverage Under COBRA," available at www.dol.gov/ebsa/publications/cobraemployer.html.

- A statement that the general notice does not fully describe COBRA or the plan and that more complete information is available from the plan administrator and in the plan's summary plan description (SPD).

Election Notice: The election notice must be provided to the qualified beneficiaries within 14 days after the plan administrator receives notice that a qualifying event has occurred. The election notice is required to include:

- The name of the plan and the name, address, and telephone number of the plan's COBRA administrator;
- Identification of the qualifying event;
- Identification of the qualified beneficiaries (by name or by status);
- An explanation of the qualified beneficiaries' right to elect COBRA continuation coverage;
- The date coverage will terminate (or has terminated) if COBRA continuation coverage is not elected;
- How to elect COBRA continuation coverage;
- What will happen if COBRA continuation coverage isn't elected or is waived;
- What COBRA continuation coverage is available, for how long, and (if it is for less than 36 months), how it can be extended for disability or second qualifying events;
- How COBRA continuation coverage might terminate early;
- Premium payment requirements, including due dates and grace periods;
- A statement of the importance of keeping the plan administrator informed of the addresses of qualified beneficiaries; and
- A statement that the election notice does not fully describe COBRA or the plan and that more information is available from the plan administrator and in the plan's SPD.

Some qualified beneficiaries may want to consider and compare health coverage alternatives to COBRA continuation coverage, such as coverage that is available through the Health Insurance Marketplace (Marketplace). Qualified beneficiaries may be eligible for a premium tax credit (a tax credit to help pay for some or all of the cost of coverage in plans offered through the Marketplace) and cost-sharing reductions (amounts that lower out-of-pocket costs for deductibles, coinsurance, and copayments), and may find that Marketplace coverage is more affordable than COBRA.

The Children's Health Insurance Program Reauthorization Act of 2009 (CHIPRA) specifies that an employer that maintains a group health plan in a State that provides premium assistance[2] for the purchase of coverage under a group health plan is required to notify each employee of potential opportunities currently available for premium assistance in the State in which the employee resides.[3]

[2] The CHIPRA notice requirement applies to an employer that maintains a group health plan in a State that provides premium assistance under a State Medicaid plan under title XIX of the Social Security Act (SSA), or child health assistance under a State child health plan under title XXI of the SSA.

[3] The Department of Labor provided guidance regarding this notice requirement and announced the availability of a model notice on February 4, 2010 at 75 FR 5808.

The Department of Labor has model notices that plans may use to satisfy the requirement to provide the general notice and election notice under COBRA, and the notice regarding premium assistance under CHIPRA. The COBRA model election notice was revised on May 8, 2013 to help make qualified beneficiaries aware of other coverage options that would soon become available in the Marketplace. Today, DOL is issuing a Notice of Proposed Rulemaking, as well as updated versions of the model general notice and model election notice that reflect that the Marketplace is now open and that better describes special enrollment rights in Marketplace coverage. DOL is also issuing a revised CHIPRA notice with similar updates related to Marketplace coverage.

Q1: Where can I get a copy of the Department of Labor's newest model notices?

The model general notice and model election notice are available on the DOL website at www.dol.gov/ebsa/cobra.html and the model CHIPRA notice is available at http://www.dol.gov/ebsa/compliance_assistance.html. (The model notices are available in modifiable, electronic form). As with the earlier model notices, in order to use the model properly, the plan administrator must complete it by filling in the blanks with the appropriate plan information.

Contemporaneous with the issuance of these FAQs, DOL is also issuing a notice of proposed rulemaking to update its regulations with respect to the COBRA model notices. Until rulemaking is finalized and effective, DOL will consider use of the model notices available on its website, appropriately completed, to constitute compliance with the notice content requirements of COBRA.

Limitations on Cost-Sharing under the Affordable Care Act

Public Health Service (PHS) Act section 2707(b), as added by the Affordable Care Act, provides that a non-grandfathered group health plan shall ensure that any annual cost-sharing imposed under the plan does not exceed the limitations provided for under sections 1302(c)(1) of the Affordable Care Act. Section 1302(c)(1) limits an enrollee's out-of-pocket costs.[4]

For plan or policy years beginning in 2014, the annual limitation on out-of-pocket costs in effect under Affordable Care Act section 1302(c)(1) is $6,350 for self-only coverage and $12,700 for coverage other than self-only coverage. Beginning with the 2015 plan or policy year and for plan or policy years thereafter, the annual limitation on out-of-pocket costs is increased by the premium adjustment percentage described under Affordable Care Act section 1302(c)(4). HHS has proposed that after applying the premium adjustment percentage, the annual limitation on out-of-pocket costs for 2015 would be $6,600 for self-only coverage and $13,200 for coverage other than self-only coverage.[5]

[4] The annual limitation on out-of-pocket costs is also applied to non-grandfathered individual market coverage through the essential health benefits package requirements of PHS Act section 2707(a). On April 1, 2014, Public Law No. 113-93 was enacted. Section 213 of that law repeals the limitation on deductibles in the small group market that was previously required in this market under section 2707(b) of the PHS Act and section 1302(c)(2) of the Affordable Care Act.

[5] Patient Protection and Affordable Care Act; Exchange and Insurance Market Standards for 2015 and Beyond; Proposed Rule, 79 FR 15808 (Mar. 21, 2014).

Previous FAQs provided guidance on out-of-pocket maximums.[6] Set forth below are FAQs addressing additional questions about out-of-pocket maximums.

Q2: If an out-of-network provider charges an amount greater than the plan's or issuer's allowed amount, does individual spending for the amount in excess of the allowed amount (also known as balance billing) count toward the out-of-pocket maximum?

The Departments previously stated in an FAQ[7] that if a plan includes a network of providers, the plan may, but is not required to, count out-of-pocket spending for out-of-network items and services towards the plan's annual out-of-pocket maximum. A plan that counts such spending towards the out-of-pocket maximum may use any reasonable method for doing so. For example, if the plan covers 75% of the usual, customary, and reasonable amount (UCR) charged for services provided out-of-network and the participant pays the remaining 25% of UCR plus any amount charged by the out-of-network provider in excess of UCR, the 25% of UCR paid by the participant may reasonably be counted, in full or in part, toward the out-of-pocket maximum without including any amount charged above UCR paid by the participant.

Q3: With respect to the annual out-of-pocket maximum, how should large group market coverage and self-insured group health plans treat an individual's out-of-pocket costs for a brand name prescription drug, in circumstances in which a generic was available and medically appropriate?

As the Departments previously stated in guidance on how to apply annual and lifetime dollar limits under section 2711 of the Public Health Service Act,[8] large group market coverage and self-insured group health plans have discretion to define "essential health benefits." For example, a plan may include only generic drugs, if medically appropriate (as determined by the individual's personal physician) and available, while providing a separate option (not as part of essential health benefits) of electing a brand name drug at a higher cost sharing amount. If, under this type of plan design, a participant or beneficiary selects a brand name prescription drug in circumstances in which a generic was available and medically appropriate (as determined by the individual's personal physician), the plan may provide that all or some of the amount paid by the participant or beneficiary (e.g., the difference between the cost of the brand name drug and the cost of the generic drug) is not required to be counted towards the annual out-of-pocket maximum. For ERISA plans, the SPD must explain which covered benefits will not count towards an individual's out-of-pocket maximum.

In determining whether a generic is medically appropriate, a plan may use a reasonable exception process. For example, the plan may defer to the recommendation of an individual's

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[6] See Affordable Care Act Implementation FAQs, Part XII, Q2, available at http://www.dol.gov/ebsa/faqs/faq-aca12.html and http://www.cms.gov/CCIIO/Resources/Fact-Sheets-and-FAQs/aca_implementation_faqs12.html; Affordable Care Act Implementation FAQs, Part XVIII, Q2-Q5, available at http://www.dol.gov/ebsa/faqs/faq-aca18.html and http://www.cms.gov/CCIIO/Resources/Fact-Sheets-and-FAQs/aca_implementation_faqs18.html.

[7] See ACA Implementation FAQs Part XVIII, Q4, available at www.dol.gov/ebsa/faqs/faq-aca18.html and http://www.cms.gov/CCIIO/Resources/Fact-Sheets-and-FAQs/aca_implementation_faqs18.html.

[8] CMS, **Frequently Asked Questions on Essential Health Benefits Bulletin, Q10 (**February 17, 2012) http://www.cms.gov/CCIIO/Resources/Files/Downloads/ehb-faq-508.pdf

personal physician, or it may offer an exceptions process meeting the requirements of 45 CFR 156.122(c).

For non-grandfathered health plans in the individual and small group markets that must provide coverage of the essential health benefit package under section 1302(a) of the Affordable Care Act, additional requirements apply.

Q4: If large group market coverage or self-insured group health plan has a reference-based pricing structure, under which the plan pays a fixed amount for a particular procedure (for example, a knee replacement), which certain providers will accept as payment in full, how does the out-of-pocket limitation apply when an individual uses a provider that does not accept that amount as payment in full?

Reference pricing aims to encourage plans to negotiate cost effective treatments with high quality providers at reduced costs. At the same time, the Departments are concerned that such a pricing structure may be a subterfuge for the imposition of otherwise prohibited limitations on coverage, without ensuring access to quality care and an adequate network of providers.

Accordingly, the Departments invite comment on the application of the out-of-pocket limitation to the use of reference based pricing. The Departments are particularly interested in standards that plans using reference-based pricing structures should be required to meet to ensure that individuals have meaningful access to medically appropriate, quality care. Please send comments by August 1, 2014 to E-OHPSCA-FAQ.ebsa@dol.gov.

Until guidance is issued and effective, with respect to a large group market plan or self-insured group health plan that utilizes a reference-based pricing program, the Departments will not consider a plan or issuer as failing to comply with the out-of-pocket maximum requirements of PHS Act section 2707(b) because it treats providers that accept the reference amount as the only in-network providers, provided the plan uses a reasonable method to ensure that it provides adequate access to quality providers.

For non-grandfathered health plans in the individual and small group markets that must provide coverage of the essential health benefit package under section 1302(a) of the Affordable Care Act, additional requirements apply.

Coverage of Preventive Services

PHS Act section 2713 and the interim final regulations relating to coverage of preventive services[9] require non-grandfathered group health plans and health insurance coverage offered in the individual or group market to provide benefits for, and prohibit the imposition of cost-sharing requirements with respect to, the following:

- Evidenced-based items or services that have in effect a rating of "A" or "B" in the current recommendations of the United States Preventive Services Task Force (USPSTF) with respect to the individual involved, except for the recommendations of the USPSTF

[9] 75 FR 41726 (July 19, 2010).

regarding breast cancer screening, mammography, and prevention issued in or around November 2009, which are not considered current;

- Immunizations for routine use in children, adolescents, and adults that have in effect a recommendation from the Advisory Committee on Immunization Practices (ACIP) of the Centers for Disease Control and Prevention (CDC) with respect to the individual involved;
- With respect to infants, children, and adolescents, evidence-informed preventive care and screenings provided for in comprehensive guidelines supported by the Health Resources and Services Administration (HRSA); and
- With respect to women, evidence-informed preventive care and screening provided for in comprehensive guidelines supported by HRSA, to the extent not already included in certain recommendations of the USPSTF.[10]

If a recommendation or guideline does not specify the frequency, method, treatment, or setting for the provision of that service, the plan or issuer can use reasonable medical management techniques to determine any such coverage limitations.[11]

These requirements do not apply to grandfathered health plans.[12]

Q5: The USPSTF recommends that clinicians ask all adults about tobacco use and provide tobacco cessation interventions for those who use tobacco products. What are plans and issuers expected to provide as preventive coverage for tobacco cessation interventions?

As stated earlier, plans may use reasonable medical management techniques to determine the frequency, method, treatment, or setting for a recommended preventive service, to the extent not specified in the recommendation or guideline regarding that preventive service. Evidence-based clinical practice guidelines can provide useful guidance for plans and issuers.[13] The Departments will consider a group health plan or health insurance issuer to be in compliance with the

[10] "Women's Preventive Services: Required Health Plan Coverage Guidelines" (HRSA Guidelines) were adopted and released on August 1, 2011, based on recommendations developed by the Institute of Medicine (IOM) at the request of HHS. These recommended women's preventive services are required to be covered without cost-sharing, for plan years (or, in the individual market, policy years) beginning on or after August 1, 2012.

[11] See 29 CFR 2590.715-2713(a)(4) and 45 CFR 147.130(a)(4).

[12] In addition, the HRSA Guidelines exempt group health plans established or maintained by certain religious employers (and any group health insurance coverage provided in connection with such plans) from any requirement to cover contraceptive services that would otherwise apply. Additionally, accommodations are available for group health plans (and any group health insurance coverage provided in connection with such plans) established or maintained by certain non-grandfathered, non-profit eligible organizations with religious objections to contraceptive services with respect to the requirement to cover contraceptive services. See 78 FR 39870 (July 2, 2013) and http://www.cms.gov/CCIIO/Resources/Regulations-and-Guidance/Downloads/preventive-services-guidance-6-28-2013.pdf.

[13] See, e.g., Public Health Service-sponsored Clinical Practice Guideline, *Treating Tobacco Use and Dependence: 2008 Update*, available at: http://www.ahrq.gov/professionals/clinicians-providers/guidelines-recommendations/tobacco/index.html#Clinic. See also Centers for Disease Control and Prevention, Coverage for Tobacco Use Cessation Treatments, available at: http://www.cdc.gov/tobacco/quit_smoking/cessation/pdfs/coverage.pdf, for a discussion of scientific evidence regarding barriers for tobacco users accessing proven cessation treatments.

requirement to cover tobacco use counseling and interventions, if, for example, the plan or issuer covers without cost-sharing:

1. Screening for tobacco use; and,
2. For those who use tobacco products, at least two tobacco cessation attempts per year. For this purpose, covering a cessation attempt includes coverage for:

    - Four tobacco cessation counseling sessions of at least 10 minutes each (including telephone counseling, group counseling and individual counseling) without prior authorization; and
    - All Food and Drug Administration (FDA)-approved tobacco cessation medications (including both prescription and over-the-counter medications) for a 90-day treatment regimen when prescribed by a health care provider without prior authorization.

This guidance is based on the Public Health Service-sponsored Clinical Practice Guideline, Treating Tobacco Use and Dependence: 2008 Update, available at: http://www.ahrq.gov/professionals/clinicians-providers/guidelines-recommendations/tobacco/index.html#Clinic.

Health FSA Carryover and Excepted Benefits

Excepted benefits provided under a group health plan or health insurance coverage generally are exempt from the Health Insurance Portability and Accountability Act (HIPAA) and Affordable Care Act market reform requirements of the Employee Retirement Income Security Act (ERISA), the PHS Act, and the Code.[14] Under previous regulations issued by the Departments, (the HIPAA excepted benefits regulations)[15] health FSAs generally constitute excepted benefits if:

1. The employer also makes available group health plan coverage that is not limited to excepted benefits for the year to the class of participants by reason of their employment; and
2. The arrangement is structured so that the maximum benefit payable to any employee participant in the class cannot exceed:
    a. Two times the employee's salary reduction election for the arrangement for the year; or,
    b. If greater, cannot exceed $500 plus the amount of the participant's salary reduction election).

[14] Note, to the extent a health FSA is not excepted benefits, the Departments' interim final rules provide that PHS Act section 2711's annual limits requirements do not apply to health FSAs. See 29 CFR 2590.715-2711(a)(2)(ii) and 45 CFR 147.126(a)(2)(ii). Moreover, to the extent a health FSA is not excepted benefits, but is integrated with other coverage as part of a group health plan and the other coverage alone would comply with the requirements of PHS Act section 2713, the fact that benefits under the health FSA by itself are limited does not violate PHS Act section 2713 because the combined benefit satisfies the requirements. Other market reforms, such as PHS Act section 2719 regarding internal claims and appeals and external review do apply, however, apply to FSA coverage that is not excepted benefits.

[15] See 26 CFR 54.9831-1(c)(3)(v), 29 CFR 2590.732(c)(3)(v), and 45 CFR 146.145(c)(3)(v).

On October 31, 2013, the Department of the Treasury and Internal Revenue Service issued guidance[16] modifying the "use-or-lose" rule for health FSAs to allow up to $500 of unused amounts remaining at the end of a plan year in a health FSA to be paid or reimbursed to plan participants for qualified medical expenses incurred during the following plan year, provided that the plan does not also incorporate a grace period. The guidance provided that the carryover of up to $500 does not affect the maximum amount of salary reduction contributions that the participant is permitted to make under section 125(i) of the Code ($2,500 adjusted for inflation after 2012).

Q6: How is a permissible carryover amount for a health FSA taken into account with regards to the maximum benefits payable limit for health FSAs under the excepted benefit regulations?

Unused carry over amounts remaining at the end of a plan year in a health FSA that satisfy the modified "use-or-lose" rule should not be taken into account when determining if the health FSA satisfies the maximum benefit payable limit prong under the excepted benefits regulations.

Summary of Benefits and Coverage

PHS Act section 2715, as added by the Affordable Care Act and incorporated by reference into ERISA and the Code, directs the Departments to develop standards for use by a group health plan and a health insurance issuer offering group or individual health insurance coverage in compiling and providing a summary of benefits and coverage (SBC) that "accurately describes the benefits and coverage under the applicable plan or coverage." On February 14, 2012, the Departments published final regulations regarding the SBC.[17] At the same time, the Departments published a notice announcing the availability of templates, instructions, and related materials authorized for implementing the disclosure provisions under PHS Act section 2715 for the first year of applicability (that is, for SBCs and the uniform glossary provided with respect to coverage beginning before January 1, 2014).[18]

The Departments stated that updated materials would be issued for later years.[19] The Departments issued FAQs in April 2013 providing guidance for SBCs provided with respect to coverage beginning on or after January 1, 2014, and before January 1, 2015 ("the second year of applicability").[20]

Q7: What templates should plans and issuers use for the SBCs and the uniform glossary required to be provided after the second year of applicability?

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[16] See IRS Notice 2013-71, available at http://www.irs.gov/pub/irs-drop/n-13-71.pdf.
[17] See 26 CFR 54.9815-2715, 29 CFR 2590.715-2715, and 45 CFR 147.200, published at 77 FR 8668 (February 14, 2012).
[18] See 77 FR 8706 (February 14, 2012).
[19] See id. at 8707. See also ACA Implementation FAQs, Part VIII, Q24, available at www.dol.gov/ebsa/faqs/faq-aca8.html and http://www.cms.gov/CCIIO/Resources/Fact-Sheets-and-FAQs/aca_implementation_faqs8.html.
[20] See ACA Implementation FAQs Part XIV, available at www.dol.gov/ebsa/faqs/faq-aca14.html and http://www.cms.gov/CCIIO/Resources/Fact-Sheets-and-FAQs/aca_implementation_faqs14.html.

An updated SBC template (and sample completed SBC) were made available at http://cciio.cms.gov and http://www.dol.gov/ebsa/healthreform in April 2013 for the second year of applicability. Until further guidance is issued, these documents continue to be authorized. There are no changes to the uniform glossary or the "Why This Matters" language for the SBC. There are also no changes to the Instructions for Completing the SBC (for either group or individual health coverage, as applicable), including the special rule providing that, "[t]o the extent a plan's terms that are required to be described in the SBC template cannot reasonably be described in a manner consistent with the template and instructions, the plan or issuer must accurately describe the relevant plan terms while using its best efforts to do so in a manner that is still as consistent with the instructions and template format as reasonably possible."

Q8: Certain specific safe harbors and other enforcement relief were provided by the Departments related to the requirement to provide an SBC and a uniform glossary for the first and second years of applicability.[21] Will this relief be extended?

Yes. As stated in previous FAQs,[22] the Departments' basic approach to Affordable Care Act implementation is to work together with employers, issuers, States, providers and other stakeholders to help them come into compliance with the new law and [to work] with families and individuals to help them understand the new law and benefit from it, as intended. Compliance assistance is a high priority for the Departments. Our approach to implementation is, and will continue to be, marked by an emphasis on assisting (rather than imposing penalties on) plans, issuers and others that are working diligently and in good faith to understand and come into compliance with the new law."

Until further guidance is provided, previously-issued enforcement and transition relief guidance continues to apply with respect to:

- Affordable Care Act Implementation FAQs Part VIII, Q2 (regarding the Departments' basic approach to implementation of the SBC requirements during the first year of applicability);[23]
- Affordable Care Act Implementation FAQs Part VIII, Q5 (regarding use of carve-out arrangements);[24]
- Affordable Care Act Implementation FAQs Part IX, Q1 (regarding the circumstances in which an SBC may be provided electronically);[25]

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[21] See ACA Implementation FAQs Part XIV, Q5, available at www.dol.gov/ebsa/faqs/faq-aca14.html and http://www.cms.gov/CCIIO/Resources/Fact-Sheets-and-FAQs/aca_implementation_faqs14.html.

[22] See ACA Implementation FAQs Part I, Q1 (available at www.dol.gov/ebsa/faqs/faq-aca.html and http://www.cms.gov/CCIIO/Resources/Fact-Sheets-and-FAQs/aca_implementation_faqs.html); FAQs Part VIII Q2 (available at www.dol.gov/ebsa/faqs/faq-aca8.html and http://www.cms.gov/CCIIO/Resources/Fact-Sheets-and-FAQs/aca_implementation_faqs8.html); and FAQs Part IX Q8 (available at www.dol.gov/ebsa/faqs/faq-aca9.html and http://www.cms.gov/CCIIO/Resources/Fact-Sheets-and-FAQs/aca_implementation_faqs9.html).

[23] Available at http://www.dol.gov/ebsa/faqs/faq-aca8.html and http://www.cms.gov/CCIIO/Resources/Fact-Sheets-and-FAQs/aca_implementation_faqs8.html.

[24] Available at http://www.dol.gov/ebsa/faqs/faq-aca8.html and http://www.cms.gov/CCIIO/Resources/Fact-Sheets-and-FAQs/aca_implementation_faqs8.html.

[25] Available at www.dol.gov/ebsa/faqs/faq-aca9.html and http://www.cms.gov/CCIIO/Resources/Fact-Sheets-and-FAQs/aca_implementation_faqs9.html.

- Affordable Care Act Implementation FAQs Part IX, Q8 (regarding penalties for failure to provide the SBC or uniform glossary);[26]
- Affordable Care Act Implementation FAQs Part IX, Q9 (regarding the coverage examples calculator);[27] and related information related to use of the coverage examples calculator;[28]
- Affordable Care Act Implementation FAQs Part IX, Q10 (regarding an issuer's obligation to provide an SBC with respect to benefits it does not insure);[29]
- Affordable Care Act Implementation FAQs Part IX, Q13 (regarding expatriate coverage);[30]
- Affordable Care Act Implementation FAQs Part X, Q1 (regarding Medicare Advantage);[31]
- Affordable Care Act Implementation FAQs Part XIV, Q2 (regarding providing information about MEC and MV without changing the SBC template);[32]
- Affordable Care Act Implementation FAQs Part XIV, Q3 (removal of the row on the SBC template related to annual limits information);[33]
- Affordable Care Act Implementation FAQs Part XIV, Q6 (an enforcement safe harbor related to closed blocks of business);[34]
- Affordable Care Act Implementation FAQs Part XIV, Q7 (regarding the anti-duplication rule for student health insurance coverage);[35] and
- The Special Rule contained in the Instruction Guides for Group and Individual Coverage.[36]

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[26] Available at www.dol.gov/ebsa/faqs/faq-aca9.html and http://www.cms.gov/CCIIO/Resources/Fact-Sheets-and-FAQs/aca_implementation_faqs9.html.

[27] Available at www.dol.gov/ebsa/faqs/faq-aca9.html and http://www.cms.gov/CCIIO/Resources/Fact-Sheets-and-FAQs/aca_implementation_faqs9.html.

[28] Available at www.dol.gov/ebsa/faqs/faq-aca9.html and http://www.cms.gov/CCIIO/Resources/Fact-Sheets-and-FAQs/aca_implementation_faqs9.html.

[29] Available at www.dol.gov/ebsa/faqs/faq-aca9.html and http://www.cms.gov/CCIIO/Resources/Fact-Sheets-and-FAQs/aca_implementation_faqs9.html.

[30] Available at www.dol.gov/ebsa/faqs/faq-aca9.html and http://www.cms.gov/CCIIO/Resources/Fact-Sheets-and-FAQs/aca_implementation_faqs9.html. See also FAQs Part XIII, available at http://www.dol.gov/ebsa/faqs/faq-aca13.html and http://www.cms.gov/CCIIO/Resources/Fact-Sheets-and-FAQs/aca_implementation_faqs13.html.

[31] Available at http://www.dol.gov/ebsa/faqs/faq-aca10.html and http://www.cms.gov/CCIIO/Resources/Fact-Sheets-and-FAQs/aca_implementation_faqs10.html.

[32] Available at www.dol.gov/ebsa/faqs/faq-aca14.html and http://www.cms.gov/CCIIO/Resources/Fact-Sheets-and-FAQs/aca_implementation_faqs14.html.

[33] Available at www.dol.gov/ebsa/faqs/faq-aca14.html and http://www.cms.gov/CCIIO/Resources/Fact-Sheets-and-FAQs/aca_implementation_faqs14.html.

[34] Available at www.dol.gov/ebsa/faqs/faq-aca14.html and http://www.cms.gov/CCIIO/Resources/Fact-Sheets-and-FAQs/aca_implementation_faqs14.html.

[35] Available at www.dol.gov/ebsa/faqs/faq-aca14.html and http://www.cms.gov/CCIIO/Resources/Fact-Sheets-and-FAQs/aca_implementation_faqs14.html.

[36] See What This Plan Covers and What it Costs: Instruction Guide for Group Coverage, February 2012 edition (available at http://www.dol.gov/ebsa/pdf/SBCInstructionsGroup.pdf and http://www.cms.gov/CCIIO/Resources/Files/Downloads/instructions-group-final.pdf) and What This Plan Covers and What it Costs: Instruction Guide for Individual Health Insurance Coverage, February 2012 edition (available at http://www.dol.gov/ebsa/pdf/SBCInstructionsIndividual.pdf and http://www.cms.gov/CCIIO/Resources/Files/Downloads/instructions-individual-final.pdf).

This guidance supersedes any previous subregulatory guidance (including FAQs) stating that certain enforcement relief for the SBC and uniform glossary requirements is limited to the first or second year of applicability.

Smoking Cessation

Goal(s):

- Promote use that is consistent with National Guidelines and medical evidence.
- Promote use of high value products

Length of Authorization:

3-6 months

Requires PA:

- Non-preferred drugs
- Nicotine replacement therapy (NRT) for more than 6 months in the absence of behavioral counseling
- Varenicline treatment for more than 12 weeks

Covered Alternatives:

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

Approval Criteria		
1. What diagnosis is being treated?	Record ICD10 code	
2. Is the diagnosis for tobacco dependence (ICD10 F17200)?	**Yes:** Go to #3	**No:** Pass to RPh. Deny; medical appropriateness
3. Is the request for a preferred NRT product?	**Yes:** Go to #5	**No:** Go to #4
4. Is the request for varenicline?	**Yes:** Go to #5	**No:** Go to #7
5. Has patient quit?	**Yes:** Approve NRT for 6 additional months or approve varenicline for 12 additional weeks	**No:** Go to #6
6. Is the patient enrolled in a smoking cessation behavioral counseling program [e.g. Quit Line at: 800-QUIT-NOW (800-784-8669)].	**Yes:** Approve NRT for 6 additional months or approve varenicline for 12 additional weeks	**No:** Pass to RPh. Deny; medical appropriateness

Approval Criteria		
7. Will the prescriber change to a preferred product? Message: • Preferred products do not require a PA for initial treatment. • Preferred products are evidence-based reviewed for comparative effectiveness and safety by the Pharmacy and Therapeutics (P&T) Committee.	**Yes:** Inform prescriber of covered alternatives in class	**No:** Approve treatment for up to 6 months

P&T Review: *7/16 (MH); 4/12*
Implementation: *7/23/12*

Section 7.0

New Discussion Items

Severe Inflammatory Skin Disease

Questions:

1) Which additional diagnoses need to be added to the severe inflammatory skin disease line to carry out the intent of the ICD-10 Dermatology review regarding prioritization of atopic dermatitis and similar skin conditions?
2) How should the severe inflammatory skin disease guideline note be modified to better carry out the intent of the ICD-10 Dermatology review?
3) Should wording be added to the severe inflammatory skin disease guideline note to specify when expensive medications for atopic dermatitis are covered per the ICD-10 reviewer recommendations?

Question source: P&T staff, CCO medical directors, HERC staff

Issues:

1) During the 2012 ICD-10 Dermatology review, the HERC accepted changes included adding atopic dermatitis and similar inflammatory skin diseases to the line that previously had only had psoriasis, with a guideline stating that only moderate/severe forms of these diseases were included on this covered line and defining what was meant by moderate/severe. However, most of the ICD-10 codes for the atopic dermatitis diagnoses intended for coverage on this line were never added. Currently, only 2 atopic dermatitis ICD-10 codes are on line 424 SEVERE INFLAMMATORY SKIN DISEASE (the "other" and "unspecified" codes). The majority of atopic dermatitis diagnoses are on line 530 ATOPIC DERMATITIS, which is not referenced in the guideline note for severe inflammatory skin disease. It is unclear which atopic dermatitis/eczema diagnoses were intended for line 424.

   HERC staff sought to identify all the possible ICD-10 diagnoses that might be used for conditions intended for inclusion on line 424 by the ICD-10 reviewers, and make recommendations as to which codes should be added to this line. Additionally, HERC staff sought to ensure that all diagnoses appearing on line 424 also appeared on an uncovered line, and to ensure that GN 21, SEVERE INFLAMMATORY SKIN DISEASE was applied to all these lines to clarify that only the moderate/severe forms of these skin conditions were included on the upper line and the mild forms were included on uncovered lines.

   The ICD-10 reviewers intended that moderate/severe forms of the following conditions be included on line 424:
   ~~**MODERATE/**~~**SEVERE INFLAMMATORY SKIN DISEASE**
   ICD 10 codes to be placed on this line for the following conditions:
   a. Psoriasis
   b. Atopic dermatitis
   c. Lichen planus
   d. Darier disease (inherited epidermal disorder)
   e. Pityriasis rubra pilaris
   f. Discoid lupus

2) GN 21 SEVERE INFLAMMATORY SKIN DISEASE needs modifications to clarify what diagnoses are intended for inclusion, and to include all relevant lines. There have been several questions

raised about the intent of GN21 SEVERE INFLAMMATORY SKIN DISEASE. This guideline is attached only to the psoriasis lines (424, 539). There have been questions raised as to which lines it should apply to in order to clarify the intent of non-coverage of mild disease. There is a second guideline for mild psoriasis; it is unclear to reviewers when a condition is covered on line 430 based on the two current guidelines; there is also concern that having two guidelines is clunky and a suggestion has been made to combine them.

3) Additionally, wording should be considered to clarify that expensive medications such as tacrolimus and Elidel for atopic dermatitis are included only as second line therapy. During the ICD-10 review, the following wording was proposed, but not included in the final guideline:

> The prevalence of atopic dermatitis is approximately 10% in children and possibly 1% in adults. Up to 1/3 of children may have moderate-to-severe disease. The prevalence of moderate-to-severe disease in adults is unknown. The vast majority of moderate-severe disease may be adequately controlled with topical corticosteroids, especially in children.
>
> <u>First-line agents</u>
> Topical corticosteroids
> Narrowband UVB
> Cyclosporine (1 year limit)
> Methotrexate
> Azathioprine
>
> <u>Second-line agents</u>
> 1) Topical pimecrolimus and topical tacrolimus

Current guideline notes:

GUIDELINE NOTE 21, SEVERE INFLAMMATORY SKIN DISEASE

Lines 424,539

Severe inflammatory skin disease is defined as having functional impairment (e.g. inability to use hands or feet for activities of daily living, or significant facial involvement preventing normal social interaction) AND one or more of the following:

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

For severe psoriasis, 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.

See GUIDELINE NOTE 57 MILD PSORIASIS for the definition of mild psoriasis included on Line 539.

GUIDELINE NOTE 57, MILD PSORIASIS

Lines 424,539

Mild psoriasis is defined as uncomplicated, having:

- No functional impairment; and/or,
- Involving less than 10% of body surface area and no involvement of the, foot, or mucous membranes.

See GUIDELINE NOTE 21 SEVERE INFLAMMATORY SKIN DISEASE for the definition of moderate/severe psoriasis included on Line 424.

Severe Inflammatory Skin Disease

Dermatitis and eczema and similar condition diagnoses

ICD-10 Code	Code description	Current Line(s)
various	Diabetes with diabetic dermatitis	Diabetes lines,530
H01.11	Allergic dermatitis of eyelid	552 MILD ECZEMATOUS AND OTHER HYPERTROPHIC OR ATROPHIC CONDITIONS OF SKIN
H01.13	Eczematous dermatitis of eyelid	552
H60.54	Acute eczematoid otitis externa	531 CONTACT DERMATITIS AND OTHER ECZEMA
L20.0	Besnier's prurigo	530 ATOPIC DERMATITIS
L20.81	Atopic neurodermatitis	530
L20.82	Flexural eczema	530
L20.83	Infantile (acute) (chronic) eczema	552
L20.84	Intrinsic (allergic) eczema	530
L20.89	Other atopic dermatitis	424 SEVERE INFLAMMATORY SKIN DISEASE 530
L20.9	Atopic dermatitis, unspecified	424,530
L23	Allergic contact dermatitis	531
L24	Irritant contact dermatitis	531
L25	Unspecified contact dermatitis	531
L26	Exfoliative dermatitis	502 ERYTHEMATOUS CONDITIONS
L27	Dermatitis due to substances taken internally	566 DERMATITIS DUE TO SUBSTANCES TAKEN INTERNALLY
L30	Nummular, infective, and other dermatitis	531
L40.2	Acrodermatitis continua	424,539 Mild psoriasis; dermatophytosis: Scalp, hand, body
L71.2	Perioral dermatitis	502
L90.4	Acrodermatitis chronica atrophicans	552

Severe Inflammatory Skin Disease

Other inflammatory skin disease diagnoses codes of possible interest

ICD-10 Code	Code description	Current Line(s)
H01.12	Discoid lupus erythematosus of eyelid	424 SEVERE INFLAMMATORY SKIN DISEASE
L40.0	Psoriasis vulgaris	424,539 MILD PSORIASIS; DERMATOPHYTOSIS: SCALP, HAND, BODY
L40.1	Generalized pustular psoriasis	424,539
L40.4	Guttate psoriasis	424,539
L40.50	Arthropathic psoriasis, unspecified	46,356 (Rheumatoid arthritis lines)
L40.8	Other psoriasis	424,539
L40.9	Psoriasis, unspecified	424,539
L41	Parapsoriasis	424,539
L43	Lichen planus	424, 480 LICHEN PLANUS
L44.0	Pityriasis rubra pilaris	424 539 654
L93.0	Discoid lupus erythematosus	424, 502 ERYTHEMATOUS CONDITIONS
Q82.8	Other specified congenital malformations of skin (used for Darier disease)	654 DERMATOLOGICAL CONDITIONS WITH NO OR MINIMALLY EFFECTIVE TREATMENTS OR NO TREATMENT NECESSARY

Severe Inflammatory Skin Disease

HERC staff recommendations:

1) Add additional ICD-10 diagnoses to line 424 SEVERE INFLAMMATORY SKIN DISEASE:
   a) L20.82 (Flexural eczema)
   b) L20.83 (Infantile (acute) (chronic) eczema)
   c) L20.84 (Intrinsic (allergic) eczema)
   d) Q82.8 (Other specified congenital malformations of skin)
2) Add the following coding specification to line 424
   a) "ICD-10 Q82.8 is included on this line only for Darier disease."
3) Add L20.83 (Infantile (acute) (chronic) eczema) to line 530 ATOPIC DERMATITIS and remove from line 552 MILD ECZEMATOUS AND OTHER HYPERTROPHIC OR ATROPHIC CONDITIONS OF SKIN
   a) A form of atopic dermatitis
4) Rename line 552 ~~MILD ECZEMATOUS AND~~ OTHER HYPERTROPHIC OR ATROPHIC CONDITIONS OF SKIN
   a) Eczema diagnoses now on line 424 and 530
5) Rename line 531 CONTACT DERMATITIS AND ~~OTHER ECZEMA~~ NON-INFECTIOUS OTITIS EXTERNA
   a) No eczema diagnoses on this line; large number of non-infectious otitis externa diagnoses on this line
6) Rename line 530 ATOPIC DERMATITIS; MILD ECZEMA
7) Ensure that all diagnoses on line 424 also appear on an unfunded line for mild forms of disease
   a) Add H01.12 (Discoid lupus erythematosus of eyelid) to line 502 ERYTHEMATOUS CONDITIONS
8) Delete GN57
   a) Merge into GN21
9) Modify GN21 as shown below
   a) Attach GN21 to lines
      i) 480 LICHEN PLANUS
      ii) 502 ERYTHEMATOUS CONDITIONS
      iii) 530 ATOPIC DERMATITIS
      iv) 654 DERMATOLOGICAL CONDITIONS WITH NO OR MINIMALLY EFFECTIVE TREATMENTS OR NO TREATMENT NECESSARY
   b) Better specify when a diagnosis is included on the upper line
   c) Consider wording to specify that more expensive medications for atopic dermatitis/eczema are second line.

GUIDELINE NOTE 21, SEVERE INFLAMMATORY SKIN DISEASE

Lines 424,480,502,530,539,654

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

The conditions above are included on line 424 if severe, ~~Severe inflammatory skin disease is~~ defined as having functional impairment (e.g. inability to use hands or feet for activities of daily living, or significant facial involvement preventing normal social interaction) AND one or more of the following:

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

The conditions above are included on line 480, 502, 530, 539, or 654 if mild, ~~Mild psoriasis is~~ defined as uncomplicated, having:

- No functional impairment; and/or,
- Involving less than 10% of body surface area and no involvement of the, foot, or mucous membranes.

For severe psoriasis, 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, fist line agents include topical corticosteroids, narrowband UVB, cyclosporine, methotrexate, and azathioprine. Second line agents include topical pimecrolimus and topical tacrolimus and should be limited to those who fail or have contraindications to first line agents.

~~See GUIDELINE NOTE 57 MILD PSORIASIS for the definition of mild psoriasis included on Line 539.~~

~~**GUIDELINE NOTE 57, MILD PSORIASIS**~~

~~*Lines 424,539*~~

~~Mild psoriasis is defined as uncomplicated, having:~~

- ~~No functional impairment; and/or,~~
- ~~Involving less than 10% of body surface area and no involvement of the, foot, or mucous membranes.~~

~~See GUIDELINE NOTE 21 SEVERE INFLAMMATORY SKIN DISEASE for the definition of moderate/severe psoriasis included on Line 424.~~

Medication assisted treatment in residential treatment programs

Question: In residential treatment programs for opioid use disorder, is medication assisted treatment a necessary component?

Question source: David Labby and Maggie Bennington Davis, HealthShare of Oregon; Behavioral Health Advisory Panel (BHAP)

Issue: A CCO has raised the issue that there are patients admitted for residential treatment who are not being offered MAT and there is a concern for high levels of relapse among these patients. HERC was asked to review the evidence on the effectiveness of residential treatment for opioid use disorder, with and without medication assisted treatment (MAT).

Medication assisted treatment may include buprenorphine, methadone, or naloxone. Medications are provided in the context of intensive behavioral interventions as part of the residential treatment stay.

Some have raised concerns about medication assisted treatment, such as: the belief that MAT just trades one addiction for another, that it should only be used short-term, that it increases the risk of overdose, that MAT hinders the recovery process, or that it is not better than abstinence.

HERC's Behavioral Health Advisory Panel (BHAP) met August 1, 2017 and deliberated on adopting a new guideline note requiring MAT to be offered by residential treatment programs. Key issues that were raised at that meeting included:

- Confirmation by the OHA State Opioid Treatment Authority, John McIlveen, that the goal is to increase options and MAT availability. We have received federal grant money from SAMSHA to help increase MAT.
- Consensus that programs need to offer MAT.
- Access to MAT, particularly in rural areas, is of concern.
- Tri-county metro area is working on developing standards, and they include a requirement that programs must offer MAT.
- There may be a delayed implementation given the need to raise awareness and build capacity across the state based on the proposed guideline note. BHAP recommended delaying until January 1, 2018 for implementation.

Background

PEW

> Only 23 percent of publicly funded treatment programs reported offering any FDA-approved medications to treat substance use disorders, and less than half of private sector treatment programs reported that their physicians prescribed FDA-approved medications

Medication assisted treatment in residential treatment programs

From Malivert, 2012

> Therapeutic communities (TCs) are drug-free residential settings, whose goal is to maintain abstinence and to socially rehabilitate drug users. In these settings, substance use disorder is considered as a general behavior not related to the substance but to the subject themselves. TCs use a hierarchical model, based on peers, with treatment stages that reflect increased levels of personal and social responsibilities. Peer influence, mediated through a variety of group processes, is used to help individuals to assimilate social norms and develop more effective social skills. Activities throughout the day aim at social rehabilitation. During a TC program, residents have the opportunity to progress in the TC hierarchy, becoming a peer who manages group activities.

From SAMSHA, 2014

- In the 1990s the NIH Consensus Panel on Effective Medical Treatment of Opiate Addiction concluded that opioid addiction is a treatable medical disorder and explicitly rejected notions that addiction is self-induced or a failure of willpower. The panel called for a commitment to providing effective treatment for opioid addiction and for Federal and State efforts to reduce the stigma attached to MAT and to expand MAT through increased funding and less restrictive regulation.

Abraham, 2014

- Study comparing provision of MAT and physician availability at public and private addiction treatment programs
- Include 595 specialty SUD treatment programs from 2007 to 2010 via face-to-face interviews, mailed surveys, and telephone\ interviews with treatment program administrators.
- Publically funded programs provided much less MAT than privately funded programs
    - Buprenorphine 24.4% (public) versus 38.3% (private)
    - Injectable naltrexone 9% (public) versus 15.9% (private)
- Lower rates of on staff physicians at publically funded programs and lower rates of availability of MAT exist

<u>Prioritized List Status</u>

Medication assisted treatment in residential treatment programs

Line: 4
Condition: SUBSTANCE USE DISORDER (See Guideline Notes 64,65)
Treatment: MEDICAL/PSYCHOTHERAPY
ICD-10: F10.10,F10.20-F10.21,F11.10,F11.20-F11.21,F12.10,F12.20-F12.21,F13.10, F13.20-F13.21,F14.10,F14.20-F14.21,F15.10,F15.20-F15.21,F16.10,F16.20-F16.21,F18.10,F18.20-F18.21,F19.10,F19.20-F19.21,Z71.51
CPT: 90785,90832-90840,90846-90853,90882,90887,96101,96150-96155,97810-97814,98966-98969,99051,99060,99201-99239,99324-99357,99366,99408, 99409,99415,99416,99441-99449,99487-99498,99605-99607
HCPCS: G0396,G0397,G0406-G0408,G0410,G0411,G0425-G0427,G0459,G0463-G0467,G0469,G0470,G0508,G0509,H0004-H0006,H0010-H0016,H0018-H0020,H0032-H0035,H0038,H0048,H2010,H2013,H2033,H2035,T1006, T1007,T1502

Evidence summary

Nielson, 2016: Study not included due to length:
http://onlinelibrary.wiley.com/doi/10.1002/14651858.CD011117.pub2/epdf

- Cochrane systematic review of RCTs for MAT and opioid use disorder (with prescription opioids)
- RCTs examining maintenance opioid agonist treatments that made the following two comparisons:
  1. full opioid agonists (methadone, morphine, oxycodone, levo-alpha-acetylmethadol (LAAM), or codeine) versus different full opioid agonists or partial opioid agonists (buprenorphine) for maintenance treatment and
  2. full or partial opioid agonist maintenance versus placebo, detoxification only, or psychological treatment (without opioid agonist treatment).
- 6 RCTs, with 607 participants
- Results:
  Comparing methadone and buprenorphine
  - Moderate quality evidence from two studies that there is no difference between methadone and buprenorphine in self-reported opioid use (risk ratio (RR) 0.37, 95%confidence interval (CI) 0.08 to 1.63) or opioid positive urine drug tests (RR 0.81, 95%CI 0.56 to 1.18).
  - Low quality evidence from three studies of no difference in retention between buprenorphine and methadone maintenance treatment (RR 0.69, 95%CI 0.39 to 1.22). There was moderate quality evidence from two studies of no difference between methadone and buprenorphine on adverse events (RR 1.10, 95% CI 0.64 to 1.91).

  Comparing MAT to detoxification or psychological treatment (2 outpatient, 1 hospital)

  - Low quality evidence from three studies favouring maintenance buprenorphine treatment over detoxification or psychological treatment in terms of fewer opioid positive urine drug tests (RR 0.63, 95% CI 0.43 to 0.91) and self-reported opioid use in the past 30 days (RR 0.54, 95% CI 0.31 to 0.93). There was no difference on days of unsanctioned opioid use (standardised mean difference (SMD) -0.31, 95% CI -0.66 to 0.04). There was moderate quality evidence favouring buprenorphine maintenance over detoxification or psychological treatment on retention in treatment (RR 0.33, 95% CI 0.23 to 0.47). There was moderate quality evidence favouring buprenorphine maintenance over detoxification or psychological treatment on adverse events (RR 0.19, 95% CI 0.06 to 0.57).
- Author conclusions: There was low to moderate quality evidence supporting the use of maintenance agonist pharmacotherapy for pharmaceutical opioid dependence. Methadone or buprenorphine appeared equally effective. Maintenance treatment with buprenorphine appeared more effective than detoxification or psychological treatments.

Mattick, 2009
http://onlinelibrary.wiley.com/doi/10.1002/14651858.CD002209.pub2/abstract;jsessionid=A2D6A46D169D974AA0A301A2147F7B11.f02t03

- Cochrane systematic review of MAT vs no MAT for opioid dependence
- 11 RCTs, 1969 participants
- Results: Methadone appeared statistically significantly more effective than non-pharmacological approaches in retaining patients in treatment and in the suppression of heroin use as measured by self-report and urine/hair analysis (6 RCTs, RR = 0.66; 95%CI: 0.56-0.78), but not statistically different in criminal activity (3 RCTs, RR=0.39; 95%CI: 0.12-1.25) or mortality (4 RCTs, RR=0.48; 95%CI: 0.10-2.39).

Mattick, 2014
http://onlinelibrary.wiley.com/doi/10.1002/14651858.CD002207.pub4/full

- Cochrane systematic review comparing buprenorphine with placebo and methadone maintenance
- 31 trials (5430 participants)
- There is high quality of evidence that buprenorphine was superior to placebo medication in retention of participants in treatment at all doses examined. Specifically, buprenorphine retained participants better than placebo: at low doses (2 - 6 mg), 5 studies, 1131 participants, risk ratio (RR) 1.50; 95% confidence interval (CI) 1.19 to 1.88; at medium doses (7 - 15 mg), 4 studies, 887 participants, RR 1.74; 95% CI 1.06 to 2.87; and at high doses (≥ 16 mg), 5 studies, 1001 participants, RR 1.82; 95% CI 1.15 to 2.90. However, there is moderate

quality of evidence that *only* high-dose buprenorphine (≥ 16 mg) was more effective than placebo in suppressing illicit opioid use measured by urinanalysis in the trials, 3 studies, 729 participants, standardised mean difference (SMD) -1.17; 95% CI -1.85 to -0.49.

- Authors' conclusions: Buprenorphine is an effective medication in the maintenance treatment of heroin dependence, retaining people in treatment at any dose above 2 mg, and suppressing illicit opioid use (at doses 16 mg or greater) based on placebo-controlled trials. However, compared to methadone, buprenorphine retains fewer people when doses are flexibly delivered and at low fixed doses. If fixed medium or high doses are used, buprenorphine and methadone appear no different in effectiveness (retention in treatment and suppression of illicit opioid use). Methadone is superior to buprenorphine in retaining people in treatment, and methadone equally suppresses illicit opioid use.

Malivert, 2012
http://www.academia.edu/15852177/Effectiveness_of_Therapeutic_Communities_A_Systematic_Review

- Systematic review of studies of therapeutic communities (drug-free) residential settings on retention in treatment and/or substance use
- 12 studies of 3,271 participants, mixture of prospective and retrospective designs, mostly U.S. based
- Programs ranged from 3-24 months, f/u 6 months to 6 years
- Not limited to opioid use disorder, cocaine dependence was the most common
- 20-90% had tried another treatment program prior to the current
- Results:
    - On average participants stayed within the program 1/3 of the planned time (38-180 days)
    - Program cessation most often occurred during the first 15-30 days
    - Completion rate ranged from 9-56%, 27-70% stayed for at least 50% of the time
    - Substance use decreased during the stay, but relapse was frequent after leaving the therapeutic community 21-100%
    - Treatment completion most important predictor of abstinence at f/u. Other important predictors were length of program.
    - Psychiatric comorbidities not a confounder

Minozzi, 2014 Study not included due to length:
http://onlinelibrary.wiley.com/doi/10.1002/14651858.CD007210.pub3/epdf

- Cochrane systematic review of trials in adolescents with opioid use disorder
- Randomized or controlled clinical trials

- 2 trials involving 189 participants, but only 1 study relevant, which included 154 participants, compared maintenance treatment with buprenorphine-naloxone and detoxification with buprenorphine.
- Maintenance treatment appeared to be more efficacious in retaining patients in treatment (drop-out risk ratio (RR) 0.37; 95% confidence interval (CI) 0.26 to 0.54), but not in reducing the number of patients with a positive urine test at the end of the study (RR 0.97; 95% CI 0.78 to 1.22).
- Self-reported opioid use at one-year follow-up was significantly lower in the maintenance group, even though both groups reported a high level of opioid use (718 per 1000 versus 524 per 1000) (RR 0.73; 95% CI 0.57 to 0.95). More patients in the maintenance group were enrolled in other addiction treatment programmes at 12-month follow-up (RR 1.33; 95% CI 0.94 to 1.88).
- The quality of the evidence was low.
- No serious side effects of buprenorphine therapy.

Smith, 2006 Study not included due to length:
http://onlinelibrary.wiley.com/doi/10.1002/14651858.CD005338.pub2/abstract

- Cochrane systematic review of RCTS of therapeutic communities for substance use disorder
- 7 studies
- Results:
    - TC versus community residence: no significant differences for treatment completion
    - Residential versus day TC: attrition (first two weeks), and abstinence rates at six months significantly lower in the residential treatment group
    - Standard TC versus enhanced abbreviated TC: number of employed higher in standard TCRR 0.78 (95%CI 0.63, 0.96).
    - Three months versus six months programme within modified TC, and six months versus 12 months programme within standard TC: completion rate higher in the three months programme and retention rate (40 days) significantly greater with the 12 months than 6 months programme.
    - Two trials evaluated TCs within a prison setting: one reported significantly fewer re-incarcerated 12 months after release from prison in the TC group compared with no treatment, RR 0.68 (95% CI 057, 0.81). In the other, people treated in prison with TC compared with Mental Health Treatment Programmes showed significantly fewer re-incarcerations RR 0.28 (95%CI 0.13, 0.63), criminal activity 0.69 (95% CI 0.52, 0.93) and alcohol and drug offences 0.62 (95% CI 0.43, 0.90) 12 months after release from prison.
- Author conclusions: There is little evidence that TCs offer significant benefits in comparison with other residential treatment, or that one type of TC is better than another. Prison TC may be better than prison on its own or Mental Health

Treatment Programmes to prevent re-offending post-release for inmates. The evidence is limited.

Policy Landscape

CMS, 2016

https://www.cms.gov/Outreach-and-Education/Outreach/Partnerships/Downloads/CMS-Opioid-Misuse-Strategy-2016.pdf

HHS priority areas

The U.S. Department of Health and Human Services announced an opioid misuse strategy with the goals of: (1) decreasing opioid overdoses and overall overdose mortality, and (2) decreasing the prevalence of opioid use disorder. To align with and achieve these goals, CMS convened a cross-agency working group to develop CMS's opioid strategy. The 3 priority areas are:

- Address opioid prescribing practices to reduce opioid use disorders and overdose
- Expand use and distribution of naloxone
- Expand use of MAT to reduce opioid use disorders and overdose

SAMSHA, 2014

http://store.samhsa.gov/shin/content/SMA12-4214/SMA12-4214.pdf

Medication-Assisted Treatment For Opioid Addiction in Opioid Treatment Programs, Treatment Improvement Protocol 43

- Reviews the history of opioid addiction and perceptions
- Agrees with NIDA's principles in their 1999 report
- Methadone maintenance treatment has the longest successful track record in patients addicted to opioids for more than a year and has been shown to control withdrawal symptoms, stabilize physiologic processes, and improve functionality. Studies also have found that methadone maintenance treatment reduces criminality, noncompliance with HIV/AIDS therapy, seroconversion to HIV/AIDS, and mortality associated with opioid addiction (Appel et al. 2001; Ball and Ross 1991).
- Control of withdrawal symptoms often is insufficient treatment to prevent a relapse to opioid abuse, and detoxification alone may yield only short-term benefits… Therefore, when detoxification from short-acting opioids is provided, the consensus panel recommends linkage to ongoing psychosocial treatment, with or without additional maintenance therapy with an opioid antagonist such as naltrexone. Comprehensive, long-term opioid agonist maintenance remains the treatment with the best track record of controlling opioid use and saving lives, although opioid partial agonist therapy is promising. Access and easy transfer to this care should remain available as part of any detoxification program.
- If a patient in an OTP is referred to a residential program that does not offer or allow onsite opioid pharmacotherapy (i.e., when other residential options are

unavailable) or methadone or buprenorphine dispensing or administration, some programs allow resident patients to travel to the OTP for medication. Some States allow exceptions to regulations governing OTP attendance and take-home medications so that concurrent treatment is possible.

- If a patient has a mild or moderate opioid use disorder without meeting criteria for tolerance/withdrawal, opioid agonist medications that will themselves produce physical dependence must be carefully considered due to the difficulty experienced by many of the discontinuation of opioids on which an individual has become physically dependent. Other options such as psychotherapy or antagonist pharmacotherapy such as oral/injectable naltrexone treatment should be considered.

CMS 2014
Letter to states

- The use of medications in combination with behavioral therapies to treat SUDs can help reestablish normal brain functioning, reduce cravings, and prevent relapse. The medications used can manage the symptoms of substance use withdrawal that often prompt relapse and allow individuals to utilize other treatments, such as behavioral therapy. In addition, these medications and therapies can contribute to lowering a person's risk of contracting HIV or hepatitis C by reducing the potential for relapse.
- For individuals with alcohol dependence, MAT was associated with fewer inpatient admissions. Total healthcare costs were 30 percent less for individuals receiving MAT than for individuals not receiving MAT.
- Medical costs decreased by 33 percent for Medicaid patients over three years following their engagement in treatment. This included a decline in expenditures in all types of health care settings including hospitals, emergency departments, and outpatient centers.
- Research shows that when treating SUDs, a combination of medication and behavioral therapies is the most effective.

Documentation of Behavioral Therapy: A state Medicaid agency or contracted MCO may require evidence that the patient seeking an FDA-approved addiction medication is being referred to or has already started to receive behavioral therapy services along with their medication. Presently, 20 states and the District of Columbia require documentation of behavioral therapy with use of buprenorphine-naloxone and 18 states for the use of injectable naltrexone. *Care should be used to avoid making such requirements unduly burdensome such that they effectively limit appropriate access to pharmacotherapy.*

State strategies
States that have implemented strong evidence-based MAT programs tend to support financing and care provision structures that provide pharmacological, medical, counseling and other supports within an integrated physical health and behavioral health system.

National Institute on Drug Abuse (NIDA), 2012
https://www.drugabuse.gov/sites/default/files/podat_1.pdf

- Research based guide on the treatment of drug abuse
- Research has shown that methadone maintenance is more effective when it includes individual and/or group counseling, with even better outcomes when patients are provided with, or referred to, other needed medical/psychiatric, psychological, and social services (e.g. employment or family services).
- Combined interventions - Research has demonstrated the effectiveness of treatment approaches using contingency management (CM) principles, which involve giving patients tangible rewards to reinforce positive behaviors such as abstinence. Studies conducted in both methadone programs and psychosocial counseling treatment programs demonstrate that incentive-based interventions are highly effective in increasing treatment retention and promoting abstinence from drugs.
- Principles of drug treatment (excerpts) –
    - Comprehensive care
    - Individualized treatment planning that may include, in addition to counseling or psychotherapy, a patient may require medication, medical services, family therapy, parenting instruction, vocational rehabilitation, and/or social and legal services. For many patients, a continuing care approach provides the best results, with the treatment intensity varying according to a person's changing needs.
    - Medications are an important element of treatment for many patients, especially when combined with counseling and other behavioral therapies.
- Medically assisted detoxification is only the first stage of addiction treatment and by itself does little to change long-term drug abuse. Although acute physical symptoms of withdrawal can, for some, pave the way for long-term addiction, addicted individuals can achieve long-term abstinence. Thus, patients should be encouraged to continue drug treatment.
- Drug addiction treatment is cost-saving according to several conservative estimates. Every dollar invested in addiction treatment programs yields a return of between $4 and $7 in reduced drug-related crime, criminal justice costs, and theft. When savings related to healthcare are included, total savings can exceed costs by a ratio of 12 to 1.

Medication assisted treatment in residential treatment programs

Guidelines

Summary and links available here: https://aspe.hhs.gov/report/review-medication-assisted-treatment-guidelines-and-measures-opioid-and-alcohol-use

American Society of Addiction Medicine, 2015

- National Practice Guideline for the Use of Medications in the Treatment of Addiction Involving Opioid Use
- The treatment setting described as Level 1 treatment in the ASAM Criteria may be a general outpatient location such as a clinician's practice site. The setting as described as Level 2 in the ASAM Criteria may be an intensive outpatient treatment or partial hospitalization program housed in a specialty addiction treatment facility, a community mental health center, or another setting. The ASAM Criteria describes Level 3 or Level 4 treatment respectively as a residential addiction treatment facility or hospital.
- The choice of available treatment options for addiction involving opioid use should be a shared decision between clinician and patient.
- Methadone is a treatment option recommended for patients who are physiologically dependent on opioids, able to give informed consent, and who have no specific contraindications for agonist treatment when it is prescribed in the context of an appropriate plan that includes psychosocial intervention. [buprenorphine and naltrexone are also discussed]

WHO, 2014

- Guidelines for the Identification and Management of Substance Use and Substance Use Disorders in Pregnancy
- Pertinent recommendations: Pregnant women dependent on opioids should be encouraged to use opioid maintenance treatment whenever available rather than to attempt opioid detoxification. **(**Strength of recommendation: Strong; Quality of evidence: Very low**)**
- Pregnant patients with opioid dependence should be advised to continue or commence opioid maintenance therapy with either methadone or buprenorphine. **(**Strength of recommendation: Strong; Quality of evidence: Very low**)**

British Association for Psychopharmacology, 2012

- Evidence-Based Guidelines for the Pharmacological Management of Substance Abuse, Harmful Use, Addiction, and Co-Morbidity: Recommendations from BAP
- Methadone maintenance treatment (MMT) is an appropriate treatment option for opioid-dependent patients. It is effective in reducing heroin use, injecting, and sharing of injecting equipment (**A**).
- Buprenorphine maintenance treatment (BMT) is an appropriate treatment option for opioid-dependent patients. It is effective in reducing heroin use (**A**).

- Both methadone and buprenorphine are effective treatments. Opioid-dependent patients should be offered either medication, guided by patient choice and safety considerations (**A**).
- MMT or BMT should be provided in conjunction with psychosocial interventions such as regular counselling (**B**).
- Highly supervised injectable diamorphine maintenance treatment should be considered for patients who have failed to respond to optimised MMT or BMT (**B**).
- We do not recommend injectable methadone treatment at present, although further studies are warranted (**C**).

Centre for Addiction and Mental Health, Canada, 2011
Buprenorphine/Naloxone for Opioid Dependence: Clinical Practice Guideline (Canada)

- Prior to initiating maintenance opioid agonist treatment the patient should meet the diagnostic criteria for opioid dependence. (Level III, Grade A)
- The decision to initiate opioid agonist therapy with either buprenorphine-naloxone or methadone maintenance should be guided by the individual clinical circumstances and the patient's preferences. (Level III, Grade I)
- Prior to initiation of buprenorphine-naloxone treatment, the patient must provide informed consent and there must be physician documentation that the patient has been informed of the physical dependence on the medication and possible long-term nature of the maintenance treatment. **(**Level III, Grade A**)**

<u>Quality Metrics</u>
A number of health care systems are using MAT as part of quality metrics

Measure	**Group**
Initiation of pharmacotherapy upon new episode of opioid dependence	Washington circle group
Maintenance pharmacotherapy for substance abuse	APA
OAT as first line of defense for at least 90 days of treatment at beginning of a new treatment episode	VHA
Duration of OAT for selected SUD patients	VHA
Maintenance pharmacotherapy for opiate dependence at empirically based dosages: (1) offered; (2) filled; (3) refused medication; or (4) contraindicated	VHA
Counseling on psychosocial and pharmacologic treatment options for opioid addiction	APA; Physician Consortium for Performance Improvement; NCQA

Medication assisted treatment in residential treatment programs

HERC Staff summary

Opioid addiction is a chronic medical disorder. The most effective treatment includes a combination of psychosocial and pharmacologic interventions, along with other services. Medication assisted treatment with methadone and buprenorphine are evidence-based and supported by major national and federal organizations as well as being a statewide priority. A number of health systems are using uptake and duration of MAT as a core quality indicator. Detoxification alone is likely ineffective. Behavioral interventions are a critical component of any program.

BHAP recommends that HERC adopts the proposed guideline. Minor modifications were made to clarify what MAT is, and that opioid substitution therapy must be offered. They believe that the implementation will require provider engagement across the state.

HERC Staff & BHAP recommendations

1) Adopt a new Guideline Note:

GUIDELINE NOTE XXX, MEDICATION-ASSISTED TREATMENT OF OPIOID DEPENDENCE

Line 4

In patients who meet criteria for opioid use disorder, programs that offer treatment of opioid use disorder must offer patients a variety of evidence-based interventions including behavioral interventions, social support, and Medication Assisted Treatment (MAT) and are individualized to the patient's needs. Intensive programs, such as inpatient residential treatment programs, are required to inform patients about MAT and to offer access to and support for MAT (including at least one form of opioid substitution therapy) if patients elect to receive it, to be included on this line.

MAT includes pharmacotherapy with opioid substitution therapy (methadone and buprenorphine) and opioid antagonists (naltrexone).

Detoxification alone is likely ineffective for producing long-term benefit and should be followed by a formal substance use disorder individualized treatment plan.

In pregnant women with opioid dependence, comprehensive treatment (including opioid substitution therapy) is included on this line.

Buprenorphine Implants

Question: Should the procedure code for implantation of buprenorphine be included on lines 500/660 on the Prioritized List?

Question source: Behavioral Health Advisory Panel, Pharmacy and Therapeutics (P&T) Committee, HERC staff, HSD

Issue: At the August, 2017 BHAP meeting, the placement of the CPT code for the insertion of the buprenorphine implant was discussed.

From the August, 2017 BHAP minutes:

> BHAP discussed the HERC staff recommendation to add the CPT code for buprenorphine implant insertion to the substance abuse line. There was considerable concern among BHAP members about the relative cost of the implant vs the sublingual formulation. Gokaldas reported that for Multnomah County patients, the cost is $10,000/yr for implant ($5,000 per implant every 6 months) and the sublingual form is $100/month or $1200 per year. It was noted that the P&T PA criteria restricted use to very stable patients, which is probably the group that least needs this type of treatment. Livingston noted that other states are considering using the implants in the prison population at release from prison, but there are no studies on this population regarding outcomes. BHAP members suggested adding buprenorphine implants to line 500 for the studied population (i.e. patients stable on 8mg or less of sublingual buprenorphine for at least 6 months with stable housing, etc.) as it is much less cost-effective that the sublingual formulation. BHAP suggested adding buprenorphine implants to line 660 for all other populations, as it is an unproven therapy for those patients (not studied, no evidence).

CPT 11981 (Insertion, non-biodegradable drug delivery implant) is currently on lines 6 REPRODUCTIVE SERVICES and 191 CUSHING'S SYNDROME; HYPERALDOSTERONISM, OTHER CORTICOADRENAL OVERACTIVITY, MEDULLOADRENAL HYPERFUNCTION. Substance abuse diagnoses such as F11.10 (Opioid abuse) and F11.2 (Opioid dependence) are on line 4 SUBSTANCE USE DISORDER. Implantable buprenorphine is only available commercially as Probuphine.

P&T reviewed an implant form of buprenorphine in June, 2016. Their review included only 1 RCT (N=173) of patients randomized with either oral or implanted buprenorphine (Rosenthal et al 2016). The primary efficacy end point was the difference in proportion of responders, defined as participants with at least 4 of 6 months without evidence of illicit opioid use (based on urine test and self-report composites) by treatment group. A total of 81/84 (96.4%) of patients in the implant group responded to therapy versus 78/89 (87.6%) patients in the SL group. The difference was 8.8% (1-sided 97.5% CI, 0.009 to infinity; $p<0.001$ for noninferiority; $p=0.03$ for superiority) for the primary endpoint (NNT = 12).

P&T concluded in their drug class review that

1) New evidence is still insufficient to determine if there is any difference in efficacy/effectiveness or safety between different opioid dependence treatments, including different buprenorphine formulations.
2) New evidence is insufficient to determine if a specific subpopulation may benefit more with a specific drug or formulation approved for opioid dependence.

To qualify for the buprenorphine implant per P&T PA criteria, a patient must

1) have a diagnosis of opioid use disorder (opioid dependence or addiction)

2) be in a comprehensive treatment program for substance abuse that includes psychosocial support system(s)
3) have a prescriber enrolled in the Oregon Prescription Drug Monitoring Program (PDMP) who has verified at least once in the past 6 months that the patient has not been prescribed any opioid analgesics from other prescribers
4) been clinically stable on 8 mg daily or less of buprenorphine or equivalent for at least 6 months
5) Be clinically stable and suitable for Probuphoine treatment meeting all of the following:
    a. no reported illicit opioid use
    b. low to no desire/need to use illicit opioids
    c. no reports of significant withdrawal symptoms
    d. stable living environment
    e. participation in a structured activity/job
    f. consistent participation in recommended cognitive behavioral therapy/peer support program

Wholesale acquisition costs:

1) Buprenorphine 8 mg SL $1,680 per year
2) Probuphine 74.2mg implant $9,900 per year

Claims: there have been no claims submitted for implantable buprenorphine in the past year

HERC staff summary

There is limited evidence regarding the efficacy of implantable buprenorphine compared to either oral buprenorphine or oral buprenorphine/naloxone. The only studied population to date was a very stable group of patients on a very low dose of buprenorphine. P&T has reviewed this data and recommends coverage only for the very limited population studied to date. However, BHAP recommended non-coverage given the significantly higher cost of the implant, making it non-cost effective, and the limited data on efficacy. The cost of the implant is approximately 6 fold higher than for the oral formulation ($1,680 for 8mg Suboxone compared to $9,900 for Probuphine per year based on WAC).

Buprenorphine Implants

HERC staff recommendations:

1) Add implantable buprenorphine for the studied population to line 500 CONDITIONS FOR WHICH CERTAIN INTERVENTIONS RESULT IN MARGINAL CLINICAL BENEFIT OR LOW COST-EFFECTIVENESS and add an entry to GN172 as shown below

GUIDELINE NOTE 172, INTERVENTIONS WITH MARGINAL CLINICAL BENEFIT OR LOW COST-EFFECTIVENESS FOR CERTAIN CONDITIONS

The following interventions are prioritized on Line 500 for the conditions listed here:

CPT/HCPCS code	INTERVENTION	Rationale	Date of Last Review/Link to Meeting Minutes
11981	Implantable buprenorphine for opioid use disorder for patients who are clinically stable on 8 mg daily or less of buprenorphine or equivalent for at least 6 months	Not cost effective compared to equally efficacious alternative formulations	November, 2017

2) Add buprenorphine implants for all other populations to line 660 CONDITIONS FOR WHICH CERTAIN TREATMENTS HAVE NO CLINICALLY IMPORTANT BENEFIT OR HAVE HARMS THAT OUTWEIGH BENEFITS; UNPROVEN TREATMENTS and add an entry to GN173 as shown below

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

The following treatments are prioritized on Line 660, CONDITIONS FOR WHICH CERTAIN TREATMENTS HAVE NO CLINICALLY IMPORTANT BENEFIT OR HAVE HARMS THAT OUTWEIGH BENEFITS; UNPROVEN TREATMENTS for the conditions listed here:

CPT/HCPCS code	INTERVENTION	Rationale	Date of last Review
11981	Implantable buprenorphine for opioid use disorder for patients other than those who are clinically stable on 8 mg daily or less of buprenorphine or equivalent for at least 6 months	Unproven treatment	November, 2017

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Class Update: Substance Use Disorders

Date of Review: September 2016 **Date of Last Review:** January 2015

Current Status of PDL Class:
See **Appendix 1**.

Purpose for Class Update:
Increases in misuse and abuse of opioids and subsequent increases in accidental opioid-related deaths have caught the attention of policy makers in the United States (U.S.) and in Oregon. On July 22, 2016, the Comprehensive Addiction and Recovery Act (CARA) was enacted which authorizes the federal government to strengthen opioid prevention and treatment programs and improve community access to naloxone. Improved practices in opioid prescribing will likely lead to decreased prescribing of opioids but it may be at the expense of increased illicit opioid use (i.e., heroin, synthetic fentanyl, prescription opioids) for persons dependent on or addicted to opioids. Illicit opioid use is a major cause of mortality from acute causes (e.g., overdose, traffic accidents) and transmission of blood-borne infections like HIV and Hepatitis C due to injection drug use. A review of new published data and updated clinical practice guidelines for management of substance use disorders will help inform whether current Oregon Health Plan (OHP) policies remain appropriate to access to these medications.

Research Questions:
1. Is there new evidence for differences in efficacy between drug therapies for alcohol use disorder or opioid use disorder?
2. Is there new evidence for differences in harms between drug therapies for alcohol use disorder or opioid use disorder?
3. Are there subpopulations based on demographics (i.e., adolescents, elderly, women, criminal justice offenders) or practice settings (i.e., rehabilitation/addiction center, clinics, private physician offices or patient self-administration) in which a drug for alcohol use disorder or opioid use disorder may be more effective or less harmful than other drugs?

Conclusions:
- Treatment for opioid use disorder was last reviewed by the Pharmacy and Therapeutics Committee in January 2015 and treatment for alcohol use disorder was last reviewed in July 2014. Since then, two high quality systematic reviews from the Agency for Healthcare Research and Quality (AHRQ) and the Cochrane Collaboration, and one high quality clinical practice guideline from the Veterans Affairs and Department of Defense (VA/DoD) were especially informative.

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Alcohol Use Disorder

- There is high quality evidence for use of acamprosate and oral naltrexone to decrease alcohol consumption in patients with alcohol use disorder when used concurrently with psychosocial interventions; however, there is insufficient evidence to support their use based on an improvement in clinically relevant health outcomes (i.e., morbidity or mortality) alone.
    - The number needed to treat [NNT] to prevent one person from returning to *any* drinking is 12 persons (95% Confidence Interval [CI], 8 to 26; 16 trials; n=4847) for acamprosate and 20 persons (95% CI, 11 to 500; 16 trials; n=2347) for oral naltrexone 50 mg daily.[1]
    - Oral naltrexone is associated with statistically significant improvement in prevention of returning to *heavy* drinking (NNT 12; 95% CI, 8 to 26; 19 trials; n=2875) but acamprosate is not associated with an improvement.[1]
- There is no statistically significant association with return to *any* drinking or return to *heavy* drinking with extended-release injectable naltrexone; however, there was a statistically significant association with reduction in *heavy* drinking days (weighted mean difference [WMD] -4.6%; 95% CI, -8.5% to -0.56%; 2 trials; n=926), although it is unclear if this difference is clinically meaningful.[1]
- There is insufficient evidence to adequately support an association between disulfiram use and preventing return to *any* drinking or improvement in other alcohol consumption outcomes.[1] However, blinded studies may be incapable of distinguishing a difference between disulfiram and control groups due to high attrition and fear for disulfiram-ethanol reactions. Blinded studies may be incompatible for disulfiram research; when data from open-labeled studies are pooled, there is moderate quality evidence that disulfiram is safe and efficacious for treatment of alcohol use disorder in supervised settings.[2]
- There is low quality evidence that suggests off-label use of topiramate may be useful in decreasing alcohol consumption.[1]
- There is high quality evidence of no difference between acamprosate and oral naltrexone in return to *any* drinking (RD 0.02; 95% CI, -0.03 to 0.08); return to *heavy* drinking (RD 0.01; 95% CI, -0.05 to 0.06); or percent of drinking days (WMD -2.98%; 95% CI, -13.4 to 7.5%).[1] There is insufficient evidence to compare extended-release injectable naltrexone or disulfiram with other drugs for treatment of alcohol use disorder.
- There is insufficient evidence to demonstrate differences in harms for medications used to treat alcohol use disorder.
- The updated clinical practice guideline from the Veterans Affairs and Department of Defense (VA/DoD) for the management of substance abuse disorders strongly recommends that treatment choice between acamprosate, disulfiram, naltrexone (oral or extended-release injection) or topiramate be individualized based on specific needs and patient preferences.[3] In all cases, strong psychosocial interventions are needed to successfully treat patients with alcohol use disorder.[3]

Opioid Use Disorder

- Moderate quality evidence from 2 trials demonstrates no difference between methadone and buprenorphine maintenance treatment in terms of self-reported opioid use (risk ratio [RR] 0.37; 95% CI, 0.08 to 1.63) or positive opioid urine drug screens (RR 0.81; 95% CI, 0.56 to 1.18).[4] Low quality evidence from 3 trials demonstrates no difference in treatment retention between methadone and buprenorphine maintenance treatment programs (RR 0.69; 95% CI, 0.39 to 1.22).[4]
- Maintenance treatment with buprenorphine is more effective than detoxification treatment alone or psychosocial treatment alone, based on low quality evidence that assessed self-reported opioid use in the last 30 days (RR 0.54; 95% CI, 0.31 to 0.93), urine drug screens (RR 0.63; 95% CI, 0.43 to 0.91), and treatment retention (RR 0.33; 95% CI, 0.23 to 0.47).[4]
- There is moderate quality evidence from 2 trials of no difference in rates of adverse events between methadone and buprenorphine maintenance treatment (RR 1.10; 95% CI, 0.64 to 1.91).[4]
- For patients with a diagnosis of opioid use disorder, the VA/DoD strongly recommends buprenorphine/naloxone or methadone in an Opioid Treatment Program depending on specific patient needs or preferences.[3] Alternatively, buprenorphine without naloxone is strongly recommended to be used in

patients who are pregnant, and extended-release injectable naloxone is recommended as an option for patients for whom buprenorphine/naloxone or methadone is contraindicated, unacceptable, or unavailable, and who have established opioid abstinence for a sufficient period of time. In all cases, strong psychosocial interventions are needed to successfully treat patients with opioid use disorder.[3]

Sub-groups

- There is insufficient evidence to confirm which treatments for alcohol or opioid use disorders are more or less effective or safe in older or younger subgroups, by gender, racial or ethnic minorities, smokers or nonsmokers, or those with certain coexisting conditions.[1] However, the VA/DoD strongly recommend that sublingual buprenorphine (without naloxone) be reserved for pregnant patients when used to treat opioid use disorder.[3]
- When compared to non-pharmacological treatment, there is low quality evidence that opioid agonist treatment (methadone or buprenorphine) and naltrexone may not be effective reducing illicit drug use in criminal justice offenders.[6] However, there is moderate quality evidence that naltrexone treatment reduces criminal activity as evidenced by decreased re-incarceration rates.[6]
- There is moderate quality evidence that disulfiram is more effective in supervised settings.[2] Otherwise, there is insufficient evidence to know with certainty whether buprenorphine products are more effective or safer when given in designated Opioid Treatment Programs or in private physician offices, or whether daily supplies should be administered or multi-day supplies may be administered. Methadone is restricted to designated Opioid Treatment Programs.

Recommendations:

- Continue to require clinical prior authorization (PA) criteria for all buprenorphine products and the naltrexone extended-release injection product based on recommended amendments in Appendix 4.
- Remove buprenorphine sublingual tablets from the OHP fee-for-service Preferred Drug List (PDL) and restrict use to pregnant females as required by clinical PA criteria in Appendix 4.
- After review of comparative drug costs in the executive session, no other changes to the OHP PDL were made.

Previous Conclusions:

- New evidence is still insufficient to determine if there is any difference in efficacy/effectiveness or safety between different opioid dependence treatments, including different buprenorphine formulations.
- New evidence is insufficient to determine if a specific subpopulation may benefit more with a specific drug or formulation approved for opioid dependence.

Previous Recommendations:

- No further review or research needed at this time.

Background:

Substance Use Disorders (SUD) can develop in individuals who use alcohol, opioids, or other addicting drugs in harmful quantities.[3] About 9% of adults in the U.S. have a non-tobacco SUD, and about 25% of all Americans will develop a non-tobacco SUD over the course of a lifetime.[3] Excessive alcohol use and illicit drug use, including illicit prescription drug use, costs $223.5 billion and $193.5 billion, respectively, each year in the U.S. according to the latest available estimates from the Centers for Disease Control and Prevention (CDC) and U.S. Department of Justice.[3] Excessive alcohol use in the U.S. results in about 88,000 premature deaths each year from acute (e.g., alcohol poisoning, motor vehicle accidents) and chronic causes (e.g., liver disease, hypertension, heart disease, stroke, pancreatitis).[3]

Illicit opioid use (heroin or prescription opioids) is also a major cause of mortality from acute causes (e.g., overdose, traffic accidents) and transmission of blood-borne infections like HIV and Hepatitis C due to injection drug use. An estimated 400,000 persons have used heroin in the past month in the U.S. and 4 million persons have reported nonmedical use of prescription pain relievers.[7] Worldwide, opioid use disorder has resulted in 11 million life-years lost from health problems, disabilities, and early death from opioid-related conditions.[7] When tobacco use is included, SUDs are the leading actual cause of death in the U.S.[3]

The Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-V) specifically recognizes SUDs related to substances such as tobacco, alcohol, opioids, cannabis, sedatives, anxiolytics, and 5 other substances.[8] According to the DSM-V, SUDs are associated with a pattern of inappropriate substance use that adversely affects one's personal or professional life or results in noticeable distress.[8] In persons with SUDs, there is an underlying change in the way the brain functions that may persist beyond detoxification that can result in repeated relapses and intense cravings when exposed to different drug-related stimuli.[8] These addictive substances alter brain circuitry involved in complex functions like motivation and decision-making and alter natural reward mechanisms for essential substances like food and water.[3] Pleasure normally experienced with stimuli such as food or social interactions are diminished with repeated use of addicting substances.[3]

Over 16 million adults in the U.S. had a diagnosis of alcohol use disorder in 2014 (10.6 million males and 5.7 million females).[9] In adolescents aged 12-17 years, it was estimated that 679,000 had alcohol use disorder which was fairly equally diagnosed between boys and girls.[9] Unfortunately, only 1 in 10 patients are treated for alcohol use disorder and treatment options remain underutilized despite their potential to improve health outcomes.[1] Treatments for alcohol use disorder include a combination of cognitive behavioral therapy, motivational enhancement therapy, 12-step programs (e.g., Alcoholic Anonymous), and pharmacotherapy. Pharmacotherapy options for patients with alcohol use disorder include oral options like disulfiram, acamprosate, and naltrexone, as well as extended-release injectable naltrexone. All of these treatments have been approved by the U.S. Food and Drug Administration (FDA) for treatment of alcohol dependence in patients who are able to abstain from alcohol. Outcomes studied have been primarily limited to reduction in alcohol consumption: return to any drinking, return to heavy drinking, drinking days, heavy drinking days (≥4 drinks per day for women; ≥5 for men), or drinks per drinking day. Off-label use of topiramate and gabapentin for alcohol use disorder has also shown some benefit, whereas drugs like baclofen, buspirone, antidepressants, and antipsychotics have not consistently shown benefit.[3]

Opioid analgesics have been used for decades to manage pain, but they can also produce feelings of euphoria, tranquility and sedation that lead to substantial misuse and abuse of these drugs. A person will build tolerance to regular use of opioids, including heroin, which can result in the desire for higher and higher doses to achieve the intended effect but at the expense of serious adverse events such as respiratory suppression and death. With the recent dramatic increase in misuse of prescription opioids and ease of accessibility of opioids, including heroin, it is imperative that physicians understand how to diagnose and navigate treatment strategies with their patients. From 2007 to 2014, the number of private insurance claim lines with an opioid dependence diagnosis increased 3,203%, with most of the claims associated with persons between 19-35 years of age.[10] On July 22, 2016, the Comprehensive Addiction and Recovery Act (CARA) was enacted which authorizes the federal government to strengthen opioid prevention and treatment programs, and improve community access to naloxone.[11]

Medically supervised treatment of long-acting opioid agonists for acute withdrawal symptoms (i.e., detoxification) can improve a patient's health and facilitate participation in a rehabilitation program.[7] However, detoxification alone is not helpful to produce long-term recovery and may increase a patient's risk for overdose due to lost tolerance for opioids.[7] The most effective approach is to relieve symptoms of detoxification with methadone or buprenorphine and then gradually reduce the dose to allow the patient to adjust to the absence of an opioid.[7] However, only licensed addiction-treatment programs and physicians who have completed specific training for opioid drugs can administer opioids to treat opioid use disorder. Some non-opioid medications, such as the centrally-acting

α-2 agonist clonidine, are also used off-label to manage the autonomic over-activity associated with opioid withdrawal. Loperamide, prochlorperazine and nonsteroidal anti-inflammatory drugs (NSAIDs) can also be used in combination to manage other withdrawal symptoms.

Opioid maintenance treatment, with methadone or buprenorphine/naloxone most commonly utilized, reduces withdrawal and cravings and has long been used in the treatment of heroin or prescription opioid dependence for rehabilitation purposes.[7] Oral and extended-release injectable naltrexone formulations are also approved by the FDA for opioid dependence in patients who can abstain from opioids. The regular dosing of a long-acting opioid lessens the sense of euphoria or intoxication that is usually associated with each illicit drug dose and has demonstrated reduction in illicit opioid use, mortality, criminal activity, HIV risk behavior and seroconversion, as well as improved physical and mental health and social functioning.[4] Concurrent psychosocial support is essential to address some of the psychological and social problems that can be associated with opioid use disorder.[4]

Methadone is a mu-opioid agonist and an N-methyl-D-aspartate (NMDA) antagonist given as a single daily dose for opioid dependence in approved Opioid Treatment Programs (i.e., 'methadone clinics'). Previous data show that methadone has strong evidence that demonstrates effectiveness in reducing mortality and substance use, improving physical and mental health outcomes, reducing criminal activity and reducing risk for HIV and risk behaviors.[4] However, methadone is not without harms. Adverse effects may include prolonged QT interval which rarely result in Torsade de pointes, and respiratory depression associated with titrating the drug. Opioid Treatment Programs have strict guidelines for dosing, supervised treatment and associated services. The optimal dosage of methadone for retention in treatment is at least 60 mg daily but many patients will require higher doses.[7]

Buprenorphine is a partial opioid agonist and has lower intrinsic activity at the opioid receptor, but due to its very high affinity for the receptor, buprenorphine possesses antagonist properties that block the effects of other opioids. Buprenorphine has a favorable safety profile compared to methadone due to its limited effects on the respiratory system and also has evidence for reduced mortality similar to methadone.[4] Unlike methadone which is 100% bioavailable as an oral formulation, buprenorphine has poor bioavailability and must be developed in formulations that are not swallowed orally (e.g., sublingual, buccal, transdermal, etc.). For treatment of opioid-dependence (and not pain), a buprenorphine sublingual formulation is available and buprenorphine/naloxone buccal and sublingual formulations are available. Buprenorphine and naloxone are usually formulated in 4:1 to discourage injection of the drug. The low dose of naloxone does not precipitate withdrawal symptoms unless it is injected. These products (C-III) are not as highly controlled as methadone (C-II) and can be provided by physicians who have received a waiver from the Substance Abuse and Mental Health Services Administration (SAMSHA), have completed 8 hours of buprenorphine training, and have a special Drug Enforcement Administration (DEA) number.[7] Previously, these physicians were limited to caring for 30 patients at a time, but that number was increased to 275 patients in July 2016.[7]

There are no guidelines that specify when to refer a patient to an Opioid Treatment Program for methadone or buprenorphine maintenance treatment. Both drugs have demonstrated improvement in clinical outcomes in multiple randomized clinical trials (RCTs). High-quality evidence supports the use of medication-assisted treatment using methadone or buprenorphine/naloxone over psychosocial treatment alone to improve outcomes.[7] Choice of drug typically comes down to individual clinician and patient preferences. Methadone can be dispensed in Opioid Treatment Programs only, whereas buprenorphine can also be prescribed by physicians in office-based settings, including primary care, outpatient specialty SUD treatment facilities, and mental health clinics. Considerations include cost; concomitant medical (e.g., heart disease) and psychiatric conditions; the availability of methadone clinics; the availability of physicians trained in administering buprenorphine; and the risk of diversion when determining which option is most appropriate. For example, an office-based treatment program may not be suitable for patients with a concurrent substance abuse disorder (e.g., alcohol, sedatives, anxiolytics) or even patients who regularly use sedative-hypnotics like benzodiazepines.[5] Buprenorphine is more expensive than methadone, and the private office charges for buprenorphine might exceed the usual

costs of a methadone clinic.[7] However, buprenorphine may be safer than methadone during induction and early stabilization phases of treatment. Buprenorphine can also be administered in physician offices which can improve access to opioid maintenance treatment.[7]

Evidence from one RCT also shows that extended-release injectable opioid antagonist naloxone can be successfully used to treat opioid use disorder.[7] The long-acting formulation can be given in both general healthcare and specialty substance use disorder treatment settings. There is insufficient evidence at this time to recommend oral naltrexone because it requires a highly motivated patient to be successful and it has not consistently demonstrated superiority to control groups at treatment retention or in opioid consumption.[3] Patients who initiate naltrexone treatment must be free of opioid dependence (e.g., >7 days without acute withdrawal symptoms), which should be confirmed based on an opioid-free urine sample and a naloxone challenge (intramuscular or intravenous administration of 0.8 to 1.6 mg of naloxone; or alternatively, 50 mg or oral naloxone with no subsequent withdrawal symptoms).[7]

Clinically important outcomes for studies that assess efficacy of substance use disorders can include: treatment retention/completion; illicit substance use or any alcohol consumption; risk behaviors (injecting, sexual, polysubstance use, overdoses, hospital admissions); quality of life as assessed by validated scales (e.g., WHO Quality of Life scale), employment, physical health as assessed by validated scales (e.g., 36-item Short Form), adverse effects and aberrant opioid-related behaviors (e.g., multiple prescribers, lost medications, or unauthorized dose increases).[4]

Methods:

A Medline literature search for new systematic reviews and RCTs assessing clinically relevant outcomes to active controls, or placebo if needed, was conducted. The Medline search strategy used for this review is available in **Appendix 3**, which includes dates, search terms and limits used. The OHSU Drug Effectiveness Review Project, Agency for Healthcare Research and Quality (AHRQ), Cochrane Collection, National Institute for Health and Clinical Excellence (NICE), Department of Veterans Affairs, BMJ Clinical Evidence, and the Canadian Agency for Drugs and Technologies in Health (CADTH) resources were manually searched for high quality and relevant systematic reviews. When necessary, systematic reviews are critically appraised for quality using the AMSTAR tool and clinical practice guidelines using the AGREE tool. The FDA website was searched for new drug approvals, indications, and pertinent safety alerts. Finally, the AHRQ National Guideline Clearinghouse (NGC) was searched for updated and recent evidence-based guidelines.

The primary focus of the evidence is on high quality systematic reviews and evidence-based guidelines. Randomized controlled trials will be emphasized if evidence is lacking or insufficient from those preferred sources.

New Systematic Reviews:

<u>Alcohol Use Disorder</u>

The Agency for Healthcare Research and Quality (AHRQ) conducted a systematic review on the efficacy of various medications used for the treatment of alcohol use disorder.[1] Eligible studies were double-blind RCTs that enrolled adults with alcohol use disorder that evaluated an FDA-approved medication or off-label medication (i.e., baclofen, buspirone, citalopram, fluoxetine, sertraline, topiramate, quetiapine, and others) for at least 12 weeks against placebo or another medication in an outpatient setting.[1] Studies were required to assess one of the following outcomes: 1) consumption – return to any drinking, return to heavy drinking, drinking days, heavy drinking days (≥4 drinks per day for women; ≥5 for men), drinks per drinking day; 2) health outcomes – accidents (i.e., motor vehicle crashes), injuries, quality of life, function, and mortality; or 3) adverse effects.[1] Adequacy of randomization, allocation concealment, similarity of groups and baseline, blinding, attrition, validity and reliability of measures, whether intention-to-treat analysis was used, and methods of handling missing data were considered in assessment of the risk of bias of the studies.[1] Meta-analyses of RCTs were conducted using random-effects models.[1] Weighted mean differences

(WMD) with 95% CIs were used for continuous outcomes.[1] Risk differences (RD) with 95% CI were conducted for binary outcomes.[1] Studies with high or unclear risk of bias were excluded from the main analaysis but were included in sensitivity analyses.[1] The I^2 statistic was calculated to assess for statistical heterogeneity.[1] Publication bias was assessed when possible (≥10 studies in a meta-analysis) by examination of funnel plots. Strength of evidence was graded as high, moderate, low or insufficient based on 4 key domains: risk of bias, consistency, directness and precision.[1] A total of 123 studies were included.[1] Most studies assessed acamprosate (27 studies; n=7519), naltrexone (53 studies, n=9140) or both.[1] Treatment duration ranged from 12 to 52 weeks.[1] In most cases, psychosocial interventions were also given to participants.[1] Most studies enrolled patients after detoxification or required a period of sobriety before randomization.[1]

Both acamprosate and oral naltrexone improve alcohol consumption outcomes.[1] The NNT to prevent one person from returning to any drinking is 12 persons (95% CI, 8 to 26; 16 trials; n=4847) for acamprosate and 20 persons (95% CI, 11 to 500; 16 trials; n=2347) for oral naltrexone 50 mg daily.[1] Acamprosate was not associated with an improvement in return to heavy drinking but oral naltrexone is associated with statistically significant improvement (NNT 12; 95% CI, 8 to 26; 19 trials; n=2875).[1] There was no statistically significant association with return to any drinking or return to heavy drinking with extended-release injectable naltrexone; however, there was a statistically significant association with reduction in heavy drinking days (WMD -4.6%; 95% CI, -8.5% to -0.56%; 2 trials; n=926).[1] There is insufficient evidence for disulfiram to adequately support an association with preventing return to any drinking or improvement in other alcohol consumption outcomes.[1] However, the largest disulfiram trial to date (n=605) did report fewer drinking days for patients who returned to drinking.[1] Meta-analyses of head-to-head RCTs that compared acamprosate with oral naltrexone did not find a statistically significant difference between these 2 medications in return to any drinking (RD 0.02; 95% CI, -0.03 to 0.08); return to heavy drinking (RD 0.01; 95% CI, -0.05 to 0.06) or percent of drinking days (WMD -2.98%; 95% CI, -13.4 to 7.5%).[1] There was insufficient evidence to support most medications used off label for alcohol use disorder.[1] The exceptions are topiramate and valproic acid.[1] Topiramate is associated with fewer drinking days (WMD -6.5%; 95% CI, -12.0% to -1.0%; 2 trials; n=541), heavy drinking days (WMD -9.0%; 95% CI, -15.3% to -2.7%; 3 trials; n=691) and drinks per drinking day (WMD -1.0; 95% CI, -1.6 to -0.48; 3 trials; n=691).[1] Valproic acid demonstrated some efficacy in consumption outcomes in patients with bipolar disorder.[1] Trials primarily focused on consumption outcomes; very few trials reported health outcomes and those that did were not powered to assess health outcomes.[1] There was also insufficient evidence to make fair estimations of potential adverse events with these agents due to inadequate precision.[1] In general, adverse events occurred more often in active treatment groups than placebo, but differences were not statistically significant.[1] In head-to-head trials of naltrexone and acamprosate, no statistically significant differences in withdrawal due to adverse events were observed.[1] Compared with placebo, patients treated with acamprosate had a higher risk of anxiety (number needed to harm [NNH] 7); diarrhea (NNH 11) and vomiting (NNH 42); patients treated with naltrexone had a higher risk for dizziness (NNH 16) and vomiting (NNH 24).[1]

Overall, acamprosate and oral naltrexone (50 mg/day) have the best evidence for treatment alcohol use disorder when used concurrently with psychosocial interventions; however, evidence is limited to alcohol consumption outcomes, including evidence for alcohol abstinence but health outcomes are still lacking.[1] A summary of the evidence extracted from the AHRQ report is summarized in **Table 1**. The mean age of participants was generally in the 40s.[1] There is insufficient evidence to confirm which treatments are more or less effective or safe in older or younger subgroups, different sex groups, racial or ethnic minorities, smokers or nonsmokers, and those with certain coexisting conditions.[1] Most trials of acamprosate were conducted in Europe while most trials of naltrexone were conducted in the U.S.[1] The few U.S.-based acamprosate trials did not find the drug to be efficacious, which may be related to the sources that the patients were recruited from (inpatient treatment programs vs. advertisements).[1] Overall, most trials were conducted in specialized outpatient treatment settings and very little evidence from primary care settings is available.[1]

Table 1. Summary of Findings and Strength of Evidence for the Efficacy of Medications use to Treat Alcohol Use Disorder Versus Placebo (*Agency for Healthcare Research and Quality*).[1]

Medication	Outcome	N (studies)	N (subjects)	Finding	Effect Size (95% CI)	NNT	SOE
Acamprosate vs. Placebo	Return to any drinking	16	4,847	Reduced by acamprosate	RD -0.09 (-0.14 to -0.04)	12	Moderate
	Return to heavy drinking	7	2,496	No difference	RD -0.01 (-0.04 to 0.03)	NA	Moderate
	Percentage of drinking days	13	4,485	Reduced by acamprosate	WMD -8.8 (-12.8 to -4.8)	NA	Moderate
Disulfiram vs Placebo	Return to any drinking	2	492	No difference	RD -0.04 (-0.11 to 0.03)	NA	Low
Naltrexone 50 mg oral vs. Placebo	Return to any drinking	16	2,347	Reduced by naltrexone	RD -0.05 (-0.10 to -0.00)	20	Moderate
	Return to heavy drinking	19	2,875	Reduced by naltrexone	RD -0.09 (-0.13 to -0.04)	12	Moderate
	Percentage of drinking days	15	1,992	Reduced by naltrexone	WMD -5.4 (-7.5 to -3.2)	NA	Moderate
	Percentage of heavy drinking days	6	521	Reduced by naltrexone	WND -4.1 (-7.6 to -0.61)	NA	Moderate
Naltrexone injection vs. Placebo	Return to any drinking	2	939	No difference	RD -0.04 (-0.10 to 0.03)	NA	Low
	Return to heavy drinking	2	615	No difference	RD -0.01 (-0.14 to 0.13)	NA	Low
	Percentage of heavy drinking days	2	926	Reduced by naltrexone	WMD -4.6 (-8.5 to -0.56)	NA	Low
Topiramate vs. Placebo	Percentage of drinking days	2	521	Reduced by topiramate	WMD -8.5 (-15.9 to -1.1)	NA	Moderate
	Percentage of heavy drinking days	2	521	Reduced by topiramate	WMD -11.5 (-18.3 to -4.8)	NA	Moderate
	Number of drinks per drinking day	2	521	Reduced by topiramate	WMD -1.1 (-1.7 to -0.4)	NA	Moderate
Other drugs	The evidence is insufficient to determine the efficacy of other medications because of inconsistency, imprecision, or lack of sufficient studies in the literature (e.g., amitriptyline, aripiprazole, atomoxetine, baclofen, buspirone, citalopram, desipramine, fluoxetine, fluvoxamine, gabapentin, imipramine, olanzapine, ondansetron, paroxetine, quetiapine, varenicline, viloxazine).						

Abbreviations: CI = confidence interval; N = number; NA = not applicable; NNT = number needed to treat; RD = risk difference; SOE = strength of evidence; WMD = weighted mean difference.

Disulfiram appears to be successful for alcohol use disorder in patients who are compliant or supervised in real-world settings, but the efficacy of disulfiram in clinical trials has been conflicting which has led to controversy around use of the drug based on poorly designed trials. A systematic review with meta-analysis was conducted to determine whether disulfiram treatment is more effective in open-label studies rather than in blinded trials because of the negative psychological impact participants may have in blinded trials because of fear of the disulfiram-ethanol reaction (DER).[2] The hypothesis was that blinded trials would not show a difference in efficacy between disulfiram and control groups because fear of DER would dissuade compliance in all groups.[2] All controlled trials that evaluated use of disulfiram in patients with alcohol use disorder were eligible for inclusion.[2] These studies included both blind and open-label designs, both supervised and unsupervised.[2] The methodological quality of the studies was analyzed according to the Cochrane Collaboration's tool for assessing risk of bias.[2] Efficacy outcomes were analyzed using a random-effects model, due to high heterogeneity in the studies, and by calculating the Hedge's *g* effect-size for each trial with the uncertainty of each result expressed by their 95% CIs.[2] An effect size of 0.2 to 0.3 is thought to be a 'small' treatment effect, about 0.5 a 'medium' treatment effect, and 0.8 to infinity a 'large' treatment effect.[2] Publication bias was assessed using funnel plots and heterogeneity was assessed by calculating the I^2 value (range 0% to 100%, with 0%-40% considered unimportant heterogeneity).[2] The primary endpoint of the meta-analysis was the combined effect-size at the end of treatment for the primary outcomes studied. Primary outcomes included: total abstinence; proportion of abstinent days to treatment days; mean days of alcohol use; no relapse; time to first heavy drinking day; or 3 or more weeks of consecutive abstinence.

Overall, 23 studies were eligible for inclusion in the meta-analysis.[2] The studies were published between 1973 and 2010; most were from the U.S. (10) study durations of 8 to 52 weeks.[2] Most participants in the studies were males and 2 studies evaluated adolescents.[2] In addition, 6 of the studies evaluated a population of cocaine abusers who also had an alcohol use disorder.[2] The results of the meta-analysis found significant success rate for disulfiram compared to controls (g=0.58; 95% CI, 0.35 to 0.82; I^2=72%).[2] A funnel plot analysis indicated possible publication bias but the summary effect size remained significant after correcting for missing studies (g=0.53 to g-0.63; p<0.001).[2] A subgroup analysis that compared blinded RCTs to open-label RCTs found that open-label RCTs found a significant superiority of disulfiram versus controls (g=0.70; 95% CI, 0.46 to 0.93; I^2=65%) whereas the blinded RCTs found no efficacy with disulfiram compared to controls (g=0.01; 95% CI, -0.29 to 0.32; I^2=43%).[2] When blinded trials were excluded, the funnel plot showed symmetry which demonstrated that there was no publication bias among those types of studies.[2] A subgroup analysis by supervision categories found disulfiram to be significantly superior to controls when medication compliance was supervised (g=0.82; 95% CI, 0.59 to 1.05; I2=46%) but not when treatment was unsupervised (g=0.26; 95% CI, -0.02 to 0.53).[2] No publication bias was found when studies were broken down by supervision categories.[2] In another subgroup analysis by control group, disulfiram was statistically significantly superior to naltrexone (g=0.77; 95% CI, 0.52 to 1.02; I^2=26%) and to acamprosate (g=0.76; 95% CI, 0.04 to 1.48; I^2=81%).[2] In terms of safety, disulfiram was associated with an increased risk for adverse events compared to controls (RR 1.40; 95% CI, 1.01 to 1.94).[2] Out of studies that reported adverse events totaling 962 participants, 8 subjects reported a serious adverse event that required hospitalization but most continued the disulfiram study after discharge.[2] A total of 13 deaths were reported (disulfiram groups = 6; control groups = 6; unspecified = 6).[2] The authors concluded that blinded studies were incapable of distinguishing a difference between treatment groups and thus are incompatible with disulfiram research.[2] Open-labeled trials in supervised settings have shown disulfiram to be safe and efficacious comparted to other abstinence supportive pharmacological treatments (naltrexone, acamprosate, topiramate) or to no disulfiram for alcohol use disorder.[2]

Opioid Use Disorder

The efficacy and safety of maintenance opioid agonist therapy for the treatment of pharmaceutical opioid dependence was recently evaluated in a systematic review by the Cochrane Collaboration.[4] All RCTs that evaluated at least 30 days of full opioid agonist maintenance treatment (i.e., methadone) against another full opioid agonist or partial opioid agonist (buprenorphine) for opioid use disorder were eligible for inclusion.[4] In addition, RCTs that evaluated full or partial opioid agonist maintenance therapy for opioid use disorder versus placebo, psychosocial treatment only (without opioid agonist treatment), or detoxification only were also eligible for inclusion.[4] Eligible RCTs had to enroll patients who were primarily dependent on prescription opioids rather than heroin.[4] The primary outcomes studied were 1) illicit opioid use; 2) illicit opioid use at end of treatment; and 3) retention. Overall, 6 RCTs met inclusion criteria (n=607).[4] Three studies compared methadone with buprenorphine and 3 studies compared buprenorphine to either buprenorphine taper or brief intervention and referral to treatment.[4] The mean duration of the studies was 105 days.[4] The mean age of participants was 31.6 years and 77% were male.[4] Five of the trials took place in the U.S. but the evidence was somewhat limited by their open-label design and small sample sizes (53 to 204 participants).[4] There was enough consistency in the way the trials collected and reported primary outcomes to pool data on key outcome measures.[4] Moderate quality evidence from 2 trials demonstrates no difference between methadone and buprenorphine maintenance treatment in terms of self-reported opioid use (risk ratio [RR] 0.37; 95% CI, 0.08 to 1.63) or positive opioid urine drug screens (RR 0.81; 95% CI, 0.56 to 1.18).[4] Low quality evidence from 3 trials demonstrates no difference in treatment retention between methadone and buprenorphine maintenance treatment programs (RR 0.69; 95% CI, 0.39 to 1.22).[4] In addition, there is moderate quality evidence from 2 trials of no difference in rates of adverse events between methadone and buprenorphine maintenance treatment (RR 1.10; 95% CI, 0.64 to 1.91).[4] Buprenorphine maintenance treatment may be superior to detoxification treatment alone or psychosocial treatment alone in terms of self-reported opioid use in the last 30 days (RR 0.54; 95% CI, 0.31 to 0.93) and positive opioid urine drug screens (RR 0.63; 95% CI, 0.43 to 0.91) based on low quality evidence.[4] In addition, buprenorphine maintenance treatment is superior to detoxification treatment alone or psychosocial treatment alone in terms of treatment retention (RR 0.33; 95% CI, 0.23 to 0.47) and adverse events (RR 0.19; 95% CI, 0.06 to 0.57) based on moderate quality evidence.[4] Overall, the authors concluded that

there is low to moderate quality evidence to support the use of methadone or buprenorphine maintenance therapy for opioid dependence but further research may change the overall findings from this review.[4]

The effectiveness of pharmacological interventions for illicit drug-using (abuse or dependence) offenders (i.e., subject to the criminal system) in reducing drug use, criminal activity, or both, was recently evaluated in a systematic review by the Cochrane Collaboration.[6] The systematic review was conducted because trials in the criminal justice setting are largely lacking, and continuity of care is critical for the treatment of individuals who transition between prison and the community.[6] All RCTs that assessed the efficacy of any pharmacological intervention that is designed to reduce, eliminate or prevent relapse of drug use or criminal activity, or both, in drug-using offenders were eligible for inclusion.[6] Control interventions could be no treatment, minimal treatment, waiting list, treatment as usual, or other treatment (pharmacological or psychosocial).[6] Where studies reported a number of different follow-up periods, the longest time reported was used to provide the most conservative estimate of effectiveness.[6] Alcohol and tobacco use was excluded from drug use outcomes data.[6] Fourteen (n=2647) trials lasting between 6 months and 4 years met inclusion criteria but most studies had small sample sizes.[6] Thirteen studies used methadone as an intervention and most trials were conducted in prison.[6] In general, the trials included evaluated methadone, buprenorphine, or naltrexone compared to no intervention, other non-pharmacological treatments (e.g., counselling) or other pharmacological drugs.[6] The methodological quality of the included trials was mostly unclear as methods were generally poorly described.[6] According to the investigators, the biggest threats to risk of bias were open label study designs (performance and detection bias) and incomplete outcome data (attrition bias).[6] Heterogeneity between studies prevented the ability to pool some data; however, 11 studies were included in the meta-analysis.[6] When compared to non-pharmacological treatment, there was low quality evidence that opioid agonist treatment (methadone or buprenorphine) was not effective at reducing drug use based on objective dichotomous data (i.e., hair and urine analysis) (RR 0.72; 95% CI, 0.51 to 1.00; n=237), self-reported subjective dichotomous data (yes/no) (RR 0.61; 95% CI, 0.31 to 1.18; n=317) or self-reported continuous data (SMD -0.62; 95% CI, -0.85 to -0.39; n=510).[6] No statistically significant differences in individual treatments were found between methadone and buprenorphine in self-reported dichotomous data of drug use (yes/no) (RR 1.04; 95% CI, 0.69 to 1.55; n=370) or continuous data of drug use (amount of drug use) (MD 0.70; 95% CI, -5.33 to 6.73; n=81) or in criminal activity (RR 1.25; 95% CI, 0.83 to 1.88).[6] There was also low quality evidence that naltrexone was not effective at reducing drug use (RR 0.69; 95% CI, 0.28 to 1.70; n=63) but there was moderate quality evidence that naltrexone treatment reduced criminal activity as evidenced by re-incarceration (RR 0.40; 95% CI, 0.21 to 0.74; n=114).[6] In a separate systematic review that looked specifically at female drug-using offenders, the only trial identified used buprenorphine which did not significantly reduce self-reported drug use compared to placebo in this population (RR 0.58; 95% CI, 0.25 to 1.35; n=36).[12] Low retention rates after prison release significantly limit adequate follow-up of all trials in these systematic reviews.

New Guidelines:

<u>VA/DoD Clinical Practice Guideline for the Management of Substance Abuse Disorders</u>[3]

The Department of Veterans Affairs (VA) and Department of Defense (DoD) Evidence-based Practice Work Group facilitates the development of clinical practice guideline for the VA and DoD populations. In December 2015, the VA/DoD published an update of their clinical practice guideline for the evaluation, treatment and management of substance abuse disorders.[3] The guideline workgroup used the Grading of Recommendations Assessment, Development and Evaluation (GRADE) system to assess the quality of the evidence base and assign a grade for the strength of each recommendation.[3] For example, a strong recommendation indicates the workgroup was highly confident based on evidence that benefits related to the recommendation outweigh risks.[3] The VA/DoD emphasizes that medical management for substance abuse disorders is a shared decision-making process that must provide strategies to increase medication adherence, as well as monitoring of substance use and its consequences.[3] Management of substance use disorders must also support abstinence through education and referral to support groups.[3]

Alcohol Use Disorder

The VA/DoD recommend all patients in general medical and mental healthcare settings be screened for unhealthy alcohol use every year using the 3-item Alcohol Use Disorders Identification Test-Consumption (AUDIT-C) questionnaire or the Single-item Alcohol Screening Questionnaire (SASQ) [*strong recommendation*].[3] A single initial intervention regarding alcohol-related risks and advice to abstain or drink within the established limits is recommended for patients without documented alcohol use disorder that screen positive for unhealthy alcohol use by the nationally established age and gender-specific limits for daily and weekly consumption in Table 2 [*strong recommendation*].[3]

Table 2. Nationally Established Age- and Gender-specific limits for Daily and Weekly Alcohol Consumption.[3]

- Men aged ≤65 y: ≤4 standard drinks per day and ≤14 per week
- Men aged >65 y and all women: ≤3 standard drinks per day and ≤7 per week
- Patients with contraindications including potential drug-drug interactions: 0 drinks per day

For patients with substance use disorders, there is insufficient evidence to recommend for or against using a standardized assessment that would determine initial intensity and setting of substance use disorder care rather than the clinical judgment of trained providers.[3]

In addition to offering one or more recognized non-pharmacological interventions (Behavioral Couples Therapy for alcohol use disorder; Cognitive Behavioral Therapy for substance abuse disorders; Community Reinforcement Approach; Motivational Enhancement Therapy; and/or 12-step Facilitation), any of the following specific pharmacotherapy options is recommended for moderate-severe alcohol use disorder based on RCTs and several systematic reviews/meta-analyses [*strong recommendation*][3]:

- Acamprosate
- Disulfiram
- Naltrexone (oral or extended-release)
- Topiramate

In the absence of contraindications, there is insufficient evidence to recommend routine use of one of the recommended medications over another; thus, treatment choice should be individualized based on specific needs and patient preferences.[3]

For management of moderate to severe alcohol withdrawal, a benzodiazepine is recommended with adequate monitoring [*strong recommendation*].[3] Pharmacotherapy strategies for managing alcohol withdrawal should include a predetermined fixed medication (i.e., given in advance of the emergence of anticipated withdrawal) with a tapering schedule and an additional medication available as needed; alternatively, treatment may be only given when signs or symptoms of withdrawal occur (e.g., as needed dosing) [*strong recommendation*].[3] Non-benzodiazepine alternatives such as carbamazepine, gabapentin, or valproic acid are recommended for managing mild to moderate alcohol withdrawal in patients from whom risks of benzodiazepines outweigh benefits (e.g., inadequate monitoring available, abuse liability, or allergy/adverse reactions) [weak recommendation].[3] The VA/DoD strongly recommend against the use of alcohol to manage medically supervised withdrawal.[3]

Opioid Use Disorder

For patients with a diagnosis of opioid use disorder, the VA/DoD recommends any of the following specific medications considering patient preferences [*strong recommendation*][3]:

- Buprenorphine/naloxone
- Methadone in an Opioid Treatment Program

Specific recommendations for treatment of opioid use disorder are also recommended[3]:
- Buprenorphine alone without naloxone in pregnant women for whom buprenorphine is indicated [*weak recommendation*]
- The method of buprenorphine treatment (i.e., Opioid Treatment Program or office-based) should be individualized for the patient [strong recommendation]
- Extended-release injectable naloxone is an option for patients for whom opioid agonist treatment is contraindicated, unacceptable, unavailable, or discontinued and who have established abstinence for a sufficient period of time [*strong recommendation*]
- There is insufficient evidence to recommend for or against oral naltrexone for the treatment of opioid use disorder
- Addiction-focused Medical Management alone or in conjunction with another psychosocial intervention is recommended at initiation of office-based buprenorphine [*strong recommendation*][3]

The VA/DoD do not recommend withdrawal management unless patients are stabilized from opioid use disorder because it substantially increases risk for relapse and overdose [*strong recommendation*].[3] In such cases, administration of long-term opioid agonists (methadone, buprenorphine) is preferred over short tapers because it is more effective and less harmful.[3] A taper of opioids using methadone or buprenorphine can be used if medically supervised in patients that 1) require abstinence from opioids; 2) wish to receive non-opioid agonist treatment (extended-release naloxone injection); 3) have minimal symptoms of opioid dependency; or 4) are in a profession that does not permit opioid agonist treatment [*strong recommendation*].[3] Clonidine may be used for withdrawal management as a second-line agent in patients with opioid use disorder who may have contraindications to methadone or buprenorphine [*strong recommendation*].[3]

The VA/DoD do not have specific pharmacotherapy recommendations for or against management of cannabis use disorder, cocaine use disorder or methamphetamine use disorder because of insufficient evidence.[3]

New Safety Alerts:
None identified.

New Formulations or Indications:
PROBUPHINE (buprenorphine) [C-III] implant device for subdermal use was approved by the FDA in May 2016.[13] The device is not available in retail pharmacies and must be inserted and removed by the certified prescriber.[13] The implants can only be obtained through a restricted Risk Evaluation and Mitigation Strategy (REMS) program that requires specialized training for physicians on insertion and removal techniques, as well as the risks for accidental overdose, misuse and abuse of opioids.[13] Certification for use of PROBUPHINE, which must be renewed every 12 months, must be achieved before use of the device.[13]

The approved indication is for the maintenance treatment of opioid dependence in patients who have achieved and sustained prolonged clinical stability of no more than 8 mg daily of a sublingual (SL) or buccal buprenorphine-containing product.[13] Treatment should accompany counseling and other psychosocial support.[13] Four implants are inserted subdermally in the upper arm for 6 months and are removed by the end of the sixth month.[13]

The efficacy of the implant is based on evidence from one double-blind, double-dummy, 6-month RCT (n=173) that compared the 4 simultaneous 80 mg buprenorphine implants with sublingual buprenorphine in adults who met DSM-IV-TR criteria for opioid dependence.[14] All patients in the trial were clinically stable on at least 6 months on SL buprenorphine at 8 mg per day or less.[14] Patients randomized to the SL buprenorphine group remained on their pre-enrollment dose (75% were taking 8 mg daily). Patients are eligible for the implant based on the enrollment in the clinical trial and manufacturer prescribing information[13]:

- no reported illicit opioid use
- no reports of significant withdrawal symptoms
- low to no desire/need to use illicit opioids
- no hospitalizations (addiction or mental health issues), emergency room visits, or crisis interventions in the past 90 days
- stable living environment, participation in a structured activity/job that contributes to the community, consistent participation in recommended cognitive behavioral therapy/peer support program
- consistent compliance with clinic visit requirements

The 4 implants contained 80 mg of buprenorphine each and yield similar plasma concentrations at a range (0.5-1.0 ng/mL) comparable to 8 mg per day or less of SL buprenorphine.[14] The primary efficacy end point was the difference in proportion of responders, defined as participants with at least *4 of 6 months* without evidence of illicit opioid use (based on urine test and self-report composites) by treatment group.[14] A total of 81/84 (96.4%) of patients in the implant group responded to therapy versus 78/89 (87.6%) patients in the SL group.[14] The difference was 8.8% (1-sided 97.5% CI, 0.009 to infinity; p<0.001 for noninferiority; p=0.03 for superiority) for the primary endpoint (NNT = 12).[14] In a sensitivity analysis for all randomized participants, with all missing urine samples imputed as positive for opioids and no illicit opioid use for all 6 months, 70/87 (80.5%) patients in the implant group and 60/90 (66.7%) in the SL buprenorphine group remained opioid-free, resulting in a proportion difference of 13.8% (1-sided 97.5% CI, 0.010 to infinity; p<0.001 for noninferiority; p=0.03 for superiority).[14] Drug-related adverse events were consistent with the known safety profile of buprenorphine and the subdermal implantation procedures (local site adverse events).[14]

Randomized Controlled Trials:

A total of 108 citations were manually reviewed from the literature search. After manual review, most citations were excluded because of wrong study design (i.e., observational), lack of control group, hospital setting, or outcome studied (i.e., non-clinical). The remaining trials are briefly described in the table below. Full abstracts are included in **Appendix 2**.

Table 3: Description of Randomized Comparative Clinical Trials.

Alcohol Use Disorder				
Study	Comparison	Population	Primary Outcome	Results
O'Malley, et al.[15] DB, PC, PG, RCT 8 weeks N=128	1. Naltrexone 25 mg/d + naltrexone 25 mg PRN once per day (≥2 hrs prior to drinking situations). Max 50 mg/day. 2. Placebo targeted + placebo daily	Ages 18-25 years reporting ≥4 heavy drinking days (≥4 drinks/women or ≥5 drinks/men) in past 4 weeks.	Outcome 1: % days abstinent (PDA) Outcome 2 % heavy drinking days (PHDD) Self-reported drinking by web-based diary	PDA: 1. 56.6% (SD 22.52) 2. 62.5% (SD 15.57) LSMD -2.55; 95% CI, -8.46 to 3.36) PHDD: 1. 21.6% (SD 16.05) 2. 22.9% (SD 13.20) LSMD -1.44; 95% CI, -6.60 to 3.71)

Opioid Use Disorder				
D'Onofrio, et al.[16] SC, OL, RCT 30 days N=329	1. Referral to addiction services 2. Referral to addiction services + Brief Negotiation Interview (BNI) 3. Referral to addiction services + BNI + 3-day supply of buprenorphine (8 mg day 1, 16 mg days 2 and 3) to bridge until first clinic visit.	Ages ≥18 years reporting to ED with DSM-IV criteria for opioid dependence and positive UDS for opioids nonmedical prescription opioid or heroin use in past 30 days	Engagement in treatment (enrollment and receiving formal addiction treatment	1. 38/102 (37%; 95% CI, 28 to 47%) 2. 50/111 (45%; 95% CI, 36 to 54%) 3. 89/114 (78%; 95% CI, 70 to 85%; p<0.001 vs. other 2 comparisons)
Lee, et al.[17] MC, OL, RCT 6 months	1. VIVITROL (naltrexone ER) inj once per month 2. Usual care (brief counseling, referral to addiction services)	Criminal justice offenders ages 18-60 years with opioid dependence per DSM-IV criteria but currently opioid free per UDS and willing to try opioid-free treatment	Time to an opioid-relapse event during the 6-month treatment phase (defined as ≥10 days opioid use in a 28-day period)	Time to first relapse: 1. 10.5 weeks 2. 5.0 weeks (HR 0.49; 95% CI, 0.36 to 0.68) Total participants with relapse: 1. 66 (43%) 2. 99 (64%) (OR 0.43; 95% CI, 0.28 to 0.65)

Abbreviations: CO = cross-over; DB = double-blind; ED = emergency department; ER = extended-release; LSMD = least squares mean difference; MC = multi-centered; MD = mean difference; MME = morphine milligram equivalents; NRS = numerical rating scale (range 0-10); OL = open label; PC = placebo-controlled; PG = parallel group; RCT = randomized clinical trial; SC = single center; SD = standard deviation.

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Appendix 1: Current Status on Preferred Drug List

ROUTE	FORMULATION	BRAND	GENERIC	PDL
ORAL	TABLET DR	ACAMPROSATE CALCIUM	ACAMPROSATE CALCIUM	Y
SUBLINGUAL	FILM	SUBOXONE	BUPRENORPHINE HCL/NALOXONE HCL	Y
SUBLINGUAL	TAB SUBL	BUPRENORPHINE HCL	BUPRENORPHINE HCL	Y
SUBLINGUAL	TAB SUBL	BUPRENORPHINE-NALOXONE	BUPRENORPHINE HCL/NALOXONE HCL	Y
SUBLINGUAL	TAB SUBL	ZUBSOLV	BUPRENORPHINE HCL/NALOXONE HCL	Y
ORAL	TABLET	NALTREXONE HCL	NALTREXONE HCL	Y
BUCCAL	FILM	BUNAVAIL	BUPRENORPHINE HCL/NALOXONE HCL	N
ORAL	TABLET	ANTABUSE	DISULFIRAM	N
ORAL	TABLET	DISULFIRAM	DISULFIRAM	N
INTRAMUSC	SUS ER REC	VIVITROL	NALTREXONE MICROSPHERES	N

Appendix 2: Abstracts of Clinical Trials

O'Malley, et al.
Reduction of Alcohol Drinking in Young Adults by Naltrexone: A Double-Blind, Placebo-Controlled, Randomized Clinical Trial of Efficacy and Safety. *J Clin Psychiatry* (2015).

Objective: Naltrexone, an opioid antagonist, may facilitate reduction in drinking among young adults. We compared the efficacy and safety of naltrexone administered daily plus targeted dosing with placebo to reduce drinking in heavy drinking young adults.
Methods: Randomized, double-blind, placebo-controlled study, outpatient research center, March 2008-January 2012. Participants were ages 18-25, reporting ≥4 heavy drinking days in the prior 4 weeks. Interventions included naltrexone 25 mg daily plus 25 mg targeted (at most daily) in anticipation of drinking (n=61) or daily/targeted placebo (n=67). All received a personalized feedback session and brief counseling every other week. Primary outcomes were percent days heavy drinking (PHDD) and percent days abstinent (PDA) over the 8-week treatment period. Secondary outcomes included drinks/drinking day and percent days with estimated blood alcohol levels ≥0.08 g/dL.
Results: Of 140 randomized, 128 began treatment, comprising the evaluable sample. During treatment, PHDD (Naltrexone M=21.60, SD=16.05; Placebo M=22.90, SD=13.20) (p=0.58) and PDA (Naltrexone M=56.60, SD=22.52; Placebo M=62.50, SD=15.75) (p=0.39) did not differ by group. Naltrexone significantly reduced drinks per drinking day (Naltrexone M=4.90, SD=2.28; Placebo M=5.90, SD=2.51) (p=0.009) and percentage of drinking days with estimated BAC ≥0.08 g/dL (Naltrexone M=35.36, SD=28.40; Placebo M=45.74, SD=26.80) (p=0.042). There were no serious adverse events. Sleepiness was more common with naltrexone.
Conclusions: Naltrexone did not reduce frequency of drinking or heavy drinking days, but reduced secondary measures of drinking intensity. While effects were modest, the risk-benefit ratio favors offering naltrexone to help young adult heavy drinkers reduce their drinking.

D'Onofrio, et al.
Emergency Department–Initiated Buprenorphine/Naloxone Treatment for Opioid Dependence: A Randomized Clinical Trial. *JAMA* (2015).

IMPORTANCE: Opioid-dependent patients often use the emergency department (ED) for medical care.
OBJECTIVE: To test the efficacy of 3 interventions for opioid dependence: (1) screening and referral to treatment (referral); (2) screening, brief intervention, and facilitated referral to community-based treatment services (brief intervention); and (3) screening, brief intervention, ED-initiated treatment with buprenorphine/naloxone, and referral to primary care for 10-week follow-up (buprenorphine).
DESIGN, SETTING, AND PARTICIPANTS: A randomized clinical trial involving 329 opioid-dependent patients who were treated at an urban teaching hospital ED from April 7, 2009, through June 25, 2013.
INTERVENTIONS: After screening, 104 patients were randomized to the referral group, 111 to the brief intervention group, and 114 to the buprenorphine treatment group.
MAIN OUTCOMES AND MEASURES: Enrollment in and receiving addiction treatment 30 days after randomization was the primary outcome. Self-reported days of illicit opioid use, urine testing for illicit opioids, human immunodeficiency virus (HIV) risk, and use of addiction treatment services were the secondary outcomes.
RESULTS: Seventy-eight percent of patients in the buprenorphine group (89 of 114 [95%CI, 70%-85%]) vs 37%in the referral group (38 of 102 [95% CI, 28%-47%]) and 45%in the brief intervention group (50 of 111 [95% CI, 36%-54%]) were engaged in addiction treatment on the 30th day after randomization (p< 0.001). The buprenorphine group reduced the number of days of illicit opioid use per week from 5.4 days (95% CI, 5.1-5.7) to 0.9 days (95% CI, 0.5-1.3) versus a reduction

from 5.4 days (95% CI, 5.1-5.7) to 2.3 days (95% CI, 1.7-3.0) in the referral group and from 5.6 days (95% CI, 5.3-5.9) to 2.4 days (95% CI, 1.8-3.0) in the brief intervention group (p<0.001 for both time and intervention effects; p=0.02 for the interaction effect). The rates of urine samples that tested negative for opioids did not differ statistically across groups, with 53.8% (95% CI, 42%-65%) in the referral group, 42.9% (95% CI, 31%-55%) in the brief intervention group, and 57.6% (95% CI, 47%-68%) in the buprenorphine group (p=0.17). There were no statistically significant differences in HIV risk across groups (p=0.66). Eleven percent of patients in the buprenorphine group (95% CI, 6%-19%) used inpatient addiction treatment services, whereas 37% in the referral group (95% CI, 27%-48%) and 35% in the brief intervention group (95% CI, 25%-37%) used inpatient addiction treatment services (p< .001).
CONCLUSIONS AND RELEVANCE: Among opioid-dependent patients, ED-initiated buprenorphine treatment vs brief intervention and referral significantly increased engagement in addiction treatment, reduced self-reported illicit opioid use, and decreased use of inpatient addiction treatment services but did not significantly decrease the rates of urine samples that tested positive for opioids or of HIV risk. These findings require replication in other centers before widespread adoption.

Lee, et al.
Extended-Release Naltrexone to Prevent Opioid Relapse in Criminal Justice Offenders. *N Engl J Med* (2016).

BACKGROUND: Extended-release naltrexone, a sustained-release monthly injectable formulation of the full mu-opioid receptor antagonist, is effective for the prevention of relapse to opioid dependence. Data supporting its effectiveness in U.S. criminal justice populations are limited.
METHODS: In this five-site, open-label, randomized trial, we compared a 24-week course of extended-release naltrexone (Vivitrol) with usual treatment, consisting of brief counseling and referrals for community treatment programs, for the prevention of opioid relapse among adult criminal justice offenders (i.e., persons involved in the U.S. criminal justice system) who had a history of opioid dependence and a preference for opioid-free rather than opioid maintenance treatments and who were abstinent from opioids at the time of randomization. The primary outcome was the time to an opioid-relapse event, which was defined as 10 or more days of opioid use in a 28-day period as assessed by self-report or by testing of urine samples obtained every 2 weeks; a positive or missing sample was computed as 5 days of opioid use. Post-treatment follow-up occurred at weeks 27, 52, and 78.
RESULTS: A total of 153 participants were assigned to extended-release naltrexone and 155 to usual treatment. During the 24-week treatment phase, participants assigned to extended-release naltrexone had a longer median time to relapse than did those assigned to usual treatment (10.5 vs. 5.0 weeks, P<0.001; hazard ratio, 0.49; 95% confidence interval [CI], 0.36 to 0.68), a lower rate of relapse (43% vs. 64% of participants, P<0.001; odds ratio, 0.43; 95% CI, 0.28 to 0.65), and a higher rate of opioid-negative urine samples (74% vs. 56%, P<0.001; odds ratio, 2.30; 95% CI, 1.48 to 3.54). At week 78 (approximately 1 year after the end of the treatment phase), rates of opioid-negative urine samples were equal (46% in each group, P = 0.91). The rates of other prespecified secondary outcome measures — self-reported cocaine, alcohol, and intravenous drug use, unsafe sex, and reincarceration — were not significantly lower with extended-release naltrexone than with usual treatment. Over the total 78 weeks observed, there were no overdose events in the extended-release naltrexone group and seven in the usual-treatment group (p= 0.02).
CONCLUSIONS: In this trial involving criminal justice offenders, extended-release naltrexone was associated with a rate of opioid relapse that was lower than that with usual treatment. Opioid-use prevention effects waned after treatment discontinuation.

Appendix 3: Medline Search Strategy

Ovid MEDLINE(R) without Revisions 1996 to July Week 2 2016

1 exp Buprenorphine, Naloxone Drug Combination/ or exp Buprenorphine/ 3133
2 exp Naltrexone/ 4363
3 exp Prescription Drug Misuse/ or exp Opioid-Related Disorders/ or exp Substance-Related Disorders/ 134079
4 1 or 2 7341
5 3 and 4 3247
6 limit 5 to (english language and humans and yr="2015 -Current" and (clinical trial, all or clinical trial or comparative study or controlled clinical trial or meta analysis or multicenter study or practice guideline or pragmatic clinical trial or randomized controlled trial or systematic reviews)) 77

Ovid MEDLINE(R) without Revisions 1996 to July Week 2 2016

1 acamprosate.mp. 641
2 exp Disulfiram/ 760
3 exp Naltrexone/ 4363
4 exp Alcoholism/ 27319
5 exp Substance-Related Disorders/ 133713
6 exp Alcohol Deterrents/ 1461
7 1 or 2 1308
8 4 or 5 or 6 134283
9 7 and 8 1247
10 limit 9 to (english language and humans and yr="2014 -Current" and (clinical trial, all or clinical trial or comparative study or controlled clinical trial or meta analysis or multicenter study or practice guideline or pragmatic clinical trial or randomized controlled trial or systematic reviews)) 31

Buprenorphine and Buprenorphine/Naloxone Products

Goals:
- Encourage use of buprenorphine products on the Preferred Drug List.
- Restrict use of buprenorphine products under this PA to management of opioid use disorder.
- Restrict use of oral transmucosal buprenorphine monotherapy products (without naloxone) to pregnant patients or females actively trying to conceive.

Length of Authorization:
Up to 6 months

Requires PA:
- Buprenorphine sublingual tablets
- Buprenorphine/naloxone buccal film (Bunavail), sublingual film (Suboxone) and sublingual tablets (Zubsolv)
- Buprenorphine (Probuphine) subdermal implants

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

Approval Criteria		
1. What diagnosis is being treated?	Record ICD10 code.	
2. Is the prescription for opioid use disorder (opioid dependence or addiction)?	**Yes:** Go to #3	**No:** Pass to RPh. Deny; medical appropriateness

Approval Criteria		
3. Is the patient part of a comprehensive treatment program for substance abuse that includes psychosocial support system(s)?	**Yes:** Go to #4	**No:** Pass to RPh. Deny; medical appropriateness. Buprenorphine therapy must be part of a comprehensive treatment program that includes psychosocial support.
4. Is the prescriber enrolled in the Oregon Prescription Drug Monitoring Program (www.orpdmp.com) and has the prescriber verified at least once in the past 6 months that the patient has not been prescribed any opioid analgesics from other prescribers?	**Yes:** Go to #5	**No:** Pass to RPh. Deny; medical appropriateness
5. Is the requested medication a preferred agent?	**Yes:** Go to #7	**No:** Go to #6
6. Will the prescriber switch to a preferred product? Note: Preferred products are reviewed and designated as preferred agents by the Oregon Pharmacy & Therapeutics Committee based on published medical evidence for safety and efficacy.	**Yes:** Inform prescriber of covered alternatives in class.	**No:** Go to #7
7. Is the request for the buprenorphine implant system (Probuphine)?	**Yes:** Go to #8	**No:** Go to #9
8. Has the patient been *clinically stable* on 8 mg daily or less of Suboxone or Subutex (or equivalent, see Table 1) for at least 6 months? Note: see Table 1 for definition of clinical stability and for equivalent dosing of other buprenorphine products.	**Yes:** if <u>all</u> criteria in Table 1 met, approve 4 implants for 6 months	**No:** Pass to RPh. Deny; medical appropriateness

Approval Criteria		
9. Is the prescription for a transmucosal formulation of buprenorphine (film, tablet) with an average daily dose of more than 24 mg (e.g., more than 24 mg/day or 48 mg every other day)?	**Yes:** Pass to RPh. Deny; medical appropriateness	**No:** Go to #10
10. Is the prescribed product a buprenorphine monotherapy product (i.e., without naloxone)	**Yes:** Go to #11	**No:** Go to #13
11. Is the patient pregnant or a female actively trying to conceive?	**Yes:** Go to #13	**No:** Go to #12
12. Does the patient have a contraindication or intolerance to buprenorphine/naloxone combination products that prevents successful management of opioid use disorder?	**Yes:** Go to #13	**No:** Pass to RPh. Deny; medical appropriateness
13. What is the patients' pharmacy-of-choice? Document pharmacy name and NPI or address in PA record. Lock patient into their pharmacy-of-choice for 6 months.	Inform prescriber patient will be locked into a single pharmacy for all prescriptions. Go to #14	
14. What is the expected length of treatment?	Document length of therapy: _____ Approve for anticipated length of treatment or 6 months, whichever is shorter.	

Table 1. Criteria for Approved Use of Probuphine (buprenorphine implant).[1]

PROBUPHINE implants are only for use in patients who meet ALL of the following criteria:
• Patients should not be tapered to a lower dose for the sole purpose of transitioning to PROBUPHINE • Stable transmucosal buprenorphine dose (of 8 mg per day or less of a sublingual Subutex or Suboxone sublingual tablet or its transmucosal buprenorphine product equivalent) for 3 months or longer without any need for supplemental dosing or adjustments: o Examples of acceptable daily doses of transmucosal buprenorphine include: ▪ Subutex (buprenorphine) sublingual tablet (generic equivalent) 8 mg or less ▪ Suboxone (buprenorphine and naloxone) sublingual tablet (generic equivalent) 8 mg/2 mg or less ▪ Bunavail (buprenorphine and naloxone) buccal film 4.2 mg/0.7 mg or less ▪ Zubsolv (buprenorphine and naloxone) sublingual tablets 5.7 mg/1.4 mg or less

Consider the following factors in determining clinical stability and suitability for PROBUPHINE treatment: • no reported illicit opioid use • low to no desire/need to use illicit opioids • no reports of significant withdrawal symptoms • stable living environment • participation in a structured activity/job that contributes to the community • consistent participation in recommended cognitive behavioral therapy/peer support program • stability of living environment • participation in a structured activity/job
Reference: PROBUPHINE (buprenorphine implant for subdermal administration) [Prescribing Information]. Princeton, MJ: Braeburn Pharmaceuticals, Inc., May 2016.

P&T Review: *9/16 (AG); 1/15 (AG); 9/09; 5/09*
Implementation: *TBD; 9/1/13; 1/1/10*

Naltrexone Extended Release Inj. (Vivitrol®)

Goal(s):

- Promote safe and cost effective therapy for the treatment of alcohol and opioid dependence.

Length of Authorization:

Up to 6 months

Covered Alternatives:

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

Approval Criteria	
1. What diagnosis is being treated?	Record ICD10 code.

Approval Criteria		
2. Will the prescriber switch to a preferred product? Note: Preferred products are reviewed and designated as preferred agents by the Oregon Pharmacy & Therapeutics Committee based on published medical evidence for safety and efficacy.	**Yes:** Inform prescriber of covered alternatives in class.	**No:** Go to #3
3. Does the patient have a diagnosis of alcohol dependence (DSM-IV-TR) or alcohol use disorder (DSM-V)?	**Yes:** Go to #4	**No:** Go to #5
4. Has the requesting prescriber provided documentation and/or confirmation of abstinence from alcohol as assessed by the provider or by objective testing?	**Yes:** Go to #9	**No:** Pass to RPh. Deny; medical appropriateness. Patients must have demonstrated alcohol abstinence prior to administration.
5. Does the patient have a diagnosis of opioid dependence (DSM-IV-TR) or opioid use disorder (DSM-V)?	**Yes:** Go to #6	**No:** Pass to RPh. Deny; medical appropriateness.
6. Is the prescriber enrolled in the Oregon Prescription Drug Monitoring Program (www.orpdmp.com) and has the prescriber verified at least once in the past 6 months that the patient has not been prescribed any opioid analgesics from other prescribers?	**Yes:** Go to #7	**No:** Pass to RPh. Deny; medical appropriateness.
7. Is the patient physiologically free of opioid dependence for ≥7 days, as confirmed by: a. Negative urine drug screen for opioids (including heroin) and their metabolites; and b. Negative naloxone challenge test (0.8 to 1.6 mg of IM/IV naloxone; or alternatively, 50 mg or oral naloxone with no subsequent withdrawal symptoms)?	**Yes:** Go to #8	**No:** Pass to RPh. Deny; medical appropriateness.

Approval Criteria		
8. Has the patient tried and failed first-line oral opioid agonists (buprenorphine/naloxone or methadone) if for the treatment of opioid dependency; or is the patient unable to take oral therapy or requires injectable therapy due to poor adherence?	**Yes:** Go to #9	**No:** Pass to RPh. Deny; medical appropriateness.
9. Is the patient part of a comprehensive treatment program for substance abuse that includes psychosocial support system(s)?	**Yes:** Approve one 380 mg injection every 4 weeks for up to 6 months.	**No:** Pass to RPh. Deny; medical appropriateness. Naltrexone extended-release injection therapy must be part of a comprehensive treatment program that includes psychosocial support.

P&T Review: 9/16 (AG); 1/15 (AG); 5/14; 11/13
Implementation: 1/1/14

Enzyme Replacement Therapy Guideline

Questions:

1) Should the enzyme replacement therapy guideline be modified?
2) Should the entry to GN173 clarify what is excluded for enzyme replacement therapy?

Question source: CCO pharmacy director, Pharmacy and Therapeutics staff

Issue: In 2012, enzyme replacement therapy for Hunter's syndrome (Elaprase, idursulfase) was reviewed and found to have no clinical efficacy. A guideline note was created to specify that enzyme replacement therapy was only included on an unfunded line except for treatment of infantile Pompe's disease. With the new GN173 process, an entry was added in August, 2017 specifying that enzyme replacement therapy was include on line 660. GN67 was not modified or deleted as part of this process.

In conversations with P&T staff, begun by a question from Carly Rodriguez, Pharm.D. from MODA, it has become clear that there are now several drugs in the enzyme replacement therapy class for various inborn errors of metabolism. However, P&T has not reviewed these drugs with the understanding that HERC intended that they not be covered. P&T plans to internally look at these drug reviews to determine if any actually have a significant clinical benefit. Also, the question was raised by Dr. Rodriguez about whether other enzyme replacement therapies, such as pancreatic enzyme replacement, were meant to be included in the non-coverage for "enzyme replacement therapy." Pancreatic enzyme replacement is standard and accepted therapy for exocrine pancreatic insufficiency resulting from cystic fibrosis, chronic pancreatitis, or other cause.

There is also a HCPCS code listed in GN173 which applies to the home administration of such enzyme replacement therapies (HCPCS S9357 Home infusion therapy, enzyme replacement intravenous therapy; (e.g., imiglucerase); administrative services, professional pharmacy services, care coordination, and all necessary supplies and equipment (drugs and nursing visits coded separately), per diem). However, the HERC intends that the drugs themselves should not be covered and the HCPCS code has been suggested for deletion from the guideline note to reduce confusion. S9357 is on lines 60 METABOLIC DISORDERS, 147 GLYCOGENOSIS, 650 ENDOCRINE AND METABOLIC CONDITIONS WITH NO OR MINIMALLY EFFECTIVE TREATMENTS OR NO TREATMENT NECESSARY, but the current GN does not apply to line 60, which contains the diagnosis for Hunter's syndrome. However, other CPT and HCPCS codes are found in GN172 or 173 as well as other lines, with the GN entry specifying when it is non-covered.

Pompe's disease is on line 147 and the dysfunction lines.

GUIDELINE NOTE 67, ENZYME REPLACEMENT THERAPY

Lines 147,650

Enzyme replacement therapy for infantile Pompe's disease is included on Line 147. All other enzyme replacement therapies are included on Line 650.

HERC staff recommendations:

1) Amend GN67 to reflect the new entry on line 660/GN173
    a. Delete line 650 ENDOCRINE AND METABOLIC CONDITIONS WITH NO OR MINIMALLY EFFECTIVE TREATMENTS OR NO TREATMENT NECESSARY
    b. Add line 660 NO CLINICALLY IMPORTANT BENEFIT OR HAVE HARMS THAT OUTWEIGH BENEFITS
    c. Add wording to clarify that enzyme replacement therapy for conditions such as exocrine pancreatic insufficiency are not included in this guideline

GUIDELINE NOTE 67, ENZYME REPLACEMENT THERAPY

Lines 147,~~650~~, 660

Enzyme replacement therapy for infantile Pompe's disease is included on Line 147. All other enzyme replacement therapies for inborn errors of metabolism are included on Line ~~*650*~~, *660.*

2) Delete HCPCS S9357 Home infusion therapy, enzyme replacement intravenous therapy; (e.g., imiglucerase); administrative services, professional pharmacy services, care coordination, and all necessary supplies and equipment (drugs and nursing visits coded separately), per diem) from lines 60 METABOLIC DISORDERS and 650 ENDOCRINE AND METABOLIC CONDITIONS WITH NO OR MINIMALLY EFFECTIVE TREATMENTS OR NO TREATMENT NECESSARY

3) Modify the entry to GN173 regarding enzyme replacement therapy as shown below

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

The following treatments are prioritized on Line 660, CONDITIONS FOR WHICH CERTAIN INTERVENTIONS HAVE NO CLINICALLY IMPORTANT BENEFIT OR HAVE HARMS THAT OUTWEIGH BENEFITS; UNPROVEN INTERVENTIONS for the conditions listed here:

CPT/HCPCS code	INTERVENTION	Rationale	Date of last Review
S9357	Enzyme replacement therapy (e.g. idursulfase and similar medications) for all inborn error of metabolism conditions except infantile Pompe's disease	No clinically important benefit	August, 2012

4) Recommend to P&T staff that similar enzyme replacement therapies be internally reviewed. If a medication is found to be efficacious, the GN173 entry will be modified to reflect coverage for that medication/condition after HERC review.

Noninvasive tests for liver fibrosis for hepatitis C – FibroSure update

Question: Should FibroTest/FibroSure be allowed as a noninvasive tests for liver fibrosis for hepatitis C?

Question source: HSD, CCOs

Issue:
Two issues need to be addressed:

1. Reconsider coverage of FibroTest/FibroSure

   FibroTest/FibroSure was not included as a covered test when the Coverage Guidance on Noninvasive Liver Testing for the Treatment of Hepatitis C was incorporated into the Prioritized List. This was based on the fact that we had defined *a priori*, that for a noninvasive test to be an acceptable alternative to liver biopsy, the Area Under the Receiver Operator Curve (AUROC) needed to have the characteristics of a "good" or "excellent" test (defined as an AUROC ≥0.8 and AUROC ≥0.9, respectively).

   FibroTest
   Median AUROC 0.79 (range 0.70 to 0.89)
   ●○○○ *(Very low confidence)*

   Hepascore®
   Median AUROC 0.79 (range 0.69 to 0.82)
   ●○○○ *(Very low confidence)*

   Compared to other included tests:

   ●●●○ *(Moderate confidence)*
   Transient Elastography
   AUROC 0.89 (95% CI 0.86 to 0.91)
   ●●●○ *(Moderate confidence)*

   Acoustic Radiation Force Impulse Imaging
   AUROC 0.88 (95% CI 0.81 to 0.96)
   ●●○○ *(Low confidence)*

   Shear Wave Elastography
   AUROC 0.88 (95% CI 0.85 to 0.91)
   ●●○○ *(Low confidence)*

ELF™
Median AUROC 0.81 (range 0.72 to 0.87)
●○○○ *(Very low confidence)*

FibroMeter™
Median AUROC 0.82 (range 0.78 to 0.85)
●○○○ *(Very low confidence)*

FIBROSpect® II
Median AUROC 0.86 (range 0.77 to 0.95)
●○○○ *(Very low confidence)*

Over the last few months, we have heard that FibroSure is more readily available than many of the acceptable tests and so there are considerable barriers to getting tested in some parts of the state. Oftentimes, the imaging tests are only available with access to a hepatologist and there can be long delays in these appointments. Many of the CCOs are doing active case-finding related to the risk corridor as there is interest in making sure that CCOs are offering the treatment to those who are eligible.

The Pharmacy and Therapeutics Committee, at their 9/28/2017 meeting, adopted language allowing FibroSure to confirm F2 or greater.

The net result is that this test (FibroSure) underperformed slightly compared to some of the others, but it is the only readily available test across the state. CCOs and HSD have expressed interest in making this test available for OHP members to help facilitate increased numbers of individuals becoming eligible for treatment with direct acting antivirals (DAAs).

2. Guideline Note 76 provides direction for which noninvasive liver tests are included in the funded region based on Fibrosis Score. Given that as of January 1, 2018, coverage for DAAs will be included for ≥F2, the specific detail about an F3 cutoff will no longer be necessary. This can simply be deleted.

<u>Prioritized List Status</u>
GUIDELINE NOTE 76, Diagnostic testing for liver fibrosis to guide treatment of hepatitis C in non-cirrhotic patients

Line 199

If a fibrosis score of ≥F2 is the threshold for antiviral treatment of Hepatitis C, the following are included on this line:

Imaging tests:

- Transient elastography (FibroScan®)
- Acoustic radiation force impulse imaging (ARFI) (Virtual Touch™ tissue quantification, ElastPQ)
- Shear wave elastography (SWE) (Aixplorer®)

Blood tests (only if imaging tests are unavailable):

- Enhanced Liver Fibrosis (ELF™)
- Fibrometer™
- FIBROSpect® II

If a fibrosis score of ≥F3 is the threshold for antiviral treatment of Hepatitis C, one or more of the following are included on this line:

Imaging tests:

- Transient elastography (FibroScan®)
- Acoustic radiation force impulse imaging (ARFI)
- Shear wave elastography (SWE)

Magnetic resonance elastography is included on this line for ≥F2 or ≥F3 only when at least one imaging test (FibroScan, ARFI, and SWE) has resulted in indeterminant results, a second one is similarly indeterminant, contraindicated or unavailable, and MRE is readily available.

Noninvasive tests are covered no more often than once per year.

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

Background on Test Definitions

Blood tests	Components of test/algorithm
Proprietary tests	
ELF™ Test (Enhanced Liver Fibrosis)	Hyaluronic acid, tissue inhibitor of metalloproteinase 1, and procollagen III amino terminal peptide
FibroMeter™	Alanine aminotransferase (ALT), α_2-macroglobulin, gamma-glutamyl transpeptidase (GGT), aspartate aminotransferase (AST), platelet count, prothrombin index, urea, and patient's age and gender
FIBROSpect® II	Hyaluronic acid, tissue inhibitor of metalloproteinase, and α_2-macroglobulin

Blood tests	Components of test/algorithm
FibroSure® (FibroTest®)	α2-macroglobulin, haptoglobin, apolipoprotein A1, total bilirubin and gamma-glutamyl transpeptidase (GGT), and patient's age and gender ActiTest® is similar, with the addition of alanine aminotransferase (ALT)
Hepascore® (FibroScore®)	α_2-macroglobulin, hyaluronic acid, gamma-glutamyl transferase (GGT), bilirubin, and patient's age and gender

HERC Staff Recommendations:

1) Modify Guideline Note 76 as follows:

GUIDELINE NOTE 76, Diagnostic testing for liver fibrosis to guide treatment of hepatitis C in non-cirrhotic patients

Line 199

Given that ~~If~~ a fibrosis score of ≥F2 is the threshold for antiviral treatment of Hepatitis C, the following are included on this line:

Imaging tests:
- Transient elastography (FibroScan®)
- Acoustic radiation force impulse imaging (ARFI) (Virtual Touch™ tissue quantification, ElastPQ)
- Shear wave elastography (SWE) (Aixplorer®)

Blood tests (only if imaging tests are unavailable):
- Enhanced Liver Fibrosis (ELF™)
- Fibrometer™
- FIBROSpect® II
- FibroSure® (FibroTest®)

~~If a fibrosis score of ≥F3 is the threshold for antiviral treatment of Hepatitis C, one or more of the following are included on this line:~~

~~Imaging tests:~~
- ~~Transient elastography (FibroScan®)~~
- ~~Acoustic radiation force impulse imaging (ARFI)~~
- ~~Shear wave elastography (SWE)~~

Magnetic resonance elastography is included on this line for ≥F2 ~~or ≥F3~~ only when at least one imaging test (FibroScan, ARFI, and SWE) has resulted in indeterminant results, a second one is similarly indeterminant, contraindicated or unavailable, and MRE is readily available.

Noninvasive tests are covered no more often than once per year.

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

2) Decide whether or not to also allow Hepascore, with the same AUROC but lower confidence interval (no known requests for this test).

3) Acknowledge that there will be a discrepancy between the Coverage Guidance and the Prioritized List Guideline Note with the inclusion of the additional serum test(s), however, staff does not recommend reopening the Coverage Guidance at this time.

HEALTH EVIDENCE REVIEW COMMISSION (HERC)

COVERAGE GUIDANCE: NONINVASIVE TESTING FOR LIVER FIBROSIS IN PATIENTS WITH CHRONIC HEPATITIS C

Approved 10/6/2016

HERC Coverage Guidance

If a fibrosis score of ≥F2 is the threshold for antiviral treatment of hepatitis C, the following are recommended for coverage *(weak recommendation)*:

Imaging tests:

- Transient elastography (FibroScan®)
- Acoustic radiation force impulse imaging (ARFI) (Virtual Touch™ tissue quantification, ElastPQ)
- Shear wave elastography (SWE) (Aixplorer®)

Blood tests (only if imaging tests are unavailable):

- Enhanced Liver Fibrosis (ELF™)
- Fibrometer™
- FIBROSpect® II

If a fibrosis score of ≥F3 is the threshold for antiviral treatment of hepatitis C, one or more of the following are recommended for coverage *(strong recommendation*):f

Imaging tests:

- Transient elastography (FibroScan®)
- Acoustic radiation force impulse imaging (ARFI)
- Shear wave elastography (SWE)

Magnetic resonance elastography is recommended for coverage for ≥F2 or ≥F3 only when at least one imaging test (FibroScan, ARFI, and SWE) has resulted in indeterminant results, a second one is similarly indeterminant, contraindicated or unavailable, and MRE is readily available *(weak recommendation).*

Noninvasive tests should be performed no more often than once per year *(weak recommendation).*

The following tests are not recommended for coverage for the detection of liver fibrosis to guide treatment decisions with antivirals in chronic hepatitis C *(strong recommendation):*

Imaging tests

- Real time tissue elastography

Blood tests (proprietary):

- Hepascore® (FibroScore®)
- FibroSure® (FibroTest®)

Blood tests (non-proprietary):

- Age-platelet index
- AST-platelet ratio index (APRI)
- AST-ALT ratio
- Cirrhosis discriminant score (Bonacini index)
- FIB-4
- Fibro-α score
- FibroIndex
- Fibronectin discriminant score
- FibroQ
- Fibrosis–cirrhosis index
- Fibrosis index
- Fibrosis probability index (Sud index)
- Fibrosis–protein index
- Fibrosis Routine Test
- Forns index
- Globulin–albumin ratio
- Göteborg University Cirrhosis Index (GUCI)
- HALT-C model (Hepatitis C Antiviral Long-Term Treatment Against Cirrhosis)
- King's score
- Lok index
- MP3 score
- Pohl index
- Sabadell NIHCED index (Non-Invasive Hepatitis-C–Related Cirrhosis Early Detection)
- Significant fibrosis index
- Zeng index

Note: Definitions for strength of recommendation are provided in Appendix A *GRADE Informed Framework Element Description*.

RATIONALE FOR DEVELOPMENT OF COVERAGE GUIDANCES AND MULTISECTOR INTERVENTION REPORTS

Coverage guidances are developed to inform coverage recommendations for public and private health plans in Oregon as they seek to improve patient experience of care, population health and the cost-effectiveness of health care. In the era of the Affordable Care Act and health system transformation, reaching these goals may require a focus on population-based health interventions from a variety of sectors as well as individually-focused clinical care. Multisector intervention reports will be developed to address these population-based health interventions or other types of interventions that happen outside of the typical clinical setting.

HERC selects topics for its reports to guide public and private payers based on the following principles:

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

Our reports are based on a review of the relevant research applicable to the intervention(s) in question. For coverage guidances, which focus on clinical interventions and modes of care, evidence is evaluated using an adaptation of the GRADE methodology. For more information on coverage guidance methodology, see Appendix A.

Multisector interventions can be effective ways to prevent, treat or manage disease at a population level. For some conditions, the HERC has reviewed evidence and identified effective interventions, but has not made coverage recommendations, as many of these policies are implemented in settings beyond traditional healthcare delivery systems.

GRADE-INFORMED FRAMEWORK

The HERC develops recommendations by using the concepts of the Grading of Recommendations Assessment, Development and Evaluation (GRADE) system. GRADE is a transparent and structured process for developing and presenting evidence and for carrying out the steps involved in developing recommendations. There are several elements that determine the strength of a recommendation, as listed in the table below. The HERC reviews the evidence and makes an assessment of each element, which in turn is used to develop the recommendations presented in the coverage guidance box. Estimates of effect are derived from the evidence presented in this document. The level of confidence in the estimate is determined by the Commission based on assessment of two independent reviewers from the Center for Evidence-based Policy. Unless otherwise noted, estimated resource allocation, values and preferences, and other considerations are assessments of the Commission.

Coverage question: Should noninvasive testing for liver fibrosis for chronic hepatitis C be recommended for coverage?				
Outcomes	**Estimate of Effect for Outcome/ *Confidence in Estimate***	**Resource allocation**	**Values and Preferences**	**Other considerations**
Hepatitis-related morbidity/ progression *(Critical outcome)*	Diagnostic strategies have not been directly compared to assess the effect on hepatitis-related morbidity or progression.	Non-invasive imaging tests are generally less costly than liver biopsy, but more costly than serum tests. Given that both serum and noninvasive tests are less invasive that biopsy, it is likely that more patients will be referred for, and receive treatment with noninvasive testing. Some	Most patients would strongly prefer to have a noninvasive test over a liver biopsy in order to avoid the procedural risks associated with the biopsy. Policy makers will need to balance the value of this greater access to less	Guidelines are mixed in their recommendations about the use of serum biomarker testing as an adjunct or alternative to imaging. Many of the serum biomarkers are commonly obtained and inexpensive.
Need for liver biopsy *(Critical outcome)*	No studies directly addressed whether the use of noninvasive tests reduce the need for liver biopsy. However, in clinical practice, these tests are used to replace liver biopsy. Therefore, their diagnostic operating characteristics, in comparison to liver biopsy, are reported here as AUROC for ≥F2, and tests with adequate diagnostic performance may be indirectly assumed to reduce the use of liver biopsy: Magnetic Resonance Elastography AUROC 0.88 (95%CI 0.84 to 0.91)			

Coverage question: Should noninvasive testing for liver fibrosis for chronic hepatitis C be recommended for coverage?				
Outcomes	**Estimate of Effect for Outcome/ *Confidence in Estimate***	**Resource allocation**	**Values and Preferences**	**Other considerations**
	●●●○ *(Moderate confidence)* Transient Elastography AUROC 0.89 (95% CI 0.86 to 0.91) ●●●○ *(Moderate confidence)* Acoustic Radiation Force Impulse Imaging AUROC 0.88 (95% CI 0.81 to 0.96) ●●○○ *(Low confidence)* Shear Wave Elastography AUROC 0.88 (95% CI 0.85 to 0.91) ●●○○ *(Low confidence)* Real-time Tissue Elastography AUROC 0.69 (95% CI NR) ●○○○ *(Very low confidence)* Platelet count Median AUROC 0.71 (range 0.38 to 0.94) ●○○○ *(Very low confidence)* Platelet count Median AUROC 0.71 (range 0.38 to 0.94) ●○○○ *(Very low confidence)*	patients who have noninvasive tests may also still require additional testing if findings are inconclusive. In cases where treatment decisions are based on the results of these tests, false positives may lead to high treatment costs; false negatives may lead to undertreatment or delayed treatment. MRE is much more expensive than the other imaging tests.	sensitive/specific tests with the potential undertreatment or overtreatment that could occur as a result of the inferior accuracy of these tests compared to liver biopsy.	Many institutions may only have one type of imaging modality available. It could be equally appropriate to do a second imaging test versus going straight to liver biopsy depending on the institution and availability of nearby alternatives.

Coverage question: Should noninvasive testing for liver fibrosis for chronic hepatitis C be recommended for coverage?				
Outcomes	**Estimate of Effect for Outcome/ *Confidence in Estimate***	**Resource allocation**	**Values and Preferences**	**Other considerations**
	Hyaluronic acid Median AUROC 0.75 (range 0.65 to 0.88) ●○○○ *(Very low confidence)* Age-platelet index Median AUROC 0.74 (range 0.64 to 0.79) ●●○○ *(Low confidence)* APRI Median AUROC 0.77 (range 0.58 to 0.95) ●○○○ *(Very low confidence)* AST-ALT ratio Median AUROC 0.59 (range 0.50 to 0.82) ●○○○ *(Very low confidence)* Bonacini index Median AUROC 0.66 (range 0.58 to 0.71) ●●○○ *(Low confidence)* ELF™ Median AUROC 0.81 (range 0.72 to 0.87) ●○○○ *(Very low confidence)*			

Coverage question: Should noninvasive testing for liver fibrosis for chronic hepatitis C be recommended for coverage?				
Outcomes	**Estimate of Effect for Outcome/ *Confidence in Estimate***	**Resource allocation**	**Values and Preferences**	**Other considerations**
	FIB-4 Median AUROC 0.74 (range 0.61 to 0.81) ●○○○ *(Very low confidence)* FibroIndex Median AUROC 0.76 (0.58 to 0.86) ●○○○ *(Very low confidence)* FibroMeter™ Median AUROC 0.82 (range 0.78 to 0.85) ●○○○ *(Very low confidence)* FIBROSpect® II Median AUROC 0.86 (range 0.77 to 0.95) ●○○○ *(Very low confidence)* FibroTest® Median AUROC 0.79 (range 0.70 to 0.89) ●○○○ *(Very low confidence)* Forns index Median AUROC 0.76 (0.60 to 0.86) ●○○○ *(Very low confidence)*			

Coverage question: Should noninvasive testing for liver fibrosis for chronic hepatitis C be recommended for coverage?				
Outcomes	**Estimate of Effect for Outcome/ *Confidence in Estimate***	**Resource allocation**	**Values and Preferences**	**Other considerations**
	Hepascore® Median AUROC 0.79 (range 0.69 to 0.82) ●○○○ *(Very low confidence)* Pohl index Median AUROC 0.52 (range 0.52 to 0.53) ●●○○ *(Low confidence)*			
Quality of life *(Critical outcome)*	No data identified			
Testing-related adverse events *(Important outcome)*	No data identified			
Change in treatment plan *(Important outcome)*	No data identified			
Balance of benefits and harms: Given the good (F2) and excellent (F3) performance of the recommended imaging tests and the potential harms of liver biopsy, the balance is strongly in favor of offering these tests as an option for patients for whom hepatitis C direct-acting antiviral therapy is being considered. Because these tests sometimes return inconclusive results, additional testing including liver biopsy may still be required for some patients. Though they are inferior to the recommended imaging tests, blood tests also have a good performance at the F2 threshold and have a favorable balance when imaging tests are unavailable and biopsy is not required.				

Rationale: The diagnostic operating characteristic of the recommended imaging tests are good to excellent (defined as an AUROC ≥0.8). Patient-oriented health outcomes are not available. However, given the characteristics of the tests, the strong values and preferences for noninvasive tests when results are comparable, and the improved individual-level resource allocation, these tests are recommended for coverage. The strong recommendation for imaging tests when the cutoff is F3 is due to the excellent performance at this level of cutoff (defined as an AUROC ≥0.9) and the other factors in favor of their use. The weak recommendation at the F2 cutoff is based on "good" but not "excellent" performance, and the high societal cost of treating patients at levels of fibrosis who are not at short-term risk.

The diagnostic operating characteristics of the blood tests are variable. Though tests recommended at the F2 threshold can accurately assess the fibrosis stage F2 or higher, they are inferior to the imaging tests at this level, and expert input suggests less clinically reliable, and so are recommended only when imaging tests are unavailable. No existing blood test can accurately distinguish between F2 and F3. Therefore, blood tests cannot be recommended (alone or in combination with noninvasive imaging tests) when the treatment planning revolves around an accurate diagnosis of F3. Many of the non-recommended blood tests have fair to poor operating characteristics regardless of the treatment threshold.

MRE is much more expensive than the other imaging tests and thus is only recommended when available after two other imaging tests fail to return useful results.

Recommendation:

If a fibrosis score of ≥F2 is the threshold for antiviral treatment of hepatitis C, the following are recommended for coverage *(weak recommendation)*:

Imaging tests:

- Transient elastography (FibroScan®)
- Acoustic radiation force impulse imaging (ARFI) (Virtual Touch™ tissue quantification, ElastPQ)
- Shear wave elastography (SWE) (Aixplorer®)

Blood tests (only if imaging tests are unavailable):

- Enhanced Liver Fibrosis (ELF™)
- Fibrometer™

- FIBROSpect® II

If a fibrosis score of ≥F3 is the threshold for antiviral treatment of hepatitis C, one or more of the following are recommended for coverage *(strong recommendation*):

Imaging tests:

- Transient elastography (FibroScan®)
- Acoustic radiation force impulse imaging (ARFI)
- Shear wave elastography (SWE)

Magnetic resonance elastography is recommended for coverage for ≥F2 or ≥F3 only when at least one imaging test (FibroScan, ARFI, and SWE) has resulted in indeterminant results, a second one is similarly indeterminant, contraindicated or unavailable, and MRE is readily available *(weak recommendation).*

Noninvasive tests should be performed no more often than once per year *(weak recommendation).*

Other imaging and blood tests are not recommended for coverage *(strong recommendation).*

*The Quality of Evidence rating was assigned using information from the editing sources and judgments made by CEbP staff based on direction from the subcommittee.

Note: GRADE framework elements are described in Appendix A. A GRADE Evidence Profile is provided in Appendix B.

EVIDENCE OVERVIEW

Clinical background

Hepatitis C virus (HCV) is a major cause of liver disease in the United States, and chronic hepatitis C infection is the leading indication for liver transplantation (Centers for Disease Control and Prevention [CDC], 2016). The CDC estimates that 3.5 million people in the United States are currently infected with HCV, though the precise number is not known. One study cited by the CDC estimated that around 15,000 deaths were attributable to HCV in 2007. Well established modes of transmission for HCV infection include injection drug use and receipt of blood products prior to 1992. According to the CDC, the prevalence of HCV infection among injection drug users ranges from about 30% for younger users (aged 18 to 30) to 70-90% for older injection drug users.

The natural history of HCV infection is variable, and 15-25% of people will clear the infection and not develop chronic hepatitis C. Between 5% and 20% of those with HCV infection will develop cirrhosis, generally over the course of 20 to 30 years, and between 1% and 5% will die from HCV-related liver disease (CDC, 2016). There are no highly accurate tools to predict which individuals with chronic hepatitis C will go on to develop cirrhosis.

The United States Preventive Services Task Force recommends birth-cohort screening for hepatitis C for anyone born between 1945 and 1965. HCV testing is also recommended for those in high risk groups included people with a history of injection drug use, those who received blood products before 1992, those with HIV infection, and those born to HCV-positive mothers (CDC, 2016).

Before 2013, treatment for chronic hepatitis C relied on interferon and ribavirin, sometimes with the addition of a protease inhibitor in the case of genotype 1 infections. These treatments were long (24 to 48 weeks), entailed a high burden of adverse effects, and response rates were highly variable. The advent of direct-acting antiviral treatments (i.e. sofosbuvir, simeprevir, and others) appears to have improved the success rates (as measured by the surrogate marker of sustained virologic response at 12 weeks) and acceptability of treatment, though at considerable cost.

Traditionally, staging of chronic hepatitis C infection was done by examining histologic specimens from liver biopsies of the liver for evidence of fibrosis. The METAVIR fibrosis stage is the most commonly used measure for assessing the histologic degree of hepatic fibrosis:

- F0 = No fibrosis
- F1 = Portal fibrosis without septa
- F2 = Portal fibrosis with few septa
- F3 = Portal fibrosis with numerous septa without cirrhosis
- F4 = Cirrhosis

Progression from fibrosis to cirrhosis is associated with complications of end-stage liver disease including portal hypertension, portosystemic encephalopathy, and hepatocellular carcinoma.

Noninvasive tests of liver fibrosis and cirrhosis have developed as an alternative to biopsy for staging chronic hepatitis C infection.

Indications

In patients with chronic hepatitis C infection, the likelihood of progression is closely correlated with the presence and severity of liver fibrosis (Chou et al., 2013). Thus, tests to diagnose the presence and ascertain the degree of fibrosis are indicated in the staging of patients with chronic hepatitis C, particularly when that information is relevant to decisions about HCV treatment. For instance, accurate determination of fibrosis stage is essential when treatment eligibility decisions are made on the basis of fibrosis severity. Beyond decisions about HCV treatment, tests to determine the presence of cirrhosis may be indicated in order to ensure appropriate supportive care and screening for complications of cirrhosis for these patients.

Until recently, the only options for staging fibrosis in hepatitis C patients was histological examination of the liver by percutaneous, transjugular, transfemoral, or laparoscopic surgical biopsy. However, biopsy entails procedural risks (including bleeding, infection, and pain), and the results are prone to sampling and interpretation errors. Despite these drawbacks, liver biopsy remains the "gold standard" for the diagnosis of fibrosis and cirrhosis (Chou et al., 2013).

The accuracy of noninvasive tests of liver fibrosis are measured against the reference standard of the results from a liver biopsy, using these definitions:

- **Sensitivity** refers to the proportion of patients who actually have the condition in question who have a positive test result.
- **Specificity** refers to the proportion of patients who really do not have the condition in question who have a negative test result.
- **Positive likelihood ratio** is the ratio of the probability of a positive test result in a patient with the condition to the probability of a positive test result in a patient without the condition. Likelihood ratios are most useful when the pre-test probability of the condition is known and the post-test probability at which treatment would be recommended is well established.
- **Negative likelihood ratio** is the ratio of the probability of a negative test in a patient with the condition to the probability of a negative test in a patient without the condition.
- The receiver operating curve **(ROC)** is a graphical illustration of the trade-off between sensitivity and specificity for an index diagnostic test (specifically for a test that has continuous rather than binary, or yes/no results) compared to a reference standard. The "index" test refers to the test that we are looking at to see how good it is. The reference standard has sometimes been referred to as the "gold standard," but given that some reference standards are not themselves perfectly accurate the terminology has shifted to "reference standard."

- The area under the receiver operating curve **(AUROC)** is an overall measure of how well the index test compares to the reference standard across a range of possible cutoffs. An index test that has cutoff value that allows perfect sensitivity and specificity (i.e. perfect classification of those with and without the condition) would have an AUROC of 1.0, while an AUROC of 0.5 represents a useless test (no better than a coin flip, on average). A test with an AUROC of 0.80-0.89 is generally regarded as a good test, while tests with an AUROC >0.90 are regarded as excellent tests. These distinctions are conventional, but arbitrary.

Technology description

Noninvasive techniques for staging liver fibrosis include imaging and blood tests. Five types of imaging tests are available: transient elastography (TE), acoustic radiation force impulse imaging (ARFI), shear wave elastography (SWE), magnetic resonance elastography (MRE), and real-time tissue elastography (RTE).

Transient Elastography (FibroScan®) measures the velocity of a low-frequency (50 Hz) elastic shear wave propagating through the liver. The velocity of the wave indicates the tissue stiffness, with the stiffer the tissue, the faster the shear wave propagates. The patient lies supine during the procedure, which takes less than five minutes.

Acoustic radiation force impulse imaging (Virtual Touch™ tissue quantification, ElastPQ) measures the speed of short-duration acoustic pulses that propagate shear waves and generate localized displacements in liver tissue. Commercial ultrasound machines can be easily modified to implement ARFI.

Shear wave elastography (Aixplorer® Supersonic Imagine) creates ultrasonic beams that are focused on liver tissues, and a very high frame rate ultrasound imaging sequences monitors the transient propagation of the shear waves in real time. This procedure can be implemented on commercial ultrasound machines.

Magnetic resonance elastography images the propagation characteristics of a shear wave in the liver using a modified phase-contrast method. Almost the entire liver can be analyzed with MRE, and it can be used effectively in patients with obesity or ascites. This procedure is more costly and more time consuming than the other imaging techniques.

Real-time tissue elastography constructs elasticity images of the liver by measuring the tissue strain induced by compression from a high-frequency ultrasound scanner. Tissue compression produces strain in the tissue, where the strain is smaller in harder tissue than in softer tissue.

Five proprietary blood testing protocols are available in the U.S., which use a combination of biochemical markers and patented algorithms to determine fibrosis stage. There are 25 additional blood tests that are not proprietary. The components of these blood tests are shown in Table 1 below. The most common components of the blood tests are platelet count, aspartate aminotransferase (AST), and alanine aminotransferase (ALT). About half of the tests include patient's age in the algorithm.

Table 1: Blood Tests for Measuring Liver Fibrosis in Patients with Hepatitis C

Blood tests	Components of test/algorithm
Proprietary tests	
ELF™ Test (Enhanced Liver Fibrosis)	Hyaluronic acid, tissue inhibitor of metalloproteinase 1, and procollagen III amino terminal peptide
FibroMeter™	Alanine aminotransferase (ALT), α_2-macroglobulin, gamma-glutamyl transpeptidase (GGT), aspartate aminotransferase (AST), platelet count, prothrombin index, urea, and patient's age and gender
FIBROSpect® II	Hyaluronic acid, tissue inhibitor of metalloproteinase, and α_2-macroglobulin
FibroSure® (FibroTest®)	α2-macroglobulin, haptoglobin, apolipoprotein A1, total bilirubin and gamma-glutamyl transpeptidase (GGT), and patient's age and gender ActiTest® is similar, with the addition of alanine aminotransferase (ALT)
Hepascore® (FibroScore®)	α_2-macroglobulin, hyaluronic acid, gamma-glutamyl transferase (GGT), bilirubin, and patient's age and gender
Non-proprietary tests	
Age–platelet index	Platelet count and patient's age
AST–platelet ratio index (APRI)	Platelet count and aspartate aminotransferase (AST)
AST–ALT ratio	Aspartate aminotransferase (AST) and alanine aminotransferase (ALT)
Cirrhosis discriminant score (Bonacini index)	Platelet count, aspartate aminotransferase (AST), alanine aminotransferase (ALT), prothrombin index, presence of ascites, and presence of spider angiomata
FIB-4	Platelet count, aspartate aminotransferase (AST), alanine aminotransferase (ALT), and patient's age
Fibro-α score	Platelet count, aspartate aminotransferase (AST), alanine aminotransferase (ALT), and α-Fetoprotein
FibroIndex	Platelet count, aspartate aminotransferase (AST), and gamma globulin
Fibronectin discriminant score	Platelet count, aspartate aminotransferase (AST), albumin, and fibronectin
FibroQ	Platelet count, aspartate aminotransferase (AST), alanine aminotransferase (ALT), prothrombin index, and patient's age
Fibrosis–cirrhosis index	Platelet count, Alkaline phosphatase, bilirubin, and albumin

Blood tests	Components of test/algorithm
Fibrosis index	Platelet count and albumin
Fibrosis probability index (Sud index)	Aspartate aminotransferase (AST), total cholesterol, insulin resistance, alcohol intake, and patient's age
Fibrosis–protein index	α_2-macroglobulin and hemopexin
Fibrosis Routine Test	Platelet count, aspartate aminotransferase (AST), α-Fetoprotein, albumin, and patient's age
Forns index	Platelet count, gamma-glutamyl transpeptidase (GGT), cholesterol, and patient's age
Globulin–albumin ratio	Globulin and albumin
Göteborg University Cirrhosis Index (GUCI)	Platelet count, aspartate aminotransferase (AST), and prothrombin index
HALT-C model (Hepatitis C Antiviral Long-Term Treatment Against Cirrhosis)	Platelet count, tissue metalloproteinase inhibitor 1 (TIMP-1), and hyaluronic acid
King's score	Platelet count, aspartate aminotransferase (AST), international normalized ratio (INR), and patient's age
Lok index	Platelet count, aspartate aminotransferase (AST), alanine aminotransferase (ALT), and international normalized ratio (INR)
MP3 score	Matrix metalloproteinase-1 (MMP-1) and procollagen III propeptide
Pohl index	Platelet count, aspartate aminotransferase (AST), and alanine aminotransferase (ALT)
Sabadell NIHCED index (Noninvasive Hepatitis-C–Related Cirrhosis Early Detection)	Platelet count, aspartate aminotransferase (AST), alanine aminotransferase (ALT), prothrombin time, right hepatic lobe atrophy, splenomegaly, caudate lobe hypertrophy, and patient's age
Significant fibrosis index	Haptoglobin, α_2-macroglobulin, tissue metalloproteinase inhibitor 1 (TIMP-1), matrix metalloproteinase-2 (MMP-2), and gamma-glutamyl transpeptidase (GGT)
Zeng index	α_2-macroglobulin, gamma-glutamyl transpeptidase (GGT), hyaluronic acid, and patient's age

Adapted from Chou & Wasson (2013)

Key Questions and Outcomes

The following key questions (KQ) guided the evidence search and review described below. For additional details about the review scope and methods please see Appendix C.

1. What is the comparative effectiveness of noninvasive tests for the diagnosis and management of hepatic fibrosis in patients with chronic hepatitis C?
2. Does the comparative effectiveness of noninvasive tests of liver fibrosis in patients with chronic hepatitis C vary based on:
    a. Duration of infection
    b. Fibrosis score
    c. Body habitus
    d. Operator/interpreter training or experience
    e. Co-existence of other etiologies of liver disease (e.g., non-alcoholic steatohepatitis)
3. What are the comparative diagnostic operating characteristics of tests of liver fibrosis?
4. What is the evidence for the timing of the initial testing for fibrosis and intervals for subsequent reassessment of fibrosis?

Critical outcomes selected for inclusion in the GRADE table were hepatitis-related morbidity/progression, need for liver biopsy, and quality of life. Important outcomes selected for inclusion in the GRADE table were testing-related adverse events and change in treatment plan (especially a decision to begin antiviral therapy).

Evidence Review

We identified no randomized controlled evidence on the use of noninvasive tests of liver fibrosis compared to liver biopsy with respect to clinical outcomes in hepatitis C infection.

We identified a poor quality systematic review and meta-analysis of six studies reporting on the relative prognostic value of liver biopsy, FibroTest®, FIB-4, and APRI for predicting overall survival. All of the tests offered statistically significant prognostic value for overall survival with AUROCs of 0.58 for APRI (95% CI 0.53 to 0.63), 0.68 for FIB-4 (95% CI 0.58 to 0.78), 0.77 for biopsy (95% CI 0.62 to 0.93), and 0.80 for FibroTest® (95% CI 0.76 to 0.95). The authors did not describe the methodologic rigor of the included studies. There was significant heterogeneity in the included studies (for example, in one study of APRI and FIB-4 in HCV patients, 68% of the patients had HIV co-infection). Lastly, the review was authored by the inventor of the FibroTest® and two employees of the company that market the test.

A more recent study (Vergniol et al., 2014) examined the prognostic value of evolving measurements of liver stiffness. In this study, about 1,025 people with chronic hepatitis C and two recorded measurements of liver stiffness (separated by >1,000 but <1,500 days) recorded between 2004 and 2008 were included. The average age of included patients was 52 years, half were men, the average BMI was 25 kg/m^2, and about 12% reported excessive alcohol consumption. During the mean follow-up period of three years (after the second measurement of liver stiffness), 16% of patients achieved sustained

virologic response from HCV treatment. Survival data was available for 95% of patients; of those, 35 patients had died and 7 had undergone liver transplantation. Twenty-one of the deaths were from liver-related causes. In the univariate analysis, several factors were associated with statistically significantly increased hazard ratios for death: age (HR 1.03, 95% CI 1.01 to 1.06), male sex (HR 2.25, 95% CI 1.17 to 4.43), baseline liver stiffness measurement (HR 4.27, 95% CI 2.94 to 6.22), follow-up liver stiffness measurement (HR 5.47, 95% CI 3.82 to 7.84), and change in liver stiffness measurement (HR 1.25, 95% CI 1.16 to 1.36). Unusually, alcohol abuse appeared to have a protective effect in this study (HR 0.42, 95% CI 0.18 to 0.97). In the multivariate analysis, baseline liver stiffness measurement (HR 5.76, 95% CI 3.74 to 8.87), change in liver stiffness measurement (HR 1.19, 95% CI 1.11 to 1.28), and achievement of SVR (HR 0.19, 95% CI 0.05 to 0.80) were statistically significant independent predictors of death. Overall, the authors concluded that patients with low-baseline liver stiffness measurements, those who achieve SVR, and those with non-cirrhotic baseline liver stiffness measurements and stable or decreasing measurements at follow-up all have an excellent prognosis. Conversely, patients with cirrhotic baseline liver stiffness measurement or those with advancing significant fibrosis have a poorer prognosis.

Cross-sectional data has correlated liver stiffness measurements by TE with the presence of portal hypertension (Kim et al., 2013), but TE has not been demonstrated in prospective studies to predict clinical outcomes related to portal hypertension in hepatitis C patients. A prospective cohort study of nearly 900 Japanese patients with HCV investigated the correlation between liver stiffness measurements by TE and the development of hepatocellular carcinoma (HCC) over a mean follow-up of 3 years (Masuzaki et al., 2009). Compared to a reference value of less than 10 kilopascals (kPa), various cut-offs of liver stiffness were associated with relative risk of HCC ranging from 16 to 45.

The remainder of the identified systematic reviews summarized diagnostic accuracy studies of various tests compared to a reference standard of liver biopsy. Most of these studies report diagnostic performance by way of sensitivity, specificity, and AUROC. A test that perfectly matches the diagnoses assigned by the reference test would have an AUROC of 1. Conventionally, tests with an AUROC of 0.9 to 1 are considered excellent, 0.8-0.89 are good, 0.7-0.79 are fair, and below 0.7 are poor, and though widely used, these distinctions are arbitrary.

Magnetic Resonance Elastography

Singh et al., 2015

This is a good quality systematic review and meta-analysis of patient-level data to determine the diagnostic performance of magnetic resonance elastography (MRE) compared to liver biopsy as the reference standard. The use of patient-level data in the meta-analysis allowed them to perform stratified analyses to determine if the diagnostic performance of MRE varied based on sex, obesity, or the etiology of the liver disease, and also allowed the authors to reduce the risk of spectrum bias and standardize diagnostic cut-offs for various fibrosis stages. The authors included 12 studies that met inclusion criteria and for which they were able to obtain the individual participant data (n=697). Overall, the included studies were judged to be at low to moderate risk of bias. Three of the studies did not adequately report on blinding procedures, raising the possibility of review bias.

Among the included patients, the average age was 55 years old, the majority were males (60%), and the average BMI was 27. Nearly half of the participants had HCV-related liver disease (47%), with smaller numbers of patients with HBV, NAFLD, ALD, AIH, or other miscellaneous etiologies. The distribution of fibrosis level on biopsy was 19.5% F0, 19.4% F1, 15.5% F2, 15.9% F3, and 29.7% F4.

The diagnostic operating characteristics of MRE from the meta-analysis, including both positive and negative likelihood ratios, are reported in Table 2 below.

Table 2: Diagnostic Operating Characteristics of MRE

Fibrosis Stage	AUROC (95% CI)	Sensitivity	Specificity	Positive LR	Negative LR
Any: ≥F1	0.84 (0.76 - 0.92)	0.73	0.79	3.48	0.34
Significant: ≥F2	0.88 (0.84 - 0.91)	0.79	0.81	4.16	0.26
Advanced: ≥F3	0.93 (0.90 - 0.95)	0.85	0.85	5.67	0.18
Cirrhosis: F4	0.92 (0.90 - 0.94)	0.91	0.81	4.79	0.11

In the subgroup and sensitivity analysis, the diagnostic performance of MRE did not significantly vary based on sex, presence of obesity, or etiology of liver disease. In this review, MRE had a failure rate of about 4%, and this was most commonly due to interference from hepatic iron overload.

Overall, the authors concluded that MRE was highly accurate for diagnosing fibrosis and cirrhosis regardless of BMI or the etiology of chronic liver disease.

Transient Elastography

Steadman et al., 2013

This is a good-quality, comprehensive technology assessment of transient elastography (TE) for the diagnosis of significant fibrosis in adults with chronic liver disease. Overall, 57 studies reporting diagnostic performance of TE compared with liver biopsy were included. The results were stratified by the etiology of liver disease, and 13 of the included studies were in patients with HCV. The included studies were methodologically rigorous with the authors rating nearly 80% of them as high quality.

The diagnostic operating characteristics of TE (in HCV patients only) from the meta-analysis are reported in Table 3 below.

Table 3: Diagnostic Operating Characteristics of Transient Elastography

Fibrosis Stage	AUROC (95% CI)	Sensitivity	Specificity	Positive LR	Negative LR
Significant: ≥F2	0.89 (0.86 - 0.91)	0.76	0.86	5.43	0.28
Advanced: ≥F3	0.92 (0.89 - 0.94)	0.88	0.91	9.7	0.13
Cirrhosis: F4	0.94 (0.92 - 0.96)	0.85	0.91	9.4	0.16

The authors also performed a basic economic analysis to calculate the incremental cost per correct diagnosis gained by liver biopsy over TE. In the subgroup of patients with HCV, the incremental cost per correct diagnosis using biopsy ranged from $1,861 for patients with F2 disease to $3,260 for patients with F3 disease. The authors were careful to note that their economic modeling does not account for the practice of monitoring progression of liver fibrosis and observe that the common practice in Alberta, Canada is yearly TE and biopsy every 3-5 years.

Overall, the authors concluded that TE was an accurate method for diagnosing fibrosis or cirrhosis and was less costly than liver biopsy.

Acoustic Radiation Force Impulse Imaging

Nierhoff et al., 2013

This is a good-quality systematic review and meta-analysis of the diagnostic operating characteristics of ARFI in patients with chronic liver disease using liver biopsy as the reference standard. The authors included 36 studies (both published manuscripts and abstracts) of nearly 4,000 patients. Among the included studies, 7 examined only patients with HCV as the etiology of their liver disease while another 18 studies reported on populations with mixed etiologies of chronic liver disease, including HCV. The methodologic quality of the included studies was mixed, and about half of the studies had potential flaws related to spectrum bias (bias introduced because the range and distribution of disease severity in the study is not representative of the overall population of people with the condition) and review bias (bias introduce when the interpreter of the index test is already aware of the result of the reference test, or vice-versa). The main reported measure of diagnostic performance was AUROC. The results of the meta-analysis of the HCV only and mixed etiology studies are reported in Table 4 below.

Table 4: AUROC of Acoustic Radiation Force Impulse (ARFI) Imaging Tests

Fibrosis Stage	AUROC – HCV only studies (95% CI)	AUROC – Mixed studies (95% CI)
Significant: ≥F2	0.88 (0.81 - 0.96)	0.83 (0.80 - 0.86)
Advanced: ≥F3	0.93 (0.89 - 0.97)	0.87 (0.85 - 0.90)
Cirrhosis: F4	0.92 (0.85 - 0.99)	0.91 (0.89 - 0.93)

One possible explanation for the poorer diagnostic performance in the mixed studies is the finding in subgroup analysis that higher BMI is associated with reduced diagnostic accuracy and a higher failure rate for testing.

Overall, the authors concluded that the diagnostic performance of ARFI is good to excellent for detecting fibrosis and cirrhosis. The authors also note that their findings are consistent with those of an earlier, smaller meta-analysis of ARFI using individual participant data.

Acoustic Radiation Force Impulse (ARFI) vs. Transient Elastography (TE)

Bota et al., 2013

This is a good-quality systematic review and meta-analysis of studies comparing ARFI and TE to a reference standard of liver biopsy for the evaluation of fibrosis. The authors included 13 trials; 10 of the trials reported diagnostic accuracy of ARFI and TE for the diagnosis of significant fibrosis (≥F2), and all the trials reported diagnostic accuracy for cirrhosis (F4). The etiology of liver disease in each study was variable, and all but one study included patients with chronic hepatitis C. The authors observed that failure rates (i.e. inability to obtain any valid measurements) were higher for TE (6.6%) than ARFI (2.1%), and five of the trials only included patients with valid ARFI and TE. The authors' risk of bias assessment for most studies was low. The results of the meta-analysis are reported in Table 5 below.

Table 5: Diagnostic Operating Characteristics of ARFI and TE

Test and Fibrosis Stage	AUROC (95% CI)	Sensitivity	Specificity	Positive LR	Negative LR
ARFI: ≥F2	0.85 (0.82 - 0.88)	0.74	0.83	4.29	0.31
TE: ≥F2	0.87 (0.83 - 0.89)	0.78	0.84	4.79	0.26
ARFI: F4	0.93 (0.91 - 0.95)	0.87	0.87	6.48	0.15
TE: F4	0.93 (0.91 - 0.95)	0.89	0.87	6.79	0.13

Overall, the authors concluded that there were no significant differences in the diagnostic accuracy of ARFI and TE. They note that while the higher failure rate for TE is concerning, new and more sensitive probes may mitigate this limitation.

Blood Tests

Dozens of blood tests and related interpretive indices or scores have been proposed for the diagnosis of fibrosis or cirrhosis in patients with HCV. The components of these tests are discussed in detail in the technology description section of this report.

Chou & Wasson, 2013

This is a good-quality systematic review of blood tests for the diagnosis of fibrosis and cirrhosis in patients with HCV. The authors did not perform a meta-analysis but present results for measures of diagnostic accuracy as medians and ranges. The number of studies for each test and the authors' GRADE assessment of the strength of evidence are provided in Table 6 below.

The results of the review of these tests are also summarized in Table 6. Because of the large number of tests as well as the various cut-offs used for each test, only the AUROC (median and range) are presented in this table.

Table 6: Studies of Blood Tests for Liver Fibrosis

Test	Number of studies	Strength of evidence	Fibrosis (≥F2) AUROC median (range)	Cirrhosis AUROC median (range)
Platelet count	18	Moderate	0.71 (0.38 - 0.94)	0.89 (0.64 - 0.99)
Hyaluronic acid	8	Moderate	0.75 (0.65 - 0.88)	0.90 (0.80 - 0.97)
Age-platelet index	11	Moderate	0.74 (0.64 - 0.79)	0.86 (0.64 - 0.91)
AST-platelet ratio index	7	High	0.77 (0.58 - 0.95)	0.84 (0.54 - 0.97)
AST-ALT ratio	32	High	0.59 (0.50- 0.82)	0.72 (0.52 - 0.91)
Bonacini index	12	Moderate	0.66 (0.58 - 0.71)	0.74 (0.61 - 0.91)
ELF™	8	Moderate	0.81 (0.72 - 0.87)	0.88 (0.78 - 0.91)
FIB-4	19	Moderate	0.74 (0.61 - 0.81)	0.87 (0.83 - 0.92)
FibroIndex	9	Moderate	0.76 (0.58 - 0.86)	0.86 (0.78 - 0.92)
Fibrometer™	8	Moderate	0.82 (0.78 - 0.85)	0.91 (0.89 - 0.94)
FIBROSpect® II	7	Low	0.86 (0.77 - 0.90)	NR
FibroTest®	32	High	0.79 (0.70 - 0.89)	0.86 (0.71 - 0.92)
Forns index	22	High	0.76 (0.60 - 0.86)	0.87 (0.85 - 0.91)
GUCI	5	Low	NR	0.82 (0.78 - 0.86)
Hepascore®	12	High	0.79 (0.69 - 0.82)	0.89 (0.88 - 0.94)
Lok index	10	Moderate	NR	0.80 (0.61 - 0.91)
Pohl index	12	Low	0.52 (0.52 - 0.53)	0.65 (0.64 - 0.66)

The Chou & Wasson review also summarized the results of trials making direct comparisons between APRI or FibroTest® and various other blood tests. Very few of these direct comparisons showed substantial differences in the median AUROC for fibrosis, but median differences in excess of 0.05 are reported in Table 7 below. Only one of the direct comparisons (APRI vs. AST-ALT ratio) for the diagnosis of cirrhosis exceed a median difference in AUROC of greater than 0.05; in those studies APRI was more accurate than the AST-ALT ratio.

Table 7. Studies of Direct Comparisons between Two Blood Tests

Number of studies	Test A AUROC median	Test B AUROC median	Median difference (range)
13	APRI 0.76	AST-ALT ratio 0.58	0.17 (-0.06 to 0.23)
4	APRI 0.74	Bonacini index 0.66	0.08 (0.07 to 0.09)
8	APRI 0.79	Fibrometer™ 0.84	-0.06 (-0.07 to -0.02)
8	APRI 0.76	Platelet count 0.67	0.08 (-0.06 to 0.53)
3	APRI 0.69	Pohl index 0.52	0.17 (0.13 to 0.23)
3	FibroTest® 0.78	FibroIndex 0.72	0.08 (0.02 to 0.10)

The authors also include 9 studies that report on the use of combinations of blood tests or indices. Four studies reported on diagnostic performance of the Sequential Algorithm for Fibrosis Evaluation that combines results from APRI and FibroTest®. In two studies of patients with fibrosis (≥F2), the algorithm had an AUROC of 0.90 and 0.94. In 3 studies of cirrhosis, the algorithm had a median AUROC of 0.87. The remaining combinations of tests or indices were only studied in single trials.

The authors point out several limitations of the review, the most important of which is the binary interpretation of presence or absence of clinically significant fibrosis. As they note, "Measures that incorporate the accuracy of tests at each fibrosis stage would therefore be more informative than estimates based on dichotomized classifications." Additionally, because nearly all the included studies grouped patients with both lesser stages of fibrosis and cirrhosis, it was not possible to ascertain the diagnostic performance of blood tests for less severe fibrosis independent from the diagnostic accuracy of the full spectrum of significant fibrosis, and distinguishing between F2 and F3 is not possible. Overall, the authors conclude that a variety of blood tests are moderately useful for the identification of clinically significant fibrosis in patients with HCV.

Shear Wave Elastography

Li et al., 2016

This is a good-quality systematic review and meta-analysis of diagnostic accuracy studies of real-time shear wave elastography (SWE) for staging liver fibrosis. The authors identified eight studies with a total of 934 patients comparing SWE to a reference standard of liver biopsy. Most patients in the included studies had chronic viral hepatitis, but the precise breakdown was not provided. The included studies were generally at low risk of bias, though three were judged to be susceptible to disease progression

bias because of the time difference between the two tests. The diagnostic operating characteristics from the meta-analysis are reported in Table 8 below.

Table 8. Diagnostic Operating Characteristics for Shear Wave Elastography

Fibrosis Stage	AUROC (95% CI)	Sensitivity	Specificity	Positive LR	Negative LR
Significant: ≥F2	0.88 (0.85 - 0.91)	0.85	0.81	4.47	0.18
Advanced: ≥F3	0.94 (0.92 - 0.96)	0.90	0.81	4.73	0.12
Cirrhosis: F4	0.92 (0.89 - 0.94)	0.87	0.88	7.25	0.15

The authors note that the primary limitations of their review include the small number of studies and the inability to perform subgroup analysis by etiology of chronic liver disease.

The authors observe that compared with reported diagnostic accuracy of other modalities, SWE is comparable to TE and ARFI for diagnosis of cirrhosis, and comparable to ARFI but better than TE for the diagnosis of significant fibrosis (≥F2). Overall, the authors conclude that the diagnostic accuracy of SWE for fibrosis staging is good.

Real-Time Tissue Elastography

Kobayashi et al., 2014

This is a good-quality systematic review and meta-analysis of diagnostic accuracy studies of real-time tissue elastography (RT-TE) compared to a reference standard of liver biopsy. The authors identified 15 trials including over 1,600 patients. Ten of 15 studies included patients with HCV. The authors expressed concerns over the risk of bias in several included studies related to patient selection bias and the absence of pre-specified cut-off values for the index tests. They also identified possible publication bias in their funnel plots. The meta-analytic results for sensitivity and specificity are reported in Table 9 below.

Table 9. Diagnostic Operating Characteristics for Real-Time Tissue Elastography

Fibrosis Stage	AUROC (95% CI)	Sensitivity (95% CI)	Specificity (95% CI)	Positive LR (95% CI)	Negative LR (95% CI)
Significant: ≥F2	0.69 (NR)	0.79 (0.75 - 0.83)	0.76 (0.68 - 0.82)	3.29 (NR)	0.27 (NR)
Advanced: ≥F3	0.86 (NR)	0.82 (0.75 - 0.88)	0.81 0.72 - 0.88)	4.31 (NR)	0.22 (NR)
Cirrhosis: F4	0.72 (NR)	0.74 (0.63 - 0.82)	0.84 0.79 - 0.88)	4.6 (NR)	0.30 (NR)

Overall, the authors conclude that, "RTE is not highly accurate for any cut-off stage of fibrosis."

Direct Comparisons of FibroTest®, FIB-4, APRI, and TE

Houot et al., 2016

This is a poor-quality systematic review and meta-analysis of trials making direct comparisons between FibroTest®, APRI, FIB-4, and TE compared to a reference standard of liver biopsy. The authors identified 71 trials, of which 37 included only patients with HCV. The main purpose of the review was to determine whether there were differences between the AUROC of these tests for the diagnosis of advanced fibrosis (defined here as ≥F2) or cirrhosis. The review did not provide information on the methodologic quality of the included studies. The authors applied three meta-analytic methods to ascertain whether the differences in test performance were statistically significant: an indirect pooled AUROC difference, a standard pooled AUROC difference, and a Bayesian pooled AUROC difference. Among the HCV-only studies, the differences in AUROC for most comparisons were generally small (<0.05). In the indirect pooled analysis, only one comparison showed a statistically significant difference in favor of TE over APRI for diagnosis of cirrhosis. In the standard pooled analysis FibroTest® was favored over TE and APRI for diagnosis of fibrosis; TE and FIB-4 were favored over APRI for the diagnosis of cirrhosis. In the Bayesian pooled analysis, FibroTest® was favored over APRI for the diagnosis of fibrosis and TE and FIB-4 were favored over APRI for the diagnosis of cirrhosis. This review is subject to potential conflict of interest as the senior author is the inventor of FibroTest® and the study was funded in part by BioPredictive, the company that markets FibroTest®.

Factors Influencing Accuracy of TE

Perazzo et al., 2015

This is a narrative review article that summarizes research on various factors that influence the accuracy and interpretation of transient elastography. The authors identify four factors that are associated with overestimation of fibrosis by TE: heightened necroinflammatory activity as denoted by alanine transaminases greater than 10 times the upper limit of normal, extrahepatic cholestasis and hepatic

congestion, non-fasting status, and the presence of severe steatosis. The authors also note that the reliability of TE measurements is modified by operator experience and propose a definition of an experienced operator as greater than 100 examinations. Similarly, large ranges of inter-observer variability are reported in the literature and discrepancies between assessments of adjacent fibrosis stages are more common. The authors suggest that longitudinal follow-up and examination by the same experienced operator may prove most accurate.

We did not identify any evidence that addresses the question of initial timing of staging or the appropriate intervals for re-staging using non-invasive tests. The systematic review of TE did observe that the common practice in Alberta, Canada is to perform non-invasive tests to assess fibrosis stage every 3 to 5 years.

EVIDENCE SUMMARY

Although an imperfect test itself, liver biopsy remains the reference standard by which noninvasive tests of liver fibrosis and cirrhosis are judged. There is no direct comparative evidence that examines the effects of different diagnostic strategies on the predetermined clinical outcomes:

- Hepatitis-related morbidity/progression
- Need for liver biopsy
- Quality of life
- Testing-related adverse events
- Change in treatment plan

Furthermore, there is only sparse evidence on the value and reliability of prognostic information obtained from noninvasive tests. However, there are a large number of studies comparing the diagnostic accuracy of noninvasive tests of liver fibrosis to the reference standard of liver biopsy. Many of these studies (see Appendix D) demonstrated good or excellent performance of non-invasive tests for the detection of various levels of fibrosis; in general, imaging studies appear to have greater ability to distinguish between intermediate stages of fibrosis (i.e. between F2 and F3), while blood tests appear to be suitable for establishing the presence of significant fibrosis (≥F2) or cirrhosis (F4).

OTHER DECISION FACTORS

Resource Allocation

The price of noninvasive tests is generally significantly less than liver biopsy and avoids the costs associated with harms from liver biopsy. However, noninvasive testing is likely to be done at a higher frequency than liver biopsy and the increased number of total procedures may somewhat reduce the cost-savings associated with avoiding liver biopsy. The more significant cost driver is the impact noninvasive testing may have on determining the eligible population for treatment with hepatitis C. Health plans have prioritized treatment of hepatitis C patients with the newer expensive medications both because of the high cost of these medications and the prevalence of chronic hepatitis C infection in

the general population. The cutoff point for some plans in Oregon include only treating persons with a score of F3 or above. This requires testing that can accurately distinguish between the cutoff points for treatment. If a test has a high false positive rate, that would lead more people into a hepatitis C treatment pathway (increasing overall costs of the population in the near term). If a test has a high false negative rate, then people with more advanced fibrosis who may particularly benefit from treatment would not qualify for treatment (decreasing health system costs, but at the expense of fewer eligible people receiving appropriate treatment).

Values and preferences

Patients would highly value avoiding an invasive procedure as long as the information provided by a noninvasive test was comparable. There would be minimal variability in this preference. From a population perspective, it would be very important that these tests can accurately distinguish between those persons who would benefit the most from the very expensive treatment versus others who may be able to delay or avoid treatment altogether.

POLICY LANDSCAPE

Quality measures

No quality measures were identified when searching the National Quality Measures Clearinghouse.

Payer coverage policies

The Oregon Medicaid fee-for-service Approval Criteria for Hepatitis C Direct-Acting Antivirals requires liver fibrosis staging by either:

- A biopsy, transient elastography (FibroScan®), or serum test (FibroSure®) to indicate advanced fibrosis (METAVIR F3) or cirrhosis (METAVIR F4)
- Radiologic, laboratory (APRI score >1.5 or FIB-4 score >3.25), or clinical evidence (ascites, portal hypertension) of cirrhosis

The Washington Health Care Authority outlines the treatment policy for patients with HCV, with the accepted diagnostic tests for liver damage including imaging procedures (FibroScan®, ARFI, SWE) and blood tests (FibroSure®, APRI). The Table 10 below shows the allowed tests and cutoffs used to stage liver fibrosis to determine hepatitis C treatments.

Table 10: Washington Health Care Authority Accepted Diagnostic Tests and Procedures to Stage Liver Damage in Patients with Chronic HCV Infection

METAVIR Score	Biopsy	FibroScan®	Elastography (ARFI/PSWE)	FibroSure®	APRI	Other Imaging
F4	F4	≥ 12.5 kPa	≥ 2.34 m/s	≥ 0.75	≥ 2.0	Cirrhosis
F3	F3	9.6 - 12.4 kPa	2.01 - 2.33 m/s	0.58 - 0.74	1.5 - 1.9	
F2	F2	7.1 - 9.5 kPa	1.38 - 2.0 m/s	0.49 - 0.57	1.0 - 1.4	
F1/0	F1/0	≤ 7.0 kPa	≤ 1.37 m/s	≤ 0.48	≤ 0.9	

On May 27, 2016, a United States District Court issued a preliminary injunction requiring the Washington Medicaid program to cover direct-acting antiviral medications for Medicaid clients with hepatitis C, regardless of the extent of liver fibrosis.

Coverage policies for noninvasive tests of liver fibrosis were searched for four commercial payers: Aetna, Cigna, Moda, and Regence. Transient elastography (FibroScan®) is covered by three of these payers: Aetna, Cigna, and Moda. MRE for staging liver fibrosis is covered by only Moda. None of the other imaging tests are covered by these payers. Three of the four payers do not cover the blood tests for staging liver fibrosis. Moda Health covers the blood tests FibroSure®, FIBROSpect®, APRI, ActiTest®, and Hepascore®.

Aetna's precertification criteria for direct-acting antivirals require the staging of liver disease by liver biopsy, METAVIR scores, FibroScan® score, APRI score, radiological imaging consistent with cirrhosis (i.e., evidence of portal hypertension), or physical findings or clinical evidence consistent with cirrhosis as attested by the prescribing physician. The Regence Medical Policy Manual states that, "Liver biopsy is typically recommended prior to the initiation of antiviral therapy." Coverage policies for direct-acting antivirals for Cigna and Moda do not indicate specific methods for staging of liver fibrosis.

For Medicare, no National Coverage Determinations or Local Coverage Determinations related to noninvasive tests for liver fibrosis were identified.

Professional society guidelines

American Association for the Study of Liver Disease (AASLD) and Infectious Disease Society of America (IDSA) Guideline, 2016

The AASLD and IDSA guideline endorses the use of biopsy, imaging, and/or noninvasive markers to evaluate advanced fibrosis in HCV patients for treatment planning and to ascertain whether additional screening and management of cirrhosis is needed (Class I, Level A). It also endorses the continued monitoring of liver disease in those who defer treatment, but does not specify the use of noninvasive tests or provide an optimal interval for re-assessment.

Regarding noninvasive tests, the AASLD and IDSA guideline makes the following statements:

- “No single method is recognized to have high accuracy alone and each test must be interpreted carefully. A recent publication of the Agency for Healthcare Research and Quality found evidence in support of a number of blood tests; however, at best, they are only moderately useful for identifying clinically significant fibrosis or cirrhosis.”
- “Vibration-controlled transient liver elastography is a noninvasive way to measure liver stiffness and correlates well with measurement of substantial fibrosis or cirrhosis in patients with chronic HCV infection. The measurement range does overlap between stages.”
- “The most efficient approach to fibrosis assessment is to combine direct biomarkers and vibration-controlled transient liver elastography. A biopsy should be considered for any patient who has discordant results between the 2 modalities that would affect clinical decision making. For example, one shows cirrhosis and the other does not. The need for liver biopsy with this approach is markedly reduced.”
- “Alternatively, if direct biomarkers or vibration-controlled transient liver elastography are not available, the AST-to-platelet ratio index (APRI) or FIB-4 index score can help, although neither test is sensitive enough to rule out substantial fibrosis. Biopsy should be considered in those in whom more accurate fibrosis staging would impact treatment decisions. Individuals with clinically evident cirrhosis do not require additional staging (biopsy or noninvasive assessment).”

European Association for the Study of the Liver (EASL) and Asociación Latinoamericano para el Estudio del Hígado (ALEH), 2015

This is a comprehensive clinical practice guideline on the use of noninvasive tests for evaluating liver disease across a variety of etiologies. In general, EASL/ALEH endorse the use of noninvasive tests of liver fibrosis. Specific recommendations and statements include:

- "Non-invasive tests should always be interpreted by specialists in liver disease, according to the clinical context, considering the results of other tests (biochemical, radiological and endoscopic) and taking into account the recommended quality criteria for each test and its possible pitfalls (A1)."
- "TE is a fast, simple, safe and easy to learn procedure that is widely available. Its main limitation is the impossibility of obtaining results in case of ascites or morbid obesity and its limited applicability in case of obesity and limited operator experience (A1)."
- "TE should be performed by an experienced operator (>100 examinations) following a standardized protocol with the patient, fasting for at least 2 hours, in the supine position, right arm in full abduction, on the midaxillary line with the probe-tip placed in the 9th to 11th intercostal space with a minimum of 10 shots (A1)."
- "Although alternative techniques, such as pSWE/ARFI or 2D-SWE seem to overcome limitations of TE, their quality criteria for correct interpretation are not yet well defined (A1)."
- "MR elastography is currently too costly and time consuming for routine clinical practice use and seems more suited for research purposes (A1)."
- "When compared in HCV patients, the different patented tests have similar levels of performance in diagnosing significant fibrosis and cirrhosis (A1). Although non-patented tests might have lower diagnostic accuracy than patented tests, they are not associated with additional costs, are easy to calculate, and are widely available (A2)."
- "Among the different available strategies, algorithms combining TE and serum biomarkers appear to be the most attractive and validated one (A2). In patients with viral hepatitis C, when TE and serum biomarkers results are in accordance, the diagnostic accuracy is increased for detecting significant fibrosis but not for cirrhosis. In cases of unexplained discordance, a liver biopsy should be performed if the results would change the patient management (A1)."

The EASL/ALEH guideline includes the following proposed algorithm for noninvasive testing in HCV patients.

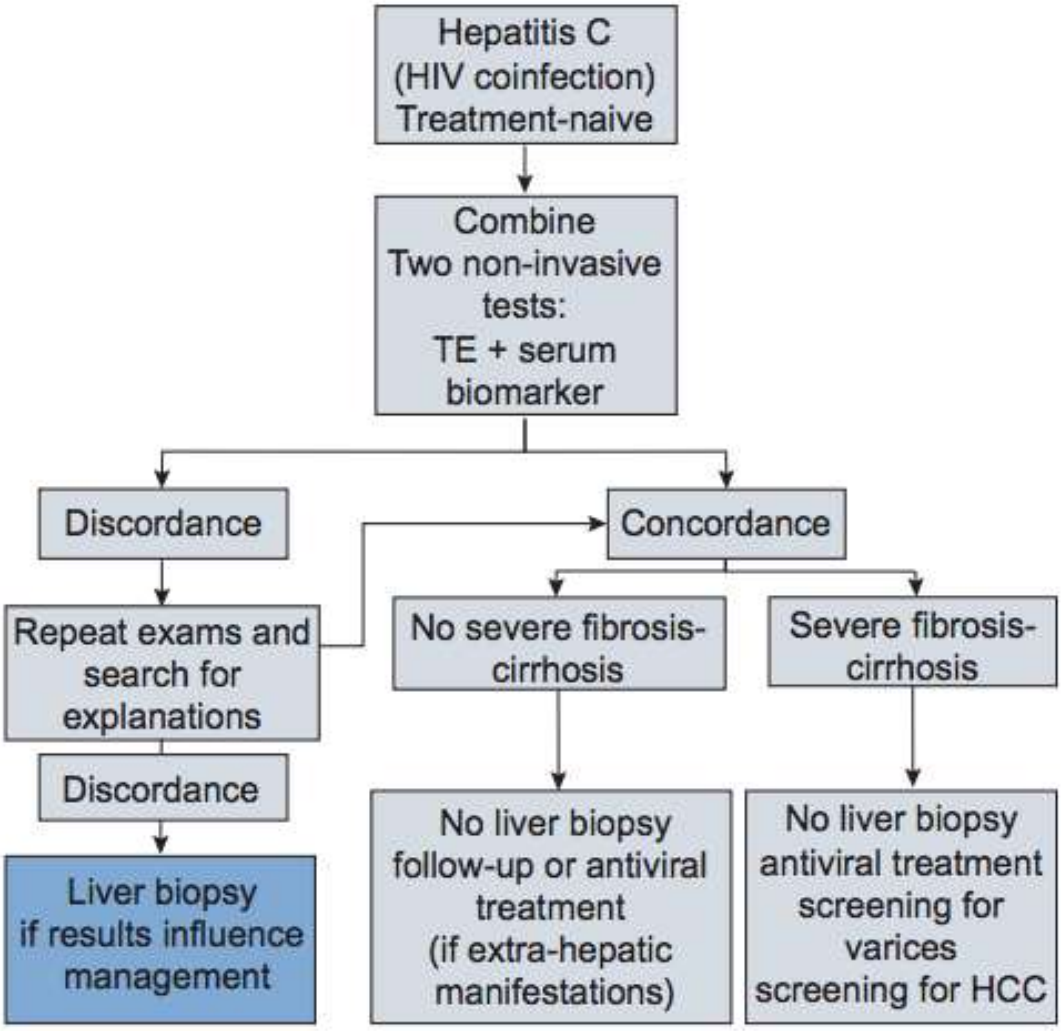

Fig. 1. Proposed algorithm for the use of non-invasive tests in treatment-naive patients with Hepatitis C with or without HIV coinfection.

National Institute for Health and Care Excellence (NICE), 2015

NICE issued medical technology guidance on the use of Virtual Touch™ Quantification (VTq, a proprietary system for performing ARFI) for diagnosing and monitoring liver fibrosis in chronic hepatitis B and C. The panel endorsed the use of VTq as an option for assessing liver fibrosis in chronic hepatitis B or C. They concluded that VTq is as accurate as transient elastography and cost modelling suggested that VTq would likely to be cost saving compared to transient elastography and liver biopsy.

Scottish Intercollegiate Guidelines Network (SIGN), 2013

SIGN published a comprehensive guideline on the management of hepatitis C in 2013 including recommendations regarding the use of noninvasive tests for diagnosing fibrosis and cirrhosis. The SIGN guideline states that while biochemical markers may be able to distinguish cirrhosis from less degrees of fibrosis, "intermediate stages are not distinguishable." Thus, SIGN recommends that biochemical markers should not be considered an alternative to biopsy for staging intermediate levels of fibrosis, but may be used in place of biopsy to diagnose cirrhosis (B recommendations, 2++ evidence). The guideline does offer that measurement of liver stiffness by noninvasive testing may be considered a "recommended best practice based on the clinical experience of the guideline development group."

Society of Radiologists in Ultrasound Consensus Conference Statement, 2015

This consensus conference statement (Barr et al., 2015) asserts that elastography (using either ultrasound or magnetic resonance techniques) can be used to diagnose liver fibrosis in patients "without overt decompensated cirrhosis." The panel stated that elastography should be used to group patients into three categories: those with minimal fibrosis (F0 or F1), those with a high likelihood of cirrhosis (F4), and those with values in between suggesting moderate to severe fibrosis (F2 and F3). The panel also proposed consensus diagnostic thresholds which are reproduced in Table 11.

Table 11: Consensus of Suggested Thresholds in Patients with Hepatitis C

Device	No Clinically Significant Fibrosis: METAVIR Stage < F2, Unlikely to Need Follow-up	Advanced Fibrosis and/or Cirrhosis: METAVIR Stage of F4 and Some Stages of F3 – Clinically Significant Fibrosis
TE FibroScan® (Echosens)	<7 kPa (1.5 m/sec)	>15 kPa (2.2 m/sec)
Siemens pSWE	1.2 m/sec (Siemens suggests <1.34 m/sec, <5.6 kPa)	>2.2 m/sec (>15 kPa)
Philips pSWE	<5.7 kPa (1.37 m/sec)	>2.2 m/sec (>15 kPa)
2D SWE (SuperSonic Imagine)	<7 kPa (1.5 m/sec)	>2.2 m/sec (>15 kPa)
MR elastography (GE, Siemens, Philips)	<3.0 kPa* (27–30)	>5.0 kPa*

*MR elastography is reported as shear modulus, while U.S. elastography techniques are reported in Young modulus. The Young modulus is three times the shear modulus.

World Health Organization, 2014

The WHO released a comprehensive guideline in 2014 focused on management of hepatitis C in resource limited settings. In general, the guideline states that noninvasive tests should be favored over liver biopsy and "in resource-limited settings, it is suggested that aminotransferase/platelet ratio index (APRI) or FIB4 be used for the assessment of hepatic fibrosis rather than other noninvasive tests that

require more resources such as elastography or Fibrotest." (Conditional recommendation, low quality evidence)

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APPENDIX A. GRADE INFORMED FRAMEWORK – ELEMENT DESCRIPTIONS

Element	Description
Balance between desirable and undesirable effects	The larger the difference between the desirable and undesirable effects, the higher the likelihood that a strong recommendation is warranted. The narrower the gradient, the higher the likelihood that a weak recommendation is warranted
Quality of evidence	The higher the quality of evidence, the higher the likelihood that a strong recommendation is warranted
Resource allocation	The higher the costs of an intervention—that is, the greater the resources consumed—the lower the likelihood that a strong recommendation is warranted
Values and preferences	The more values and preferences vary, or the greater the uncertainty in values and preferences, the higher the likelihood that a weak recommendation is warranted
Other considerations	Other considerations include issue about the implementation and operationalization of the technology or intervention in health systems and practices within Oregon.

Strong recommendation

In Favor: The subcommittee is confident that the desirable effects of adherence to a recommendation outweigh the undesirable effects, considering the quality of evidence, cost and resource allocation, and values and preferences.

Against: The subcommittee is confident that the undesirable effects of adherence to a recommendation outweigh the desirable effects, considering the quality of evidence, cost and resource allocation, and values and preferences.

Weak recommendation

In Favor: The subcommittee concludes that the desirable effects of adherence to a recommendation probably outweigh the undesirable effects, considering the quality of evidence, cost and resource allocation, and values and preferences, but is not confident.

Against: The subcommittee concludes that the undesirable effects of adherence to a recommendation probably outweigh the desirable effects, considering the quality of evidence, cost and resource allocation, and values and preferences, but is not confident.

Quality or strength of evidence rating across studies for the treatment/outcome[1]

High: The subcommittee is very confident that the true effect lies close to that of the estimate of the effect. Typical sets of studies are RCTs with few or no limitations and the estimate of effect is likely stable.

Moderate: The subcommittee is moderately confident in the 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. Typical

[1] Includes risk of bias, precision, directness, consistency and publication bias

sets of studies are RCTs with some limitations or well-performed nonrandomized studies with additional strengths that guard against potential bias and have large estimates of effects.

***Low*:** The subcommittee's confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect. Typical sets of studies are RCTs with serious limitations or nonrandomized studies without special strengths.

***Very low*:** The subcommittee has very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect. Typical sets of studies are nonrandomized studies with serious limitations or inconsistent results across studies.

APPENDIX B. GRADE EVIDENCE PROFILE

Quality Assessment for MRE (Confidence in Estimate of Effect)							
No. of Studies	**Study Design(s)**	**Risk of Bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other Factors**	**Quality**
Hepatitis related morbidity/progression (Critical outcome)							
0							Insufficient
Need for liver biopsy (Critical outcome)							
12	Diagnostic accuracy studies (cross-sectional or cohort designs)	Low	Not serious	Serious	Not serious		Moderate confidence ●●●○
Quality of life (Critical outcome)							
0							Insufficient
Testing related adverse events (Important outcome)							
0							Insufficient
Change in treatment plan (Important outcome)							
0							Insufficient

Quality Assessment for TE (Confidence in Estimate of Effect)							
No. of Studies	**Study Design(s)**	**Risk of Bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other Factors**	**Quality**
Hepatitis related morbidity/progression (Critical outcome)							
2	Prospective prognostic studies	Moderate to high	Not serious	Serious	Serious		Very low confidence ●○○○
Need for liver biopsy (Critical outcome)							
57	Diagnostic accuracy studies (cross-sectional or	Low	Not serious	Serious	Not serious		Moderate confidence ●●●○

Quality Assessment for TE (Confidence in Estimate of Effect)							
No. of Studies	**Study Design(s)**	**Risk of Bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other Factors**	**Quality**
	cohort designs)						
Quality of life (Critical outcome)							
0							Insufficient
Testing related adverse events (Important outcome)							
0							Insufficient
Change in treatment plan (Important outcome)							
0							Insufficient

Quality Assessment for ARFI (Confidence in Estimate of Effect)							
No. of Studies	**Study Design(s)**	**Risk of Bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other Factors**	**Quality**
Hepatitis related morbidity/progression (Critical outcome)							
0							Insufficient
Need for liver biopsy (Critical outcome)							
36	Diagnostic accuracy studies (cross-sectional or cohort designs)	Moderate	Not serious	Serious	Not serious		Low confidence ●●○○
Quality of life (Critical outcome)							
0							Insufficient
Testing related adverse events (Important outcome)							
0							Insufficient
Change in treatment plan (Important outcome)							
0							Insufficient

Quality Assessment for SWE (Confidence in Estimate of Effect)							
No. of Studies	**Study Design(s)**	**Risk of Bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other Factors**	**Quality**
Hepatitis related morbidity/progression (Critical outcome)							
0							Insufficient
Need for liver biopsy (Critical outcome)							
8	Diagnostic accuracy studies (cross-sectional or cohort designs)	Low to Moderate	Not serious	Serious	Not serious		Low confidence ●●○○
Quality of life (Critical outcome)							
0							Insufficient
Testing related adverse events (Important outcome)							
0							Insufficient
Change in treatment plan (Important outcome)							
0							Insufficient

Quality Assessment for RT-TE (Confidence in Estimate of Effect)							
No. of Studies	**Study Design(s)**	**Risk of Bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other Factors**	**Quality**
Hepatitis related morbidity/progression (Critical outcome)							
0							Insufficient
Need for liver biopsy (Critical outcome)							
15	Diagnostic accuracy studies (cross-sectional or cohort designs)	Moderate	Not serious	Serious	Unclear	Possible publication bias	Very low confidence ●○○○
Quality of life (Critical outcome)							

Quality Assessment for RT-TE (Confidence in Estimate of Effect)							
No. of Studies	**Study Design(s)**	**Risk of Bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other Factors**	**Quality**
0							Insufficient
Testing related adverse events (Important outcome)							
0							Insufficient
Change in treatment plan (Important outcome)							
0							Insufficient

Quality Assessment for Platelet count (Confidence in Estimate of Effect)							
No. of Studies	**Study Design(s)**	**Risk of Bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other Factors**	**Quality**
Hepatitis related morbidity/progression (Critical outcome)							
0							Insufficient
Need for liver biopsy (Critical outcome)							
18	Diagnostic accuracy studies (cross-sectional or cohort designs)	Moderate	Not serious	Serious	Serious		Very low confidence ●○○○
Quality of life (Critical outcome)							
0							Insufficient
Testing related adverse events (Important outcome)							
0							Insufficient
Change in treatment plan (Important outcome)							
0							Insufficient

Quality Assessment for Hyaluronic acid (Confidence in Estimate of Effect)							
No. of Studies	**Study Design(s)**	**Risk of Bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other Factors**	**Quality**
Hepatitis related morbidity/progression (Critical outcome)							
0							Insufficient
Need for liver biopsy (Critical outcome)							
8	Diagnostic accuracy studies (cross-sectional or cohort designs)	Moderate	Not serious	Serious	Serious		Very low confidence ●○○○
Quality of life (Critical outcome)							
0							Insufficient
Testing related adverse events (Important outcome)							
0							Insufficient
Change in treatment plan (Important outcome)							
0							Insufficient

Quality Assessment for Age-platelet index (Confidence in Estimate of Effect)							
No. of Studies	**Study Design(s)**	**Risk of Bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other Factors**	**Quality**
Hepatitis related morbidity/progression (Critical outcome)							
0							Insufficient
Need for liver biopsy (Critical outcome)							
11	Diagnostic accuracy studies (cross-sectional or cohort designs)	Moderate	Not serious	Serious	Not Serious		Low confidence ●●○○
Quality of life (Critical outcome)							
0							Insufficient

Quality Assessment for Age-platelet index (Confidence in Estimate of Effect)							
No. of Studies	**Study Design(s)**	**Risk of Bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other Factors**	**Quality**
Testing related adverse events (Important outcome)							
0							Insufficient
Change in treatment plan (Important outcome)							
0							Insufficient

Quality Assessment for APRI (Confidence in Estimate of Effect)							
No. of Studies	**Study Design(s)**	**Risk of Bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other Factors**	**Quality**
Hepatitis related morbidity/progression (Critical outcome)							
6	Retrospective prognostic studies	High	Not serious	Serious	Not serious		Very low confidence ●○○○
Need for liver biopsy (Critical outcome)							
7	Diagnostic accuracy studies (cross-sectional or cohort designs)	Moderate	Not serious	Serious	Serious		Very low confidence ●○○○
Quality of life (Critical outcome)							
0							Insufficient
Testing related adverse events (Important outcome)							
0							Insufficient
Change in treatment plan (Important outcome)							
0							Insufficient

Quality Assessment for AST-ALT ratio (Confidence in Estimate of Effect)							
No. of Studies	**Study Design(s)**	**Risk of Bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other Factors**	**Quality**
Hepatitis related morbidity/progression (Critical outcome)							
0							Insufficient
Need for liver biopsy (Critical outcome)							
32	Diagnostic accuracy studies (cross-sectional or cohort designs)	Moderate	Not serious	Serious	Serious		Very low confidence ●○○○
Quality of life (Critical outcome)							
0							Insufficient
Testing related adverse events (Important outcome)							
0							Insufficient
Change in treatment plan (Important outcome)							
0							Insufficient

Quality Assessment for Bonacini index (Confidence in Estimate of Effect)							
No. of Studies	**Study Design(s)**	**Risk of Bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other Factors**	**Quality**
Hepatitis related morbidity/progression (Critical outcome)							
0							Insufficient
Need for liver biopsy (Critical outcome)							
12	Diagnostic accuracy studies (cross-sectional or cohort designs)	Moderate	Not serious	Serious	Not serious		Low confidence ●●○○
Quality of life (Critical outcome)							

Quality Assessment for Bonacini index (Confidence in Estimate of Effect)							
No. of Studies	**Study Design(s)**	**Risk of Bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other Factors**	**Quality**
0							Insufficient
Testing related adverse events (Important outcome)							
0							Insufficient
Change in treatment plan (Important outcome)							
0							Insufficient

Quality Assessment for ELF™ (Confidence in Estimate of Effect)							
No. of Studies	**Study Design(s)**	**Risk of Bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other Factors**	**Quality**
Hepatitis related morbidity/progression (Critical outcome)							
0							Insufficient
Need for liver biopsy (Critical outcome)							
8	Diagnostic accuracy studies (cross-sectional or cohort designs)	Moderate	Not serious	Serious	Serious		Very low confidence ●○○○
Quality of life (Critical outcome)							
0							Insufficient
Testing related adverse events (Important outcome)							
0							Insufficient
Change in treatment plan (Important outcome)							
0							Insufficient

Quality Assessment for FIB-4 (Confidence in Estimate of Effect)							
No. of Studies	**Study Design(s)**	**Risk of Bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other Factors**	**Quality**
Hepatitis related morbidity/progression (Critical outcome)							
6	Retrospective prognostic studies	High	Not serious	Serious	Not serious		Very low confidence ●○○○
Need for liver biopsy (Critical outcome)							
19	Diagnostic accuracy studies (cross-sectional or cohort designs)	Moderate	Not serious	Serious	Serious		Very low confidence ●○○○
Quality of life (Critical outcome)							
0							Insufficient
Testing related adverse events (Important outcome)							
0							Insufficient
Change in treatment plan (Important outcome)							
0							Insufficient

Quality Assessment for FibroIndex (Confidence in Estimate of Effect)							
No. of Studies	**Study Design(s)**	**Risk of Bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other Factors**	**Quality**
Hepatitis related morbidity/progression (Critical outcome)							
0							Insufficient
Need for liver biopsy (Critical outcome)							
9	Diagnostic accuracy studies (cross-sectional	Moderate	Not serious	Serious	Serious		Very low confidence ●○○○

Quality Assessment for FibroIndex (Confidence in Estimate of Effect)							
No. of Studies	**Study Design(s)**	**Risk of Bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other Factors**	**Quality**
	or cohort designs)						
Quality of life (Critical outcome)							
0							Insufficient
Testing related adverse events (Important outcome)							
0							Insufficient
Change in treatment plan (Important outcome)							
0							Insufficient

Quality Assessment for FibroMeter™ (Confidence in Estimate of Effect)							
No. of Studies	**Study Design(s)**	**Risk of Bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other Factors**	**Quality**
Hepatitis related morbidity/progression (Critical outcome)							
0							Insufficient
Need for liver biopsy (Critical outcome)							
8	Diagnostic accuracy studies (cross-sectional or cohort designs)	Moderate	Not serious	Serious	Serious		Very low confidence ●○○○
Quality of life (Critical outcome)							
0							Insufficient
Testing related adverse events (Important outcome)							
0							Insufficient
Change in treatment plan (Important outcome)							
0							Insufficient

Quality Assessment for FIBROSpect® II (Confidence in Estimate of Effect)							
No. of Studies	**Study Design(s)**	**Risk of Bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other Factors**	**Quality**
Hepatitis related morbidity/progression (Critical outcome)							
0							Insufficient
Need for liver biopsy (Critical outcome)							
7	Diagnostic accuracy studies (cross-sectional or cohort designs)	Moderate	Not serious	Serious	Serious		Very low confidence ●○○○
Quality of life (Critical outcome)							
0							Insufficient
Testing related adverse events (Important outcome)							
0							Insufficient
Change in treatment plan (Important outcome)							
0							Insufficient

Quality Assessment for FibroTest® (Confidence in Estimate of Effect)							
No. of Studies	**Study Design(s)**	**Risk of Bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other Factors**	**Quality**
Hepatitis related morbidity/progression (Critical outcome)							
6	Retrospective prognostic studies	High	No serious	Serious	Serious		Very low confidence ●○○○
Need for liver biopsy (Critical outcome)							
32	Diagnostic accuracy studies (cross-sectional or	Moderate	Not serious	Serious	Serious		Very low confidence ●○○○

Quality Assessment for FibroTest® (Confidence in Estimate of Effect)							
No. of Studies	**Study Design(s)**	**Risk of Bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other Factors**	**Quality**
	cohort designs)						
Quality of life (Critical outcome)							
0							Insufficient
Testing related adverse events (Important outcome)							
0							Insufficient
Change in treatment plan (Important outcome)							
0							Insufficient

Quality Assessment for Forns index (Confidence in Estimate of Effect)							
No. of Studies	**Study Design(s)**	**Risk of Bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other Factors**	**Quality**
Hepatitis related morbidity/progression (Critical outcome)							
0							Insufficient
Need for liver biopsy (Critical outcome)							
7	Diagnostic accuracy studies (cross-sectional or cohort designs)	Moderate	Not serious	Serious	Serious		Very low confidence ●○○○
Quality of life (Critical outcome)							
0							Insufficient
Testing related adverse events (Important outcome)							
0							Insufficient
Change in treatment plan (Important outcome)							
0							Insufficient

Quality Assessment for Hepascore® (Confidence in Estimate of Effect)							
No. of Studies	**Study Design(s)**	**Risk of Bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other Factors**	**Quality**
Hepatitis related morbidity/progression (Critical outcome)							
0							Insufficient
Need for liver biopsy (Critical outcome)							
12	Diagnostic accuracy studies (cross-sectional or cohort designs)	Moderate	Not serious	Serious	Serious		Very low confidence ●○○○
Quality of life (Critical outcome)							
0							Insufficient
Testing related adverse events (Important outcome)							
0							Insufficient
Change in treatment plan (Important outcome)							
0							Insufficient

Quality Assessment for Pohl index (Confidence in Estimate of Effect)							
No. of Studies	**Study Design(s)**	**Risk of Bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other Factors**	**Quality**
Hepatitis related morbidity/progression (Critical outcome)							
0							Insufficient
Need for liver biopsy (Critical outcome)							
12	Diagnostic accuracy studies (cross-sectional or cohort designs)	Moderate	Not serious	Serious	Not serious		Low confidence ●●○○
Quality of life (Critical outcome)							

Quality Assessment for Pohl index (Confidence in Estimate of Effect)							
No. of Studies	**Study Design(s)**	**Risk of Bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other Factors**	**Quality**
0							Insufficient
Testing related adverse events (Important outcome)							
0							Insufficient
Change in treatment plan (Important outcome)							
0							Insufficient

APPENDIX C. METHODS

Scope Statement

Populations

Adults and children with chronic hepatitis C infection

Population scoping notes: *None*

Interventions

Noninvasive tests of liver fibrosis (e.g., acoustic radiation force impulse imaging, transient elastography, magnetic resonance elastography, biochemical tests with predictive algorithms)

Intervention exclusions: *None*

Comparators

Liver biopsy, other interventions listed above

Outcomes

Critical: Hepatitis-related morbidity/progression, need for liver biopsy, quality of life

Important**:** Testing-related adverse events, change in treatment plan (especially decision to begin antiviral therapy)

Considered but not selected for the GRADE table: *None*

Key Questions

1. What is the comparative effectiveness of noninvasive tests for the diagnosis and management of hepatic fibrosis in patients with chronic hepatitis C?

2. Does the comparative effectiveness of noninvasive tests of liver fibrosis in patients with chronic hepatitis C vary based on:
   a. Duration of infection
   b. Fibrosis score
   c. Body habitus
   d. Operator/interpreter training or experience
   e. Co-existence of other etiologies of liver disease (e.g., non-alcoholic steatohepatitis)

3. What are the comparative diagnostic operating characteristics of tests of liver fibrosis?

4. What is the evidence for the timing of the initial testing for fibrosis and intervals for subsequent reassessment of fibrosis?

Search Strategy

A full search of the core sources was conducted to identify systematic reviews, meta-analyses, technology assessments, and clinical practice guidelines using terms for each of the studied interventions. Searches of core sources were limited to citations published after 2010.

The core sources searched included:

Agency for Healthcare Research and Quality (AHRQ)
Blue Cross/Blue Shield Health Technology Assessment (HTA) program
BMJ Clinical Evidence
Canadian Agency for Drugs and Technologies in Health (CADTH)
Cochrane Library (Wiley Interscience)
Hayes, Inc.
Institute for Clinical and Economic Review (ICER)
Medicaid Evidence-based Decisions Project (MED)
National Institute for Health and Care Excellence (NICE)
Tufts Cost-effectiveness Analysis Registry
Veterans Administration Evidence-based Synthesis Program (ESP)
Washington State Health Technology Assessment Program

A MEDLINE search was then conducted to identify randomized control trials, systematic reviews, meta-analyses, and technology assessments published after the end search date of the most recent SR for each studied intervention.

Searches for clinical practice guidelines were limited to those published since 2010. A search for relevant clinical practice guidelines was also conducted, using the following sources:

Australian Government National Health and Medical Research Council (NHMRC)
Centers for Disease Control and Prevention (CDC) – Community Preventive Services
Choosing Wisely
Institute for Clinical Systems Improvement (ICSI)
National Guidelines Clearinghouse
New Zealand Guidelines Group
NICE
Scottish Intercollegiate Guidelines Network (SIGN)
United States Preventive Services Task Force (USPSTF)
Veterans Administration/Department of Defense (VA/DOD)

Inclusion/Exclusion Criteria

Studies were excluded if they were not published in English or did not address the scope statement.

APPENDIX D: TEST CHARACTERISTICS

Noninvasive Tests with Good or Excellent Accuracy by Pooled or Median AUROC

Test	Pooled/Median AUROC ≥F2 (95% CI/Range)	Pooled/Median AUROC ≥F3 (95% CI/Range)
MRE	0.88 (0.84 - 0.91)	0.93 (0.90 - 0.95)
TE	0.89 (0.86 - 0.91)	0.92 (0.89 - 0.94)
ARFI	0.88 (0.81 - 0.96)	0.93 (0.89 - 0.97)
SWE	0.88 (0.85 - 0.91)	0.94 (0.92 - 0.96)
RT-TE		0.86 (NR)
ELF™	0.81 (median) (Range 0.72 - 0.87)	
Fibrometer™	0.82 (median) (Range 0.78 - 0.85)	
FIBROSpect® II	0.86 (median) (Range 0.77 - 0.90)	

Noninvasive Tests with Fair or Poor Accuracy by Median AUROC

Test	Median AUROC ≥F2 (Range)
Platelet count	0.71 (0.38 - 0.94)
Hyaluronic acid	0.75 (0.65 - 0.88)
Age-platelet index	0.74 (0.64 - 0.79)
APRI	0.77 (0.58 - 0.95)
AST-ALT ratio	0.59 (0.50 - 0.82)
Bonacini index	0.66 (0.58 - 0.71)
FIB-4	0.74 (0.61 - 0.81)
FibroIndex	0.76 (0.58 - 0.86)
FibroTest®	0.79 (0.70 - 0.89)
Forns index	0.76 (0.60 - 0.86)
Hepascore®	0.79 (0.69 - 0.82)
Pohl index	0.52 (0.52 - 0.53)

Illustrative Effects of Reported Cut-Offs on Sensitivity and Specificity

MRE (Singh et al., 2015)

Fibrosis Stage	Cut-off	Sensitivity	Specificity
≥F2	3.66 kPa	0.79	0.81
≥F3	4.11 kPa	0.85	0.85

TE (Steadman et al., 2013)

Fibrosis Stage	Cut-off	Sensitivity	Specificity
≥F2	7.4 (SD ±1.5) kPa	0.80	0.81
≥F3	9.9 (SD ±2.4) kPa	0.84	0.87

ARFI (selected individual studies included in Nierhoff et al., 2013)

Fibrosis Stage	Cut-off	Sensitivity	Specificity
≥F2	1.22 m/s	1.0	0.71
	1.37 m/s	0.69	0.92
	1.63 m/s	0.59	1.0
≥F3	1.71 m/s	1.0	0.73
	1.73 m/s	0.93	0.85

SWE (selected individual studies included in Li et al., 2016)

Fibrosis Stage	Cut-off	Sensitivity	Specificity
≥F2	7.2 kPa	0.86	0.86
	8.6 kPa	0.78	0.93
≥F3	9.1 kPa	0.92	0.85
	10.46 kPa	0.89	0.80

APRI (Chou & Wasson, 2013)

Fibrosis Stage	Cut-off	Sensitivity	Specificity
≥F2	≥0.5 to >0.55	0.81	0.55
	≥1.5	0.37	0.95
F4	≥1.0	0.77	0.75
	≥2.0	0.48	0.94

ELF™ (Chou & Wasson, 2013)

Fibrosis Stage	Cut-off	Sensitivity	Specificity
≥F2	>8.75	0.86	0.62
	>9.78	0.84	0.80

FIB-4 (Chou & Wasson, 2013)

Fibrosis Stage	Cut-off	Sensitivity	Specificity
≥F2	≥1.45	0.64	0.68
	≥3.25	0.5	0.79
F4	≥1.45	0.90	0.58
	≥3.25	0.55	0.92

Fibrometer™ (Chou & Wasson, 2013)

Fibrosis Stage	Cut-off	Sensitivity	Specificity
≥F2	>0.419 to >0.59	0.69	0.81

FIBROSpect® II (Chou & Wasson, 2013)

Fibrosis Stage	Cut-off	Sensitivity	Specificity
≥F2	>0.36	0.95	0.66
	≥0.42	0.67	0.74

FibroTest® (Chou & Wasson, 2013)

Fibrosis Stage	Cut-off	Sensitivity	Specificity
≥F2	>0.10 to >0.22	0.92	0.38
	>0.70 to >0.80	0.22	0.96
F4	>0.56	0.85	0.77
	>0.73 to >0.862	0.56	0.81

APPENDIX E. APPLICABLE CODES

CODES	DESCRIPTION
ICD-10 Diagnosis Codes	
B18.2	Chronic viral hepatitis C
CPT Codes	
0346T	Ultrasound elastography (with diagnosis code)
91200	Liver elastography, mechanically induced shear wave (e.g. vibration), without imaging, with interpretation and report
91299	Other diagnostic gastroenterology procedures
0001M	Infectious disease, HCV, six biochemical assays (ALT, A2-macroglobulin, apolipoprotein A-1, total bilirubin, GGT, and haptoglobin) utilizing serum, prognostic algorithm reported as scores of fibrosis and necroinflammatory activity in liver
81599	Unlisted multianalyte assay with algorithm
82172	Apolipoprotein
82246	Bilirubin
82977	Glutamiltransferase, gamma (GGT)
83010	Hepatoglobin; quantitative
83519	Immunoassay, analyte quantitative by radiopharmaceutical technique
83520	Immunoassay NOS
83883	Nephelometry, each analyte not elsewhere specified
84450	Transferase; aspartate amino (AST) (SGOT)
84460	Transferase; alanine amino (ALT) (SGPT)

Note: Inclusion on this list does not guarantee coverage

Section 8.0

Coverage Guidances

Opportunistic Salpingectomy for Ovarian Cancer Prevention

Draft Coverage Guidance for VbBS Consideration

November 9, 2017

Oregon Health Authority

Oregon Health & Science University

Center For Evidence-based Policy

Background

- Ovarian cancer has been thought to begin in the ovary. Newer research suggests that at least some of these cancers may actually begin in the ends of the falllopian tube
- Factors that increase the risk of ovarian cancer include age of 40 or older, family history of ovarian cancer, BRCA1 or BRCA2 gene mutations, nulliparous
- Lifetime risk of ovarian cancer is 1.3%
  - Fifth leading cause of cancer death among women
- No effective screening test for ovarian cancer

Background

- Opportunistic salpingectomy
  - Removal of fallopian tubes during pelvic surgery for another indication
  - Performed in women at average risk for ovarian cancer to reduce their ovarian cancer risk while conserving the ovaries
- Procedure can be completed through open, laparoscopic, robotic, or vaginal surgery
- Most commonly performed on women undergoing a hysterectomy for benign indications
- Also used in place of tubal ligation for women desiring sterilization

Scope Statement

- Populations
  - Women at average risk of ovarian cancer who are undergoing pelvic surgery
- Interventions
  - Opportunistic salpingectomy
- Comparators
  - No intervention; oral contraceptive pills

Scope Statement

- Critical Outcomes
  - Ovarian cancer incidence
  - Mortality and morbidity
  - Ovarian function (e.g., premature menopause)
- Important Outcomes
  - Operative time and length of hospital stay
  - Harms

Scope Statement

Key Questions

1. What is the comparative effectiveness of an opportunistic salpingectomy for the prevention of ovarian cancer?
2. How does the comparative effectiveness of opportunistic salpingectomy vary by:
    a. Age
    b. Race or ethnicity
    c. Patient history, including previous pelvic surgeries
    d. Baseline risk within an average-risk screening population (as ascertained by risk assessment tools)
    e. Type of and indication for pelvic surgery
    f. Laparoscopic versus open approach
    g. Total versus partial salpingectomy
3. What are the harms of an opportunistic salpingectomy?

Evidence Sources

- Darelius et al., 2017
  - Fair-quality systematic review of salpingectomy to reduce risk of ovarian cancer (quality of the systematic review was downgraded because the search strategy missed a small case-control study)
  - This systematic review used adapted GRADE methodology to rate the confidence in the estimates of effect
- Kho et al., 2017
  - Good-quality systematic review of operative outcomes for benign hysterectomy with or without opportunistic salpingectomy
  - Included 10 studies: 8 retrospective cohort studies and 2 RCTs

Evidence Sources

- Madsen et al., 2015
  - Good-quality population registry-based case-control study assessing the effects of tubal ligation or indicated salpingectomy on ovarian cancer risk
- Lessard-Anderson et al., 2014
  - Fair-quality nested case-control study assessing the effects of tubal sterilization technique on the risk of ovarian cancer
- Falconer et al., 2015
  - Good-quality population-based retrospective cohort study assessing the effects of indicated salpingectomy on ovarian cancer risk
- Song, Lee, Kim, Heo, & Kim, 2016
  - Fair-quality retrospective cohort study comparing the effects of laparoscopic myomectomy with or without opportunistic salpingectomy on operative outcomes and ovarian reserve

Evidence Review

Outcomes	Estimate of Effect for Outcome/ *Confidence in Estimate*
Ovarian cancer incidence, morbidity, and mortality *(Critical outcome)*	Salpingectomy for any indication vs. no surgery Incidence rate of ovarian cancer 13.0 vs. 24.4 per 100,000 person-years AHR 0.65 (95% CI 0.52 to 0.81, p = .05) NNT = 8,770 Bilateral salpingectomy is associated with reduced odds of epithelial ovarian cancer vs. no surgery AOR 0.58 (95% CI 0.36 to 0.95) Unilateral salpingectomy is not associated with a statistically significant reduction in the risk of epithelial ovarian cancer vs. no surgery AOR 0.90 (95% CI 0.72 to 1.12) Excisional tubal sterilization is not associated with a statistically significant reduction in the risk of ovarian cancer AOR (0.36, 95% CI 0.13 to 1.02) ●●○○ *(Very low confidence, based on 1 retrospective cohort study and 2 case-control studies)*

Evidence Review

Outcomes	Estimate of Effect for Outcome/ *Confidence in Estimate*
Ovarian function *(Critical outcome)*	No differences in surrogate measures of ovarian function at 3 to 6 months ●●○○ *(Low confidence, based on 2 RCTs and 1 cohort study)*
Operative time *(Important outcome)*	No difference in operative time between hysterectomy alone and hysterectomy with salpingectomy MD 2.4 minutes (95% CI -12.5 to 17.3 minutes) ●●○○ *(Low confidence, based on 4 cohort studies)*

Evidence Review

Outcomes	Estimate of Effect for Outcome/ *Confidence in Estimate*
Length of hospital stay *(Important outcome)*	Shorter length of stay when hysterectomy with salpingectomy is compared to hysterectomy alone MD -0.18 days (95% CI -0.27 to -0.10 days) ●●○○ *(Low confidence, based on 4 cohort studies)*
Harms *(Important outcome)*	No differences in surgical complication rates, blood loss, reoperation, or readmission when hysterectomy with salpingectomy is compared to hysterectomy alone ●●○○ *(Low confidence, based on 9 studies with mixed designs)*

Evidence Summary

- No direct evidence that opportunistic salpingectomy reduces the risk of ovarian cancer
- Indirect evidence from case-control and cohort studies suggests an association between salpingectomy (for any indication) and reduced risk of ovarian cancer
  - These studies are subject to indication and detection bias
- Most studies of opportunistic salpingectomy have not found significant differences in ovarian endocrine function, surgical complications, operative time, or hospital length of stay

Guidelines

- American College of Obstetricians and Gynecologists (2015)
  - Prophylactic salpingectomy may provide an opportunity to prevent ovarian cancer
  - The surgeon and patient should discuss the potential benefits
- European Menopause and Andropause Society (2017)
  - Opportunistic bilateral salpingectomy may prevent ovarian cancer
  - Procedure should be recommended for hysterectomy for benign conditions
  - Bilateral salpingectomy should be preferred to tubal ligation for women seeking sterilization

Guidelines

- Society of Gynecologic Oncology (2013)
  - Salpingectomy should be considered at the time of pelvic surgery, after completion of childbearing
  - Salpingectomy should be considered in lieu of tubal ligation
- Scottish Intercollegiate Guidelines Network (2013)
  - Does not mention opportunistic salpingectomy for average-risk women (only for high-risk women)

Policy Landscape: Public Payers

- Washington Medicaid
  - No coverage policy for opportunistic salpingectomy was identified for Washington Medicaid
  - Washington Medicaid does not cover salpingectomy when performed solely for the purpose of sterilization
- Medicare
  - No National Coverage Determinations or Local Coverage Determinations were identified for salpingectomy

Policy Landscape: Private Payers

- Aetna considers opportunistic salpingectomy in low-risk women to be experimental and investigational because of insufficient evidence of its effectiveness
- No coverage policy on opportunistic salpingectomy was identified for the other three payers that were assessed: Cigna, Moda, and Regence

Public Comment

- No public comments were submitted

Discussion

Resource Allocation:

Opportunistic salpingectomy would add a small to moderate cost to the overall surgical cost. However, gynecological surgeries that would be eligible for opportunistic salpingectomy are extremely common, and ovarian cancer is relatively uncommon. The cost-effectiveness of opportunistic salpingectomy is unknown given the limited evidence demonstrating decreased ovarian cancer as well as variability in the point estimates. The prevalence of gynecological procedures compared to the infrequency of ovarian cancer would decrease the potential cost-effectiveness.

Values and Preferences:

Women would likely strongly prefer strategies that would result in a lower risk of ovarian cancer. There would likely be low variability in this preference if there is no harm associated with the intervention.

Discussion

Other Considerations

Currently, obstetricians and gynecologists are sometimes offering salpingectomy for tubal sterilization for the potential benefits of ovarian cancer prevention. However, the entire billed claim for the sterilization procedure is often being denied in these cases, because the salpingectomy is not an add-on code, but rather the primary technique that is being used for the sterilization.

Discussion

Balance of benefits and harms:

There is very low confidence that salpingectomy may result in reduced rates of epithelial ovarian cancer from a limited number of indirect studies. There appears to be a dose-response effect: bilateral salpingectomy appears to be associated with greater cancer risk reduction benefit than unilateral salpingectomy. The evidence demonstrates no significant perioperative and short-term harms of opportunistic salpingectomy, although there is low confidence in this outcome. Long-term harms are unknown. The evidence shows a balance in favor of opportunistic salpingectomy, but it is limited by indirectness and concerns about indication and detection bias.

Discussion

Rationale:

There is limited indirect evidence to suggest that opportunistic salpingectomy may substantially decrease the rate of ovarian cancer without short-term harms. Although promising, there is no information available about potential long-term harms, and there would be a significant cost given the prevalence of gynecological procedures. Patient preferences also drive the balance in favor of opportunistic salpingectomy. Therefore, the balance of benefits, harms, and patient preferences weigh in favor of opportunistic salpingectomy, but the evidence is too weak to support an increased reimbursement rate. Noncoverage is resulting in denials of some surgeries (i.e., tubal sterilization).

DRAFT: Coverage Guidance

Opportunistic salpingectomy during gynecological procedures is recommended for coverage, without an increased payment (i.e., using a form of reference-based pricing) (*weak recommendation*)

Health Evidence Review Commission (HERC)

Coverage Guidance:

Opportunistic Salpingectomy for Ovarian Cancer Prevention

DRAFT for VbBS/HERC meeting materials 11/9/2017

HERC Coverage Guidance

Opportunistic salpingectomy during gynecological procedures is recommended for coverage, without an increased payment (i.e., using a form of reference-based pricing) (*weak recommendation*).

Note: Definitions for strength of recommendation are in Appendix A. *GRADE Informed Framework Element Description*.

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Oregon Health Authority

Table of Contents

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Rationale for development of coverage guidances and multisector intervention reports

Coverage guidances are developed to inform coverage recommendations for public and private health plans in Oregon as plan administrators seek to improve patient experience of care, population health, and the cost-effectiveness of health care. In the era of public and private sector health system transformation, reaching these goals requires a focus on maximizing the benefits and minimizing the harms and costs of health interventions. Multisector intervention reports will be developed to address these population-based health interventions or other types of interventions that occur outside of the typical clinical setting.

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

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

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

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

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GRADE-Informed Framework

HERC develops recommendations by using the concepts of the Grading of Recommendations, Assessment, Development, and Evaluation (GRADE) system. GRADE is a transparent and structured process for developing and presenting evidence and for performing the steps involved in developing recommendations. The table below lists the elements that determine the strength of a recommendation. HERC reviews the evidence and makes an assessment of each element, which in turn is used to develop the recommendations presented in the coverage guidance box. Estimates of effect are derived from the evidence presented in this document. The level of confidence in the estimate is determined by HERC based on the assessment of two independent reviewers from the Center for Evidence-based Policy. In some cases, no systematic reviews or meta-analyses encompass the most current literature. In those cases HERC may describe the additional evidence or alter the assessments of confidence in light of all available information. Such assessments are informed by clinical epidemiologists from the Center for Evidence-based Policy. Unless otherwise noted, estimated resource allocation, values and preferences, and other considerations are assessments of HERC.

Should opportunistic salpingectomy be recommended for coverage for ovarian cancer risk reduction?

Outcomes	**Estimate of Effect for Outcome/** ***Confidence in Estimate***	**Resource Allocation**	**Values and Preferences**	**Other Considerations**
Ovarian cancer incidence, morbidity, and mortality *(Critical outcome)*	Salpingectomy for any indication vs. no surgery Incidence rate of ovarian cancer 13.0 vs. 24.4 per 100,000 person-years AHR 0.65 (95% CI 0.52 to 0.81, p = .05) Bilateral salpingectomy is associated with reduced odds of epithelial ovarian cancer vs. no surgery aOR 0.58 (95% CI 0.36 to 0.95) Unilateral salpingectomy is not associated with a statistically significant reduction in the risk of epithelial ovarian cancer vs. no surgery aOR 0.90 (95% CI 0.72 to 1.12) Excisional tubal sterilization is not associated with a statistically significant reduction in the risk of ovarian cancer aOR (0.36, 95% CI 0.13 to 1.02)	Opportunistic salpingectomy would add a small to moderate cost to the overall surgical cost. However, gynecological surgeries that would be eligible for opportunistic salpingectomy are extremely common, and ovarian cancer is relatively uncommon. The cost-effectiveness of opportunistic salpingectomy is unknown given the	Women would likely strongly prefer strategies that would result in a lower risk of ovarian cancer. There would likely be low variability in this preference if there is no harm associated with the intervention.	Currently, obstetricians and gynecologists are sometimes offering salpingectomy for tubal sterilization for the potential benefits of ovarian cancer prevention. However, the entire billed claim for the sterilization procedure is often being denied in these cases, because the salpingectomy is not

Should opportunistic salpingectomy be recommended for coverage for ovarian cancer risk reduction?

Outcomes	Estimate of Effect for Outcome/ *Confidence in Estimate*	Resource Allocation	Values and Preferences	Other Considerations
	●●○○ *(Very low confidence, based on 1 retrospective cohort study and 2 case-control studies)*	limited evidence demonstrating decreased ovarian cancer as well as variability in the point estimates. The prevalence of gynecological procedures compared to the infrequency of ovarian cancer would decrease the potential cost-effectiveness.		an add-on code, but rather the primary technique that is being used for the sterilization.
Ovarian function *(Critical outcome)*	No differences in surrogate measures of ovarian function at 3 to 6 months ●●○○ *(Low confidence, based on 2 RCTs and 1 cohort study)*			
Operative time *(Important outcome)*	No difference in operative time between hysterectomy alone and hysterectomy with salpingectomy MD 2.4 minutes (95% CI -12.5 to 17.3 minutes) ●●○○ *(Low confidence, based on 4 cohort studies)*			
Length of hospital stay *(Important outcome)*	Shorter length of stay when hysterectomy with salpingectomy is compared to hysterectomy alone MD -0.18 days (95% CI -0.27 to -0.10 days) ●●○○ *(Low confidence, based on 4 cohort studies)*			
Harms *(Important outcome)*	No differences in surgical complication rates, blood loss, reoperation, or readmission when hysterectomy with salpingectomy is compared to hysterectomy alone ●●○○ *(Low confidence, based on 9 studies with mixed designs)*			

Balance of benefits and harms: There is very low confidence from a limited number of indirect studies that salpingectomy may result in reduced rates of epithelial ovarian cancer. There appears to be a dose-response effect: bilateral salpingectomy appears to be associated with greater cancer risk reduction benefit than unilateral salpingectomy. The evidence demonstrates no significant perioperative or short-term harms of opportunistic salpingectomy, although there is low confidence in this outcome. Long-term harms are unknown. The evidence shows a balance in favor of opportunistic salpingectomy, but it is limited by indirectness and concerns about indication and detection bias.

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Should opportunistic salpingectomy be recommended for coverage for ovarian cancer risk reduction?

Outcomes	Estimate of Effect for Outcome/ *Confidence in Estimate*	Resource Allocation	Values and Preferences	Other Considerations
Rationale: There is limited indirect evidence to suggest that opportunistic salpingectomy may substantially decrease the rate of ovarian cancer without short-term harms. Although promising, there is no information available about potential long-term harms, and there would be a significant cost given the prevalence of gynecological procedures. Patient preferences also drive the balance in favor of opportunistic salpingectomy. Therefore, the balance of benefits, harms, and patient preferences weigh in favor of opportunistic salpingectomy, but the evidence is too weak to support an increased reimbursement rate. Noncoverage is resulting in denials of some surgeries (i.e., tubal sterilization).				
Recommendation: Opportunistic salpingectomy during gynecological procedures is recommended for coverage, without an increased payment (i.e., using a form of reference-based pricing) (*weak recommendation*).				

Note: GRADE-informed framework elements are described in Appendix A. A GRADE Evidence Profile is in Appendix B.

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Clinical Background

Approximately 1.3% of women will be diagnosed with ovarian cancer at some point during their lifetime (National Cancer Institute [NCI], n.d.). Ovarian cancer is the fifth leading cause of cancer death among women, and 14,276 women in the United States died from ovarian cancer in 2013 (Centers for Disease Control and Prevention [CDC], 2017). The five-year survival rate for ovarian cancer is 46.5%, according to data from 2007 to 2013 (NCI, n.d.). Factors that increase the risk of ovarian cancer include being aged 40 or older, having a family history of ovarian cancer or BRCA1 or BRCA2 gene mutations; being of Eastern European or Ashkenazi Jewish ancestry; and being nulliparous (CDC, 2017). Currently, there is no effective screening test for ovarian cancer (CDC, 2017).

The most common type of ovarian cancer is epithelial ovarian cancer (EOC). The cellular origin and pathogenesis of EOC, particularly of the high-grade serous type, is the subject of ongoing research. One hypothesis posits that most high-grade serous EOCs arise from precancerous lesions of the distal fallopian tubes known as serous tubal intraepithelial carcinoma (STIC) that is associated with mutations in the p53 tumor suppressor gene (Li, Fadare, Kong, & Zheng, 2012).

Opportunistic salpingectomy is the removal of the fallopian tubes during pelvic surgery for another indication to reduce the risk of epithelial carcinoma of the fallopian tube, ovary, or peritoneum. Opportunistic salpingectomy is a relatively new strategy to prevent ovarian cancer. The traditional understanding of ovarian carcinogenesis is that the ovarian surface epithelium undergoes metaplastic changes, leading to the different histologic types of EOC. A more recent understanding of epithelial ovarian carcinogenesis is that serous, endometrioid, and clear cell carcinomas are derived from the fallopian tube and the endometrium, not directly from the ovary (American College of Obstetricians and Gynecologists, 2015).

Indications

An opportunistic salpingectomy is performed for women at average risk for ovarian cancer to reduce their ovarian cancer risk and to conserve the ovaries. The procedure is most commonly performed on women undergoing a hysterectomy for benign indications, and the procedure is also used in place of tubal ligation for women desiring sterilization. Women at high risk of ovarian cancer are typically advised to undergo salpingo-oophorectomy after completion of childbearing to reduce their risk of ovarian cancer.

Salpingectomy is an option for women who desire surgical sterilization. Compared with other tubal sterilization procedures, postpartum partial salpingectomy is among the most effective techniques for preventing unintended pregnancy (Peterson, Xia, Hughes, Wilcox, Ratliff Tylor, & Trussell, 1996).

Technology Description

Opportunistic salpingectomy involves removal of the distal one-third (fimbria and infundibulum, portion of ampulla) of both fallopian tubes, however, the entire tube can also be removed. The surgery can be completed through open, laparoscopic, robotic, or vaginal surgery.

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Evidence Review

Darelius et al., 2017

This is a fair-quality systematic review of salpingectomy to reduce the risk of EOC. The review used an adapted GRADE methodology to rate the confidence in the estimates of effect. The quality of the systematic review was downgraded because the search strategy missed a small case-control study that reported on the effects of salpingectomy, thus raising a question as to the completeness of the search.

Although the initial scope of the systematic review was focused on salpingectomy at the time of hysterectomy for benign indications, because the authors identified no direct studies of opportunistic salpingectomy, they opted to include studies examining the effects of indicated salpingectomy (common indications include ectopic tubal pregnancy, hydrosalpinx, endometriosis, and pelvic inflammatory disease) on EOC risk reduction. Thus, the authors stated that the results should be interpreted as describing the effects of salpingectomy per se, as opposed to opportunistic salpingectomy at the time of gynecological or pelvic surgery for benign causes.

The review summarized the results of two large observational studies that compared the effects of indicated salpingectomy to no surgery on the risk of ovarian cancer. The authors of the systematic review assessed both studies as having a high risk of bias because of indication and detection bias, and thus rated the quality of evidence for ovarian cancer risk reduction as very low. These studies (Madsen et al., 2014; Falconer et al., 2015) and the small case-control study that was not included in the systematic review (Lessard-Anderson et al., 2014) are discussed separately below.

Three studies included in the systematic reviews (two RCTs and one cohort study) reported on measures of postoperative ovarian endocrine function after hysterectomy with opportunistic salpingectomy. Two of the studies found no statistically significant difference in anti-Müllerian hormone levels at three months after surgery. The third study compared the effects of total bilateral salpingectomy to partial bilateral salpingectomy on several hormonal and imaging-based indicators of ovarian function and found no statistically significant differences in any of the outcomes at six months. Because of concerns about small samples, short follow-up periods, and the reliance on biochemical and imaging markers of ovarian function, the systematic review authors rated the quality of evidence for ovarian function as low.

Five studies included in the systematic review (four cohort studies and one case series) reported on surgical complications for opportunistic or indicated salpingectomy. None of the included studies found statistically significant differences in the surgical complication rate, but the authors rated the quality of evidence as very low because of the use of historical controls as comparators in three of the four studies.

Six studies included in the systematic review (one RCT and five cohort studies) compared the effects on operative time of hysterectomy with or without salpingectomy. Two studies did not report the surgical approach, and the remaining three studies used different laparoscopic techniques. The single small RCT (n = 30) found no statistically significant difference in operative time (115.2 minutes for hysterectomy alone compared to 115.7 minutes for hysterectomy with salpingectomy, p = .97). In a meta-analysis of four of the five cohort studies (a fifth was excluded because of an “extreme, skewed distribution”), salpingectomy resulted in a mean difference of 2.4 minutes of added operative time (95% CI -12.5 to 17.3 minutes). The level of heterogeneity was high, and the authors rated the quality of evidence as low.

Five studies included in the systematic review (all cohort studies) compared the effects on length of stay of hysterectomy with or without salpingectomy. In a meta-analysis of four of the five cohort studies (a fifth was again excluded because of an "extreme, skewed distribution"), the mean difference in the length of stay was 0.18 days shorter when salpingectomy was added to hysterectomy (95% CI -0.27 to -0.10 days), but the authors stated that these estimates were at high risk of bias because of the use of historical controls. The authors rated the quality of evidence as very low.

Overall, the systematic review authors concluded that there is insufficient evidence on the effects of opportunistic salpingectomy on ovarian cancer risk reduction and uncertainty about the potential complications.

Kho et al., 2017

This is a good-quality systematic review of 10 studies (eight retrospective cohort studies and two RCTs) examining operative outcomes for benign hysterectomy with or without opportunistic salpingectomy. Four of the cohort studies were rated good quality, three were fair quality, and one was poor quality; one of the RCTs was rated poor quality and one was rated good quality. Some of the included studies were also included in the review by Darelius et al. (2017).

Nine of the included studies reported on operative time; seven found no differences between the groups. One study found a median increase in operative time of 16.3 minutes, and another study found a mean decrease in operative time of five minutes, but only when salpingectomy was added to total laparoscopic hysterectomy (not in conjunction with vaginal or total abdominal hysterectomy).

Nine of the included studies reported on estimated blood loss; eight found no difference in blood loss between the groups. The remaining study found less estimated blood loss in the opportunistic salpingectomy group (median of 100 mL vs. 150 mL, $p < .01$). Studies that reported on the incidence of blood transfusion or change in hemoglobin found no differences.

Nine of the included studies reported on hospital length of stay. Four of the cohort studies found shorter lengths of stay with opportunistic salpingectomy (mean reductions ranging from 0.3 to 0.43 days). The remaining studies found no statistically significant differences in the length of stay.

Surgical complications were reported in nine of the included studies. The complications included infection, fever, need for reoperation, emergency visits, readmission, and intraoperative complications. None of the included studies found these complications to be more likely when opportunistic salpingectomy was performed compared to hysterectomy alone.

Overall, the systematic review authors concluded that the addition of opportunistic salpingectomy to benign hysterectomy did not increase operative time, operative blood loss, or the rate of operative complications.

Madsen et al., 2015

This is a good-quality population registry-based case-control study assessing the effects of tubal ligation or indicated salpingectomy on the risk of ovarian cancer in women in Denmark. The study used several comprehensive population-based registries. Cases were defined as a first diagnosis of histologically verified EOC in women between the ages of 30 and 84 with no previous cancer diagnosis. Exposures were ascertained from the National Patient Register, which contains information on nearly all surgical procedures performed since 1977. For each case, 15 randomly selected, date-of-birth-matched

concurrent controls were selected. Tubal ligation was associated with reduced odds of any EOC after adjustment for age, parity, infertility, endometriosis, pelvic inflammatory disease, and hysterectomy (adjusted odds ratio [aOR] 0.87, 95% CI 0.78 to 0.98). Bilateral salpingectomy was also associated with a reduction in any EOC after adjustment for age, parity, and tubal ligation (aOR 0.58, 95% CI 0.36 to 0.95). Unilateral salpingectomy was not associated with a statistically significant reduction in the odds of any EOC after adjustment (aOR 0.90, 95% CI 0.72 to 1.12). The main limitations of this study were the low numbers of tubal ligations and salpingectomies and indication bias.

Lessard-Anderson et al., 2014

This is a fair-quality nested case-control study assessing the effect of a tubal sterilization technique on the risk of EOC in women in the Rochester Epidemiology Project. Cases were defined as women with a new diagnosis of serous EOC or primary peritoneal cancer (PPC) diagnosed between 1966 and 2009 while residing in Olmstead County. Cases were age-matched to two controls from the general population of women living in Olmstead County. Exposures were ascertained through review of operative and pathology reports; complete salpingectomy, partial salpingectomy, and distal fimbriectomy were all classified as excisional tubal sterilization. In the analysis, adjustments were made for previous hysterectomy or salpingo-oophorectomy, contraceptive use, endometriosis, infertility, and parity. There were 194 cases and 388 matched controls; 14 of the cases (7.2%) and 46 (11.9%) of the controls had undergone any tubal sterilization, and five of the cases (2.6%) and 25 of the controls (6.4%) had undergone excisional tubal sterilization. Excisional tubal sterilization reduced the adjusted odds of EOC or PPC by 64%, but the result was not statistically significant (aOR 0.36, 95% CI 0.13 to 1.02). When sensitivity analyses were performed by excluding serous borderline tumors, excluding partial salpingectomy, or both, the results remained non-statistically significant. Limitations of the study included the small sample size, changing patterns of oral contraceptive use during the studied period, and lack of information about familial cancer history.

Falconer et al., 2015

This is a good-quality population-based retrospective cohort study that assessed the effects of indicated salpingectomy on ovarian cancer risk in women in Sweden. The study relied on comprehensive nationwide registries to identify women who had undergone one of four procedures (hysterectomy, hysterectomy with bilateral salpingo-oophorectomy (BSO), salpingectomy, or tubal sterilization) and women with incident ovarian or tubal cancer (borderline tumors were excluded). Information on parity and educational attainment was also obtained from national registries. In the overall analysis with full adjustment for age, parity, and educational attainment, salpingectomy was associated with a reduced risk of ovarian cancer (adjusted hazard ratio [AHR] 0.65, 95% CI 0.52 to 0.81). By comparison, hysterectomy (AHR 0.79, 95% CI 0.70 to 0.88) and tubal sterilization (AHR 0.72, 95% CI 0.64 to 0.81) showed slightly lower risk reduction, and hysterectomy with BSO showed the greatest risk reduction (AHR 0.06, 95% CI 0.03 to 0.12). Bilateral salpingectomy (AHR 0.35, 95% CI 0.17 to 0.73) was associated with a greater risk reduction than unilateral salpingectomy (AHR 0.71, 95% CI 0.56 to 0.91), which could be interpreted as evidence of a dose-response effect. The incidence rate of ovarian cancer was 25.2 per 100,000 person-years in the unexposed group, compared to 13.0 per 100,000 person-years in the salpingectomy group. The main limitation of this study is confounding by indication; the most common reasons for salpingectomy were ectopic pregnancy (which may confer protection against ovarian cancer)

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or conditions involving tubal inflammation (infection, endometriosis, and hydrosalpinx), which are thought to confer greater risk of ovarian cancer.

Song, Lee, Kim, Heo, & Kim, 2016

This is a fair-quality retrospective cohort study comparing the effects of laparoscopic myomectomy with or without opportunistic salpingectomy on operative outcomes and ovarian reserve. Overall, 45 patients had laparoscopic myomectomy with opportunistic salpingectomy and 65 patients had laparoscopic myomectomy without salpingectomy. The two groups were similar with respect to baseline characteristics. For all outcomes, including ovarian reserve (as assessed by rate of decline of anti-Müllerian hormone levels at three months), operative time, conversion to laparotomy, estimated blood loss, need for transfusion, and operative complications, there were no statistically significant differences between the two groups. The authors concluded that the addition of opportunistic salpingectomy to laparoscopic myomectomy does not result in decreased ovarian reserve or increased operative complications. The major limitations of this study stem from the small sample size, the "relatively advanced reproductive age" of most participants (average age was approximately 43 years old in both groups), and questions of generalizability because all of the procedures were performed by attending surgeons at four institutions.

Evidence Summary

There is no direct evidence that opportunistic salpingectomy at the time of gynecological or pelvic procedures for benign indications or sterilization reduces the risk of EOC. Indirect evidence from case-control and cohort studies suggests an association between salpingectomy per se and a reduced risk of EOC, but these studies are subject to indication and detection bias. Most studies that have compared the addition of opportunistic salpingectomy to a gynecological or pelvic procedure without salpingectomy have not found significant differences in ovarian endocrine function, surgical complications, operative time, or length of stay.

Policy Landscape

Payer Coverage Policies

Medicaid

No coverage policy for opportunistic salpingectomy was identified for Washington's Medicaid program. In addition, Washington Medicaid does not cover salpingectomy when performed solely for the purpose of sterilization.

Medicare

No Medicare National Coverage Determinations or Local Coverage Determinations were identified for salpingectomy.

Private Payers

Coverage policies for opportunistic salpingectomy were assessed for Aetna, Cigna, Moda, and Regence. Aetna considers opportunistic salpingectomy in low-risk women to be experimental and investigational because of insufficient evidence of its effectiveness. No coverage policy on opportunistic salpingectomy was identified for Cigna, Moda, or Regence.

Professional Society Guidelines

The American College of Obstetricians and Gynecologists (2015) guideline on *Salpingectomy for Ovarian Cancer Prevention* includes these recommendations:

- The surgeon and patient should discuss the potential benefits of removal of the fallopian tubes during a hysterectomy in women at population risk of ovarian cancer who are not having an oophorectomy.
- When counseling women about laparoscopic sterilization methods, clinicians can communicate that bilateral salpingectomy can be considered a method that provides effective contraception.

The American College of Obstetricians and Gynecologists guideline states that prophylactic salpingectomy may provide an opportunity to prevent ovarian cancer, but that randomized controlled trials are needed to support the validity of this approach.

A European Menopause and Andropause Society position statement (Perez-Lopez et al., 2017) states that opportunistic bilateral salpingectomy may prevent ovarian cancer, and the procedure should be recommended in cases of hysterectomy for benign conditions. In addition, bilateral salpingectomy should be preferred to tubal ligation for women seeking sterilization.

The *Clinical Practice Statement: Salpingectomy for Ovarian Cancer Prevention* from the Society of Gynecologic Oncology (2013) states, "For women at population risk (average) for ovarian cancer, salpingectomy should be considered (after completion of childbearing) at the time of hysterectomy, in lieu of tubal ligation, and also at the time of other pelvic surgery."

The guidelines from the Scottish Intercollegiate Guidelines Network (2013) on *Management of Epithelial Ovarian Cancer* do not mention opportunistic salpingectomy for average-risk women.

Quality Measures

No quality measures related to salpingectomy were identified when searching the National Quality Measures Clearinghouse.

References

Evidence Sources

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Coverage guidance is prepared by the Health Evidence Review Commission (HERC), HERC staff, and subcommittee members. The evidence summary is prepared by the Center for Evidence-based Policy at Oregon Health & Science University (the Center). This document is intended to guide public and private purchasers in Oregon in making informed decisions about health care services.

The Center is not engaged in rendering any clinical, legal, business or other professional advice. The statements in this document do not represent official policy positions of the Center. Researchers involved in preparing this document have no affiliations or financial involvement that conflict with material presented in this document.

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Appendix A. GRADE-Informed Framework Element Descriptions

Element	Description
Balance of benefits and harms	The larger the difference between the desirable and undesirable effects, the higher the likelihood that a strong recommendation is warranted. An estimate that is not statistically significant or has a confidence interval crossing a predetermined clinical decision threshold will be downgraded.
Quality of evidence	The higher the quality of evidence, the higher the likelihood that a strong recommendation is warranted
Resource allocation	The higher the costs of an intervention—that is, the greater the resources consumed in the absence of likely cost offsets—the lower the likelihood that a strong recommendation is warranted
Values and preferences	The more values and preferences vary, or the greater the uncertainty in values and preferences, the higher the likelihood that a weak recommendation is warranted
Other considerations	Other considerations include issues about the implementation and operationalization of the technology or intervention in health systems and practices within Oregon.

Strong recommendation

In Favor: The subcommittee concludes that the desirable effects of adherence to a recommendation outweigh the undesirable effects, considering the balance of benefits and harms, resource allocation, values and preferences and other factors.

Against: The subcommittee concludes that the undesirable effects of adherence to a recommendation outweigh the desirable effects, considering the balance of benefits and harms, resource allocation, values and preferences and other factors.

Weak recommendation

In Favor: The subcommittee concludes that the desirable effects of adherence to a recommendation probably outweigh the undesirable effects, considering the balance of benefits and harms, resource allocation, values and preferences and other factors., but further research or additional information could lead to a different conclusion.

Against: The subcommittee concludes that the undesirable effects of adherence to a recommendation probably outweigh the desirable effects, considering the balance of benefits and harms, cost and resource allocation, and values and preferences, but further research or additional information could lead to a different conclusion.

Confidence in estimate rating across studies for the intervention/outcome

Assessment of confidence in estimate includes factors such as risk of bias, precision, directness, consistency and publication bias.

High: The subcommittee is very confident that the true effect lies close to that of the estimate of the effect. Typical sets of studies are RCTs with few or no limitations and the estimate of effect is likely stable.

Moderate: The subcommittee is moderately confident in the estimate of effect: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different. Typical sets of studies are RCTs with some limitations or well-performed nonrandomized studies with additional strengths that guard against potential bias and have large estimates of effects.

Low: The subcommittee's confidence in the estimate of effect is limited: The true effect may be substantially different from the estimate of the effect. Typical sets of studies are RCTs with serious limitations or nonrandomized studies without special strengths.

Very low: The subcommittee has very little confidence in the estimate of effect: The true effect is likely to be substantially different from the estimate of effect. Typical sets of studies are nonrandomized studies with serious limitations or inconsistent results across studies.

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Appendix B. GRADE Evidence Profile

Quality Assessment (Confidence in Estimate of Effect)							
No. of Studies	**Study Design(s)**	**Risk of Bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other Factors**	**Quality**
Ovarian Cancer Incidence, Morbidity, and Mortality							
2	Observational	Moderate	Serious	Not serious	Serious	Possible dose-response effect	Very low ●○○○
Ovarian Function							
3	Mixed	Moderate	Serious	Not serious	Not serious		Low ●●○○
Operative Time							
4	Observational	Moderate	Not serious	Not serious	Not serious		Low ●●○○
Length of Stay							
4	Observational	Moderate	Not serious	Not serious	Not serious		Low ●●○○
Harms							
9	Mixed	Moderate	Not serious	Not serious	Not estimable		Low ●●○○

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Appendix C. Methods

Scope Statement

Populations

Women at average risk of ovarian cancer who are undergoing pelvic surgery

Population scoping notes: None

Interventions

Opportunistic salpingectomy

Intervention exclusions: None

Comparators

No intervention, oral contraceptive pills

Outcomes

Critical: Ovarian cancer incidence, mortality and morbidity, ovarian function (e.g., premature menopause)

Important: Operative time and length of hospital stay, harms

Considered but not selected for the GRADE table: None

Key Questions

KQ1: What is the comparative effectiveness of an opportunistic salpingectomy for the prevention of ovarian cancer?

KQ2: How does the comparative effectiveness of opportunistic salpingectomy vary by:

a) Age
b) Race or ethnicity
c) Patient history, including previous pelvic surgeries
d) Baseline risk within an average-risk screening population (as ascertained by risk assessment tools)
e) Type of and indication for pelvic surgery
f) Laparoscopic versus open approach
g) Total versus partial salpingectomy

KQ3: What are the harms of an opportunistic salpingectomy?

Search Strategy

A full search of the core sources was conducted to identify systematic reviews, meta-analyses, and technology assessments meeting the criteria for the scope described above. Searches of core sources were limited to citations published after 2012. The following core sources were searched:

Agency for Healthcare Research and Quality (AHRQ)
Blue Cross/Blue Shield Center for Clinical Effectiveness
Canadian Agency for Drugs and Technologies in Health (CADTH)
Cochrane Library (Wiley Online Library)

Institute for Clinical and Economic Review (ICER)
Medicaid Evidence-based Decisions Project (MED)
National Institute for Health and Care Excellence (NICE)
Tufts Cost-effectiveness Analysis Registry
Veterans Administration Evidence-based Synthesis Program (ESP)
Washington State Health Technology Assessment Program

A MEDLINE search was also conducted to identify systematic reviews, meta-analyses, and technology assessments, using the search term salpingectomy. The search was limited to publications in English published since 2012. In addition, a MEDLINE search was conducted for studies published after the search dates of the Darelius et al. systematic review (2017). The search was limited to publications in English published after September 2015 (the end search date for the Darelius et al. systematic review, which was judged to be the most comprehensive review on this topic).

Searches for clinical practice guidelines were limited to those published since 2012. A search for relevant clinical practice guidelines was also conducted using MEDLINE and the following sources:

Australian Government National Health and Medical Research Council (NHMRC)
Canadian Agency for Drugs and Technologies in Health (CADTH)
Centers for Disease Control and Prevention (CDC) – Community Preventive Services
National Guidelines Clearinghouse
National Institute for Health and Care Excellence (NICE)
Scottish Intercollegiate Guidelines Network (SIGN)
United States Preventive Services Task Force (USPSTF)
Veterans Administration/Department of Defense (VA/DOD) Clinical Practice Guidelines

Inclusion/Exclusion Criteria

Studies were excluded if they were not published in English, did not address the scope statement, or were study designs other than systematic reviews, meta-analyses, technology assessments, randomized controlled trials, observational studies, or clinical practice guidelines.

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Appendix D. Applicable Codes

CODES	DESCRIPTION
CPT Codes	
58150	Total abdominal hysterectomy (corpus and cervix), with or without removal of tube(s), with or without removal of ovary(s);
58180	Supracervical abdominal hysterectomy (subtotal hysterectomy), with or without removal of tube(s), with or without removal of ovary(s)
58260	Vaginal hysterectomy, for uterus 250 g or less;
58262	Vaginal hysterectomy, for uterus 250 g or less; with removal of tube(s), and/or ovary(s)
58290	Vaginal hysterectomy, for uterus greater than 250 g;
58291	Vaginal hysterectomy, for uterus greater than 250 g; with removal of tube(s) and/or ovary(s)
58541	Laparoscopy, surgical, supracervical hysterectomy, for uterus 250 g or less;
58542	Laparoscopy, surgical, supracervical hysterectomy, for uterus 250 g or less; with removal of tube(s) and/or ovary(s)
58543	Laparoscopy, surgical, supracervical hysterectomy, for uterus greater than 250 g;
58544	Laparoscopy, surgical, supracervical hysterectomy, for uterus greater than 250 g; with removal of tube(s) and/or ovary(s)
58544	Laparoscopy, surgical, with vaginal hysterectomy, for uterus greater than 250 g; with removal of tube(s) and/or ovary(s)
58550	Laparoscopy, surgical, with vaginal hysterectomy, for uterus 250 g or less;
58552	Laparoscopy, surgical, with vaginal hysterectomy, for uterus 250 g or less; with removal of tube(s) and/or ovary(s)
58553	Laparoscopy, surgical, with vaginal hysterectomy, for uterus greater than 250 g;
58661	Laparoscopy, surgical; with removal of adnexal structures (partial or total oophorectomy and/or salpingectomy)
58570	Laparoscopy, surgical, with total hysterectomy, for uterus 250 g or less;
58571	Laparoscopy, surgical, with total hysterectomy, for uterus 250 g or less; with removal of tube(s) and/or ovary(s)
58572	Laparoscopy, surgical, with total hysterectomy, for uterus greater than 250 g;
58573	Laparoscopy, surgical, with total hysterectomy, for uterus greater than 250 g; with removal of tube(s) and/or ovary(s)
58600	Ligation or transection of fallopian tube(s), abdominal or vaginal approach, unilateral or bilateral
58661	Laparoscopy, surgical; with removal of adnexal structures (partial or total oophorectomy and/or salpingectomy)
58670	Laparoscopy, surgical; with fulguration of oviducts (with or without transection)
58671	Laparoscopy, surgical; with occlusion of oviducts by device (e.g., band, clip, or Falope ring)
58700	Salpingectomy, complete or partial, unilateral or bilateral (separate procedure)
58720	Salpingo-oophorectomy, complete or partial, unilateral or bilateral (separate procedure)
58940	Oophorectomy, partial or total, unilateral or bilateral;

Note: Inclusion on this list does not guarantee coverage.

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CG-Opportunistic Salpingectomy for Ovarian Cancer Prevention

Question: How should the Coverage Guidance *Opportunistic Salpingectomy for Ovarian Cancer Prevention* be applied to the Prioritized List?

Question source: EbGS, HERC Staff

Issue: The Evidence-based Guidelines Subcommittee approved a draft Coverage Guidance that recommends opportunistic salpingectomy for coverage, only when there is not an additional fee associated with it. They agreed that it was important that coverage not be denied for appropriate procedures (such as tubal sterilization, or hysterectomy for cervical cancer) just because an opportunistic salpingectomy was performed. Given the limited evidence, however, it was not felt appropriate for opportunistic salpingectomy to justify additional procedural fees.

Prioritized List Status

Line:	**6**
Condition:	REPRODUCTIVE SERVICES (See Guideline Notes 64,65,68,162)
Treatment:	CONTRACEPTION MANAGEMENT; STERILIZATION
ICD-10:	Z30.011-Z30.9,Z31.61-Z31.69,Z39.2
CPT:	11976,11981-11983,55250,55450,57170,58300,58301,58340,58565,58600-58615, 58670,58671,74740,98966-98969,99051,99060,99070,99078,99184,99201-99239, 99281-99285,99291-99404,99408-99449,99468-99480,99487-99498,99605-99607
HCPCS:	G0396,G0397,G0406-G0408,G0425-G0427,G0463-G0467,G0490,G0508,G0509, S4981,S4989,T1015

Relevant gynecological lines

25 Dysplasia of cervix and cervical carcinoma in situ, cervical condyloma
37 Ectopic pregnancy; hydatidiform mole; choriocarcinoma
51 Acute pelvic inflammatory disease
61 Torsion of ovary
63 Spontaneous abortion; missed abortion
133 Cancer of cervix
157 Cancer of colon, rectum, small intestine and anus
191 Cancer of breast; at high risk of breast cancer
209 Cancer of uterus
239 Cancer of ovary
286 Cancer of vagina, vulva, and other female genital organs
312 Gender dysphoria/transexualism
395 Endometriosis and adenomyosis
403 Uterine leiomyoma and polyps
420 Menstrual bleeding disorders
428 Noninflammatory disorders and benign neoplasms of ovary, fallopian tubes and uterus; ovarian cysts; gonadal dysgenisis
464 Uterine prolapse; cystocele
467 Gonadal dysfunction, menopausal management
529 Chronic pelvic inflammatory disease, pelvic pain syndrome, dyspareunia
555 Dysmenorrhea
565 Peritoneal adhesion
578 Congenital anomalies of female genital organs excluding vagina
619 Prevention services with limited or no evidence of effectiveness

New ICD 10 code

Z40.03 Encounter for prophylactic removal of fallopian tube(s)

CPT	Description	Placement 1/18 list
58150	Total abdominal hysterectomy (corpus and cervix), with or without removal of tube(s), with or without removal of ovary(s)	25,37,51,63,133,157,209,239,286,312,395,403,420,464,529,555
58180	Supracervical abdominal hysterectomy (subtotal hysterectomy), with or without removal of tube(s), with or without removal of ovary(s)	37,51,209,239,286,312,403,420,529,555
58260	Vaginal hysterectomy, for uterus 250 g or less;	25,37,51,133,209,239,286,312,395,403,420,464,529,555
58262	Vaginal hysterectomy, for uterus 250 g or less; with removal of tube(s), and/or ovary(s)	25,51,209,312,395,403,420,464,529
58290	Vaginal hysterectomy, for uterus greater than 250 g;	25,51,209,286,312,395,403,420,464,529,555
58291	Vaginal hysterectomy, for uterus greater than 250 g; with removal of tube(s) and/or ovary(s)	25,51,209,312,395,403,420,464,529
58541	Laparoscopy, surgical, supracervical hysterectomy, for uterus 250 g or less;	37,51,209,239,286,312,403,420,529,555
58542	Laparoscopy, surgical, supracervical hysterectomy, for uterus 250 g or less; with removal of tube(s) and/or ovary(s)	37,51,209,239,286,312,403,420,529,555
58543	Laparoscopy, surgical, supracervical hysterectomy, for uterus greater than 250 g;	37,51,209,239,286,312,403,420,529,555
58544	Laparoscopy, surgical, supracervical hysterectomy, for uterus greater than 250 g; with removal of tube(s) and/or ovary(s)	37,51,209,239,286,312,403,420,529,555
58550	Laparoscopy, surgical, with vaginal hysterectomy, for uterus 250 g or less;	25,37,51,133,209,239,286,312,395,403,420,464,529,555
58552	Laparoscopy, surgical, with vaginal hysterectomy, for uterus 250 g or less; with removal of tube(s) and/or ovary(s)	25,37,51,133,209,239,286,312,395,403,420,464,529,555
58553	Laparoscopy, surgical, with vaginal hysterectomy, for uterus greater than 250 g	25,37,51,133,209,239,286,312,395,403,420,464,529,555
58570	Laparoscopy, surgical, with total hysterectomy, for uterus 250 g or less;	25,37,51,133,209,239,286,312,395,403,420,464,529,555
58571	Laparoscopy, surgical, with total hysterectomy, for uterus 250 g or less; with removal of tube(s) and/or ovary(s)	25,37,51,133,209,239,286,312,395,403,420,464,529,555
58572	Laparoscopy, surgical, with total hysterectomy, for uterus greater than 250 g;	25,37,51,133,209,239,286,312,395,403,420,464,529,555
58573	Laparoscopy, surgical, with total hysterectomy, for	25,37,51,133,209,239,286,312,

CPT	Description	Placement 1/18 list
	uterus greater than 250 g; with removal of tube(s) and/or ovary(s)	395,403,420,464,529,555
58600	Ligation or transection of fallopian tube(s), abdominal or vaginal approach, unilateral or bilateral	6
58661	Laparoscopy, surgical; with removal of adnexal structures (partial or total oophorectomy and/or salpingectomy)	37,51,61,191,239,286,312,395, 428,467,529,565,578
58670	Laparoscopy, surgical; with fulguration of oviducts (with or without transection)	6
58671	Laparoscopy, surgical; with occlusion of oviducts by device (eg, band, clip, or Falope ring)	6
58700	Salpingectomy, complete or partial, unilateral or bilateral (separate procedure)	37,51,61,428,529,578
58720	Salpingo-oophorectomy, complete or partial, unilateral or bilateral (separate procedure)	37,51,61,239,312,428,529,578
58940	Oophorectomy, partial or total, unilateral or bilateral;	37,51,61,191,239,312,395,428, 467,529,565,578,619

HERC Staff Summary

Opportunistic salpingectomy may be used with a variety of gynecologic surgeries. Pairing of the procedure with the ICD 10 code anywhere in the funded region of the Prioritized List will allow the claim to process. Placing both the diagnostic and procedure code for opportunistic salpingectomy on the reproductive line would allow it to be covered during sterilization and other gynecologic surgeries. If further evidence of effectiveness emerges, it could be added to Line 3. A guideline would need to be added to clarify the intent around reference-based pricing.

HERC Staff Recommendations:

1. Add ICD 10 code Z40.03 *Encounter for prophylactic removal of fallopian tube(s)* to Line 6 *Reproductive Services*
2. Add CPT code 58700 to Line 6
3. Add a guideline note

GUIDELINE NOTE XXX, OPPORTUNISTIC SALPINGECTOMY

Line 6

Opportunistic salpingectomy during gynecologic procedures is included on Line 6, when it does not involve an increased payment (i.e., using a form of reference-based pricing) or require a change in the setting in which the procedure would be performed (e.g. necessitate a hospital setting instead of an ambulatory surgical center).

HERC Coverage Guidance: Opportunistic Salpingectomy for Ovarian Cancer Prevention
Disposition of Public Comments

Commenters

Identification	Stakeholder
	No public comment was submitted

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Section 9.0

Previously Discussed Items

Eteplirsen for the Treatment of Duchenne Muscular Dystrophy
November, 2017

Question: How should eteplirsen (Exondys 51) for the treatment of Duchenne muscular dystrophy (DMD) be prioritized?

Question source: HERC, Pharmacy and Therapeutics (P&T) staff, OHA leadership

Issue: At the September, 2017 VBBS meeting, the VBBS voted unanimously to place eteplirsen (Exondys 51) on line 660 due to lack of evidence of efficacy. The P&T drug review of etplirsen was reviewed, and the discussion amongst VBBS members was that there was insufficient evidence of effectiveness shown in the 3 trials to date of the drug. There was testimony at the September meeting from an expert on Duchenne muscular dystrophy, Dr. Erika Finanger, as well as from several families affected by the disease, regarding their experiences with eteplirsen. Representatives from Sarepta Pharmaceuticals spoke to the fact that the drug has FDA approval. It was noted that with current indications an estimated 3-4 OHP patients would qualify for this medication based on having the exon 51 mutation form of Duchenne muscular dystrophy. The subcommittee expressed compassion for the DMD community and noted that there was need for improved care for that condition.

The VBBS recommendation for placing eteplirsen on line 660 was discussed at the September, 2017 HERC meeting. At the HERC meeting, the HERC voted 8-1 to table the eteplirsen decision until several issues raised at the HERC meeting could be addressed. These issues and the additional information requested are outlined below.

1) The HERC heard testimony from Mike Donabedian of Sarepta Pharmaceuticals that P&T had removed the age requirement which had restricted the drug to those over 5 years of age and removed the requirement for ambulatory statues before voting to send the topic to HERC for consideration of placement below the funding line. He asked how P&T could vote to improve access to the drug while sending it to HERC to potentially be placed on an unfunded line. HERC staff has consulted with P&T staff, and the explanation for this apparent discrepancy is that P&T could not make distinctions about what patient groups might obtain benefit from eteplirsen based on the very limited published clinical data and therefore felt that their PA criteria needed to follow the wording of the FDA approval. The P&T did not have any intention of implying by this change that they thought eteplirsen should be prioritized above or below the funding line. This change was simply to align PA criteria with FDA labeling per usual procedure. The P&T makes recommendations for prior-authorization criteria and preferred drug status on the Practitioner Managed Prescription Drug Plan, which are the extent of their decision-making. HERC uses the P&T drug evaluation reports to make OHP prioritization decisions.
2) The HERC heard testimony from families and advocates that there were patient-centered outcomes that were reported to the FDA via family testimony that was not included in the VBBS summary or discussion. HERC staff have reviewed the FDA transcript from the April, 2016 hearing on eteplirsen. The following is the most pertinent information included on patient-centered outcomes reported by family members:
    a. Page 125: “Through social media requests, 8 of the 12 participants in study 202 agreed to be interviewed. All of these boys were over the age of 7 and in the decline phase of ambulation. And importantly, we interviewed the 3 largest decliners in the study, including the 2 patients who lost ambulation early and a boy who broke his tibia. These interviews took place after the boys had been receiving therapy for 3 years. We also

interviewed 3 boys from study 204. In total, 11 boys participated. For the boys that we interviewed, who were all between the ages of 10 and 13 and on drug for over 3 years, we saw a decrease in spontaneous falls, the ability to walk after a fracture, and the stabilization or improvement in fatigue, and the maintenance of ADLs in the non-ambulatory boys."

HERC staff have consulted with P&T staff. The non-published, family-derived information on eteplirsen summarized above or other information contained in the FDA transcript would not be considered to be of high enough quality to be considered in a DERP or a P&T review and would not change the P&T recommendation on this medication.

Additionally, the P&T report noted that in their review of the second published study on eteplirsen, "All patients treated with eteplirsen had progressive decline in other functional outcomes including NSAA scores with no apparent difference from the untreated historical control."

3) The HERC heard testimony from families that there were no reported side effects of eteplirsen. The FDA Adverse Events Reporting System was queried:
    a. 13 cases with a total of 23 adverse reactions were reported in 2016 and 2017:
        i. 3 deaths
        ii. 6 administrative site reactions
        iii. 6 respiratory disorders
        iv. 5 cardiac disorders
        v. 4 infections
        vi. 3 procedural complications
        vii. 2 skin and subcutaneous disorders
        viii. 2 vascular disorders
        ix. 2 other
        x. 1 psychiatric disorder
        xi. 1 musculoskeletal disorder
        xii. 1 hepatobiliary disorder

    It cannot be discerned from the FDA database whether these adverse reactions were due to eteplirsen or due to the natural history of DMD, like all such adverse event reporting data. It cannot be discerned if the rates of these adverse reactions were higher than expected for the DMD population.
4) The HERC requested information on other insurance coverage of eteplirsen. HERC staff has determined that Anthem does not cover eteplirsen and considers it experimental. Aetna and Cigna cover eteplirsen. Aetna restricts to ambulatory patients, and withdrawals approval if the patient loses time on the 6 min walk test or becomes non-ambulatory. Cigna did not have any identified coverage criteria. Arkansas Medicaid is not covering eteplirsen due to considering it experimental (personal communication). According to DERP, Alabama, Arizona, California, Colorado, Minnesota, Missouri, New York, Oklahoma, and Washington. Arizona Medicaid all cover eteplirsen with or without restrictions. Some Medicaid programs restrict eteplirsen prescriptions to those written by neurologists, some restrict the initial length of prescribing. Minnesota Medicaid requires patients to not be enrolled in ongoing Exondys 51 clinical trials. California Medicaid requires patients receiving an initial prescription of eteplirsen to be 4 years or older. Washington Medicaid requires patients receiving an initial eteplirsen prescription to be

7 years or older. Missouri Medicaid requires patients to be ambulatory. Washington Medicaid and UnitedHealthcare require patients to walk at least 300 meters in the 6-minute walk test. Missouri Medicaid specifies that patients prescribed eteplirsen must be concurrently receiving glucocorticoid therapy. Before initiating an eteplirsen prescription, Washington Medicaid requires patients to have been on glucocorticoid therapy for at least 24 weeks. California Medicaid grant continuation for members who have "responded to therapy." UnitedHealthcare continues therapy if medical records confirm that a patient is ambulatory without an assistive device. Washington Medicaid allows for continuation if patients are ambulatory, stable with pulmonary and cardiac function, and continue glucocorticoid therapy. Missouri Medicaid allows for continuation if patients "maintain or demonstrate a less than expected decline." Minnesota Medicaid has a similar standard for patients to have "maintained or increased in physical function from baseline or progression has been slower than otherwise would have been expected."

5) There was discussion at the HERC meeting about other expert bodies reviewing eteplirsen. HERC staff have determined that NICE is reviewing this medication, with outcomes that were expressed to be of interest to the HERC, with expected completion of the review in 2018. These outcomes include:
    a. walking ability (ambulation)
    b. muscle function
    c. muscle strength (upper and lower)
    d. ability to undertake activities of daily living
    e. cardiac function
    f. lung function
    g. time to wheelchair
    h. number of falls
    i. time to scoliosis
    j. mortality
    k. adverse effects of treatment health-related quality of life (for patients and carers [caregivers]).

Eteplirsen for the Treatment of Duchenne Muscular Dystrophy
November, 2017

Evidence (included from the September 2017 meeting materials)

1) **eteplirsen (Exondys 51)**
    a. General: In approximately 13% of patients with DMD, the cause is a mutation in exon 51 of the pre-mRNA. Eteplirsen binds to exon 51 of dystrophin pre-mRNA leading to exclusion of this exon and formation of a partially functional, truncated dystrophin protein.
    b. Eteplirsen has conditional FDA approval with a specification in the medication labeling that it "has no proven clinical benefit." Final FDA approval will depend on the results of a large ongoing trial expected to have published results in the next few years.
    c. Evidence (see the P&T medication review)
        i. 3 studies (N=25); 1 randomized placebo controlled trial and 2 open-label studies. All subjects were ambulatory. Primary outcome was dystrophin protein level in muscle tissue. Clinical outcomes included change in 6-minute walking distance. All studies found to be poor quality with significant methodologic flaws.
            1. Study 1: RCT of 12 pts for 24 weeks (randomized (1:1:1) to eteplirsen 50 mg/kg weekly, eteplirsen 30 mg/kg weekly, or placebo). No difference was observed in the 6-minute walk distance at 24 weeks compared to placebo. Change in dystrophin level from baseline could not be assessed.
            2. Study 2: extension of study 1 to 3.5 years. Control patients from study 1 were treated with eteplirsen (50 mg/kg weekly or 30 mg/kg weekly) and all patients were compared to historical controls from Belgium and Italy. Patients treated with eteplirsen had an average dystrophin level that was 0.93% of the normal protein level in healthy patients. No significant difference in 6 minute walk test was found at 48 weeks. Overall, compared to the historical control, patients treated with eteplirsen experienced a benefit of 162 meters at 36 months (3 years) in the 6MWT (p=0.0005). The manufacturer also claimed that only 2 patients (16.7%) treated with eteplirsen lost ambulation over 4 years compared to 76.9% (10/13) of untreated historical controls. However, when results are evaluated as a function of age, 6 patients (4 less than 14 years of age and 2 still ambulatory between 13 and 14 years of age) appear to have similar disease progression and functional decline compared to their age-matched, untreated historical controls. All patients treated with eteplirsen had progressive decline in other functional outcomes including NSAA scores with no apparent difference from the untreated historical control.
                a. Note: "There is a high risk of selection, performance, detection, and reporting bias in this study and efficacy results should not be considered in the decision-making process."
            3. Study 3: an ongoing, unpublished, interim analysis of an open-label study trial of 13 patients treated with eteplirsen 30 mg/kg weekly for 48 weeks. Mean change in dystrophin level from baseline to 48 weeks was

0.28% of normal (0.16% at baseline vs. 0.44% at 48 weeks; p=0.008). Change in dystrophin protein level has not been validated as a surrogate outcome in DMD and there is no evidence to support it is correlated to clinical outcomes. The minimum change in dystrophin level which may result in a clinical improvement has not been established. No functional outcomes were evaluated in this study.

4. P&T study critique: Efficacy of eteplirsen for DMD remains to be established. Data from Western blot analysis suggests that some patients may not respond to treatment with little to no improvement in dystrophin levels. The FDA recommended further post-marketing studies to evaluate efficacy at higher doses. Studies failed to demonstrate improvement in functional outcomes even in patients treated for more than 4 years, and labeling for eteplirsen specifies that a clinical benefit has not been established. Furthermore, though a slight change in level of dystrophin level was observed (<1% of normal), changes did not correlate with any clinical improvement. It remains to be determined if changes in dystrophin correlate to clinical outcomes, and the FDA has required further studies to evaluate functional improvements in patients with DMD. FDA approval of eteplirsen was highly controversial because it conflicted with the recommendation by the external advisory committee who expressed multiple concerns with the studies, including: industry funding, blinding procedures, assays used, small sample size, and very minimal change from baseline.
5. Safety: The safety population included a total of 114 patients treated with at least one dose of eteplirsen. Only 36 patients have been treated for more than 6 months and 12 have been treated for more than 1 year. Serious adverse events occurred in 6 patients (5.3%) and were consistent with expected events for a population of patients with DMD.

ii. Summary: Efficacy of eteplirsen for DMD remains to be established. The studies published to date were found to have serious methodological flaws. Studies failed to demonstrate improvement in functional outcomes even in patients treated for more than 4 years, and labeling for eteplirsen specifies that a clinical benefit has not been established. Furthermore, though a slight change in level of dystrophin level was observed (<1% of normal), changes do not correlate with any clinical improvement. Additionally, there are significant methodological concerns and a high risk of bias in available studies.

d. Wholesale Acquisition Cost:

60923028410 - EXONDYS 51	ETEPLIRSEN INTRAVEN 500MG/10ML VIAL	09 - WHN	$800.00000
60923036302 - EXONDYS 51	ETEPLIRSEN INTRAVEN 100 MG/2ML VIAL	09 - WHN	$800.00000

1. Note: vials are single use. The cost is $800/ml regardless of vial size

2. A 25kg patient dosed at 30 mg/kg/week would require 750mg/wk (one 500mg vial at $8000 + three 100mg vials at $4800), giving an estimated yearly cost of $665,600

HERC staff summary:
Eteplirsen has evidence of a small (<1%) increase in the surrogate outcome of dystrophin levels, but this increase does not have any known clinical significance. Additionally, there is no published evidence of improved clinical outcomes such as 6 minute walk distances, hospitalizations, etc. with eteplirsen treatment. This is a very high cost medication. There are adverse events reported to the FDA, including death, although it is unclear whether these adverse events are due to the medication or the natural history of the disease. The family reported patient-centered outcomes have not been peer reviewed or published and therefore would not be considered by the P&T in their drug class review and would not change the P&T recommendations. NICE is conducting a review with patient centered outcomes expected within the next year.

Eteplirsen for the Treatment of Duchenne Muscular Dystrophy
November, 2017

HERC staff recommendations:

1) Make no change to the prior VBBS recommendation to prioritize eteplirsen (Exondys 51) to line 660 and add the following entry to GN173 due to no established clinical benefit based on published studies. Reconsider this decision when the NICE review on eteplirsen is published.

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

The following treatments are prioritized on Line 660, CONDITIONS FOR WHICH CERTAIN TREATMENTS HAVE NO CLINICALLY IMPORTANT BENEFIT OR HAVE HARMS THAT OUTWEIGH BENEFITS; UNPROVEN TREATMENTS, for the conditions listed here:

CONDITION	**CPT/HCPCS Code**	**TREATMENT**	**Rational**	**Date of Last Review/Link to Meeting Minutes**
Duchenne muscular dystrophy		eteplirsen (Exondys 51)	No clinically important benefit	November, 2017

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Proposed Highly Specialised Technology Evaluation

Eteplirsen for treating Duchenne muscular dystrophy

Draft scope (pre-referral)

Draft remit/evaluation objective

To evaluate the benefits and costs of eteplirsen within its licensed indication for treating of Duchenne muscular dystrophy for national commissioning by NHS England.

Background

Muscular dystrophies are a group of genetic disorders which cause muscle weakness and progressive disability. Duchenne muscular dystrophy is one of the most common and severe forms. It is caused by the presence of different types of mutations on the X-chromosome in the gene for dystrophin, a protein that is important for maintaining normal muscle structure and function. The main types of mutation are deletions (where part of the gene is deleted), insertions (where an additional piece of DNA is inserted into the gene), duplications (when part of the gene is repeated) and point mutations (when individual letters in the DNA code are changed, altering the information needed to produce a protein). These mutations cause muscle fragility that progressively leads to weakness and loss of walking ability during childhood and adolescence. About 60% of Duchenne muscular dystrophy is due to deletions within the dystrophin gene. In this case, part of the gene is deleted and a technique called splicing can be used to restore a functional genetic code. The genetic code for dystrophin is dispersed over exons. Exons are connected by introns, which do not contain the functional genetic code. When a part of the gene is deleted, splicing is a process that removes introns so that the protein translation between exons can be maintained.

Boys only have one X chromosome, and thus one single copy of the dystrophin gene, hence they have a much higher probability of developing Duchenne muscular dystrophy than girls. A very small number of girls develop Duchenne muscular dystrophy.

Initial symptoms of Duchenne muscular dystrophy usually present between the ages of 1 and 3 years and children with the disease may appear weaker than other children, and have difficulty walking, standing, or climbing stairs, and may have behavioural or learning difficulties. After the age of 12 most children will need to use a wheelchair. During adolescence, breathing muscles can weaken, causing shallow breathing and a less effective cough mechanism, which can lead to chest infections. Weakness of the heart muscle, called cardiomyopathy, occurs in almost all patients by the age of 18. The life expectancy of people with Duchenne muscular dystrophy depends on

how quickly and intensely muscle weakness progresses and on how it affects the patient's ability to breathe. The average lifespan is less than 30 years.

The incidence of Duchenne muscular dystrophy is approximately 1 in 3600–6000 male live births. Approximately 11–13% of people with Duchenne muscular dystrophy is expected to have a deletion of exon 51 and therefore would be eligible for drisapersen.

In the ambulant population (people who are able to walk), increasing the time a patient is able to walk is one of the major aims of treatment. In the non-ambulant population delaying the loss of further muscle function is one of the major aims of treatment. Current treatment options do not treat the underlying cause of the disease and focus on alleviating symptoms and maintaining muscle strength. Interventions may include the use of corticosteroids (associated with several side effects), creatine supplementation and physical aids (such as wheelchairs, leg braces or crutches), exercise, physiotherapy, and occasionally orthopaedic surgery. In addition, other supportive treatments such as dietetic advice, prevention and treatment of bone fragility and the management of complications of long-term steroid therapy are required. In the later stages of Duchenne muscular dystrophy, cardiac management and treatments to help improve breathing and increase oxygen levels may be needed if lung function becomes impaired.

The technology

Eteplirsen (brand name unknown, Sarepta Therapeutics) is a phosphorodiamidate morpholino oligomer and is designed to skip an exon (exon 51) of the dystrophin gene to correct the reading frame of dystrophin transcripts for the synthesis of a shorter but functional dystrophin protein. It is administered by intravenous infusion.

Eteplirsen does not currently have a marketing authorisation in the UK for treating Duchenne muscular dystrophy. It has been studied in clinical trials in ambulant males aged 7 years and older who have Duchenne muscular dystrophy resulting from a mutation that was correctable by exon 51 skipping.

Intervention(s)	Eteplirsen
Population(s)	People with Duchenne muscular dystrophy that is amenable to treatment with exon 51 skipping
Comparators	Established clinical management without eteplirsen
Outcomes	The outcome measures to be considered include: • walking ability (ambulation) • muscle function • muscle strength (upper and lower)

	• ability to undertake activities of daily living • cardiac function • lung function • time to wheelchair • number of falls • time to scoliosis • mortality • adverse effects of treatment • health-related quality of life (for patients and carers).
Nature of the condition	• disease morbidity and patient clinical disability with current standard of care • impact of the disease on carer's quality of life • extent and nature of current treatment options
Impact of the new technology	• clinical effectiveness of the technology • overall magnitude of health benefits to patients and, when relevant, carers • heterogeneity of health benefits within the population • robustness of the current evidence and the contribution the guidance might make to strengthen it • treatment continuation rules (if relevant)
Cost to the NHS and Personal Social Services (PSS), and Value for Money	• budget impact in the NHS and PSS, including patient access agreements (if applicable) • robustness of costing and budget impact information • technical efficiency (the incremental benefit of the new technology compared to current treatment) • productive efficiency (the nature and extent of the other resources needed to enable the new technology to be used) • allocative efficiency (the impact of the new technology on the budget available for specialised commissioning)

Impact of the technology beyond direct health benefits, and on the delivery of the specialised services	• whether there are significant benefits other than health • whether a substantial proportion of the costs (savings) or benefits are incurred outside of the NHS and personal and social services • the potential for long-term benefits to the NHS of research and innovation • staffing and infrastructure requirements, including training and planning for expertise.
Other considerations	Guidance will only be issued in accordance with the marketing authorisation. The use of eteplirsen is conditional on the presence of mutations in the dystrophin gene that are amenable to treatment with exon 51 skipping. The economic modelling should include the costs associated with diagnostic testing for mutations in the dystrophin gene that are amenable to treatment with exon 51 skipping in people with Duchenne muscular dystrophy who would not otherwise have been tested. A sensitivity analysis should be provided without the cost of the diagnostic test.
Related NICE recommendations and NICE Pathways	Ataluren for treating Duchenne muscular dystrophy with a nonsense mutation in the dystrophin gene (July 2016) NICE Highly Specialised Technologies guidance 3. To be reviewed in 2020. Quality Standard in development: Neurological problems (relatively uncommon neurological problems e.g. muscular dystrophy). Status: Referred. Earliest anticipated date of publication: to be confirmed.
Related National Policy	Diagnostic service for rare neuromuscular disorders (adults and children) – chapter 48 http://www.england.nhs.uk/wp-content/uploads/2012/12/pss-manual.pdf Specialist neuroscience services for children and young people – chapter 119 http://www.england.nhs.uk/wp-content/uploads/2012/12/pss-manual.pdf Department of Health, NHS Outcomes Framework 2014-2015, Nov 2013.

	https://www.gov.uk/government/uploads/system/uploads/attachment_data/file/256456/NHS_outcomes.pdf Diagnosis and management of Duchenne muscular dystrophy, Duchenne Muscular Dystrophy Care Considerations Working Group, 2011 (NICE Accredited) http://www.nice.org.uk/Media/Default/About/accreditation/accreditation-decisions/Duchenne-Muscular-Dystrophy-Care-Considerations-Working-Group-final-decision.pdf

Questions for consultation

Have all relevant comparators for eteplirsen been included in the scope? Which treatments are considered to be established clinical practice in the NHS for treating Duchenne muscular dystrophy with an exon 51-skip amenable mutation in the dystrophin gene?

The clinical trials were conducted in males aged 7 years and older with Duchenne muscular dystrophy resulting from a mutation correctable by exon 51 skipping.

- How this type of mutation currently tested in the NHS?
- Are validated tests readily available?
- Is it tested routinely in current clinical practice?
- Please describe any existing services in England for the diagnosis and management of this condition.

Are there any subgroups of people in whom the technology is expected to provide greater clinical benefits or more value for money, or other groups that should be examined separately?

NICE is committed to promoting equality of opportunity, eliminating unlawful discrimination and fostering good relations between people with particular protected characteristics and others. Please let us know if you think that the proposed remit and scope may need changing in order to meet these aims. In particular, please tell us if the proposed remit and scope:

- could exclude from full consideration any people protected by the equality legislation who fall within the patient population for which eteplirsen will be licensed;
- could lead to recommendations that have a different impact on people protected by the equality legislation than on the wider population, e.g. by

making it more difficult in practice for a specific group to access the technology;

- could have any adverse impact on people with a particular disability or disabilities.

Please tell us what evidence should be obtained to enable the Highly Specialised Technologies Evaluation Committee to identify and consider such impacts.

Do you consider the technology to be innovative in its potential to make a significant and substantial impact on health-related benefits and how it might improve the way that current need is met (is this a 'step-change' in the management of the condition)?

NICE intends to evaluate this technology through its Highly Specialised Technologies Programme. We welcome comments on the appropriateness of evaluating this topic through this process. (Information on the Institute's Highly Specialised Technologies interim methods and evaluation processes is available at: http://www.nice.org.uk/media/DE4/9A/HSTCombinedInterimProcessMethods.pdf.

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Drug Use Research & Management Program
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Salem, Oregon 97301-1079
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New Drug Evaluation: Eteplirsen injection, intravenous

Date of Review: July 2017
Generic Name: eteplirsen injection

End Date of Literature Search: 06/02/2017
Brand Name (Manufacturer): Exondys 51 (Sarepta Therapeutics, Inc.)
Dossier Received: Yes

Research Questions:

1. What is the efficacy of eteplirsen compared to placebo or currently available treatments of Duchenne Muscular Dystrophy (DMD)?
2. Is eteplirsen safe for treatment of DMD?
3. Are there any subgroups (based on age, gender, ethnicity, comorbidities, disease duration or severity) that would particularly benefit or be harmed from treatment with eteplirsen?

Conclusions:

- Efficacy of eteplirsen for DMD remains to be established. Studies failed to demonstrate improvement in functional outcomes even in patients treated for more than 4 years, and labeling for eteplirsen specifies that a clinical benefit has not been established.[1] Furthermore, though a slight change in level of dystrophin level was observed (<1% of normal), changes do not correlate with any clinical improvement. Additionally, there are significant methodological concerns and a high risk of bias in available studies.
- There is insufficient evidence that eteplirsen treatment in patients with DMD is associated with any clinical change in symptoms or functional status. Functional improvement was primarily evaluated using the 6-minute walk test (6MWT). In a single study of 12 patients, no difference was observed between patients treated with eteplirsen and placebo in the 6MWT at 24 or 48 weeks.[1] A long-term extension study evaluating functional improvement assessed with the 6MWT or North Star Ambulatory Assessment (NSAA) over 36 months compared eteplirsen to a historical control group.[2] However, significant limitations associated with this study including differing baseline characteristics between groups, inability to control for potential confounders, and differences in assessment methods limit confidence in these results. Labeling for eteplirsen specifies that a clinical benefit has not been established.[3]
- Eteplirsen was primarily evaluated in 2 studies (n=24) which examined change in the level of dystrophin protein. After 3.5 years of treatment, patients treated with eteplirsen had an average dystrophin level that was 0.93% of the normal protein level in healthy patients (as evaluated by Western blot).[1] Mean change in dystrophin level from baseline to 48 weeks was 0.28% of normal (0.16% at baseline vs. 0.44% at 48 weeks; p=0.008).[1] Change in dystrophin protein level has not been validated as a surrogate outcome in DMD and there is no evidence to support it is correlated to clinical outcomes. The minimum change in dystrophin level which may result in a clinical improvement has not been established.
- There is insufficient evidence to evaluate safety of eteplirsen for treatment of DMD. The safety population included a total of 114 patients treated with at least one dose of eteplirsen. Only 36 patients have been treated for more than 6 months and 12 have been treated for more than 1 year.[1] Serious adverse events occurred in 6 patients (5.3%) and were consistent with expected events for a population of patients with DMD.[1]
- There is insufficient evidence to evaluate differences in specific populations or subgroups.

Author: Sarah Servid, Pharm.D.
Date: July 2017

Recommendations:

- Recommend implementation of prior authorization criteria limiting use to the population studied and requiring maintained functional status with continuation of therapy (**Appendix 2**).
- Due to the lack of evidence supporting clinical efficacy of eteplirsen for the treatment of Duchenne muscular dystrophy, consider referral of eteplirsen to the Health Evidence Review Commission (HERC) for funding placement as a medication with high cost and no clinically meaningful benefit.

Background:

Duchenne muscular dystrophy (DMD) is a rare X-linked genetic disorder which results in the absence of a functional dystrophin protein. Duchenne's is the most common type of muscular dystrophy occurring in approximately 1 in 5000 to 7250 patients age 5 to 24 years.[1,4] Currently, in the Oregon Health Plan (OHP) population, approximately 70 fee-for-service patients and more than 300 patients enrolled in coordinated care organizations have a diagnosis of muscular dystrophy. Available claims data for OHP is unable to distinguish between patients with various types of muscular dystrophy. Based on this data and the estimated prevalence of mutations amenable to exon 51 skipping, approximately 3-4 OHP patients may be eligible for this medication. Without a functional dystrophin protein, muscle fibers degenerate and are eventually replaced with adipose and fibrotic tissue.[1] Patients with DMD experience progressive muscle deterioration leading to pulmonary problems, dilated cardiomyopathy, arrhythmias, and increased risk for thrombotic events. In many patients, these complications lead to wheelchair dependence between the ages of 8-16 and death before the age of 20.[1,5] Only 25% of patients remain ambulatory by age 16.[1] There is currently no curative treatment, and therapy focuses on improving symptoms, enhancing quality of life, and decreasing disease progression.[4] Guidelines from the American Academy of Neurology recommend glucocorticoids as first-line treatment in children over 5 years of age to improve muscle and pulmonary function and reduce risk of scoliosis.[5] Other non-pharmacological therapies which are often essential in disease management include physical therapy and use of support devices such as braces and wheelchairs.[4] As the disease progresses, mechanical ventilation and spinal surgery may be used to improve pulmonary function and decrease pain from scoliosis and vertebral fractures.[4]

Recently the FDA approved eteplirsen, an oligonucleotide indicated for patients with DMD who have a confirmed mutation of the DMD gene that is amenable to exon 51 skipping.[3] In approximately 13% of patients with DMD, exon 51 is included in pre-mRNA and one or more nearby exons are deleted.[1] This results in a shift in the reading-frame as the protein is formed and leads to reduction or absence of dystrophin protein. Eteplirsen binds to exon 51 of dystrophin pre-mRNA leading to exclusion of this exon, partially restoring the reading-frame, and forming a potentially functional, truncated dystrophin protein. In untreated patients with DMD, documented dystrophin levels typically range from 0 to 0.4% of normal healthy patients.[1] Experts suggests that dystrophin levels less than 3% of normal are typically associated with a phenotype of DMD.[1] It is unclear whether increases in dystrophin protein level in patients with DMD correlate to clinical outcomes. Similarly, the minimum change in dystrophin level which may result in a clinical improvement has not been established. Some experts suggest that very minimal improvements may constitute a beneficial change in dystrophin level while others suggest that dystrophin levels at 10-20% of normal would likely correlate to clinically significant changes in muscle symptoms or function.[1,6] In patients with Becker muscular dystrophy, a less severe form of the muscular dystrophy, dystrophin protein levels are on average 80% of normal.[1]

Efficacy outcomes which are clinically important in patients with DMD include muscle strength, functional status, quality of life, disease progression, and mortality. Functional improvement is often evaluated using the 6-minute walk test (6MWT) and the North Star Ambulatory Assessment (NSAA) score. The 6MWT evaluates the distance a patient is able to walk in 6 minutes and evaluates both function and endurance.[7] In healthy children less than 7 years of age, the distance patients are able to walk is expected to remain stable or improve over time with estimated mean walk distances ranging from 500-700 meters.[2,8,9] The minimum clinically important difference in the 6MWT for patients with DMD is approximately 30 meters.[7] The NSAA evaluates 17 functional activities including standing, walking, standing up from a chair, standing on 1 leg, climbing/descending step, moving from lying to sitting, rising from the floor, jumping, hopping,

and running.[1] Each item is evaluated on a 3 point scale with a total score ranging from 0 to 34. NSAA scores less than 16 are more often correlated with 6MWT of less than 300 meters and scores greater than 30 correlate moderately with 6MWT of more than 400 meters.[10] The NSAA is considered a more comprehensive measure of functional status compared to other functional assessments, but score is often very dependent on patient effort.[1] The minimum clinically important difference in NSAA score has not been determined. Other functional assessments include timed measures of rising from a sitting or supine position, 10-meter run/walking time, or time to climb 4 stairs.[7]

See **Appendix 1** for **Highlights of Prescribing Information** from the manufacturer, indications, dosage and administration, formulations, contraindications, warnings and precautions, adverse reactions, drug interactions and use in specific populations.

Clinical Efficacy:
Eteplirsen was evaluated in 3 poor quality studies with significant flaws (1 randomized placebo controlled trial and 2 open-label studies). All patients in these trials were ambulatory and on a stable dose of corticosteroids for at least 6 months. Study 1 was a double-blind, randomized, dose-response, placebo-controlled study for 24 weeks. It included 12 white, male, pediatric patients (age range 7-13, mean 9.4 years) with a mean 6-minute walking distance at baseline of 363 meters (substantially decreased from the mean distance of 500-700 meters expected in healthy children).[11] Patients were randomized (1:1:1) to eteplirsen 50 mg/kg weekly, eteplirsen 30 mg/kg weekly, or placebo.[11] After 24 weeks, patients were enrolled in a long-term open-label extension study (Study 2). In this study, patients initially randomized to the placebo group were re-randomized to eteplirsen 30 or 50 mg/kg/week for which data is available up to 240 weeks (4.6 years).[1] The primary outcomes for these studies included the level of dystrophin protein in muscle tissue (measured as a percentage of the expected normal levels in healthy patients without DMD) and change in the 6MWT.[11] Study 3 is an ongoing, unpublished, interim analysis of an open-label study which evaluated the change in dystrophin levels for 13 male patients treated with eteplirsen 30 mg/kg weekly for up to 48 weeks.[1]

No difference was observed in the 6MWT at 24 weeks compared to placebo.[11] In addition, the long-term extension study failed to demonstrate a statistically significant difference in 6MWT upon comparison to placebo at 48 weeks.[1] Since all patients were re-randomized to treatment, the manufacturer attempted to compare eteplirsen to a control group generated from two DMD natural history cohorts of patients in an open-label extension of the primary study. Patients were matched to 13 historical controls based on corticosteroid use, available longitudinal data for the 6MWT, age (less than or greater than 7 years), and genotype.[1,2] Patients were not matched on the basis of the 6MWT distance though mean distance was similar between groups at baseline (363 vs. 358 meters).[2] Overall, compared to the historical control, patients treated with eteplirsen experienced a benefit of 162 meters at 36 months (3 years) in the 6MWT ($p=0.0005$).[1] The manufacturer also claimed that only 2 patients (16.7%) treated with eteplirsen lost ambulation over 4 years compared to 76.9% (10/13) of untreated historical controls.[1] However, when results are evaluated as a function of age, 6 patients (4 less than 14 years of age and 2 still ambulatory between 13 and 14 years of age) appear to have similar disease progression and functional decline compared to their age-matched, untreated historical controls.[1] All patients treated with eteplirsen had progressive decline in other functional outcomes including NSAA scores with no apparent difference from the untreated historical control.[1]

There are significant concerns and inherent limitations of using a historical control group and conclusions cannot be made from this fatally flawed study. Performance on the 6MWT is susceptible to expectation bias and coaching which significantly confounds the benefit observed in an open-label trial when compared to a historical cohort. For example, in patients treated with eteplirsen, the maximum distance achieved in the 6MWT was recorded, whereas the standard approach for historical controls was to classify patients as non-ambulatory if they were unable to complete the 6MWT.[1] If a standard assessment for the 6MWT was applied to both groups, several patients treated with eteplirsen may have been classified as non-ambulatory. It is also unclear whether physical therapy programs were similar between the treatment group and historical control.[1,2] In addition, there were significant differences between groups in steroid

regimens used and the mean age at initiation of steroid treatment (6.4 years in historical control vs. 5.2 years in treatment group).[1] These differences affect interpretation and bias results in favor of eteplirsen treatment. Historical control patients also had a lower mean NSAA scores at baseline, indicating greater disease severity and could bias results in favor of eteplirsen treatment.[1] The historical control population was selected after publication of results in eteplirsen trials and was not specified *a priori.* There is a high risk of selection, performance, detection, and reporting bias in this study and efficacy results should not be considered in the decision-making process.

The additional outcome in Study 1 and 2 was mean change in percent of dystrophin-positive fibers from baseline.[1] Biopsies through week 48 were collected from the biceps and week 180 biopsies were collected from the deltoid.[1] Because different muscle groups are known to have varying levels of dystrophin protein, comparisons of the deltoid biopsy at week 180 to earlier samples taken from the biceps are difficult to interpret. Evaluation of a different muscle group may result in varying levels of dystrophin protein. Dystrophin level was assessed using both immunofluorescence and Western blot techniques. These provide very different insight into perceived benefit of eteplirsen. Western blot is a quantitative method whereas immunofluorescence is used to identify localization of a protein in a particular tissue and is considered to be less quantitative.[1] Due to significant methodological and technical issues with the initial analyses, the FDA concluded that the results were unreliable and uninterpretable.[12] The FDA required a blinded re-analysis of available biopsies by 3 independent evaluators.[1]

After 3.5 years of treatment, patients treated with eteplirsen (both 30 and 50 mg/kg/week) had an average dystrophin level that was 0.93% of the normal protein level in healthy patients (as evaluated by Western blot).[1] Approximately one-third of patients had no change in dystrophin level or changes that were below the level of quantification (0.24% of normal).[1] Only one patient had a dystrophin level greater than 2% and none had a level greater than 3% of normal.[1] Overall, re-analyzed biopsies did not confirm the initial study findings and did not support the dose dependent effect seen in earlier trials. In addition, there was a poor correlation between results of immunofluorescence and Western blot analyses, and results of the immunofluorescent tests varied between treatment groups.

Despite re-analysis of biopsy samples, there are several significant limitations which should be taken into consideration. Only 3 patients had baseline samples that were evaluable upon re-analysis, and therefore, the change in dystrophin level from baseline could not be assessed.[1] Furthermore, immunofluorescent samples at 48 weeks (11 months) and Western blot analysis at 180 weeks (3.5 years) were processed differently and were not comparable with earlier samples.[1] There was also significant intra-patient variability upon Western blot analysis at 180 weeks. At least 3 patients had analyses which differed by more than 0.7% of normal between samples evaluated at 180 weeks.[1] Furthermore, the methods used to select the group of historical controls is unclear, and they may not represent a random sample of comparative patients, decreasing confidence in the results which indicate protein level was only 0.93% of normal.[1] In addition, biopsy samples were stored for approximately 3 years before re-analyzed and the stability of the protein over time was not evaluated.[1]

Study 3 is an ongoing, unpublished, open-label study including 13 male patients treated with eteplirsen 30 mg/kg weekly for up to 48 weeks (mean age of 8.9 years).[1] Data was available from 12 of these patients.[1] The primary outcome evaluated change in dystrophin protein level (evaluated using Western blot analysis). No functional outcomes were evaluated in this study. Protein levels that were below the level of quantification (0.24%) were analyzed using several imputation methods including minimum (0%), maximum (0.24%), and actual measured values. Results were consistent between all analyses, and demonstrated statistically significant differences in dystrophin level compared to baseline.[1] Mean change in dystrophin level from baseline to 48 weeks was 0.28% of normal (0.16% at baseline vs. 0.44% at 48 weeks; p=0.008).[1] At 48 weeks, approximately 60% of patients treated in this study had no change in dystrophin level or had a change less than 0.25% compared to the normal level in a health patient. Only one patient had a dystrophin level greater than 1% and none had a level greater than 2% of normal.[1] These changes in dystrophin levels are not clinically significant and do not translate into any clinical meaningful benefit.

Efficacy of eteplirsen for DMD remains to be established. Data from Western blot analysis suggests that some patients may not respond to treatment with little to no improvement in dystrophin levels.[1] The FDA recommended further post-marketing studies to evaluate efficacy at higher doses.[1] Studies failed to demonstrate improvement in functional outcomes even in patients treated for more than 4 years, and labeling for eteplirsen specifies that a clinical benefit has not been established.[1] Furthermore, though a slight change in level of dystrophin level was observed (<1% of normal), changes did not correlate with any clinical improvement. It remains to be determined if changes in dystrophin correlate to clinical outcomes, and the FDA has required further studies to evaluate functional improvements in patients with DMD.[3] FDA approval of eteplirsen was highly controversial because it conflicted with the recommendation by the external advisory committee who expressed multiple concerns with the studies, including: industry funding, blinding procedures, assays used, small sample size, and very minimal change from baseline.

Clinical Safety:

The safety population included a total of 114 patients treated with at least 1 dose of eteplirsen. Only 36 patients have been treated for more than 6 months and 12 have been treated for more than 1 year.[1] Because the population is small and the majority of these trials were not placebo-controlled, there is limited data available regarding adverse effects and safety. Serious adverse events occurred in 6 patients (5.3%) and included wound infection, vomiting, fractures, decreased oxygen saturation, and viral lymphadenitis.[1] All events were thought to be unrelated to treatment. One patient, who had preexisting cardiomyopathy, experienced a decreased left ventricular ejection and discontinued treatment.[1] In general, serious and severe adverse effects were consistent with expected events for a population of patients with DMD. However, there is insufficient data to assess short-term or long-term safety of eteplirsen.

Table 1. Pharmacology and Pharmacokinetic Properties.[3]

Parameter	
Mechanism of Action	Eteplirsen binds to exon 51 of dystrophin pre-mRNA, resulting in exclusion of this exon during mRNA processing in patients with genetic mutations that are amenable to exon 51 skipping. Skipping of exon 51 allows for formation of a truncated dystrophin protein.
Distribution and Protein Binding	Protein binding: 6-17% Volume of distribution at steady state: 600 mL/kg
Elimination	Approximately 67% of eteplirsen is renally cleared Majority of drug elimination occurred within 24 hours
Half-Life	3-4 hours
Metabolism	No hepatic metabolism apparent

Abbreviations:

Comparative Clinical Efficacy:

Clinically Relevant Endpoints:

1) Functional or symptom improvement
2) Quality of life
3) Disease progression
4) Serious adverse events
5) Study withdrawal due to an adverse event

Primary Study Endpoint:

1) Mean change in the percentage of dystrophin-positive fibers
2) Change in the 6-minute walk test at 48 weeks

Table 2. Comparative Evidence Table.

Ref./Study Design	Drug Regimens/ Duration	Patient Population	N	Efficacy Endpoints	ARR/ NNT	Safety Outcomes	ARR/ NNH	Risk of Bias/ Applicability
1. Mendell, et al. 2013.[11] Exondys 51 FDA Medical Review.[1] Exondys 51 FDA Summary Review.[12] DB, PC, Phase IIB RCT	1. Eteplirsen 30 mg/kg/ week 2. Eteplirsen 50 mg/kg/ week 3. Placebo/ delayed tx After 24 weeks patients in the placebo group were randomized to one of the treatment groups in an open label extension study up to 48 weeks. Patients have been continued in the extension study for greater than 4 years.	Demographics: - Mean age: 9.4 years - Deflazacort 18-25 mg/day: 8/12 (67%) - Prednisone: 4/12 (33%) - Mean 6MWT: 363 m (range 261-456) Key Inclusion Criteria: - Boys age 7 to 13 - Confirmed DMD deletions potentially correctable by exon 51 skipping - 6MWT of 200-400 m - On stable glucocorticoid tx for ≥24 weeks - Stable cardiac and pulmonary function Key Exclusion Criteria: - None	ITT: 1. 4 2. 4 3. 4 mITT: 1. 2 2. 4 3. 4 Attrition: All patients completed 48 weeks	Primary Endpoints (ITT):[1] Mean change in percent of dystrophin-positive fibers from baseline to 12 or 24 weeks[T]** 1. 13% 2. 2% 3. -1% P-values NR Mean change in percent of dystrophin-positive fibers from baseline to 48 weeks** 1. 9% 2. 10% 3. -1% P-values NR Mean percent of normal dystrophin at 180 weeks (SD) with Western blot analysis[12] 1. 0.96% (0.95) 2. 0.91% (0.79) Mean change in 6MWT at 48 weeks (SE) 1. -153.4 m (38.7) 2. 21 m (38.2) 3. -68.4 m (37.6) p-values NR Secondary Endpoints (ITT): Mean change in 6MWT at 24 weeks (SE) 1. -128.2 m (31.6) 2. -0.3 m (31.2) 3. -25.8 m (30.6) p-values NR	NA NA NA NA	No serious or treatment -emergent adverse effects reported at 48 weeks.	NA	**Risk of Bias (low/high/unclear)**: Selection Bias: UNCLEAR. Randomization methods and allocation concealment were unclear. Average baseline 6MWT in patients randomized to 30 mg/kg/week was ~40 m less than other groups. Performance Bias: UNCLEAR. Methods of blinding were not stated. Placebo consisted of phosphate buffered saline. Placebo or eteplirsen was diluted in normal saline and infused over 60 minutes. Detection Bias: HIGH. Biopsy samples were not processed consistently at all time points leading to unclear changes over time. Use of immunofluorescent staining was less quantitative than Western blot analysis. Re-analysis by blinded, independent pathologists (reported here) resulted in significantly differing protein levels. Analysis confirmed by Western blot at 180 weeks. Multiple methodological limitations reduce confidence in the results and limit ability to make conclusions regarding dystrophin level. Attrition Bias: HIGH. All patients remained in the study up to 48 weeks. Use of ITT appropriate. The mITT population excludes 2 patients who had rapid disease progression and became non-ambulatory despite treatment and increases in dystrophin-positive fibers. Reporting Bias: HIGH. Funding provided by Sarepta Therapeutics who was involved in data interpretation and editing the manuscript. Results of multiple post-hoc analyses emphasized. Results of immunofluorescent assays may be misleading as they describe the percent of fibers stained with an intensity ***above the background of the image*** and DO NOT correspond to a percent of normal levels expected in a healthy patient. **Applicability**: Patient: Small population limits ability to make conclusions. Patients were on stable dose of corticosteroid and ambulatory at baseline. Intervention: Effective dose not established. Comparator: Placebo appropriate to determine efficacy. No dose-response observed. Use of an open-label, non-controlled extension study after 24 weeks limits ability to make long-term efficacy or safety conclusions. Outcomes: Dystrophin measured using immunofluorescence, confirmed by Western blot. As reported, outcomes do not correspond to percent of normal levels expected in a healthy patient and may be misleading. Due to significant methodological issues, the change from baseline could not be determined. Correlation of 6MWT or other functional outcomes with dystrophin levels is unclear. Setting: Initial 24 weeks conducted at Nationwide Children's Hospital, open-label extension study conducted at 10 sites throughout the United States.

Abbreviations [alphabetical order]: 6MWT = 6 minute walk test; ARR = absolute risk reduction; CI = confidence interval; DB = double blind; ITT = intention to treat; m = meters; mITT = modified intention to treat; N = number of subjects; NA = not applicable; NNH = number needed to harm; NNT = number needed to treat; NS = not significant; PC = placebo-controlled; PP = per protocol, RCT = randomized controlled trial; SE = standard error; tx = treatment

Percentages were evaluated with immunofluorescent assays and represent the percent of fibers stained with an intensity ***above the background* of the image and DO NOT correspond to a percent of normal levels expected in a healthy patient.

[†]Data for 30mg/kg/week group collected at 24 weeks, 50mg/kg/week collected at 12 weeks, and placebo collected at both times.

References:

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Appendix 1: Prescribing Information Highlights

HIGHLIGHTS OF PRESCRIBING INFORMATION These highlights do not include all the information needed to use EXONDYS 51™ safely and effectively. See full prescribing information for EXONDYS 51.

EXONDYS 51 (eteplirsen) injection, for intravenous use
Initial U.S. Approval: 2016

INDICATIONS AND USAGE

EXONDYS 51 is an antisense oligonucleotide indicated for the treatment of Duchenne muscular dystrophy (DMD) in patients who have a confirmed mutation of the DMD gene that is amenable to exon 51 skipping. This indication is approved under accelerated approval based on an increase in dystrophin in skeletal muscle observed in some patients treated with EXONDYS 51 *[see Clinical Studies (14)]*. A clinical benefit of EXONDYS 51 has not been established. Continued approval for this indication may be contingent upon verification of a clinical benefit in confirmatory trials. (1)

DOSAGE AND ADMINISTRATION

- 30 milligrams per kilogram of body weight once weekly (2.1)
- Administer as an intravenous infusion over 35 to 60 minutes (2.1, 2.3)
- Dilution required prior to administration (2.2)

DOSAGE FORMS AND STRENGTHS

Injection:

- 100 mg/2 mL (50 mg/mL) in single-dose vial (3)
- 500 mg/10 mL (50 mg/mL) in single-dose vial (3)

CONTRAINDICATIONS

None (4)

ADVERSE REACTIONS

The most common adverse reactions (incidence ≥35% and higher than placebo) were balance disorder and vomiting (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Sarepta Therapeutics, Inc. at 1-888-SAREPTA (1-888-727-3782) or FDA at 1-800FDA-1088 or *www.fda.gov/medwatch*.
Revised: 09/2016

Appendix 2: Prior Authorization Criteria

Drugs for Duchenne Muscular Dystrophy

Goal(s):
- Encourage use of corticosteroids which have demonstrated long-term efficacy
- Restrict use of eteplirsen and deflazacort to patients with Duchenne Muscular Dystrophy and limit use of deflazacort to patients with contraindications or serious intolerance to other oral corticosteroids

Length of Authorization:
- 6 months

Requires PA:
- Eteplirsen
- Deflazacort

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

Approval Criteria		
1. What diagnosis is being treated?	Record ICD10 code.	
2. Is the diagnosis funded by OHP?	**Yes:** Go to #3	**No:** Pass to RPh. Deny; not funded by the OHP.
3. Is the request for treatment of Duchenne Muscular Dystrophy?	**Yes:** Go to #4	**No:** Pass to RPh. Deny; medical appropriateness. Note: Eteplirsen and deflazacort are not indicated for other forms of muscular dystrophy or other diagnoses.
4. Is the request for continuation of eteplirsen treatment?	**Yes:** Go to **Renewal Criteria**	**No:** Go to #5

Approval Criteria		
5. Is the request for deflazacort?	**Yes:** Go to #6	**No:** Go to #8
6. Is the patient ≥ 5 years of age?	**Yes:** Go to #7	**No:** Pass to RPh. Deny; medical appropriateness.
7. Does the patient have a documented contraindication or intolerance to oral prednisone that is not expected to crossover to deflazacort?	**Yes:** Approve for up to 12 months. Document contraindication or intolerance reaction.	**No:** Pass to RPh. Deny; medical appropriateness. Recommend trial of another oral corticosteroid.
8. Does the patient have a diagnosis of Duchenne Muscular Dystrophy with one of the following genetic mutations amenable to exon 51 skipping: • Deletion of exons 45 to 50 • Deletion of exons 48 to 50 • Deletion of exons 49 and 50 • Deletion of exon 50 OR • Deletion of exon 52?	**Yes:** Go to #9 Document genetic testing.	**No:** Pass to RPh, Deny; medical appropriateness.
9. Has the patient been on a stable dose of corticosteroid for at least 6 months?	**Yes:** Go to #10	**No:** Pass to RPh. Deny; medical appropriateness.
10. Has baseline functional assessment been evaluated using a validated tool such as the 6-minute walk test or North Star Ambulatory Assessment?	**Yes:** Document baseline functional assessment and approve for up to 6 months	**No:** Pass to RPh. Deny; medical appropriateness.

Renewal Criteria		
1. Has the patient's baseline functional status been maintained at or above baseline level or not declined more than expected given the natural disease progression?	**Yes:** Approve for up to 6 months Document functional status.	**No:** Pass to RPh, Deny; medical appropriateness.

P&T/DUR Review: *07/17 (SS)*
Implementation: *TBD*