Health Evidence Review Commission

March 10, 2016

1:30 PM

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

Section 1.0

Call to Order

AGENDA

HEALTH EVIDENCE REVIEW COMMISSION

Wilsonville Training Center, Rooms 111-112

March 10, 2016

1:30-4:30 pm

(All agenda items are subject to change and times listed are approximate)

#	Time	Item	Presenter	Action Item
1	1:30 PM	Call to Order	Som Saha	
2	1:35 PM	Approval of Minutes (1/14/16)	Som Saha	X
3	1:40 PM	Director's Report	Darren Coffman	
4	1:50 PM	Value-based Benefits Subcommittee Report	Ariel Smits Cat Livingston	X
5	2:15 PM	Review of Scoping Statements and Scoring for Proposed New Coverage Guidance Topics	Adam Obley Cat Livingston	X
6	2:45 PM	Prioritization of Coverage Guidance Topics	Cat Livingston	X
7	3:00 PM	Skin Substitutes for Chronic Skin Ulcers • EbGS Recommended Coverage Guidance • VbBS Recommended Prioritized List Changes	Adam Obley Cat Livingston	X
8	3:30 PM	Metabolic and Bariatric Surgery • HTAS Recommended Coverage Guidance Preliminary Review • Introduction to Prioritized List Issues	Adam Obley Cat Livingston	
9	4:20 PM	Next Steps • Schedule next meeting – 5/19/16 Wilsonville Training Center, Rooms 111-112	Som Saha	
10	4:30 PM	Adjournment	Som Saha	

Note: Public comment will be taken on each topic per HERC policy at the time at which that topic is discussed.

MINUTES

HEALTH EVIDENCE REVIEW COMMISSION
Clackamas Community College
Wilsonville Training Center, Rooms 111-112
Wilsonville, Oregon
January 14, 2016

Members Present: Susan Williams, MD; Chair Pro Tempore; Beth Westbrook, PsyD; Irene Croswell, RPh; Mark Gibson; Gerald Ahmann, MD, PhD; Derrick Sorweide, DO; Chris Labhart; Holly Jo Hodges, MD; Gary Allen, DMD.

Members Absent: Som Saha, MD, MPH, Chair; Wiley Chan, MD; Leda Garside, RN, MBA; Wiley Chan, MD; Vern Saboe, DC.

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

Also Attending: Jesse Little, Kim Wentz, MD, MPH, (Oregon Health Authority); Erica Pettigrew, MD (OHSU); Valerie King, MD MPH, Adam Obley, MD, MPH, Craig Mosbaek (OHSU Center for Evidence Based Policy); Nancy Noe (Johnson & Johnson); Renee Taylor (Dexcom).

Call to Order

Susan Williams, MD, Chair Pro Tempore of the Health Evidence Review Commission (HERC), called the meeting to order and role was called.

Minutes Approval

MOTION: To approve the minutes of the November 12, 2015 meeting as presented. CARRIES 10-0.

Director's Report

Membership update
Darren Coffman thanked Dr. Gerald Ahmann for his years of service, noting this is his last meeting. Dr. Kevin Olson, VbBS Chair (and former Health Services Commission member) was nominated by Governor Kate Brown to fill the post vacated by Dr. Ahmann and will have a Senate confirmation hearing in February.

Coffman thanked an absent Dr. Vern Saboe for his years of service and noted that Saboe will now be moving from the Evidence-based Guidelines Subcommittee to the Value-based Benefits Subcommittee. Governor Brown nominated Dr. Kimberly Tippens (naturopath and acupuncturist) to fill the complementary and alternative medicine post on HERC (also to be Senate confirmed in February). Dr. Tippens will also serve on the Evidence-based Guidelines Subcommittee.

Prioritized List update
Staff determined there is not a need for a possible additional Prioritized List for 2016; the errata process to correct issues with ICD-10-CM conversion is working well.

Statewide back pain guidelines
Coffman discussed retiring three evidence-based clinical guidelines on back pain. He stated the Commission stopped work on clinical guidelines in 2012 to focus on coverage guidances. Coverage guidances have been developed from the following three clinical guidelines and so they are no longer needed.

- Guideline on the Evaluation and Management of Low Back Pain (October 2011)
- Guideline for Advanced Imaging for Low Back Pain (April 2012)
- Guideline for Percutaneous Interventions for Low Back Pain (June 2012)

MOTION: To retire the three guidelines on the management of back pain. Carries: 10-0.

ICD-10-CM coding changes for meeting materials and guideline inclusion
Staff will change the ICD-10 codes in all meeting materials and guidelines to remove terminal "x's" which are there to indicated that all further digit "daughter" codes are included. The ICD-10 codes will terminate at the digit that includes all daughter codes. Codes will remain in guidelines only when absolutely necessary.

Biennial Review topics (1/1/2018)
The 2018 biennial review is starting. Smits is requesting suggestions for topics. Topics proposed to date include obesity (subject of a new taskforce), merging the two low birth weight lines into a single prematurity line, and review of coverage for uncomplicated inguinal hernia. Coffman added the project should be wrapped up this calendar year.

Value-based Benefits Subcommittee (VbBS) Report on Prioritized List Changes
Meeting materials page 73-117

Ariel Smits reported the VbBS met earlier in the day, January 14, 2016. She summarized the subcommittee's recommendations.

RECOMMENDED CODE MOVEMENT (effective 10/1/16)

- Move the diagnosis code for Barrett's esophagus without dysplasia from an uncovered line to a covered line with a guideline change allowing long-term proton pump inhibitor therapy
- Move the diagnosis codes for Barrett's esophagus with dysplasia from an uncovered line to the covered esophageal cancer line, a line title was change to reflect this inclusion
- Move the eosinophilic esophagitis diagnosis code from one covered line to another
- Move several conditions of the mouth with no treatment from a covered line to an uncovered line
- Add procedure codes for acupuncture and chiropractic/osteopathic manipulation to the scoliosis line
- Move the procedure code for placement of artificial discs from the scoliosis line to the covered back surgery line
- Delete the procedure codes for epidural steroid injections from the back conditions line and add to the Services Recommended for Non-Coverage Table

- Delete the procedure codes for maintenance of intrathecal pumps from the back condition lines
- Various straightforward coding changes

RECOMMENDED GUIDELINE CHANGES (effective 10/1/16)

- Edit the wording of the guideline regarding disease of the lips to clarify the included ICD-10 codes
- Edit the surgical back guideline to remove the requirement for 6 months of conservative therapy prior to a patient being eligible for surgery on the uncovered back surgery line; add epidural steroid injections to the list of uncovered procedures
- Edit the guideline for advanced imaging for low back conditions to specify that repeat imaging is only covered for significant changes in a patient's condition, and to return to the old definition of radiculopathy as neurologic changes rather than just radiating pain
- The epidural steroid injection guideline and the intrathecal pump maintenance guideline were deleted

MOTION: To accept the VbBS recommendations on Prioritized List changes not related to coverage guidances, as stated. See the VbBS minutes of 1/14/16 for a full description. Carries: 10-0.

Topic Rescan for 2013 Approved Coverage Guidances

Meeting materials page 119-232

Livingston led the discussion. The process calls for the identification of Population, Intervention, Comparator, Outcomes (PICO) and Key Questions (KQ) for each topic, followed by posting for public comment for 7 days and a review of the literature search results. EbGS and HTAS have reviewed each topic.

The Commission discussed the scope documents (meetings materials pages 119-232). There was limited discussion and no change to the proposed documents.

Retire this coverage guidance and defer to United States Preventive Services Task Force (USPSTF):

- Cervical cancer screening

Reassess the need to review pending completion of an outside report:

- Coronary artery calcium scoring (CACS) - delay pending AHRQ review
- Coronary computed tomography angiography (CCTA) - delay pending AHRQ review
- Treatment of attention deficit/hyperactivity disorder in children (ADHD) - delay pending NICE review

Review and update now, according to priority order:

- Recurrent acute otitis media
- Continuous glucose monitoring in diabetes mellitus
- Diagnosis of sleep apnea in adults

Reaffirm the current coverage guidance and rescan in another two years:

- Neuroimaging headache
- Induction of labor

- Carotid endarterectomy
- Self-monitoring of blood glucose for Type 1 & Type 2 Diabetes
- PET scanning fir breast cancer
- MRI for breast cancer diagnosis
- Vertebroplasty, sacroplasty and kyphoplasty

MOTION: To approve the recommendations on the need to update the 2013 approved coverage guidances as presented. Carries 10-0.

Coverage Guidance Topic: Nitrous Oxide Use for Labor Pain Management
Meeting materials page 234-266

Livingston and Valerie King, MD from the Center for Evidence-based Policy, reviewed the evidence resulting in the draft coverage guidance from the Evidence-based Guidelines Subcommittee (EbGS).

The primary evidence source is from an Agency for Healthcare Research and Quality (AHRQ) report, retrievable from:
http://www.effectivehealthcare.ahrq.gov/ehc/products/260/1175/CER67_NitrousOxideLaborPain_FinalReport_20120817.pdf

Clinical Background:

- In the U.S., pain relief during childbirth is most commonly delivered through epidural anesthesia.
- 61% of women who had singleton vaginal births elected epidural anesthesia.
- Other pain control options include opioids, hydrotherapy, sterile water injections, psychoprophylaxis, and labor support as well as inhaled nitrous oxide.
- Inhaled nitrous oxide is widely used for childbirth pain relief outside of the United States.
- Nitrous oxide (N20) is a non-flammable, tasteless, odorless gas.
- For childbirth-related pain, N2O is typically administered as a 50% nitrous oxide/50% oxygen mixture.
- Nitrous oxide reduces the sensation of pain and provides some anti-anxiety effects.
- In comparison to epidural anesthesia, women using N2O retain full mobility.
- Nitrous oxide is rapidly cleared from the maternal system with normal respiration.
- Because the effects of N2O wear off quickly, other pain management methods can be used soon after N2O.
- Nitrous oxide can be used in the first or second stages of labor and is indicated for women intending a vaginal birth.
- Nitrous oxide can also be used in the third stage of labor for immediate postpartum procedures (e.g., perineal repair, manual placenta removal).
- Costs in the Portland-Metro region:
    - Epidural: $1,050-$2,400
    - Nitrous oxide: $15-$100

Evidence Summary: King read through the GRADE-Informed Framework (meeting materials pages 235-237).

Summary:

- Nitrous oxide is often used in dentistry and can be used by most pregnant women for pain in labor, as an alternative to or in addition to other pain-relieving measures.
- There do not appear to be any ill effects for infants.
- Women can experience unpleasant side effects such as nausea, vomiting, and lightheadedness.
- Most women who use nitrous oxide find it helpful and would want it again in another birth.
- The benefits of nitrous oxide seem to outweigh any harms.
- There is little recent published data about its use in U.S. settings, but there are an increasing number of new use locations.

Discussion:

Livingston said many implementation barriers such as licensure, payment, monitoring, and billing codes exist that are not HERC's tasks to tackle. Westbrook asked if there is a way to encourage providers to include options of pain management at the informed consent phase. For example, a person may not know an epidural is not available when having a home-birth. None were put forth.

MOTION: To approve the proposed coverage guidance for Nitrous Oxide Use for Labor Pain Management as recommended by EbGS. Carries 10-0.

MOTION: To approve the proposed guideline and coding changes for the Prioritized List as recommended by VbBS. Carries 10-0.

Approved Coverage Guidance:

HERC Coverage Guidance

Nitrous oxide for labor pain is recommended for coverage *(weak recommendation).*

Changes for the Prioritized List of Health Services:

1) Advise HSD to consider reimbursement options for the use of nitrous oxide.
2) Add a new guideline note:

GUIDELINE NOTE XXX NITROUS OXIDE FOR LABOR PAIN

Line 1

Nitrous oxide for labor pain is included on this line.

Coverage Guidance Topic: Indications for Proton Beam Therapy

Meeting materials page 268-367

Obley presented the proposed coverage guidance from the Health Technology Assessment Subcommittee (HTAS).

Proton beam therapy is a different way to deliver radiation in cancer treatment and in certain non-malignant conditions. The benefit is protons are less likely to damage surrounding tissue. It is twice as

expensive as conventional radiation. It may be used as a primary treatment with curative intent or as salvage treatment in recurrent disease.

Obley read through the Evidence Summary document (*Meeting materials page 274):*

Evidence Summary

- Bone cancer – low quality evidence of effectiveness, unknown risk, higher cost
- Brain, spinal, and paraspinal tumors – very low quality evidence of incremental benefit and higher costs
- Esophageal cancer – no evidence on effectiveness, unknown risk, higher cost
- Head and neck cancers – very low quality evidence of comparable benefits, fewer harms, higher costs, but patient preference
- Liver cancer – low quality evidence of comparable benefits and harms, higher costs
- Lung cancer – low quality evidence of comparable benefits, similar risk, higher cost
- Ocular tumors – moderate quality evidence of greater benefits with fewer harms
- Pediatric cancers – very low quality evidence of comparable benefits, fewer harms, potential health impact over decades
- Prostate cancer – low quality evidence of similar benefits, similar risk, higher cost
- Ocular hemangiomas – very low quality evidence of comparable benefits and harms
- Other benign tumors – no evidence on effectiveness, unknown risk compared to alternative, higher cost

Livingston read the GRADE-Informed Framework (meeting materials page 288-290) and highlighted what translated to the recommended box language. Public comment was received in support of PBT for many cancer conditions including cancers of the brain, spine, paraspine, breast, head and neck, prostate, lung, liver and pediatric cancers. Among core issues raised by experts/public are recurrent cancers, definition of pediatric, and longevity of benefit. There are no treatment centers in Oregon; patients would have to travel to Seattle or another clinic outside of Oregon.

There was some discussion about the definition of "pediatric." Wentz said the American Academy of Pediatrics considers pediatric up to 21. Hodges asserted age 19 is used for DME. Sorweide added, when this issue came up with the experts, they said if a person develops a brain tumor between age 18 and 21, it is considered a pediatric tumor rather than an adult-onset tumor.

MOTION: To approve the proposed coverage guidance for Indications for Proton Beam Therapy as recommended by HTAS. Carries 10-0.

MOTION: To approve the proposed guideline and coding changes for the Prioritized List recommended by VbBS. Carries 10-0.

Approved Coverage Guidance:

HERC Coverage Guidance

Proton beam therapy (PBT) is recommended for coverage for malignant ocular tumors (*strong recommendation*).

Proton beam therapy is recommended for coverage *(weak recommendation)* for:

- malignant brain, spinal, skull base, paranasal sinus, and juxtaspinal tumors
- pediatric malignant tumors (incident cancer under age 21)

Proton beam therapy is not recommended for coverage for cancer of the bone, breast, oropharynx, nasopharynx, esophagus, liver, lung, or prostate or for gynecologic or gastrointestinal cancers, lymphoma, sarcoma, thymoma, seminoma, arteriovenous malformation or ocular hemangiomas *(weak recommendation).*

Changes for the Prioritized List of Health Services:

1) **Add proton beam therapy codes (77520, 77522, 77523,77525) to the following lines:**
    a. 97 CHILDHOOD LEUKEMIAS
    b. 133 GRANULOMATOSIS WITH POLYANGIITIS
    c. 195 CANCER OF BREAST; AT HIGH RISK OF BREAST CANCER
    d. 205 CANCER OF BONES
    e. 242 ACUTE PROMYELOCYTIC LEUKEMIA
    f. 280 CANCER OF SKIN, EXCLUDING MALIGNANT MELANOMA
    g. 292 CANCER OF ORAL CAVITY, PHARYNX, NOSE AND LARYNX
    h. 402 ACUTE MYELOID LEUKEMIA
    i. 403 MYELOID DISORDERS
2) **Remove proton beam therapy codes** from Line 377 BENIGN NEOPLASM OF RESPIRATORY AND INTRATHORACIC ORGANS
3) **Add a new guideline note**

    GUIDELINE NOTE XXX PROTON BEAM THERAPY FOR CANCER

    Lines 97, 117, 130, 133, 195, 205, 242, 280, 292, 299, 377, 402, 403

    Proton beam therapy is included on lines 117 CANCER OF EYE AND ORBIT, 130 BENIGN NEOPLASM OF THE BRAIN AND SPINAL CORD and 299 CANCER OF BRAIN AND NERVOUS SYSTEM.

    Proton beam therapy is included on lines 133, 205, and 292 only for: malignant skull base, paranasal sinus (including lethal midline granuloma), spinal, and juxtaspinal tumors.

    Proton beam therapy is additionally included on lines 97, 195, 242, 280, 402, and 403 only for pediatric malignant tumors (incident cancer under age 21.)

Elective Surgery and Tobacco Cessation

Williams asked Commissioners to share their thoughts about requiring smoking cessation for a period of time before any elective surgery, which the commission indicated that wanted to discuss further at the November meeting.

Hodges said elective surgery is everything that does not have to be done straight from the Emergency Department. Sorweide expressed concerned that we may be asked to study and supply a risk assessment for each and every procedure. Gibson said he thinks this focus on surgical outcomes is an investment in the health of the population. Williams shared her worry about appeals, lawsuits and potentially denying access to care for patients with addictions. Livingston shared concern about treatment of patients with the additional challenged of mental illness issues.

The commission asked staff to consider further and bring options to the next meeting.

Public Comment

There was no public comment at this time.

Adjournment

Meeting adjourned at 3:40 pm. Next meeting will be from 1:30-4:30 pm on Thursday, March 10, 2016 at Clackamas Community College Wilsonville Training Center, Rooms 111-112, Wilsonville, Oregon.

Section 2.0

VbBS Report

Prioritized List Errata for March 2016

1) Added L20.9 (Atopic dermatitis, unspecified) to line 535 ATOPIC DERMATITIS
2) Added P07.30 (Preterm newborn, unspecified weeks of gestation) and P07.32 (Preterm newborn, gestational age 29 completed weeks) to line 17 VERY LOW BIRTH WEIGHT (UNDER 1500 GRAMS). All other preterm newborn P17.3 family codes are already on line 17
3) Moved K44.0 (Diaphragmatic hernia with obstruction, without gangrene) and K44.1 (Diaphragmatic hernia with gangrene) from line 172 COMPLICATED HERNIAS; UNCOMPLICATED INGUINAL HERNIA IN CHILDREN AGE 18 AND UNDER; PERSISTENT HYDROCELE to line 385 ESOPHAGITIS; ESOPHAGEAL AND INTRAESOPHAGEAL HERNIAS
    a. Line 385 contains the CPT codes for diaphragmatic hernia repair
    b. The ICD-9 code equivalent is on line 385
4) Moved E51.2 (Wernicke's encephalopathy) from line 122 NUTRITIONAL DEFICIENCIES to line 205 CHRONIC ORGANIC MENTAL DISORDERS INCLUDING DEMENTIAS to pair with hospitalization CPT codes
5) The following neonatal conditions were moved
    a. Moved P78.89 (Other specified perinatal digestive system disorders) from line 2 to line 105 CONGENITAL ANOMALIES OF DIGESTIVE SYSTEM AND ABDOMINAL WALL EXCLUDING NECROSIS; CHRONIC INTESTINAL PSEUDO-OBSTRUCTION
    b. Moved the following codes from line 2 BIRTH OF NEWBORN to line 186 SEPTICEMIA
        i. P36 Sepsis of newborn
            1. ECMO codes on 186 needed to pair with ECMO codes
6) Added Q30.0 Choanal atresia to line 124 CHOANAL ATRESIA and removed from line 665 MISCELLANEOUS CONDITIONS WITH NO OR MINIMALLY EFFECTIVE TREATMENTS OR NO TREATMENT NECESSARY
7) M79.7 (fibromyalgia) was removed from line 607 DISORDERS OF SOFT TISSUES and left on the fibromyalgia line
8) Z51.0 (Encounter for antineoplastic radiation therapy) was added to all the cancer lines with radiation therapy codes and HSD was advised to remove it from the Informational List
9) Z51.12 (Encounter for antineoplastic immunotherapy) was added to all the cancer lines with chemotherapy and HSD was advised to remove it from the Informational List
10) The nerve block codes were moved to the Ancillary Procedures File effective January 1, 2015, but several of these codes were mistakenly not moved. CPT 64505-64530 were removed from all lines on the Prioritized List and HSD was advised to add them to the Ancillary Procedures File.
11) Added ICD-10 M93.0 (Acute/chronic slipped upper femoral epiphysis) to line 360 CLOSED FRACTURE OF EXTREMITIES (EXCEPT MINOR TOES) where the CPT code series 27175-27181 (Repair of femoral slipped epiphysis) will pair. Removed M93.0 from line 85 FRACTURE OF HIP

12) Removed G0458 (Low dose rate (ldr) prostate brachytherapy services, composite rate) from all current lines and added to line 334 CANCER OF PROSTATE GLAND. This code was moved from 334 to 8 other lines in 2015 as some type of data input error.
13) GN 42 was corrected. These changes were adopted at the October, 2015 VBBS/HERC meetings but were not included in the January 1, 2016 PL in error.

GUIDELINE NOTE 42, CHEMODENERVATION FOR CHRONIC MIGRAINE

Line 414

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

1) have chronic migraine defined as headaches on at least 15 days per month of which at least 8 days are with migraine
2) has not responded to or have contraindications to at least three prior pharmacological prophylaxis therapies (beta-blocker, calcium channel blocker, anticonvulsant or tricyclic antidepressant)
3) treatment is administered in consultation with a neurologist or headache specialist.

Treatment is limited to two ~~injections~~ treatments given 3 months apart. Additional treatment requires documented positive response to therapy. Positive response to therapy is defined as a reduction of at least ~~6~~ 7 headache days per month compared to baseline headache frequency.

Straightforward Issues—March, 2016

Code	Code Description	Line(s) Involved	Issue	Recommendation(s)
20924	Tendon graft, from a distance (eg, palmaris, toe extensor, plantaris)	436 INTERNAL DERANGEMENT OF KNEE AND LIGAMENTOUS DISRUPTIONS OF THE KNEE, RESULTING IN SIGNIFICANT INJURY/IMPAIRMENT	Alison Little, MD requested that 20924 be added to the knee line for use in ACL reconstruction. 20924 appears on 7 other lines.	Add 20924 to line 436
D62	Acute posthemorrhagic anemia	122 NUTRITIONAL DEFICIENCIES 152 ACQUIRED HEMOLYTIC ANEMIAS	D62 is currently on line 122, which does not have hospitalization codes, and this condition may require inpatient treatment. Line 152 has inpatient CPT codes	Add D62 to line 152 Remove D62 from line 122
96150-96155	Health and behavior assessment	3 PREVENTION SERVICES WITH EVIDENCE OF EFFECTIVENESS	Line 3 needs to have screening procedure codes which are not currently there. This code series is on approximately 170 other lines.	Add 96150-96155 to line 3
64505 64508 64510 64517 64520 64530	Injection, anesthetic agent	3 PREVENTION SERVICES WITH EVIDENCE OF EFFECTIVENESS	Several anesthetic injections are found on line 3 and there is no diagnoses on this line that need to pair with these codes.	Remove 64505, 64508, 64510, 64517, 64520, and 64530 from line 3
L66.2 L66.3 L66.8 L66.9	Folliculitis decalvans Perifolliculitis capitis abscedens Other cicatricial alopecia Cicatricial alopecia, unspecified	517 HIDRADENITIS SUPPURATIVA; DISSECTING CELLULITIS OF THE SCALP 588 DISEASE OF NAILS, HAIR AND HAIR FOLLICLES	Folliculitis decalvans and cicatricial alopecia are conditions very similar to dissecting cellulitis of the scalp, and are treated in similar ways. L66.3 is the most commonly used code for dissecting cellulitis of the scalp.	Add L66.2, L66.8 and L66.9 to line 517 Remove L66.2, L66.3, L66.8 and L66.9 from line 588

Straightforward Issues—March, 2016

Code	Code Description	Line(s) Involved	Issue	Recommendation(s)
92507-92508 92526 92607-92609 92633 Inpatient and ICU codes	Speech therapy services	501 CALCIUM PYROPHOSPHATE DEPOSITION DISEASE (CPPD) AND HYDROXYAPETITE DEPOSITION DISEASE	A series of CPT codes for speech therapy appear on line 501 with no diagnosis which is appropriate to pair. Inpatient and ICU and similar codes appear on this line and are not appropriate.	Remove 92507-92508, 92526, 92607-92609, and 92633 from line 501 Remove all CPT codes for inpatient care.
E11.49 E11.59 E11.628	Type 2 diabetes mellitus with other diabetic neurological complication Type 2 diabetes mellitus with other circulatory complications Type 2 diabetes mellitus with other skin complications	169 PREVENTIVE FOOT CARE IN HIGH RISK PATIENTS	HSD requested that E11.49 and E11.59 and E11.628 pair with CPT 11721 (Debridement of nail(s) by any method(s); 6 or more) which appears on line 169. Similar diagnosis codes appear on line 169	Add E11.49 and E11.59 and E11.628 to line 169
27175-27185	Treatment of slipped femoral epiphysis	431 ACUTE PERIPHERAL MOTOR AND DIGITAL NERVE INJURY 360 CLOSED FRACTURE OF EXTREMITIES (EXCEPT MINOR TOES) 508 PERIPHERAL ENTHESOPATHIES	27175-27185 pair with slipped femoral epiphysis diagnosis codes on line 360; no appropriate diagnoses appear on lines 431 or 508	Remove 27175-27185 from lines 431 and 508

Straightforward Issues—March, 2016

Code	Code Description	Line(s) Involved	Issue	Recommendation(s)
96904	Whole body integumentary photography, for monitoring of high risk patients with dysplastic nevus syndrome or a history of dysplastic nevi, or patients with a personal or familial history of melanoma	234 MALIGNANT MELANOMA OF SKIN 280 CANCER OF SKIN, EXCLUDING MALIGNANT MELANOMA 631 BENIGN NEOPLASMS OF SKIN AND OTHER SOFT TISSUES	HSD requested review of the placement of 96904. This code appears on a large number of lines that do not contain relevant diagnoses. It needs to be added to line 234 to pair with melanoma, line 280 to pair with D48.5 which codes for dysplastic nevus syndrome, and line 631 to pair with various melanocytic nevi codes.	Add 96904 to lines 234, 280 and 631 Remove 96904 from lines 60,217,363,378,413,430,493,525, 535,536,544 and 548

Rosacea

Issue: Multiple rosacea ICD-10 codes were identified on lines other than line 525 ROSACEA; ACNE. No rosacea diagnosis codes are currently on line 525. Additionally, several CPT codes for treatment of hidradenitis are found on line 525 when this diagnosis (with appropriate CPT codes) is found on line 517 HIDRADENITIS SUPPURATIVA; DISSECTING CELLULITIS OF THE SCALP.

HERC staff recommendations:

1) Add roseacea ICD-10 diagnosis codes to line 525 ROSACEA; ACNE and remove from line 507 ERYTHEMATOUS CONDITIONS
    a. L71.1 Rhinophyma
    b. L71.8 Other rosacea
    c. L71.9 Rosacea, unspecified
2) Remove hidradenitis treatment CPT codes from lines 378 ACNE CONGLOBATA (SEVERE CYSTIC ACNE), 525 ROSACEA; ACNE and 631 BENIGN NEOPLASMS OF SKIN AND OTHER SOFT TISSUES
    a. CPT 11450-11471 (Excision of skin and subcutaneous tissue for hidradenitis)
    b. Already on appropriate other lines (517 HIDRADENITIS SUPPURATIVA; DISSECTING CELLULITIS OF THE SCALP, 520 DISORDERS OF SWEAT GLANDS)

Vitamin A Deficiencies

Issue: several diagnoses related to Vitamin A deficiency are on the incorrect lines. Vitamin A deficiency can cause ulceration of the conjunctiva or cornea and night blindness. The main treatment is high dose vitamin A supplementation. Ophthalmology evaluation may be necessary, although there is no surgical treatment or other ophthalmology intervention for these conditions. Xerosis is dry eyes, and does not need ophthalmology treatment. Corneal ulcers due to vitamin A supplementation may require treatment, as might keratomalacia.

These diagnoses should be placed on the vitamin deficiency line. The diagnostic ophthalmology visit should be covered as a diagnostic visit, but further ophthalmology visits would not pair.

ICD-10 Code	Code Description	Current Placement
E50.0	Vitamin A deficiency with conjunctival xerosis	456 EXOPHTHALMOS AND CYSTS OF THE EYE AND ORBIT
E50.1	Vitamin A deficiency with Bitot's spot and conjunctival xerosis	456
E50.2	Vitamin A deficiency with corneal xerosis	456
E50.3	Vitamin A deficiency with corneal ulceration and xerosis	456
E50.4	Vitamin A deficiency with keratomalacia	122 NUTRITIONAL DEFICIENCIES 315 CORNEAL OPACITY AND OTHER DISORDERS OF CORNEA
E50.5	Vitamin A deficiency with night blindness	122 455 DISORDERS OF REFRACTION AND ACCOMMODATION
E50.6	Vitamin A deficiency with xerophthalmic scars of cornea	122
E50.7	Other ocular manifestations of vitamin A deficiency	122
E50.8	Other manifestations of vitamin A deficiency	122
E50.9	Vitamin A deficiency, unspecified	122

HERC staff recommendations:

1) Add E50.0-E50.3 to line 122 NUTRITIONAL DEFICIENCIES and remove from line 456 EXOPHTHALMOS AND CYSTS OF THE EYE AND ORBIT
2) Add E50.3 to line 249 CORNEAL ULCER; SUPERFICIAL INJURY OF EYE AND ADNEXA
3) Remove E50.5 from line 455 DISORDERS OF REFRACTION AND ACCOMMODATION

2018 Biennial Review

Merging Selected Neonatal Lines

Issue: There are multiple lines on the Prioritized List which related to the birth of an infant or to newborn medical conditions. Many of these lines contain basically the same treatment CPT codes—hospitalization codes, NICU codes, and pediatric intensive care codes. Each also contains diagnosis codes for possibly serious newborn conditions which might require nursery or NICU care. These lines are generally all in the highest priority area of the Prioritized List.

These lines were reviewed by the ICD-10 neonatology reviewers, who made few suggestions for change. However, HERC staff feel that many of these lines should be merged together due to very similar diagnoses, having only one or a few diagnoses, or having diagnoses that are equally important to treat compared to another line.

The following 26 lines contain newborn conditions. Lines for conditions which require specific surgical interventions, such as congenital heart disease or cleft palate, are not included in this list and are not recommended by staff for merging at this time.

2 BIRTH OF INFANT—contains ICD-10 codes for newborns affected by various maternal conditions/infections/exposures, multiple gestation, possible birth defects, observation for suspected conditions in newborns, infants with serious infections such as sepsis, as well as normal newborns with no suspected conditions

11 RESPIRATORY CONDITIONS OF FETUS AND NEWBORN—contains ECMO codes

15 CONGENITAL INFECTIOUS DISEASES—contains diagnoses that might be used for an extended period

16 CONGENITAL SYPHILIS— contains diagnoses that might be used for an extended period

17 VERY LOW BIRTH WEIGHT (UNDER 1500 GRAMS)—contains ICD-10 codes for premature infants, as well as a subset of brain injury and bleeding codes (intraventricular hemorrhage and hypoxic ischemic encephalopathy).

18 NEONATAL MYASTHENIA GRAVIS

19 FEEDING PROBLEMS IN NEWBORNS

21 SYNDROME OF "INFANT OF A DIABETIC MOTHER" AND NEONATAL HYPOGLYCEMIA

22 OMPHALITIS OF THE NEWBORN AND NEONATAL INFECTIVE MASTITIS

23 LOW BIRTH WEIGHT (1500-2500 GRAMS)—contains ICD-10 codes for premature infants, mostly overlapping with line 17

27 INTRACRANIAL HEMORRHAGES; CEREBRAL CONVULSIONS, DEPRESSION, COMA, AND OTHER ABNORMAL CERERAL SIGNS OF THE NEWBORN

31 DRUG WITHDRAWAL SYNDROME IN NEWBORN

34 SEVERE BIRTH TRAUMA FOR BABY—contains mostly intracranial hemorrhage diagnoses, which are missing from line 27

35 NEONATAL THYROTOXICOSIS

36 HEMATOLOGICAL DISORDERS OF FETUS AND NEWBORN

43 DISORDERS RELATING TO LONG GESTATION AND HIGH BIRTHWEIGHT—contain ICD-10 codes for large for gestational age and post-term infants

45 HYPOCALCEMIA, HYPOMAGNESEMIA AND OTHER ENDOCRINE AND METABOLIC DISTURBANCES SPECIFIC TO THE FETUS AND NEWBORN
77 POLYCYTHEMIA NEONATORUM, SYMPTOMATIC
92 NECROTIZING ENTEROCOLITIS IN FETUS OR NEWBORN—contains multiple surgical codes for intestinal procedures
106 HEMOLYTIC DISEASE DUE TO ISOIMMUNIZATION, ANEMIA DUE TO TRANSPLACENTAL HEMORRHAGE, AND FETAL AND NEONATAL JAUNDICE—contains light therapy codes
146 CONDITIONS INVOLVING THE TEMPERATURE REGULATION OF NEWBORNS
149 ANEMIA OF PREMATURITY OR TRANSIENT NEONATAL NEUTROPENIA
283 HYDROPS FETALIS
296 ADRENAL OR CUTANEOUS HEMORRHAGE OF FETUS OR NEONATE
353 MILD/MODERATE BIRTH TRAUMA FOR BABY
648 EDEMA AND OTHER CONDITIONS INVOLVING THE SKIN OF THE FETUS AND NEWBORN—contains conditions that require no treatment

Additionally, staff have identified multiple neonatal diagnoses on the dysfunction lines which are not included on current neonatal disease specific lines. Line 2 BIRTH OF INFANT contains many diagnoses that could be moved to disease specific lines as well.

Staff feel that some or many of these 26 lines can be merged together. There are several ways to do this. There could be a merging of conditions of the same organ system together as larger lines such as "NEONATAL ENDOCRINE AND METABOLIC DISORDERS," "HEMATOLOGICAL DISORDERS OF FETUS AND NEWBORN," and "PREMATURITY." Many of the conditions currently on line 2 BIRTH OF INFANT would be moved onto one of these new lines, leaving mainly normal newborn codes and observation for suspected condition codes on line 2. Lines considered for merging would need to contain diagnoses that are only seen in the neonatal period, and that have no disease specific sequelae (other than conditions included on the dysfunction lines). This type of lumping would result in approximately 10 lines rather than 26. The advantage of this strategy is that is reduces arbitrary differences between similar lines and makes the Prioritized List somewhat less confusing and arbitrary.

There could also be more extensive merging, with most lines merged into an expanded line 2 BIRTH OF INFANT. All diagnoses for this line would conditions of the newborn which do not persist much past the neonatal period (other than sequelae which are on the dysfunction lines) and which do not require specialized treatments represented by CPT codes other than hospital/NICU/pediatric intensive care codes (i.e. surgery, light therapy, ECMO, etc.). Conditions of similar seriousness already appear on line 2. Thirteen lines would be merged into line 2 in this scenario. Two additional lines would be created, one for neonatal hemorrhages and similar diagnoses, and one for jaundice and neonatal hemolytic disease. This scenario would merge the 26 lines into approximately 5 lines. The advantage of this scenario is that it reflects the reality of care. A newborn who does not appear healthy or normal is evaluated and receives nursery or NICU care in much the same way regardless of the eventual diagnosis. These conditions are all identified and treated in similar ways (i.e. have the same CPT codes),

have similar prioritization (i.e. are all important to treat), and generally have similar prognoses. Separating these conditions into so many lines seems arbitrary.

A third scenario would have minimal line merging. This could consist of merging a few lines, such as the two low birth weight lines, that have no real reason to be separated, but would leave the majority of current lines as is. This scenario would reduce the number of lines to approximately 20. The advantage of this strategy is that it reflects how these conditions have been prioritized for the past 25 years and is consistent with the recommendations of the Neonatology ICD-10 reviewers.

In all scenarios, staff would move certain diagnoses as they are identified as being on incorrect lines, and try to place diagnoses only found on the dysfunction lines onto specific disease lines. Staff have identified many diagnoses that would fall into this category.

<u>HERC staff recommendation</u>:

1) Discuss merging strategies for the neonatal lines and give staff guidance on which merging scenario is preferred by the Commission
    a. Minimal line merging
    b. Merge lines into organ system groups
    c. Merge lines into a few large lines
    d. In all cases, incorrectly placed codes will be identified and more appropriate placement recommended

Neonatal Line Scoring (does not include congenital heart disease or other congenital anomaly lines)

Line	Score	Comments
2 BIRTH OF INFANT	5000	Hand moved to line position
10 GALACTOSEMIA	5625	Affects for extended period
11 RESPIRATORY CONDITIONS OF FETUS AND NEWBORN	5600	Do not merge—has unique treatment CPTs
13 CONGENITAL HYPOTHYROIDISM	4875	Affects for extended period
14 PHENYLKETONURIA (PKU)	4875	Affects for extended period
15 CONGENITAL INFECTIOUS DISEASES	4800	Affects for extended period
16 CONGENITAL SYPHILIS	4800	Affects for extended period
17 VERY LOW BIRTH WEIGHT (UNDER 1500 GRAMS)	4800	
18 NEONATAL MYASTHENIA GRAVIS	4400	
19 FEEDING PROBLEMS IN NEWBORNS	4400	
21 SYNDROME OF "INFANT OF A DIABETIC MOTHER" AND NEONATAL HYPOGLYCEMIA	4000	
22 OMPHALITIS OF THE NEWBORN AND NEONATAL INFECTIVE MASTITIS	4000	
23 LOW BIRTH WEIGHT (1500-2500 GRAMS)	4000	
27 INTRACRANIAL HEMORRHAGES; CEREBRAL CONVULSIONS, DEPRESSION, COMA, AND OTHER ABNORMAL CERERAL SIGNS OF THE NEWBORN	3600	
31 DRUG WITHDRAWAL SYNDROME IN NEWBORN	3300	
34 SEVERE BIRTH TRAUMA FOR BABY	3300	Diagnoses overlap with line 27
35 NEONATAL THYROTOXICOSIS	3200	
36 HEMATOLOGICAL DISORDERS OF FETUS AND NEBORN	3200	
43 DISORDERS RELATING TO LONG GESTATION AND HIGH BIRTHWEIGHT	3000	
45 HYPOCALCEMIA, HYPOMAGNESEMIA AND OTHER ENDOCRINE AND METABOLIC DISTURBANCES SPECIFIC TO THE FETUS AND NEWBORN	3000	
77 POLYCYTHEMIA NEONATORUM, SYMPTOMATIC	2500	
92 NECROTIZING ENTEROCOLITIS IN FETUS OR NEWBORN	2400	Do not merge—has unique treatment CPTs
106 HEMOLYTIC DISEASE DUE TO ISOIMMUNIZATION, ANEMIA DUE TO TRANSPLACENTAL HEMORRHAGE, AND FETAL AND NEONATAL JAUNDICE	2240	Do not merge—has unique treatment CPTs
146 CONDITIONS INVOLVING THE TEMPERATURE REGULATION OF NEWBORNS	2000	
149 ANEMIA OF PREMATURITY OR TRANSIENT NEONATAL NEUTROPENIA	2000	
283 HYDROPS FETALIS	1200	

296 ADRENAL OR CUTANEOUS HEMORRHAGE OF FETUS OR NEONATE	1120	
353 MILD/MODERATE BIRTH TRAUMA FOR BABY	750	
648 EDEMA AND OTHER CONDITIONS INVOLVING THE SKIN OF THE FETUS AND NEWBORN	0	No treatment necessary

Line merging – fewer line merges proposal

1) Merge line 15 CONGENITAL INFECTIOUS DISEASES and 16 CONGENITAL SYPHILIS
    a. Same score, syphilis is an infectious disease
2) Merge line 17 VERY LOW BIRTH WEIGHT (UNDER 1500 GRAMS) and line 23 LOW BIRTH WEIGHT (1500-2500 GRAMS)
    a. Similar scoring, mostly overlapping diagnosis codes
3) Merge line 21 SYNDROME OF "INFANT OF A DIABETIC MOTHER" AND NEONATAL HYPOGLYCEMIA, 35 NEONATAL THYROTOXICOSIS, and line 45 HYPOCALCEMIA, HYPOMAGNESEMIA AND OTHER ENDOCRINE AND METABOLIC DISTURBANCES SPECIFIC TO THE FETUS AND NEWBORN
    a. All are endocrine issues for neonates
    b. Scoring varies between 3000 and 4000
4) Merge lines 36 HEMATOLOGICAL DISORDERS OF FETUS AND NEBORN, 77 POLYCYTHEMIA NEONATORUM, SYMPTOMATIC, 149 ANEMIA OF PREMATURITY OR TRANSIENT NEONATAL NEUTROPENIA
    a. All are hematologic issues for neonates
    b. Scoring varies between 2000 and 3200
5) Merge lines 27 INTRACRANIAL HEMORRHAGES; CEREBRAL CONVULSIONS, DEPRESSION, COMA, AND OTHER ABNORMAL CERERAL SIGNS OF THE NEWBORN and 34 SEVERE BIRTH TRAUMA FOR BABY
    a. Line 34 contains nearly all diagnosis codes for intracranial hemorrhages. Other diagnoses include other CNS injuries
    b. Scoring is nearly identical

Diaphragmatic Hernia

Question: Where should obstructed or gangrenous diaphragmatic hernia be prioritized?

Question source: HERC staff

Issue: ICD-10 K44.0 (Diaphragmatic hernia with obstruction, without gangrene) and K44.1 (Diaphragmatic hernia with gangrene) were moved from line 172 COMPLICATED HERNIAS; UNCOMPLICATED INGUINAL HERNIA IN CHILDREN AGE 18 AND UNDER; PERSISTENT HYDROCELE to line 385 ESOPHAGITIS; ESOPHAGEAL AND INTRAESOPHAGEAL HERNIAS as an errata in January 2016. Line 385 contains the CPT codes for diaphragmatic hernia repair that need to pair with these diagnoses and the ICD-9 code equivalent for these diagnoses was on line 385. This errata was done to allow pairing of these diagnoses with appropriate treatment. Uncomplicated diaphragmatic hernia (K44.9 Diaphragmatic hernia without obstruction or gangrene) is on line 516 ESOPHAGITIS AND GERD; ESOPHAGEAL SPASM; ASYMPTOMATIC DIAPHRAGMATIC HERNIA, which is appropriate as the major issue with this diagnosis is GERD type symptoms and complications.

The ICD-10 Gastroenterology reviewers had intentionally moved the diaphragmatic hernia codes to the upper line as they felt that any obstructed or gangrenous hernia should be prioritized together and relatively high on the Prioritized List.

Expert Input

Dr. Kimberly Ruscher, pediatric surgeon

> If you need to pair the K44 codes with treatment, I would keep them under the complicated hernia line…gangrenous or complicated hernias are just as dangerous as other complicated hernias. The reason I say this is that whether the hernia is in the diaphragm, the abdominal wall, inguinal region, or an internal hernia, if there is an obstruction we have to treat it by treating the hernia, and if gangrene is present the patient's life will be threatened. Thus, I think that the most straightforward thing is to pair gangrenous/obstructed diaphragmatic hernia and treatment on the line for complicated hernias.

HERC staff recommendations:

1) Add ICD-10 K44.0 (Diaphragmatic hernia with obstruction, without gangrene) and K44.1 (Diaphragmatic hernia with gangrene) to line 172 COMPLICATED HERNIAS; UNCOMPLICATED INGUINAL HERNIA IN CHILDREN AGE 18 AND UNDER; PERSISTENT HYDROCELE and remove from line 385 ESOPHAGITIS; ESOPHAGEAL AND INTRAESOPHAGEAL HERNIAS
2) Add the CPT codes for repair of complicated diaphragmatic hernia to line 172 and remove from line 385
    a. 39503 Repair, neonatal diaphragmatic hernia, with or without chest tube insertion and with or without creation of ventral hernia
    b. 39540 Repair, diaphragmatic hernia (other than neonatal), traumatic; acute
    c. 39541 Repair, diaphragmatic hernia (other than neonatal), traumatic; chronic
    d. 39560 Resection, diaphragm; with simple repair (eg, primary suture)
    e. 39561 Resection, diaphragm; with complex repair (eg, prosthetic material, local muscle flap)
3) Change the line title for line 385
    a. Condition: ESOPHAGITIS; GERD~~; ESOPHAGEAL AND INTRAESOPHAGEAL HERNIAS~~

Balloon angioplasty and Intravascular Stenting

Issue: During the 2016 CPT code review of intra-arterial mechanical thrombectomy, similar procedures were identified that are currently being covered and which appear to have limited evidence of effectiveness. 61630 (Balloon angioplasty, intracranial (eg, atherosclerotic stenosis), percutaneous) and 61635 (Transcatheter placement of intravascular stent(s), intracranial (eg, atherosclerotic stenosis), including balloon angioplasty, if performed) were new CPT codes for 2006 and do not appear to have been reviewed extensively at the time of their placement on the Prioritized List. At some point between 2006 and present, 61635 was placed on the non-covered list.

Current Placement

61630 Balloon angioplasty, intracranial (eg, atherosclerotic stenosis), percutaneous: line 200 SUBARACHNOID AND INTRACEREBRAL HEMORRHAGE/HEMATOMA; CEREBRAL ANEURYSM; COMPRESSION OF BRAIN.

61635 Transcatheter placement of intravascular stent(s), intracranial (eg, atherosclerotic stenosis), including balloon angioplasty, if performed: Services Recommended for Non-Coverage Table

Evidence

1) **NICE 2012** Endovascular stent insertion for intracranial atherosclerotic disease
    a. Current evidence on the efficacy of endovascular stent insertion for intracranial atherosclerotic disease shows no substantial differences in clinical outcomes compared with medical treatment after 1–2 years. Evidence on its safety shows that there is a significant risk of periprocedural stroke and death. Therefore, this procedure should only be used in the context of research.
2) **VISSIT**; RCT of balloon angioplasty/stent vs medical management for intracranial stenosis http://jama.jamanetwork.com/article.aspx?articleid=2208809
    a. **Zaidat 2015**, VISSIT
        i. N=112 patients randomized to medical management alone vs medical management plus balloon-expandable stent placement
            1. Enrollment stopped early due to early analysis finding negative outcomes
        ii. RESULTS The 30-day primary safety end point occurred in more patients in the stent group (14/58; 24.1%[95%CI, 13.9%-37.2%]) vs the medical group (5/53; 9.4%[95%CI, 3.1%-20.7%]) (*P* = .05). Intracranial hemorrhage within 30 days occurred in more patients in the stent group (5/58; 8.6%[95%CI, 2.9%-19.0%]) vs none in the medical group (95%CI, 0%-5.5%) (*P* = .06). The 1-year primary outcome of stroke or hard TIA occurred in more patients in the stent group (21/58; 36.2%[95%CI, 24.0-49.9]) vs the medical group (8/53; 15.1% [95%CI, 6.7-27.6]) (*P* = .02).Worsening of baseline disability score (modified Rankin Scale) occurred in more patients in the stent group (14/58; 24.1%[95%CI, 13.9%-37.2%]) vs the medical group (6/53; 11.3%[95%CI, 4.3%-23.0%]) (*P* = .09).The EuroQol-

5D showed no difference in any of the 5 dimensions between groups at 12-month follow-up.

iii. CONCLUSIONS Among patients with symptomatic intracranial arterial stenosis, the use of a balloon-expandable stent compared with medical therapy resulted in an increased 12-month risk of added stroke or TIA in the same territory, and increased 30-day risk of any stroke or TIA. These findings do not support the use of a balloon-expandable stent for patients with symptomatic intracranial arterial stenosis.

3) **SAMMPRIS**; RCT of stenting vs aggressive medical management for acute stroke and intracranial artery stenosis
   a. **Chimowitz 2011**, SAMMPRIS RCT early outcomes
      i. N=451 patients (enrolment stopped early due to serious negative outcomes) randomized to either aggressive medical management alone or aggressive medical management plus stenting
      ii. The primary endpoint was any of the following: stroke or death within 30 days after enrolment, ischemic stroke in the territory of the qualifying artery beyond 30 days of enrolment, or stroke or death within 30 days after a revascularization procedure of the qualifying lesion during follow-up
      i. Results: 30-day rate of stroke or death was 14.7% in the PTAS group (nonfatal stroke, 12.5%; fatal stroke, 2.2%) and 5.8% in the medical-management group (nonfatal stroke, 5.3%; non–stroke-related death, 0.4%) (P = 0.002). Beyond 30 days, stroke in the same territory occurred in 13 patients in each group. The probability of the occurrence of a primary end-point event over time differed significantly between the two treatment groups (P = 0.009), with 1-year rates of the primary end point of 20.0% in the PTAS group and 12.2% in the medical-management group.
      ii. Conclusions: In patients with intracranial arterial stenosis, aggressive medical management was superior to PTAS with the use of the Wingspan stent system, both because the risk of early stroke after PTAS was high and because the risk of stroke with aggressive medical therapy alone was lower than expected.
   b. **Derdeyn 2014**, SAMMPRIS RCT later outcomes
      i. N=451 patients (follow up of Chimowitz paper)
      ii. Findings During a median follow-up of 32·4 months, 34 (15%) of 227 patients in the medical group and 52 (23%) of 224 patients in the stenting group had a primary endpoint event. The cumulative probability of the primary endpoints was smaller in the medical group versus the percutaneous transluminal angioplasty and stenting (PTAS) group (p=0·0252). Beyond 30 days, 21 (10%) of 210 patients in the medical group and 19 (10%) of 191 patients in the stenting group had a primary endpoint. The absolute differences in the primary endpoint rates between the two groups were 7·1% at year 1 (95% CI 0·2 to 13·8%;

p=0·0428), 6·5% at year 2 (−0·5 to 13·5%; p=0·07) and 9·0% at year 3 (1·5 to 16·5%; p=0·0193). The occurrence of the following adverse events was higher in the PTAS group than in the medical group: any stroke (59 [26%] of 224 patients *vs* 42 [19%] of 227 patients; p=0·0468) and major haemorrhage (29 [13%] of 224 patients *vs* 10 [4%] of 227 patients; p=0·0009).

iii. Conclusions: The early benefit of aggressive medical management over stenting with the Wingspan stent for highrisk patients with intracranial stenosis persists over extended follow-up. Our findings lend support to the use of aggressive medical management rather than PTAS with the Wingspan system in high-risk patients with atherosclerotic intracranial arterial stenosis.

4) **Teleb 2014**, review of endovascular management for intracranial atherosclerotic disease
   a. Early studies of angioplasty for intracranial atherosclerotic disease found very high rates of complications
      i. Complication rates as high as 50%, including dissections, emboli and rupture
      ii. Newer studies with new technology have found better outcomes
         1. "Some studies have suggested that restenosis and outcomes in balloon angioplasty without stenting are similar to those with stenting"
         2. These studies defined success as being a reduction in stenosis to less than 50%; outcomes such as stroke and death not used
5) **Cruz-Flores 2008**, Cochrane review of angioplasty for intracranial atherosclerosis
   a. N=79 articles (case series)
   b. The safety profile of the procedure showed an overall perioperative rate of stroke of 7.9% (95% confidence intervals (CI) 5.5% to 10.4%), perioperative death of 3.4% (95% CI 2.0% to 4.8%), and perioperative stroke or death of 9.5% (95% CI 7.0% to 12.0%).
   c. No comments can be made on the effectiveness of the procedure
      1. At present there is insufficient evidence to recommend angioplasty with or without stent placement in routine practice for the prevention of stroke in patients with intracranial artery stenosis. The descriptive studies show that the procedure is feasible although carries a significant morbidity and mortality risk

<u>Other expert guidelines</u>

1) **Jauch 2013** AHA/ASA guidelines for the treatment of acute stroke http://stroke.ahajournals.org/content/44/3/870 (study not included in packet due to length)
   a. The usefulness of emergent intracranial angioplasty and/or stenting is not well established. These procedures should be used in the setting of clinical trials *(Class IIb; Level of Evidence C)*. (New recommendation)

b. The usefulness of emergent angioplasty and/or stenting of the extracranial carotid or vertebral arteries in unselected patients is not well established *(Class IIb; Level of Evidence C)*. Use of these techniques may be considered in certain circumstances, such as in the treatment of acute ischemic stroke resulting from cervical atherosclerosis or dissection *(Class IIb; Leve of Evidence C)*. Additional randomized trial data are needed.

HERC staff summary

Good evidence finds that intracranial vascular stenting results in significantly worse outcomes that medical management of intracranial vascular stenosis. Intracranial balloon angioplasty appears to be much less studied, but has similar or worse outcomes than stenting in the studies identified.

HERC staff recommendations:

1) Remove 61630 (Balloon angioplasty, intracranial (eg, atherosclerotic stenosis), percutaneous) from line 200 SUBARACHNOID AND INTRACEREBRAL HEMORRHAGE/HEMATOMA; CEREBRAL ANEURYSM; COMPRESSION OF BRAIN and place on the Services Recommended for Non-Coverage List
    a. No evidence of effectiveness and evidence of harm
2) Affirm placement of 61635 (Transcatheter placement of intravascular stent(s), intracranial (eg, atherosclerotic stenosis), including balloon angioplasty, if performed) on the Services Recommended for Non-Coverage Table

Balloon Dilation of Intracranial Vasospasm

Question: Should balloon dilation of intracranial vasospasm be removed from the Prioritized List?

Question source: HERC staff

Issue: New CPT codes 61650 and 61651 (Endovascular intracranial prolonged administration of pharmacologic agent(s) other than for thrombolysis, arterial, including catheter placement diagnostic angiography, and imaging guidance) were reviewed at the November, 2015 VBBS/HERC meeting and were added to the Services Recommended for Non-Coverage Table due to lack of evidence of effectiveness for this therapy. During this review, HERC staff noted that the level and type of evidence for intracranial vasodilator therapy was similar to the evidence for intracranial balloon dilation for intracranial vasospasm. Currently, balloon dilation (CPT 61640-61642 Balloon dilation of intracranial vasospasm, percutaneous) appears on line 200 SUBARACHNOID AND INTRACEREBRAL HEMORRHAGE/HEMATOMA; CEREBRAL ANEURYSM; COMPRESSION OF BRAIN Treatment: BURR HOLES, CRANIECTOMY/CRANIOTOMY.

Both Intracranial vasodilator therapy and balloon dilation are used for treatment of cerebral vasospasm after intracranial hemorrhage. The major treatment of cerebral vasospasm appears to be administration of medications via peripheral or central IV.

In 2012, the use of balloon dilation of intracranial vasospasm for treatment of transient cerebral ischemia (TIA) was reviewed by HERC and found to be experimental.

Evidence

1) **Abruzzo 2012**, review of the safety and efficacy of transluminal balloon angioplasty (TBA) and intra-arterial vasodilator infusion therapy (IAVT) for management of posthemorrhagic cerebral vasospasm (PHCV)
    a. N=12 studies for balloon angioplasty (361 patients)
        i. All studies case series, most retrospective
    b. N=7 studies for IAVT (109 patients)
        i. 6 retrospective case series, 1 prospective case series
    c. Major risks for balloon angioplasty identified, including cerebral artery rupture (reported to be 1-5% in large case series), thromboembolic complications (4-5% of cases), ischemic stroke, arterial dissection
    d. The technical efficacy of TBA reversing cerebral vasoconstriction in patients with PHCV is in the 80-100% range. Clinical series have reported improvements in TCD velocities, luminal caliber assessed by DSA and cerebral blood flow. More importantly, it has been demonstrated that TBA reduces neurological deficits in patients with PHCV and that early treatment (<2 h from symptom onset) significantly increases the probability of sustained clinical improvement. Technically successful restoration of normal or near normal luminal caliber is achieved in the majority of TBA procedures. Case series report angiographic

improvement in 82-100% of patients. On the other hand, clinical success varies widely, with reversal of DCI in 31-77% of patients.

e. There is no significant evidence that the intervention results in better long term clinical outcomes relative to medical management.
f. TBA may be beneficial and may be considered for flow limiting PHCV involving the proximal intradural cerebral arteries (ICA, M1, VA, basilar artery, A1, P1) symptomatic with cerebral ischemia and refractory to maximal medical therapy.
g. The assessment shows that for the indications described above, TBA and IAVT are classified as Class IIb, Level B interventions according to the American Heart Association guidelines, and Level 4, Grade C interventions according to the University of Oxford Centre for Evidence Based Medicine guidelines.

2) Velat 2011, review and meta-analysis of therapies for intracranial vasospasm
   a. Identified 1 RCT on prophylactic balloon angioplasty vs no treatment
      i. N=85 patients with balloon angioplasty vs 94 control
   b. Patients undergoing prophylactic TBA experienced a non-significant reduction in DIND incidence (*P*=0.30). A significant decrease in therapeutic angioplasty (*P* = 0.03) was observed, however, for patients who had prophylactic TBA compared to controls. A high rate of vessel perforation was observed during the trial, resulting in three iatrogenic deaths.
   c. Although anecdotal reports suggest that TBA provides durable relief of vasospasm, no RCTs using therapeutic angioplasty alone have been published to date.
   d. Nimodipine is the only treatment that provided a significant benefit across multiple studies.

3) Kimball 2011, review of endovascular management of cerebral vasospasm
   a. N=27 studies (1028 patients) for balloon angioplasty
      i. 26 retrospective case series, 1 RCT
      ii. Included prophylactic studies excluded from Abruzzo 2012. Concluded that "prophylactic treatment, however, has been associated with potential risks, and the data have not shown an improvement in clinical outcome after prophylactic treatment."
   b. Improvements in vessel diameters as well as neurological deficits were observed in most studies following balloon angioplasty
   c. Complications of balloon angioplasty including vessel perforation, hemorrhage and death
   d. In summary, endovascular intervention for clinically identified vasospasm may be indicated as when medical management has failed or when there is a concern for complications from medical management.

Expert guidelines

1) **Conolly 2012**, AHA/ASA guidelines for management of subarachnoid hemorrhage (link to pdf included in November, 2015 packet)

a. Oral nimodipine should be administered to all patients with aSAH *(Class I; Level of Evidence A*
b. Maintenance of euvolemia and normal circulating blood volume is recommended to prevent DCI *(Class I; Level of Evidence B).*
c. Prophylactic hypervolemia or balloon angioplasty before the development of angiographic spasm is not recommended *(Class III; Level of Evidence B).*
d. Induction of hypertension is recommended for patients with DCI unless blood pressure is elevated at baseline or cardiac status precludes it *(Class I; Level of Evidence B).*
e. Cerebral angioplasty and/or selective intra-arterial vasodilator therapy is reasonable in patients with symptomatic cerebral vasospasm, particularly those who are not rapidly responding to hypertensive therapy *(Class IIa; Level of Evidence B*).

2) **Deringer 2011**, Neurocritical Care Society consensus statement (link to pdf included in November, 2015 packet)
   a. There was wide international variation in the use of endovascular therapies with some groups strongly recommending their use and other not utilizing them at all
   b. Recommendation: Endovascular treatment using intra-arterial vasodilators and/or angioplasty may be considered for vasospasm related DCI (moderate quality evidence-strong recommendation).
   c. Recommendation: The timing and triggers of endovascular treatment of vasospasm remains unclear, but generally rescue therapy for ischemic symptoms that remain refractory to medical treatment should be considered. The exact timing is a complex decision which should consider the aggressiveness of the hemodynamic intervention, the patients' ability to tolerate it, prior evidence of large artery narrowing, and the availability of and the willingness to perform angioplasty or infusion of intra-arterial agents (moderate quality evidence—strong recommendation).
3) **Steiner 2013**, European Stroke Organization guideline of treatment of subarachnoid hemorrhage (link to pdf included in November, 2015 packet)
   a. no recommendations for balloon angioplasty or intra-arterial vasodilators

Summary:
Some preliminary evidence from retrospective case series finds that balloon angioplasty may be useful for treatment of intracranial vasospasm following aneurysmal subarachnoid hemorrhage, but its effectiveness needs to be verified by prospective RCTs. This procedure is recommended as a possible therapy after failure of optimal medical management by expert guidelines which rate the underlying evidence to be of low to moderate strength. There is risk of serious adverse events including arterial rupture and death from this procedure. The best available evidence does not find improvement in long term outcomes with balloon angioplasty vs optimal medical management.

HERC staff recommendation:

1) Option 1: Remove CPT 61640-61642 Balloon dilation of intracranial vasospasm, percutaneous) from line 200 SUBARACHNOID AND INTRACEREBRAL HEMORRHAGE/HEMATOMA; CEREBRAL ANEURYSM; COMPRESSION OF BRAIN and place on the Services Recommended for Non-Coverage Table
    a. Evidence shows efficacy at best similar to optimal medical management
    b. Evidence of harm from treatment not seen with optimal medical management
2) Option 2: leave CPT 61640-61642 on line 200 and adopt the following new guideline note
    a. There is good evidence that prophylactic use is not effective and is harmful
    b. Expert guidelines recommend use only with failure of optimal medical management

GUIDELINE NOTE XXX BALLOON DILATION OF INTRACRANIAL VASOSPASM

Line 200

Balloon dilation of intracranial vasospasm is included on this line only for patients with flow limiting posthemorrhagic cerebral vasospasm involving the proximal intradural cerebral arteries symptomatic with cerebral ischemia and refractory to maximal medical therapy.

Breast/Chest Surgery Requirements for Gender Dysphoria
Other Coverage Concerns for Gender Dysphoria

Questions:

1) Should the gender dysphoria guideline be modified to remove the requirement for 1 year of cross sex hormone therapy prior to breast/chest surgery?
2) Should laser hair removal be a covered treatment for pre-operative site preparation?
3) What is the HERC policy regarding revisions to previous gender dysphoria related surgeries?
4) Should smoking cessation be required prior to genital surgery for gender dysphoria?
5) Do we need to add PT procedure codes to the gender dysphoria line to allow pre- and post-procedure therapy for vaginoplasty?
6) Should other procedures requested by patients be considered for addition to the gender dysphoria line?

Question sources:

1) Stephanie Detlefsen, MD, and Heather M. Leffler, MSW, LCSW, Kaiser Permanente Gender Pathways Clinic/Transgender Care Team
2) CCO medical director; OHSU transgender surgical team
3) Joyce Liu, MD, Medicaid medical director for Kaiser Permanente NW
4) HERC staff
5) HERC staff
6) Patients

Issues:

Issue 1: The current gender dysphoria guideline requires 1 year of cross-sex hormone therapy prior to bilateral mastectomy for female-to-male transgender patients or breast augmentation surgeries for male-to-female transgender patients. The Kaiser medical team caring for their transgender population is requesting that this requirement be removed. It is not consistent with WPATH guidelines and is not a requirement for various private insurers, and so is causing confusion and denials of service for the Kaiser program.

The issue raised by the Kaiser clinicians appears to specifically concern female-to-male transitioning persons. When patients are not able to tolerate the side effects of testosterone, they are being denied chest/breast surgery.

An OHP CCO medical director also raised a question about whether requiring 1 year of living as the desired gender is required by WPATH prior to breast/chest surgery. The current HERC guideline requires this step prior to surgery for both breast/chest surgery and for genital surgery.

From Dr. Detlefsen

I want to remind HERC that WPATH creates their guidelines as a world standard on how to treat these patients. Gender is a spectrum and everyone's gender identity is very personal and the choice of hormones, surgery, etc is very individualized. Gender is a spectrum hence treatment is a spectrum. Testosterone has a fair amount of side effects... WPATH writes the guidelines we all follow and more and more patients are obtaining surgical benefits. I'm not sure if you know, but as of January 1st ALL Kaiser members have surgical benefits (with rare exception) and we are following the WPATH guidelines for all of them except OHP members due to the HERC language around the 1 year testosterone requirement prior to top surgery.

I cannot speak for other organizations, but Heather has informally outreached to "other" organizations and they too (mostly due to strict UM interpretation) are not performing top surgery based on HERC language. UM committees often have complex goals that reach beyond clinical care goals. It is not common that patients don't want testosterone but it happens and again I think this is a moot point. Gender is spectrum and everyone's gender identity is different whether cis-gendered, trans-tendered or other. I have included WPATH's language below. I think their wording is quite blunt. I know evidence based scientists hate to hear we don't have a lot of data but we don't have good demographic data on the transgender population due to numerous barriers but that should not prevent us from caring for these patients humanely…Heather and I would be happy to discuss this further with HERC because ultimately, the issue is this: is it ethical to force patients to take medications they do not want to take, which has side effects they want to avoid, when there are clear guidelines from WPATH that says it is not necessary and there is no clinical literature that shows hormones increases the "success" for chest masculinization surgery?

From Dr. Jens Urs Berli, OHSU Plastic and Reconstructive Surgery

Not every patient qualifies for testosterone based on their preexisting conditions (i.e. coronary artery disease, polycythemia vera, exacerbation of psychiatric comorbidities)…Although hormonal treatment for 12 months in the male to female patient is strongly encouraged, there may also here be patients that do not qualify for estrogen treatment (i.e. previous deep venous thrombosis/pulmonary embolus).

Breast construction/reconstruction guidance should be modified to remove that term "medical" from the contra-indication exemption to allow for a broader application. There may be patients for whom hormone therapy is not desirable due to being of an older generation, may have cancer risks or other medical or psychiatric issues and that don't meet strict contra-indication but may have associate undesirable risks.

Issue 2: Another issue raised by a provider was the question of whether we cover laser hair removal for surgical site preparation, or only electrolysis. HERC added electrolysis (CPT 17380) to the gender dysphoria line with a limitation to surgical site preparation last fall, but did not

add laser hair removal due to the nonspecific nature of the CPT code (CPT 17999 Unlisted procedure, skin, mucous membrane and subcutaneous tissue). CPT 17999 is currently listed as Ancillary.

The CCOs are finding considerable difficulty in identifying providers for electrolysis who have Medicaid billing numbers and who are willing to contract with them. The CCOs have questions about what is actually required for surgical site preparation.

Expert Input: Dr. Daniel Dugi, OHSU urology, gender affirming surgery provider
From materials he gives to prospective patients:

> **Permanent hair removal:** As the skin of the penis and scrotum is used to make the new vagina, it is important to permanently remove hair from this area before surgery. This is to avoid having hair within the vagina. Options for hair removal include electrolysis and laser hair removal. Electrolysis is the most permanent form of hair removal. Laser hair removal may not be as effective in the long-term or in individuals with lighter hair color. I recommend electrolysis. We will provide you with a letter of medical necessity and a diagram showing the pattern for hair removal (see Dr. Dugi's handout in packet). Hair removal is the biggest delay in moving forward with surgery! Not all hair grows at the same time, and it takes at least three cycles of hair growth to achieve adequate hair removal. This may take anywhere between 3-12 months depending on how stubborn your hair is. The earlier you can start with this process, the better.

From Dr. Dugi's letter to the Commission:

> Laser hair removal should be added as an option for pre-surgical site hair removal. While not all patient will be good candidates for laser hair removal (vs electrolysis) prior to gender-affirming surgery, some people will be good candidates for this less expensive, less painful, and more efficient method of hair reduction should be an option, consistent with best medical practices and patient autonomy.
>
> As a urologist and genital reconstructive surgeon, it is my professional opinion that these treatments are medically necessary. I have seen firsthand the impact these procedures have on the quality of life and safely of the transgender patient I work with.

Expert input: Heather Onoday, NP, OHSU Dermatology

> From our perspective, when doing billing for hair laser that is medically necessary, the typical code that we utilize is 17110 or 17111. It is based on number of follicles treated, so most of the time the 17111 is used.
>
> The laser is very effective for permanent hair reduction. Essentially, a patient typically requires approximately 5 to 6 treatments to remove approximately 90% of their hair. Over the course of many months to years they may get a small percentage of the hair back, but generally speaking there is a very large quantity of hair permanently removed (10-25% may recur over a varied time period of months to years). This is comparable to electrolysis

which also offers permanent hair reduction. There's not yet an actual method of complete permanent removal available.

Laser Treatments are spaced approximately 4 to 6 weeks apart, to accommodate the changes in hair growth cycles. The advantages of hair laser over electrolysis are that it is a smaller number of overall treatments required and pain is reduced due to the very short time of treatment required, typically the groin area or chest area is an approximately 10 to 15 minute procedure. Electrolysis allows for very blonde or white hair to be treated, whereas hair laser does require that there is at least some pigmentation to the hair. This accounts for the majority of patients-it is a very rare patient who does not have some pigment within their hair follicles.

From Dr. Jens Urs Berli, OHSU Plastic and Reconstructive Surgery

Laser hair removal should be added as an option for pre-surgical site hair removal. A combined approach of electrolysis and laser hair removal may at times be more effective. Pre-genital surgery: last hair removal is an integral part of the preoperative preparation. Hair that grows within the neourethra can lead to urinary obstruction and infection. Growth of intravaginal hair is stigmatizing and undesired. I therefore strongly support presurgical laser hair removal as an alternative for those who cannot tolerate electrolysis.

From Megan Bird, MD and Amy Penkin, submitted testimony

The advantages of hair laser over electrolysis are that it requires a small number of overall treatments and pain is reduced due to the reduction in treatments. A typical groin or chest area is approximately 10 to 15 min procedure with laser treatments, compared to electrolysis, which can require 16-20 hours of treatments. Electrolysis, however, can be more effective for treatment very blonder or white hair.

We also support adding a code or modifying guidance to allow for expanding the length of time for a single daily electrolysis session from 30 minutes to up to two hours for patients who can't use laser removal and have sufficient pain management. This will reduce the overall number of sessions needed, which is critical for patients who must travel for treatments.

Issue 3: Kaiser Permanente has contacted HERC staff for guidance on policy for coverage of revisions to previous sex reassignment surgery. Dr. Megan Bird also contacted HERC for clarification of coverage for revisions and repairs.

From Dr. Liu:

We have a request from a 55 yo transgender women (M-> F) who had surgery 30 years ago. She had full SRS including a vaginoplasty in 1986. Her vagina was very small from the beginning and she would like to have a functional vagina and there is newer technology available.

Based on your interpretation of the relatively new transgender benefit do you think this revision should be covered? She meets the other HERC requirements for the surgery but this is the first revision we have been asked to cover. Thanks so much for your help on this.

From: Dr. Megan Bird

I have had a couple of patients who have had surgery out of state or out of country now living in Oregon. They have either chronic pain or a surgical complication of the procedure (fistula, erosion) and needed revision but were denied. I know one gave up and did not pursue appeal as they should have. I would suggest something on the order of revisions of covered service may be done in cases of chronic pain or surgical complication. There is no guidance in WPATH as you said. There is no real literature on the subject but it makes sense that if the original surgery would have been covered and they had a complication to cover the revision. I would like to avoid revisions for cosmetic reasons (for example the labia are uneven on a vaginoplasty) as I don't think that is a good use of resources.

From: Dr. Daniel Dugi, OHSU reconstructive urologist

Guidance for revision surgery should be clarified for pain complications or other medical complications. As we endeavor to treat care for gender dysphoria as any other medical condition that has surgery as a possible therapy, we will need to deal with and care for the inevitable complications. Research shows that complications of genital surgery are very distressing to all patients and especially transgender patients. Complications can be related to urinary or sexual function in addition to pain, and we must be able to effectively treat complications of gender-affirming surgery.

From Dr. Jens Urs Berli, OHSU Plastic and Reconstructive Surgery

Revision surgery may include: vaginal strictures, urethral strictures, extrusion of phallic prosthesis, testicular prosthesis, implant associated problems (i.e. capsular contracture), pain from nerve entrapment, excess scar formation (hypertrophic scars, keloids). All patients should be able to access revisions to manage above mentioned complications, many of which are associated with pain, medical risk and continued dysphoria.

From Megan Bird, MD and Amy Penkin, submitted testimony

Fistulas [lines 234 and 303] and urethral strictures of stenosis [line 184] are covered, but others are not currently covered (surgical wound breakdown, abscess). For patients with chronic pain or surgical complications it is appropriate to provide for revision of the original surgery to obtain the outcome necessary.

Note: abscess and necrosis of surgical wound is covered on line 230

There is no guidance in the current WPATH version regarding revisions to surgeries, other than obvious need to treat surgical complications.

Issue 4: Dr. Dugi (the only surgeon performing genital gender dysphoria surgery in Oregon) strongly feels that smoking cessation is required prior to vaginoplasty surgery.

From Dr. Dugi's surgical information packet:

> **Smoking** I require that people not smoke or use any nicotine or tobacco products for at least 6 weeks before surgery and at least 6 weeks after surgery - and it is best for your overall health to never start again!. This includes e-cigarettes, nicotine gum, and nicotine patches. Nicotine is a very powerful drug that decreases blood flow to the tissues that need this nutrition after surgery. Research shows that people who smoke even 1 cigarette a day have a **10-time increased risk of surgery failure**. Second hand smoke exposure should be avoided as well for all of the above reasons. Your primary care provider and tobacco cessation groups can be very helpful in this process. Vaginoplasty is an affirming procedure, and we do not want you to have wound healing complications that lead to a less than desired result. This is so important, that as a policy for all my patients, a urine nicotine test will be performed as part of your pre-surgery lab tests, and we will reschedule if you have not been able to quit.
>
> He uses a urine cotinine test 2 weeks prior to surgery to confirm smoking cessation**.**

Issue 5: Dr. Dugi requires pelvic physical therapy pre- and post-operatively for vaginoplasty. There are currently no PT CPT codes on the current gender dysphoria line.

From Dr. Dugi's surgical materials:

> **Physical therapy** Creating the vagina requires making a space between the pelvic muscles. These muscles normally work to support your organs and help with control of urination and bowel movements. You will need to learn what it feels like to contract and relax these muscles, as being good at relaxing these muscles will make dilation of the vaginal later on much more comfortable. You will meet with a physical therapist who specializes in pelvic muscle function before and after surgery to help teach you these techniques.

<u>Pelvic physical therapy CPT codes</u>:
97001 Physical therapy evaluation
97002 Physical therapy re-evaluation
97110 Therapeutic procedure, 1 or more areas, each 15 minutes; therapeutic exercises to develop strength and endurance, range of motion and flexibility
97140 Manual therapy techniques (eg, mobilization/ manipulation, manual lymphatic drainage, manual traction), 1 or more regions, each 15 minutes
97530 Therapeutic activities, direct (one-on-one) patient contact (use of dynamic activities to improve functional performance), each 15 minutes

Issue 6: A patient has contacted the HERC to request consideration of the addition of facial feminization and chest liposuction (CPT 15877) to the gender dysphoria line. Other patient testimony was received regarding the need to cover facial feminization. For more information about these requests, please see the submitted testimony available on the HERC secure website.

Current Prioritized List Guideline

GUIDELINE NOTE 127, GENDER DYSPHORIA

Line 317

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

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

1. have persistent, well-documented gender dysphoria
2. have the capacity to make a fully informed decision and to give consent for treatment
3. have any significant medical or mental health concerns reasonably well controlled
4. have a comprehensive mental health evaluation provided in accordance with Version 7 of the World Professional Association for Transgender Health (WPATH) Standards of Care (www.wpath.org).

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

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

Electrolysis (CPT 17380) is only included on this line for surgical site electrolysis as part of pre-surgical preparation for chest or genital surgical procedures also included on this line. It is not included on this line for facial or other cosmetic procedures or as pre-surgical preparation for a procedure not included on this line.

Mammoplasty (CPT 19316, 19324-19325, 19340, 19342, 19350, 19357-19380) is only included on this line when 12 continuous months of hormonal (estrogen) therapy has failed to result in breast tissue growth of Tanner Stage 5 on the puberty scale OR there is a medical contraindication to hormonal therapy.

From WPATH 7.0 (not included in the packet due to length)

Criteria for mastectomy and creation of a male chest in FtM patients:

1. Persistent, well-documented gender dysphoria;
2. Capacity to make a fully informed decision and to consent for treatment;
3. Age of majority in a given country (if younger, follow the *SOC* for children and adolescents);
4. If significant medical or mental health concerns are present, they must be reasonably well controlled.

Hormone therapy is not a prerequisite.

Criteria for breast augmentation (implants/lipofilling) in MtF patients:

1. Persistent, well-documented gender dysphoria;
2. Capacity to make a fully informed decision and to consent for treatment;
3. Age of majority in a given country (if younger, follow the *SOC* for children and adolescents);
4. If significant medical or mental health concerns are present, they must be reasonably well controlled.

Although not an explicit criterion, it is recommended that MtF patients undergo feminizing hormone therapy (minimum 12 months) prior to breast augmentation surgery. The purpose is to maximize breast growth in order to obtain better surgical (aesthetic) results.

Other policies

1) **Cigna 2015**
    a. Has no hormone requirement prior to female to male chest surgery
    b. Does not appear that mammoplasty is a covered service
2) **Aetna 2015**
    a. Note: mammoplasty is not a covered services
    b. Aetna considers gender reassignment surgery medically necessary when all of the following criteria are met:
        i. Requirements for mastectomy for female-to-male patients:
            1. Single letter of referral from a qualified mental health professional (see Appendix); and
            2. Persistent, well-documented gender dysphoria (see Appendix); and
            3. Capacity to make a fully informed decision and to consent for treatment; and
            4. Age of majority (18 years of age or older); and

5. If significant medical or mental health concerns are present, they must be reasonably well controlled.
6. Note that a trial of hormone therapy is not a pre-requisite to qualifying for a mastectomy.

HERC staff recommendations:

1) Modify the gender dysphoria guideline as shown below
    a. Removes hormone requirement prior to female-to-male type chest/breast surgeries
        i. Consistent with other insurance carriers and WPATH guidelines
    b. Modifies the requirement for hormone (estrogen) therapy prior to mammoplasty, allowing for "any contraindication" which could include intolerance of the medication or medical conditions which preclude use
        i. Alternate: remove any requirement for estrogen therapy prior to mammoplasty
    c. Removes the requirement for a year of living as the desired gender prior to breast/chest surgery
        i. Consistent with other insurance carriers and WPATH guidelines
    d. Clarifies when surgical revisions are a covered service
    e. Add requirement for smoking cessation prior to genital surgeries
        i. Evidence of improved outcomes; agrees with Dr. Dugi's recommendations
2) Add laser hair removal for surgical site preparation (CPT 17110, 17111) to line 317 GENDER DYSPHORIA
    a. 17110: Destruction (eg, laser surgery, electrosurgery, cryosurgery, chemosurgery, surgical curettement), of benign lesions other than skin tags or cutaneous vascular proliferative lesions; up to 14 lesions
    b. 17111: 15 or more lesions
    c. Modify the guideline note as shown below regarding hair removal
3) Add pelvic physical therapy to line 317 GENDER DYSPHORIA
    a. 97001 Physical therapy evaluation
    b. 97002 Physical therapy re-evaluation
    c. 97110 Therapeutic procedure, 1 or more areas, each 15 minutes; therapeutic exercises to develop strength and endurance, range of motion and flexibility
    d. 97140 Manual therapy techniques (eg, mobilization/ manipulation, manual lymphatic drainage, manual traction), 1 or more regions, each 15 minutes
    e. 97530 Therapeutic activities, direct (one-on-one) patient contact (use of dynamic activities to improve functional performance), each 15 minutes
    f. Modify the guideline note as shown below to specify use only for pre- and post-operative therapy for included genital surgery.

GUIDELINE NOTE 127, GENDER DYSPHORIA

Line 317

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

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

1. have persistent, well-documented gender dysphoria
2. have the capacity to make a fully informed decision and to give consent for treatment
3. have any significant medical or mental health concerns reasonably well controlled
4. have a comprehensive mental health evaluation provided in accordance with Version 7 of the World Professional Association for Transgender Health (WPATH) Standards of Care (www.wpath.org).

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

1. have persistent, well documented gender dysphoria
2. for genital surgeries, have completed twelve months of continuous hormone therapy as appropriate to the member's gender goals unless hormones are not clinically indicated for the individual
3. for genital surgeries, have completed twelve months of living in a gender role that is congruent with their gender identity unless a medical and a mental health professional both determine that this requirement is not safe for the patient
4. have the capacity to make a fully informed decision and to give consent for treatment
5. have any significant medical or mental health concerns reasonably well controlled
6. for breast/chest surgeries, have one referral from a mental health professional provided in accordance with version 7 of the WPATH Standards of Care.
7. For genital surgeries, have two referrals from mental health professionals provided in accordance with version 7 of the WPATH Standards of Care.
8. For genital surgeries, be abstinent from tobacco products for 6 weeks prior to surgery, to be confirmed by urine cotinine testing.

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

Mammoplasty (CPT 19316, 19324-19325, 19340, 19342, 19350, 19357-19380) is only included on this line when 12 continuous months of hormonal (estrogen) therapy has failed to result in breast tissue growth of Tanner Stage 5 on the puberty scale OR there is any ~~a medical~~ contraindication to hormonal therapy.

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

Pelvic physical therapy (CPT 97001, 97001, 97110, 97140, and 97530) is included on this line only for pre- and post-operative therapy related to genital surgeries also included on this line.

Acupuncture for Tobacco Cessation

Question: Should limits be placed on the use of acupuncture for tobacco cessation?

Question source: HERC staff

Issue: Acupuncture (CPT 97810-97814) is included on line 5 TOBACCO DEPENDENCE but currently has no mention/limits in the acupuncture guideline. The ACA does not require coverage for acupuncture treatment for smoking cessation.

Line: 5
Condition: TOBACCO DEPENDENCE (See Guideline Notes 4,64,65)
Treatment: MEDICAL THERAPY/BEHAVIORAL COUNSELING
ICD-10: F17.200-F17.228,F17.290-F17.299,Z71.6
CPT: 96150-96154,97810-97814,98966-98969,99078,99201-99215,99224,99324-99350, 99366,99406,99407,99415,99416,99441-99449,99487-99498,99605-99607
HCPCS: D1320,G0425-G0427,G0436,G0437,G0459,G0463,G0466,G0467,G0469,G0470, G9016,H0038,S9453

Current guideline

GUIDELINE NOTE 92, ACUPUNCTURE (ADAPTED FROM THE OCT. 1, 2015 PRIORITIZED LIST†)
Lines 1,208,351,415,467,532,543 (Lines 351 and 532 represent lines 374 and 545 from the Oct. 1, 2015 Prioritized List†)
Inclusion of acupuncture (CPT 97810-97814) on the Prioritized List has the following limitations:
Line 1 PREGNANCY
Acupuncture pairs on Line 1 for the following conditions.

Hyperemesis gravidarum
ICD-10-CM: O21.0, O21.1
Acupuncture pairs with hyperemesis gravidarum when a diagnosis is made by the maternity care provider and referred for acupuncture treatment for up to 12 sessions of acupressure/acupuncture.

Breech presentation
ICD-10-CM: O32.1
Acupuncture (and moxibustion) is paired with breech presentation when a referral with a diagnosis of breech presentation is made by the maternity care provider, the patient is between 33 and 38 weeks gestation, for up to 6 visits.

Back and pelvic pain of pregnancy
ICD-10-CM: O99.89
Acupuncture is paired with back and pelvic pain of pregnancy when referred by maternity care provider/primary care provider for up to 12 sessions.

Line 208 DEPRESSION AND OTHER MOOD DISORDERS, MILD OR MODERATE

Acupuncture is paired with the treatment of post-stroke depression only. Treatments may be billed to a maximum of 30 minutes face-to-face time and limited to 12 total sessions, with documentation of meaningful improvement.

Line 351 DISORDERS OF SPINE WITH NEUROLOGIC IMPAIRMENT (Line 374 from the Oct. 1, 2015 Prioritized List†)

Acupuncture is included on Line 351 (Line 374 from the Oct. 1, 2015 Prioritized List†) only for pairing with disorders of the spine with myelopathy and/or radiculopathy represented by ICD-10-CM G83.4, M47.2, M50.0, M50.1, M51.0, M51.1, M54.1), for up to 12 sessions.

Line 415 MIGRAINE HEADACHES

Acupuncture pairs on Line 415 for migraine (ICD-10-CM G43.0, G43.1, G43.5, G43.7, G43.8, G43.9), for up to 12 sessions.

Line 467 OSTEOARTHRITIS AND ALLIED DISORDERS

Acupuncture pairs on Line 467 for osteoarthritis of the knee only (ICD-10-CM M17), for up to 12 sessions.

*Line 532 ACUTE AND CHRONIC DISORDERS OF SPINE WITHOUT NEUROLOGIC IMPAIRMENT (Line 545 from the Oct. 1, 2015 Prioritized List†)

Acupuncture pairs on Line 532 (Line 545 from the Oct. 1, 2015 Prioritized List†) with the low back diagnoses appearing on this line (ICD-10-CM M51.36, M51.86, M54.5, M99.03, S33.5, S33.9, S39.092, S39.82, S39.92). Acupuncture pairs with chronic (>90 days) neck pain diagnoses on this line (ICD-10-CM M53.82, M54.2, S13.4, S13.8), for up to 12 sessions.

*Line 543 TENSION HEADACHES

Acupuncture is included on Line 543 for treatment of tension headaches (ICD-10-CM G44.2), for up to 12 sessions.

The development of this guideline note was informed by a HERC evidence-based guideline. See http://www.oregon.gov/oha/herc/Pages/blog-low-back-non-pharmacologic-intervention.aspx

Evidence:

1) **White 2014**[i]**,** Cochrane review of acupuncture for smoking cessation
    a. N=38 studies
        i. N=3 studies (393 patients) comparing acupuncture to waiting list control
        ii. N=19 studies (1,588 patients) comparing active acupuncture to sham acupuncture
    a. Based on three studies, acupuncture was not shown to be more effective than a waiting list control for long-term abstinence, with wide confidence intervals and evidence of heterogeneity (n = 393, risk ratio [RR] 1.79, 95% confidence interval [CI] 0.98 to 3.28, I^2 = 57%). Compared with sham acupuncture, the RR for the short-term effect of acupuncture was 1.22 (95% CI 1.08 to 1.38), and for the long-term effect was 1.10 (95% CI 0.86 to 1.40). Acupuncture was less effective than nicotine replacement therapy (NRT). There was no evidence that acupuncture is superior to psychological interventions in the short- or long-term.
    b. Moderate quality of evidence of no long term benefit for acupuncture on smoking cessation, although evidence of short term effect
    c. Wide variety of acupuncture protocols. Details of included studies' intervention frequency/duration as well as adjunct therapy, if any (studies only listed here if full articles were available):
    i. Bier 2002: 20 sessions over 4 wks. Three arms: true acupuncture, true acupuncture + intensive ed program, sham acupuncture + intensive ed program
    ii. Clavel 1985: single session. *Adjunct therapy: 3 one-hour sessions of group therapy in first month
    iii. Clavel 1992: 3 sessions over one month
    iv. Cottraux 1983: 3 weekly sessions
    v. Fritz 2013: 5 weekly 20 min sessions of b/l auriculotherapy
    vi. He 1997: Both groups received combination of body electroacupuncture, ear acupuncture and ear acupressure (genuine vs sham points), 6 treatments over 3 wks + 6 plant seeds taped to "correct" or "incorrect" points on the ear and subjects instructed to press on each seed 100x on 4 occasions daily
    vii. Lagrue 1980: facial acupuncture vs sham acupuncture, day 0 and day 7. *Adjunct therapy: "standardised advice"
    viii. Waite 1998: lung point in ear vs control patella point. *Both groups received one 20-minute session of acupuncture w electrical stimulation followed by placement of seed on needle site. Instructed to press seed with desire to smoke.ix. White 1998: acupuncture with electrical stim to lung points in both ears vs sham acupuncture to mastoid bone. Days 1,3, 7. *Adjunct therapy: counseling by a nurse
    x. Wu 2007: indwelling auricular needles in active vs sham points, 4 points retained for one week, then replaced. 8 wk tx period. *Adjunct therapy: counseling from nurse
    d. **Authors' conclusions** Although pooled estimates suggest possible short-term effects there is no consistent, bias-free evidence that acupuncture, acupressure, or laser therapy have a sustained benefit on smoking cessation for six months or

more. However, lack of evidence and methodological problemsmean that no firm conclusions can be drawn.

2) **Patnode 2015[ii]: USPSTF Review of Reviews.** (article not included in meeting materials due to length)

a. Includes all types of behavioral and pharmacotherapy interventions. In total, reviewed 638 abstracts and 114 full-text reviews for possible inclusion, narrowing down to 54 systematic reviews which met eligibility criteria. Identifies 2 reviews on acupuncture (White 2014 and Di 2014) and classifies them both as "good." Additionally, it evaluates Cheng 2012's review of acupoint stimulation as "fair." No other reviews regarding acupuncture or acupressure identified.

b. Authors' conclusions: Concluded that "evidence on the use of...complementary and alternative therapies was limited and not definitive."

3) **McRobbie 2007[iii]: NICE Rapid Review of Non NHS Treatments for Smoking Cessation** (Study not included in meeting materials due to length)

a. 19 reviews narrowed to 9 reviews after further exclusion based on poor quality, no systematic method, or review of reviews. Included White's Cochrane review from 2006. Additionally, 21 studies were narrowed to 14 studies after exclusion for not being an RCT. Further, of those 14 studies, 13 were included in the Cochrane Review. Only one new RCT (Docherty 2003) was included, but it was examining laser therapy and thus is not relevant to this lit review.

b. Since this NICE Review relied heavily on an old Cochrane review, this is less relevant to HERC's current lit review.

c. **Authors' conclusion**: Marginal effect compared to placebo in short-term but no evidence of efficacy in long-term abstinence rates. Level 1+ evidence "well-conducted meta-analyses, systematic reviews of RCTs, or RCTs (including cluster RCTs) with a low risk of bias."

4) **Cheng 2012[iv]** Systematic Review and Meta-Analysis in American Journal of Chinese Medicine.

a. n = 20 studies total
n = 9 studies evaluating smoking cessation rate at 3,6 months
n = 3 studies evaluating daily cigarette consumption

b. Includes 13 of same acupuncture studies as White 2014 Cochrane.

c. Combined all types of acupoint stimulation (acupuncture, acupressure, laser therapy) and all types of controls into single analysis. White 2014 comments that this likely explains the differences in the reviews.

d. Smoking cessation RR 1.24 (95% CI 1.07,1.43) immediately after tx, 1.70 (1.17,2.46) at 3 months, 1.79 (1.13,2.82) at 6 months compared to control or sham interventions.

d. Authors' conclusions: "Acupoint stimulation increases smoking cessation rate and reduces daily cigarette consumption. Multi-modality treatment,

especially acupuncture combined with smoking cessation education..., can help."

5) **Di 2014**[v] (Drug and Alcohol Dependence Journal) "A Meta-Analysis of Ear-Acupuncture, Ear-Acupressure and Auriculotherapy for Cigarette Smoking Cessation"
   a. Did not take body acupuncture or laser therapy into account.
   b. n = 25 RCTs, two pools: 1) comparing to inactive control and 2) comparing to other smoking cessation specific treatment.
   c. Pool 1) immediate RR = 1.77 (1.39, 2.25), 3 months RR = 1.54 (1.14, 2.08), 6 months RR = 2.01 (1.23, 3.28), insufficient data for 12 months. Pool 2) "no superiority or inferiority...[immediately] or at 3 and 6 month follow-ups." Small trials.
   d. Authors' conclusions: Ear acupuncture, ear acupressure and auriculotherapy is superior to inactive controls for smoking cessation immediately and at 3 months and 6 months.
6) **Tahiri 2012**[vi] Meta-analysis in American Journal of Medicine
   a. n = 6 acupuncture trials (823 patients). All 6 were included in Di 2014 meta-analysis and 5 of them included in White 2014. The sixth RCT (Kerr 2008) was classified as laser therapy and excluded from White 2014.
   b. OR = 3.53 (1.03,12.07)
   c. Very wide confidence interval.
   d. Authors' conclusions: "acupuncture...may help smokers quit."

Expert input:
From Laura Ocker, Lac

February 18 2016

I think 12 acupuncture treatments is a good starting point for pain / chronic pain conditions. For smoking cessation, more treatment would be warranted (assuming the patient is truly making progress). For smoking cessation, my recommendation to patients is 2-3 visits per week the first two or three weeks and then 1-2 times per week for several weeks following. Then I am available for a few follow-up appointments throughout the year when stressors trigger the urge to start smoking again. **So, I'd say 18 treatments would be better.** For the person who is truly making progress. If I treat them 3-5 times and they show no signs of cutting down or quitting, I suggest they pursue other options or come back when they feel more ready.

Would be great to combine acupuncture with CBT or other therapies, but I wouldn't necessarily make it a requirement. If someone is doing really well with acupuncture alone, they may not need the additional support. Or vice versa. Also, there are times when medications are not appropriate, such as pregnancy or for patients who are medication-adverse, and this is another good area for acupuncture.

I'd say 18 treatments is a good number for private practice. Although in community health center / community acupuncture settings where a patient can come in more easily and more often for a drop-in treatment (and where you're more likely to be seeing Medicaid patients and people with multiple chronic health conditions and other significant life stressors) up to 24-30 treatments (IF MAKING PROGRESS) would be completely reasonable.

I would recommend 18. I would expect my colleagues to be ethical enough to not treat past the first couple of weeks if the patient has not quit or substantially reduced the number of cigarettes per day.

March 2015

I think that smoking cessation may be one of those conditions, like so many others, for which we see a high degree of efficacy in clinical practice, but for which there may not adequate evidence to support the use of acupuncture as a treatment option from a coverage standpoint. My colleagues and I find that acupuncture and Oriental medicine is a helpful therapy for smoking cessation - in that it reduces cravings and withdrawal symptoms and reduces associated symptoms such as anxiety, rage, nervousness, frustration, etc. Acupuncture alone, or often combined with other therapies, such as CBT or use of nicotine products gradually weaned under a physician's guidance, is very helpful to people who would like to quit smoking. I would like to see acupuncture remain an option for smoking cessation.

HERC staff summary

Four meta-analyses (White 2014, Di 2014, Cheng 2012, and Tahiri 2012) came to varying conclusions, either finding superiority of acupuncture over control/sham at 0-6 months or inconclusive. The differences between the meta-analyses was most attributable to differing methods of pooling. In general, the widely varying acupuncture techniques and protocols used in RCTs let to the inability to draw firm conclusions on effectiveness.

The general staff conclusion is that acupuncture may be helpful for smoking cessation, and is definitely not harmful. The number of visits used in study protocols ranged from 3-20, but were generally fewer than recommended by experts. There is insufficient evidence about the need to pair acupuncture with other therapies for smoking cessation.

HERC staff recommendations:

1) Modify GN92 Acupuncture as shown below
    a. 18 visits maximum

GUIDELINE NOTE 92, ACUPUNCTURE (ADAPTED FROM THE OCT. 1, 2015 PRIORITIZED LIST†)

Lines 1,208,351,415,467,532,543 (Lines 351 and 532 represent lines 374 and 545 from the Oct. 1, 2015 Prioritized List†)

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

Line 1 PREGNANCY

Acupuncture pairs on Line 1 for the following conditions.

Hyperemesis gravidarum

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

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

Breech presentation

ICD-10-CM: O32.1

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

Back and pelvic pain of pregnancy

ICD-10-CM: O99.89

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

Line 5 TOBACCO DEPENDENCE

Acupuncture is included on this line for a maximum of 18 sessions.

Line 208 DEPRESSION AND OTHER MOOD DISORDERS, MILD OR MODERATE

Acupuncture is paired with the treatment of post-stroke depression only. Treatments may be billed to a maximum of 30 minutes face-to-face time and limited to 12 total sessions, with documentation of meaningful improvement.

Line 351 DISORDERS OF SPINE WITH NEUROLOGIC IMPAIRMENT (Line 374 from the Oct. 1, 2015 Prioritized List†)

Acupuncture is included on Line 351 (Line 374 from the Oct. 1, 2015 Prioritized List†) only for pairing with disorders of the spine with myelopathy and/or radiculopathy represented by ICD-10-CM G83.4, M47.2, M50.0, M50.1, M51.0, M51.1, M54.1), for up to 12 sessions.

Line 415 MIGRAINE HEADACHES

Acupuncture pairs on Line 415 for migraine (ICD-10-CM G43.0, G43.1, G43.5, G43.7, G43.8, G43.9), for up to 12 sessions.

Line 467 OSTEOARTHRITIS AND ALLIED DISORDERS

Acupuncture pairs on Line 467 for osteoarthritis of the knee only (ICD-10-CM M17), for up to 12 sessions.

*Line 532 ACUTE AND CHRONIC DISORDERS OF SPINE WITHOUT NEUROLOGIC IMPAIRMENT (Line 545 from the Oct. 1, 2015 Prioritized List†)

Acupuncture pairs on Line 532 (Line 545 from the Oct. 1, 2015 Prioritized List†) with the low back diagnoses appearing on this line (ICD-10-CM M51.36, M51.86, M54.5, M99.03, S33.5, S33.9, S39.092, S39.82, S39.92). Acupuncture pairs with chronic (>90 days) neck pain diagnoses on this line (ICD-10-CM M53.82, M54.2, S13.4, S13.8), for up to 12 sessions.

*Line 543 TENSION HEADACHES

Acupuncture is included on Line 543 for treatment of tension headaches (ICD-10-CM G44.2), for up to 12 sessions.

The development of this guideline note was informed by a HERC evidence-based guideline. See http://www.oregon.gov/oha/herc/Pages/blog-low-back-non-pharmacologic-intervention.aspx

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[i] White, Adrian R., et al. "Acupuncture and related interventions for smoking cessation." *Cochrane Database Syst Rev* 1 (2014).

[ii] Patnode, Carrie D., et al. "Behavioral Counseling and Pharmacotherapy Interventions for Tobacco Cessation in Adults, Including Pregnant Women: A Review of Reviews for the US Preventive Services Task Force." *Annals of internal medicine* 163.8 (2015): 608-621.

[iii] McRobbie, Hayden, et al. "Rapid Review of Non NHS Treatments for Smoking Cessation." NICE (2007).

[iv] Cheng, Hsiao-Min, et al. "Systematic review and meta-analysis of the effects of acupoint stimulation on smoking cessation." *The American journal of Chinese medicine* 40.03 (2012): 429-442.

[v] Di, Yuan Ming, et al. "A meta-analysis of ear-acupuncture, ear-acupressure and auriculotherapy for cigarette smoking cessation." *Drug and alcohol dependence* 142 (2014): 14-23.

[vi] Tahiri, Mehdi, et al. "Alternative smoking cessation aids: a meta-analysis of randomized controlled trials." *The American journal of medicine* 125.6 (2012): 576-584.

Hyperbaric Oxygen Guideline

Question: Should the hyperbaric oxygen guideline be clarified/simplified?

Question source: HERC staff, CCO medical directors

Issue: The current hyperbaric oxygen guideline is confusing to many readers. HERC staff has worked to clarify language for this guideline.

Dr. Carl Stevens, a medical director with CareOregon, has suggested modifications to the guideline to clarify language. One specific request was to apply the requirement for re-evaluation of the wound healing to all conditions listed in the guideline, as all may or may not respond to hyperbaric oxygen therapy

Further staff suggested clarifications are:

1) Clarifying that there are many conditions included in this line (such as carbon monoxide poisoning, air embolism, etc.) which are not included in the guideline as the guideline is just a list of limitations for certain ICD-10 codes or restrictions on certain conditions
2) Applying the same restrictions as now apply to diabetic gangrenous wounds regarding need for reassessment at 30 days, etc. to all conditions that this restriction applied to in the CMS coverage determination, as the original intent was to mirror this. CMS applies restrictions to diabetic wounds of the lower extremities, peripheral ischemia, crush injuries, compromised skin grafts, osteoradionecrosis, and soft tissue radionecrosis.

Other issues found on review:

1) The ICD-10 code for osteoradionecrosis of the jaw is incorrect. Currently M27.8 (Other specified diseases of jaws) is included on this line, while the correct code is M27.2 (Inflammatory conditions of jaws) which is only on a dental line.

Guideline history

1) 2011, reviewed osteomyelitis and determined no evidence to support coverage
2) 2013, modified guideline wording to improve readibility
3) 2014, coverage guidance on hyperbaric oxygen was adopted and a modified guideline was adopted to reflect the coverage guidance recommendations. The diabetic wound portions of the guideline note were adopted with exact wording from the coverage guidance, except the addition of the requirement for re-evaluation every 30 days. This requirement was added to address medical director concerns and was based on the CMS coverage determination.
    a. Note: the CMS coverage determination actually applied the requirement for 30 day re-evaluation to ALL conditions treated with hyperbaric oxygen, not just diabetic wounds

Current guideline note:

GUIDELINE NOTE 107, HYPERBARIC OXYGEN

Line 337

Hyperbaric oxygen is a covered service only under the following circumstances:

- when paired with ICD-10-CM codes E11.5x and E11.621, E11.622 and E11.623 for diabetic wounds with gangrene OR diabetic wounds of the lower extremities in patients who meet the all of the following criteria:
    - Patient has Type 1 or Type 2 diabetes and has a lower extremity wound that is due to diabetes, AND
    - Patient has a wound classified as Wagner grade III or higher, AND
    - Patient has failed an adequate course of standard wound therapy including arterial assessment, with no measurable signs of healing after at least thirty days, AND
    - Wounds must be evaluated at least every 30 days during administration of hyperbaric oxygen therapy. Continued treatment with hyperbaric oxygen therapy is not covered if measurable signs of healing have not been demonstrated within any 30-day period of treatment.
- when paired with ICD-10-CM codes M27.8 for osteoradionecrosis of the jaw only
- when paired with ICD-10-CM codes O08.0, M60.000-M60.09 only if the infection is a necrotizing soft-tissue infection
- when paired with ICD-10 CM codes S07.xxx,S17.xxx,S38.xxx,S47.1xxA-S47.1xxD,S47.2xxA-S47.2xxD,S47.9xxA-S47.9xxD, S57.xxx,S67.xxx, S77.xxx,S87.xxx,S97.xxx, T79.Axx only for posttraumatic crush injury of Gustilo type III B and C
- when paired with ICD-10--CM codes T66.xxxA only for osteoradionecrosis and soft tissue radiation injury
- when paired with ICD-10-CM codes T86.820-T86.829,T82.898A/T82.898D, T82.9xxA/T82.9xxD, T83.89xA/T83.89xD, T83.9xxA/T83.9xxD, T84.89xA/T84.89xD, T84.9xxA/T84.9xxD, T85.89xA/T85.89xD, T859xxA/T859xxD only for compromised myocutaneous flaps

HERC staff recommendations:

1) Remove M27.8 (Other specified diseases of jaws) from line 337 and add M27.2 (Inflammatory conditions of jaws) to line 337
    a. M27.2 is the correct ICD-10 code for osteoradionecrosis of the jaw
2) Modify GN107 as shown below

[easier to read format]

GUIDELINE NOTE 107, HYPERBARIC OXYGEN

Line 337

Hyperbaric oxygen therapy is included on this line, subject to the following limitations:

1. Courses of treatment for wounds or ulcers are limited to 30 days after the initial treatment; additional 30 day treatment courses are only covered for patients with incomplete wound/infection resolution AND measurable signs of healing
2. For the diagnoses specified below, inclusion on this line is subject to the following additional limitations:
    a. Codes appearing on this line from ICD-10-CM E08-E13 are included only when they are diabetic wound ulcers of the lower extremities which are Wagner grade 3 or higher (that is, involving bone or gangrenous) and show no measurable signs of healing after 30 days of adequate standard wound therapies including arterial assessment
    b. ICD-10-CM M27.2 is included on this line for osteoradionecrosis of the jaw only
    c. ICD-10-CM O08.0 and M60.0 are included on this line only if the infection is a necrotizing soft-tissue infection
    d. ICD-10-CM S07, S17, S38, S47.1, S47.2, S47.9, S57, S67, S77, S87, S97, T79.A are included on this line only for posttraumatic crush injury of Gustilo type III B and C
    e. ICD-10-CM T66.XXXA-T66.XXXD are included on this line only for osteoradionecrosis and soft tissue radiation injury
    f. ICD-10-CM T86.82, T82.898, T82.9, T83.89, T83.9, T84.89, T84.9, T85.89, T85.9 are included on this line only for compromised myocutaneous flaps

[edited guideline format]

GUIDELINE NOTE 107, HYPERBARIC OXYGEN

Line 337

A course of ~~H~~hyperbaric oxygen treatment is included on this line ~~a covered service~~ subject to the following limitations: ~~only under the following circumstances~~:

1. Courses of treatment for wounds or ulcers are limited to 30 days after the initial treatment; additional 30 day treatment courses are only covered for patients with incomplete wound/infection resolution AND measurable signs of healing

~~when paired with ICD-10-CM codes E11.5x and E11.621, E11.622 and E11.623 for diabetic wounds with gangrene OR diabetic wounds of the lower extremities in patients who meet the all of the following criteria:~~

~~a. Patient has Type 1 or Type 2 diabetes and has a lower extremity wound that is due to diabetes, AND~~

~~b. Patient has a wound classified as Wagner grade III or higher, AND~~
~~c. Patient has failed an adequate course of standard wound therapy including arterial assessment, with no measurable signs of healing after at least thirty days, AND~~
~~d. Wounds must be evaluated at least every 30 days during administration of hyperbaric oxygen therapy. Continued treatment with hyperbaric oxygen therapy is not covered if measurable signs of healing have not been demonstrated within any 30-day period of treatment.~~

2. For the diagnoses specified below, inclusion on this line is subject to the following additional limitations:
    a. Codes appearing on this line from ICD-10-CM E08-E13 are included only when they are diabetic wound ulcers of the lower extremities which are Wagner grade 3 or higher (that is, involving bone or gangrenous) and show no measurable signs of healing after 30 days of adequate standard wound therapies including arterial assessment
    b. ~~when paired with~~ ICD-10-CM ~~M27.8~~ M27.2 is included on this line for osteoradionecrosis of the jaw only
    c. ~~when paired with~~ ICD-10-CM O08.0 and M60.0 are included on this line only if the infection is a necrotizing soft-tissue infection
    d. ~~when paired with diagnosis codes included on this line from~~ ICD-10-CM S07, S17, S38, S47.1, S47.2, S47.9, S57, S67, S77, S87, S97, T79.A are included on this line only for posttraumatic crush injury of Gustilo type III B and C
    e. ~~when paired with~~ ICD-10-CM T66.XXXA-T66.XXXD are included on this line only for osteoradionecrosis and soft tissue radiation injury
    f. ~~when paired with~~ ICD-10-CM T86.82, T82.898, T82.9, T83.89, T83.9, T84.89, T84.9, T85.89, T85.9 are included on this line only for compromised myocutaneous flaps

Pectus Excavatum and Pectus Carinatum

Question: Should pectus excavatum and pectus carinatum be moved to a higher priority line on the Prioritized List?

Question source: Kimberly Ruscher, MD, pediatric surgeon, through coverage guidance topic nomination process and direct contact with HERC; Garret Zallen from PeaceHealth through coverage guidance topic nomination process.

Issue: Currently, pectus excavatum (ICD-10 Q67.6) and pectus carinatum (Q67.7) are on line 665 MISCELLANEOUS CONDITIONS WITH NO OR MINIMALLY EFFECTIVE TREATMENTS OR NO TREATMENT NECESSARY. There are no surgical repair codes on line 665. These conditions are generally considered cosmetic.

Pectus excavatum is the most common congenital deformity of the anterior wall of the chest, in which several ribs and the sternum grow abnormally. This produces a caved-in or sunken appearance of the chest. It can either be present at birth or not develop until puberty. Pectus excavatum is sometimes considered to be cosmetic; however, depending on the severity, it can impair cardiac and respiratory function and cause pain in the chest and back. People with the condition may experience negative psychosocial effects. Pectus excavatum is sometimes referred to as cobbler's chest, sunken chest, the crevasse, or funnel chest. The severity of pectus excavatum is determined by the Haller index. The patient's Haller is calculated by obtaining the ratio of the transverse diameter (the horizontal distance of the inside of the ribcage) and the anteroposterior diameter (the shortest distance between the vertebrae and sternum) from a chest CT scan. A Haller Index of greater than 3.25 is generally considered severe, while normal chest has an index of 2.5. Surgical correction is done with implants (cosmetic results only) or a more extensive surgical correction, generally with the Nuss procedure in which a metal bar is placed to push the sternum outward; this procedure allows correction of cardiopulmonary issues as well as the cosmetic chest defect. Magnetic mini-movers and vacuum bells are also used, which are non-surgical attempts at correction.

Pectus carinatum, also called pigeon chest, is a deformity of the chest characterized by a protrusion of the sternum and ribs. It is normally treated with bracing. Surgical correction is done for very severe cases.

Poland syndrome (ICD-10 Q79.8), a more severe form of chest wall deformity, is coded with the generic ICD-10 code Q79.8 (Other congenital malformations of musculoskeletal system) which is currently on line 530 DEFORMITIES OF UPPER BODY AND ALL LIMBS. Poland syndrome is a rare birth defect characterized by underdevelopment or absence of the pectoralis chest muscle on one side of the body, and usually has finger and hand abnormalities on the same side. Additional muscles in the chest wall and adjacent areas can be missing or underdeveloped. There may also be rib cage abnormalities, such as shortened ribs. In most cases, the abnormalities in the chest area do not cause health problems or affect movement.

From Dr. Ruscher

I am a Pediatric Surgeon here in Oregon, currently working at Sacred Heart Medical Center at Riverbend in Springfield and at Shriner's Hospital in Portland. One of my areas of interest is caring for children and young adults with chest wall deformities. This email is to ask that you review two conditions, Pectus Carinatum, Q67.7 and Pectus excavatum, Q67.6, to include treatment. I would like to present public comment during the January meeting, and will provide written testimony and reference materials ahead of that time. Regarding this matter, I have no conflicts of interest; specifically, I am a salaried employee of PeaceHealth, and am not compensated for my work at Shriners. I would not benefit in any way from a change in coverage for these conditions.

Pectus carinatum (incidence 1 in 1000) and pectus excavatum (incidence 1 in 500) are common chest wall deformities affecting children. Until the early 20th century, there were no treatments available. Nearly 100 years ago, surgeons developed procedures for these conditions. The surgery was quite invasive and for some children had devastating complications. In many cases, the treatment was worse than the disease. After this time, chest wall deformities were treated as cosmetic and only the worst patients were sent for surgery. Further, little was known in the medical literature about the long term effects of untreated chest wall deformities.

The teaching that chest wall deformities are cosmetic has persisted, though the knowledge about and therapy for these conditions has improved greatly. Research has clearly demonstrated that there are long-term physiological effects especially of having pectus excavatum, and that modern therapies are safe and effective. Pectus carinatum can be completely treated in 90-95% of children with a simple bracing protocol, and pectus excavatum can be diagnosed with little work-up and treated with a minimally invasive surgery.

From Dr. Ruscher's coverage guidance review request

Q5: What is the specific intervention that requires an evidence review?
Bracing for pectus carinatum; Surgery for pectus excavatum
Q6: What patients or group(s) of patients does your question involve?
Any patient with pectus carinatum; Patients with pectus excavatum with moderate defect, Haller index of 3.25 or higher, or co-morbidities (cardiac compression, shortness of breath, chest pain, cardiac rhythm abnormalities)
Q7: What treatment alternatives are relevant to your question?
Pectus carinatum- bracing is 90-95% effective; failure of bracing would require surgery for treatment. Pectus excavatum- other treatments (magnet mini-mover or vacuum bell) are under trial but have not demonstrated long term efficacy.
Q8: Describe any health-related outcomes (benefits or harms) of interest.
Pectus carinatum - bracing could fail, especially if started too late in life. Pectus excavatum - complications of surgery or from the implant could occur.

Q9: Why are you suggesting this topic? How would a HERC coverage guidance be useful to patients, providers or policy makers? Check all that apply

- Intervention is more effective
- Intervention has fewer harms
- Other (please specify) These defects were formerly considered cosmetic or to have no good treatments. New research is available.

Q10: Why did you decide to bring this topic to the HERC's attention? Why should the HERC spend its time on this over other topics?
These are common conditions (for example, pectus excavatum affects at least 1 in 500) that cause physical and emotional problems in the short and long term, with good treatment options. Bracing for pectus carinatum is especially cost -effective compared to surgery.

From Mr. Zallen's coverage guidance review request

Q5: What is the specific intervention that requires an evidence review?
Thoracoscopic assisted Pectus Excavatum repair
Q6: What patients or group(s) of patients does your question involve?
Pectus Excavatum
Q7: What treatment alternatives are relevant to your question?
There is no effective non-surgical treatment
Q8: Describe any health-related outcomes (benefits or harms) of interest.
Improved cardiac function and improved lifestyle
Q9: Why are you suggesting this topic? How would a HERC coverage guidance be useful to patients, providers or policy makers? Check all that apply

- Intervention is more effective
- Intervention has fewer harms

Q10: Why did you decide to bring this topic to the HERC's attention? Why should the HERC spend its time on this over other topics?
One in 500 people suffer from chest wall deformities and Pectus Excavatum is the most common. It has physiological consequences as well as significant body image issues in those who have PE.

Current Prioritized List status

Q67.6 (pectus excavatum) is on line 665 MISCELLANEOUS CONDITIONS WITH NO OR MINIMALLY EFFECTIVE TREATMENTS OR NO TREATMENT NECESSARY
Q67.7 (pectus carinatum) is on line 665
Q76.6-Q76.9 (congential malformation of ribs/sternum/bony thorax) are on line 530 DEFORMITIES OF UPPER BODY AND ALL LIMBS

21740 Reconstructive repair of pectus excavatum or carinatum; open
21742 minimally invasive approach (Nuss procedure), without thoracoscopy
21743 minimally invasive approach (Nuss procedure), with thoracoscopy
All appear on line 530 DEFORMITIES OF UPPER BODY AND ALL LIMBS

Evidence—pectus excavatum

1) **de Oliveira Carvalho 2014**, Cochrane review of surgical interventions for pectus excavatum
    a. No RCT or quasi-RCTs found that met inclusion criteria
2) **Johnson 2008**, review of cardiopulmonary outcomes of pectus excavatum repair
    a. N=11 studies (387 patients), various surgical methods
    b. Postoperative total lung capacity for patients who had Ravitch repair was significantly lower (SMD, 0.71 [CI -1.06, -0.36]; I2 =19.6%) than preoperative. Based on 2 studies after removal of the Nuss bar, FEV1 was significantly increased from preoperative values (SMD, 0.39 [CI, 0.03, 0.74]; I2 = 0%). Stroke volume increased after surgery (SMD, 0.40 [CI, 0.10, 0.70]; I2 = 0%) after Ravitch repair. There was a trend toward improved exercise tolerance, but it was not statistically significant.
    c. Conclusions: Total lung capacity was decreased after Ravitch repair, and FEV1 was increased after Nuss bar removal. Stroke volume may be increased after Ravitch repair. Exercise tolerance was not improved after either type of surgical repair.
3) **Guntheroth 2007**, review of studies on cardiac function outcomes of pectus excavatum surgery
    a. N=5 studies (118 patients, 82 controls)
    b. No improvements were found in left ventricular size, stroke volume, and cardiac output after surgery in 4 of 5 studies, using radionuclides, 2-dimensional echocardiography, radiographic planimetry, and cardiac output by the Fick method. Only a single study, with volumes calculated by squaring the diameter of the left ventricle from M-mode echocardiography, reported an increase (22%) in left ventricular stroke volume after operation, but that increased (17%) in the investigators' unoperated controls.
    c. In conclusion, there is no reliable documentation of improved cardiac function from thoracic surgery for pectus excavatum.
4) **Malek 2006,** review and meta-analysis of cardiac outcomes of surgical repair of pectus excavatum
    a. N=8 studies (169 patients)
    b. Random-effects modeling yielded a mean weighted effect size (ES) for cardiovascular function that was statistically significant (ES, 0.59; 95% confidence interval, 0.25 to 0.92; $p < 0.0006$).
    c. *Conclusions:* The findings of the present study indicated that surgical repair of the pectus excavatum significantly improves cardiovascular function and contradicts arguments that surgical repair is primarily cosmetic yielding minimal physiologic improvement.
5) **Malek 2006,** review and meta-analysis of pulmonary outcomes of surgical repair of pectus excavatum
    a. N=12 studies (313 patients)

b. Random-effects modeling yielded a mean weighted effect size (ES) for pulmonary function which was statistically nonsignificant (ES = 0.08, 95% CI = -0.20 to 0.35; P = 0.58). The findings of the present study indicated that surgical repair of pectus excavatum does not significantly improve pulmonary function. These findings, however, may be a result of testing pulmonary function under conditions in which pectus excavatum does not manifest itself.

Submitted evidence—pectus excavatum

1) **Jayaramakrishnan 2013**, systematic review
    a. N=22 papers, studies grouped by type of repair
    b. Nuss repair (N=4 studies)
        i. Pulmonary function and exercise tolerance 3-6 months post-op decreased
        ii. Studies after 6 months found improvement in pulmonary and cardiac function
        iii. The majority of the studies performed post-bar removal demonstrated a small but significant improvement in pulmonary function
    c. Ravich procedure
        i. Early post op to 8 months post-op, studies found no improvement in or reduced pulmonary function. Late post-op (1 study) found modest improvement in pulmonary function only in a subgroup with severely reduced pulmonary function (FEV1 < 75% predicted) preoperatively.
        ii. Significant improvements in cardiac function including right ventricular diastolic volume indexes were noted.
    d. Other procedures:
        i. Reduced pulmonary function found short and long term
    e. Conclusions: Pectus repair using minimally invasive Nuss technique and Ravitch procedure cause an early decrease in the pulmonary function. However, a small, but significant, return of function does occur during the late postoperative period. Cardiac function increases during the early postoperative period, an improvement that is sustained [improvement noted to be modest]. In contrast, pectus repair using other techniques has not shown similar improvements.

2) Chao 2015
    a. Retrospective case series of 168 adults undergoing modified Nuss repair
    b. There was an increase in right atrium (15.1%), tricuspid annulus (10.9%), and right ventricular outflow tract (6.1%) size after surgery (all P<0001). Right ventricular cardiac output measured in a subset of 42 patients improved by 38%.
    c. No change in chamber size or cardiac output occurred before and after bar removal surgery in the control group.
        i. Note: control group had previously had surgery and were undergoing bar removal. N=17 pts, average time after initial Nuss surgery 3 years

d. Exercise capacity or other patient centered outcomes not studied
e. ECHO readers not blinded to type of surgery
f. CONCLUSIONS: Surgical correction of PE deformity caused a significant improvement in right heart chamber size and cardiac output.

3) O'Keefe 2013

a. Case series, N=67 patients (excluded patients with connective tissue disorders or other co-morbidities)
b. Cardiopulmonary outcomes, standardized for height and weight, showed significant improvements in FEV-1 as (pre) 81.1±17.0 vs post 89.8±20.5*, FVC: 91.2±18.6 vs 98.9±22.9*, O2 pulse: 75.8±14.4 vs 80.5±18.3* (each as % predicted). Both the self-ratings of appearance (2.5±0.8 vs 4.4±0.5) and ability to exercise (3.3±0.7 vs 4.3±0.6, scale 1–5) increased significantly.
c. No improvements seen in cardiac dynamics at rest
d. Conclusions: the results of this study show a modest improvement in pulmonary function and exercise testing in moderate to severe pectus defects when repaired with the Nuss procedure. However, it is the impact on appearance and the perceived exercise tolerance that show the greatest improved with pectus repair.

4) **Maagaard 2013/Tang 2012** (appear to be reporting on same patient group)

a. Prospective case series of 75 patients (49 with PE, 26 controls)
    i. Haller index of PE patients 5.3 +/- 2.3 pre-operatively (i.e. more severely affected patients)
b. PE patients underwent Nuss procedure
c. Preoperatively, PE patients had lower maximum cardiac index. Cardiac index increased significantly 1 year after surgery, and there was no difference between PE patients and controls at 3 years post-op
d. Forced expiratory volume (FEV1) was significantly lower in PE patients prior to surgery; there was no significant difference found between groups post-operatively
e. Before operation, the patients exercised less than the controls, and there was no difference in training level one year after the operation, although this was mainly due to less activity in the control group.

5) **Krueger 2010**

a. Prospective case series of 17 patients studied with intraoperative ECHO during PE repair with Ravitch-Shamberger technique
b. End diastolic RV diameter, area, and volume all significant increased after surgery. LV ejection fraction also significantly increased after surgery
c. No correlation found in degree of RV function improvement and degree of pre-op degree of chest wall deformity
d. No report regarding clinical impact, exercise tolerance change, or other outcomes

6) Kelly 2005

a. Autopsy series of 62 patients
    i. 35 died of other causes

ii. 21 found to have co-existing conditions or syndromes
iii. 1 died of complications of pectus repair in 1947
iv. 5 children cause of death not mentioned
v. No data on severity of pectus deformity
vi. Pectus excavatum patients tended to die earlier (P = .0001). However, pectus excavatum patients who survived past the age of 56 years tended to survive longer than their matched controls (P = .0001).

Evidence—Pectus carinatum

1) **Kravarusic 2006,** case series of chest bracing for pectus carinatum
    a. N=24 patients
    b. Nineteen (79.2%) patients have completed initial treatment (mean CP time, 4.3 F 2.1 months). There were 3 patients (12.5%) who were noncompliant, and 2 (8.3%) are still in the initial CP phase of therapy. Fourteen (58.3%) patients are presently in maintenance phase, nocturnally braced, and 2 (8.3%) have completed therapy. In patients completing initial treatment, the pectus carinatum protrusion (pre 22 F 6 vs post 6.0 F 6.2) and subjective appearance (change + 1.8F0.4) showed a significant improvement (P > .001 for both) with no change in exercise tolerance.
    c. Conclusion: Compressive bracing results in a significant subjective and objective improvement in PC appearance in skeletally immature patients. However, patient compliance and diligent follow up appear to be paramount for the success of this method of treatment. Further studies are required to show the durability of this method of treatment.
2) **Desmarais 2013**, review of pectus carinatum
    a. Recent evidence confirms that children with pectus carinatum have a disturbed body image and a reduced quality of life. Treatment has been shown to improve the psychosocial outcome of these patients.
    b. A growing body of literature, however, now supports the use of orthotic bracing as a nonoperative alternative in select patients.

Submitted evidence—pectus carinatum

1) Knudsen 2015
    a. Prospective case series (N=28 patients)
    b. Disease-specific health-related quality of life was improved by 33% (95% CI: 23; 44%)—the instrument used included all questions about perceived appearance and how this affected life
    c. The improvement for generic mental health-related quality of life was 7% (95% CI: 3; 12%). The improvement in self-esteem was 9% (95% CI: 2; 17%)
    d. No significant improvement in depression or anxiety
    e. Conclusion: This study confirms positive effects of surgical correction of pectus carinatumon health-related quality of life and self-esteem.

Other policies

1) **NICE 2009**
    a. Current evidence on the safety and efficacy of placement of pectus bar for pectus excavatum (also known as MIRPE [minimally invasive repair of pectus excavatum] or the Nuss procedure) is adequate to support its use
    b. Key efficacy outcomes in the review were cosmetic appearance and patient satisfaction
        i. Outcomes listed in review were improved quality of life, self-esteem and cosmetic appearance scores
2) **Cigna 2009**
    a. Under many benefit plans, surgery for chest wall deformities is not covered when performed solely for the purpose of improving or altering appearance or self-esteem or to treat psychological symptomatology or psychosocial complaints related to one's appearance.
    b. If coverage for surgical repair of chest wall deformities is available, the following conditions of coverage apply.
        i. CIGNA covers surgical repair of severe pectus excavatum as medically necessary when imaging studies (e.g., computerized tomography [CT] scans, radiographs) confirm a pectus index (i.e., Haller index) greater than 3.25 and EITHER of the following criteria is met:
            1. Pulmonary function studies demonstrate at least a moderately severe restrictive lung defect.
            2. Cardiac imaging (e.g., echocardiography, stress echocardiography, magnetic resonance imaging [MRI]) demonstrates findings consistent with external compression.
    c. CIGNA covers surgical repair of pectus carinatum as medically necessary when there is documented evidence of significant physical functional impairment (e.g., cardiac or respiratory insufficiency), and the procedure is expected to correct the impairment
    d. CIGNA covers the surgical repair of a chest deformity associated with Poland syndrome as medically necessary when rib formation is absent.
3) **Aetna 2015** Aetna considers surgical repair of severe pectus excavatum deformities that cause functional deficit medically necessary when done for medical reasons in members who meet all of the following criteria:
    a. Well-documented evidence of complications arising from the sternal deformity. Complications include but may not be limited to:
        i. Asthma
        ii. Atypical chest pain
        iii. Cardiopulmonary impairment documented by respiratory and/or cardiac function tests
        iv. Exercise limitation
        v. Frequent lower respiratory tract infections; *and*

b. An electrocardiogram or echocardiogram has been done if a heart murmur or known heart disease is present to define the relationship of the cardiac problem to the sternal deformity; a*nd*
c. A CT scan of the chest demonstrates a pectus index, derived from dividing the transverse diameter of the chest by the anterior-posterior diameter, greater than 3.25.
d. Aetna considers surgical repair of pectus excavatum cosmetic when criteria are not met.
e. Aetna considers the following interventions for the treatment of pectus excavatum experimental and investigational because their effectiveness has not been established;
    i. The magnetic mini-mover procedure
    ii. The vacuum bell
    iii. Dynamic Compression System
f. Aetna considers surgical reconstruction of musculo-skeletal chest wall deformities associated with Poland's syndrome that cause functional deficit medically necessary
g. Aetna considers bracing and surgical procedures to correct pectus carinatum cosmetic because this deformity does not cause physiologic disturbances from compression of the heart or lungs.

4) **<u>United Indications for Coverage</u>**
    a. Surgical repair of pectus excavatum is considered reconstructive and medically necessary when the following criteria has been met:
        i. Pectus Excavatum
            1. Imaging studies confirm Haller index greater than 3.25; and
            2. The functional impairment is defined by one or more of the following:
                a. For restrictive lung capacity the total lung capacity is documented in the physician current office notes as <80% of the predicted value; or
                b. There is cardiac compromise as demonstrated by decreased cardiac output on the echocardiogram; or
                c. There is objective evidence of exercise intolerance as documented by:
                    i. Cardiopulmonary exercise testing that is below the predicted values; or
                    ii. Exercise pulmonary function tests that are below the predicted values and show restrictive lung disease
        ii. Pectus Carinatum
            1. It is extremely uncommon that pectus carinatum will cause a functional/physiological deficit. Pectus carinatum is not a congenital anomaly; it is a developmental condition of the cartilage that generally occurs during an adolescents growth

spurt. (Goretsky, 2004) Requests for coverage of repair of pectus carinatum will be reviewed by a UHC Medical Director on a case by case basis.

5) **HealthPartners Indications for Coverage**
   a. Pectus Excavatum:
      i. All of the following criteria must be met for coverage of repair of pectus excavatum:
         1. A Pectus/ Haller Index greater than 3.25 (calculated by using chest measurements from a CT scan of the area of the chest with the greatest depression.)
         2. Exercise limitation with symptoms OR chest pain related to pectus excavatum present for more than six months and unresponsive to more conservative treatment. Documentation of either of these is required.
         3. Diminished cardiopulmonary function during exercise, documented by lung/cardiac function tests (i.e. 20% depression of cardiopulmonary function.); and
         4. Cardiologist/pulmonologist concurs with need for surgical correction.
      ii. Pectus Carinatum repair is not covered unless there is documentation in the medical record of related functional problems.
      iii. Repairs for cosmetic reasons are not covered.

HERC staff summary:

Pectus excavatum: The literature is conflicting regarding whether surgical repair of pectus excavatum improves cardiac or pulmonary function or exercise tolerance, based on large case series and case-control studies. At best, there is a modest improvement in cardiopulmonary function long term, with short term decreases in pulmonary function after surgery. The vast majority of the literature reports on intermediate outcomes such as cardiac ejection fraction or forced expiratory volume, rather than patient oriented outcomes such as exercise tolerance. Cases with severe deformities causing measurable cardiac or pulmonary impairment or patients with certain co-morbidities may benefit more from surgical intervention than less impacted individuals.

Pectus carinatum: There is no evidence that surgical correction or bracing of this condition improves cardiac or pulmonary outcomes or improves other health outcomes. Correction of this condition appears to be solely cosmetic.

HERC staff recommendations:

1) Keep Q67.7 (pectus carinatum) on line 665 MISCELLANEOUS CONDITIONS WITH NO OR MINIMALLY EFFECTIVE TREATMENTS OR NO TREATMENT NECESSARY
    a. Treatment is cosmetic
2) Move Q67.6 (pectus excavatum) from line 665 MISCELLANEOUS CONDITIONS WITH NO OR MINIMALLY EFFECTIVE TREATMENTS OR NO TREATMENT NECESSARY to line 530 DEFORMITIES OF UPPER BODY AND ALL LIMBS
    a. CPT codes for Nuss procedures and other repair procedures (CPT 21740-21743) are on line 530 and would pair with this diagnosis
    b. Similar conditions Q76.6-Q76.9 (congential malformation of ribs/sternum/bony thorax) are on line 530
    c. Movement would continue non-coverage for this condition due to the prioritization of line 530 below the current funding line
    d. Very severe cases could be reviewed for surgical repair through the exceptions process. The CCO medical directors report approving cases through the co-morbidity rule when cardiac or pulmonary dysfunction has been present.
    b. Alternative:
        i. Add Q67.6 to line 406 BENIGN CONDITIONS OF BONE AND JOINTS AT HIGH RISK FOR COMPLICATIONS in addition to adding to line 530 and removing from line 665.
        ii. Add Q79.8 (Other congenital malformations of musculoskeletal system) to line 406 and keep on line 530.
        iii. Add a new guideline note shown as the first entry below

HERC staff recommended wording:

GUIDELINE NOTE XXX PECTUS EXCAVATUM

Lines 406, 530

Pectus excavatum (ICD-10 Q67.6) is included on line 406 only for patients with all of the following

1) severe deformity (Haller index >3.25) AND
2) exercise limitation with symptoms related to pectus excavatum present for more than six months and unresponsive to more conservative treatment AND
3) Documented pulmonary or cardiac dysfunction demonstrated by either
    a. pulmonary function studies demonstrating at least a moderately severe restrictive lung defect OR
    b. Cardiac effects to include cardiac compression or displacement, bundle branch block or other cardiac pathology secondary to compression of the heart AND
4) cardiologist/pulmonologist concurs with need for surgical correction AND
5) these conditions are reasonably expected to be relieved with surgery.

Otherwise, this condition is included on line 530.

ICD-10 Q79.8 is included on line 406 only for Poland syndrome. Other diagnoses using this code are on line 530. Surgical reconstruction of musculo-skeletal chest wall deformities associated with Poland's syndrome are only included on line 406 when causing functional deficit(s).

Dr. Ruscher suggested guideline wording:

GUIDELINE NOTE XXX PECTUS EXCAVATUM

Lines 406, 530

Pectus excavatum (ICD-10 Q67.6) is included on line 406 only for patients with

1) severe deformity (Haller index >3.25), history of failed repair, progression of deformity AND one of either
    a. Cardiac effects to include cardiac compression or displacement, mitral valve prolapse, bundle branch block or other cardiac pathology secondary to compression of the heart, OR
    b. Pulmonary function studies demonstrating at least a moderately severe restrictive lung defect, OR
    c. Exercise limitation with symptoms, OR
    d. Atypical chest pain, OR
    e. Poland syndrome or connective tissue disorder, OR
    f. Paradoxical movement of the chest wall with deep inspiration, OR
    g. Significant body image disturbance
2) AND these conditions are reasonably expected to be relieved with surgery.

Otherwise, this condition is included on line 530.

Disposition of submitted literature

1) Li 2015
    a. Case study; higher level of evidence found
2) Kinuya 2005
    a. Case series of 3 patients; higher level of evidence found
3) Tardy 2015
    a. Prospective case control series; PE patients had decreased maximal exercise tolerance compared to controls
    b. Report was a letter with little data provided; unclear if peer reviewed
4) Sigalet 2003
    a. Included in Jayaramakrishnan 2013
5) Lawson 2005
    a. Included in Jayaramakrishnan 2013
6) Coln 2006
    a. Included in Jayaramakrishnan 2013
7) Redlinger 2010
    a. Examined outcomes in Marfan patients with PE; did not directly address question for this review
8) St Peter 2011
    a. Study regarding new measure for PE severity; Did not directly address question for this review
9) Koumbourlis 2015
    a. General review of condition; no specific evidence supporting treatment included
10) Castellani 2010
    a. Included in Jayaramakrishnan 2013
11) Sigalet 2007
    a. Included in Jayaramakrishnan 2013
12) Jaroszewski 2009
    a. Case study; higher level of evidence available
13) Poston 2014
    a. Involved index used to measure severity of disease; did not address the question at hand
14) Kaguraoka 1992
    a. Older study; newer studies available

Retractile Testicles

Question: Should the diagnosis code for retractile testicles (Q55.22) be returned to a covered line?

Question source: David Lashley, MD, pediatric urologist

Issue: during the ICD-10 urology review, ICD-9 752.52 and ICD-10 Q55.22 (retractile testicles) were moved from line 98 UNDESCENDED TESTICLE to line 662 GENITOURINARY CONDITIONS WITH NO OR MINIMALLY EFFECTIVE TREATMENTS OR NO TREATMENT NECESSARY, as there is no effective treatment for this condition.

Dr. Lashley has raised concerns that this condition needs continued monitoring by the patient's PCP, and in many cases, by a pediatric urologist. The initial consultation for this condition is covered, but not any follow up visits for monitoring. While he agrees that there is no treatment for this condition, he feels that it should be on a covered line to allow monitoring.

Retractile testis is considered as a testis that is located at the upper scrotum or lower inguinal canal and that can be made to descend completely into the scrotum without resistance by manual reduction but returns to its original position. Retractile testis has traditionally been considered as a variant of normal testis because it usually descends into the scrotum during adolescence and shows no difference in testicular volume or childbearing capacity compared with the normal testis. However, **Bae (2012)** found that 14% of boys with retractile testicle develop undescended testicle and require orchiopexy. That article concludes "Retractile testis has a risk of requiring orchiopexy. The risk is higher in the population diagnosed at a younger age. Boys with retractile testis should be observed periodically until the testis is descended in the normal position."

From Dr. Lashley:

> PCP's send us a lot of kids with a concern about undescended testicle..?25% or more of the time the testicles are retractile and do not require surgery. No problem…they are new patient visits so they get covered regardless of the diagnosis. I tell the family:
>
> Retractile testicles: The family and I talked about treatment options for retractile testicles. Etiologies of retractile testicles were discussed with the family including the benign nature of this condition, the lack of association with the future development of testicular cancer, and the tendency for the testicles to drop permanently into the scrotum normally between now and puberty. The family and I talked about the fact that surgery in general is not indicated as a treatment of retractile testicles. Alternative treatment options were discussed with the patient in detail. All questions were answered. The family gave fully informed consent to proceed with conservative therapy for their retractile testicles at this time.
>
> On occasion (7-12%) these retractile testicles may "ascend" with the child's linear

growth and subsequently require surgical repair. For this reason I recommend that annual genital examinations at his well child visits continue to document the ability to bring the testicles into the dependant scrotum. I would be happy to see him back if there are ongoing questions or concerns. The patient/family was given instructions to call for incomplete descent of the testicles over time, scrotal/groin/abdominal pain, especially if associated with nausea, vomiting, swelling redness, etc.

so when the pcp checks the next year and can not get the testicle(s) into the scrotum they send them back for re eval. if the testicle is ascended..i am covered as the dx is now above the line. if the testicle is still retractile then i am not covered. it is a total hassle because pcp's will send the kids back to us with undescended testicle diagnosis and thus will not have the follow up visit authorized. i did not realize the retractile code is now BTL so i have a few claims which will not pay. The pcp's want to serve their patients so they often refer BTL diagnosis with ATL codes..which gets them in my door..but then i am often stuck trying to get paid for a BTL visit.

Utilization: For the period 1/1/14-9/30/15, more than >10000 billings (in any diagnosis position), with 4,402 are in the primary diagnosis position on the billing

HERC staff recommendation:

1) Remove ICD-10 Q55.22 (retractile testicle) from line 662 GENITOURINARY CONDITIONS WITH NO OR MINIMALLY EFFECTIVE TREATMENTS OR NO TREATMENT NECESSARY and add to line 98 UNDESCENDED TESTICLE
    a. Will allow specialty consultation and monitoring visits

Telemedicine for Retinopathy of Prematurity

Question: Should remote screening and monitoring (CPT 92227 and 92228) of infants for retinopathy of prematurity (ROP) be a covered service?

Question source: Dr. Michael Chiang, ophthalmologist at Casey Eye Institute

Issue: Premature infants in rural NICU's may not have access to pediatric ophthalmologists for the detection and treatment of retinopathy of prematurity, a leading treatable cause of childhood blindness in the US. Remote screening and monitoring via telemedicine is becoming increasingly common, and is endorsed by the American Academy of Pediatrics and the American Academy of Ophthalmology. Currently, remote imaging for retinal disease detection or monitoring (CPT 92227 and 92228) is on the diabetes lines, and on the chorioretinal inflammation line and the birth trauma line. Retinopathy of prematurity (ICD-10 H35.1) is located on line 278 RETINOPATHY OF PREMATURITY.

Fierson et al (2015) reviewed telemedicine for ROP. (http://pediatrics.aappublications.org/content/pediatrics/135/1/e238.full.pdf study not included in packet due to length)The review included 8 level one studies (1715 patients). The PPV was found to be 62-100%, and the NPV was found to be 68-100%. The final conclusion of the paper was that telemedicine was a useful adjunct to bedside binocular indirect ophthalmoscopy, but should not replace it. The paper reviews technical issues which should be addressed in future studies.

Current list status:
H35.1 (Retinopathy of prematurity) is on line 278 RETINOPATHY OF PREMATURITY
P07.2 (Extreme immaturity of newborn) is on lines 17 VERY LOW BIRTH WEIGHT (UNDER 1500 GRAMS) and 23 LOW BIRTH WEIGHT (1500-2500 GRAMS)
P07.3 (Preterm newborn) is on lines 17 and 23

92227 (Remote imaging for detection of retinal disease (eg, retinopathy in a patient with diabetes) with analysis and report under physician supervision, unilateral or bilateral) is on lines 8, 30, 100, 353, and 365
92228 (Remote imaging for monitoring and management of active retinal disease (eg, diabetic retinopathy) with physician review, interpretation and report, unilateral or bilateral) is on lines 100, 353, and 365

HERC staff recommendations:

1) Add CPT 92227 (Remote imaging for detection of retinal disease (eg, retinopathy in a patient with diabetes) with analysis and report under physician supervision, unilateral or bilateral) and 92228 (Remote imaging for monitoring and management of active retinal disease (eg, diabetic retinopathy) with physician review, interpretation and report, unilateral or bilateral) to lines 17 VERY LOW BIRTH WEIGHT (UNDER 1500 GRAMS) and 23 LOW BIRTH WEIGHT (1500-2500 GRAMS) and 278 RETINOPATHY OF PREMATURITY

Issue Summaries from the 3-10-2016 VbBS meeting

Implantable Cardiac Event Monitors

Question: Should implantable cardiac event monitors be a covered service?

Question source: Tracy Muday, MD, OHP Medical Director

Issue: Implantable cardiac event monitors (CPT 33282 and HCPCS C1764) are currently Excluded. Dr. Muday received a request for placement of this device for evaluation of cryptogenic stroke. The HSC reviewed this device in 2000 and placed it on the Excluded List; the rationale and documentation for this decision is not available. The minutes note that this decision was made with the input of specialty groups familiar with the procedure. This device has not been reviewed since 2000.

An insertable cardiac monitor, also referred to as an implantable loop recorder (ILR), is a small insertable device that continuously monitors heart rhythms and records them either automatically or when a hand-held patient assistant is used. Unlike Holter monitors (monitor for 1-7 days) or external cardiac loop recorders (monitor for 3-4 weeks), the ILR's record for about 3 years. They are most commonly used to evaluate fainting spells/transient loss of consciousness that remain unexplained after initial evaluation. ILRs are also used for evaluation of seizures, recurrent palpitations, lightheadedness and dizziness.

Cryptogenic ischemic stroke, one in which the origin of the emboli cannot be determined after full evaluation (e.g. ECG, 24 hours of telemetry, echocardiogram, carotid ultrasound), make up nearly a quarter of all ischemic strokes. There is growing interest in the use of ICLRs to identify occult paroxysmal atrial fibrillation in patients with cryptogenic stroke (MED 2015).

Code	Code description	Placement
33282	Implantation of patient-activated cardiac event recorder	Services recommended for non-coverage table
33284	Removal of an implantable, patient-activated cardiac event recorder	290 COMPLICATIONS OF A PROCEDURE ALWAYS REQUIRING TREATMENT
C1764	Event recorder, cardiac (implantable)	Ancillary

Evidence

1) **MED 2015**, Implantable Loop Recorders for the Evaluation of Cryptogenic Stroke
    a. There is no high-quality comparative evidence on the use of implantable cardiac loop records or other ambulatory monitoring modalities on the initiation of oral anticoagulation or stroke recurrence in patients diagnosed with occult atrial fibrillation.
    b. In the past two years, four systematic reviews found increased detection of occult atrial fibrillation by ILCRs compared to other ambulatory monitoring efforts. However, these reviews do not report on change in management nor

impact on stroke recurrence (Afzal et al., 2015; Dussault et al., 2015; Kishore et al., 2014; Sposato et al., 2015). None of the systematic reviews identified head-to-head comparative trials of different ICLR devices or extended monitoring devices. The limited data available for inclusion in the reviews were based on observational trials with short follow up periods.

c. In a small, poor-quality cohort study of 61 patients receiving ICLRs, all received weeklong serial ECGs as well. The authors reported that within the first week of use, ILCR compared to serial ECG detected cases of intermittent atrial fibrillation at a 3:1 ratio. The authors did not discuss the potential clinical significance of this finding. This study did not observe any recurrent stroke or TIAs in their short follow-up period.
d. In a fair-quality, industry funded, RCT of 441 patients, higher rates of stroke and lower use of oral anticoagulation were observed in those randomized to conventional monitoring compared to ICLRs (i.e. baseline and serial ECGs every 6 months, thus not meeting strict inclusion criteria). At 6-and 12-months follow-up, the ICM group compared to controls had statistically significantly higher percentages of participants that received anticoagulation (6 months: 10.1% vs. 4.6%, P=0.04 and 12 months: 14.7% vs. 6.0%, P=0.007).
e. Among the included studies, adverse events were rare and included site infection, pocket erosion, pain, and irritation. A single patient experienced device failure from sub-optimal placement preventing rhythm detection.
f. Summary: Patients with ischemic stroke found to have atrial fibrillation on initial evaluation experience decreased risk of recurrent stroke with the use of oral anticoagulation therapy. In patients with cryptogenic stroke, despite an extensive initial evaluation without detection of atrial fibrillation, the use of prolonged monitoring demonstrates increased detection of paroxysmal or occult atrial fibrillation. The current literature is limited on the impact of the detection of occult atrial fibrillation through prolonged monitoring and subsequent initiation of anticoagulation on stroke recurrence. Clinicians and researchers are advocating for more comparative research to be conducted on ICLRs and their use in cryptogenic stroke, as well as the clinical impact of detecting occult atrial fibrillation in those with cryptogenic stroke.

2) **Parry 2010**, review of ILR for evaluation of unexplained syncope
   a. Conclusion: The ILR has entered routine clinical practice over the last 15 years with surprisingly few rigorous data. In this era of evidence-based practice, this requires to be addressed with a focus on high quality trials of up-to-the minute technology. In the interim, the ILR offers a useful adjunct in the investigation of unexplained syncope, particularly where an arrhythmic cause is suspected. Further controlled data are required to inform clinical practice with attention focused on empowering ILR-guided diagnosis, establishing the optimal timing of ILR use in syncope and embracing new technological advancements

Expert groups

1) **European Society of Cardiology 2009**, (http://europace.oxfordjournals.org/content/11/5/671 study not included in packet due to length) ILR position statement
    a. For management of transient loss of consciousness (TLoC)
        i. Class I. ILR is indicated:
            1. In an early phase of evaluation of patients with recurrent syncope of uncertain origin who have:
                a. absence of high-risk criteria that require immediate hospitalization or intensive evaluation and
                b. a likely recurrence within battery longevity of the device (Level of evidence A)
            2. In high-risk patients in whom a comprehensive evaluation did not demonstrate a cause of syncope or lead to specific treatment (Level of evidence B)
        ii. Class II A. ILR may be indicated:
            1. To assess the contribution of bradycardia before embarking on cardiac pacing in patients with suspected or certain neurally mediated syncope presenting with frequent or traumatic syncopal episodes (Level of evidence B)
        iii. Class II B. ILR may be indicated:
            1. In patients with T-LOC of uncertain syncopal origin in order to definitely exclude an arrhythmic mechanism (Level of evidence C)
    b. For diagnosis of undocumented palpitations
        i. Class IIA: ILRs may be indicated in selected cases with severe infrequent symptoms when ELRs and other ECG monitoring systems fail to document the underlying cause (Level of evidence B). The outcome of asymptomatic arrhythmias remains uncertain.
    c. For diagnosis of atrial fibrillation
        i. Continuous monitoring by implantable devices further increases the detection of AF, but it is hampered by misdetections and artefacts.
        ii. Technological improvements are required for significant reduction of maldetection. Manual analysis can improve diagnostic yield if stored electrograms are provided. The results of some on-going studies with new generation devices are awaited
        iii. The clinical relevance of Loop Recorders to guide medical and device therapy has yet to be demonstrated
    d. For risk stratification after MI
        i. The clinical usefulness of ILR to guide medical and device therapy in patients surviving myocardial infarction has yet to be demonstrated
        ii. ILRs have a potential role in identifying the correlation between symptoms and suspected ventricular tachyarrhythmia in selected high-risk patients affected by Brugada ECG pattern, long or short QT,

hypertrophic cardiomyopathy, and arrhythmogenic right ventricular dysplasia.

Other policies

1) **NICE 2010** http://guidance.nice.org.uk/cg109 (Study not included in packet due to length)
    a. For evaluation of transient loss of consciousness (TLoC) in adults: For people with a suspected cardiac arrhythmic cause of syncope, offer an ambulatory ECG and do not offer a tilt test as a first-line investigation. The type of ambulatory ECG offered should be chosen on the basis of the person's history (and, in particular, frequency) of TLoC. For people who have TLoC infrequently (less than once every 2 weeks), offer an implantable event recorder.
2) **Aetna 2015**
    a. Aetna considers an implantable loop recorder (e.g., Reveal Insertable Loop Recorder by Medtronic, Inc.) medically necessary for evaluation of recurrent unexplained episodes of pre-syncope, syncope, "seizures", palpitations, or dizziness when both of the following criteria are met:
        i. A cardiac arrhythmia is suspected as the cause of the symptoms; *and*
        ii. Either of the following criteria is met:
            1. For persons with heart failure, prior myocardial infarction or significant ECG abnormalities (see appendix), noninvasive ambulatory monitoring, consisting of 30-day presymptom external loop recordings or MCT, fails to establish a definitive diagnosis; *or*
            2. For persons without heart failure, prior myocardial infarction or significant ECG abnormalities (see appendix), symptoms occur so infrequently and unpredictably (less frequently than once per month) that noninvasive ambulatory monitoring (MCT or external loop recorders) are unlikely to capture a diagnostic ECG.
    b. Aetna considers implantable loop recorders experimental and investigational for all other indications because their effectiveness for indications other than the ones listed above has not been established.
3) **Cigna 2015**
    a. Cigna covers the use of an implantable loop recorder (CPT codes 33282, 33284, 93285, 93291, 93297, 93298, 93299, C1764, E0616) as medically necessary for the evaluation of recurrent unexplained episodes of fainting when ALL of the following criteria are met:
        i. cardiac arrhythmia is suspected to be the cause of fainting
        ii. noninvasive ambulatory monitoring failed to establish a definitive diagnosis because the symptoms occur so infrequently and unpredictably that the length of the monitoring period may have been inadequate to capture a diagnostic electrocardiogram (ECG) rhythm disorder
        iii. tilt-table testing is negative or nondiagnostic

HERC staff summary:
The use of implantable loop recorders (ILRs) appears to have evidentiary support and expert recommendations for use for evaluation of recurrent transient loss of consciousness in patients in whom a comprehensive evaluation including noninvasive ambulatory monitoring did not demonstrate a cause of the TLoC or lead to specific treatment, and in whom a cardiac cause is suspected, and in whom an event is expected to recur within the battery life of the ILR.

The use of ILRs for evaluation for possible atrial fibrillation as the cause of cryptogenic stroke appears to be an area of active research and controversy.

HERC staff recommendations:

1) Add coverage for the use of implantable loop recorders (ILRs) for the evaluation of recurrent transient loss of consciousness in selected patients. Do not add coverage for other indications due to their experimental nature
    a. Advise HSD to add CPT 33282 (Implantation of patient-activated cardiac event recorder) to the Diagnostic Procedures File and remove from the Services Recommended for Non-Coverage Table
    b. Advise HSD to add HCPCS C1764 (Event recorder, cardiac (implantable)) to the Diagnostic Procedures File and remove from the Ancillary List
    c. Adopt the following Diagnostic Guideline Note

DIAGNOSTIC GUIDELINE DX, IMPLANTABLE LOOP RECORDERS
Use of an implantable cardiac loop recorder (ILR) is a covered service only when the patient meets all of the following criteria:

1) The evaluation is for recurrent transient loss of consciousness (TLoC); and
2) A comprehensive evaluation including noninvasive ambulatory cardiac monitoring did not demonstrate a cause of the TLoC; and
3) A cardiac arrhythmia is suspected to be the cause of the TLoC; and
4) There is a likely recurrence of the TLoC within the battery longevity of the device.

ILRs are not a covered service for evaluation of cryptogenic stroke or any other indication.

Electric Tumor Treatment Fields for Glioblastoma

Question: Should electric tumor treatment field therapy be covered for initial treatment of glioblastoma?

Question source: Andy Luther, MD, OHP medical director

Issue: Electric tumor treatment field therapy (ETTF) involves a portable device which delivers low-intensity, intermediate frequency electric fields via non-invasive, transducer arrays. It is thought to physically interfere with tumor cell division. Glioblastoma is a very difficult to treat cancer of the brain with a typical life expectancy with current therapy of 1-2 years. Standard treatment involves surgical resection, radiation therapy, and chemotherapy.

ETTF therapy was reviewed for treatment of recurrent glioblastoma in May, 2014. At that time, little evidence was found to support its effectiveness and it was found to be less cost effective than conventional therapy for recurrent glioblastoma. The HCPCS codes for this therapy (HCPCS A4555 and E0766) were placed on the Services Recommended for Non-Coverage Table.

ETTF recently received FDA approval for initial treatment of glioblastoma. This approval was based on the results of a single trial of 695 participants.

A4555	Electrode/transducer for use with electrical stimulation device used for cancer treatment, replacement only
E0766	Electrical stimulation device used for cancer treatment, includes all accessories, any type

From Dr. Luther:

> … had a request for the Optune "tumor treating fields" system for treatment of glioblastoma in conjunction with temozolomide. It was FDA approved in October for certain patients, but Up-To-Date is fairly cautious about it's use given data available so far. We have an unfortunate patient that it might be appropriate for, and of course it is very expensive, OHP coverage not clear. There is now (as of October) an indication for treatment for newly diagnosed glioblastoma, after rad/chemo, in conjunction with ongoing temozolomide. I think the ancillary GL only addresses recurrent glioblastoma, so this may deserve another look, as it seems likely to keep coming up.

Originally approved entry in the Services Recommended for Non-Coverage Table
ELECTRONIC TUMOR TREATMENT FIELDS
Most recent review date: May, 2014
Electronic tumor treatment field therapy (ETTF; HCPCS A4555 and E0766) has been found to have significantly lower cost effectiveness compared to conventional chemotherapy for treatment of recurrent glioblastoma. See VBBS/HERC minutes from 5/8/14 for details [link].

Current entry in the Services Recommended for Non-Coverage Table

HCPCS A4555, E0766	Electronic tumor treatment field (ETTF) therapy	June, 2014	Found to have comparable effectiveness to conventional treatments, but significantly higher cost[3]

Evidence

Stupp 2015 (http://www.ncbi.nlm.nih.gov/pubmed/?term=26670971 Study not included due to length)

1) Randomized, non-controlled trial, open label trial of temozolomide chemotherapy alone vs temozolomide chemotherapy followed by TTF therapy for initial treatment of glioblastoma
2) N=695 patients (466 TTF+chemo, 229 chemo alone)
    a. Trial stopped after analysis of 315 patients (280 actually included in analysis after exclusions)
    b. Excluded patients who progressed rapidly after initial diagnosis and thus had the poorest prognoses
3) Intention to treat trial, endpoint was progression free survival
4) Median follow up 38 months (range, 18-60 months).
5) Median progression-free survival in the intent-to-treat population was 7.1 months (95%CI, 5.9-8.2 months) in the TTFields plus temozolomide group and 4.0 months (95%CI, 3.3-5.2 months) in the temozolomide alone group (hazard ratio [HR], 0.62 [98.7%CI, 0.43-0.89]; *P* = .001). Median overall survival in the per-protocol population was 20.5 months (95%CI, 16.7-25.0 months) in the TTFields plus temozolomide group (n = 196) and 15.6 months (95%CI, 13.3-19.1 months) in the temozolomide alone group (n = 84) (HR, 0.64 [99.4%CI, 0.42-0.98]; *P* = .004).
6) Further data analysis and follow up will be done; however, control patients were allowed to cross over to the ETTF group after official study termination and therefore future study results will be difficult to interpret
7) Significant differences in chemotherapy received by the TFF and control groups
    a. Number of cycles of temozolomide in the TTF group until disease progression=6 vs 4 cycles in the control group
    b. Second line chemotherapy received in 67% of the TTF group vs 57% of the temozolomide alone group
    c. Unclear if due to benefit of TTF (longer healthy life) or whether the additional chemotherapy explains some or all of the observed TTF benefit
    d. Question about whether the open-label use of TTF impacted provider or patient decision making regarding additional therapies (see **Sampson 2015** critique)
8) No increase in adverse events seen in the TTF group compared to the temozolomide alone group
9) CONCLUSIONS AND RELEVANCE In this interim analysis of 315 patients with glioblastoma who had completed standard chemoradiation therapy, adding TTFields to maintenance temozolomide chemotherapy significantly prolonged progression-free and overall survival.

10) Industry sponsored trial

Major guidelines:

NCCN 2015

1) ETTF mentioned as a possible therapy option for treating recurrent glioblastoma
    a. "Consider alternating electric field therapy for glioblastoma (category 2B)"
    b. No change from recommendation reviewed by HERC in 2014
2) No mention of ETTF as possible therapy for treatment of initial treatment of glioblastoma

European Society for Medical Oncology 2014

(http://annonc.oxfordjournals.org/content/early/2014/04/29/annonc.mdu050 Guideline not included due to length)

1) Reviewed ETTF as treatment for recurrent glioblastoma and did not find evidence to support its use
2) Use for initial treatment of glioblastoma was not reviewed

HERC staff summary:

The current evidence to support the use of electric tumor treatment fields in the initial treatment of glioblastoma is based on a single trial, which had questions regarding the trial methodology. No major specialty group is currently including ETTF as a recommended treatment for initial glioblastoma treatment. However, this does appear to be a rapidly evolving field and a promising treatment.

HERC staff recommendations:

1) Do not add ETTF (HCPCS A4555 and E0766) as an initial treatment for glioblastoma
2) Amend the entry to the Services Recommended for Non-Coverage as shown below

HCPCS A4555, E0766	Electronic tumor treatment field (ETTF) therapy	June, 2014 (Affirmed March 2016) March, 2016	For recurrent glioblastoma: Found to have comparable effectiveness to conventional treatments, but significantly higher cost[3] For initial treatment of glioblastoma: Experimental[2]

Footnotes 2 and 3 refer to OARs

Introduction to Issues Regarding Services for Autism and Dementia

Questions:

1) Should autism and dementia diagnoses continue to appear on the dysfunction lines, or should they only appear on the specific lines for these conditions?
    a. If moved off the dysfunction lines, what services should pair with autism and dementia diagnoses that currently only pair with them on the dysfunction lines?
2) What guideline restrictions should be placed on rehabilitative and habilitative services for autism and dementia and other behavioral health conditions?
3) Should the current rehabilitation services guideline be modified?

Question sources: HERC staff, OHA, HSD, medical directors

Issues: Autism and dementia both have unique lines (lines 197 AUTISM SPECTRUM DISORDERS and 206 CHRONIC ORGANIC MENTAL DISORDERS INCLUDING DEMENTIAS), but also appear on the four dysfunction lines. The services available on the dysfunction lines are far more extensive than those on the autism and dementia specific lines, including PT/OT/Speech services, and, for autism, inpatient and SNF care. HERC staff would like to discuss whether autism and dementia should be removed from the dysfunction lines; if so, what types of services that now appear on the dysfunction lines should be added to the condition specific lines to continue to pair with these diagnoses?

As background, the evidence base/literature for PT and OT services is not robust. The majority of the literature focuses on a specific modality (for example, ultrasound or soft tissue mobilization) and its effectiveness for treatment of a specific condition. There are some studies of PT as a general service for certain conditions, such as back pain, but again, this literature is limited to one or a set of closely related conditions. In general, the evidence supporting the use of PT and OT for most services is weak or lacking. Most Medicaid programs and private insurers use medical necessity and, in some cases, arbitrary number limits to manage the use of these services.

If autism and dementia are removed from the dysfunction lines, GN6 Rehabilitative Therapies will no longer apply to these conditions. This GN could be added to the autism and dementia lines in its current form; or some modified guideline could be applied. HERC staff would like to discuss what restrictions, if any, should be placed on PT/OT/Speech services for autism, dementia, and similar behavioral health conditions. As background for this discussion, VBBS/HERC members will need to have information on possible conflicts between GN6 as it applies to behavioral health services and national laws and regulations.

1) GN6 may conflict with several national laws and regulations
    a. EPSDT laws (Title XIX). The Early and Periodic Screening, Diagnostic and Treatment (EPSDT) benefit provides comprehensive and preventive health care services for children under age 21 who are enrolled in Medicaid.
    b. CMS rules regarding habilitative services
    c. Federal Mental Health Parity laws

   d. Essential Health Benefit (EHB) discrimination language
2) Pending guidance for the Oregon Department of Justice regarding legal issues with GN6
3) Possible issues with Oregon's Medicaid waiver and CMS requirements and rules for these types of services.

A new CMS regulation was issued in January, 2016 which impacts the types of restrictions for habilitative services which might be governed by GN6, Rehabilitative Services, such as many of the PT, OT and speech services for autism and dementia (see published rule in meeting packet). Habilitative services are defined as "health care services and devices that help a person keep, learn, or improve skills and functioning for daily living (habilitative services). Examples include therapy for a child who is not walking or talking at the expected age. These services may also include physical and occupational therapy, speech-language pathology and other services for people with disabilities in a variety of inpatient and/or outpatient settings." The new rule states:

> The state must not impose limits on habilitative services and devices that are more stringent than limits on rehabilitative services and devices (see 45 CFR 156.115(a)(5)(ii)). This provision is effective immediately and requires that states review the coverage in the ABP to ensure that limits are in compliance with this provision.
>
> Separate coverage limits must also be established for rehabilitative and habilitative services and devices (see 45 CFR 156.115(a)(5)(iii)) for plan years beginning on or after January 1, 2017. A combined limit that cannot be exceeded based on medical necessity is not permissible. States will need to assess any existing limits on this coverage to determine if an amendment to the ABP SPA is required.

Additional concerns about GN6 in general have been raised by various CCO medical directors and by HERC staff. HERC staff would like to discuss possible revisions to GN6 as it applies to non-behavioral health conditions. Some specific concerns include:

1) General concerns among the CCOs about the language and desire to eliminate the clause about 30 additional visits per year being authorized for "exceptional circumstances." This clause is considered difficult to interpret.
2) Consideration of the addition of pulmonary rehabilitation to the guideline. The current guideline has a global limit for the combination of PT, OT, speech and cardiac rehabilitation services
3) Cardiac rehabilitation involves more than just PT, and the cardiac lines are not even mentioned in the guideline note. Cardiac rehabilitation should considered for removal from the guideline note.
4) HERC staff has reviewed a 2015 MED report on PT/OT services in other state Medicaid programs, which finds Oregon to be more restrictive than nearly all other states, particularly for children. Staff would like to discuss consideration of removal of the strict numerical limit on visits, possibly only for children. Historically, the limit on

services was quite low and the current 30 visit all-encompassing limit was an expansion of coverage.

HSD has rules and regulations regarding when PT and OT services are appropriate. These are published as OARs.

1. OAR definition of Medical Appropriateness:
    a. Service is consistent with symptoms or treatment of the health condition
    b. Generally recognized as effective
    c. Not for convenience of provider, patient or vendor
    d. Most cost effective alternative
2. OAR definition of Medical Necessity:
    a. If less than 30+ visits won't be effective
    b. Patient will suffer harm if not treated with more than 30

MED 2015 Summary of state policies on coverage of PT, OT and speech therapy

1) Survey of 10 states policies/coverage
2) Common elements that states use to determine medical necessity are:
    a. Referral by a licensed health care practitioner
    b. Diagnosis requiring skilled professional services
    c. Reasonable expectation of improvement
    d. Plan of care with measurable goals and outcomes
    e. Additional elements states may consider include:
        i. Acute vs chronic conditions
        ii. Therapeutic goals (e.g., improvement, maintenance, prevention of deterioration)
3) Quantitative visit limits
    a. Few states specify limits on coverage for children, even those states with limits on adult services.
    b. States with no limits or limits only on the number of units billable per day for adults and children: Alabama, Colorado, Minnesota
    c. Arizona - Adults: 15 outpatient visits and 25 inpatient days/year each for PT and OT; Children: Limits not specified
    d. Maine - No more than 1 unit/day of supervised modalities per modality; Maintenance care: 2 visits/year, or 6 visits/year if needed to maintain function; Sensory integration: 2 visits/year, 1 evaluation or re-evaluation per condition or event; no limits specified for children
    e. Michigan - Up to 144 units/year (rehabilitative or habilitative) or after 24 visits in 60 days in the home setting (adults or children not specified)
    f. New York - 20 visits per year of PT and 20 visits of OT for adults; no limits for children
    g. Washington - adults limited to 24 units of PT and 24 units of OT per year with additional limits by procedure; no limits for children

h. Wisconsin - up to 35 units of PT and 35 units of OT per year, additional available by PA approval; same for adults and children over age 3

Current guideline

GUIDELINE NOTE 6, REHABILITATIVE THERAPIES

Lines 34,50,61,72,75,76,78,85,95,96,135,136,140,154,157,164,182,187,188,200,201,205, 206,212,259,261,276,290,292,297,305,306,314,322,346,350,351,353,360,361,364,366,381, 382,392,406,413,421,423,427,428,436,447,459,467,470,471,482,490,501,512,532,558,561, 574,592,611,666 (Lines 351, 366 and 532 represent lines 374, 412 and 545 from the Oct. 1, 2015 Prioritized List†)

A total of 30 visits per year of rehabilitative therapy (physical, occupational and speech therapy, and cardiac and vascular rehabilitation) are included on these lines when medically appropriate. Additional visits, not to exceed 30 visits per year, may be authorized in exceptional circumstances, such as in cases of rapid growth/development.

Physical, occupational and speech therapy, and cardiac and vascular rehabilitation are only included on these lines when the following criteria are met:

1. therapy is provided by a licensed physical therapist, occupational therapist, speech language pathologist, physician, or other practitioner licensed to provide the therapy,
2. there is objective, measurable documentation of clinically significant progress toward the therapy plan of care goals and objectives,
3. the therapy plan of care requires the skills of a medical provider, and
4. the client and/or caregiver cannot be taught to carry out the therapy regimen independently.

No limits apply while in a skilled nursing facility for the primary purpose of rehabilitation, an inpatient hospital or an inpatient rehabilitation unit.

Spinal cord injuries, traumatic brain injuries, or cerebral vascular accidents are not subject to the visit limitations during the first year after an acute injury.

HERC staff recommendations:

1) Discuss whether autism and dementia should remain on the dysfunction lines
    a. If autism and dementia are removed from the dysfunction lines, discuss which services should be added to the disease specific lines
        i. The Behavioral Health Advisory Panel (BHAP) may need to be tasked with review of the appropriateness of certain CPT codes
    b. See Appendix A for details
2) Give staff feedback and direction on guideline(s) for rehabilitative services and habilitative services for behavioral health conditions such as autism and dementia. Possible options include, but are not limited to:
    a. Applying GN6 Rehabilitative Services to the autism and dementia lines, in an edited form or in the current form
    b. Creating a new guideline for habilitative and rehabilitative services for behavioral health conditions such as autism and dementia
3) Give staff feedback and direction on possible revisions to GN6 Rehabilitative Therapies for physical health conditions. Possible options include, but are not limited to:
    a. Consider deleting the guideline entirely and allow HSD to create rules on appropriate use of services
    b. Consider deleting the number of visit limits and only include wording about medical necessity
    c. Consider removing the additional 30 visit clause for "rapid growth and development" and have the GN apply only to adults; no limits for children

Appendix A

Diagnoses which appear on the Dysfunction lines related to autism and/or dementia

1) Autism related diagnoses on both the dysfunction lines and line 197 AUTISM SPECTRUM DISORDERS
    a. F84.0 Autistic disorder
    b. F84.3 Other childhood disintegrative disorder
    c. F84.8 Other pervasive developmental disorders
2) Autism related diagnoses appearing only on the dysfunction lines
    a. F84.2 Rett's syndrome
3) Dementia related diagnoses appearing on the dysfunction lines and on line 206 CHRONIC ORGANIC MENTAL DISORDERS INCLUDING DEMENTIAS
    a. F01.5 Vascular dementia
    b. F03.9 Unspecified dementia
    c. F06.1 Catatonic disorder due to known physiological condition
    d. F06.8 Other specified mental disorders due to known physiological condition
    e. F07.89 Other personality and behavioral disorders due to known physiological condition

Services Currently Only Pairing with Autism and/or Dementia on the Dysfunction Lines

1) Services appearing on the dysfunction lines but not both lines 197 AUTISM SPECTRUM DISORDERS and 206 CHRONIC ORGANIC MENTAL DISORDERS INCLUDING DEMENTIAS
    a. Multiple procedures not felt to related to specifically to autism and dementia
        i. Examples: injections, osteotomy, arthrodesis, tracheostomy, gastroduodenostomy, colectomy, neurostimulator pumps, CMT, OMT, ophthalmologic examinations
        ii. These would still be available if paired with an appropriate diagnosis that the person with the autism or dementia condition might also have
    b. Speech therapy
        i. 92507-92508 Treatment of speech, language, voice, communication, and/or auditory processing disorder
        ii. 92521-92524 Evaluation of speech
        iii. 92526 Treatment of swallowing dysfunction and/or oral function for feeding
        iv. 92607-92609 Evaluation and therapeutic services for speech-generating augmentative and alternative communication device
        v. 92633 Auditory rehabilitation; postlingual hearing loss
    c. Speech therapy related
        i. 21084 Impression and custom preparation; speech aid prosthesis
        ii. 92526 Treatment of swallowing dysfunction and/or oral function for feeding
    d. CPT 96150-96154 Health and behavior assessment
    e. PT Services

i. 97012 Application of a modality to 1 or more areas; traction, mechanical
ii. 97022 Application of a modality to 1 or more areas; whirlpool
iii. 97110-97129 Therapeutic procedure
iv. 97140 Manual therapy techniques
v. 97150 Therapeutic procedure(s), group (2 or more individuals)
vi. 97530 Therapeutic activities, direct (one-on-one) patient contact (use of dynamic activities to improve functional performance)
vii. 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)
viii. 97542 Wheelchair management (eg, assessment, fitting, training)
ix. 97760-97762 Orthotic(s) management and training

f. 99070 Supplies and materials (except spectacles), provided by the physician or other qualified health care professional over and above those usually included with the office visit or other services rendered (list drugs, trays, supplies, or materials provided)
g. 99078 Physician or other qualified health care professional qualified by education, training, licensure/regulation (when applicable) educational services rendered to patients in a group setting (eg, prenatal, obesity, or diabetic instructions)
h. 99184 Initiation of selective head or total body hypothermia in the critically ill neonate
i. 99281-99285 ER visits
j. 99291-99292 ICU care
k. 99354-99355 Prolonged evaluation and management or psychotherapy service(s) (beyond the typical service time of the primary procedure) in the office or other outpatient setting requiring direct patient contact beyond the usual service
l. 99356-99360 Prolonged service in the inpatient or observation setting
m. 99363-99364 Anticoagulant management
n. 99367-99368 Medical team conference with interdisciplinary team of health care professionals
o. 99374-99375 Supervision of a patient under care of home health agency
p. 99377-99378 Supervision of a hospice patient
q. 99379-99380 Supervision of a nursing facility patient (patient not present) requiring complex and multidisciplinary care modalities involving regular development and/or revision of care plans by that individual, review of subsequent reports of patient status, review
r. 99381-99429 Preventive medicine evaluation and management or service, alcohol and drug screening
s. 99379-99380 Supervision of a nursing facility patient (patient not present) requiring complex and multidisciplinary care modalities involving regular development and/or revision of care plans by that individual

t. 99468-99480 NICU/PICU

2) Services appearing on the dysfunction lines but not line 197 AUTISM SPECTRUM DISORDERS (already appear on line 206)
    a. 97001-97004 PT evaluation and re-evaluation
    b. 97532 Development of cognitive skills to improve attention, memory, problem solving (includes compensatory training), direct (one-on-one) patient contact, each 15 minutes
    c. 99217-99220 Inpatient observation
    d. 99221-99239 Inpatient hospital care
    e. 99304-99318 SNF care
    f. 99605-99607 Medication therapy management service(s) provided by a pharmacist

Section 3.0

Coverage Guidance Topic Selection

SCOPE STATEMENT FOR HERC COVERAGE GUIDANCE

GENETIC TESTING OF THYROID NODULES

Population description	Adults with cytologically indeterminate thyroid nodules after fine needle aspiration (FNA) *Population scoping notes: None*
Intervention(s)	Multigene expression assay performed on FNA specimens *Intervention exclusions: None*
Comparator(s)	Usual care
Outcome(s) (up to five)	Critical: Mortality, thyroid cancer-related morbidity, quality of life Important: Change in management, harms resulting from testing (including overtreatment and undertreatment) *Considered but not selected for GRADE Table: None*
Key questions	1. Are multigene expression assays performed on thyroid nodule FNA specimens analytically valid? 2. Are multigene expression assays performed on thyroid nodule FNA specimens clinically valid? a. Do these tests predict the likelihood of thyroid cancer? b. Do these tests offer prognostic information when thyroid cancer is present? c. Do these tests predict responsiveness to certain treatments? 3. Are multigene expression assays performed on thyroid nodule FNA specimens clinically useful? a. Do these tests change the management plans selected by physicians and patients? b. Do these tests result in changes in patient-important clinical outcomes?

SCOPE STATEMENT FOR HERC COVERAGE GUIDANCE

NONINVASIVE TESTING FOR LIVER FIBROSIS IN CHRONIC HEPATITIS C PATIENTS

Population description	Adults and children with chronic hepatitis C infection *Population scoping notes: None*
Intervention(s)	Non-invasive tests of liver fibrosis (e.g., acoustic radiation force impulse imaging, transient elastography, magnetic resonance elastography, biochemical tests with predictive algorithms) *Intervention exclusions: None*
Comparator(s)	Liver biopsy, other interventions listed above
Outcome(s) (up to five)	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 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 non-invasive 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?

SCOPE STATEMENT FOR HERC COVERAGE GUIDANCE

PROSTATIC URETHRAL LIFT FOR TREATMENT OF BENIGN PROSTATIC HYPERTROPHY

Population description	Men with benign prostatic hypertrophy (BPH) and lower urinary tract symptoms (LUTS) *Population scoping notes: None*
Intervention(s)	Prostatic urethral lift (PUL) procedure *Intervention exclusions: None*
Comparator(s)	Medical management (alpha blockers and 5-alpha reductase inhibitors), transurethral resection of the prostate (TURP), bipolar TURP, photoselective vaporization of the prostate (PVP), holmium laser enucleation of the prostate (HoLEP), transurethral incision of the prostate (TUIP), transurethral needle ablation of the prostate (TUNA), transurethral microwave thermotherapy (TUMT), bipolar transurethral elctrovaporization of the prostate (TUVP), thulium laser vaporization/resection of the prostate
Outcome(s) (up to five)	Critical: Quality of life Important: Need for re-operation, urinary incontinence, erectile dysfunction, symptom improvement (e.g., International Prostate Symptom Score (IPSS) or American Urological Association Symptom Index (AUASI) scores) *Considered but not selected for GRADE Table: Flow rate, post-void residual, post-procedural catheterization time, urinary retention*
Key questions	1. What is the comparative effectiveness of prostatic urethral lift (PUL) for men with lower urinary tract symptoms from BPH? a. Does comparative effectiveness vary by baseline symptom severity? b. Does the age of the patient or duration of symptoms affect the comparative effectiveness? 2. What are the comparative harms of prostatic urethral lift (PUL) for men with lower urinary tract symptoms from BPH?
Contextual questions	1. In what settings (outpatient, ambulatory surgical center, inpatient) and with what types of anesthesia or analgesia can PUL be safely performed?

SCOPE STATEMENT FOR HERC COVERAGE GUIDANCE

SACRAL NERVE STIMULATION FOR NON-OBSTRUCTIVE URINARY RETENTION

Population description	Adults and children with non-obstructive urinary retention *Population scoping notes: None*
Intervention(s)	Sacral nerve stimulation *Intervention exclusions: None*
Comparator(s)	Intermittent self-catheterization, in-dwelling urinary catheters, urethral dilatation
Outcome(s) (up to five)	Critical: Quality of life, development of chronic kidney disease, avoidance of surgical urinary diversion Important: Urinary tract infections, harms *Considered but not selected for GRADE Table: Ability to void spontaneously, post-void residuals, reduced need for catheterization, improved urodynamic measures, procedural harms*
Key questions	1. What is the comparative effectiveness of sacral nerve stimulation for the treatment of non-obstructive urinary retention? 2. Does the comparative effectiveness of sacral nerve stimulation vary by: a. Etiology of non-obstructive urinary retention b. Anatomic location (sacral nerve root) of electrode c. Observed effectiveness in the evaluation stage of a 2-stage technique d. Duration of symptom prior to implantation 3. What are the comparative harms of sacral nerve stimulation?

SCOPE STATEMENT FOR HERC COVERAGE GUIDANCE

DIGITAL BREAST TOMOSYNTHESIS (3D MAMMOGRAPHY) FOR BREAST CANCER SCREENING IN AVERAGE RISK WOMEN

Population description	Women between the ages of 40 and 74 years referred for breast cancer screening *Population scoping notes: Exclude women with a personal history of breast cancer or ductal carcinoma in situ; BRCA mutations*
Intervention(s)	Digital breast tomosynthesis (3-D mammography) in conjunction with standard digital mammography *Intervention exclusions: None*
Comparator(s)	*Standard 2-D mammography with or without computer-aided diagnosis* *Considered but not selected: No screening, MRI*
Outcome(s) (up to five)	Critical: Breast cancer morbidity, mortality, quality of life Important: Cancer detection rate, recall rate for false positive tests including additional invasive and non-invasive testing *Considered but not selected for GRADE Table: All-cause mortality, radiation exposure PPV for recalls, PPV for biopsies.*
Key questions	1. What is the effectiveness of digital breast tomosynthesis as a primary screening modality in women referred for breast cancer screening? 2. Does the the intervention as a primary screening modality vary by the following characteristics: a. Age b. Breast density c. Baseline risk within an average-risk screening population (as ascertained by risk assessment tools) d. Screening interval 3. In a screening population, how do the diagnostic test characteristics of the intervention compare to those of standard 2-D mammography?

SCOPE STATEMENT FOR HERC COVERAGE GUIDANCE

Fecal Microbiota Transplants for C. difficile

Population description	Adults and children with Clostridium difficile infection (CDI) *Population scoping notes: None*
Intervention(s)	Fecal microbiota transplantation (FMT) by any route *Intervention exclusions: None*
Comparator(s)	Oral or intravenous metronidazole, oral or rectal vancomycin, oral rifaximin, oral fidaxomicin, bile acid sequestrants, probiotics, combinations of these treatments
Outcome(s) (up to five)	Critical: Mortality, CDI-related morbidity (including hospitalizations), symptom resolution without recurrence Important: Latrogenic infections, harms from intervention (e.g., colon perforation, antibiotic side effects) *Considered but not selected for GRADE Table: None*
Key questions	1. What is the comparative effectiveness of FMT for patients with CDI? 2. Does the effectiveness, harm, or patient acceptance of FMT for CDI vary by: a. Initial vs recurrent vs refractory infection b. Previous treatment regimen c. Severity of infection d. Route of administration e. Donor characteristics

CHANGE LOG

Date	Change	Rationale
2/4/2016	EbGS moved probiotics before combination treatments in the list of comparators.	Clarity

SCOPE STATEMENT FOR HERC COVERAGE GUIDANCE

GENETIC TESTS FOR SELECTION OF ANTIDEPRESSANT THERAPY

Population description	Adults or children with major depressive disorder who are initiating or changing anti-depressant medications *Population scoping notes: None*
Intervention(s)	Genetic testing to inform the selection of anti-depressant medications *Intervention exclusions: None*
Comparator(s)	Usual care
Outcome(s) (up to five)	Critical: Depression remission, functional improvement, quality of life Important: Timing to remission, depression improvement *Considered but not selected for GRADE Table: None*
Key questions	1. Are genetic tests to guide selection of anti-depressant medications analytically valid? 2. Are genetic tests to guide selection of anti-depressant medications clinically valid? a. Do these tests predict the likelihood of responding to anti-depressant medications? b. Do these tests predict the likelihood of discontinuation of anti-depressant medictions? 3. Are genetic tests to guide selection of anti-depressant medications clinically useful? a. Do these tests change the treatments selected by physicians and patients? 4. Do these tests improve depression or quality of life outcomes for patients? 5. Does the clinical utility of these tests vary by: a. Whether the depression is an initial or recurrent episode b. Chronicity c. Severity of depression 6. Does the use of genetic testing to guide use of anti-depressant medication reduce total health care costs?

SCOPE STATEMENT FOR HERC COVERAGE GUIDANCE

INTERVENTIONS TO REDUCE TOBACCO USE DURING PREGNANCY

Population description	Women during pregnancy and the postpartum period *Population scoping notes: Includes all forms of tobacco, including e-cigarettes*
Intervention(s)	Screening for tobacco use, pharmacotherapy, behavioral interventions (telephonic, in person, individual, group), Internet based interventions, and multisector interventions such as policy, systems, and environmental change *Intervention exclusions: None*
Comparator(s)	No care, usual care, other studied interventions
Outcome(s) (up to five)	Critical: Pregnancy complications, low birth weight, perinatal/infant death Important: Abstinence from tobacco during pregnancy, long-term tobacco abstinence *Considered but not selected for GRADE Table:* Maternal exposure to secondhand smoke, health benefits to mothers.
Key questions	1. What interventions are most effective and most cost-effective to: a. Reduce tobacco-related perinatal/infant morbidity and mortality? b. Reduce tobacco use prevalence in pregnant women? c. Sustain tobacco abstinence after delivery among women who quit tobacco use during pregnancy? 2. Does effectiveness vary by socioeconomic factors such as race, ethnicity, income and educational attainment? 3. What models of care would allow these interventions to be implemented most effectively and cost-effectively?

SCOPE STATEMENT FOR HERC COVERAGE GUIDANCE

GASTROINTESTINAL MOTILITY TESTS

Population description	Adults and children with suspected gastrointestinal motility disorders (e.g., gastroparesis, colonic pseudo-obstruction, slow-transit constipation) *Population scoping notes: None*
Intervention(s)	Radiographic and capsule-based gastrointestinal motility tests: • Gastric emptying scintigraphy • Radiopaque marker testing • Barium small bowel follow through • Colonic scintigraphy • Whole gut scintigraphy • Wireless motility capsule • Isotope breath tests *Intervention exclusions: None*
Comparator(s)	Empiric therapy, diagnosis based on clinical criteria/assessment tools, other listed interventions
Outcome(s) (up to five)	Critical: Quality of life, morbidity (including hospitalization) Important: Change in management, patient-reported symptoms, harms of intervention *Considered but not selected for GRADE Table: Need for additional testing, diagnostic accuracy (will be reported as contextual information), need for further testing*
Key questions	1. What is the comparative effectiveness of gastrointestinal motility tests for patients with suspected motility disorders? 2. What is the diagnostic accuracy of gastrointestinal motility tests in patients with suspected motility disorders? 3. What are the harms of gastrointestinal motility tests for patients with suspected motility disorders? 4. Do these tests have additional clinical utility over using clinical assessment without invasive testing?

SCOPE STATEMENT FOR HERC COVERAGE GUIDANCE

TIMING OF LONG-ACTING REVERSIBLE CONTRACEPTIVE PLACEMENT

Population description	Women in the post-partum or post-abortal period who desire contraception *Population scoping notes: None*
Intervention(s)	Offering immediate post-partum or post-abortal placement of a long-acting reversible contraceptive (LARC) *Intervention exclusions: None*
Comparator(s)	Usual care: Offering immediate non-LARC forms of contraception, scheduling delayed LARC placement, delaying discussion of options until 6 weeks post-partum or post-abortion
Outcome(s) (up to five)	Critical: Unintended pregnancies, abortions Important: Presence of LARC at one year, need for alternate/replacement contraception, harms *Considered but not selected for GRADE Table: Device expulsion, discontinuation of contraception for any reason other than desire to conceive*
Key questions	1. What is the comparative effectiveness of offering immediate post-partum or post-abortal placement of a long-acting reversible contraceptive? 2. What are the harms of immediate post-partum or post-abortal placement of a long-acting reversible contraceptive?

SCOPE STATEMENT FOR HERC COVERAGE GUIDANCE

PERCUTANEOUS INTERVENTIONS FOR LOW BACK PAIN

Population description	Adults with acute, subacute, or chronic low back pain with or without radiculopathy *Population scoping notes: None*
Intervention(s)	Epidural, facet joint, or sacroiliac corticosteroid injections *Intervention exclusions: None*
Comparator(s)	Other injection therapies (e.g., local anesthetics, hyaluronic acid, or saline), physical therapy, home exercise programs, medications (e.g., oral corticosteroids, opioids, nonsteroidal anti-inflammatory drugs), complementary and alternative therapies (e.g., acupuncture, yoga, chiropractic therapy, Alexander technique), soft tissue injections, ablative interventions, surgery, no treatment
Outcome(s) (up to five)	Critical: Short-term function, long-term function, long-term risk of undergoing surgery Important: Adverse events, change in utilization of comparators (e.g., opioids, surgery) *Considered but not selected for GRADE Table: Immediate-, short- and long-term pain, immediate-term function*
Key questions	1. What is the comparative effectiveness of corticosteroid injection therapies for low back pain? 2. Does the effectiveness of corticosteroid injection therapies for low back pain vary based on: a. Duration of back pain b. Etiology of back or radicular pain (e.g., stenosis, disc herniation) c. Choice of corticosteroid, dose, or frequency d. Anatomic approach e. Use of imaging guidance f. Previous back surgery g. Response to previous diagnostic injections h. Response to previous injection therapies 3. What are the harms of corticosteroid injection therapies for low back pain?
Contextual questions	1. Does the use of these therapies influence subsequent utilization of health care resources (e.g., chiropractic, opioids, acupuncture, physical therapy)? 2. Does the effectiveness of these interventions depend on prior treatments the patient has received?

Summary of changes to Topic Scoring system

Scoring:	Score 0	Score 1	Score 2	Score 3
Disease Burden (morbidity/mortality, individual perspective)	Inconsequential	Minor	Moderate	~~Major~~High
Prevalence of Condition~~/Population affected~~	~~Minimal~~Rare	Low	Moderate	High~~ly prevalent~~
Uncertainty of ~~Efficacy~~Effectiveness/Harms	~~No controversy~~None	~~Low uncertainty~~Low	Moderate	High ~~uncertainty~~
Variation in Care/ Controversy/Variance between standard of care and evidence	~~Standard Of Care in Oregon aligns w/evidence; low abuse~~None	~~Little controversy/abuse/variation~~Low	~~Some controversy/abuse/variation~~Moderate	~~SOC differs from evidence, or frequently abused~~High
~~Cost/~~Magnitude of Economic Impact of ~~CG~~ Intervention (population level, includes downstream costs)	~~No conceivable cost impact~~None	~~Low potential to save costs (short-term or downstream)~~Low	Moderate	~~High potential for savings (short-term or downstream)~~High
Potential of intervention to improve health outcomes	None	Low	Moderate	High
Public/Professional Interest	~~Not in the public eye; general public would have little understanding of the issue.~~None	~~Some members of the public would be interested in/aware of this topic~~Low	~~Frequent media coverage or prevalent conditions~~Moderate	~~Hot button issue with significant public controversy~~High
~~Relevant subgroup information is available (e.g. race, gender, comorbid conditions)~~Potential of Intervention to Reduce Health Disparities	None ~~or unknown~~	~~Not directly relevant or very low quality~~Low	~~Relevant, but low quality, or less relevant but high quality~~Moderate	~~Relevant and high quality~~High

Meaningful CG (~~High Impact~~Multiplier for the sum of scores above)	No "theory of change" for how CG would increase alignment of practice/evidence	Minor change possible through promotion/precert/metrics, etc.	Moderate change possible through promotion/precert/metrics, etc.	Levers (denials, precerts, bundling, metrics) available to purchasers to align care with recommendation

Summary of changes:

1. Clarify that the disease burden is from the individual perspective (not population). Prevalence row takes care of population.
2. Changed “Population Affected” row to “Prevalence of Condition” for clarity.
3. Changed “Uncertain Efficacy/Harms” to “Uncertainty of Effectiveness/Harms” for precision and clarity.
4. Added a new row on potential of intervention to improve health outcomes.
5. Changed “Variation/Controversy” to “Variation in Care/Controversy/Variance Between Standard of Care and Evidence” for precision and clarity, and to allow the scores to have a simpler descriptor.
6. Changed “Cost/Economic Impact” to “Magnitude of Economic Impact of Intervention” for precision and clarity. Impact of coverage guidance itself on cost is dealt with in the multiplier row at the bottom.
7. Changed “Public Interest” to “Public/Professional Interest” to capture topics of interest to health professionals.
8. Changed “Relevant subgroup information available (e.g. race, gender, comorbid conditions)”. The point of this row was to reduce disparities, so changed it to be more direct.
9. Changed “Meaningful CG” by replacing the descriptor “High Impact” with “Multiplier for sum of scores above” to clarify the role of this row in scoring.
10. Changed most of the scoring descriptions to None, Low, Moderate and High for consistency. Moved descriptive language to row name where needed. The exception was on the Meaningful CG row where we left them in for clarity, and added “, etc. to the scores for 1 and 2 to allow for the ranking of multi-sector interventions.

CG Topic Selection 2016--Retirements

Staff recommends retiring the following coverage guidance topics, as new topics will have a higher priority:

Topic	Rationale
Telepsychiatry and Telecounseling	Implementation challenges/coverage guidance unlikely to influence care
Nitric oxide for the diagnosis and management of asthma	Lack of community interest, limited evidence base, insufficient controversy to merit an in-depth review
Transitional care interventions to prevent readmissions for people with heart failure	Implementation challenges/coverage guidance unlikely to influence care
Treatments for acquired nontraumatic cognitive impairment/dementia	Implementation challenges/coverage guidance unlikely to influence care

Topic:

Digital Breast Tomosynthesis (3d Mammography) for Breast Cancer Screening in Average Risk Women						
Scoring:	**Score 0**	**Score 1**	**Score 2**	**Score 3**	**Scoring**	**Notes**
Disease Burden (morbidity/mortality)	Inconsequential	Minor	Moderate	Major	3	
Prevalence/Population affected	Minimal	Low	Moderate	Highly prevalent	3	
Uncertain Efficacy/Harm	No controversy	Low uncertainty	Moderate	High uncertainty	3	
Variation/ Controversy	Standard Of Care in Oregon aligns w/evidence; low abuse	Little controversy/abuse/variation	Some controversy/abuse/variation	SOC differs from evidence, or frequently abused	3	
Magnitude of economic impact of intervention (population level, includes downstream costs)	No impact	Low impact	Moderate impact	High impact	2	
Potential of intervention to improve health outcomes	No impact	Minimal impact	Moderate impact	High impact	2	
Public/Professional Interest	Not in the public eye; general public would have little understanding of the issue.	Some members of the public would be interested in/aware of this topic	Frequent media coverage	Hot button issue with significant public controversy	3	
Potential of interventions to reduce health disparities	None or unknown	Low impact	Moderate impact	High impact	1	
Base score					20	
Meaningful Coverage Guidance (Multiplier sum of other scores)	No "theory of change" for how CG would increase alignment of practice/evidence	Minor change possible through promotion/precert/metrics	Moderate change possible through promotion/precert/metrics	Levers (denials, precerts, bundling, metrics) available to purchasers to align care with recommendation	3	
Totals					60	0

Scoping notes:

Topic:

Fecal Microbiota Transplants for C. difficile						
Scoring:	**Score 0**	**Score 1**	**Score 2**	**Score 3**	**Scoring**	**Notes**
Disease Burden (morbidity/mortality)	Inconsequential	Minor	Moderate	Major	2	
Prevalence/Population affected	Minimal	Low	Moderate	Highly prevalent	1	
Uncertain Efficacy/Harm	No controversy	Low uncertainty	Moderate	High uncertainty	3	
Variation/ Controversy	Standard Of Care in Oregon aligns w/evidence; low abuse	Little controversy/abuse/variation	Some controversy/abuse/variation	SOC differs from evidence, or frequently abused	3	
Magnitude of economic impact of intervention (population level, includes downstream costs)	No impact	Low impact	Moderate impact	High impact	1	
Potential of intervention to improve health outcomes	No impact	Minimal impact	Moderate impact	High impact	2	
Public/Professional Interest	Not in the public eye; general public would have little understanding of the issue.	Some members of the public would be interested in/aware of this topic	Frequent media coverage	Hot button issue with significant public controversy	3	
Potential of interventions to reduce health disparities	None or unknown	Low impact	Moderate impact	High impact	0	
Meaningful Coverage Guidance	No "theory of change" for how CG would increase alignment of practice/evidence	Minor change possible through promotion/precert/metrics	Moderate change possible through promotion/precert/metrics	Levers (denials, precerts, bundling, metrics) available to purchasers to align care with recommendation	3	
Totals					45	0

Scoping notes:

Topic:

Genetic Tests for Selection of Antidepressant Therapy						
Scoring:	**Score 0**	**Score 1**	**Score 2**	**Score 3**	**Scoring**	**Notes**
Disease Burden (morbidity/mortality)	Inconsequential	Minor	Moderate	Major	3	
Prevalence/Population affected	Minimal	Low	Moderate	Highly prevalent	3	
Uncertain Efficacy/Harm	No controversy	Low uncertainty	Moderate	High uncertainty	3	
Variation/ Controversy	Standard Of Care in Oregon aligns w/evidence; low abuse	Little controversy/abuse/variation	Some controversy/abuse/variation	SOC differs from evidence, or frequently abused	2	Medicare and VA cover this test
Magnitude of economic impact of intervention (population level, includes downstream costs)	No impact	Low impact	Moderate impact	High impact	2	
Potential of intervention to improve health outcomes	No impact	Minimal impact	Moderate impact	High impact	2	
Public/Professional Interest	Not in the public eye; general public would have little understanding of the issue.	Some members of the public would be interested in/aware of this topic	Frequent media coverage	Hot button issue with significant public controversy	1	
Potential of interventions to reduce health disparities	None or unknown	Low impact	Moderate impact	High impact	0	
Meaningful Coverage Guidance	No "theory of change" for how CG would increase alignment of practice/evidence	Minor change possible through promotion/precert/metrics	Moderate change possible through promotion/precert/metrics	Levers (denials, precerts, bundling, metrics) available to purchasers to align care with recommendation	3	
Totals					48	0

Scoping notes:

Topic:

Interventions to Reduce Tobacco Use During Pregnancy						
Scoring:	**Score 0**	**Score 1**	**Score 2**	**Score 3**	**Scoring**	**Notes**
Disease Burden (morbidity/mortality)	Inconsequential	Minor	Moderate	Major	3	
Prevalence/Population affected	Minimal	Low	Moderate	Highly prevalent	2	
Uncertain Efficacy/Harm	No controversy	Low uncertainty	Moderate	High uncertainty	3	
Variation/ Controversy	Standard Of Care in Oregon aligns w/evidence; low abuse	Little controversy/abuse/variation	Some controversy/abuse/ variation	SOC differs from evidence, or frequently abused	3	Multisector interventions underutilized, variation in clinical interventions
Magnitude of economic impact of intervention (population level, includes downstream costs)	No impact	Low impact	Moderate impact	High impact	3	
Potential of intervention to improve health outcomes	No impact	Minimal impact	Moderate impact	High impact	3	
Public/Professional Interest	Not in the public eye; general public would have little understanding of the issue.	Some members of the public would be interested in/aware of this topic	Frequent media coverage	Hot button issue with significant public controversy	3	
Potential of interventions to reduce health disparities	None or unknown	Low impact	Moderate impact	High impact	3	
Meaningful Coverage Guidance	No "theory of change" for how CG would increase alignment of practice/evidence	Minor change possible through promotion/precert/metrics	Moderate change possible through promotion/precert/ metrics	Levers (denials, precerts, bundling, metrics) available to purchasers to align care with recommendation	2	
Totals					46	0

Scoping notes:

Topic:

Gastrointestinal motility tests						
Scoring:	**Score 0**	**Score 1**	**Score 2**	**Score 3**	**Scoring**	**Notes**
Disease Burden (morbidity/mortality)	Inconsequential	Minor	Moderate	Major	2	
Prevalence/Population affected	Minimal	Low	Moderate	Highly prevalent	1	
Uncertain Efficacy/Harm	No controversy	Low uncertainty	Moderate	High uncertainty	2	Uncertain utility not efficacy/harm
Variation/ Controversy	Standard Of Care in Oregon aligns w/evidence; low abuse	Little controversy/abuse/variation	Some controversy/abuse/ variation	SOC differs from evidence, or frequently abused	2	
Magnitude of economic impact of intervention (population level, includes downstream costs)	No impact	Low impact	Moderate impact	High impact	1	
Potential of intervention to improve health outcomes	No impact	Minimal impact	Moderate impact	High impact	1	
Public/Professional Interest	Not in the public eye; general public would have little understanding of the issue.	Some members of the public would be interested in/aware of this topic	Frequent media coverage	Hot button issue with significant public controversy	0	
Potential of interventions to reduce health disparities	None or unknown	Low impact	Moderate impact	High impact	0	
Meaningful Coverage Guidance	No "theory of change" for how CG would increase alignment of practice/evidence	Minor change possible through promotion/precert/metrics	Moderate change possible through promotion/precert/ metrics	Levers (denials, precerts, bundling, metrics) available to purchasers to align care with recommendation	3	
Totals					27	0

Scoping notes:

Topic:

Timing of Long-Acting Reversible Contraceptive Placement						
Scoring:	**Score 0**	**Score 1**	**Score 2**	**Score 3**	**Scoring**	**Notes**
Disease Burden (morbidity/mortality)	Inconsequential	Minor	Moderate	Major	3	
Prevalence/Population affected	Minimal	Low	Moderate	Highly prevalent	3	
Uncertain Efficacy/Harm	No controversy	Low uncertainty	Moderate	High uncertainty	2	
Variation/ Controversy	Standard Of Care in Oregon aligns w/evidence; low abuse	Little controversy/abuse/variation	Some controversy/abuse/variation	SOC differs from evidence, or frequently abused	3	Due to reimbursement issues and high expulsion rate
Magnitude of economic impact of intervention (population level, includes downstream costs)	No impact	Low impact	Moderate impact	High impact	3	
Potential of intervention to improve health outcomes	No impact	Minimal impact	Moderate impact	High impact	3	
Public/Professional Interest	Not in the public eye; general public would have little understanding of the issue.	Some members of the public would be interested in/aware of this topic	Frequent media coverage	Hot button issue with significant public controversy	2	
Potential of interventions to reduce health disparities	None or unknown	Low impact	Moderate impact	High impact	3	
Meaningful Coverage Guidance	No "theory of change" for how CG would increase alignment of practice/evidence	Minor change possible through promotion/precert/metrics	Moderate change possible through promotion/precert/metrics	Levers (denials, precerts, bundling, metrics) available to purchasers to align care with recommendation	3	
Totals					66	0

Scoping notes:

Topic:

Percutaneous Interventions for Low Back Pain						
Scoring:	**Score 0**	**Score 1**	**Score 2**	**Score 3**	**Scoring**	**Notes**
Disease Burden (morbidity/mortality)	Inconsequential	Minor	Moderate	Major	1	
Prevalence/Population affected	Minimal	Low	Moderate	Highly prevalent	3	
Uncertain Efficacy/Harm	No controversy	Low uncertainty	Moderate	High uncertainty	3	
Variation/ Controversy	Standard Of Care in Oregon aligns w/evidence; low abuse	Little controversy/abuse/variation	Some controversy/abuse/variation	SOC differs from evidence, or frequently abused	3	
Magnitude of economic impact of intervention (population level, includes downstream costs)	No impact	Low impact	Moderate impact	High impact	2	1000 per year with imaging before and during
Potential of intervention to improve health outcomes	No impact	Minimal impact	Moderate impact	High impact	1	
Public/Professional Interest	Not in the public eye; general public would have little understanding of the issue.	Some members of the public would be interested in/aware of this topic	Frequent media coverage	Hot button issue with significant public controversy	1	
Potential of interventions to reduce health disparities	None or unknown	Low impact	Moderate impact	High impact	1	
Meaningful Coverage Guidance	No "theory of change" for how CG would increase alignment of practice/evidence	Minor change possible through promotion/precert/metrics	Moderate change possible through promotion/precert/metrics	Levers (denials, precerts, bundling, metrics) available to purchasers to align care with recommendation	3	
Totals					45	0

Scoping notes:

Topic:

Recurrent Acute Otitits Media in Children						
Scoring:	**Score 0**	**Score 1**	**Score 2**	**Score 3**	**Scoring**	**Notes**
Disease Burden (morbidity/mortality)	Inconsequential	Minor	Moderate	Major	2	
Prevalence/Population affected	Minimal	Low	Moderate	Highly prevalent	1	
Uncertain Efficacy/Harm	No controversy	Low uncertainty	Moderate	High uncertainty	2	
Variation/ Controversy	Standard Of Care in Oregon aligns w/evidence; low abuse	Little controversy/abuse/variation	Some controversy/abuse/variation	SOC differs from evidence, or frequently abused	2	
Magnitude of economic impact of intervention (population level, includes downstream costs)	No impact	Low impact	Moderate impact	High impact	2	
Potential of intervention to improve health outcomes	No impact	Minimal impact	Moderate impact	High impact	2	
Public/Professional Interest	Not in the public eye; general public would have little understanding of the issue.	Some members of the public would be interested in/aware of this topic	Frequent media coverage	Hot button issue with significant public controversy	1	
Potential of interventions to reduce health disparities	None or unknown	Low impact	Moderate impact	High impact	2	
Meaningful Coverage Guidance	No "theory of change" for how CG would increase alignment of practice/evidence	Minor change possible through promotion/precert/metrics	Moderate change possible through promotion/precert/metrics	Levers (denials, precerts, bundling, metrics) available to purchasers to align care with recommendation	3	
Totals					42	0

Scoping notes:

	Topic: Continuous Glucose Monitoring in Diabetes Mellitus						
	Scoring:	**Score — 0**	**Score — 1**	**Score — 2**	**Score — 3**	**Score**	**Notes**
1	Disease Burden (morbidity/mortality, individual perspective)	Inconsequential	Minor	Moderate	High	3	
2	Prevalence of Condition	Rare	Low	Moderate	High	3	
3	Uncertainty of Effectiveness/Harms	None	Low	Moderate	High	2	
4	Variation in Care/ Controversy/ Variance Between Standard of Care and Evidence	None	Low	Moderate	High	2	
5	Magnitude of Potential Economic Impact of Intervention (population level, includes downstream costs)	None	Low	Moderate	High	2	
6	Potential of Intervention to Improve Health Outcomes	None	Low	Moderate	High	2	
7	Public/Professional Interest	None	Low	Moderate	High	2	
8	Potential of Intervention to Reduce Health Disparities	None	Low	Moderate	High	2	
9	Meaningful Coverage Guidance (Multiplier for scores above)	No "theory of change" for how CG would increase alignment of practice/evidence	Minor change possible through promotion/precert/ metrics, etc.	Moderate change possible through promotion/precert/ metrics, etc.	Levers (denials, precerts, bundling, metrics) available to purchasers to align care with recommendation	3	
				Total Score (Sum of first 8 rows multiplied by row 9)		**54**	

Scoping notes:

	Topic: Genetic Testing of Thyroid Nodules						
	Scoring:	**Score — 0**	**Score — 1**	**Score — 2**	**Score — 3**	**Score**	**Notes**
1	Disease Burden (morbidity/mortality, individual perspective)	Inconsequential	Minor	Moderate	High	1	
2	Prevalence of Condition	Rare	Low	Moderate	High	1	
3	Uncertainty of Effectiveness/Harms	None	Low	Moderate	High	3	
4	Variation in Care/ Controversy/ Variance Between Standard of Care and Evidence	None	Low	Moderate	High	2	
5	Magnitude of Potential Economic Impact of Intervention (population level, includes downstream costs)	None	Low	Moderate	High	1	
6	Potential of Intervention to Improve Health Outcomes	None	Low	Moderate	High	1	
7	Public/Professional Interest	None	Low	Moderate	High	1	
8	Potential of Intervention to Reduce Health Disparities	None	Low	Moderate	High	0	
9	Meaningful Coverage Guidance (Multiplier for scores above)	No "theory of change" for how CG would increase alignment of practice/evidence	Minor change possible through promotion/precert/ metrics, etc.	Moderate change possible through promotion/precert/ metrics, etc.	Levers (denials, precerts, bundling, metrics) available to purchasers to align care with recommendation	3	
				Total Score (Sum of first 8 rows multiplied by row 9)		**30**	

Scoping notes:

	Noninvasive Testing for Liver Fibrosis in Chronic Hepatitis C Patients						
	Scoring:	**Score — 0**	**Score — 1**	**Score — 2**	**Score — 3**	**Score**	**Notes**
1	Disease Burden (morbidity/mortality, individual perspective)	Inconsequential	Minor	Moderate	High	2	
2	Prevalence of Condition	Rare	Low	Moderate	High	2	
3	Uncertainty of Effectiveness/Harms	None	Low	Moderate	High	1	
4	Variation in Care/ Controversy/ Variance Between Standard of Care and Evidence	None	Low	Moderate	High	2	Controversy about frequency
5	Magnitude of Potential Economic Impact of Intervention (population level, includes downstream costs)	None	Low	Moderate	High	2	Because of Hep. C treatments
6	Potential of Intervention to Improve Health Outcomes	None	Low	Moderate	High	2	
7	Public/Professional Interest	None	Low	Moderate	High	1	
8	Potential of Intervention to Reduce Health Disparities	None	Low	Moderate	High	1	
9	Meaningful Coverage Guidance (Multiplier for scores above)	No "theory of change" for how CG would increase alignment of practice/evidence	Minor change possible through promotion/precert/ metrics, etc.	Moderate change possible through promotion/precert/ metrics, etc.	Levers (denials, precerts, bundling, metrics) available to purchasers to align care with recommendation	3	
				Total Score (Sum of first 8 rows multiplied by row 9)		**39**	

Scoping notes:

	Prostatic Urethral Lift For Treatment Of Benign Prostatic Hypertrophy						
	Scoring:	**Score — 0**	**Score — 1**	**Score — 2**	**Score — 3**	**Score**	**Notes**
1	Disease Burden (morbidity/mortality, individual perspective)	Inconsequential	Minor	Moderate	High	2	
2	Prevalence of Condition	Rare	Low	Moderate	High	1	
3	Uncertainty of Effectiveness/Harms	None	Low	Moderate	High	3	
4	Variation in Care/ Controversy/ Variance Between Standard of Care and Evidence	None	Low	Moderate	High	2	
5	Magnitude of Potential Economic Impact of Intervention (population level, includes downstream costs)	None	Low	Moderate	High	1	
6	Potential of Intervention to Improve Health Outcomes	None	Low	Moderate	High	2	
7	Public/Professional Interest	None	Low	Moderate	High	1	
8	Potential of Intervention to Reduce Health Disparities	None	Low	Moderate	High	0	
9	Meaningful Coverage Guidance (Multiplier for scores above)	No "theory of change" for how CG would increase alignment of practice/evidence	Minor change possible through promotion/precert/ metrics, etc.	Moderate change possible through promotion/precert/ metrics, etc.	Levers (denials, precerts, bundling, metrics) available to purchasers to align care with recommendation	3	
				Total Score (Sum of first 8 rows multiplied by row 9)		**36**	

Scoping notes:

	Sacral Nerve Stimulation for Non-Obstructive Urinary Retention						
	Scoring:	**Score — 0**	**Score — 1**	**Score — 2**	**Score — 3**	**Score**	**Notes**
1	Disease Burden (morbidity/mortality, individual perspective)	Inconsequential	Minor	Moderate	High	2	
2	Prevalence of Condition	Rare	Low	Moderate	High	1	
3	Uncertainty of Effectiveness/Harms	None	Low	Moderate	High	3	
4	Variation in Care/ Controversy/ Variance Between Standard of Care and Evidence	None	Low	Moderate	High	2	
5	Magnitude of Potential Economic Impact of Intervention (population level, includes downstream costs)	None	Low	Moderate	High	1	
6	Potential of Intervention to Improve Health Outcomes	None	Low	Moderate	High	2	
7	Public/Professional Interest	None	Low	Moderate	High	0	
8	Potential of Intervention to Reduce Health Disparities	None	Low	Moderate	High	0	
9	Meaningful Coverage Guidance (Multiplier for scores above)	No "theory of change" for how CG would increase alignment of practice/evidence	Minor change possible through promotion/precert/ metrics, etc.	Moderate change possible through promotion/precert/ metrics, etc.	Levers (denials, precerts, bundling, metrics) available to purchasers to align care with recommendation	3	
				Total Score (Sum of first 8 rows multiplied by row 9)		**33**	

Scoping notes:

	Sleep Apnea Diagnosis in Adults						
	Scoring:	**Score — 0**	**Score — 1**	**Score — 2**	**Score — 3**	**Score**	**Notes**
1	Disease Burden (morbidity/mortality, individual perspective)	Inconsequential	Minor	Moderate	High	2	
2	Prevalence of Condition	Rare	Low	Moderate	High	2	
3	Uncertainty of Effectiveness/Harms	None	Low	Moderate	High	1	
4	Variation in Care/ Controversy/ Variance Between Standard of Care and Evidence	None	Low	Moderate	High	2	
5	Magnitude of Potential Economic Impact of Intervention (population level, includes downstream costs)	None	Low	Moderate	High	2	
6	Potential of Intervention to Improve Health Outcomes	None	Low	Moderate	High	2	
7	Public/Professional Interest	None	Low	Moderate	High	1	
8	Potential of Intervention to Reduce Health Disparities	None	Low	Moderate	High	0	
9	Meaningful Coverage Guidance (Multiplier for scores above)	No "theory of change" for how CG would increase alignment of practice/evidence	Minor change possible through promotion/precert/ metrics, etc.	Moderate change possible through promotion/precert/ metrics, etc.	Levers (denials, precerts, bundling, metrics) available to purchasers to align care with recommendation	3	
				Total Score (Sum of first 8 rows multiplied by row 9)		**36**	

Scoping notes:

	Ultrasound-Enhanced Catheter Directed Thrombolysis for Deep Vein Thrombosis						
	Scoring:	**Score — 0**	**Score — 1**	**Score — 2**	**Score — 3**	**Score**	**Notes**
1	Disease Burden (morbidity/mortality, individual perspective)	Inconsequential	Minor	Moderate	High	2	
2	Prevalence of Condition	Rare	Low	Moderate	High	1	
3	Uncertainty of Effectiveness/Harms	None	Low	Moderate	High	3	
4	Variation in Care/ Controversy/ Variance Between Standard of Care and Evidence	None	Low	Moderate	High	2	
5	Magnitude of Potential Economic Impact of Intervention (population level, includes downstream costs)	None	Low	Moderate	High	1	
6	Potential of Intervention to Improve Health Outcomes	None	Low	Moderate	High	1	
7	Public/Professional Interest	None	Low	Moderate	High	0	
8	Potential of Intervention to Reduce Health Disparities	None	Low	Moderate	High	0	
9	Meaningful Coverage Guidance (Multiplier for scores above)	No "theory of change" for how CG would increase alignment of practice/evidence	Minor change possible through promotion/precert/ metrics, etc.	Moderate change possible through promotion/precert/ metrics, etc.	Levers (denials, precerts, bundling, metrics) available to purchasers to align care with recommendation	2	
				Total Score (Sum of first 8 rows multiplied by row 9)		**20**	

Scoping notes:

	Ultrasound-Enhanced Catheter Directed Thrombolysis for Pulmonary Embolism						
	Scoring:	**Score — 0**	**Score — 1**	**Score — 2**	**Score — 3**	**Score**	**Notes**
1	Disease Burden (morbidity/mortality, individual perspective)	Inconsequential	Minor	Moderate	High	3	
2	Prevalence of Condition	Rare	Low	Moderate	High	1	
3	Uncertainty of Effectiveness/Harms	None	Low	Moderate	High	3	
4	Variation in Care/ Controversy/ Variance Between Standard of Care and Evidence	None	Low	Moderate	High	1	
5	Magnitude of Potential Economic Impact of Intervention (population level, includes downstream costs)	None	Low	Moderate	High	0	
6	Potential of Intervention to Improve Health Outcomes	None	Low	Moderate	High	1	
7	Public/Professional Interest	None	Low	Moderate	High	0	
8	Potential of Intervention to Reduce Health Disparities	None	Low	Moderate	High	0	
9	Meaningful Coverage Guidance (Multiplier for scores above)	No "theory of change" for how CG would increase alignment of practice/evidence	Minor change possible through promotion/precert/ metrics, etc.	Moderate change possible through promotion/precert/ metrics, etc.	Levers (denials, precerts, bundling, metrics) available to purchasers to align care with recommendation	2	
				Total Score (Sum of first 8 rows multiplied by row 9)		**18**	

Scoping notes:

Section 4.0

Coverage Guidances

HEALTH EVIDENCE REVIEW COMMISSION (HERC)

COVERAGE GUIDANCE: SKIN SUBSTITUTES FOR CHRONIC SKIN ULCERS

DRAFT for VbBS/HERC meeting materials 3/10/2016

HERC Coverage Guidance

Skin substitutes for chronic venous leg ulcers and chronic diabetic foot ulcers are recommended for coverage *(weak recommendation)* when all of the following criteria are met:

1. Product is recommended for the type of ulcer being treated (see table below)
2. FDA indications and contraindications are followed, if applicable
3. Wound has adequate arterial flow (ABI > 0.7), no ongoing infection and a moist wound healing environment
4. For patients with diabetes, Hba1c level is < 12.
5. Prior appropriate wound care therapy (including but not limited to appropriate offloading, multilayer compression dressings and smoking cessation counseling) has failed to result in significant improvement (defined as at least a 50 percent reduction in ulcer surface area) of the wound over at least 30 days
6. Ulcer improves significantly over 6 weeks of treatment with skin substitutes, with continued significant improvement every 6 weeks required for coverage of ongoing applications
7. Patients is able to adhere to the treatment plan

The following products are recommended/not recommended for coverage as shown below. All recommendations are weak recommendations.

Product	Diabetic foot ulcers	Venous leg ulcers
Dermagraft	Recommended	Not recommended
Apligraf	Recommended	Recommended
OASIS Wound Matrix	Recommended	Recommended
Epifix	Not recommended	Not recommended
Grafix	Not recommended	Not recommended
Graftjacket	Not recommended	Not recommended
Talymed	Not recommended	Not recommended
Theraskin	Not recommended	Not recommended
Other skin substitutes	Not recommended	Not recommended

The use of skin substitutes is not recommended for coverage of chronic skin ulcers other than venous leg ulcers and diabetic foot ulcers (e.g. pressure ulcers) *(weak recommendation).*

Note: Definitions for strength of recommendation are provided in Appendix A *GRADE Informed Framework Element Description*.

RATIONALE FOR GUIDANCE DEVELOPMENT

The HERC selects topics for guideline development or technology assessment based on the following principles:

- Represents a significant burden of disease
- Represents important uncertainty with regard to efficacy or harms
- Represents important variation or controversy in clinical care
- Represents high costs, significant economic impact
- Topic is of high public interest

Coverage guidance development follows standard methodology to translate evidence reviews into a policy decision. Coverage guidances are based on a thorough review of the evidence by the Evidence-based Guideline Subcommittee or the Heath Technology Assessment Subcommittee. The evidence review used in the coverage guidance development process may use existing systematic reviews of the evidence on a given topic and incorporate additional individual studies published more recently than the included systematic reviews. Included evidence sources are generally published within the last three to five years. A full description of the evidence review methodology is included in each coverage guidance as an appendix. The translation of the evidence review to a policy decision is based on a GRADE-informed framework, as described below

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.

Note: The Quality of Evidence rating was assigned by the primary evidence source, not the HERC Subcommittee. The GRADE framework elements are described in Appendix A. A GRADE Evidence Profile is provided in Appendix B.

Apligraf® / Graftskin

Coverage question: Should Apligraf® be recommended for coverage for treatment of chronic skin ulcers?		
Outcomes	**Estimate of Effect for Outcome/ *Confidence in Estimate***	**Resource allocation**
Deep soft tissue or bone infection *(Critical outcome)*	DFU[1]: osteomyelitis 2.7% vs 10.4% (p = 0.4) ●●○○ *(low certainty of no benefit, based on one good quality RCT)* DFU (Apligraf vs Theraskin): One amputation due to infection with Theraskin vs none for Apligraf (p-value not reported) ●○○○ (very low certainty of no comparative benefit, based on one fair quality RCT) VLU: osteomyelitis 8.1% vs 0% (no statistical analysis)	Incremental cost for adding Apligraf to a patient's course of treatment for a small leg ulcer (<25 cm^2) under Medicare FFS (using average national prices for October, 2015) would range from $771.20 for a single application in an ambulatory surgery center to $4,553.81 for three applications in the physician's office setting. Prices are somewhat higher for foot ulcers due to higher physician fees/bundled fees for application.

[1] DFU: Diabetic Foot Ulcer; VLU: Venous Leg Ulcer

Coverage question: Should Apligraf® be recommended for coverage for treatment of chronic skin ulcers?		
Outcomes	**Estimate of Effect for Outcome/** ***Confidence in Estimate***	**Resource allocation**
	●○○○ *(very low certainty of benefit, based on one good quality RCT)*	Product is sold in 44 cm^2 sheets. Up to 3 applications appear to be the maximum necessary based on included studies.
Complete wound healing *(Critical outcome)*	DFU: RR 1.5, 1.96 (p = 0.01, 0.03) ●●●○ *(moderate certainty of benefit, based on two good quality RCTs)* DFU (Apligraf vs Theraskin): 47.1% vs 66.7% (p-value not reported) ●○○○ (very low certainty of no comparative benefit, based on one fair quality RCT) VLU: RR 2.38 (p < 0.001) ●●○○ *(low certainty of benefit, based on one good quality RCT)* Unspecified non-healing ulcers: 100% vs 75% (p < 0.01) ●○○○ *(very low certainty of benefit, based on one poor quality RCT)*	
Quality of life *(Critical outcome)*	No evidence identified.	
Time to complete wound healing *(Important outcome)*	DFU: No evidence identified. VLU: 61 vs 191 days (statistical analysis not provided) ●●○○ *(low certainty of benefit, based on one good quality RCT)* Unspecified non-healing ulcers: 7 vs 51 weeks (statistical analysis not provided)	

Coverage question: Should Apligraf® be recommended for coverage for treatment of chronic skin ulcers?		
Outcomes	**Estimate of Effect for Outcome/ *Confidence in Estimate***	**Resource allocation**
	●○○○ *(very low certainty of benefit, based on one poor quality RCT)*	
Adverse effects *(Important outcome)*	DFU: Pooled data from 4 RCTs showed similar incidence of cellulitis, dermatitis, and peripheral edema with Apligraf® vs control (statistical analysis not reported) ●●○○ *(low certainty of no harm, based on four good quality RCT)* VLU: Infection rates of 8.2% vs 7.8% (statistical analysis not reported) ●○○○ *(very low certainty of no harm, based on one good quality RCT)*	
Rationale: Apligraf is recommended for coverage for venous leg ulcers and diabetic foot ulcers, based on improved complete wound healing, low variability in patient preference, and despite its cost. A strong recommendation was not made because only 2/5 of the predefined critical/important outcomes were addressed by the evidence and in favor of Apligraf for DFU. Coverage is recommended only when other conditions exist for wound healing (see Other Considerations section, below).		
Recommendation: Apligraf is recommended for coverage for diabetic foot ulcers and venous leg ulcers *(weak recommendation)* when conditions necessary for wound healing are present. Payers may wish to consider bundled payment, reference pricing, or other effective alternatives for smaller ulcers, as this product is sold in units of 44 cm^2 and has a short shelf life, which may lead to waste.		

Dermagraft®

Coverage question: Should Dermagraft® be recommended for coverage for treatment of chronic skin ulcers?		
Outcomes	**Estimate of Effect for Outcome/ *Confidence in Estimate***	**Resource allocation**
Deep soft tissue or bone infection *(Critical outcome)*	DFU: Osteomyelitis incidence 8.6% in both intervention and control groups ●○○○ *(very low certainty of no benefit, based on one fair quality RCT)*	Incremental cost for adding Dermagraft® to a patient's course of treatment for a small leg ulcer (<25 cm^2) under Medicare FFS (using average national prices for October, 2015) would range from $771.20 for a single application in an ambulatory surgery center to $11,960.80 for eight applications in the hospital outpatient setting. Up to 4 applications total appears equivalent efficacy to 8 applications. Product is sold in 37.5 cm^2 sheets.
Complete wound healing *(Critical outcome)*	DFU: OR 1.64 (95% CI, 1.10 to 2.43) in pooled data from 3 fair quality RCTs; one poor quality RCT with 38.5% versus 31.7% (p = 0.138) ●●○○ *(low certainty of benefit, based on three fair quality concordant RCTs and one poor quality discordant RCT)* *DFU (Dermagraft vs OASIS): 84.6% vs 76.9%, p = 0.62* ●○○○ *(very low certainty of no comparative benefit, based on one fair quality RCT)* VLU: RR 1.83 (95% CI, 0.47 to 7.21) and RR 3.04 (95%, CI 0.95 to 9.68) ●○○○ *(very low certainty of no benefit, based on two fair quality RCTs)*	
Quality of life *(Critical outcome)*	No evidence identified.	
Time to complete wound healing *(Important outcome)*	DFU: 13 weeks vs 28 weeks(statistical analysis not reported) ●●○○ *(low certainty of benefit, based on four poor to fair quality RCTs)* DFU (Dermagraft vs OASIS): 40.90 vs 35.67 days, p = 0.73	

	●○○○ (very low certainty of no comparative benefit, based on one fair quality RCT) VLU: 35 weeks vs 74 weeks, (statistical analysis not reported) ●○○○ *(very low certainty of benefit, based on one fair quality RCT)*	
Adverse effects *(Important outcome)*	DFU: 19% vs 32%, p = 0.007; second RCT no difference in rates of AE. ●○○○ *(very low certainty of benefit, based on two fair quality RCTs)* VLU: Similar number of AEs in all groups, statistical analysis not reported ●○○○ *(very low certainty of no harm, based on one fair quality RCT)*	
Rationale: Dermagraft is recommended for coverage for diabetic foot ulcers based on evidence of reduced time to wound healing and a higher likelihood of complete wound healing than usual care, with low variability in patient values and preferences. The recommendation is weak because of the low certainty of the evidence, and relatively high cost. Dermagraft is not recommended for coverage for venous leg ulcers based on insufficient evidence of benefit for any critical or important outcome and lack of FDA approval for this indication.		
Recommendation: Dermagraft is not recommended for coverage for venous leg ulcers *(weak recommendation)* Dermagraft is recommended for coverage for diabetic foot ulcers *(weak recommendation)* when conditions necessary for wound healing are present. Payers may wish to consider bundled payment, reference pricing, or other effective alternatives for smaller ulcers, as this product is sold in units of 37.5 cm^2 and has a short shelf life, which may lead to waste.		

OASIS® Wound Matrix

Coverage question: Should OASIS® Wound Matrix be recommended for coverage for treatment of chronic skin ulcers?		
Outcomes	**Estimate of Effect for Outcome/** ***Confidence in Estimate***	**Resource allocation**
Deep soft tissue or bone infection *(Critical outcome)*	No evidence identified.	Incremental cost for adding OASIS Wound Matrix to a patient's course of treatment for a small leg ulcer (<25 cm^2) under Medicare FFS (using average national prices for October, 2015) would be $235.69 for a single application in an ambulatory surgery center. In a physician's office, the cost would be $10.72 per cm^2 plus physician's fees of $143.73. The manufacturer recommends re-application every three to seven days as needed. Product is sold in units of varying sizes, the smallest of which is 10.5 cm^2. One study of DFU showed an average of 10 sheets. One study of VLU reported an average of 8 sheets. Study showed equivalence of 8 sheets of Oasis to 3 sheets of Dermagraft for DFU. One Medicare LCD limits to 12 weeks of therapy.
Complete wound healing *(Critical outcome)*	DFU: 49% vs 28% (p = 0.06) at 12 weeks; 54% vs 32% (p=0.021)at 12 weeks ●●○○ *(low certainty of benefit, based on two fair quality RCTs with inconsistency in comparator groups)* DFU *(OASIS vs Dermagraft): 76.9% vs 84.6%, p = 0.62* ●○○○ *(very low certainty of no comparative benefit, based on one fair quality RCT)* VLU: 80% vs 65% at 8 weeks (p < 0.05); 83% vs 46% at 16 weeks (p < 0.001); 55% vs 34% at 12 weeks, (p = 0.02) ●●○○ *(low certainty of benefit, based on three fair to good quality RCTs with inconsistency in comparator groups)*	
Quality of life *(Critical outcome)*	No evidence identified.	
Time to complete wound healing *(Important outcome)*	DFU: 5.4 vs 8.3 weeks, statistical analysis not reported; 67 vs 73 days (p = 0.245) ●●○○ *(low certainty of no benefit, based on two fair quality RCTs)* DFU (OASIS vs Dermagraft): 35.67 vs 40.90 days, p = 0.73 ●○○○ (very low certainty of no comparative benefit, based on one fair quality RCT) VLU: 63% vs 40% expected to heal at 12 weeks, p = 0.0226	

Coverage question: Should OASIS® Wound Matrix be recommended for coverage for treatment of chronic skin ulcers?		
Outcomes	**Estimate of Effect for Outcome/ *Confidence in Estimate***	**Resource allocation**
	●○○○ *(very low certainty of benefit, based on one good quality RCT*	
Adverse effects *(Important outcome)*	DFU: Approximately equal number of AEs between groups, statistical analysis not reported ●○○○ *(very low certainty of no benefit, based on one fair quality RCT)* VLU: Approximately equal number of AEs between groups, statistical analysis not reported ●○○○ *(very low certainty of no benefit, based on one good quality RCT)*	
Rationale: OASIS Wound Matrix is recommended for coverage for venous leg ulcers based on low-certainty evidence that it improves complete wound healing and time to complete wound healing, with low variability in values and preferences. OASIS Wound matrix is recommended for coverage for diabetic foot ulcers based on low certainty evidence of benefit of improved wound healing, low variability in values and preferences.		
Recommendation: OASIS is recommended for coverage for diabetic foot ulcers and venous leg ulcers (*weak recommendation*), when conditions necessary for wound healing are present.		

EpiFix®

Coverage question: Should EpiFix® be recommended for coverage for treatment of chronic skin ulcers?	
Outcomes	**Estimate of Effect for Outcome/ *Confidence in Estimate***
Deep soft tissue or bone infection *(Critical outcome)*	No evidence identified.

Coverage question: Should EpiFix® be recommended for coverage for treatment of chronic skin ulcers?	
Outcomes	**Estimate of Effect for Outcome/ *Confidence in Estimate***
Complete wound healing *(Critical outcome)*	DFU: 92% versus 8% (p < 0.0001) ●○○○ *(very low certainty of benefit, based on one RCT of fair quality)*
Quality of life *(Critical outcome)*	No evidence identified.
Time to complete wound healing *(Important outcome)*	No evidence identified.
Adverse effects *(Important outcome)*	No evidence identified.
Rationale: Epifix is not recommended for coverage due to insufficient evidence of effectiveness and the availability of effective alternatives *(weak recommendation).*	
Recommendation: EpiFix is not recommended for coverage for chronic skin ulcers (*weak recommendation*).	

Grafix®

Coverage question: Should Grafix® be recommended for coverage for treatment of chronic skin ulcers?	
Outcomes	**Estimate of Effect for Outcome/ *Confidence in Estimate***
Deep soft tissue or bone infection *(Critical outcome)*	DFU: "Wound-related infection" (undefined) 18.0% vs 36.2%, p = 0.044●○○○ *(very low certainty of benefit, based on one RCT of poor quality)*

Coverage question: Should Grafix® be recommended for coverage for treatment of chronic skin ulcers?	
Outcomes	**Estimate of Effect for Outcome/ *Confidence in Estimate***
Complete wound healing *(Critical outcome)*	DFU: 62% vs 21%, p < 0.01 ●○○○ *(very low certainty of benefit, based on one RCT of poor quality)*
Quality of life *(Critical outcome)*	No evidence identified.
Time to complete wound healing *(Important outcome)*	DFU: 42 days vs 69.5 days (statistical analysis not reported) ●○○○ *(very low certainty of benefit, based on one RCT of poor quality)*
Adverse effects *(Important outcome)*	DFU: 44% vs 66% (p = 0.031) ●○○○ *(very low certainty of benefit, based on one RCT of poor quality)*
Rationale: Grafix is not recommended for coverage for chronic skin ulcers due to insufficient evidence of effectiveness and the availability of effective alternatives *(weak recommendation).*	
Recommendation: Grafix is not recommended for coverage for chronic skin ulcers *(weak recommendation).*	

Graftjacket®

Coverage question: Should Graftjacket® be recommended for coverage for treatment of chronic skin ulcers?	
Outcomes	**Estimate of Effect for Outcome/ *Confidence in Estimate***
Deep soft tissue or bone infection *(Critical outcome)*	One trial had a single pt with hallux amputation due to infection in the treatment group and zero in control. ●○○○ *(very low certainty of harm, based on one RCT of poor quality)*

Coverage question: Should Graftjacket® be recommended for coverage for treatment of chronic skin ulcers?	
Outcomes	**Estimate of Effect for Outcome/** ***Confidence in Estimate***
Complete wound healing *(Critical outcome)*	DFU, vs moist dressing: 70% vs 46% (p = 0.03) DFU, vs Curasol: 86% vs 29% (p = 0.006) ●●○○ *(very low certainty of benefit, based on two poor to fair quality RCTs)*
Quality of life *(Critical outcome)*	No evidence identified.
Time to complete wound healing *(Important outcome)*	DFU: 11.92 vs 13.5 weeks and 5.7 vs 6.8 weeks, not significant ●○○○ *(very low certainty of no benefit, based on two poor to fair quality RCTs)*
Adverse effects *(Important outcome)*	DFU: Wound infection 21.4% vs 35.7%,statistical analysis not reported ●○○○ *(very low certainty of no harm, based on one poor quality RCT)*
Rationale: Graftjacket is not recommended for coverage because of the very low evidence of benefit for the critical outcome of complete wound healing, and a lack of efficacy for improving time to complete wound healing. Given only one application is required, fewer resources would be needed which would be an argument in favor, however, there is insufficient evidence to justify if even at the lower cost, this would provide significant benefit to patients.	
Recommendation: Graftjacket is not recommended for coverage for chronic skin ulcers (*weak recommendation*).	

Talymed®

Coverage question: Should Talymed® be recommended for coverage for treatment of chronic skin ulcers?	
Outcomes	**Estimate of Effect for Outcome/** ***Confidence in Estimate***
Deep soft tissue or bone infection *(Critical outcome)*	No evidence identified.
Complete wound healing *(Critical outcome)*	VLU: 86% vs 45% (p = 0.0005) ●○○○ *(very low certainty of benefit, based on one good quality RCT)*
Quality of life *(Critical outcome)*	No evidence identified.
Time to complete wound healing *(Important outcome)*	No evidence identified.
Adverse effects *(Important outcome)*	VLU: No significant treatment-related AEs ●○○○ *(very low certainty of no benefit, based on one good quality RCT)*
Rationale: Talymed is not recommended for coverage because of very low certainty of benefit, a lack of strong patient preferences for this, alternatives available, and its high cost.	
Recommendation: Talymed is not recommended for coverage for chronic skin ulcers (*weak recommendation*).	

TheraSkin®

Coverage question: Should Theraskin® be recommended for coverage for treatment of chronic skin ulcers?	
Outcomes	**Estimate of Effect for Outcome/** ***Confidence in Estimate***
Deep soft tissue or bone infection *(Critical outcome)*	DFU (Theraskin vs Apligraf): One amputation for infection, compared to none with Apligraf ●○○○ (very low certainty of no comparative benefit, based on one RCT of fair quality)
Complete wound healing *(Critical outcome)*	DFU (Theraskin vs Apligraf): 66.7% vs 41.3% (p = 0.21) ●○○○ (very low certainty of no comparative benefit, based on one RCT of fair quality)
Quality of life *(Critical outcome)*	No evidence identified.
Time to complete wound healing *(Important outcome)*	No evidence identified.
Adverse effects *(Important outcome)*	No evidence identified.
Rationale: Theraskin is not recommended for coverage because of insufficient evidence of benefit (limited evidence suggesting it is comparable to another effective product), a lack of strong patient preferences for this, alternatives available, and its cost.	
Recommendation: TheraSkin is not recommended for coverage for chronic skin ulcers (*weak recommendation*).	

EVIDENCE OVERVIEW

Clinical background

Diabetic foot ulcers (DFUs), venous leg ulcers (VLUs), and decubitus ulcers can be serious wounds, leading to severe health outcomes such as amputations and death. Diabetic foot ulcers are the result of atherosclerosis that impedes blood flow to the extremities and peripheral neuropathy that reduces the ability to sense injuries from extended pressure or other causes. Diabetic foot ulcers can lead to infections such as osteomyelitis and amputation. Appropriate treatment of these wounds can minimize the negative health outcomes and improve patient quality of life. Treatment for diabetic foot ulcers include cleaning, dressing, debridement, and pressure relief (Wound, Ostomy, and Continence Nurses Society, 2012). During the past 20 years, the prevalence of diabetes among adults in Oregon has more than doubled, to 9% in 2011. Among adults covered by the Oregon Health Plan, 17% have diabetes (Oregon Heart Disease and Stroke and Diabetes Prevention Programs, 2013). The annual incidence of foot ulcers among Medicare patients with diabetes is 6% (Margolis et al., 2011).

Venous leg ulcers are caused by chronic venous insufficiency. Treatment for venous leg ulcers include cleaning and dressing the wound, hemodynamic support to control the underlying disorder that caused the ulcer (e.g., medication or vascular bypass procedures), compression bandages, and compression stockings. The lifetime incidence of venous leg ulcers is about 1% (O'Meara, Al-Kurdi, & Ovington, 2008).

Decubitus ulcers or pressure ulcers (commonly called bed sores or pressure ulcers) occur when patients are unable to reposition themselves, most commonly in hospitals, long-term care facilities, and at home. Sustained pressure on a specific part of the body (often a bony prominence such as hip or sacrum) for long periods of time can cause a pressure ulcer. Treatment includes removing the pressure from the affected area, skin protection, debridement of necrotic tissues, cleaning, and dressing. Data from the National Nursing Home Survey indicate that 11% of nursing home residents had pressure ulcers (Park-Lee & Caffrey, 2009).

Skin substitutes have been used to treat ulcers that do not heal with the standard treatments. The most common use for skin substitutes is for the treatment of diabetic foot ulcers, venous leg ulcers, and decubitus ulcers. The etymologies of these ulcers make the wounds slower to heal, and the usual wound treatments are not always sufficient to ensure complete healing.

Indications

Skin substitutes are indicated for the treatment of chronic wounds, usually defined as having not healed within 30 days, having not responded to initial treatment, or persisting despite appropriate care. Skin substitutes were originally designed to treat burns, but now the most common usage is treating diabetic foot ulcers, venous leg ulcers, and decubitus ulcers.

Technology description

Skin substitutes promote healing and wound closure by mimicking or substituting for the skin structure. The skin substitute is designed to help the healing process by stimulating the host to regenerate lost

tissue and replace the wound with functional skin. Skin substitutes can be categorized (Snyder, Sullivan, & Schoelles, 2012) based upon how they are derived or produced:

- Products derived from human donor tissue
- Products derived from living human or animal tissues and cells
- Acellular animal –derived products
- Biosynthetic products

Currently, there are over 73 skin substitute products approved by the FDA for use in humans. While skin substitute products can be broadly grouped according to their source materials, the products are all sufficiently unique as to make generalization of efficacy across categories impracticable.

Table 1 shows skin substitute products available in the United States, categorized by how the product is derived and thus regulated by the FDA. This list of skin substitutes was created from the evidence and policy sources, and may not be complete. Products in the same category may not be equivalent in terms of effectiveness (Snyder, Sullivan, & Schoelles, 2012).

Human-derived skin substitute products that are minimally processed are regulated by the FDA as human cells, tissues, and cellular and tissue-based products (HCT/Ps). With HCT/Ps, tissue is obtained from human donors then processed and used in the same role in the patient (e.g., skin for skin, tendon for tendon). These HCT/Ps are regulated as human tissue intended for transplantation as long as the processing and clinical use are consistent with “Minimal Manipulation” and “Homologous Use” as defined in 21 CFR 1271. Products regulated as HCT/Ps must be registered with the FDA but are not required to demonstrate safety or effectiveness.

Cellular-derived material for wound healing cultured from human-derived tissues are regulated using the Biologics License Application (under the Federal Public Health Service Act) or with premarket approval (PMA) or as a Humanitarian Use Device obtained through a humanitarian device exemption depending on their composition and primary mode of action. The application for products regulated under the PMA process must include scientifically valid clinical studies demonstrating that the product is effective and safe.

Acellular animal-derived products and synthetic products are regulated under Section 510(k) of the Food, Drug and Cosmetic Act. This requires a premarket submission to the FDA to demonstrate that the device is substantially equivalent, i.e., at least as safe and effective, to a legally marketed device that is not subject to PMA. Submitters can compare their device to a device that was legally marketed prior to May 28, 1976 or a device which has been previously found to be substantially equivalent through the 510(k) process (Snyder, Sullivan, & Schoelles, 2012).

Table 1: Skin Substitutes

Products derived from human donor tissue, minimally processed	Products derived from living human and/or animal tissue	Acellular animal-derived products	Biosynthetic products
AlloDerm Regenerative Tissue Matrix	Apligraf®/Graftskin	Acell UBM Hydrafted Wound Dressing	Epicel™
Allpatch HD™	Dermagraft®	Acell UMB Lyophilized Wound Dressing	Hyalomatrix® (Laserskin®)
Alloskin™	AlloMax™	Aongen™ Collagen Matrix	Hyalomatrix®
Cymetra® Micronized AlloDerm	Celaderm®	Atlas Wound Matrix	Jaloskin®
Dermacell® and Arthroflex®	OrCel™	Avagen Wound Dressing	Suprathel®
Flex HD®	TransCyte™	Biobrane®	Talymed®
GammaGraft®		Collagen Sponge (Innocoll)	
Graftjacket® Regenerative Tissue Matrix		Collagen Wound Dressing (Oasis Research)	
Graftjacket® Express Scaffold		Collaguard®	
Matrix HD™		CollaSorb™	
Memoderm™		CollaWound™	
Puros® Dermis		Collexa®	
Repliform®		Collieva®	
TheraSkin®		Coreleader Colla-Pad	
		Dermadapt™ Wound Dressing	
		DressSkin	
		EndoForm Dermal Template™	
		Excellagen	
		E-Z Derm™	
		FortaDerm™ Wound Dressing	
		Helicoll	
		Integra® Dermal Regeneration Template	
		Integra™ Bilayer Matrix Wound Dressing	

Products derived from human donor tissue, minimally processed	Products derived from living human and/or animal tissue	Acellular animal-derived products	Biosynthetic products
		Integra™ Flowable Wound Matrix LTM Wound Dressing MatriStem Matristem Micromatrix® Matristem® Burn Matrix MatriStem® Wound Matrix Matrix Collagen Wound Dressing Medline Collagen Wound Dressing OASIS Burn Matrix™ OASIS Wound Matrix ™ Primatrix™ Primatrix™ Dermal Repair Scaffold SIS Wound Dressing II SS Matrix™ Stimulen™ Collagen TheraPorm™ Standard/Sheet Unite® Biomatrix Unite™ Biomatrix	

The following skin substitute products may not be available for chronic wounds in the US: Dermagen, EpiDex, Hyalograft, Kaloderm, Matriderm, PermaDerm, StrataGraft/ExpressGraft, and Xelma.

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 D.

1. What is comparative effectiveness of different types of skin substitutes compared with wound care alternatives for individuals with chronic skin ulcers? Include consideration of:
    a. Age
    b. Body mass index (BMI)
    c. Comorbidities

d. Site of ulcer
e. Ulcer etiology (e.g. infectious, pressure or circulatory).
f. Wound severity
g. Prior need for skin substitute
h. Failure of prior therapies

2. What adverse events are associated with skin substitutes?
3. What are contraindications to the use of skin substitutes?

Critical outcomes selected for inclusion in the GRADE table: deep soft tissue or bone infection, complete wound healing, and quality of life. *Important outcomes* selected for inclusion in the GRADE table: time to complete wound healing and adverse effects.

Evidence overview

Four systematic reviews and two additional RCTs address the use of skin substitutes for chronic skin ulcers; they are summarized in Tables 2 and 3. The outcomes considered critical for purposes of this coverage guidance are deep soft tissue or bone infection, complete wound healing, and quality of life. Time to complete wound healing and adverse effects are considered important outcomes. Complete wound healing is generally defined as "full epithelialization with no drainage, no exudate or eschar (scab) present" (Snyder, Sullivan & Schoelles, 2012, p. 48).

Although some products may have similar components or substrates, "[t]he results obtained from studies of a single product […] cannot be extrapolated to all products in a group because of differences in product components and healing properties" (Snyder, Sullivan & Schoelles, 2012, p. 48). Therefore, the results are organized by product type below.

Results are also separated by indication (diabetic foot ulcer or venous leg ulcer; the search did not identify any evidence for skin substitutes in the treatment of decubitus ulcers). Effectiveness for one type of wound cannot be extrapolated across indications "because of the difference in etiology and pathophysiology" between different types of wounds (Snyder, Sullivan & Schoelles, 2012, p. 56).

One limitation of the body of evidence is a lack of standardization of comparators. Some trials compare one skin substitute versus another, but many use "usual care" in the control group. Some treatments that fall into the category of usual care can include (but are not limited to):

- Diabetic Foot Ulcers – usual care techniques:
  - Nonadherent gauze dressing (Mepitel), covered with a secondary dressing including saline-moistened gauze and dry gauze
  - Saline-moistened, nonadherent gauze (Teapore) covered with a layer of saline-moistened gauze followed by dry gauze and petrolatum gauze layer
  - Nonadherent interface + saline moistened gauze
  - Saline moistened gauze
- Venous Leg Ulcers – usual care techniques:
  - Tegapore (gauze bolster), zinc oxide-impregnanted, paste bandage (Unna boot), and self-adherent elastic wrap

- Multilayered compression therapy

The body of evidence is also limited in the evidence addressing the considerations in Key Question 1. Where possible, discussion of study inclusion/exclusion criteria are presented.

Table 2. Summary of Included Systematic Reviews

Systematic Review (Quality) Total N	Population No. and Type of Included Studies	Skin Substitute Category	Outcomes of Interest
Game (2015) (Fair) N = 1461	Diabetic foot ulcers: 11 RCTs 1 Cohort 1 Case-control	• Allogeneic fetal fibroblasts on polyglactic matrix (Dermagraft) • Tissue engineered sheet of fibroblast/keratinocyte co-culture (Graftskin) • Living keratinocytes and fibroblasts (Apligraf®) • Amniotic membrane wound graft (Epifix)	• Complete wound healing • Time to complete wound healing
Felder (2012) (Fair) N = 2043	Chronic foot ulcers (diabetic, angiopathic, venous stasis, pressure-induced, or infected): 15 RCTs 1 Cohort 5 SRs	• Bilayer of neonatal keratinocytes and fibroblasts on hyaluronic acid matrix (Apligraf/Graftskin) • Neonatal fibroblasts and keratinocytes cultured onto bovine collagen matrix (OrCel) • Cryopreserved split-thickness skin allograft (TheraSkin) • Allogeneic fetal fibroblasts on polyglactic matrix (Dermagraft) • Autologous cultured keratinocytes on hyaluronic acid-derived,	• Complete wound healing • Time to complete wound healing • Infection rate • Complications • Ulcer recurrence

Systematic Review (Quality) Total N	Population No. and Type of Included Studies	Skin Substitute Category	Outcomes of Interest
		perforated lamina (Laserskin) • Decellularized cadaveric dermis (Graftjacket®) • Bovine collagen and chondroitin-6-sulfate scaffold with silicone covering (Synthetic Integra)	
Jones (2013) (Good) N = 438	Venous leg ulcers: 5 RCTs	• Allogenic bilaminar Composite Cultured Skin (OrCel™) • Cultured epidermal allograft (Autoderm™) • Products derived from live human/animal tissue (Apligraf®, Dermagraft®)	• Complete wound healing • Time to complete healing • Rate of change in ulcer area • Pain • Adverse events
Snyder (2012) (Good) N = 1,829	Diabetic foot ulcers: 12 RCTs Vascular leg ulcers: 6 RCTs	• Products derived from human donor tissue (Graftjacket®) • Products derived from live human/animal tissue (Apligraf®, Dermagraft®) • Acellular animal derived products (OASIS® Wound Matrix) • Biosynthetic products (Talymed®)	• Wound infection • Complete wound healing • Time to complete wound healing • Adverse events • Quality of life surrogate outcomes (return to baseline activities of daily living and function, pain reduction)

Table 3. Summary of Included Randomized Controlled Trials identified in additional Medline search

RCT (Quality) Total N	Population	Skin Substitute Category	Outcomes of Interest
Lavery 2014 (Poor) N = 97	Diabetic foot ulcers	• Placenta-derived human viable wound matrix (Grafix®)	• Complete wound healing • Time to complete healing • Adverse events • Wound-related infections

EVIDENCE SUMMARY

Snyder [AHRQ] (2012)

The AHRQ systematic review by Snyder, Sullivan and Schoelles (2012) included 18 RCTs (12 on DFUs, 6 on VLUs). Of the 18 studies, eight were assessed as a low risk of bias, nine as a moderate risk of bias, and one with an unclear risk of bias. The review authors limited study inclusion to RCTs that had a minimum of 10 patients per treatment arm. In addition to the outcomes described in Table 1, the AHRQ review evaluated wound recurrence, need for amputation, need for hospitalization, return to baseline activities of daily living and function, pain reduction, and exudate and odor reduction.

Felder (2012)

The systematic review by Felder, Goyal, and Attinger (2012) included 15 RCTs and one prospective cohort study as well as five systematic reviews. This SR was concerned with chronic foot ulcers of any origin. There is significant overlap in included studies (nine RCTS) between the AHRQ SR (Snyder, Sullivan and Schoelles, 2012) and this SR. Felder and colleagues (2012) included five additional studies (3 DFU, 1 VLU, 1 non-healing foot ulcer) that were not included in the AHRQ review (Snyder, Sullivan and Schoelles, 2012). Of these five, one was assessed at low risk of bias, one at moderate risk of bias, and three at high risk of bias. Rate of complete wound healing was the primary outcome; secondary outcomes included time to complete wound healing, infection rates, and ulcer recurrence.

Jones [Cochrane] (2013)

The Jones systematic review (Jones, Nelson and Al-Hity, 2013) focused on the treatment of VLUs and included five RCTs on the use of skin substitutes, two of which overlap with the AHRQ review (Snyder, Sullivan and Schoelles, 2012). Of the remaining three studies, one is rated as unclear risk of bias, one at low risk of bias, and one at moderate risk of bias. Authors included any randomized study, regardless of

publication status or language, in which skin grafts or skin replacements for venous leg ulcers were compared against any other intervention (only studies involving skin substitutes are summarized in this coverage guidance), and which reported on the primary outcomes of wound healing, time to complete healing, or absolute rate of change of ulcer area.

Game (2015)

A systematic review by Game and colleagues (2015) assessed the effectiveness of various interventions for diabetic foot ulcers. This is the second update of a systematic review undertaken by the International Working Group of the Diabetic Foot (IWGDF) in 2006 and first updated in June 2010. Game and colleagues (2015) included all controlled studies, both prospective and retrospective, that evaluated treatment of chronic foot ulcers in adults (age 18 and older) with type 1 or type 2 diabetes. Primary outcomes were healing, time to healing, and reduction in wound area. The 2015 review included 11 RCTs relevant to skin substitutes; all but three of them overlap with the other SRs included in this report. Of those three, one was rated at medium risk of bias and the others at high risk of bias.

Apligraf® / Graftskin

Apligraf®, known previously as Graftskin, is a "living cell based bilayered skin substitute derived from bovine type 1 collagen and human fibroblasts and keratinocytes derived from neonatal foreskins" (Snyder, Sullivan, and Schoelles, 2012, pg 38).

The FDA has approved Apligraf®

> For use with standard therapeutic compression for the treatment of non-infected partial and full-thickness skin ulcers due to venous insufficiency of greater than 1 month duration and which have not adequately responded to conventional ulcer therapy. Apligraf is also indicated for use with standard diabetic foot ulcer care for the treatment of full-thickness neuropathic diabetic foot ulcers of greater than three weeks' duration which have not adequately responded to conventional ulcer therapy and which extend through the dermis but without tendon, muscle, capsule or bone exposure.
>
> Apligraf is contraindicated for use on clinically infected wounds. Apligraf is contraindicated in patients with known allergies to bovine collagen. Apligraf is contraindicated in patients with a known hypersensitivity to the components of the Apligraf agarose shipping medium." of non-infected partial and full-thickness skin ulcers due to venous insufficiency of greater than 1 month duration and which have not adequately responded to conventional ulcer therapy. Apligraf is also indicated for use with standard diabetic foot ulcer care for the treatment of full-thickness neuropathic diabetic foot ulcers of greater than three weeks' duration which have not adequately responded to conventional ulcer therapy and which extend through the dermis but without tendon, muscle, capsule or bone exposure (Snyder, Sullivan, and Schoelles, 2012, pg 38).

The prescribing information contains a caution; “The safety and effectiveness of Apligraf have not been established for patients receiving greater than 5 device applications.”

Inclusion criteria for trials of Apligraf® varied in the size and severity of wounds. Minimum duration was 2-4 weeks. Patients were excluded for conditions that would impair wound healing such as poor glycemic control (identified in one trial as hemoglobin A1c ≥12), active infection, immunocompromise (either from underlying disease, radiation, chemotherapy, or recent corticosteroid use), evidence of skin cancer at or near the wound, renal or hepatic impairment, drug or alcohol abuse, and Charcot foot or inability to offload the ulcer. Some studies excluded patients whose ulcers responded to usual care in a 7-14 day run-in period. The majority of patients were male and in their 50s or 60s.

Three early studies (Sabolinski, 1996; Falanga, 1998; Falanga & Sabolinski, 1999) all used the same protocol of up to five applications within the first 21 days of treatment. Ulcers were re-examined every few days and if less than 50% of the previous application “took,” researchers applied the product again, up to five times in total. The earliest study reported that 70% of patients got 1-3 grafts; the others did not report how many applications were required. A 2009 study re-examined patients at 4 and 8 weeks after initial application and re-applied as necessary. “In the Apligraf group, 13 of the 33 subjects required only 1 application of Apligraf, and 15 and 5 subjects received 2 or 3 applications, respectively. On average, subjects received 1.8 Apligraf applications during the course of the study” (Edmonds, 2009, pg. 14). The comparative study of Apligraf® vs TheraSkin® (DiDomenico, 2011) put no limits on the number of applications and allowed them at clinician discretion, they report an average of 1.53 applications (SD = 1.65).

Chang, 2000 used only a single application for all subjects, and reported on costs thusly:

At our institution, professional fee reimbursement for all skin graft procedures averages $1 350. A single 7-inch disk of Apligraf costs $1000 to the third-party insurer or the patient. The reimbursement for a 3- to 5-day hospital stay, including operating room and recovery room costs, average $8000-$11,000 for a Medicare patient. Therefore, Apligraf application in these patients costs $7000 to $10,000 less that an autologous skin graft. Moreover, further cost reductions may be possible as demand for this product increases. Finally, wound closure yields may further be improved with multiple applications of TESG and as the optimal dressing and management of TESG-treated wounds in this patient population become better defined (Chang, 2000, pg. 49).

Critical Outcome: Deep Soft Tissue or Bone Infection

The AHRQ review (Snyder, Sullivan and Schoelles, 2012) included one trial that reported cases of osteomyelitis in patients with DFUs treated with either Apligraf®/Graftskin or usual care. The RCT compared Apligraf® to saline-moistened gauze (treatment group, n = 112; usual care group, n = 96). There was a significantly lower incidence of osteomyelitis in the Apligraf® group compared to usual care (2.7% vs 10.4%, p = 0.04).

For VLUs, the AHRQ review included a single RCT comparing Apligraf® to compression therapy (treatment group, n = 161; usual care group, n = 136) that reported incidence of osteomyelitis. Approximately eight percent of patients receiving Apligraf® developed osteomyelitis at the study site, compared with no patients in the comparison group developing a bone infection (no statistical analysis conducted).

Critical Outcome: Complete Wound Healing

Snyder and colleagues (2012) included three RCTs comparing Apligraf® to usual care. Two of the trials included patients with DFUs (total n = 280) and the third trial focused on VLUs (n = 275). The AHRQ review (Snyder, Sullivan and Schoelles, 2012) found the use of Apligraf® was associated with significantly greater percentage of wound closures compared to usual care for patients with DFUs at 12 weeks (Trial 1, n=72, 52% vs 26%, p=0.03, relative risk 1.96, 95% CI 1.05 to 3.66; Trial 2, n=208, 56% vs 38%, p=0.01, relative risk 1.5, 95% CI 1.11 to 2.04) and patients with VLUs at 12 weeks (53% vs 22%, p<0.001, relative risk 2.38, 95% CI 1.67 to 3.39).

Felder and colleagues (2012) included two additional RCTs comparing Apligraf® to usual care. The first was a subgroup analysis of a larger study which looked at 120 patients whose ulcers had been present for at least one year, comparing Apligraf® to multilayer compression wrap. In this hard-to-heal subgroup, complete healing occurred by six months in 47% of subjects receiving Apligraf® versus 19% of the control subjects. The second study included by Felder (2012) compared Apligraf® against saline gauze dressing in patients with chronic foot ulcers of any etiology who had undergone limb revascularization within 60 days. Complete closure by six months occurred in 100% of Apligraf® patients, compared to 75% of usual care patients ($p < 0.01$).

Apligraf® vs Theraskin®

One RCT included in the AHRQ review (Snyder, Sullivan and Schoelles, 2012) evaluated the comparative effectiveness of Apligraf® and Theraskin® for DFUs (n = 28). Average wound size was similar between groups. There were no significant differences reported in complete wound closure between the two products (Apligraf® 41% vs Theraskin® 67%, p=0.21).

Critical Outcome: Quality of Life

No SRs or RCTs reported on the effect of Apligraf® on validated quality of life indicators. One RCT included in the AHRQ review reported on pain, noting that it improved significantly in both Apligraf® and control groups (Snyder, Sullivan and Schoelles, 2012).

Important Outcome: Time to Complete Wound Healing

Snyder and colleagues (2012) included one RCT that reported on the time to complete wound healing in the use of Apligraf® for VLU. In the single RCT, patients who received Apligraf® experienced shorted median time to wound closure (61 days) compared with usual care (i.e., Unna boot) (191 days).

Felder and colleagues (2012) included one RCT of patients with chronic foot ulcers who had recently (60 days) undergone limb revascularization, which found mean time to healing with Apligraf® was seven weeks, compared to 15 weeks in the group treated with saline-gauze dressing (p = 0.0021).

Important Outcome: Adverse Effects

The AHRQ review (Snyder, Sullivan and Schoelles, 2012) included four studies that reported on adverse effects from Apligraf® for a total of 332 patients treated with the product and 283 patients treated with usual care. Two RCTs (N = 28 and N = 72) reported only "serious adverse events" in the treatment and follow-up phases, and these were roughly equivalent (3-5 patients in each group). One trial only reported on osteomyelitis, which is discussed above. In the fourth RCT (N = 297), there were approximately equal incidences of cellulitis (15.5% vs 13.2%), dermatitis (8.7% vs 8.8%), and peripheral edema (5.0% vs 5.0%) in the Apligraf® group compared to usual care.

Although not explicitly stated as a critical outcome, one trial reported on the incidence of death. Six cases of death reported in the Apligraf® group compared with five cases in the usual care group (reasons not described); there were no other deaths reported across the three other trials.

Felder and colleagues (2012) included one additional study (a subgroup of a previous study, separating out 120 patients with hard-to-heal venous ulcers present longer than one year) that reported infection rates of 8.2% in the Apligraf® treatment group (n = 72) versus 7.8% in the usual care control group (n = 48).

In addition to the adverse effects described above, trials also reported relatively rare incidence of rashes, pain, urinary tract infection, pain, dyspnea, congestive heart failure, accidental injury, pharyngitis, asthenia, arrhythmia, arthralgia, increased cough, erythema, and kidney failure.

Dermagraft®

Dermagraft® is a "cryopreserved human fibroblast-derived dermal substitute on a bioabsorbable polyglactin mesh scaffold. The fibroblasts are obtained from human newborn foreskin tissue" (Snyder, Sullivan and Schoelles, 2012, pg 38). It is indicated by the FDA

> [f]or use in the treatment of full-thickness diabetic foot ulcers greater than six weeks' duration which extend through the dermis, but without tendon muscle, joint capsule or bone exposure. Dermagraft® should be used in conjunction with standard wound care regimens and in patients that have adequate blood supply to the involved foot. Dermagraft is contraindicated for use in ulcers that have signs of clinical infection or in ulcers with sinus tracts. Dermagraft is contraindicated in patients with known hypersensitivity to bovine products, as it may contain trace amounts of bovine proteins from the manufacturing medium and storage solution (Snyder, Sullivan and Schoelles, 2012, pg 38).

The FDA prescribing information contains a caution than Dermagraft has not been studied in patients receiving greater than 8 device applications.

Trials of Dermagraft® included patients with adequate glycemic control and evidence of adequate circulation as measured by ankle brachial pressure index (ABPI). Patients were excluded for evidence of active infection, impaired mobility, and significant comorbidities such as HIV, severe peripheral vascular

disease, or a bleeding disorder. Patients were also generally excluded if their ulcers responded to usual care during a run-in or screening period. Average age ranged from 55 to 72 years.

Application regimens for Dermagraft® are diverse in the literature. Earlier trials involved weekly applications for up to 7 or 8 treatments (Gentzkow, 1996; Naughton, 1997; Marston, 2003). A study in 2003 divided patients into three different treatment arms; weekly applications for up to 12 weeks and a total of four applications at 0, 1, 4, and 8 weeks had identical efficacy (5/13 wounds healed). The most recent trial in this report (Omar, 2004) used this same 0, 1, 4, and 8 protocol and had a similar result (5/10 ulcers healed).

Critical Outcome: Deep Soft Tissue or Bone Infection

The AHRQ review (Snyder, Sullivan and Schoelles, 2012) identified one RCT comparing Dermagraft® to saline-moistened gauze in the treatment of DFU that reported on incidence of osteomyelitis. Rates were 8.6% in both the intervention and the control groups.

Critical Outcome: Complete Wound Healing

Snyder and colleagues (2012) included three RCTs that reported on complete wound healing in the use of Dermagraft® for DFUs. All three RCTs on DFUs found that patients receiving Dermagraft® experienced greater rates of complete wound healing compared to usual care at 12 weeks. A meta-analysis found Dermagraft to be more effective for achieving wound closure compared to usual care (saline-moistened gauze) for patients with DFUs (odds ratio 1.64; 95% CI 1.10 to 2.43).

Felder and colleagues (2012) identified one additional RCT of Dermagraft® in care of DFUs, in which the metabolic activity of the graft was assessed and patients in the treatment arm were stratified by whether or not the Dermagraft® was “metabolically active within the therapeutic range” (Felder, 2012, p. 150). At twelve weeks, the rate of complete healing was 38.5% in the entire treatment group and 31.7% in the control group (p = 0.138), but was 50.8% in the “metabolically active” Dermagraft® group.

Snyder and colleagues (2012) identified one RCT that included patients with VLUs, which found greater rates of complete wound healing in the Dermagraft® group at 12 weeks, although this finding was not statistically significant (28% vs 15%, p=0.30, relative risk 1.83, 95% CI 0.47 to 7.21).

Jones and colleagues (2013) identified one additional RCT of Dermagraft® versus usual care in VLUs that used a four-piece protocol. They pooled this data with the results of the aforementioned RCT and found that “There was no evidence of overall benefit associated with four pieces of dermal skin replacement (at baseline, one, four and eight weeks) in the two studies (RR 3.04, 95% CI 0.95 to 9.68), when pooled using a fixed-effect model (44 participants)” (Jones, Nelson, and Al-Hity, 2013, p. 10).

Dermagraft® vs OASIS®

One RCT included in the AHRQ review (Snyder, Sullivan and Schoelles, 2012) evaluated the comparative effectiveness of Dermagraft® and OASIS® for DFUs (n = 26). Average wound size was similar between groups (p = 0.94). There were no significant differences reported in complete wound closure between the two products (Dermagraft® 84.6% vs OASIS® 76.9%, p = 0.62).

Critical Outcome: Quality of Life

No SRs or RCTs reported on the effect of Dermagraft® on validated quality of life indicators or surrogate measures.

Important Outcome: Time to Complete Wound Healing

Felder and colleagues (2012) identified four RCTs that reported on time to complete healing for DFUs treated with Dermagraft®. In all four trials, generally speaking, healing was faster in the Dermagraft® group than in the control. A fair quality small RCT testing three different Dermagraft® regimens against usual care (N=50) found that weekly application of Dermagraft® resulted in mean time to healing of 12 weeks, while less frequent applications and usual care led to healing times greater than 12 weeks. A second, fair quality RCT (N=235) assessed the metabolic activity of the Dermagraft® product prior to application and found an improvement in healing time (13 weeks vs 28 weeks) only when the product was "metabolically active within the therapeutic range" (Felder, Goyal, and Attinger, 2012, p. 150). A poor quality RCT (N=281) published the same year had identical results (13 weeks vs 28 weeks), while the final RCT in this review (also poor quality, N=245) demonstrated that time to healing was significantly faster with Dermagraft than with control (p = 0.04)

Similarly, the one RCT included in the AHRQ review (Snyder, Sullivan and Schoelles, 2012) on the use of Dermagraft® for patient with VLUs found shorter wound closure time in the Dermagraft group compared with usual care (35 weeks vs 74 weeks).

Dermagraft® vs OASIS®

One RCT included in the AHRQ review (Snyder, Sullivan and Schoelles, 2012) evaluated the comparative effectiveness of Dermagraft® and OASIS® for DFUs (n = 26). There were no significant differences reported in time to complete wound closure between the two products (Dermagraft 40.90 ± 32.32 days vs OASIS® 35.67 ± 41.47 days, p = 0.73).

Important Outcome: Adverse Effects

Two trials identified by Felder and colleagues (2012) reported on adverse effects with Dermagraft®. One trial (n = 314) found that compared to usual care (saline-moistened gauze), patients who received Dermagraft® had lower rates of adverse effects (i.e., infection, osteo and cellulitis) (19% vs 32%, p=0.007). In the second trial, patients in the Dermagraft® groups had similar rates of adverse events (undefined, statistical significance not reported in the AHRQ review). Unrelated AEs in this study (N = 53) included syncope, skin excoriation, bleeding from biopsy site, latex allergy, development of bullous pemphigoid, and cerebrovascular accident.

The AHRQ review (Snyder, Sullivan and Schoelles, 2012) reported adverse events from one fair quality RCT (N=53) of Dermagraft® in treatment of VLUs. With 13-14 subjects in each treatment group, total number of adverse events was 15-18 per group, Serious adverse events were not reported in the control group; the three treatment groups each had at least one serious adverse event, with four serious events in the most intensive treatment arm.

EpiFix®

EpiFix® is derived from human amniotic membrane and is marketed both in a skin allograft form as well as an injectable form. It does not presently have any FDA indications. This evidence review identified one small RCT of EpiFix®. Patients were 56-62 years old, were 69% and 58% male in the intervention and control groups, respectively, and had ulcers averaging 2.8cm^2 in the intervention group and 3.4 cm^2 in the controls. Other inclusion/exclusion criteria were not described and significance of baseline differences were not reported.

In this RCT (Zelen, 2013), patients who had incomplete epithelialization received an additional application at weeks 2, 4, 6, 8, and 10. The authors state, "Five patients (45%) healed with one dHAM application, one (9.1%) healed with two applications, one (9.1%) healed with three applications, two (18%) healed with four applications, and one (9.1%) healed after five applications." This is an average of 2.3 applications.

Critical Outcome: Deep Soft Tissue or Bone Infection

No SRs or RCTs reported on the effect of EpiFix® on deep soft tissue or bone infection.

Critical Outcome: Complete Wound Healing

Game and colleagues (2015) identified one RCT of Epifix®, an amniotic membrane graft product, in the treatment of DFUs. This was a small pilot study in which 13 patients with an average wound size of 2.8 cm^2 were treated with EpiFix® and 12 patients with an average wound size of 3.4 cm^2 were treated with moistened gauze and silver; all patients received compression dressings. At four weeks, complete healing was 77% in the EpiFix® group and 0% in the control group ($p < 0.0001$). By six weeks, rates of complete healing were 92% and 8%, respectively ($p < 0.0001$). This is an unexpectedly low rate of healing in the control group.

Critical Outcome: Quality of Life

No SRs or RCTs reported on the effect of EpiFix® on validated quality of life indicators or surrogate measures.

Important Outcome: Time to Complete Wound Healing

No SRs or RCTs reported on the effect of EpiFix® on time to complete wound healing.

Important Outcome: Adverse Effects

No SRs or RCTs reported on the adverse effects of EpiFix®.

Grafix®

Grafix® is another product derived from cryopreserved human placental membrane. It is approved by the FDA as a "wound cover" for both acute and chronic wounds. According to the manufacturer it intends to submit a Biologics License Application for more clinical indications. This evidence review identified only one RCT of poor quality. Patients in this trial had wounds of four to 52 weeks' duration, and of one to 15 cm^2 in area. Patients were excluded for A1c ≥12, inadequate ABPI, presence of active

infection, and response to usual care during a one-week screening period. Other subject characteristics were not reported. Patients received weekly applications for up to 84 days (Lavery, 2014).

Critical Outcome: Deep Soft Tissue or Bone Infection

No SRs or RCTs reported on the effect of Grafix® on deep soft tissue or bone infection. The RCT by Lavery and colleagues (2014) did report that patients randomized to Grafix® did experience significantly fewer wound infections than the usual-care group (18.0% versus 36.2%, p = 0.044), and a trend to fewer infection-related hospitalizations (6% versus 15%, p = 0.15).

Critical Outcome: Complete Wound Healing

Lavery and colleagues (2014) conducted an RCT of Grafix® versus standard wound care for DFUs. Patient groups were similar at baseline. Complete wound healing occurred in 62% of patients treated with Grafix® and in 21% of the control group (p < 0.01). The quality of this study is poor due to having no description of randomization methodology, nor concealment or blinding efforts. The study was funded by manufacturer.

Critical Outcome: Quality of Life

No SRs or RCTs reported on the effect of Grafix® on validated quality of life indicators or surrogate measures.

Important Outcome: Time to Complete Wound Healing

In the poor quality RCT by Lavery and colleagues (2014), time to complete healing was a secondary outcome. Patients treated with Grafix® experienced complete wound healing in a median time of 42 days, compared to 69.5 days in the control group (p = 0.019).

Important Outcome: Adverse Effects

Lavery and colleagues (2014) reported that patients treated with Grafix® were less likely to experience any adverse event than patients in the control group (44% versus 66%, p = 0.031). One control group subject underwent amputation due to an adverse event; there were no amputations in the intervention arm. There was no discussion of whether any of the adverse events were thought to be related to treatment.

Graftjacket®

Graftjacket® is derived from donated human tissue, and is composed of extracellular components of human dermis (collagen, elastin, and proteoglycans). One RCT included patients with non-infected ulcers and a palpable/audible pulse to the affected extremity, but did not describe other inclusion/exclusion criteria. A second RCT included only patients with good diabetic control (Hgb A1c < 12, serum creatinine < 3.0 mg) and adequate ABPI, and excluded patients who had received biomedical or topical growth factors within 30 days. Other subject characteristics were not reported. Both RCTs used a single application in the treatment group (Brigido, 2006; Reyzelman, 2009).

Critical Outcome: Deep Soft Tissue or Bone Infection

The AHRQ review (Snyder, Sullivan and Schoelles, 2012) identified one RCT that reported wound infection rates in the use of Graftjacket®. In 46 patients treated with Graftjacket®, one patient experienced a wound infection that eventually ended with amputation; there were no cases of wound infection in the 39 control group subjects.

Critical Outcome: Complete Wound Healing

Two RCTs were included in the AHRQ review (Snyder, Sullivan and Schoelles, 2012) that evaluated the use of Graftjacket® in patients with DFUs (total n = 113). The authors of both studies report a significantly greater proportion of wound closure compared to usual care at 12 weeks (compared with moist-wound therapy dressings: 70% vs 46%, p=0.03, relative risk 1.51, 95% CI 1.02 to 2.22; compared with Curasol: 86% vs 29%, p=0.006). In the AHRQ review, one of these RCTs was assessed at moderate risk of bias; the other was determined to be at low risk of bias after author communications clarified the randomization procedures. However, Felder and colleagues (2012) point out other flaws in this second RCT, specifically that the dropout rate was twice as high in the treatment group as in the control group, that the average pretreatment wound size was biased in favor of the Graftjacket arm (3.6cm^2 in the treatment subjects versus 5.1cm^2 in the control subjects), and that the control group "had a higher percentage of foot wounds, which are more likely to be weight-bearing and therefore more difficult to heal" (Felder, Goyal and Attinger, 2012, p. 60).

Critical Outcome: Quality of Life

No SRs or RCTs reported on the effect of Graftjacket® on validated quality of life indicators or surrogate measures.

Important Outcome: Time to Complete Wound Healing

The AHRQ SR (Snyder, Sullivan and Schoelles, 2012) included two RCTs that reviewed the effectiveness of Graftjacket for DFUs. In one trial, time to complete healing was 11.92 weeks in the treatment group versus 13.5 weeks in the control group; in the other, it was 5.7 weeks in the treatment group versus 6.8 weeks in the control. While both studies reported a shortened time to would closure compared to a usual care group, neither finding was statistically significant.

Important Outcome: Adverse Effects

One RCT reported wound infection rates of 21.4% versus 35.7% in the treatment and control groups, respectively (Felder, Goyal and Attinger, 2012). The other RCT reported on a control group patient who experienced altered mental status and hypotension and another who developed an abscess; in the treatment group, one patient had an infection leading to amputation (discussed above), and a second required vascular surgery.

OASIS® Wound Matrix

OASIS® is derived from hydrolyzed bovine collagen and is approved by the FDA "[f]or the management of wounds including full thickness and partial thickness wounds, pressure ulcers, venous ulcers, ulcers caused by mixed vascular etiologies, diabetic ulcers, second-degree burns, donor sites and other

bleeding surface wounds, abrasions, traumatic wounds healing by secondary intention, dehisced surgical incisions" (Snyder, Sullivan and Schoelles, 2012, pg. ES-12). The AHRQ review identified five RCTs evaluating the effectiveness of OASIS®. Patients were enrolled with a wound of >4 weeks duration (in one trial, > 6 months). Patients with conditions that would slow wound healing were excluded from all trials, for example, malnutrition (albumin < 2.5 g/dL), poor glycemic control (A1c >12), active smoker status, inadequate circulation to the affected limb, active infection, immunosuppression, use of steroids, vascular disease, and Charcot foot.

In three trials of OASIS® for DFU, the product was re-applied as deemed clinically necessary. One RCT (Niezgoda, 2005) reported an average use of 10 sheets of OASIS per patient. A trial of OASIS compared to Dermagraft® (Landsman, 2008) reported that up to eight applications of OASIS was similarly effective to up to three applications of Dermagraft®. The third trial (Romanelli, 2010) reported an average of 5.2 days between dressing changes for OASIS patients.

Two RCTs reported on OASIS® in treatment of VLU. One (Mostow, 2005) reported an average of eight sheets per patient; the other (Romanelli, 2007) reported an average of 6.4 days between dressing changes but did not report on number of sheets of product used.

Critical Outcome: Deep Soft Tissue or Bone Infection

No SRs or RCTs reported on the effect of OASIS® on deep soft tissue or bone infection.

Critical Outcome: Complete Wound Healing

The AHRQ review (Snyder, Sullivan and Schoelles, 2012) included one RCT of patients with DFUs (n = 98), comparing OASIS® Wound Matrix with Regranex Gel (contains platelet-derived growth factor) and found greater wound closure of plantar ulcers at 12 weeks in the OASIS® group (49% vs 28%, p=0.06).

A second RCT comparing OASIS® Wound Matrix with standard care was identified after the initial search and draft coverage guidance was completed. Cazzell and colleagues (2015) published results of an open-label RCT of 82 patients comparing OASIS® to standard care for treatment of DFU. In the intervention group, OASIS was applied once each week. Patients in the control group were also seen weekly and the standard care intervention was selected by the investigator (standard care included sliver dressing, Hydrogel, wet-to-dry, alginate, Manuka honey, or triple antibiotic dressing). Ulcer measurement was standardized by use of a digital image capture and wound measurement device. At 12 weeks, wound healing was greater in the OASIS group (54%) compared with the standard care group (32%) (p=0.021). Smith and Nephew funded the study and employs three of the authors. Aside from the conflicts of interest and open-label design, the study otherwise appears to be at low risk of bias. This fair quality RCT demonstrates improved DFU wound healing at 12 weeks for patients treated with OASIS compared to standard care.

Snyder and colleagues (2012) included three RCTs of patients with VLUs that evaluated the effectiveness of OASIS® Wound Matrix (total n = 222). The trials included disparate usual care groups (petrolatum-impregnated gauze with no compression, Jaloskin containing hyaluronan, nonadherent dressing with compression bandages). However, healing rates were greater in the OASIS® Wound Matrix arms across

all three trials and follow-up periods (80% vs 65% at 8 weeks, p<0.05; 83% vs 46% at 16 weeks, p<0.001; 55% vs 34% at 12 weeks, p=0.02; respectively).

OASIS® Wound Matrix vs Dermagraft®

The AHRQ SR (Snyder, Sullivan and Schoelles, 2012) included one RCT that compared OASIS® Wound Matrix with Dermagraft® for individuals with DFUs (n = 26). The study found no significant difference in complete wound closure between the two products (Dermagraft 84.6% vs OASIS® 76.9%, p = 0.62).

Critical Outcome: Quality of Life

No SRs or RCTs reported on the effect of OASIS® on validated quality of life indicators. One RCT identified in the AHRQ review reported fewer wound dressings with OASIS® (6.46 ± 1.39 changes vs 2.54 ± 0.78), while a second reported lower pain levels in the intervention group as measured by a 10-point visual analog scale (3.7 vs 6.2, p < 0.05). A third RCT reported that 2/17 patients in the OASIS® group experienced pain, compared to 1/10 control patients.

Important Outcome: Time to Complete Wound Healing

Of the three RCTs included in the AHRQ review (Snyder, Sullivan and Schoelles, 2012) that evaluated OASIS® Wound Matrix in patients with DFUs, only one trial reported a shorter time to wound closure compared to nonadherent dressing with compression bandages (5.4 weeks vs 8.3 weeks, statistical analysis not reported). A second RCT reported 35.67 ± 41.47 days in the OASIS® arm vs 40.90 ± 32.32 days in the control (not significant). The third RCT reported average time of 67 days with OASIS® and 73 days with control (p = 0.245). All three RCTs were of fair quality.

One RCT of OASIS® in VLUs did not report time to healing, but did estimate using Cox analysis that at twelve weeks, 63% of the treatment group vs 29% of the controls would be expected to achieve complete wound healing (Snyder, Sullivan and Schoelles, 2012).

OASIS® Wound Matrix vs Dermagraft®

The AHRQ SR included one RCT that compared OASIS® Wound Matrix with Dermagraft for individuals with DFUs. The study found no significant difference in the time to wound closure between the two products (Snyder, Sullivan and Schoelles, 2012).

Important Outcome: Adverse Effects

The AHRQ SR included one RCT that compared OASIS® with Regranex growth gel (Snyder, Sullivan and Schoelles, 2012). The authors reported adverse effects in the OASIS® group (n=17) including one patient with depression/mood disorder, one patient with gastrointestinal disorder, and three patients with infections in a non-study ulcer. In the Regranex group (n=10), there was one instance of infection in a non-study ulcer, two cases of limb injury, one respiratory tract infection, one case of septic arthritis, and one skin injury.

The AHRQ SR also reported on one trial in which eight patients received OASIS® and 15 were treated with compression. In this trial, three patients in each group experienced an allergic reaction or intolerance to the secondary dressing. One patient in the OASIS® group died of cardiovascular disease; one patient in the compression group developed a new ulcer from the compression. One patient in each

group developed an infection in another (non-target) wound, one patient receiving compression developed a seroma, and one patient in each group suffered skin injury.

Talymed®

Talymed® is a wound dressing product containing poly-N-acetyl glucosamine (pGlcNAc) derived from microalgae. (Snyder, Sullivan and Schoelles, 2012, pg. 56). This evidence review identified one small pilot RCT within the AHRQ review. Patients in this trial were 59-63 years old, 25-65% male, and had wounds ranging from 2.7 to 3.6 months duration. Patients in both intervention and control groups had comorbidities including hypertension, diabetes, obesity, arthritis, and blood clotting disorders. Patients were excluded for a variety of more severe indications such as collagen vascular disease, Charcot disease, previous radiation, current hemodialysis, or insufficient ABPI.

The RCT (Kelechi, 2011) included three treatment arms (single application, application every other week, or application every three weeks). Weekly application was equivalent to control (45%, n = 9 of 20). Complete healing occurred in 86.4% (n = 19 of 22) and 65.0% (n = 13 of 20) with applications every two and every three weeks, respectively. P-value was significant for every other week versus standard care ($p < 0.01$).

Critical Outcome: Deep Soft Tissue or Bone Infection

No SRs or RCTs reported on the effect of Talymed® on deep soft tissue or bone infection.

Critical Outcome: Complete Wound Healing

The AHRQ review (Snyder, Sullivan and Schoelles, 2012) included a single RCT that evaluated the use of Talymed® in combination with usual care compared to usual care alone for VLUs (n=82). Patients receiving Talymed® with usual care every other week experienced higher wound closure rates than usual care alone at 20 weeks (86% vs 45%, p=0.0005). Snyder and colleagues (2012) note that patients receiving Talymed® once every three weeks or only receiving one application did not experience statistically significant results.

Critical Outcome: Quality of Life

No SRs or RCTs reported on the effect of Talymed® on validated quality of life indicators or surrogate measures.

Important Outcome: Time to Complete Wound Healing

No SRs or RCTs reported on the effect of Talymed® on time to complete wound healing.

Important Outcome: Adverse Effects

In the AHRQ review (Snyder, Sullivan and Schoelles, 2012), a single RCT reported “no pain, edema, or significant treatment-related adverse events occurred” (p. C-65).

TheraSkin®

TheraSkin® is a cryopreserved human skin allograft (Snyder, Sullivan and Schoelles, 2012). This evidence review identified one RCT in which TheraSkin® was used as a comparison for Apligraf® for diabetic foot ulcers, discussed above. Patients in this trial had either Type I or Type II diabetes with A1c < 12.0 and the ability to comply with an offloading regimen as well as adequate ABPI (>0.75) and absence of infection, gangrenous tissue, or abscess. The study was rated at moderate risk of bias.

Patients in the RCT (DiDomenico, 2011) received up to five applications, in accordance with the manufacturer's recommendations. Authors report that most patients received only a single application and that the mean number of applications was 1.38 (SD = 0.29).

Critical Outcome: Deep Soft Tissue or Bone Infection

The AHRQ review (Snyder, Sullivan and Schoelles, 2012) identified one RCT in which TheraSkin® was used as the comparator to Apligraf®. In this trial, one patient treated with TheraSkin® was hospitalized due to infection, but no further information is available.

Critical Outcome: Complete Wound Healing

The RCT identified in the AHRQ review (Snyder, Sullivan and Schoelles, 2012) reported complete wound healing at two time points. By 12 weeks follow up, the TheraSkin® group had 66.7% complete healing, versus 41.3% in the Apligraf® group (p = 0.21). The difference was even smaller at 20 weeks, as no more patients in the TheraSkin group experienced complete healing (66.7% vs 47.1%, p not reported).

Critical Outcome: Quality of Life

No SRs or RCTs reported on the effect of TheraSkin® on validated quality of life indicators or surrogate measures.

Important Outcome: Time to Complete Wound Healing

No SRs or RCTs reported on the effect of TheraSkin® on time to complete wound healing.

Important Outcome: Adverse Effects

No SRs or RCTs reported on the adverse effects of TheraSkin®

Summary of the Evidence

The field of biologic skin substitutes for treatment of chronic skin ulcers such as venous leg ulcers and diabetic foot ulcers is rapidly expanding with a variety of new innovations and products. An AHRQ review in 2012 identified 57 unique products, while this updated search found 73 and there are likely more. Evidence for the effectiveness and safety of these products has not kept pace with their development, however, as this review was only able to find published trials of nine products (available in the US), and none dealing with pressure ulcers. While early tests are promising for these products in the treatment of serious and occasionally life-threatening wounds, our confidence in the estimates of effectiveness is generally very low. Studies are almost universally limited by small sample size and inconsistency in control groups and what is defined as "usual care." There is virtually no evidence to

illuminate the comparative effectiveness of these products, nor to compare their effectiveness versus other alternative types of wound dressings besides moist saline gauze and compression.

Our key question regarding subgroup analysis (considerations of age, BMI, comorbidities, etc.) went largely unanswered by these studies. Where inclusion/exclusion criteria were reported, in general the patients were predominantly male, between 50-70 years of age, had hemoglobin A1c < 12.0%, had no active infectious process, and had adequate circulation to the extremity as measured by ankle-brachial pressure index (ABPI). Some trials excluded other comorbidities such as immunosuppression.

Most trials did report on the likelihood of complete wound closure, which makes comparison of results across studies possible; however, the limitation is that many studies have a short follow-up time that may miss complete healing that takes place in the usual care group at a later time. The second critical outcome was incidence of deep soft tissue or bone infection; this outcome was not widely reported and could be inferred from some studies only by the occasion of an amputation. No information was identified related to validated quality of life indicators for any of the products, although there is very limited information about pain and number of dressing changes for a few products. Time to complete healing is another outcome considered important to this review. In these early trials, the skin substitutes do appear to reduce time to wound healing but it should be noted that none of the trials had adequate blinding and many are subject to selection as well as observer bias.

In the AHRQ review, Snyder and colleagues (2012) express concern about the external validity of this body of evidence:

> The overall applicability of the evidence base is limited to a small number of skin substitute products examining diabetic foot ulcers and venous and/or arterial leg ulcers and to patients in generally good health. Although these results are consistent in showing a benefit when using skin substitutes and suggest that skin substitutes could be used in treating diabetic foot ulcers and venous leg ulcers, the patients enrolled in these studies were in generally good health and free of infected wounds, medications that would impede wound healing, clinically significant medical conditions, significant peripheral vascular disease, malnutrition, or uncontrolled diabetes. The results of these studies may not easily translate to everyday clinical situations. The expected population with chronic wounds is likely to have these conditions; therefore, the results reported in studies without these patients may not extrapolate well. The applicability of the findings to sicker patients may be limited (Snyder, Sullivan and Schoelles, 2012, p. 74).

These products are dissimilar enough that even though they can be broadly categorized by derivation, results from a trial of one product cannot be extrapolated to other products in its category. With such a large number of products, it will be challenging to have high confidence in the evidence of their effectiveness without many, many more trials.

OTHER DECISION FACTORS –

Resource Allocation

Cost for a course of treatment with skin substitutes can vary widely, depending on the product used, the number of applications required, the amount of skin substitute purchased, where it is applied (inpatient hospital, outpatient hospital, ambulatory surgical center, office) and payer reimbursement policies. Costs for a course of treatment can vary from a few hundred dollars for an in-office treatment with a low-cost skin substitute such as OASIS® Wound Matrix to several thousand dollars for multiple applications of higher cost products such as Apligraf and Dermagraft. While these products are sometimes billed separately from the physician fees for applying them (including related debridement), some payers are bundling payment in order to incentivize the use of cost-effective products. For instance, in the ambulatory surgery center setting, Medicare fee for service bundles the professional fee with the product itself. In addition, in a form of reference pricing, Medicare groups these bundles into two groups--for high-cost and low cost products—in order to encourage the use of cost-effective products. Some other payers follow Medicare's practices, but others have their own reimbursement policies.

When not bundled, prices for the skin substitute product itself are usually based on the number of square centimeters purchased, though some products are only sold in relatively large pieces (creating waste when used for small ulcers), while others can be purchased in a variety of sizes. In addition, some products are perishable and must be ordered to arrive within a few days of use; others have a longer shelf life. If these products are effective at improving time to complete ulcer healing, or preventing amputations, they could be cost-effective. However, given the low quality evidence available on most of these products, it is difficult to determine whether or not the expected improvement is sufficient to justify the cost.

For products recommended for coverage, the GRADE-informed framework above shows examples of pricing for smaller ulcers for Medicare fee-for-service in various settings. Information about costs for a course of treatment in the GRADE-informed framework and in Appendix E reflects a certain number of applications, based on FDA approval criteria, other payers' coverage criteria or averages from studies.

When multiple effective skin substitutes are available for a given indication, strategizing preferred products based on price or using alternative payment strategies may create savings for payers.

Values and preferences

Ulcers can be painful, distressing, and debilitating to patients and patients would likely be highly motivated to have effective treatment. However, few of these products have any evidence of benefit at this point and patients would be unlikely to strongly prefer skin substitutes if benefit is unclear. Skin substitutes, however, do not appear to add much burden to the patient; they would continue to require frequent wound dressings, offloading, and other mediating treatments regardless of the use of skin substitutes, so adverse effects or impact on convenience would not be a strong consideration against these products.

Other considerations

Expert input and study inclusion criteria show that skin substitutes can only be effective when other conditions necessary for wound healing exist. These conditions include the following:

1. Product is recommended for the type of ulcer being treated (see table below)
2. FDA indications and contraindications are followed, if applicable
3. Appropriate offloading has been performed
4. Wound has adequate arterial flow, no ongoing infection and a moist wound healing environment
5. Multilayer compression dressings are used (when clinically appropriate)
6. Patient has not used tobacco products 4 weeks prior to placement
7. For patients with diabetes, Hba1c level is < 12.
8. No prior failure of the same skin substitute for the ulcer being treated
9. Prior appropriate wound care therapy has failed to result in significant improvement of the wound over at least 30 days
10. Ulcer improves significantly over 6 weeks of treatment with skin substitutes, required for coverage of ongoing applications
11. Patients is able to adhere to the treatment plan

POLICY LANDSCAPE

Quality measures

No quality measures related to skin substitutes were identified on the National Quality Measures Clearinghouse.

Payer coverage policies

Among the four private payers reviewed, two payers provide coverage of skin substitute products (Aetna and Cigna) and two payers do not have coverage criteria (Moda and Regence). Washington Medicaid only covers one skin substitute (Theraskin for diabetic foot ulcers) and requires prior authorization. No National Coverage Determinations were identified. However, there are four Local Coverage Determinations (LCDs) that specify coverage of skin substitutes. Two of the LCDs detail specific products covered (L34285 and L34593), while the other two do not (L36377 and L35041). Table 4 summarizes the coverage for skin substitutes to treat diabetic foot ulcers (DFU) and venous leg ulcers (VLU) across payers. None of the skin substitute coverage policies cover decubitus ulcers. All payers reviewed, except the Medicare NCD and Washington Medicaid, cover skin substitutes when a wound has not adequately responded to standard treatments, usually within 30 days. Many coverage policies have additional indications that limit use, such as the ulcer being infection-free (Aetna, L35041, L34593, and L34285), the foot having adequate blood supply (Aetna, Cigna, L 35041, and L34593), and HbA1C < 12% (Cigna). Some payers limit the number of applications of skin substitutes, for example, a maximum of four treatments of Apligraf or Epifix in 12 weeks and wound healing must be present (Cigna), not more than 10 applications per wound (L35041), Apligraf and Epifix limited to five applications (L34593), and Graftjacket is limited to one application (L34285).

Table 4. Summary of Other Payer Coverage of Skin Substitutes

Payer	Skin Substitutes						
	Apligraf®	Dermagraft®	Epifix®	Graftjacket®	OASIS®	Primatrix®	Theraskin®
Aetna	DFU, VLU	DFU	X	DFU	DFU, VLU	X	X
Cigna	DFU, VLU	DFU	DFU, VLU	DFU	DFU, VLU	X	DFU
Washington	X	X	X	X	X	X	DFU w/ author-ization
LCD-Alabama (L34285)	DFU, VLU	DFU	DFU, VLU	DFU	DFU, VLU	X	DFU, VLU
LCD-Iowa (L34593)	DFU, VLU	DFU	DFU, VLU	DFU	DFU, VLU	DFU, VLU	DFU, VLU
LCD-Delaware (L35041)	DFU, VLU – no specific products identified						
LCD-Florida (L36377)	DFU, VLU – no specific products identified						

Key: X – product is not covered

Abbreviations: DFU – diabetic foot ulcer; LCD – local coverage determination; VLU – venous leg ulcer

Clinical Practice Guidelines

Diabetic foot ulcers

Three clinical practice guidelines address care for diabetic foot ulcers (Braun, Kim, Margolis, Peters, & Lavery, 2006; NICE, 2011; Registered Nurses' Association of Ontario, 2013). The good-quality National Institute for Health and Care Excellence (NICE) clinical practice guidelines recommend to, "Consider dermal or skin substitutes as an adjunct to standard care when treating diabetic foot ulcers, only when healing has not progressed and on the advice of the multidisciplinary foot care service" (2015, p.18). The fair-quality guideline from the Registered Nurses' Association of Ontario and Braun and colleagues (2006) poor-quality update to the Wound Healing Society guideline did not include a recommendation on use of skin substitutes.

Venous leg ulcers

Three clinical practice guidelines address care of venous leg ulcers (AAWC, 2010; Australian Wound Management Association Inc. and the New Zealand Wound Care Society Inc., 2011; SIGN, 2010). One good-quality guideline, Australian and New Zealand Clinical Practice Guideline for Prevention and Management of Venous Leg Ulcers, and one poor-quality guideline from the Association for the Advancement of Wound Care (AAWC) recommend skin substitutes for non-healing or persistent venous

leg ulcers, but do not provide recommendations on the use of specific products. The good-quality SIGN guideline found that there is insufficient evidence on which to base a recommendation for including skin substitutes, or any skin grafting.

Pressure ulcers

The good-quality Institute for Clinical Systems Improvement (ICSI) guideline recommends that clinicians refer the patient to a wound-focused physician or clinician to select the appropriate skin substitute or other biological application for the treatment of chronic skin ulcers, such as platelet gels, platelet-derived growth factor therapy, or extracellular matrix sheets.

REFERENCES

Evidence Sources

Felder, J. M., Goyal, S. S., Attinger, C. E. (2012). A systematic review of skin substitutes for foot ulcers. *Plastic and Reconstructive Surgery, 130*(1):145-64. DOI: 10.1097/PRS.0b013e318254b1ea.

Game, F. L., Apelqvist, J., Attinger, C., Hartemann, A., Hinchliffe, R. J., Londahl, M., … Jeffcoate, W.J., on behalf of the International Working Group on the Diabetic Foot (IWGDF). (2015). Effectiveness of interventions to enhance healing of chronic ulcers of the foot in diabetes: A systematic review. *Diabetes / Metabolism Research and Reviews,* accepted manuscript online. doi: 10.1002/dmrr.2707

Jones, J. E., Nelson, E. A., & Al-Hity, A. (2013). Skin grafting for venous leg ulcers. *Cochrane Database of Systematic Reviews,* 1. DOI: 10.1002/14651858.CD001737.pub4.

Lavery, L. A., Fulmer, J., Shebetka, K. A., Regulski, M., Vayser, D., Fried, D., . . . Nadarajah, J. (2014). The efficacy and safety of Grafix((R)) for the treatment of chronic diabetic foot ulcers: results of a multi-centre, controlled, randomised, blinded, clinical trial. *Int Wound J, 11*(5), 554-560. DOI:10.1111/iwj.12329.

Snyder, D. L., Sullivan, N., & Schoelles, K. M. (2012). *Skin substitutes for treating chronic wounds*. Rockville, MD: Agency for Healthcare Research and Quality (AHRQ). Retrieved from http://www.ahrq.gov/research/findings/ta/skinsubs/HCPR0610_skinsubstfinal.pdf.

Other Citations

Aetna. (2015). *Wound care*. Hartford, CT: Aetna. Retrieved from http://www.aetna.com/cpb/medical/data/200_299/0244.html.

Association for the Advancement of Wound Care (AAWC). (2010). Association for the Advancement of Wound Care venous ulcer guideline. Malvern, PA: AAWC. Retrieved from http://aawconline.org/professional-resources/resources/.

The Australian Wound Management Association Inc. and the New Zealand Wound Care Society Inc. (2011). Australian and New Zealand Clinical Practice Guideline for Prevention and Management of Venous Leg Ulcers. Retrieved from http://www.awma.com.au/publications/2011_awma_vlug.pdf.

Braun, L., Kim, P. J., Margolis, D., Peters, E. J. & Lavery, L. A. (2014). What's new in the literature: An update of new research since the original WHS diabetic foot ulcer guidelines in 2006. *Wound Repair and Regeneration, 22*, 594–604. DOI: 10.1111/wrr.12220.

Cahaba Government Benefit Administrators®, LLC. (2015). Local coverage determination (LCD): Surgery: Bioengineered skin substitutes (BSS) for the treatment of diabetic and venous stasis ulcers of the lower extremities (L34285). Washington, DC: CMS. Retrieved from https://www.cms.gov/medicare-coverage-database/details/lcd-details.aspx?LCDId=34285&ContrId=213&ver=12&ContrVer=1&CoverageSelection=Both&ArticleTy

pe=All&PolicyType=Final&s=All&KeyWord=skin&KeyWordLookUp=Title&KeyWordSearchType=And&articleId=52974&bc=gAAAABAAAAAAAA%3d%3d&.

Cazzell, S. M., Lange, D. L., Dickerson, J. E. Jr., Slade, H. B. (2015). The Management of diabetic foot ulcers with porcine small intestine submucosa tri-layer matrix: A randomized controlled trial. *Advances in Wound Care, 4*, 1-8. DOI: 10.1089/wound.2015.0645.

Centers for Medicare and Medicaid Services. (unknown). National coverage determination (NCD) for porcine skin and gradient pressure dressings (270.5). Washington, DC: CMS. Retrieved from https://www.cms.gov/medicare-coverage-database/details/ncd-details.aspx?NCDId=139&ncdver=1&CoverageSelection=Both&ArticleType=All&PolicyType=Final&s=All&KeyWord=skin&KeyWordLookUp=Title&KeyWordSearchType=And&articleId=52974&ver=3&ContrId=370&ContrVer=1&bc=gAAAABAAAAAAAA%3d%3d&.

Centers for Medicare and Medicaid Services. (2015). October 2015 ASC HCPCS codes and payment rates. Washington, DC: CMS. Retrieved from https://www.cms.gov/Medicare/Medicare-Fee-for-Service-Payment/ASCPayment/Downloads/2015-October-ASC-Addenda.zip.

Cigna. (2015). *Cigna medical coverage policy: tissue-engineered skin substitutes*. Bloomfield, CT: Cigna. Retrieved from https://cignaforhcp.cigna.com/public/content/pdf/coveragePolicies/medical/mm_0068_coveragepositioncriteria_woundhealing.pdf.

First Coast Service Options, Inc. (2015). Local coverage determination (LCD): Application of skin substitute grafts for treatment of DFU and VLU of lower extremities (L36377). Washington, DC: CMS. Retrieved from https://www.cms.gov/medicare-coverage-database/details/lcd-details.aspx?LCDId=36377&ContrId=368&ver=2&ContrVer=1&CoverageSelection=Both&ArticleType=All&PolicyType=Final&s=All&KeyWord=skin&KeyWordLookUp=Title&KeyWordSearchType=And&articleId=52974&bc=gAAAABAAAAAAAA%3d%3d&.

Institute for Clinical Systems Improvement (ICSI). (2012). Pressure ulcer prevention and treatment protocol: Health care protocol. Bloomington (MN): Institute for Clinical Systems Improvement (ICSI). Retrieved from https://www.icsi.org/_asset/6t7kxy/PressureUlcer.pdf.

Margolis, D. J., Malay, D. S., Hoffstad, O. J., Leonard, C. E., MaCurdy, T., Nava, K. L., … Siegel, K. L. (2011). *Incidence of diabetic foot ulcer and lower extremity amputation among Medicare beneficiaries, 2006 to 2008: Data Points #2*. Rockville (MD): Agency for Healthcare Research and Quality. Retrieved from http://www.ncbi.nlm.nih.gov/books/NBK65149/.

National Institute for Health and Clinical Excellence (NICE). (2011). Diabetic foot problems: prevention and management. London: NICE. Retrieved from http://www.nice.org.uk/guidance/ng19/resources/diabetic-foot-problems-prevention-and-management-1837279828933.

Novitas Solutions, Inc. (2015). Local coverage determination (LCD): Application of bioengineered skin substitutes to lower extremity chronic non-healing wounds (L35041). Washington, DC: CMS. Retrieved from https://www.cms.gov/medicare-coverage-database/details/lcd-

details.aspx?LCDId=35041&ContrId=314&ver=22&ContrVer=1&CoverageSelection=Both&ArticleType=All&PolicyType=Final&s=All&KeyWord=skin&KeyWordLookUp=Title&KeyWordSearchType=And&articleId=52974&bc=gAAAABAAAAAAAA%3d%3d&.

O'Meara, S., Al-Kurdi, D., & Ovington, L. G. (2008). Antibiotics and antiseptics for venous leg ulcers. *Cochrane Database of Systematic Reviews*, Issue 1. DOI: 10.1002/14651858.CD003557.pub2

Oregon Heart Disease and Stroke and Diabetes Prevention Programs. (2013). *Heart disease, stroke and diabetes in Oregon: 2013*. Portland, OR: Oregon Health Authority, Public Health Division. Retrieved September 9, 2015 from https://public.health.oregon.gov/DiseasesConditions/ChronicDisease/Documents/OHA8582_AllVolumes.pdf.

Park-Lee, E., & Caffrey, C. (2009). *Pressure ulcers among nursing home residents: United States, 2004*. Atlanta, GA: National Center for Health Statistics. Retrieved September 29, 2015 from http://www.cdc.gov/nchs/data/databriefs/db14.htm.

Registered Nurses' Association of Ontario (RNAO). (2013). Assessment and management of foot ulcers for people with diabetes. Toronto (ON): Registered Nurses' Association of Ontario (RNAO). Retrieved from http://rnao.ca/sites/rnao-ca/files/Assessment_and_Management_of_Foot_Ulcers_for_People_with_Diabetes_Second_Edition1.pdf.

Scottish Intercollegiate Guidelines Network (SIGN). (2010). Management of chronic venous leg ulcers. Edinburgh: SIGN. Retrieved from http://www.sign.ac.uk/guidelines/fulltext/120/index.html.

Smith & Nephew, Inc. (2015). OASIS® Wound Matrix: Frequently asked questions. Retrieved from http://www.oasiswoundmatrix.com/faq

Washington State Healthcare Authority. (2015). Physician-related services/health care professional services provider guide. Olympia, WA: Washington State Healthcare Authority. Retrieved from http://www.hca.wa.gov/medicaid/billing/Documents/guides/physician-related_services_mpg.pdf.

Wisconsin Physicians Service Insurance Corporation (2015). Local coverage determination (LCD): Application of bioengineered skin substitutes (L34593). Washington, DC: CMS. Retrieved from https://www.cms.gov/medicare-coverage-database/details/lcd-details.aspx?LCDId=34593&ContrId=143&ver=11&ContrVer=1&CoverageSelection=Both&ArticleType=All&PolicyType=Final&s=All&KeyWord=skin&KeyWordLookUp=Title&KeyWordSearchType=And&articleId=52974&bc=gAAAABAAAAAAAA%3d%3d&.

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.

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[2]

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 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.

[2] Includes risk of bias, precision, directness, consistency and publication bias

***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[3]

Apligraf® / Graftskin

Indication	Quality Assessment (Confidence in Estimate of Effect)							
	No. of Studies	Study Design(s)	Risk of Bias	Inconsistency	Indirectness	Imprecision	Other Factors	Quality
Deep Soft Tissue or Bone Infection								
DFUs	1	RCT	Low	Unknown	Direct	Precise	*None*	Low confidence in estimate of effect ●●○○
VLUs	1	RCT	Low	Unknown	Direct	Imprecise	*None*	Very low confidence in estimate of effect ●○○○
Complete Wound Healing								
DFUs	2	RCT	Low	Consistent	Direct	Precise	*None*	Moderate confidence in estimate of effect ●●●○
VLUs	1	RCT	Low	Unknown	Direct	Precise	*None*	Low confidence in estimate of effect ●●○○
Nonhealing foot ulcers – undefined	1	RCT	High	Unknown	Indirect	Precise	*None*	Very low confidence in estimate of effect ●○○○
Quality of Life								
No evidence identified								

[3] All GRADE Evidence Profiles in this Appendix are in comparison to usual care.

Indication	Quality Assessment (Confidence in Estimate of Effect)							
	No. of Studies	Study Design(s)	Risk of Bias	Inconsistency	Indirectness	Imprecision	Other Factors	Quality
Time to Complete Wound Healing								
VLUs	1	RCT	Low	Unknown	Direct	Precise	*None*	Low confidence in estimate of effect ●●○○
Nonhealing foot ulcers – undefined	1	RCT	High	Unknown	Indirect	Precise	*None*	Very low confidence in estimate of effect ●○○○
Adverse Effects								
DFUs	1	RCT	Low	Unknown	Direct	Imprecise	*None*	Very low confidence in estimate of effect ●○○○
VLUs	1	RCT	Low	Unknown	Direct	Unknown	*None*	Very low confidence in estimate of effect ●○○○

Abbreviations: DFU – diabetic foot ulcer; RCT – randomized controlled trial; VLU – venous leg ucler

Dermagraft®

Indication	Quality Assessment (Confidence in Estimate of Effect)							
	No. of Studies	Study Design(s)	Risk of Bias	Inconsistency	Indirectness	Imprecision	Other Factors	Quality
Deep Soft Tissue or Bone Infection								
DFU	1	RCT	Moderate	Unknown	Direct	Precise	None	Very low confidence in estimate of effect ●○○○
Complete Wound Healing								
DFUs	4	RCTs	Moderate to high	Inconsistent	Direct	Precise	*3 RCTs of moderate ROB are consistent, a high-risk RCT had a discrepant result*	Low confidence in estimate of effect ●●○○
VLUs	2	RCTs	Moderate	Unknown	Direct	Imprecise	*None*	Very low confidence in estimate of effect ●○○○
Quality of Life								
No evidence identified								
Time to Complete Wound Healing								
DFUs	4	RCT	Moderate to high	Consistent	Direct	Unknown	*None*	Low confidence in estimate of effect ●●○○
VLUs	1	RCTs	Moderate	Unknown	Direct	Imprecise	*None*	Very low confidence in estimate of effect ●○○○

Indication	Quality Assessment (Confidence in Estimate of Effect)							
	No. of Studies	Study Design(s)	Risk of Bias	Inconsistency	Indirectness	Imprecision	Other Factors	Quality
Adverse Effects								
DFUs	2	RCT	Moderate	Unknown	Direct	Unknown		Very low confidence in estimate of effect ●○○○
VLUs	1	RCT	Moderate	Unknown	Direct	Unknown		Very low confidence in estimate of effect ●○○○

Abbreviations: DFU – diabetic foot ulcer; RCT – randomized controlled trial; VLU – venous leg ulcer

EpiFix®

Indication	Quality Assessment (Confidence in Estimate of Effect)							
	No. of Studies	Study Design(s)	Risk of Bias	Inconsistency	Indirectness	Imprecision	Other Factors	Quality
Deep Soft Tissue or Bone Infection								
No evidence identified								
Complete Wound Healing								
DFU	1	RCT	Moderate	Unknown	Direct	Precise	*None*	Very low confidence in estimate of effect ●○○○
Quality of Life								
No evidence identified								
Time to Complete Wound Healing								
No evidence identified								

Indication	Quality Assessment (Confidence in Estimate of Effect)							
	No. of Studies	Study Design(s)	Risk of Bias	Inconsistency	Indirectness	Imprecision	Other Factors	Quality
Adverse Effects								
No evidence identified								

Abbreviations: DFU – diabetic foot ulcer; RCT – randomized controlled trial

Grafix®

Indication	Quality Assessment (Confidence in Estimate of Effect)							
	No. of Studies	Study Design(s)	Risk of Bias	Inconsistency	Indirectness	Imprecision	Other Factors	Quality
Deep Soft Tissue or Bone Infection								
DFUs	1	RCT	High	Unknown	Direct	Precise	*"Wound-related infection" not defined*	Very low confidence in estimate of effect ●○○○
Complete Wound Healing								
DFU	1	RCT	High	Unknown	Direct	Precise	*None*	Very low confidence in estimate of effect ●○○○
Quality of Life								
No evidence identified								
Time to Complete Wound Healing								
DFU	1	RCT	High	Unknown	Direct	Precise	*None*	Very low confidence in estimate of effect ●○○○

Abbreviations: DFU – diabetic foot ulcer; RCT – randomized controlled trial

Adverse Effects								
DFU	1	RCT	High	Unknown	Direct	Precise	*None*	Very low confidence in estimate of effect ●○○○

Graftjacket®

Indication	Quality Assessment (Confidence in Estimate of Effect)							
	No. of Studies	Study Design(s)	Risk of Bias	Inconsistency	Indirectness	Imprecision	Other Factors	Quality
Deep Soft Tissue or Bone Infection								
No evidence identified								
Complete Wound Healing								
DFUs	2	RCT	Moderate to high	Consistent	Unknown	Precise	*None*	Very low confidence in estimate of effect ●○○○
Quality of Life								
No evidence identified								
Time to Complete Wound Healing								
DFUs	2	RCTs	Moderate to high	Unknown	Direct	Unknown	*None*	Very low confidence in estimate of effect ●○○○
Adverse Effects								
DFUs	1	RCT	High	Unknown	Direct	Unknown	*None*	Very low confidence in estimate of effect ●○○○

Abbreviations: DFU – diabetic foot ulcer; RCT – randomized controlled trial

OASIS® Wound Matrix

Indication	Quality Assessment (Confidence in Estimate of Effect)							
	No. of Studies	Study Design(s)	Risk of Bias	Inconsistency	Indirectness	Imprecision	Other Factors	Quality
Deep Soft Tissue or Bone Infection								
No evidence identified								
Complete Wound Healing								
DFUs	1	RCT	Moderate	Unknown	Direct	Imprecise	*None*	Very low confidence in estimate of effect ●○○○
VLUs	3	RCT	Low to moderate	Unknown	Direct	Imprecise	Effectiveness varied based on type of usual care	Very low confidence in estimate of effect ●○○○
Quality of Life								
No evidence identified								
Time to Complete Wound Healing								
VLUs	3	RCTs	Low to moderate	Unknown	Direct	Imprecise	Effectiveness varied based on type of usual care	Very low confidence in estimate of effect ●○○○
Adverse Effects								
VLUs	1	RCT	Low	Unknown	Direct	Imprecise	*None*	Very low confidence in estimate of effect ●○○○
DFUs	1	RCT	Moderate	Unknown	Direct	Imprecise	*None*	Very low confidence in estimate of effect ●○○○

Abbreviations: DFU – diabetic foot ulcer; RCT – randomized controlled trial; VLU – venous leg ulcer

Talymed®

Indication	Quality Assessment (Confidence in Estimate of Effect)							
	No. of Studies	Study Design(s)	Risk of Bias	Inconsistency	Indirectness	Imprecision	Other Factors	Quality
Deep Soft Tissue or Bone Infection								
No evidence identified								
Complete Wound Healing								
VLUs	1	RCT	Low	Unknown	Direct	Imprecise	*None*	Very low confidence in estimate of effect ●○○○
Quality of Life								
No evidence identified								
Time to Complete Wound Healing								
No evidence identified								
Adverse Effects								
VLU	1	RCT	Low	Unknown	Direct	Unknown	None	Very low confidence in estimate of effect ●○○○

Abbreviations: RCT – randomized controlled trial; VLU – venous leg ulcer

TheraSkin® versus Apligraf®

Indication	Quality Assessment (Confidence in Estimate of Effect)							
	No. of Studies	Study Design(s)	Risk of Bias	Inconsistency	Indirectness	Imprecision	Other Factors	Quality
Deep Soft Tissue or Bone Infection								
DFUs		RCT	Moderate	Unknown	Indirect	Unknown	*None*	Very low confidence in estimate of effect ●○○○
Complete Wound Healing								
DFUs	1	RCT	Moderate	Unknown	Indirect	Unknown	*None*	Very low confidence in estimate of effect ●○○○
Quality of Life								
No evidence identified								
Time to Complete Wound Healing								
No evidence identified								
Adverse Effects								
No evidence identified								

Abbreviations: RCT – randomized controlled trial; DFU – diabetic foot ulcer

OASIS® versus Dermagraft®

Indication	Quality Assessment (Confidence in Estimate of Effect)							
	No. of Studies	Study Design(s)	Risk of Bias	Inconsistency	Indirectness	Imprecision	Other Factors	Quality
Deep Soft Tissue or Bone Infection								
No evidence identified								
Complete Wound Healing								
DFUs	1	RCT	Moderate	Unknown	Indirect	Unknown	*None*	Very low confidence in estimate of effect ●○○○
Quality of Life								
No evidence identified								
Time to Complete Wound Healing								
No evidence identified								
Adverse Effects								
No evidence identified								

Abbreviations: RCT – randomized controlled trial; DFU – diabetic foot ulcer

APPENDIX C. METHODS

Scope Statement

Populations

Adults with chronic skin ulcers

Population scoping notes: *Considered limiting scope to diabetic foot ulcers and venous leg ulcers, sacral decubitus ulcers, but decided on the broader definition above, considered burns and other types of wounds*

Interventions

Skin substitutes

Intervention exclusions: None

Comparators

Usual care

Outcomes

Critical: Deep soft tissue or bone infections, complete wound healing, quality of life

Important**:** Time to complete wound healing, adverse effects

Considered but not selected for the GRADE table: *Cellulitis, sepsis, death, need for surgical management, ulcer recurrence*

Key Questions

1. What is comparative effectiveness of different types of skin substitutes compared with wound care alternatives for individuals with chronic skin ulcers? Include consideration of:
    a. Age
    b. Body mass index (BMI)
    c. Comorbidities
    d. Site of ulcer
    e. Ulcer etiology (e.g. infectious, pressure or circulatory).
    f. Wound severity
    g. Prior need for skin substitute
    h. Failure of prior therapies
2. What adverse events are associated with skin substitutes?
3. What are contraindications to the use of skin substitutes?

Search Strategy

A full search of the core sources was conducted to identify systematic reviews, meta-analyses, technology assessments, and clinical practice guidelines using the terms “wound,” “ulcer,” “skin

substitute," or "bioengineered skin." Searches of core sources were limited to citations published after 2005.

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® (Ovid) search was then conducted to identify systematic reviews, meta-analyses, and technology assessments published after the search dates of the AHRQ report (Snyder et al, 2012). The search was limited to publications in English published after 2011 (the end search date for the AHRQ SR). Using the 2012 AHRQ systematic review as the predominant evidence source, a second MEDLINE® (Ovid) search was conducted to identify any randomized controlled trials published after the search dates of the AHRQ review (2011).

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, did not address the scope statement, or were study designs other than systematic reviews, meta-analyses, technology assessments, or clinical practice guidelines. A MEDLINE® search was conducted for randomized control trials published after the AHRQ systematic review.

The AHRQ systematic review (Snyder, Sullivan and Schoelles, 2012) was selected as the base systematic review for this topic based on its comprehensiveness; thus systematic reviews published prior to the AHRQ review were excluded. In addition, several systematic reviews published more recently than the AHRQ review were excluded because they did not include any additional studies that were not already summarized by the included systematic reviews. These four systematic reviews were excluded because they included only studies that were in the AHRQ systematic review:

Game , F. L., Hinchliffe, R. J., Apelqvist, J., Armstrong, D. G., Bakker, K., Hartemann, A., … Jeffcoate, W.J. (2012). A systematic review of interventions to enhance the healing of chronic ulcers of the foot in diabetes. Diabetes Metab Res Rev, 28 Suppl 1:119-41. DOI: 10.1002/dmrr.2246.

Greer , N., Foman, N., Dorrian, J., Fitzgerald, P., MacDonald, R., Rutks, I., & Wilt, T. (2012). Advanced wound care therapies for non-healing diabetic, venous, and arterial ulcers: A systematic review. VA-ESP Project #09-009.. Retrieved from http://link.springer.com/article/10.1007%2Fs40257-014-0081-9.

Hankin , C. S., Knispel, J., Lopes, M., Bronstone, A., & Maus, E. (2012). Clinical and cost efficacy of advanced wound care matrices for venous ulcers. Journal of Managed Care Pharmacy, 18(5), 375-384. Retrieved from http://www.amcp.org/WorkArea/DownloadAsset.aspx?id=15289.

Iorio, M. L.,Shuck, J., Attinger, C. E.(2014). Wound healing in the upper and lower extremities – A systematic review on the use of acellular dermal matrices. *Plastic and Reconstructive Surgery, 130*: 5S-2. DOI: 10.1097/PRS.0b013e3182615703.

The following systematic review was excluded because it only included studies found in the AHRQ systematic review or Jones and colleagues (2013):

Valle , M. F., Maruthur, N. M., Wilson, L. M., Malas, M., Qazi, U., Haberl, E., … Lazarus, G. (2014). Comparative effectiveness of advanced wound dressings for patients with chronic venous leg ulcers: A systematic review. Wound Repair and Regeneration, 22(2), 193-204. DOI: 10.1111/wrr.12151.

Finally, the following systematic review was excluded because it did not provide sufficient detail regarding outcomes reported in trials of skin substitutes:

Braun, L. R., Fisk, W. A., Lev-Tov, H., Kirsner, R.S., & Isseroff, R. R. (2014). Diabetic foot ulcer: an evidence-based treatment update. *Am J Clin Dermatol, 15*, 267–281. DOI: 10.1007/s40257-014-0081-9.

APPENDIX D. APPLICABLE CODES

CODES	DESCRIPTION
ICD-10 Diagnosis Codes	
E08.621 E09.621 E10.621 E11.621 E13.621	Diabetes mellitus due to underlying condition with foot ulcer Drug or chemical induced diabetes mellitus with foot ulcer Type I diabetes mellitus with foot ulcer Type II diabetes mellitus with foot ulcer Other diabetes mellitus with foot ulcer
L97-L97.9	Non-pressure chronic ulcer of lower limb
L89-L89.0	Pressure ulcer
L98.4	Non-pressure chronic ulcer of skin
CPT Codes	
15271	Application of skin substitute graft to trunk, arms, legs, total wound surface area up to 100 sq cm; first 25 sq cm or less wound surface area
15272	Each additional 25 sq cm wound surface, or part thereof
15275	Application of skin substitute graft to face, scalp, eyelids, mouth, neck, ears, orbits, genitalia, hands, feet, and/or multiple digits, total wound surface area up to 100 sq cm; first 25 sq cm or less wound surface area
15276	Each additional 25 sq cm wound surface, or part there of
15273	Application of skin substitute graft to trunk, arms, legs, total wound surface area greater than or equal to 100 sq cm; first 100 sq cm wound surface area, or 1% of body area of infants and children
15274	Each additional 100 sq cm wound surface area or part thereof, or each additional 1% of body area of infants and children or part thereof
15277	Application of skin substitute graft to face, scalp, eyelids, mouth, neck, ears, orbits, genitalia, hands, feet, and/or multiple digitis, total wound surface area greater than or equal to 100 sq cm; first 100 sq cm wound area, or 1% of body area of infants and children
15278	Each additional 100 sq cm wound surface area, or part thereof, or each additional 1% of body area of infants and children or part thereof
HCPCS Level II Codes	
C5271	Application of low cost skin substitute graft to trunk, arms, legs, total wound surface area up to 100 sq cm; first 25 sq cm or less wound surface area
C5272	Application of low cost skin substitute graft to trunk, arms, legs, total wound surface area up to 100 sq cm; each additional 25 sq cm wound surface area, or part thereof (list separately in addition to code for primary procedure)
C5273	Application of low cost skin substitute graft to trunk, arms, legs, total wound surface area greater than or equal to 100 sq cm; first 100 sq cm wound surface area, or 1% of body area of infants and children
C5274	Application of low cost skin substitute graft to trunk, arms, legs, total wound surface area greater than or equal to 100 sq cm; each additional 100 sq cm wound surface area, or part thereof, or each additional 1% of body area of infants and children, or
C5275	Application of low cost skin substitute graft to face, scalp, eyelids, mouth, neck, ears, orbits, genitalia, hands, feet, and/or multiple digits, total wound surface area up to 100 sq cm; first 25 sq cm or less wound surface area
C5276	Application of low cost skin substitute graft to face, scalp, eyelids, mouth, neck, ears, orbits, genitalia, hands, feet, and/or multiple digits, total wound surface area up to 100 sq cm; each additional 25 sq cm wound surface area, or part thereof (list

C5277	Application of low cost skin substitute graft to face, scalp, eyelids, mouth, neck, ears, orbits, genitalia, hands, feet, and/or multiple digits, total wound surface area greater than or equal to 100 sq cm; first 100 sq cm wound surface area, or 1% of bod
C5278	Application of low cost skin substitute graft to face, scalp, eyelids, mouth, neck, ears, orbits, genitalia, hands, feet, and/or multiple digits, total wound surface area greater than or equal to 100 sq cm; each additional 100 sq cm wound surface area, or
Q4100	Skin substitute, NOS
Q4101	Apligraf
Q4102	OASIS wound matrix
Q4103	OASIS burn matric
Q4104	Integra BMWD
Q4105	Integra DRT
Q4106	Dermagraft
Q4107	Graftjacket
Q4108	Integra Matrix
Q4110	Primatrix
Q4111	Gammagraft
Q4112	Cymetra injectable
Q4113	Graftjacket Xpress
Q4114	Integra Flowable Wound Matrix
Q4115	Alloskin
Q4116	Alloderm
Q4117	Hyalomatrix
Q4118	Matristem Micromatrix
Q4119	Matristem Wound Matrix
Q4120	Matristem Burn Matrix
Q4121	Theraskin
Q4122	Dermacell
Q4123	Alloskin
Q4124	Oaskis Tri-layer Wound Matrix
Q4125	Arthroflex
Q4126	Memoderm/derma/tranz/integup
Q4127	Taylmed
Q4128	Flexhd/Alopatchhd/matrixhd
Q4129	Unite Biomatrix
Q4131	Epifix
Q4132	Grafix core
Q4133	Grafix prime
Q4134	HMatrix
Q4135	Mediskin
Q4136	EZderm
Q4137	Amnioexcel or Biodmatrix, 1cc
Q4138	DioDfence DryFlex, 1cc
Q4139	Amniomatrix or Biodmatrix, 1cc
Q4140	Biodfence 1cm
Q4141	Alloskin ac, 1 cm
Q4142	Xcm biologic tiss matrix 1cm
Q4143	Repriza, 1cm
Q4145	Epifix, 1mg

Q4146	Tensix, 1 cm
Q4147	Architect ecm px fx 1 sq cm
Q4148	Neox 1k, 1cm
Q4149	Excellagen, 0.1cc
Q4150	Allowrap DS or Dry 1 sq cm
Q4151	AmnioBand, Guardian 1 sq cm
Q4152	Dermapure 1 square cm
Q4153	Dermavest 1 square cm
Q4154	Biovance 1 square cm
Q4155	NeoxFlow or ClarixFlo 1mg
Q4156	Neox 100 1 square cm
Q4157	Revitalon 1 square cm
Q4158	Marigen 1 square cm
Q4159	Affinity 1 square cm
Q4160	NuSheild 1 square cm
Q9349	Fortaderm, fortaderm antimic
Q9358	SergiMend, fetal
C9360	SurgiMend, neonatal
C9363	Integra Meshed Bil Wound Mat

ICD-10-PCS (Procedure Codes)						
Section	**Body System**	**Operation**	**Body Part**	**Approach**	**Device**	**Qualifier**
O (Medical and surgical)	**H** (skin and breast) **J** (subcutaneous tissue and fascia) **R** (mouth and throat)	**R** (replacement) **U** (supplement) **W** (revision)	All (0-X) except: Q finger nail R toe nail S hair	**O** (open) **3** (percu-taneous)	**J** (synthetic substitute) **K** (nonauto-logous tissue substitute)	**Z** (no qualifier)
CODES	**DESCRIPTION**					
0HR0	Skin, Scalp					
0HR1	Skin, Face					
0HR2	Skin, Right Ear					
0HR3	Skin, Left Ear					
0HR4	Skin, Neck					
0HR5	Skin, Chest					
0HR6	Skin, Back					
0HR7	Skin, Abdomen					
0HR8	Skin, Buttock					
0HR9	Skin, Perineum					
0HRA	Skin, Genitalia					
0HRB	Skin, Right Upper Arm					
0HRC	Skin, Left Upper Arm					
0HRD	Skin, Right Lower Arm					
0HRE	Skin, Left Lower Arm					
0HRF	Skin, Right Hand					
0HRG	Skin, Left Hand					
0HRH	Skin, Right Upper Leg					
0HRJ	Skin, Left Upper Leg					

0HRK	Skin, Right Lower Leg
0HRL	Skin, Left Lower Leg
0HRM	Skin, Right Foot
0HRN	Skin, Left Foot
0HRQ	Finger Nail
0HRR	Toe Nail
0HRS	Hair
0HRT	Breast, Right
0HRU	Breast, Left
0HRV	Breast, Bilateral
0HRW	Nipple, Right
0HRX	Nipple, Left

Note: Inclusion on this list does not guarantee coverage.

APPENDIX E: FREQUENCY OF APPLICATION AND COST OF SKIN SUBSTITUTES

Product	Proposed maximum covered applications	Rationale	Medicare cost information per application (National Average Fee For Service, October, 2015*)
Apligraf	5	Greater than 5 applications not studied per FDA. Early studies limited to 5 applications, and one later study found wound healing was completed within 3 applications. Cigna limits to 4 applications in 12 weeks. Two Medicare LCD limits to 5 applications.	ASC: $771 HOPD: $1,495 Phys. Off =$1,518
Derma-graft	8	The FDA prescribing information contains a caution than Dermagraft has not been studied in patients receiving greater than 8 device applications. 2003 study showed that 4 applications is equivalent to 8. Cigna limits to 8 applications in 12 weeks. One Medicare LCD limits to 8 applications.	ASC: $771 HOPD: $1,495 Phys. Off =$1,409
Epifix	5	One study limited to 5 applications. Cigna limits to 4 applications in 12 weeks. Two Medicare LCD limits to 5 applications.	ASC: $771 HOPD: $1,495 Phys. Office: $535
Grafix	12	Weekly applications up to 84 days in the one study	ASC: $771 HOPD: $1,495 Phys. Off **
Graft-jacket	1	Single application used in both studies. Cigna and one Medicare LCD limits to 1 application.	ASC: $771 HOPD: $1,495 Phys. Office: $1,672
Oasis Wound Matrix	12	One study of DFU showed an average of 10 sheets. One study of VLU reported an average of 8 sheets. Study showed equivalence of 8 sheets of Oasis to 3	ASC: $236 HOPD: $518

		sheets of Dermagraft. One Medicare LCD limits to 12 weeks of therapy.	Phys. Office: $262
Talymed	10	Study used applications every 1-3 weeks over 20 weeks. Found fewer applications ineffective.	ASC: $771 HOPD: $1,495 Phys. Office **
Thera-skin	5	Up to 5 applications received in the study, however, most patients only had 1. Cigna limits to 4 applications in 12 weeks. One Medicare LCD limits to 5 applications.	ASC: $771 HOPD: $1,495 Phys. Office: $612

ASC=ambulatory surgery center; DFU=diabetic foot ulcers; HOPD=hospital outpatient department; LCD=local coverage determination; VLU=venous leg ulcers

*Costs reported are for the smallest available product and include applicable professional fees for applying the skin substitute to a leg ulcer smaller than 25 cm^2. Fees are higher for some other body parts or larger applications.

**Physician's office average sales price (ASP) fees cannot be calculated, product not on ASP fee schedule.

References for pricing information:

Hospital outpatient bundle costs retrieved from https://www.cms.gov/apps/ama/license.asp?file=/hospitaloutpatientpps/downloads/2015-Jan-Addendum-B-File.zip

Ambulatory surgical center bundled rates retrieved from

https://www.cms.gov/Medicare/Medicare-Fee-for-Service-Payment/ASCPayment/Downloads/2015-October-ASC-Addenda.zip

Physician fees retrieved from

https://www.cms.gov/Medicare/Medicare-Fee-for-Service-Payment/PhysicianFeeSched/index.html?redirect=/PhysicianFeeSched/

October 2015 ASP Pricing file (for physician's office product fees) retrieved from:

https://www.cms.gov/Medicare/Medicare-Fee-for-Service-Part-B-Drugs/McrPartBDrugAvgSalesPrice/2015ASPFiles.html

All retrievals made October 29, 2015.

Cost information in this applications table did not affect the coverage guidance recommendations. Costs represent a single application; the appropriate number of applications for a patient may differ by product.

CG-Skin substitutes for diabetic foot ulcers and venous leg ulcers

Question: How should the Coverage Guidance on Skin Substitutes for Chronic Skin Ulcers be applied to the Prioritized List?

Question source: Evidence-based Guidelines Subcommittee (EbGS)

Issue: The EbGS made recommendation about specific skin substitutes, and about the clinical prerequisites necessary for a skin substitute to be appropriate. Many of the specific skin substitutes are hcpcs codes that are not typically included on the Prioritized List. A guideline would need to be developed addressing the prerequisites, and also indicating those skin substitutes which were found to have adequate evidence to support their use.

Skin substitutes are also covered for burns, but this was outside the scope of the Coverage Guidance.

There is information about typical number of applications and maximum number of applications based on a mixture of the evidence or other insurers. These are not consistently evidence- derived. VbBS needs to discuss whether or not maximum number of applications should be included in the Prioritized List new Guideline Note.

Current Prioritized List Status:

Line: 384
Condition: CHRONIC ULCER OF SKIN (See Guideline Notes 62,64,65)
Treatment: MEDICAL AND SURGICAL TREATMENT
ICD-10: E08.621-E08.622,E09.621-E09.622,E10.621-E10.622,E11.621-E11.622,E13.621-E13.622,I70.231-I70.25,I70.331-I70.35,I70.431-I70.45,I70.531-I70.55,I70.631-I70.65,I70.731-I70.75,I83.001-I83.029,I83.201-I83.229,I87.011-I87.019,I87.031-I87.039,I87.311-I87.319,I87.331-I87.339,L88,L89.000-L89.95,L97.101-L97.929,L98.411-L98.499
CPT: 10060,10061,11000-11047,14000-15136,15200-15221,15241-15770,15920-15958,27598,28122,28810,29445,29580-29584,36470-36479,37700-37785,64505-64530,96150-96154,97036,97605-97608,98966-98969,99051,99060,99070,99078,99184,99201-99239,99281-99285,99291-99404,99408-99416,99429-99449,99468-99480,99487-99498,99605-99607
HCPCS: D7920,G0396,G0397,G0406-G0408,G0425-G0427,G0458,G0463,G0466,G0467

Code	Code Descriptions	Current Lines
15271	Application of skin substitute graft to trunk, arms, legs, total wound surface area up to 100 sq cm; first 25 sq cm or less wound surface area	61,76,185,201,212,384
15272	Application of skin substitute graft to trunk, arms, legs, total wound surface area up to 100 sq cm; each additional 25 sq cm wound surface area, or part thereof (List separately in addition to code for primary procedure)	61,76,185,201,212,384
15273	Application of skin substitute graft to trunk, arms, legs, total wound surface area greater than or equal to 100 sq cm; first 100 sq cm	61,76,185,201,212,384

Code	Code Descriptions	Current Lines
	wound surface area, or 1% of body area of infants and children	
15274	Application of skin substitute graft to trunk, arms, legs, total wound surface area greater than or equal to 100 sq cm; each additional 100 sq cm wound surface area, or part thereof, or each additional 1% of body area of infants and children, or part thereof (List separately in addition to code for primary procedure)	Updated description Codes,61,76,185,201,212,384
15275	Application of skin substitute graft to face, scalp, eyelids, mouth, neck, ears, orbits, genitalia, hands, feet, and/or multiple digits, total wound surface area up to 100 sq cm; first 25 sq cm or less wound surface area	61,76,185,201,212,384
15276	Application of skin substitute graft to face, scalp, eyelids, mouth, neck, ears, orbits, genitalia, hands, feet, and/or multiple digits, total wound surface area up to 100 sq cm; each additional 25 sq cm wound surface area, or part thereof (List separately in addition to code for primary procedure)	61,76,185,201,212,384
15277	Application of skin substitute graft to face, scalp, eyelids, mouth, neck, ears, orbits, genitalia, hands, feet, and/or multiple digits, total wound surface area greater than or equal to 100 sq cm; first 100 sq cm wound surface area, or 1% of body area of infants and children	Updated description Codes,61,76,185,201,212,384
15278	Application of skin substitute graft to face, scalp, eyelids, mouth, neck, ears, orbits, genitalia, hands, feet, and/or multiple digits, total wound surface area greater than or equal to 100 sq cm; each additional 100 sq cm wound surface area, or part thereof, or each additional 1% of body area of infants and children, or part thereof (List separately in addition to code for primary procedure)	61,76,185,201,212,384

All Ancillary Codes

C5271	Application of low cost skin substitute graft to trunk, arms, legs, total wound surface area up to 100 sq cm; first 25 sq cm or less wound surface area
C5272	Application of low cost skin substitute graft to trunk, arms, legs, total wound

	surface area up to 100 sq cm; each additional 25 sq cm wound surface area, or part thereof (list separately in addition to code for primary procedure)
C5273	Application of low cost skin substitute graft to trunk, arms, legs, total wound surface area greater than or equal to 100 sq cm; first 100 sq cm wound surface area, or 1% of body area of infants and children
C5274	Application of low cost skin substitute graft to trunk, arms, legs, total wound surface area greater than or equal to 100 sq cm; each additional 100 sq cm wound surface area, or part thereof, or each additional 1% of body area of infants and children, or
C5275	Application of low cost skin substitute graft to face, scalp, eyelids, mouth, neck, ears, orbits, genitalia, hands, feet, and/or multiple digits, total wound surface area up to 100 sq cm; first 25 sq cm or less wound surface area
C5276	Application of low cost skin substitute graft to face, scalp, eyelids, mouth, neck, ears, orbits, genitalia, hands, feet, and/or multiple digits, total wound surface area up to 100 sq cm; each additional 25 sq cm wound surface area, or part thereof (list
C5277	Application of low cost skin substitute graft to face, scalp, eyelids, mouth, neck, ears, orbits, genitalia, hands, feet, and/or multiple digits, total wound surface area greater than or equal to 100 sq cm; first 100 sq cm wound surface area, or 1% of bod
C5278	Application of low cost skin substitute graft to face, scalp, eyelids, mouth, neck, ears, orbits, genitalia, hands, feet, and/or multiple digits, total wound surface area greater than or equal to 100 sq cm; each additional 100 sq cm wound surface area, or
Q4100	Skin substitute, NOS
Q4101	Apligraf
Q4102	OASIS wound matrix
Q4103	OASIS burn matric
Q4104	Integra BMWD
Q4105	Integra DRT
Q4106	Dermagraft
Q4107	Graftjacket
Q4108	Integra Matrix
Q4110	Primatrix
Q4111	Gammagraft
Q4112	Cymetra injectable
Q4113	Graftjacket Xpress
Q4114	Integra Flowable Wound Matrix
Q4115	Alloskin
Q4116	Alloderm
Q4117	Hyalomatrix
Q4118	Matristem Micromatrix
Q4119	Matristem Wound Matrix

Q4120	Matristem Burn Matrix
Q4121	Theraskin
Q4122	Dermacell
Q4123	Alloskin
Q4124	Oaskis Tri-layer Wound Matrix
Q4125	Arthroflex
Q4126	Memoderm/derma/tranz/integup
Q4127	Taylmed
Q4128	Flexhd/Alopatchhd/matrixhd
Q4129	Unite Biomatrix
Q4131	Epifix
Q4132	Grafix core
Q4133	Grafix prime
Q4134	HMatrix
Q4135	Mediskin
Q4136	EZderm
Q4137	Amnioexcel or Biodmatrix, 1cc
Q4138	DioDfence DryFlex, 1cc
Q4139	Amniomatrix or Biodmatrix, 1cc
Q4140	Biodfence 1cm
Q4141	Alloskin ac, 1 cm
Q4142	Xcm biologic tiss matrix 1cm
Q4143	Repriza, 1cm
Q4145	Epifix, 1mg
Q4146	Tensix, 1 cm
Q4147	Architect ecm px fx 1 sq cm
Q4148	Neox 1k, 1cm
Q4149	Excellagen, 0.1cc
Q4150	Allowrap DS or Dry 1 sq cm
Q4151	AmnioBand, Guardian 1 sq cm
Q4152	Dermapure 1 square cm
Q4153	Dermavest 1 square cm
Q4154	Biovance 1 square cm
Q4155	NeoxFlow or ClarixFlo 1mg
Q4156	Neox 100 1 square cm
Q4157	Revitalon 1 square cm
Q4158	Marigen 1 square cm
Q4159	Affinity 1 square cm
Q4160	NuSheild 1 square cm
Q9349	Fortaderm, fortaderm antimic
Q9358	SergiMend, fetal
C9360	SurgiMend, neonatal

C9363	Integra Meshed Bil Wound Mat

Recommendations:

1) Adopt a new guideline note

GUIDELINE NOTE XXX SKIN SUBSTITUTES FOR CHRONIC SKIN ULCERS
Line 384

Skin substitutes for chronic skin ulcers (venous leg ulcers and diabetic foot ulcers only) are included on Line 384 only when all of the following criteria are met:

1. Product is indicated for inclusion on this Line for the type of ulcer being treated (see table below)
2. FDA indications and contraindications are followed, if applicable
3. Wound has adequate arterial flow (ABI > 0.7), no ongoing infection and a moist wound healing environment
4. For patients with diabetes, Hba1c level is < 12.
5. Prior appropriate wound care therapy (including but not limited to appropriate offloading, multilayer compression dressings and smoking cessation counseling) has failed to result in significant improvement (defined as at least a 50 percent reduction in ulcer surface area) of the wound over at least 30 days
6. Ulcer improves significantly over 6 weeks of treatment with skin substitutes, , with continued significant improvement every 6 weeks required for coverage of ongoing applications
7. Patients is able to adhere to the treatment plan

Skin substitutes table

Product	**Diabetic foot ulcers**	**Venous leg ulcers**
Dermagraft	Included	Not included
Apligraf	Included	Included
OASIS Wound Matrix	Included	Included
Epifix	Not included	Not included
Grafix	Not included	Not included
Graftjacket	Not included	Not included
Talymed	Not included	Not included
Theraskin	Not included	Not included
Other skin substitutes	Not included	Not included

2) Discuss whether or not to include the maximum number of applications.
    a. Additional guideline note language:
        i. The maximum number of applications for each of the following skin substitutes is limited to:

Apligraf	5
Dermagraft	8
Oasis Wound Matrix	12

Skin Substitutes

Draft Coverage Guidance for VbBS Consideration

March 10, 2016

Oregon Health Authority

Oregon Health & Science University

Center For Evidence-based Policy

Background – Skin Ulcers

- Common types of skin ulcers
  - Diabetic foot ulcers (DFU)
    - Caused by atherosclerosis impeding blood flow to extremities and neuropathy that reduces person's ability to detect an injury
    - DFU can lead to infection (e.g., osteomyelitis) and amputation
  - Venous leg ulcers (VLU)
    - Caused by venous insufficiency
  - Pressure ulcers (i.e., bed sores)
    - Occurs when person is unable to reposition themselves, leading to prolonged pressure on a part of the body

Background – Treatments

- Standard treatments for skin ulcers
  - Cleaning and debridement
  - Moist dressing of the ulcer
  - Removing of any pressure on the part of the body with the ulcer (off-loading)
  - Care for the underlying conditions causing the ulcers:
    - DFU: controlling diabetes, blood pressure, etc.
    - VLU: improving circulation with compression stockings, revascularization procedures

Background – Skin Substitutes

- Skin substitutes were originally designed for the treatment of burns.
- Skin ulcers occur more frequently than burns, and skin substitutes are now used more commonly for treatment of ulcers.
- Skin substitutes are indicated for the treatment of chronic ulcers, usually defined as not healing within 30 days using standard treatments.

Background – Skin Substitutes

- Skin substitutes stimulate the body to regenerate lost tissue.
- These products do this by mimicking the body's skin structure.
- The FDA regulates skin substitutes based on how they are derived or produced:
  - Products derived from human donor tissue
  - Products derived from living human or animal tissues and cells
  - Acellular animal–derived products
  - Biosynthetic products

Background – Skin Substitutes

- There are over 70 skin substitute products approved for use in humans (see Table 1 in the CG, pp. 17-18)
- Not all products may be indicated for each type of wound (burns, DFU, VLU)

PICO Statement

- Population: Adults with chronic skin ulcers
- Intervention: Skin substitutes
- Comparator: Usual care
- Outcomes:
  - Deep soft tissue or bone infections (critical)
  - Complete wound healing (critical)
  - Quality of life (critical)
  - Time to complete wound healing (important)
  - Adverse effects (important)

Key Questions

1. What is comparative effectiveness of different types of skin substitutes compared with wound care alternatives for individuals with chronic skin ulcers? Include consideration of:
    a. Age
    b. Body mass index (BMI)
    c. Comorbidities
    d. Site of ulcer
    e. Ulcer etiology (e.g., infectious, pressure or circulatory)
    f. Wound severity
    g. Prior need for skin substitute
    h. Failure of prior therapies
2. What adverse events are associated with skin substitutes?
3. What are contraindications to the use of skin substitutes?

Evidence Sources

- Full search of core sources
  - AHRQ systematic review (Snyder, 2015) identified as the most comprehensive recent review for DFU and VLU: good-quality.
  - Other systematic reviews
    - Game (2015) for DFU: good-quality
    - Jones (2013) for VLU: good-quality
    - Felder (2012) for chronic foot ulcers: fair quality

Evidence Sources

- Medline search
  - Indexed in Medline and published 2012 - October 2015 (corresponding to dates after AHRQ systematic review search)
  - Inclusion criteria: Randomized control trials (RCT) that were not in one of the systematic reviews; product available in U.S.
  - One RCT found
  - During public comment period, one more additional RCT was published and then included in the CG

Evidence Review

- No evidence identified for treatment of pressure ulcers
- The identified evidence evaluated the effectiveness of eight skin substitutes currently sold in the US
- None of the studies found evidence for the critical outcome - quality of life
- Evidence review done separately for
  - Diabetic foot ulcers (DFU)
  - Venous leg ulcers (VLU)

Evidence Summary

Evidence shows moderate or low certainty of benefit

	Diabetic Foot Ulcers	Venous Leg Ulcers
Apligraf®	Complete wound healing: *moderate certainty of benefit* Adverse events: *low certainty of no harm*	Complete wound healing: *low certainty of benefit* Time to complete wound healing: *Low certainty of benefit*
Dermagraft®	Complete wound healing: *low certainty of benefit* Time to complete wound healing: *low certainty of benefit*	
EpiFix®		
Grafix®		

Evidence Summary

Evidence shows moderate or low certainty of benefit

	Diabetic Foot Ulcers	Venous Leg Ulcers
Graftjacket®		
OASIS®	Complete wound healing: *low certainty of benefit*	Complete wound healing: *low certainty of benefit*
Talymed®		
Theraskin®		

Public Comment

- Submitted by Soluble Systems
  - Suggested addition of three studies
    - One study was in AHRQ systematic review
    - One study was not RCT - non-comparative retrospective case series
    - One study not indexed in Medline, small (n=23), poor-quality RCT
  - Discussed coverage by other payers
- Submitted by Smith & Nephew
  - New study: Cazzell (2015) – fair quality RCT of 82 patients comparing OASIS to standard care for treatment of DFU
  - At 12 weeks, wound healing was greater in the OASIS group (54%) compared to standard care group (32%) (p=0.021)

EbGS Decision Factors

- Coverage recommendation divided by “low” versus “very low” quality evidence

Late breaking studies

- Late breaking studies
  - included RCTs, SRs, MAs
  - if submitted by end of public comment period
  - some were not indexed in Medline
- Will wait for a 2 year re-review before adding additional products (there are alternatives)

Complex reimbursement issues

- Costs of product
  - will vary by plan, setting of care, contractual issues
  - Varied number of applications, product sizes, shelf life
- Applications table (revised) included as an appendix for plan information. No max application language included in box.
- Language on reference pricing and bundling omitted

Prerequisites

- Based on combination of study criteria and expert input
- Appropriate wound care required
- Appropriate patient characteristics
  - Diabetic control (<12)
  - Adequate blood flow
  - Failure of prior therapy
  - *Participation* in tobacco cessation required

HERC Coverage Guidance – Skin Substitutes
Disposition of Public Comments

Table of Contents

Commenters

Identification	Stakeholder
A	Soluble Systems *[Submitted December 7, 2015]*
B	Smith & Nephew Advance Wound Management *[Submitted December 15, 2015]*

HERC Coverage Guidance – Skin Substitutes
Disposition of Public Comments

Public Comments

ID/#	Comment	Disposition
A1	"We would like to request that Oregon Medicaid reconsider the current non-coverage recommendation of Theraskin based on the following conclusions obtained from previously submitted clinical data. Upon review of the included references, Theraskin is as effective and at least equivalent to products currently recommended for coverage by Oregon Medicaid (Apligraf and Dermagraft)."	Thank you for your comment. We will address each of these studies individually below.
A2	"The 2011 Landman's study concluded that Theraskin healed (closed) 60% of previously non-progressing diabetic foot ulcers (DFUs) and venous leg ulcers (VLUs) at 12 weeks and 74% at 20 weeks."	Because this is a non-comparative retrospective case series, it does not meet individual inclusion criteria for the evidence review.
A3	"DiDomenico's 2011 study concluded that TheraSkin had a greater rate of wound healing than Apligraf, both at 12 weeks (66.7% vs. 41.3%) and 20 weeks (66.7% vs. 47.1%)."	This study is included in the systematic review by Snyder, Sullivan, & Schoelles (2014), and has thus already been included in the evidence review for the draft coverage guidance. DiDomenico and colleagues did not report a test of statistical significance of the difference observed in the trial; the authors of the AHRQ report found that the difference was not statistically significant (p=0.21).

HERC Coverage Guidance – Skin Substitutes
Disposition of Public Comments

ID/#	Comment	Disposition
A4	"Sanders 2014 clinical study showed wounds treated with TheraSkin are twice as likely to close by week 12, with half the number of grafts, versus wounds treated with Dermagraft."	This manuscript is not indexed in Medline and therefore was not included in the evidence review. Furthermore, this small (n=23) RCT is of poor quality because of uncertainty about allocation concealment; baseline differences in study population (particularly with respect to number of diabetes medications, peripheral arterial disease, tobacco use and wound duration before treatment); differences in the number of office visits in each treatment group and use of offloading techniques; and inadequate blinding of participants, personnel, and outcomes assessors. Additionally, two authors are paid consultants of Soluble Systems and the research was funded by Soluble Systems.
A5	"Snyder, Sullivan and Schoelles 2012 (AHRQ Review included on page 26 of Oregon's Draft Policy) evaluated the effectiveness of Apligraf and TheraSkin for DFUs with average wound sizes. The study also concluded that there were no significant differences reported in complete wound closure between the two products Apligraf 41% vs. Theraskin 67%, p=0.21."	The AHRQ systematic review concluded that there is insufficient evidence to draw conclusions about the comparative effectiveness of Theraskin and Apligraf. The single trial that informed this comparison (DiDomenico, 2011) was a small (n=28) and imprecise trial deemed to be at moderate risk of bias by the authors of the AHRQ review.

HERC Coverage Guidance – Skin Substitutes
Disposition of Public Comments

ID/#	Comment	Disposition
A6	"We respectfully recommend Oregon Medicaid to take into consideration that Theraskin is broadly and long accepted by the medical community and insurance carriers as medically and reasonably necessary therapy for the treatment of a broad range of chronic wound indications. ○ All A/B Medicare Administrative Contractors (MACs) across the U.S., including Oregon, cover Theraskin. ○ 41 Medicaid plans throughout the country, including many states surrounding Oregon, also provide Theraskin coverage. ○ Many large Private Health Plans cover Theraskin including Regence, Kaiser, Cigna, Blue Cross Independence, HCSC (BCBS IL/NM/OK/TX), Amerihealth, BCBS Highmark, United Health Care, Tricare, UPMC Health Plan, etc."	Thank you for your comment. Our review of Local Coverage Determinations (LCDs) as well as the policies of selected Medicaid programs and private health plans found that Theraskin is commonly, but not uniformly, covered.

ID/#	Comment	Disposition
A7	"Oregon Medicaid proposes a recommendation of non-coverage for Theraskin due to 'product cost being moderate compared to alternative treatment options.' Listed within the Oregon Medicaid draft policy under 'Frequency of application and cost of skin substitute' Apligraf and Dermagraft product costs were based upon clinical studies while Theraskin's product cost was based upon Medicare LCD limits. Thus, causing Theraskin associated cost-savings to appear modest when compared to alternative treatments. We respectfully recommend that Oregon Medicaid reevaluate Theraskin's product cost in a similar manner as Apligraf and Dermagraft or adults all product cost using Medicare's' LCFD maximum limits."	The right-hand column of the frequency of application document presented to EbGS was based on the maximum number of applications from the study, while lower limits were used for other products. The rationale column does note that most patients in the study only required a single application. At its November 3, 2015 meeting, the subcommittee recognized that costs and number of applications will vary by patient and that the cost of these products cannot be easily estimated at the population level. Therefore we have removed a specific number of applications for each product from the right column of the applications table and added information on application frequency used in the studies for those products recommended for coverage. However, the subcommittee still finds insufficient evidence of effectiveness to recommend this product for coverage.
B1	"In the draft guidance, the Commission recommends (with a weak recommendation) coverage of OASIS Wound Matrix for venous leg ulcers ('VLU'). We support the recommendation for coverage of OASIS for VLU, and we thank the Commission for its position."	Thank you for your comment.
B2	"By contrast, the Commission recommends against coverage of OASIS Wound Matrix for the treatment of diabetic foot ulcers ('DFU') concluding that there is 'inadequate evidence of benefit, other alternatives available, and its costliness.' We respectfully disagree with this recommendation for the reasons summarized below.	The study by Cazzell and colleagues was not indexed in Medline at the time of the search; it has subsequently been indexed. The previous RCTs of Oasis for DFU were included in the AHRQ review. Landsman, et al (2008) found no statistically significant difference between OASIS and Dermagraft for DFU wound healing at 12 weeks. Niezgoda, et al (2005) compared OASIS to Regranex Gel and found a

ID/#	Comment	Disposition
	There is new evidence, published after the 2012 Agency for Healthcare Research & Quality ('AHRQ') systematic review from supporting the use of OASIS in the treatment of diabetic foot ulcers. This evidence was not considered by the Commission. The findings from a prospective, randomized controlled trial of OASIS Ultra Trilayer Matrix versus standard care were published in 2015 in Advances in Wound Care. In this 16 week trial, 82 qualified patients were randomly assigned to 12 weeks' treatment with OASIS or standard care. The trial demonstrated that a greater proportion of the DFUs were closed by the end of the treatment period (week 12) for the OASIS group than for the standard care group (54% vs. 32%; p = 0.021). More ulcers were closed at each weekly study visit in the OASIS group than the standard care group beginning at week 3 (first visit showing ulcers closed). The overall treatment effect on proportion of ulcers closed over the 12 weeks and the interaction of treatment by week were found to be statistically significant (p = 0.047) in favor of the OASIS group. In the draft coverage guidance, the Commission defined five outcomes considered in its evaluation: ▪ Critical Outcomes – Deep soft tissue or bone infection – Complete wound healing ▪ Important Outcomes – Quality of life – Time to complete wound healing – Adverse effects The randomized, controlled study above included three of these outcomes and supports the use of OASIS compared to the standard care with statistically significant results."	difference in healing at 12 weeks that approached statistical significance (49% vs 28% respectively, p=0.06). Cazzell is an open-label RCT of 82 patients comparing OASIS to standard care for treatment of DFU. In the intervention group, OASIS was applied once each week. Patients in the control group were also seen weekly and the standard care intervention was selected by the investigator (standard care included sliver dressing, Hydrogel, wet-to-dry, alginate, Manuka honey, or triple antibiotic dressing). Ulcer measurement was standardized by use of a digital image capture and wound measurement device. At 12 weeks, wound healing was greater in the OASIS group (54%) compared with the standard care group (32%) (p=0.021). Smith and Nephew funded the study and employs three of the authors. Aside from the conflicts of interest and inadequate blinding, the study otherwise appears to be at low risk of bias. This fair quality RCT demonstrates improved DFU wound healing at 12 weeks for patients treated with OASIS compared to standard care.

ID/#	Comment	Disposition
B3	"OASIS has the same level of general acceptance by the medical community as Apligraf. While not a consideration for coverage, the Commission does review the policy landscape and payer coverage policies. Under Medicare, with respect to local coverage determinations, the policy must be based on published authoritative evidence derived from definitive RCTs or other definitive studies, and general acceptance by the medical community (standard of practice), as supported by sound medical evidence. Use of OASIS in the treatment of DFU is well established in the payer community: ▪ All of the MACs cover OASIS for VLU and DFU ▪ OASIS has positive coverage based on medical necessity from 760 private payers"	Thank you for your comment. Our review of Local Coverage Determinations (LCDs) as well as the policies of selected Medicaid programs and private health plans found that OASIS is commonly, but not uniformly, covered.
B4	"OASIS is the least costly product per application compared with Apligraf and Dermagraft. The Commission's recommendation against coverage for OASIS for DFUs is based, in part, on the Commission's conclusion that the product is costly. In fact, as is shown below, OASIS has a lower cost per application compared with Apligraf and Dermagraft—two other products recommended for coverage for diabetic foot ulcers." *See chart in submitted comments.*	OASIS does have a lower unit cost than Apligraf and Dermagraft. However, as noted in the cost comparison chart, studies which showed effectiveness of OASIS used 8 to 10 applications of this product per patient versus smaller quantities used in the studies showing effectiveness for Dermagraft and Apligraf. The subcommittee does recognize that costs and number of applications will vary by patient and that the cost of these products cannot be easily estimated at the population level.
B5	"The Commission stated in the draft guidance that OASIS 'is not recommended for coverage for diabetic foot ulcers based on inadequate evidence of benefit, other alternatives available, and its costliness.' We believe that this new evidence, together with the position taken by private and public payers as well as the relative low cost of OASIS compared to Apligraf and Dermagraft, support coverage for OASIS for the treatment of diabetic foot ulcers."	Thank you for your comment.

References Provided by Commenters

ID/#	References
A2	Landsman A. S., Cook J., Cook E., Landsman A. R., Garrett P., Yoon J., Kirkwood A., Desman E. (2011). A retrospective clinical study of 188 consecutive patients to examine the effectiveness of a biologically active cryopreserved human skin allograft (TheraSkin®) on the treatment of diabetic foot ulcers and venous leg ulcers. Foot Ankle Spec. 4(1):29-41. DOI: 0.1177/1938640010387417.
A3	DiDomenico, L., Landsman, A. R., Emch, K. J., Landsman, A. (2011). A prospective comparison of diabetic foot ulcers treated with either a cryopreserved skin allograft or a bioengineered skin substitute. *Wounds, 23*(7):184-9.
A4	Sanders, L., Landsman, A. S., Landsman, A., Keller, N., Cook, J., Cook, E., Hopson, M. (2014). A prospective, multicenter, randomized, controlled clinical trial comparing a bioengineered skin substitute to a human skin allograft. *Ostomy Wound Manage, 60*(9):26-38
B2	Cazzell, S. M., Lange, D. L., Dickerson, J. E. Jr., Slade, H. B. (2015). The Management of diabetic foot ulcers with porcine small intestine submucosa tri-layer matrix: A randomized controlled trial. *Adv Wound Care, 4*:1-8. DOI: 10.1089/wound.2015.0645.

Section 5.0

Coverage Guidances

HEALTH EVIDENCE REVIEW COMMISSION (HERC)

COVERAGE GUIDANCE: METABOLIC AND BARIATRIC SURGERY

DRAFT for 3/10/2016 VbBS/HERC meeting materials

HERC Coverage Guidance

Coverage of metabolic and bariatric surgery (including Roux-en-Y gastric bypass, gastric banding, and sleeve gastrectomy) is recommended for:

- Adult obese patients (BMI ≥ 35) with
  - Type 2 diabetes *(strong recommendation)* OR
  - at least two of the following other serious obesity-related comorbidities: hypertension, coronary heart disease, mechanical arthropathy in major weight bearing joint, sleep apnea *(weak recommendation)*
- Adult obese patients (BMI ≥ 40) *(strong recommendation)*

Metabolic and bariatric surgery is recommended for coverage in these populations only when provided in a facility accredited by the Metabolic and Bariatric Surgery Accreditation and Quality Improvement Program *(weak recommendation).*

Metabolic and bariatric surgery is not recommended for coverage in:

- Patients with BMI <35, or 35-40 without the defined comorbid conditions above *(weak recommendation)*
- Children and adolescents *(weak recommendation)*

Note: Definitions for strength of recommendation are provided in Appendix B: GRADE Informed Framework – Element Descriptions.

RATIONALE FOR GUIDANCE DEVELOPMENT

The HERC selects topics for guideline development or technology assessment based on the following principles:

- Represents a significant burden of disease
- Represents important uncertainty with regard to efficacy or harms
- Represents important variation or controversy in clinical care
- Represents high costs, significant economic impact
- Topic is of high public interest

Coverage guidance development follows to translate the evidence review to a policy decision. Coverage guidance may be based on an evidence-based guideline developed by the Evidence-based Guideline

Subcommittee or a health technology assessment developed by the Heath Technology Assessment Subcommittee. In addition, coverage guidance may utilize an existing evidence report produced by one of HERC's trusted sources, generally within the last three years.

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 bariatric surgery be recommended for coverage in adults?				
Outcomes	**Estimate of Effect for Outcome/ *Confidence in Estimate***	**Resource allocation**	**Values and Preferences**	**Other considerations**
All-cause mortality (*Critical outcome)*	Odds ratio: 0.48 (95% CI 0.35 to 0.64) Crude event rates 3.6% with surgery and 11.4% without surgery Number needed to treat = 13 ●●○○ *(low certainty based on consistent but indirect observational studies)*	Bariatric surgery costs tens of thousands of dollars per surgery, but has been shown to be cost effective across BMI thresholds and surgery types.	Patients would balance surgery and its risks with risks of living with morbid obesity. Many patients who have failed conservative attempts at weight loss may elect surgery. The benefits of decreased mortality, dramatic weight loss, and regression of diabetes are important outcomes that patients and society	The greatest benefit may be with BMI ≥ 40 but otherwise specific subpopulations which would benefit the most from bariatric surgery are not well characterized. The pre-operative requirements for achieving optimal outcomes are unclear. Given the rate of complications and need for reoperation
Major adverse cardiovascular events (*Critical outcome*)	Odds ratio: 0.54 (95% CI 0.41 to 0.70) Crude event rates 2.4% with surgery and 4.0% without surgery Number needed to treat = 62			

Coverage question: Should bariatric surgery be recommended for coverage in adults?				
Outcomes	**Estimate of Effect for Outcome/ *Confidence in Estimate***	**Resource allocation**	**Values and Preferences**	**Other considerations**
	●●○○ (*low certainty based on consistent but indirect observational studies)*		would strongly value. However, there would still be moderate variability because of the risks and costs associated with surgery, as well as the intensive peri- and post-operative follow up.	reported in the summary literature, benefit plans may wish to consider alternative payment methodologies like bundled payments or a pay-for-outcomes approach. Surgeon case volume, and to a lesser extent hospital case volume, appear to affect outcomes for patients undergoing bariatric surgery and requirements regarding surgeon or facility volume may be reasonable.
Type 2 DM remission/resolution (*Important outcome*)	Odds ratio: 3.6 to 52.4 (favoring surgery) Number needed to treat: 1 to 5			
	●●●○ *(moderate certainty based on a mix of RCTs and observational studies with consistent but imprecise effects)*			
Hypertension remission/ resolution (*Important outcome*)	Odds ratio: 2.99 to 3.12 (favoring surgery) Number needed to treat: 4			
	●●●○ *(moderate certainty based on a mix of RCTs and observational studies with consistent but imprecise effects)*			
Change in BMI (*Important outcome*)	Mean difference at 1 year: -5.5 to -33.35 kg/m^2 (favoring surgery) Pooled mean difference: -7.4 kg/m^2 (favoring surgery)			

Coverage question: Should bariatric surgery be recommended for coverage in adults?				
Outcomes	**Estimate of Effect for Outcome/ *Confidence in Estimate***	**Resource allocation**	**Values and Preferences**	**Other considerations**
	●●●○ *(moderate certainty based on a mix of RCTs and observational studies with consistent but imprecise effects)*			

Rationale: Bariatric surgery appears to lower all-cause mortality and major adverse cardiovascular events in obese adults (low certainty), and significantly reduces BMI, and results in resolution of type 2 diabetes and hypertension. The greatest benefit appears to be with BMI ≥ 40. Though bariatric surgery is costly and carries significant perioperative risks, the clear long-term positive health benefits leads to a recommendation for coverage. The strength of the recommendation is based on the fact that there is a strong benefit on critical outcomes (particularly in diabetics), and patients desiring surgery would strongly prefer this intervention. For those without diabetes, and other comorbidities are present, the evidence is less clear, leading to a weak recommendation.

Recommendation:

Coverage of metabolic and bariatric surgery (including Roux-en-Y gastric bypass, gastric banding, and sleeve gastrectomy) is recommended for:

- Adult obese patients (BMI ≥ 35 and <40) with:
  - Type 2 diabetes *(strong recommendation)* OR
  - at least two of the following other serious obesity-related comorbidities: hypertension, coronary heart disease, mechanical arthropathy in major weight bearing joint, sleep apnea *(weak recommendation)*
- Adult obese patients (BMI ≥ 40) *(strong recommendation)*

Metabolic and bariatric surgery is recommended for coverage in these populations only when provided in a facility accredited by the Metabolic and Bariatric Surgery Accreditation and Quality Improvement Program *(weak recommendation).*

Metabolic and bariatric surgery is not recommended for coverage in:

- Patients with BMI <35, or 35-40 without the defined comorbid conditions above *(weak recommendation)*

Note: GRADE framework elements are described in Appendix B. A GRADE evidence profile is provided in Appendix C.

Coverage question: Should bariatric surgery be recommended for coverage in children and adolescents?				
Outcomes	**Estimate of Effect for Outcome/ *Confidence in Estimate***	**Resource allocation**	**Values and Preferences**	**Other considerations**
All-cause mortality (*Critical outcome*)	Insufficient evidence in this population *Insufficient evidence*	High cost (tens of thousands of dollars) but may be cost effective especially given the long time horizon if weight loss is maintained. However, uncertainty about the long-term balance of benefits and harms could significantly alter estimates of cost-effectiveness.	High variability. If conservative treatments have failed, children, adolescents and their parents would be highly motivated to find an effective alternative intervention. Children may have a significant fear of surgery, but the profound social and emotional impact of obesity may override their concerns. Parents are likely to be more concerned about the long term health impacts of obesity than children, and may be concerned about the	Parental involvement in weight management plans is likely necessary to assist the effectiveness of obesity treatments (based on expert opinion). Pediatric bariatric surgery is likely to be available at only a few highly specialized centers. The American Academy of Pediatrics has 10 criteria that pediatric bariatric surgery programs should meet.
Major adverse cardiovascular events (*Critical outcome*)	Insufficient evidence in this population *Insufficient evidence*			
Type 2 DM remission/resolution (*Important outcome*)	Rates of remission of T2DM ranged from 50 to 100% ●○○○ *(very low certainty based on mostly small observational trials with imprecise effects)*			
Hypertension remission/ resolution (*Important outcome*)	Rates of remission of hypertension ranged from 50 to 100% ●○○○ (*very low certainty based on mostly small observational trials with imprecise effects)*			

Coverage question: Should bariatric surgery be recommended for coverage in children and adolescents?				
Change in BMI (*Important outcome*)	Mean weighted difference in BMI at 1 year (from baseline): -10.5 to -17.2 kg/m^2 ●●○○ *(low certainty based on mostly small observational trials)*		uncertainty about the long term benefits.	
Rationale: Bariatric surgery likely results in significant reductions in BMI (low certainty) and is associated with remission of type 2 diabetes and hypertension (very low certainty). However, coverage is not recommended because of the limited evidence about overall long-term benefits and harms of bariatric surgery in this population as well as the high variability in values and preferences.				
Recommendation: Bariatric surgery is not recommended for coverage in children and adolescents *(weak recommendation).*				

Note: GRADE framework elements are described in Appendix B. A GRADE evidence profile is provided in Appendix C.

Coverage question: Should reoperative bariatric surgery for inadequate weight loss be recommended for coverage?					
Outcomes		**Estimate of Effect for Outcome** **Confidence in Estimate of Effect**	**Resource allocation**	**Values and Preferences**	**Other considerations**
Critical outcomes	All-cause mortality	Insufficient evidence in this population *Insufficient evidence*	A second high cost procedure (tens of thousands of dollars), with a history of prior failure may be	There would be high variability in patient preferences. With a prior failure of a bariatric procedure, some patients would be hesitant to try an additional procedure	There is evidence of greater complications rates with reoperation. There is insufficient evidence in the reoperation group to
		Insufficient evidence in this population			

Coverage question: Should reoperative bariatric surgery for inadequate weight loss be recommended for coverage?					
Outcomes		**Estimate of Effect for Outcome** **Confidence in Estimate of Effect**	**Resource allocation**	**Values and Preferences**	**Other considerations**
	Major adverse cardiovascular events	*Insufficient evidence*	more costly in total and less effective, however, the cost –effectiveness in this group is unknown.	given the burdens of surgery and prior ineffectiveness. Others would be motivated to try a different procedure in hopes that it would work better. Patients seeking reoperation have likely no other good potential option given failure of multiple previous alternatives (e.g. clinical, pharmacological, nutritional, physical activity, and surgical).	know if their outcomes would be substantially different that those undergoing their first operation. A significant proportion of these patients would be going from a band to a RYGB (from a procedure with a higher failure rate to a lower failure rate).
Important outcomes	Type 2 DM remission / resolution	Insufficient evidence in this population *Insufficient evidence*			
	Hypertension remission/ resolution	Insufficient evidence in this population *Insufficient evidence*			
	Change in BMI	Mean change in BMI (from baseline): +2.4 kg/m^2 to -17.2 kg/m^2 (follow-up ranging from 8 to 48 months) ●○○○ *(very low certainty based on small case series)*			
Rationale: Reoperation is associated with higher complication rates but also effective weight loss (based on very low quality evidence). While there are not long term health outcomes available, there is no reason to believe that significant weight loss in the reoperation group would be associated with less future health benefits. Therefore, the subcommittee makes no recommendation that the coverage criteria should be different between reoperation and primary surgery. Surgeons will also evaluate their patients and consider reasons for failure when deciding if the patient is a good candidate for reoperation.					
Recommendation: No recommendation that coverage criteria for re-operation should be different than for primary surgery.					

Note: GRADE framework elements are described in Appendix B GRADE evidence profile is provided in Appendix C.

EVIDENCE OVERVIEW

Clinical background

Obesity, generally defined as a body mass index (BMI) ≥ 30 kg/m^2 in adults or above the 95th percentile of age- and sex-specific BMI growth charts in children and adolescents, is common. Information from the National Health and Nutrition Examination Survey published in 2014 provides estimates of obesity prevalence of 35% of adults, 17% of 2 to 19 year olds, and 8.1% of infants and toddlers (Ogden, Carroll, Kit, & Flegal, 2014). Obesity is a risk factor for several medical conditions including heart disease, type 2 diabetes mellitus (T2DM), stroke, cancer, sleep apnea, osteoarthritis and others. The Centers for Disease Control and Prevention estimates that obesity is the second leading cause of preventable death and will likely overtake tobacco use as the leading cause of preventable death within the next decade. Older estimates from 2009 found that medical spending attributable to obesity is between $147 billion and $210 billion annually with at least $60 billion of those costs accruing to Medicare and Medicaid programs (Finkelstein, Trogdon, Cohen, & Dietz, 2009).

Data from the Oregon Behavioral Risk Factor Surveillance system in 2009 found that the overall prevalence of adult obesity in Oregon is 24%, though the prevalence of obesity in adults covered by the Oregon Health Plan is greater at 38%. The Oregon Healthy Teens Survey in 2009 estimated that approximately 11% of 8th graders were obese. The Oregon Department of Public Health estimated that costs of obesity related medical care in the Medicaid program alone exceeded $333 million in 2006 (State of Oregon, Department of Human Services, 2012).

There are a number of commonly used medical treatments for obesity including structured programs to promote improved nutrition and physical activity, intensive behavioral counseling for individuals or families, and medications. The Food and Drug Administration (FDA) approved pharmaceutical treatments for obesity include orlistat (Xenical®, Alli®), lorcaserin (Belviq®), phentermine/topiramate (Qsymi®), liraglutide (Victoza®, Saxenda®), and bupropion/naltrexone (Contrave®). Several other medications and herbal supplements are also promoted for weight loss. The FDA also recently approved a weight loss device called the Maestro® Rechargable System that works by blocking signals along the vagal nerve.

Bariatric surgical procedures (sometimes also referred to as metabolic surgery) are another treatment option for obesity.

Indications

Bariatric surgery (alone or in conjunction with non-surgical treatments) is indicated for the treatment of obesity. Guidelines regarding indications for bariatric surgery vary based on BMI thresholds and the presence of obesity-related comorbid conditions.

Technology description

Bariatric procedures commonly performed in the United States include adjustable gastric banding (AGB), vertical sleeve gastrectomy (VSG), Roux-en-Y gastric bypass (RYGB), and biliopancreatic diversion/ duodenal switch (BPD/DS). An excellent overview of the anatomic details of these procedures is available in the executive summary of the Washington Health Technology Assessment (WA HTA) report published in April 2015 (WA HTA, 2015).

The use of bariatric surgical procedures is growing, and approximately 179,000 procedures were performed in 2013 in the United States (U.S.). The distribution of procedure types in the U.S. has shifted with greater use of vertical sleeve gastrectomy and declining use of gastric banding. The estimated number and distribution of surgical procedures in the U.S. is summarized in Table 1.

Table 1. Estimated number and distribution of bariatric surgical procedures in the United States between 2011 and 2013.

	2011	2012	2013
Total	158,000	173,000	179,000
RYGB	36.7%	37.5%	34.2%
Gastric band	35.4%	20.2%	14.0%
Sleeve gastrectomy	17.8%	33.0%	42.1%
BPD/DS	0.9%	1.0%	1.0%
Revisions	6.0%	6.0%	6.0%
Other	3.2%	2.3%	2.7%

Reproduced from the American Society of Bariatric and Metabolic Surgeons, http://connect.asmbs.org/may-2014-bariatric-surgery-growth.html.

Abbreviations: BPD/DS – Biliopancreatic diversion/duodenal switch; RYGB – Roux-en-Y gastric bypass

Adjustable gastric banding and VSG are procedures that either functionally or anatomically reduce the size of the stomach. Adjustable gastric banding, alone among the bariatric surgical procedures, is completely reversible. Roux-en-Y gastric bypass and BPD/DS are more complicated procedures that reduce the size of the stomach and connect more distal portions of the small intestine to the gastric remnant thus bypassing varying lengths of small intestine and reducing the absorption of nutrients. For this reason, these surgeries are sometimes referred to as malabsorptive procedures, with the degree of malabsorption correlating to the length of small intestine that is bypassed. Vertical sleeve gastrectomy is sometimes performed as part of a two stage procedure for patients with extremely high BMIs (the second stage of the procedure is usually a malabsorptive procedure that is more technically feasible after the initial weight loss achieved by VSG).

These procedures can be performed laparoscopically and with robotic assistance. Adjustable gastric banding is sometimes performed on an outpatient basis, but the other procedures generally require a hospital stay that varies from one to seven days after surgery depending on the procedure and patient-specific characteristics. Recovery times vary from one to four weeks. All procedures require frequent follow-up, but AGB may require a greater number of follow-up visits to make adjustments to the band (done through a port located underneath the skin of the abdomen).

All of the bariatric surgical procedures entail operative and post-operative risks, though these vary by the type of procedure. Data regarding perioperative mortality, complications, need for reoperation, and serious adverse events reported in four systematic reviews are summarized in Table 2. It should be noted that definitions of complications and adverse events varied widely across studies. Operative risks include bleeding, infection, and damage to various abdominal organs. Nausea and vomiting are common after all these procedures and the malabsorptive surgeries sometimes cause persistent diarrhea. The malabsorptive procedures are associated with an increased risk of vitamin and mineral deficiencies, and certain types of kidney stones may become more common. Gastrointestinal bleeding from ulcers occurring at the surgical anastamoses also occurs. Infections of the subcutaneous port and erosion of the gastric band into the stomach are risks unique to AGB. The overall median complication rates reported in the Washington HTA report range from 8.8% for VSG to 26.9% for BPD (WA HTA, 2015).

Table 2. Mortality, complications, reoperations, and serious adverse events reported in four systematic reviews.

	Chang (2014)	Colquitt (2014)	Puzziferri (2014)	WA HTA (2015) Range, Median
Mortality <30 days	0.08% in RCTs 0.22% in OSs	NR	NR	NR
Mortality >30 days or not specified	0.31% in RCTs 0.35% in OSs	NR	1% for bypass procedures 0.2% for banding procedures	BPD: 0%-2.9%, 1.4% LAGB: 0%-2.0%, 0.15% RYGB: 0%-4.3%, 1.94% VSG: 0%-3.9%, 0.07%
Complication rate	17% in RCTs 10% in OSs	NR	NR	BPD: 8%-83%, 26.9% LAGB: 0%-53%, 10.1% RYGB: 0%-78%, 9.2% VSG: 0%- 80%, 8.8%
Reoperation rate	7% in RCTs 6% in OSs	2%-13%	NR	BPD: 0%-30%, 3.6% LAGB: 0%-44%, 7.4% RYGB: 0%-22%, 5.8%

	Chang (2014)	Colquitt (2014)	Puzziferri (2014)	WA HTA (2015) Range, Median
				VSG: 0%-17%, 3.9%
Serious adverse event rate	NR	0-37% in surgical groups 0-25% in non-surgical groups	NR	NR

Abbreviations: BPD – Biliopancreatic diversion; LAGB – Laparoscopic adjustable gastric banding; NR – Not reported; OS – Observational study; RCT – Randomized controlled trial; RYGB – Roux-en-Y gastric bypass; VSG – Vertical sleeve gastrectomy

Key Questions

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 A.

1. Should coverage be recommended for bariatric surgery in each of the scenarios in the table below? (Note that the "resolution of diabetes" would not be an applicable outcome in scenarios 4-9)

	BMI 30 – 34.9	BMI 35 – 39.9	BMI ≥ 40
With DM2	Scenario 1	Scenario 2	Scenario 3
W/o DM2 nor other comorbidities	Scenario 4*	Scenario 5*	Scenario 6*
w/o DM2 but with other comorbidities	Scenario 7*	Scenario 8*	Scenario 9*

*Resolution of type 2 diabetes isn't a relevant outcome for this population

2. What is the appropriate minimum age for bariatric surgery?
3. What components and systems of care are associated with improved health outcomes (e.g., centers of excellence, surgeon's experience, etc.)?
4. What preoperative assessments or requirements for preoperative weight loss should be recommended in patients being considered for bariatric surgery?

Critical outcomes selected for inclusion in the GRADE table were all-cause mortality and major adverse cardiovascular events. Important outcomes selected for inclusion in the GRADE table were weight loss (change in BMI), and remission or resolution of T2DM or hypertension.

Evidence review

General Limitations

The literature on bariatric surgery is voluminous. The search conducted by Center staff yielded more than 20 systematic reviews published in the last two years (see Appendix A for a detailed methods description). These reviews span more than 600 individual studies. It should be noted that there is little consistency in the inclusion of individual studies across reviews and that many of the systematic reviews did not perform meta-analysis, in part due to high levels of heterogeneity.

Furthermore, there are important concerns about the quality of much of the published research on bariatric surgery. As the Washington HTA report summarized:

> While the comparative evidence base for either head-to-head comparisons of bariatric procedures or comparisons of bariatric surgery to nonsurgical interventions has grown considerably over time, major challenges with the quality and applicability of available studies remains. Of the 179 comparative studies identified for this evaluation, we rated only 26 (15%) to be of good quality, based on comparable groups at baseline, comparable duration of follow-up, and limited sample attrition. An additional 74 studies (41%) were rated fair quality; issues with comparability, duration of follow-up, and/or attrition were identified in these studies, but attempts were made to control for confounding in the analytic methods (e.g., survival analysis techniques, multivariate regression). However, we considered another 79 studies (44%) to be of poor quality because at least one key quality issue was present and not adequately addressed in either study design or analysis. (WA HTA, 2015, p ES-6).

Additionally, there are at least nine ongoing trials of bariatric surgery that are expected to publish results over the next four years.

Systematic Reviews Addressing Effectiveness in Adults

Eight good quality systematic reviews address the effectiveness of bariatric surgery in adults (Chang et al., 2014; Colquitt, Pickett, Loveman, & Frampton, 2014; Hayes, 2014; Kwok et al., 2014; Muller-Stich et al., 2014; Puzziferri et al., 2014; Wang et al., 2015; WA HTA, 2015). These studies are summarized in Table 3 and discussed below by systematic review.

Table 3. Summary of Systematic Reviews – Effectiveness of Bariatric Surgery for Adults

Systematic Review (Quality) Total N	No. and Type of Included Studies	Population	Outcomes of Interest
Chang, 2014 (Good) N = 161,756	37 RCTs 127 observational studies	Pre-surgical BMI (mean): 45 kg/m^2 T2DM: 26% Hypertension: 47%	Mortality (within 30 days of surgery) Complication rate BMI (mean change at 1 and 5 years) T2DM remission Hypertension remission
Colquitt, 2014 (Good) N ~ 600	7 RCTs	Average pre-surgical BMI (mean): 27 – 55 kg/m^2 5 out of 7 studies required participants have T2DM	BMI T2DM remission Hypertension remission Serious adverse events
Hayes, 2014 (Good) N = 1,734	18 controlled or comparative studies	Pre-surgical BMI (mean): 25 – 55 kg/m^2 T2DM	BMI T2DM remission
Kwok, 2014 (Good) N = 195,408	14 comparative cohorts	Most studies enrolled participants with BMI > 35 kg/m2	All-cause mortality Cardiovascular adverse events
Muller-Stich, 2014 (Good) N = 766	7 RCTs 6 Comparative observational studies	Pre-surgical BMI (mean): < 35 – 37 kg/m^2	BMI T2DM remission Hypertension remission
Puzziferri, 2014 (Good) N = 8,678	10 RCTs 8 cohort studies 11 case series	Pre-surgical BMI (mean): 44 – 61 kg/m^2	Weight loss T2DM remission Hypertension remission Perioperative mortality

Systematic Review (Quality) Total N	No. and Type of Included Studies	Population	Outcomes of Interest
Wang, 2015 (Good) N = 256	4 RCTs	Pre-surgical BMI (mean): 30 – 47 kg/m^2	BMI T2DM remission
WA HTA, 2015 (Good) N = 2,083	14 RCTs 7 comparative cohort studies	Pre-surgical BMI (mean): 30 – 56 kg/m^2	BMI T2DM remission Perioperative mortality and complications

Abbreviations: BMI – body mass index; RCT – randomized controlled trial; T2DM – type 2 diabetes mellitus; WA HTA – Washington Health Technology Assessment Program

Chang (2014)

Chang et al. (2014) is a good quality systematic review and meta-analysis of 164 contemporary studies (37 randomized controlled trials [RCTs] and 127 observational studies) of bariatric surgery published between 2003 and 2012. The included studies spanned over 161,000 patients with an average age of 45 years and an average pre-surgical BMI of 45 kg/m^2. Twenty six percent of the included patients had T2DM and 47% had hypertension. More than two years of follow-up was available for 133,000 of the included patients. Results of RCTs and observational studies were reported separately in the meta-analysis.

The review and meta-analysis focused on surgical mortality and complications, change in BMI, and resolution of obesity-related comorbid conditions. The overall rate of mortality within 30 days of surgery was 0.08% (95% confidence interval [CI] 0.01% to 0.24%) in the RCTs and 0.22% (95% CI 0.14% to 0.31%) in the observational studies. The overall complication rate was 17% (95% CI 11% to 23%) in the RCTs and 9.8% (95% CI 7.4 to 13.0) in the observational studies.

The overall mean change in BMI at 1 year was -13.53 kg/m^2 in the RCTs and -11.79 kg/m^2 in the observational studies. For those studies reporting outcomes at five years of follow-up, the overall mean change in BMI was -11.40 kg/m^2 in the RCTs and -14.32 kg/m^2 in the observational studies.

In the RCTs, the T2DM remission rates in the surgical groups was 92% (95% CI 84.68 to 97.18) compared with a rate of 17.4% (95% CI 0.98 to 69.27) in the control groups. The observational studies found a T2DM remission rate of 86.5%. In the RCTs, the hypertension remission rate was 75% (95% CI 61.52 to 86.35) in the surgical groups compared with a rate of 49% (95% CI 0 to 99%). These comparisons are both indirect and imprecise because so few of the included studies compared surgical and non-surgical

groups directly. Additionally, duration of follow-up for the studies examining comorbid conditions was unclear.

Colquitt (2014)

Colquitt et al. (2014) is a good quality systematic review by the Cochrane Collaboration that includes 22 RCTs, of which 7 studies, comprising approximately 600 patients, compared bariatric surgery to non-surgical controls. Because of differences in the characteristics of participants, interventions, and comparators, meta-analysis was considered inappropriate, and the results were reported narratively.

In terms of BMI, the included studies reported mean changes of -7.4 kg/m^2 to -33.3 kg/m^2 with surgery compared to -0.5 kg/m^2 to -4.7 kg/m^2 in non-surgical controls. The authors conclude that "the direction of the effect was consistently in favour of surgery" based on moderate quality of evidence.

In terms of remission of T2DM, the included studies reported rates of remission ranging from 42% to 90% at 12 to 24 months in surgical groups (73% to 90% if one study with a more stringent definition of A1c < 6 is excluded) compared to remission rates of 0% to 32% in non-surgical controls. The authors conclude that "more people experienced remission following surgery" based on moderate quality of evidence.

Three studies included in the Cochrane review also reported on hypertension outcomes. Two studies reported rates of reduction or discontinuation of antihypertensive medications ranging from 49% to 80% between 12 and 24 months in the surgical groups compared to 0% to 70% in non-surgical controls. One additional study reported that the proportion of patients with systolic blood pressure less than130 mmHg at 12 months was 84% in the surgical group and 79% in non-surgical controls. The authors did not draw any conclusions based on these data.

Hayes (2014)

Hayes (2014) is a good quality systematic review and health technology assessment based on 18 controlled or comparative studies of RYGB in adults with T2DM published between2007 and 2014. Seven of the included studies (5 RCTs and 2 non-randomized controlled trials) compared RYGB with non-surgical treatments while the remaining 11 compared RYGB with other bariatric surgical procedures. The average follow-up across the included studies was 12 months to 5 years.

In patients undergoing RYGB, BMI was reduced by 20 to 33% compared to baseline and T2DM remission was reported in 38 to 90% of patients. In the non-surgical treatment groups, BMI change ranged from -10% to 1%, and T2DM remission rates ranged from 0 to 33%. Based on this, Hayes concluded that RYGB is superior to intensive lifestyle or medical interventions for the treatment of T2DM. The authors further conclude that RYGB and sleeve gastrectomy are equally effective in the treatment of T2DM. Finally, the authors note that preliminary evidence (from a single study) suggests the RYGB may be equally effective for treatment of T2DM in patients with BMI<35 kg/m^2 and BMI>35 kg/m^2, but that additional studies are needed to establish the safety and effectiveness of RYGB in patients with lower BMIs.

Kwok (2014)

Kwok et al. (2014) is a good quality systematic review and meta-analysis of 14 comparative cohort studies reporting mortality and cardiovascular outcomes amongst 29,208 bariatric surgery patients and 166,200 non-surgical controls. The follow-up period of the included studies ranged from 2 years to 14.7 years. The surgical procedures in the studies included AGB, RYGB, SG, banded gastroplasty, as well as other unspecified bariatric surgical procedures. Most of the included studies reported enrolling patients with BMI >35 kg/m^2. Of the 14 included studies, 10 were deemed to be at low to moderate risk of bias, while four studies were deemed to be at moderate-high risk of bias due to concerns over loss to follow-up and inadequate adjustment for confounding. See Appendix D for a detailed description of the included studies.

In the 14 studies included in the meta-analysis of all-cause mortality, the crude event rate was 1059/29,208 (3.6%) in the surgical group and 18,962/166,200 (11.4%) in the non-surgical control group. The odds ratio (OR) for mortality in the surgical group compared with the non-surgical group was 0.48 (95% CI 0.35 to 0.64). Considering only the 10 studies that reported adjusted estimates, the association was consistent but more conservative with an odds ratio for mortality of 0.60 (95% CI 0.49 to 0.74) favoring the surgical group over the non-surgical controls.

In the four studies included in the meta-analysis of composite cardiovascular adverse events, the crude event rate was 407/17,262 (2.4%) in the surgical group and 1108/27,726 (4.0%) in the non-surgical control group. The odds ratio for composite cardiovascular adverse events in the surgical group compared with the non-surgical group was 0.54 (95% CI 0.41 to 0.70). The pooled estimates for the odds ratio of myocardial infarction and stroke for surgical patient compared to non-surgical controls were 0.46 (95% CI 0.30 to 0.69) and 0.49 (95% CI 0.32 to 0.75) respectively.

Overall, the authors conclude that long-term follow-up data from comparative cohort studies suggest that bariatric surgery is associated with lower rates of mortality (3.6% vs 11.4% for non-surgical controls, number needed to treat [NNT] = 13) and composite adverse cardiovascular events (2.4% vs 4.0% for non-surgical controls, NNT = 62).

Muller-Stich (2014)

Muller-Stich et al. (2014) is a good quality systematic review and meta-analysis of studies comparing surgical and medical treatment of T2DM in non-severely obese patients. The systematic review included seven RCTs and six comparative observational studies comprising 818 diabetic patients. All of the studies included patients with BMI <35 kg/m^2 and eight of the studies were performed exclusively in patients with BMI <35 kg/m^2; among the remaining seven studies the highest average BMI was 37.1 kg/m^2. The surgical procedures performed in the included studies were AGB, BPD, RYGB, and SG. The follow-up periods ranged from 12 to 36 months.

In the meta-analysis of studies reporting remission of T2DM, 129 of 280 patients achieved remission in the surgical group compared with 6 of 252 patients in the medical treatment group. The combined odds

ratio for T2DM resolution after surgery compared with medical treatment was 14.11 (95% CI 6.67 to 29.86).

In the meta-analysis of studies reporting change in BMI, the absolute mean difference in BMI was -5.5 kg/m^2 (95% CI -6.7 to -4.3) favoring the surgical group.

In the meta-analysis of studies reporting presence of arterial hypertension at the end of the study, the 76 of 274 patients in the surgical group and 101/189 patients in the medical treatment group had arterial hypertension. The combined odds ratio for arterial hypertension after surgery compared with medical treatment was 0.25 (95% CI 0.12 to 0.50).

The authors performed a network meta-analysis to compare the treatment effects of the different surgical procedures. Although point estimates of the odds ratio for T2DM remission compared to medical treatment ranged from 12.23 for AGB to 55.05 for RYGB, the 95% confidence intervals overlapped for all four included procedures, and all were superior to medical treatment.

Overall, the authors conclude that among non-severely obese patients with T2DM bariatric surgery results in greater short-term improvements in diabetes remission, weight loss, and arterial hypertension when compared with medical treatment.

Puzziferri (2014)

Puzziferri et al. (2014) is a good quality systematic review and meta-analysis of 29 studies with long-term follow-up and low rates of attrition. Specifically, only studies of gastric bypass, gastric band, or sleeve gastrectomy performed in patients with a BMI of >35 and that reported outcomes with a minimum of two years of follow-up and at least 80% of the original study participants were included in the review. Only 29 studies (of nearly 8,000 citations reviewed) met the inclusion criteria. Among the included studies were 10 RCTs, one matched cohort, six prospective cohorts, one retrospective cohort, and 11 case series.

Weight loss outcomes in this review were reported as percentage of mean excess weight loss (EWL). The sample size weighted mean EWL was 65.7% after gastric bypass, 64.5% after sleeve gastrectomy, and 45% after gastric banding.

Six of the included studies reported on remission of T2DM (defined as glycated hemoglobin <6.5% without medications). Sample size weighted T2DM remission rates were 66.7% after gastric bypass and 28.6% after gastric banding.

Three of the included studies reported on remission of hypertension (defined as blood pressure <140/90 without medications). The reported hypertension remission rate was 38.2% after gastric bypass and 17.4% after gastric banding.

Wang (2015)

Wang et al. (2015) is a good quality, though narrowly focused, systematic review and meta-analysis of randomized controlled trials comparing laparoscopic RYGB with sleeve gastrectomy in overweight or obese adults with T2DM. Three RCTs judged to be at low risk of bias and one RCT with an unclear risk of

bias were included. The average baseline BMI in the studies ranged from 30 to 46 kg/m^2. Laparoscopic RYGB and sleeve gastrectomy resulted in similar improvements in HbA1c, fasting plasma glucose, need for any diabetic medication, and BMI. Improvements in HDL and LDL cholesterol were statistically significantly greater in the RYGB group. The absolute or relative improvements in these outcomes compared to baseline were not included. Overall, the authors conclude that RYGB and sleeve gastrectomy offer equivalent results in terms of weight loss and T2DM remission, but that RYGB affords greater improvements in lipid parameters and may thus significantly decrease cardiovascular risk.

Washington Health Technology Assessment Report (2015)

The WA HTA report (2015) is a good quality systematic review and health technology assessment summarizing results from 179 comparative studies (35 RCTs, 59 prospective cohorts, 85 retrospective cohorts). Notably, one large cohort study with long-term follow-up, the Swedish Obese Subjects study, was not included as a primary source for the Washington HTA report because most of the patients in that study received a surgical procedure (gastroplasty) that is no longer widely performed. Only 15% of the included studies were judged to be of high quality, with an additional 41% deemed fair quality. When performing meta-analysis, the authors included only good or fair quality RCTs.

Overall or cause-specific mortality was not directly addressed in the WA HTA report because none of the included comparative studies reported those outcomes. However, the WA HTA report does note that evidence from at least one recent comparative cohort study found significantly lower all-cause mortality at 1 to 14 years of follow-up in surgical subjects (hazard ratio [HR] 0.45, 95% CI 0.36 to 0.56) (Arterburn, 2015).

The comparison of bariatric surgery to non-surgical management included 21 good- or fair-quality studies (14 RCTs, 7 comparative cohorts). These studies reported on RYGB (13 studies), AGB (6 studies), VSG (4 studies) and BPD/DS (3 studies). The non-surgical comparators included diet and lifestyle interventions and/or medical interventions (some variably defined as “intensive”). Meta-analytic results were available for weight loss and resolution of T2DM. The pooled mean difference in BMI was 7.4 (95% CI 6.2 to 8.6) favoring surgery, based on 10 studies. Resolution of T2DM had a log odds ratio of 3.62 (95% CI 2.49 to 4.73) favoring surgery, based on nine studies. Meta-analysis of studies reporting resolution of HTN was not done, but the report noted that “[o]ther individual comorbidities commonly evaluated in these comparative studies included hypertension and hyperlipidemia. In studies evaluating resolution of these conditions and/or discontinuation of relevant medications as a binary variable, bariatric surgery was associated with two- to three-fold reductions in the prevalence of these comorbidities [hypertension and hyperlipidemia] at the end of follow-up, while nonsurgical management resulted in no appreciable change from baseline…” (WA HTA, 2015, p. 34).

The WA HTA report is the only systematic review staff identified that summarizes key clinical outcomes stratified by procedure and mean pre-operative BMI. Those tables are included in Appendix G. Nine good- or fair-quality RCTs and prospective cohorts comparing bariatric surgery and non-surgical management enrolled patients with BMI<35. Seven of those studies included presence of T2DM or

metabolic syndrome as an entry criterion, while two did not report comorbid condition-based entry criteria. The authors conclude that for those with a mean pre-operative BMI of 30 to 35.9 "patterns of weight loss across procedures were similar to those in studies of patients at higher BMI" (WA HTA, 2015, p. ES-41). Furthermore, among studies of patients at lower BMI levels that reported on remission of T2DM at 12 to 24 months the results favored surgery (remission rates of 26% to 73%) over non-surgical treatment (remission rates of 0% to 16%).

Systematic Reviews Addressing Effectiveness in Children and Adolescents

Three fair or good quality systematic reviews address the effectiveness of bariatric surgery in children and adolescents (Aikenhead, Knai, & Lobstein, 2011; Black, White, Viner, & Simmons, 2013; Treadwell, Sun, & Schoelles, 2011). These studies are summarized in Table 4 and discussed below by systematic review.

Table 4. Summary of Systematic Reviews – Effectiveness of Bariatric Surgery for Children and Adolescents

Systematic Review (Quality) Total N	No. and Type of Included Studies	Population	Outcomes of Interest
Aikenhead, 2011 (Fair) N = 831	1 RCT 8 cohort studies 14 observational studies 12 case series	≤ 19 years old	BMI
Black, 2013 (Fair) N = 637	1 RCT 22 observational studies	Pre-surgical BMI (mean): 46 – 52 Age: 5 – 23 years	BMI
Treadwell, 2008 (Treadwell) N = 644	18 Observational studies	Pre-surgical BMI (mean): 46 – 52 Age: 9 – 21 years	BMI

Abbreviations: BMI – body mass index; RCT – randomized controlled trial

Aikenhead (2011)

Aikenhead et al. (2011) is a fair quality narrative systematic review of 37 studies of effectiveness of bariatric surgery spanning 831 patients age 19 years old or younger. The authors note several general limitations of the pediatric bariatric surgery literature including predominately observational study designs, small sample sizes (the largest of the included trials had 68 patients), and sparse information on low frequency outcomes.

Thirteen of the included studies (all but one observational) assessed gastric banding. Twelve of these studies reported mean BMI reductions of 8.5 kg/m^2 to 43 kg/m^2, while one study (a case report of gastric banding and truncal vagotomy in an adolescent with a rare mutation in a gene implicated in regulation of appetite and energy balance) found an increase in BMI of 2.2 kg/m^2. Rates of resolution of comorbid conditions ranged from 11 to 100%.

Eight of the included studies (all observational) assessed RYGB. The studies reported mean reductions in BMI of 9 kg/m^2 to 25 kg/m^2. The authors note that four of the studies reported on comorbid conditions and three of those four studies found 100% rates of resolution for dyslipidemia, degenerative joint disease, asthma, and gastroesophageal reflux disease.

Fourteen of the included studies (all observational) reported on other bariatric procedures (sleeve gastrectomy, BPD/DS, vertical banded gastroplasty). These studies reported mean BMI reductions of 9 kg/m^2 to 24 kg/m^2. The authors note that changes in comorbid conditions were reported in 12 of the 14 studies, but additional details are not included.

The authors' overall conclusion is that "[i]n the context of a general lack of effective tools for primary prevention or behavioural treatment of obesity, surgical treatment may be advocated as a preferred and cost-effective solution for certain children and adolescents" (Aikenhead, 2011, p. 18)

Black (2013)

Black et al. (2013) is a fair quality systematic review and meta-analysis of bariatric surgery for obese children and adolescents. Twenty-three studies (22 observational and 1 RCT) comprising 637 patients undergoing RYGB, AGB, or SG were included. The mean pre-surgical BMI was 52.4 kg/m^2 in the RYGB studies, 49.6 kg/m^2 in the SG studies, and 46.1 kg/m^2 in the AGB studies. The ages of patients in the included studies ranged from 5 to 23 years old.

Overall, the average weighted BMI difference from baseline to one year postoperatively was -13.5 kg/m^2 (95% CI -15.1 to -11.9). The greatest BMI reductions were observed in patients undergoing RYGB (average weighted difference of -17.2 kg/m^2) and the smallest BMI reductions were observed in the AGB group (average weighted difference of -10.5 kg/m^2).

The authors note that they were unable to provide summary estimates of the effects on comorbidity resolution because the data were of poor quality and adequate definitions of resolution were not provided. The rates of reported resolution of T2DM from baseline to follow-up ranged from 0 to 100% in the eight studies that reported this outcome. However, excluding one study with only a single T2DM patient who did not experience resolution, the rate of resolution for T2DM would range from 50 to 100%. The rates of reported resolution of hypertension from baseline to follow-up ranged from 50 to 100% in the 10 studies that reported this outcome.

Treadwell (2008)

Treadwell et al. (2008) is a good quality systematic review and meta-analysis of bariatric surgery for pediatric obesity. This review included 18 studies of children ages 9 to 21 years (mean age 16.7 years) with mean BMI ranging from 45.8 kg/m^2 to 51.8 kg/m^2. In 14 of the 18 studies, patients must have failed

a trial of non-surgical weight loss before undergoing bariatric surgery. Only one of the included studies reported a non-surgical control group and significant differences in baseline characteristics between the groups were noted including baseline BMI and comorbidities. Thus, the authors note that, in effect, the included studies were all case series.

Meta-analysis of change in BMI in six studies of AGB found a 95% CI of -13.7 kg/m^2 to -10.6 kg/m^2 at mean length of follow-up of one to three years. Two of the studies of AGB reported T2DM remission rates of 80 to 100% and three of the studies reported hypertension remission rates of 50 to 100%.

Meta-analysis of change in BMI in six studies of RYGB found a 95% CI of -17.8 kg/m^2 to -22.3 kg/m^2 at mean length of follow-up of one to six years. Only one of the studies of RYGB reported remission of T2DM. Three studies of RYGB reported rates of hypertension remission of 50 to 100%.

Because of the small number of studies and patients undergoing other procedures, summary information on weight changes or comorbidity resolution was not presented.

Overall, the authors conclude that there is weak to moderate evidence that AGB achieves weight loss at one year or longer and weak evidence of resolution of T2DM and hypertension. For RYGB, the authors conclude that there is weak to moderate evidence of weight loss at one year or longer, weak evidence of resolution of hypertension, and insufficient evidence of resolution of T2DM. There was insufficient evidence for any outcomes from other bariatric procedures.

Systematic Reviews Addressing Bariatric Reoperation Procedures

As the use of primary bariatric surgical procedures has increased, so too has the rate of bariatric reoperation. The term “bariatric reoperation” captures several types of procedures (conversion, correction, revision, or reversal) that are performed for various indications. Inadequate weight loss (commonly, but not uniformly, defined as <50% EWL) is the most common indication for revision or conversion procedures. Reoperation is also performed to address both acute complications (including anastomotic leaks, bleeding, strictures, obstruction, and perforation) and chronic complications (including protein calorie malnutrition, severe GERD, band erosion, late or recurrent leaks, late strictures, and band intolerance.) Reversal procedures are rare, but are sometimes performed to address intractable nausea and vomiting, excessive or uncontrolled weight loss, severe malnutrition, recurrent anastomotic ulcers, severe hypoglycemia, and recalcitrant hypocalcaemia.

In general, bariatric reoperation is thought to be more technically challenging than primary bariatric surgery, at least in part because of the likelihood of surgical adhesions from the primary procedure. Nevertheless, many reoperative bariatric procedures can still be performed laparoscopically, though the complication rates may be higher when compared with primary bariatric procedures.

Five fair quality and one low quality systematic reviews address the effectiveness of bariatric reoperative procedures (Brethauer, et al., 2014; Cheung, Switzer, Gill, Shi, & Kamali, 2014; Coblijn, Verveld, van Wagensveld, & Lagard, 2013; Elnahas, Graybiel, Farrokhyar, Gmora, Anvari, & Hong, 2013;

Mahawar, Graham, Carr, Jennings, Schroeder, Balupuri, & Small, 2015; Schouten, Japink, Meesters, Nelemans, & Greve, 2011).

These systematic reviews of bariatric reoperation provide very low certainty evidence that revisional or conversion procedures performed after an initial bariatric surgery may achieve additional weight loss (particularly those procedures that convert AGB to RYGB or BPD/DS), but at the expense of a higher rate of complications. The systematic reviews offer no evidence that bariatric reoperation improved co-morbidity resolution. Most of the studies included in the systematic reviews were not methodologically rigorous and there are concerns about publication bias in this literature. Furthermore, the indications for bariatric reoperation varied across and within individual studies.

Brethauer (2014)

Brethauer et al. (2014) is a systematic review on indications for and outcomes of reoperative bariatric surgery that was conducted by the ASMBS Bariatric Surgery Revision Taskforce. The review was supported by an unrestricted educational grant from Covidien, a company that manufactures equipment used in bariatric surgical procedures. While the review states that 175 articles were included in the systematic review, the majority of these were single center retrospective case series and the evidence tables in the review provide details on only 35 "selected studies." Thus, the degree to which the narrative review and recommendations reflect an unbiased inclusion of studies identified in the systematic review is uncertain. Furthermore, the reporting of quantitative outcomes across indications and reoperative procedures was erratic. The conclusions of the authors, summarized here with the above caveats, are 1) reoperation for inadequate or failed weight loss generally improves weight loss, and 2) complication rates are generally higher with reoperative procedures.

Cheung (2014)

Cheung et al. (2014) is a systematic review of studies of revisional bariatric surgery following laparoscopic sleeve gastrectomy. The review includes 11 studies spanning a total of 218 patients. In most of the studies patients underwent revisional procedures because of insufficient weight loss or weight regain, although the former indication was variably defined. Intractable gastroesophageal reflux disease was an additional indication in 5 of the studies. The revisional procedures included laparoscopic butterfly gastroplasty, laparoscopic omega loop mini gastric bypass, laparoscopic re-sleeve gastrectomy, laparoscopic duodenal switch, and laparoscopic or open RYGB. Nine of the studies were cases series and two studies were case-controls. The largest single study enrolled 40 patients. The primary outcomes were change in BMI at various time points. At 24 months or greater, revisional procedures were associated with reductions in BMI. Revision of LSG to gastric bypass resulted in an average change in BMI of -6.2 kg/m^2. Revision of LSG to re-sleeve gastric bypass resulted in an average change in BMI of -3.2 kg/m^2. Revision of LSG to other surgical interventions (all other conversion procedures) resulted in an average change in BMI of -17.2 kg/m^2. In the three studies that examined the effects of revisional procedures on GERD complications, there was a 100% complete resolution rate, though it should be noted that the sample size for this outcome was very small (n=15). The authors note that their review

was limited by the small number of studies and patients, the very low methodological rigor of the study designs, and the absence of postoperative complication rates after revision.

Coblijn (2013)

Coblijn et al. (2013) is a systematic review of studies of revisional bariatric surgery (LSG or LRYGB) after an initial adjustable gastric banding procedure. The review includes 15 studies of LRYGB spanning 588 patients and 8 studies of LSG spanning 286 patients. Not all studies reported the indication for revisional surgery, but in those that did the most common indication was insufficient weight loss or weight regain (approximately 65% of patients). Most of the studies were consecutive case series and there were no randomized controlled trials. The primary outcomes of interest were perioperative morbidity and mortality. In the LRYGB studies that reported this outcome there were no perioperative deaths and the overall perioperative complication rate was 8.5%. In the LSG studies that reported this outcome, there were 3 perioperative deaths and the overall perioperative complication rate was 12.2%. The rate of reoperation after the revisional procedures was 6.5% for LRYGB and 3.5% for LSG. Though weight loss was not of primary interest for this review, the authors did note that 11 of the 15 LRYGB studies reported mean EWL of 23% to 74%, though the follow-up time was not clear. Weight loss achieved with revisional LSG appeared to be nearly comparable. The authors note several limitations to their review including the very low methodological rigor of the study designs and the possibility of publication bias, particularly for studies reporting on morbidity and mortality.

Elnahas (2013)

Elnahas et al. (2013) is a systematic review of conversion bariatric procedures after failed adjustable gastric banding. The review includes 24 studies reporting outcomes of conversion to LSG (n=106 patients), LRYGB (n=514 patients), and laparoscopic BPD/DS (n=71 patients). Patients in these studies underwent the conversion procedure due to inadequate weight loss or surgical complications with AGB. All of the included studies were retrospective case series. The primary outcome of interest was weight loss measured by change in BMI or percentage EWL. The mean change in BMI at 24 to 48 months after reoperation was -2.8 kg/m^2 for LSG, -8.5 kg/m^2 for LRYGB, and -13.3 kg/m^2 for BPD/DS. The weighted mean complication rates for conversion to LSG, LRYGB, and BPD/DS were 4.1%, 10.7%, and 24.4% respectively. The authors note several limitations to their study including the very low methodological rigor of the study designs and significant heterogeneity across studies.

Mahawar (2015)

Mahawar et al. (2015) is a systematic review of studies that compare the outcomes of revisional bariatric procedures to the outcomes of the same primary procedures. The review includes 14 studies comparing revisional and primary RYGB and 7 studies comparing revisional and primary SG. The designs of the primary studies were not made explicit, but all appeared to be case-control or retrospective cohort studies. Quantitative cumulative outcomes reported in the studies comparing revisional with primary RYGB included mortality (1.3% revisional vs 0.2% primary), complications (29.5% revisional vs 13.9% primary), reoperation (8.4% revisional vs 8.6% primary), and leaks (5.8% revisional vs 1.0%

primary). Quantitative cumulative outcomes reported in the studies comparing revisional SG with primary SG included mortality (0% revisional vs 0.1% primary), complications (10.5% revisional vs 5.2% primary), reoperation (4.8% revisional vs 1.6% primary), and leaks (1.9% revisional vs 1.5% primary). Weight loss outcomes were not cumulatively analyzed because of heterogeneity in the studies, but the authors do note that most of the studies that reported on weight loss outcomes found that the weight loss achieved with revisional procedures was either inferior to (10/14 studies of RYGB, 2/5 studies of SG) or not significantly different from the weight loss achieved with primary procedures (4/14 studies of RYGB, 3/5 studies of SG). The authors do not comment on limitations of their review other than noting the absence of any level I evidence on revisional bariatric surgery.

Schouten (2011)

Schouten et al. (2011) is a systematic review of studies examining reoperation following gastric banding procedures. The review included 11 studies of re-banding, 12 studies of conversion to LRYGB, 5 studies of conversion to laparoscopic BPD/DS, and 5 studies of conversion to LSG.

Among the 11 studies that examined re-banding, the most common indications were slippage, erosion, or pouch dilation. Ten of the 11 studies presented level III or level IV evidence, while one presented level II evidence. The follow-up period varied from 8 to 48 months after reoperation. The early complication rate ranged from 0% to 11%, the late complication rate ranged from 0% to 41%, and the reoperation rate ranged from 0% to 45%. Change in BMI was reported in 6 studies and ranged from +2.4 kg/m^2 to -5.8 kg/m^2.

Among the 12 studies of conversion to LRYGB, the most common indications were insufficient weight loss, band, erosion, and pouch dilation. Ten of the 12 studies presented level III or level IV evidence, while the remaining 2 presented level II evidence. The follow-up period ranged from 8.3 to 36 months after reoperation. The early complication rate ranged from 3% to 36%, the late complication rate ranged from 2% to 23%, and the reoperation rate ranged from 0% to 20%. Change in BMI was reported in 9 studies and ranged from -6.1 kg/m^2 to -13.2 kg/m^2. Percentage EWL was reported in 2 studies and ranged from 33% to 43%.

Among the 5 studies of conversion to BPD/DS, the most common indication was insufficient weight loss. All 5 studies presented level III or level IV evidence. The follow-up period ranged from 12 to 38 months after reoperation. The early complication rate ranged from 8% to 62%, the late complication rate ranged from 20.6% to >23.5%, and the reoperation rate ranged from 0% to 20.6%. Percentage of EWL was reported in 3 studies and ranged from 44% to 70%.

Among the 5 studies of conversion to LSG, the most common indication was insufficient weight loss. Four studies presented level IV evidence while 1 study presented level II evidence. The follow-up period ranged from 12 to 24 months after reoperation. The early complication rate ranged from 0% to 13.8%, the late complication rate ranged from 0% to 10.3%, and the reoperation rate ranged from 0% to 10.3%.

Percentage of EWL was reported in 2 studies and ranged from 20% to 65.7% while change in BMI was reported in 1 study as -4.4 kg/m^2.

The authors conclude that adjustable gastric banding should remain a first line procedure with re-banding or conversion to RYGB or BPD/DS as options for managing band failure.

Systematic Reviews Addressing Patient Selection

One poor quality and two good quality systematic reviews address patient selection criteria (Ochner, Dambkowski, Teomans, Teizeira, & Xavier Pi-Sunyer, 2012; Thomas & Agrqwal, 2012; WA HTA, 2015).

Ochner (2012)

Ochner et al. (2012) is a good quality narrative systematic review of 29 studies examining the effects of preoperative weight loss requirements on postoperative outcomes. The authors note that heterogeneity in the included studies precluded formal quantitative synthesis. Overall, the included studies were mostly observations and were mixed on the effects of preoperative weight loss requirements on postoperative weight loss outcomes. As the authors note, "studies of the relation between pre- and post-operative changes in body weight range from a positive relationship (preoperative weight loss associated with greater postoperative weight loss) to a negative relationship (preoperative weight loss associated with less postoperative weight loss) and many in between (no relationship)" (Ochner et al., 2012, p. 1381). The only included RCT deemed "viable" by the authors randomized 100 patients undergoing RYGB to a group with a requirement of 10% preoperative weight loss or a group with no preoperative weigh loss requirement. At six months after surgery, patients in the preoperative weight loss group had lost 54% of excess body weight compared to 51% excess body weight loss in the in the group without a preoperative weight loss requirement, but because only 37% of the original sample was analyzed at six months there was insufficient power to detect an effect.

The review also examined studies reporting on the effects of preoperative weight loss requirements on other outcomes including resolution of comorbid conditions. One study of 90 RYGB patients found that preoperative weight loss of >5% of excess body weight was associated with shorter operative times (36 minutes on average) but no difference in complications or resolution of comorbid conditions. Another study demonstrated that patients with preoperative weight loss of >5% of excess body weight were less likely to have a postoperative length of stay of >4 days. The RCT referenced above found no difference in the complication rate or resolution of comorbid conditions at six months. A fourth study found no correlation between preoperative weight changes and remission of diabetes or hypertension.

The authors' overall conclusion is that "[g]iven the inconsistency and questionable validity of the extant research…on the question of the effect of preoperative weight loss on peri- and postoperative outcomes, it is the opinion of these authors that insufficient evidence is currently available to justify a pre-bariatric surgery weight loss mandate" (Ochner et al., 2012, p. 1386).

Thomas (2012)

Thomas & Agarwal (2012) is a poor quality systematic review of a preoperative risk stratification tool known as the obesity surgery mortality risk score (OS-MRS). The OS-MRS assigns one point each for age greater than 45 years, male gender, BMI > 50 kg/m^2, hypertension, and known risk factors for pulmonary embolism. Scores of 0 to 1 are considered class A or lowest risk, scores of 2 to 3 reflect class B or intermediate risk, and scores of 4 to 5 are class C or high risk. This review included six studies reporting on 9,382 patients evaluating the validity of OS-MRS to predict postoperative mortality risk. Overall, there were 83 death in the 9,382 patients (0.88%). There were 13 deaths among the 4,912 class A patients (0.26%), 55 deaths among the 4,124 class B patients (1.33%), and 14 deaths among the 346 class C patients (4.34%). The mortality difference between classes were statistically significant at $p<0.05$. The authors conclude that use of the OS-MRS can stratify mortality risk in patients undergoing bariatric surgery (particularly RYGB which was the predominately studied procedure in the included studies).

WA HTA (2015)

The WA HTA report included a single retrospective comparative cohort study that stratified outcomes by patient adherence to preoperative program recommendations. In the laparoscopic AGB group, patients who did not attend >75% of their pre-procedure appointments had attenuated weight loss at 12 months of follow-up (23% EWL vs 32% EWL in patients with fewer missed appointment, p=0.01). There were no differences in RYGB performance related to pre-procedure appointment adherence.

A single study included in the WA HTA report concluded that patients with congestive heart failure and cardiac arrhythmias had a significantly increased risk of post-surgical complications compared with the overall cohort (40% vs 13.4% for open RYGB, 21.1% vs 8.6% for laparoscopic RYGB, and 17.4% vs 3.1% for laparoscopic AGB, all p-values <0.001). The same study reported that patients with peripheral vascular disease undergoing RYGB had significantly increased complication rates compared to those without peripheral vascular disease (32.0% vs 8.4%, $p<0.001$).

The WA HTA report also notes that it did not find studies that stratified outcomes by smoking status or psychosocial health that met inclusion criteria.

Systematic Reviews Addressing Systems of Care

One good quality systematic review addresses the effect of systems of care on bariatric surgery outcomes (Zevin, Aggarwal, & Grantcharov, 2012).

Zevin (2012)

Zevin et al. (2012) is a good quality systematic review of volume-outcome associations in bariatric surgery. The article reviews 24 observational studies comprising almost 460,000 patients. Meta-analysis was not performed due to a high level of heterogeneity that resulted, in part, from differences in duration of follow-up and risk-adjustment.

Thirteen studies addressed the relationship between annual surgeon case volume and patient outcomes. Across the five cohort studies that were included, there was consistent evidence of improved

outcomes with increasing surgeon volume. The results of lower quality studies (primarily retrospective cohorts) were mixed, but six of the eight studies supported an association between surgeon volume and outcomes.

Seventeen studies addressed the association between hospital volume and outcomes. While the two case-control studies that were included did not support an association between facility volume and outcomes, the preponderance of retrospective case series (14/15 studies) that were included found an association between facility volume and outcomes.

The authors conclude that there is strong evidence to support the association between surgeon volume and patient outcomes, and that weaker evidence supports the association between hospital volume and outcomes. Overall, they conclude that the literature "supports the BSCOE accreditation and the bariatric surgery fellowship training programs" (Zevin et al., 2012, p. 70).

WA HTA (2015)

The WA HTA report notes that pre-procedure support groups have shown little benefit, but that there is some evidence that patients in postoperative support groups experience improvements in psychological comorbidities and achieve greater weight loss. The WA HTA report cites one RCT of 144 Hispanic-American RYGB patients randomized to "comprehensive nutrition and lifestyle support or brief, printed healthy lifestyle guidelines…" At one year after surgery, patients in the comprehensive support group had greater reductions in BMI (6.48 kg/m^2 vs 3.63 kg/m^2, $p<0.001$).

Systematic Reviews Addressing Cost-effectiveness

WA HTA (2015)

The WA HTA report (2015) performed a cost-effectiveness analysis based on a model constructed by the authors. This analysis assumed a public payer perspective. The base-case analysis compared RYGB with standard care over a 10 year time horizon; other base-case assumptions included a procedural cost of $24,277, 20% worsening in BMI after 12 months, mean BMI at baseline of 40 kg/m^2, and a discounting rate of 3%. In the base-case analysis, the incremental cost-effectiveness of RYGB compared to standard care was $37,423 per quality-adjusted life year (QALY) gained. In the deterministic sensitivity analyses, the incremental cost-effectiveness estimates ranged from $5,444 per QALY to $84,971 per QALY. The estimates were most sensitive to changes in the time horizon, the cost of the bariatric surgical procedure, maintenance of weight loss after surgery, and baseline BMI. The WA HTA cost-effectiveness estimates, stratified by procedure and baseline BMI, are included in Appendix H.

There is very sparse evidence on the cost-effectiveness of bariatric surgery in children and adolescents. The only included systematic review which addresses this question is Aikenhead et al. (2011). The conclusions of this review are limited by the small number of studies, use of economic models that are not directly applicable to the U.S., and inferences from cost-effectiveness studies of bariatric surgery in adults.

EVIDENCE SUMMARY

Despite the existence of a large number of studies and systematic reviews, there remain substantial limitations to the evidence regarding bariatric surgery. Differences in patient characteristics, choice of surgical procedure, and individual components and intensity of non-surgical management arms make it difficult to summarize effects across studies. Variable measures of weight loss and wide variation in definitions of remission or resolution of comorbid conditions pose additional problems. Many of the studies included in the reviews were non-comparative, and the comparative observational studies suffer from risk of bias related to patient selection and residual confounding. The data from RCTs is limited by questions regarding proper allocation concealment and the universal absence of blinding. Perhaps the greatest concern is the limited long term follow-up of patients from RCTs and incomplete outcomes data due to high rates of attrition in most studies.

Overall, the following conclusions can be drawn based on review of the summary literature:

1. Bariatric surgery is associated with lower rates of all-cause mortality and major adverse cardiovascular events in adults, despite a short term increased risk of perioperative mortality and complications (based on low certainty evidence from cohort studies with long term follow-up, with study populations consisting predominantly of patients with BMI ≥35).
2. Bariatric surgery is associated with significant reductions in BMI in adults, despite a short term increased risk of perioperative mortality and complications (based on moderate certainty evidence from a mix of observational and randomized trials). The effects on weight loss appear to be greatest in patients with baseline BMI ≥40 based on the BMI stratification provided in the WA HTA report.
3. Bariatric surgery is associated with remission or resolution of T2DM and hypertension in adults with BMI ≥ 35, despite a short term increased risk of perioperative mortality and complications (based on moderate certainty evidence from a mix of observational and randomized trials).
    - The effects on remission of T2DM appear to be greatest in patients with baseline BMI ≥40 based on the BMI stratification provided in the WA HTA report.
    - Preliminary evidence suggests that adults with BMI < 35 may also achieve significant reductions in BMI and improvement in comorbid T2DM and hypertension, though the long term effects are not yet clear.
4. Bariatric surgery is associated with significant reductions in BMI in children and adolescents, despite a short term increased risk of perioperative mortality and complications (based on low certainty evidence primarily from small, non-comparative observational trials of bariatric surgery for pediatric obesity).

5. Bariatric surgery is associated with remission or resolution of T2DM and hypertension in children or adolescents, despite a short term increased risk of perioperative mortality and complications (based on very low certainty evidence from a small number of trials).
6. There is no evidence-based minimum age recommendation for pediatric bariatric surgery. Patients as young as five years old were included in the studies reported in the summary literature.
7. There is low certainty conflicting evidence on the effects of preoperative weight loss requirements.
8. The obesity surgery mortality risk score (OR-MRS) is a validated preoperative assessment of perioperative mortality risk (particularly for RYGB procedures) and may be useful in selecting patients for surgery or counseling them on surgical risks.
9. Harms of bariatric surgery include a perioperative mortality rate that probably ranges from 0.10 to 2%, and an overall complication rate that is probably on the order of 8 to 25%. The estimated reoperation rate is likely between 2 and 13%. There is limited evidence from a single study that comorbid congestive heart failure, cardiac arrhythmias, and peripheral vascular disease are associated with higher rates of complications after bariatric surgery.
10. There is low certainty evidence that surgeon experience is associated with improved outcomes and very low certainty evidence that hospital bariatric surgical volume is associated with improved outcomes.
11. There is very low certainty evidence that revisional or conversion procedures performed after an initial bariatric surgery may achieve additional weight loss (particularly those procedures that convert AGB to RYGB or BPD/DS), but at the expense of a higher rate of complications. Systematic reviews offer no evidence that bariatric reoperation improved co-morbidity resolution.

OTHER DECISION FACTORS

Resource allocation

Bariatric surgery for adults is costly, but improved outcomes compared with non-surgical management may offset these costs. The WA HTA report cites total costs of bariatric surgical procedures as ranging from $17,483 for gastric banding to $36,160 for biliopancreatic diversion. By comparison, standard non-surgical care has a reported total cost of $3,746. Accounting for reductions in BMI, resolution of comorbid conditions, and complications of surgery and projecting costs and effectiveness over a 10-year horizon, bariatric surgical procedures are uniformly cost-effective at a willingness-to-pay threshold of $100,000 per QALY gained. This was true across BMI thresholds and surgical procedures. Excerpts from the economic analysis in the WA HTA report are provided in Appendix H.

Bariatric surgery for children is also costly, but improved outcomes may offset these costs, and the beneficial effects could accrue over the longer time horizon afforded by earlier intervention in children and adolescents. However, there is very limited evidence of cost-effectiveness of pediatric bariatric surgery. The pediatric cost-effectiveness information included in the review by Aikenhead et al. in 2011 used assumptions from Australia that are likely too indirect to influence deliberations on resource allocation.

Reoperations for additional weight loss are sometimes requested; a second high cost procedure (tens of thousands of dollars), with a history of prior failure is unlikely to show a favorable cost-effectiveness ratio.

Values and preferences

Adults

Most people would prefer to avoid surgery and its attendant risks if similar results could be attained through safer and less invasive interventions. However, patients who have failed to achieve adequate weight loss with less invasive interventions may decide that the superior outcomes of bariatric surgery (including long term improvements in all-cause mortality, complete remission of diabetes, and significant weight loss) outweigh the upfront risks of surgery. Overall, there would be a moderate variability given these considerations.

Children and adolescents

Similar to adults, most children and their parents would prefer to avoid surgery and its attendant risks if similar results could be attained through safer and less invasive interventions. However, patients who may have failed to achieve adequate weight loss with less invasive interventions may decide that bariatric surgery offers the best chance at weight reduction. The significant social pressures of obesity at a young age may also push children and their parents to have strong interest in an effective treatment. Children though would likely have a great fear of surgery and the associated procedures and loss of social/academic participation. However, additional uncertainties related to malnutrition in this age group and its effects on growth, development, and reproductive capacity may make surgery less appealing in children and adolescents (to their caregivers). Long term remission rates of morbid obesity and recurrence of the comorbidities are unknown; most studies report outcomes at one year, although a few studies report outcomes at up to three years. Given these considerations, there would be high variability in children's and parents preferences.

Re-operations for inadequate weight loss

There would be high variability in patient preferences regarding reoperation. With a prior failure of the procedure, some patients would be hesitant to try an additional procedure given the burdens of surgery and prior ineffectiveness, but others would be motivated to try a different procedure in hopes that it would work. Patients seeking reoperation likely have no other good option given failure of multiple previous alternatives (e.g. clinical, pharmacological, nutritional, physical activity, surgical).

Other factors

Adults

The greatest health benefits may be with BMI ≥ 40 but otherwise specific subpopulations which would benefit the most from bariatric surgery are not well characterized.

The pre-operative requirements for achieving optimal outcomes are unclear.

Given the rate of complications and need for reoperation reported in the summary literature, benefit plans may wish to consider alternative payment methodologies like bundled payments or a pay-for-outcomes approach.

Surgeon case volume, and to a lesser extent hospital case volume, appear to affect outcomes for patients undergoing bariatric surgery and requirements regarding surgeon or facility volume may be reasonable.

Children and adolescents

Parental involvement in weight management plans is likely necessary to assist the effectiveness of obesity treatments (based on expert opinion).

Pediatric bariatric surgery is likely to be available at only a few highly specialized centers. The American Academy of Pediatrics has 10 criteria that pediatric bariatric surgery programs should meet.

Re-operations for inadequate weight loss

It is unclear from the evidence which modifiable patient factors that resulted in surgical failure would predict a high likelihood of success or failure of a second procedure.

POLICY LANDSCAPE SOURCES

Quality measures

One bariatric surgery-specific quality measure was identified when searching the National Quality Measures Clearinghouse:

- Prevention and management of obesity for adults: percentage of patients with a BMI greater than or equal to 40 who have been provided with a referral to a bariatric specialist (Institute for Clinical Systems Improvement)

Payer coverage policies

Medicare (National Coverage Determination [NCD] 100.1), Washington Medicaid, Aetna, Cigna, Regence Blue Cross Blue Shield, and Moda all provide coverage of bariatric surgery. Each coverage policy outlines specific coverage criteria that must be met prior to bariatric surgery being approved. These criteria are described below and provided in more detail in Appendix E.

Age

All six payers provide coverage of bariatric surgery for adults (defined as at least 18 years), and Aetna and Cigna additionally provides coverage for adolescents (defined as an individual with completed skeletal growth). Washington limits the procedure type to LAGB only for individuals aged 18 to 20 years.

Body Mass Index

For adults, Aetna, Cigna and Moda require individuals have a BMI of greater than or equal to 40 kg/m^2, or greater than or equal to 35 kg/m^2 with specific comorbidities. Washington and NCD 100.1 cover individuals with a BMI of greater than or equal to 35 kg/m^2 with comorbidities, and Regence BCBS requires that an individual have a BMI of greater than or equal to 40 kg/m^2 or a BMI of greater than, or equal to 35 kg/m^2 with type 2 diabetes or at least two other specified comorbidities. Washington is the only identified payer that explicitly requires individuals not be pregnant at the time of the surgery.

For adolescents, Aetna covers individuals with a BMI of greater than 40 kg/m^2 who have serious comorbidities, or individuals with a BMI of greater than 50 kg/m^2 with less serious comorbidities. Cigna uses the same BMI criteria as the adult population.

Comorbidities

Diabetes is the only comorbidity specified by all five payers. Payers specify various combinations of other comorbid conditions including coronary heart disease, dyslipidemia, hypertension, lower extremity lymphatic or venous obstruction, mechanical arthopathy in major weight bearing joint, rare comorbid conditions (e.g., pseudo tumor cerebri), and obstructive sleep apnea. Aetna specifies several less severe comorbidities for adolescents with a BMI of over 50 including gastroesphageal reflux disease, intertriginous soft-tissue infection, nonalcoholic steatohepatitis, obesity-related psychosocial distress, significant impairments in daily living, and stress urinary incontinence.

Pre-Surgical Requirements

Five payers require individuals to undergo a comprehensive psychosocial evaluation and participate in a formal weight loss program prior to being approved for bariatric surgery (Aetna, Cigna, Moda, Regence BCBS, and Washington). Three payers require a separate medical evaluation (Washington, Cigna, Moda), surgical evaluation (Washington, Cigna), and nutritional evaluation (Cigna, Moda) prior to surgery. The NCD 100.1 requires that individuals have been previously unsuccessful with medical treatment for obesity.

Payers require an individual attend a formal weight loss program within six months (Washington) to two years of surgery (Aetna, Regence BCBS, Moda). The weight loss program must be greater than or equal to three (Cigna) to six months in duration (Washington, Aetna, Regence BCBS, Moda). Both Washington and Moda require that individuals lose 5% of their initial body weight as part of the weight loss program prior to surgery. Aetna's policy states that there can be no net weight gain during weight loss program attendance. Payer coverage policies include a variety of additional required program components including counseling by a registered dietitian, patient journal of participation, regular face-to-face provider visits, behavior modification, supervised exercise regimen, and hypocaloric diet changes.

Provider Requirements

Washington Medicaid and Moda state that bariatric surgery is only covered if provided by an approved facility, defined by Moda as a Center of Excellence and by Washington with specific criteria. Bariatric surgery facilities approved by Washington Medicaid must have performed a minimum of 100 bariatric surgical procedures, be under the direction of an experienced board-certified surgeon, been in operation for at least five years, have a 2% or less mortality rate, have a 15% or less morbidity rate, have at least five years of patient follow-up data, have an average of at least 50% patient weight loss at five years, and have a reoperation/revision rate of 5% or less.

The Centers for Medicaid and Medicare have approved six facilities in Oregon to perform bariatric surgery: Bay Area Hospital, Legacy Good Samaritan Hospital and Medical Center, Oregon Health & Science University, Sacred Heart Medical Center, Salem Hospital, St. Charles Medical Center – Bend.

Repeat Surgery Coverage

Aetna, Cigna and Regence BCBS address repeat bariatric surgery and outline specific circumstances under which it is covered. All three payers provide coverage to correct complication from the initial surgery, and conversion from gastric banding to sleeve gastrectomy, RYGB or BPD/DS. Aetna and Cigna specify that conversion surgery is covered for individuals who have not lost more than 50% of their body weight two years following the primary bariatric surgery. Cigna will cover the adjustment of the silicone gastric band and repeat surgery for a failed dilation of a gastric pouch. Aetna will additionally cover removal of a gastric band, replacement of adjustable band, and repeat surgery for a failed dilation of a gastric pouch.

Non-Covered Procedures

Aetna, Cigna, and Regence BCBS outline specific conditions and procedures that are not in the coverage of bariatric surgery. Across all three payers, gastroplasty ("stomach stapling"), laparoscopic gastric plication, mini gastric bypass, transoral endoscopic surgery (e.g., OverStich suturing device, StomaphX™, TOGA®), are not covered. In addition, Aetna and Cigna do not cover gastrointestinal liners (e.g., EndoBarrier™), intragastric balloon, loop gastric bypass, silastic ring vertical gastric bypass (e.g., Fobi pouch), or vagus nerve blocking. Aetna and Regence BCBS do not cover band over bypass surgeries, band or sleeve gastrectomy surgeries, sclerotherapy for the treatment of dilated gastrojejunostomy following bariatric surgery, or for gastroesophageal reflux disease in non-obese individuals. Cigna and Regence BCBS do not cover intestinal bypass (jejunoileal bypass) or restorative obesity surgery (e.g., ROSE). Regence BCBS specifically does not cover vertical banded gastroplasty; Aetna covers this procedure for members who are at increased risk of adverse consequences from Roux-en-Y gastric bypass due to certain gastrointestinal conditions (see Appendix E).

The NCD 100.1 does not provide coverage for open adjustable gastric banding, open sleeve gastrectomy, open and laparoscopic vertical banded gastroplasty, intestinal bypass surgery, and gastric balloon for treatment of obesity.

Professional society guidelines

Adults

The Institute for Clinical Systems Improvement (ICSI) (Fitch et al., 2013a) (good quality), Veterans Administration (VA) (Management of Overweight and Obesity Working Group, 2014) (good quality), the American Association of Clinical Endocrinologists, Obesity Society, American Society for Metabolic & Bariatric Surgery (Mechanick et al., 2013) (poor quality primarily), the Australian National Health and Medical Research Council (NHMRC) (NHMRC, 2013) (good quality), and the National Institute for Health and Care Excellence (NICE) (NICE, 2014) (good quality) provide recommendations on the use of bariatric surgery in adults. The guideline from the American Heart Association/American College of Cardiology/The Obesity Society (Jensen et al., 2014) (good quality) provides a summary of the evidence related to the long-term effectiveness of bariatric surgeries and the long-term effects of these procedures on varying BMI levels with and without comorbidities. The guideline does not provide clinical practice recommendations.

All identified guidelines consistently recommend bariatric surgery for individuals with a BMI of greater than 40 kg/m^2, or greater than 35 kg/m^{2}with significant comorbidities. There is some variance between guidelines in what comorbidities are considered significant. For example, only two of the five guidelines list gastroesophageal reflux disease as a significant comorbidity. Four guidelines (AACD/OS/ASMBS, ICSI, NHMRC, NICE) recommend bariatric surgery be considered for individuals with a BMI of greater than 30 kg/m^{2}who have severe comorbidities such as diabetes, and NICE recommends bariatric surgery for individuals of Asian descent with recent-onset diabetes who may have a lower BMI than other

populations. The VA determined that there was insufficient evidence to recommend the use of bariatric surgery for individuals with a BMI less than 35 kg/m^2.

The AACD/OS/ASMBS and NICE guidelines recommend individuals have pre-surgical comprehensive medical and psychological evaluations. The use of multidisciplinary teams consisting of surgical, medical, nutrition, and psychological expertise is recommended by NICE and NHMRC.

Children

The ICSI (Fitch et al., 2013b) (good quality), the Australian NHMRC (NHMRC, 2013), and NICE (NICE, 2014) provide recommendations on indications for bariatric surgery in the pediatric population. Both the ICSI and NHMRC guidelines recommend bariatric surgery as an option for adolescents with a BMI greater than 40, or greater than 35 with severe comorbidities. The NHMRC specifies that only laparoscopic gastric banding performed by a specialist bariatric/pediatric surgical team is recommended for adolescents. The guideline from ICSI is the most comprehensive and recommends detailed pre-surgical evaluations, failed attempts at weight loss through formal weight loss programs, and the use of multidisciplinary team at regional bariatric centers of excellence. ICSI further recommends that children have attained Tanner stage 4 or 5 or have bone age of ≥13 years in girls or ≥15 years in boys before considering bariatric surgery. Pediatric bariatric surgery is not recommended by NICE except in the case of exceptional circumstances.

Assessment of congruence between guidelines and evidence

In general, the clinical practice guideline recommendations for adults are supported by the available evidence. Patients with BMI ≥40 kg/m^2 or with BMI 35 to 39.9 with obesity-related comorbid conditions have been well studied in the literature, and the clinical practice guidelines reflect this stronger evidence base. The divergence in the recommendations for patients with BMI 30 to 34.9 probably reflects the smaller number of studies that specifically address this population and the shorter follow-up periods reported in these studies. Recommendations regarding pre-surgical evaluations may reflect expert practice tips, but are not directly supported by the summary literature. Similarly, recommendations regarding preoperative weight loss are based on expert opinion and are not directly supported by the summary literature.

The wider variation in the recommendations for bariatric surgery in children reflects greater uncertainty about both the effectiveness and the adverse effects of surgery. When surgery is recommended for children, there is general agreement based on expert opinion that this should be performed at regional centers of excellence.

REFERENCES

Evidence Sources

Aikenhead, A., Knai, C., & Lobstein, T. (2011). Effectiveness and cost-effectiveness of paediatric bariatric surgery: A systematic review. *Clinical Obesity, 1*(1), 12-25. DOI: 10.1111/j.1758-8111.2010.00003.x.

Black, J. A., White, B., Viner, R. M., & Simmons, R. K. (2013). Bariatric surgery for obese children and adolescents: a systematic review and meta-analysis. *Obesity Reviews, 14*(8), 634-644. DOI: 10.1111/obr.12037.

Brethauer, S. A., Kothari, S., Sudan, R., Williams, B., English, W. J., Brengman, M., … Morton, J. M. (2014). Systematic review on reoperative bariatric surgery. *Surgery for Obesity and Related Diseases, 10*(5), 952-972.

Chang, S. H., Stoll, C. R., Song, J., Varela, J. E., Eagon, C. J., & Colditz, G. A. (2014). The effectiveness and risks of bariatric surgery: an updated systematic review and meta-analysis, 2003-2012. *Journal of the American Medical Association Surgery*, *149*(3), 275-287. DOI: 10.1001/jamasurg.2013.3654.

Cheung, D., Switzer, N. J., Gill, R.S., Shi, X., & Karmali, S. (2014). Revisional bariatric surgery following failed primary laparoscopic sleeve gastrectomy: A systematic review. *Obesity Surgery, 24*(10), 1757-1763.

Coblijn, U. K., Verveld, C. J., van Wagensveld, B. A., & Lagard, S. M. (2013). Laparoscopic Roux-en-Y gastric bypass or laparoscopic sleeve gastrectomy as revisional procedure after adjustable gastric band—A systematic review. *Obesity Surgery, 23*(11), 1899-1914.

Colquitt, J. L., Pickett, K., Loveman, E., & Frampton, G. K. (2014). Surgery for weight loss in adults. *Cochrane Database of Systematic Reviews*, Issue 8. DOI: 10.1002/14651858.CD003641.pub4.

Elnahas, A., Graybiel, K., Farrokhyar, F., Gmora, S., Anvari, M., & Hong, D. (2013). Revisional surgery after failed laparoscopic adjustable gastric banding: A systematic review. *Surgical Endoscopy, 27*(3), 740-745.

Hayes, Inc. (2014). *Roux-en-Y gastric bypass for diabetes in obese and severely obese patients*. Lansdale, PA: Hayes.

Kwok, C. S., Pradhan, A., Khan, M. A., Anderson, S. G., Keavney, B. D., Myint, P. K., … Loke, Y. K. (2014). Bariatric surgery and its impact on cardiovascular disease and mortality: a systematic review and meta-analysis. *International Journal of Cardiology*, *173*(1), 20-28. DOI: 10.1016/j.ijcard.2014.02.026.

Mahawar, K. K., Graham, Y., Carr, W. R. J., Jennings, N., Schroeder, N., Balupuri, S., & Small, P. K. (2015). Revisional Roux-en-Y gastric bypass and sleeve gastrectomy: A systematic review of comparative outcomes with respective primary procedures. *Obesity Surgery, 25*(7), 1271-1280.

Muller-Stich, B. P., Senft, J. D., Warschkow, R., Kenngott, H. G., Billeter, A. T., Vit, G., … Nawroth, P. P. (2015). Surgical versus medical treatment of type 2 diabetes mellitus in nonseverely obese patients: a systematic review and meta-analysis. *Annals of Surgery, 261*(3), 421-9. DOI: 10.1097/SLA.0000000000001014.

Ochner, C. N., Dambkowski, C. L., Yeomans, B. L., Teixeira, J., & Xavier Pi-Sunyer, F. (2012). Pre-bariatric surgery weight loss requirements and the effect of preoperative weight loss on postoperative outcome. *International Journal of Obesity, 36*(11), 1380-1387. DOI: 10.1038/ijo.2012.60.

Puzziferri, N., Roshek, T. B., Mayo, H. G., Gallagher, R., Belle, S. H., & Livingston, E. H. (2014). Long-term follow-up after bariatric surgery: a systematic review. *Journal of the American Medical Association, 312*(9), 934-942. DOI: 10.1001/jama.2014.10706.

Schouten, R., Japink, D., Meesters, B., Nelemans, P. J., Greve, J. W. M. (2011). Systematic review of reoperations after gastric banding: Is a stepwise approach justified? *Surgery for Obesity and Related Diseases, 7*(1), 99-109.

Thomas, H., & Agrawal, S. (2012). Systematic review of obesity surgery mortality risk score: preoperative risk stratification in bariatric surgery. *Obesity Surgery, 22*(7), 1135-1140. DOI: 10.1007/s11695-012-0663-7.

Treadwell, J. R., Sun, F., & Schoelles, K. (2008). Systematic review and meta-analysis of bariatric surgery for pediatric obesity. *Annals of Surgery, 248*(5), 763-776. DOI: 10.1097/SLA.0b013e31818702f4.

Wang, M. C., Guo, X. H., Zhang, Y. W., Zhang, Y. L., Zhang, H. H., & Zhang, Y. C. (2015). Laparoscopic Roux-en-Y gastric bypass versus sleeve gastrectomy for obese patients with type 2 diabetes: a meta-analysis of randomized controlled trials. *American Surgeon, 81*(2), 166-71. PMID:25642879.

Washington State Health Care Authority Health Technology Assessment Program (WA HTA Report). (2015). *Bariatric surgery: Final evidence report*. Olympia, WA: Washington State Health Care Authority Health Technology Assessment Program. Retrieved from http://www.hca.wa.gov/hta/Documents/bariatric_final_rpt_040315.pdf

Zevin, B., Aggarwal, R., & Grantcharov, T. P. (2012). Volume-outcome association in bariatric surgery: a systematic review. *Annals of Surgery, 256*(1), 60-71. DOI: 10.1097/SLA.0b013e3182554c62.

Other Citations

Arterburn, D. E., Olsen, M. K., Smith, V., Livingston, E. H., Van Scoyoc, L., Yancy, W. S., … Maciejewski, M. L. (2015). Association between bariatric surgery and long-term survival. *Journal of the American Medical Association, 313*(1), 62-70. DOI: 10.1001/jama.2014.16968.

Finkelstein, E., Trogdon, J., Cohen, J., & Dietz, W. (2009). Annual medical spending attributable to obesity: payer- and service-specific estimates. *Health Affairs, 28*(5), 822-831.

Fitch, A., Everling, L., Fox, C., Goldberg, .J, Heim, C., Johnson, K., … Webb, B. (2013a). Institute for Clinical Systems Improvement. Prevention and Management of Obesity for Adults. Retrieved from https://www.icsi.org/_asset/s935hy/ObesityAdults.pdf

Fitch, A., Fox, C., Bauerly, K., Gross, A., Heim, C., Judge-Dietz, J., … Webb, B. (2013b). Institute for Clinical Systems Improvement. Prevention and Management of Obesity for Children and Adolescents. Retrieved from https://www.icsi.org/_asset/tn5cd5/ObesityChildhood.pdf

Jensen, M. D., Ryan, D. H., Apovian, C. M., Ard, J. D., Comuzzie, A. G., Donato, K. A., … Yanovski, S. Z. (2014). 2013 AHA/ACC/TOS guideline for the management of overweight and obesity in adults: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines and The Obesity Society. *Journal of the American College of Cardiology, 63*(25 Pt B), 2985-3023. Retrieved from http://dx.doi.org/10.1016/j.jacc.2013.11.004

Management of Overweight and Obesity Working Group. (2014). *VA/DoD clinical practice guideline for screening and management of overweight and obesity*. Washington (DC): Department of Veterans Affairs, Department of Defense. Retrieved from http://www.healthquality.va.gov/guidelines/CD/obesity/CPGManagementOfOverweightAndObesityFINAL041315.pdf

Mechanick, J. I., Youdim, A., Jones, D. B., Garvey, W. T., Hurley, D. L., McMahon, M. M., … Brethauer, S., American Association of Clinical Endocrinologists, Obesity Society, American Society for Metabolic & Bariatric Surgery. (2013). Clinical practice guidelines for the perioperative nutritional, metabolic, and nonsurgical support of the bariatric surgery patient--2013 update: cosponsored by American Association of Clinical Endocrinologists, the Obesity Society, and American Society for Metabolic & Bariatric Surgery. *Endocrine Practice, 19*(2), 337-72. DOI: 10.4158/EP12437.GL.

National Health and Medical Research Council. (2013). *Clinical practice guidelines for the management of overweight and obesity in adults, adolescents and children in Australia*. Melbourne (Australia): National Health and Medical Research Council. Retrieved from https://www.nhmrc.gov.au/_files_nhmrc/publications/attachments/n57_obesity_guidelines_140630.pdf

National Institute for Health and Care Excellence (NICE). (2014). *Obesity: Identification, assessment, and management of overweight and obesity in children, young people, and adults*. London: NICE. Retrieved from http://www.nice.org.uk/guidance/cg189/resources/guidance-obesity-identification-assessment-and-management-of-overweight-and-obesity-in-children-young-people-and-adults-pdf

Ogden, C., Carroll, M., Kit, B., & Flegal, K. (2014). Prevalence of Childhood and Adult Obesity in the United States, 2011-2012. *Journal of the American Medical Association, 311*(8), 806-814.

State of Oregon, Department of Human Services. (2012). *Oregon Overweight, Obesity, Physical Activity and Nutrition Facts*. Retrieved from https://public.health.oregon.gov/PreventionWellness/PhysicalActivity/Documents/Oregon_PANfactst_2012.pdf

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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.

APPENDIX A. METHODS

Scope Statement

Populations

Obese individuals who are being considered for bariatric or metabolic surgery

Population scoping notes: *Include <18. Exclude overweight (BMI<30)*

Interventions

Bariatric or metabolic surgery (Adjustable gastric banding, Roux-en-y gastric bypass, biliopancreatic diversion, duodenal switch, vertical sleeve gastrectomy)

Intervention exclusions: *Gastric balloon (not FDA approved)*

Comparators

Nonsurgical treatment (medical management, pharmacotherapy, intensive multicomponent behavioral interventions, behavioral counseling, structured weight management programs (e.g. Weight Watchers)

Outcomes

Critical: All-cause mortality, Major Cardiac Events (MACE)

Important**:** Resolution of hypertension, weight loss, resolution of type 2 diabetes

Considered but not selected for the GRADE table: Hyperlipidemia, arthritis, sleep apnea, CPAP use, medication use

Key Questions

1. Should coverage be recommended for bariatric surgery in each of the scenarios in the table below? (Note that the "resolution of diabetes" would not be an applicable outcome in scenarios 4-9)

	BMI 30-34.9	BMI 35-39.9	BMI>=40
With DM2	Scenario 1	Scenario 2	Scenario 3
W/o DM2 nor other comorbidities	Scenario 4*	Scenario 5*	Scenario 6*
w/o DM2 but with other comorbidities	Scenario 7*	Scenario 8*	Scenario 9*

*Resolution of type 2 diabetes isn't a relevant outcome for this population

2. What is the appropriate minimum age for bariatric surgery?

3. What components and systems of care are associated with improved health outcomes? (e.g., centers of excellence, surgeon's experience, etc.)
4. What preoperative assessments or requirements for preoperative weight loss should be recommended in patients being considered for bariatric surgery?

Search Strategy

A full search of the core sources was conducted to identify systematic reviews, meta-analyses, technology assessments, and clinical practice guidelines using the terms "bariatric." Searches of core sources were limited to citations published after 2004 with one exception (see inclusion criteria).

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 (WA HTA)

A recent technology assessment from the WA HTA program was identified as the most comprehensive review identified (WA HTA, 2015). A MEDLINE® (Ovid) search was then conducted to identify systematic reviews, meta-analyses, and technology assessments published after the search dates of the WA HTA report. The search was limited to publications in English published after 2014 (the end search date for the WA HTA systematic review).

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

Due to the volume of available literature related to the effectiveness of bariatric surgery in adults (Key Question #1), reviews were limited to those published after 2013. Center staff dual quality assessed the identified reviews and only included those that were rated as good quality.

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, or clinical practice guidelines. The following systematic review was excluded because it only included studies that were found in the other systematic reviews:

Ashrafian, H., Toma, T., Rowland, S. P., Harling, L., Tan, A., Efthimiou, E., … Athanasiou, T. (2014). Bariatric surgery or non-surgical weight loss for obstructive sleep apnoea? A systematic review and comparison of meta-analyses. *Obesity Surgery, 25*(7), 1239-50. DOI: 10.1007/s11695-014-1533-2.

APPENDIX B. 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 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.

[1] Includes risk of bias, precision, directness, consistency and publication bias

***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 C. GRADE EVIDENCE PROFILE

Quality Assessment (Confidence in Estimate of Effect) – Adults							
No. of Studies	**Study Design(s)**	**Risk of Bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other Factors**	**Quality**
All-cause Mortality[1]							
14	Cohort	Moderate	Consistent	Direct	No serious imprecision	Large effect size	Low confidence in estimate of effect ●●○○
Major Adverse Cardiovascular Events[1]							
4	Cohort	Moderate	Consistent	Direct	No serious imprecision	Large effect size	Low confidence in estimate of effect ●●○○
Type 2 DM Remission/Resolution[2]							
60	15 RCTs; 45 observational studies	Moderate to High	Consistent	Direct	Imprecise	None	Moderate confidence in estimate of effect ●●●○
Hypertension Remission/Resolution[2]							
52	13 RCTs; 39 observational studies	Moderate	Consistent	Direct	Imprecise	None	Moderate confidence in

Quality Assessment (Confidence in Estimate of Effect) – Adults							
No. of Studies	**Study Design(s)**	**Risk of Bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other Factors**	**Quality**
							estimate of effect ●●●○
Change in BMI[2]							
101	28 RCTs; 73 observational studies	Moderate to High	Consistent	Direct	Imprecise	None	Moderate confidence in estimate of effect ●●●○

[1] Studies from Tables 1 and 2(Kwok, 2014). Strength of evidence assessment based on Table 2 in Kwok (2014).

[2]Studies and strength of evidence assessment based on Figure 2 of Colquitt (2014), Supplemental Table 1 of Muller-Stich (2015), and the description of study quality from the WA HTA review (2015, p.27-28). Chang (2014) does not provide individual study risk of bias assessments.

Quality Assessment (Confidence in Estimate of Effect) – Children and Adolescents							
No. of Studies	**Study Design(s)**	**Risk of Bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other Factors**	**Quality**
All-cause Mortality							
0	NA	NA	NA	NA	NA	NA	Insufficient evidence
Major Adverse Cardiovascular Events							
0	NA	NA	NA	NA	NA	NA	Insufficient evidence

Quality Assessment (Confidence in Estimate of Effect) – Children and Adolescents							
No. of Studies	**Study Design(s)**	**Risk of Bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other Factors**	**Quality**
Type 2 DM Remission/Resolution[1]							
13	13 observational studies	High	Consistent	Direct	Imprecise	None	Very low confidence in estimate of effect ●○○○
Hypertension Remission/Resolution[1]							
15	15 observational studies	High	Consistent	Direct	Imprecise	None	Very low confidence in estimate of effect ●○○○
Change in BMI[1]							
28	1 RCT; 27 observational studies	High	Consistent	Direct	Imprecise	None	Low confidence in estimate of effect ●●○○

[1] Studies from Black (2013) and Treadwell (2008).

APPENDIX D. MORTALITY BENEFIT OUTCOMES FROM KWOK (2014) SYSTEMATIC REVIEW AND META-ANALYSIS

Several large cohort studies with long-term follow-up comparing bariatric surgery patients to non-surgical controls have demonstrated a consistent reduction in all-cause mortality (as summarized in the meta-analysis in Kwok 2014). In the included cohort studies that performed direct subgroup analysis by BMI, the effects of bariatric surgery appear to be stronger in patients with higher BMI, though other cohorts that report proportional hazard ratios using BMI of 35-40 kg/m2 as the reference find increasing mortality in BMI groups >40. Only two of the cohorts reported outcomes by baseline comorbidities. In the Swedish Obese Subjects study (Sjostorm, 2012), patients with T2DM may have benefited more than those without T2DM, while patients with SBP <140 may have benefited more than hypertensive patients; however, in both scenarios the 95% confidence intervals overlap. It should be noted that Sjostrom reported on the incidence of cardiovascular events rather than mortality and that 70% of the patients received vertical banded gastroplasty, a procedure that is no longer used in the United States. Scott (2013) reports on a cohort of bariatric patients compared to matched controls undergoing either orthopedic or gastrointestinal procedures. There were no significant differences based on the presence of HTN in either group or T2DM in the bariatric-orthopedic comparison; among T2DM patients in the bariatric-GI comparison, there was a slight increase in the proportional hazard of mortality. Two other cohort studies (Arterburn, 2013 and Johnson, 2013) only included patients with T2DM at baseline.

Caution should be exercised in interpreting subgroup analyses from these cohorts given the potentially small number of patients involved. Individual studies with pre-specified inclusion criteria based on comorbidities are more likely to provide accurate estimates of the effects in these groups. On balance, there is insufficient evidence from these cohort studies to conclude that the effects of bariatric surgery on long-term mortality vary based on pre-operative BMI or the presence of comorbid conditions.

Studies in the table below were reviewed in the following article: Kwok, C. S., Pradhan, A., Khan, M. A., Anderson, S. G., Keavney, B. D., Myint, P. K., … Loke, Y. K. (2014). Bariatric surgery and its impact on cardiovascular disease and mortality: a systematic review and meta-analysis. International Journal of Cardiology, 173(1), 20-28. DOI: 10.1016/j.ijcard.2014.02.026

Study	Population (surgical group)	Overall effect of surgery on mortality (95% CI)	Effect of surgery on mortality by BMI (95% CI)	Mortality effect by comorbidities (95% CI)
Adams (2007) Matched retrospective cohort	9,949 adults RYGB Avg BMI 44.9	HR 0.63 (0.53 to 0.74) (all subjects) HR 0.60 (0.45 to 0.67) (matched subjects)	BMI<45 HR 0.72 (0.53 to 0.99) BMI >45 HR 0.56 (0.43 to 0.74)	NR
Arterburn (2013) Retrospective cohort	1,395 adults 80% RYGB BMI>35 and T2DM	HR 0.54 (0.22 to 1.30)	NR	NR
Busetto (2007) Matched cohort	821 adults LAGB BMI>40	RR 0.36 (0.16 to 0.79)	BMI 40-49 RR 0.67 (0.23 to 1.94) BMI>50 RR 0.21 (0.21 to 0.75)	NR
Christou (2004) Retrospective cohort	1,035 adults RYGB Mean BMI 50.0	RR 0.11 (0.04 to 0.27)	NR	NR
Flum (2004) Retrospective cohort	3,328 adults Any gastric bypass "Morbidly obese" (by ICD codes) 13% T2DM	HR 0.67 (0.54 to 0.85)	NR	NR
Gentileschi (2012) Prospective cohort	208 adults RYGB, VSG, AGB Avg BMI 46.6 31% T2DM, 48% HTN	1/208[i] (surgical group) 4/81 (non-surgical group)	NR	NR

BMI=Body mass index (reported in kg/m^2), CAD=Coronary artery disease, HR=Hazard ratio, HTN=Hypertension, LAGB=Laparoscopic Adjustable gastric banding, NR=Not reported, RR=Relative risk,

Johnson (2013) Retrospective cohort	2,580 adults with T2DM Any bariatric surgery Avg BMI 47 82% HTN, 8.6% CAD	41/2580[ii] (surgical group) 985/13,371 (non-surgical group)	NR	NR
Maciejewski (2011) Retrospective cohort	850 adults (Vets) RYGB Avg BMI 47	HR 0.64[iii] (0.51 to 0.80)	BMI 35-39 HR 1.0 (reference)[iv] BMI 40-49 HR 1.22 (1.16 to 1.27) BMI >50 HR 1.71 (1.59 to 1.85)	NR
Miranda (2012) Retrospective cohort	2,020 adults 95% RYGB Avg BMI 49	HR 0.76 (0.60 to 0.96)	NR	NR
Peeters (2007) Prospective cohort	966 adults LAGB Avg BMI 45	HR 0.28 (0.10 to 0.85)	BMI <40 HR 0.89 BMI >40 HR 0.16	NR
Scott (2013) Retrospective Cohort	4,747 adults Any bariatric surgery "Morbid obesity" (by ICD codes) 41% T2DM, 71% HTN, 5% CAD	HR 0.72 compared to matched ortho surgery pts (0.58 to 0.89) HR 0.48 compared to matched GI surgery pts (0.39 to 0.61)	NR	Bariatric-ortho[v] HTN HR 1.02 (0.8 to 1.4) T2DM HR 1.14 (0.9 to 1.5) Bariatric-GI HTN HR 0.79 (0.6 to 1.1) T2DM HR 1.49 (1.1 to 2.0)

RYGB=Roux-en-Y gastric bypass, SBP=Systolic blood pressure (reported in mmHg), T2DM=Type 2 diabetes mellitus, VSG=Vertical sleeve gastrectomy

[i] Reported as crude event rates

[ii] Reported as crude event rates

Sjostrom (2012) Prospective cohort	2,010 adults 70% gastroplasty	HR 0.83[vi] (0.69 to 1.00)	BMI <40.8 HR 0.91 (0.70 to 1.18) BMI >40.8 HR 0.8 (0.60 to 1.06)	T2DM HR 0.63 (0.45 to 0.90) No TD2M HR 0.84 (0.67 to 1.06) SBP<140 HR 0.63 (0.46 to 0.86) SBP>140 HR 0.82 (0.64 to 1.04)
Sowemimo (2007) Retrospective cohort	908 adults Nearly all RYGB BMI>40 or >35 with comorbidities Mean BMI 54	HR 0.18 (0.09 to 0.35)	NR	NR

[iii] Reported after unadjusted Cox regression; after adjustment for covariates, the HR was 0.80 (95% CI 0.63 to 0.995). An analysis of propensity matched patients resulted in a HR of 0.83 (95% CI 0.61 to 1.14).

[iv] Reported as adjusted Cox proportional hazards

[v] Reported as Cox proportional hazards

[vi] Primary outcome in Sjostrom was not mortality but incidence of CV events (included here because of its analysis by comorbidity)

[vii] Reported as adjusted Cox proportional hazards

APPENDIX E. BARIATRIC SURGERY COVERAGE

Table E1. Bariatric Surgery Coverage – Adults

Coverage criteria	Payer				
	Washington Medicaid	Aetna[1]	Cigna[2]	Regence BCBS[3]	Moda
Patient Characteristics					
Age	18 – 20 yrs (LAGB obly) 21 – 59 yrs (all procedures)	≥ 18 yrs	≥ 18 yrs	≥ 18 yrs	≥ 18 yrs
BMI	≥ 35 with comorbidities 30-34.9 with DM2 (*see below*)	> 40 > 35 with comorbidities (*see below*)	≥ 40 ≥ 35 with comorbidities (*see below*)	≥ 40 ≥ 35 with DM2 or at least two other comorbidities (*see below*)	≥ 40 ≥ 35 with comorbidities (*see below*)
Not pregnant	√	---	---	---	---
Comorbidities					
Coronary heart disease	---	√	√	√	√
Diabetes	√	√	√	√	√
Dyslipidemia	---	---	√	√	---
Hypertension	---	√	√ (poorly controlled or pulmonary)	√	√
Lower extremity lymphatic or venous obstruction	---	---	√	---	---
Mechanical arthopathy in major weight bearing joint	√	---	√	---	√
Rare comorbid conditions (e.g., pseudo tumor cerebri)	√[4]	---	---	---	---
Sleep apnea	---	√	√	√	√
Absence of other medical conditions (e.g., multiple sclerosis)	√	---	---	---	√

Key: √ – required; --- – not in policy description

Abbreviations: BCBS – Blue Cross Blue Shield; BMI – body mass index; LAGB – laparoscopic adjustable gastric banding; yrs – years

Notes:

1. Specific to open or laparoscopic Roux-en-Y gastric bypass (RYGB), laparoscopic adjustable silicone gastric banding (LASGB), open or laparoscopic sleeve gastrectomy, open or laparoscopic biliopancreatic diversion (BPD), and duodenal switch (DS).
2. Specific to open or laparoscopic Roux-en-Y gastric bypass, open or laparoscopic adjustable silicone gastric banding (LAP-BAND®, REALIZE™), open or laparoscopic biliopancreatic diversity with duodenal switch (BPD/DS) for individuals with a BMI >50, open or laparoscopic sleeve gastrectomy, open or laparoscopic vertical banded gastroplasty
3. Roux-en-Y with an alimentary limb of 150 cm or less, sleeve gastrectomy as a stand-alone procedure, or adjustable gastric banding
4. Must be medical evidence that bariatric surgery is medically necessary and that the benefits of bariatric surgery outweigh the risk of surgical mortality

Table E2. Bariatric Surgery Coverage – Children

Coverage criteria	Payer	
	Aetna[1]	**Cigna**[2]
Patient Characteristics		
Age	Adolescents who have completed bone growth (~13 yrs in girls, ~15 yrs in boys)	Reached full expected skeletal growth
BMI	> 40 with serious comorbidities > 50 with less serious comorbidities	≥ 40 ≥ 35 with comorbidities
Comorbidities		
Coronary artery disease	---	√
Diabetes	√ (>40 BMI)	√
Dislipidemias	√ (> 50 BMI)	√
Gastroesophageal reflux disease	√ (> 50 BMI)	---
Hypertension	√ (> 50 BMI)	√ (poorly controlled or pulmonary)
Intertriginous soft-tissue infection	√ (> 50 BMI)	---
Mechanical arthropathy in a major weight bearing joint	√ (> 50 BMI)	√
Nonalcoholic steatohepatitis	√ (> 50 BMI)	---
Obesity-related psychosocial distress	√ (> 50 BMI)	---
Rare comorbid conditions (e.g., pseudo tumor cerebri)	√ (>40 BMI)	---
Significant impairments in daily living	√ (> 50 BMI)	---
Sleep apnea	√ (>40 BMI)	√
Stress urinary incontinence	√ (> 50 BMI)	---
Venous stasis disease	√ (> 50 BMI)	√

Key: √ – required; --- – not in policy description Abbreviations; BMI – body mass index; yrs - years

Notes:

1. Specific to open or laparoscopic Roun-en-Y gastric bypass (RYGB), laparoscopic adjustable silicone gastric banding (LASGB), open or laparoscopic sleeve gastrectomy, open or laparoscopic biliopancreatic diversion (BPD), and duodenal switch (DS)
2. Specific to open or laparoscopic Roux-en-Y gastric bypass, open or laparoscopic adjustable silicone gastric banding (LAP-BAND®, REALIZE™), open or laparoscopic biliopancreatic diversity with duodenal switch (BPD/DS) for individuals with a BMI >50, open or laparoscopic sleeve gastrectomy, open or laparoscopic vertical banded gastroplasty

Table E3. Pre-Surgical Requirements

Coverage criteria	Payer				
	Washington Medicaid	**Aetna[1]**	**Cigna[4]**	**Regence BCBS**	**Moda**
Patient Evaluation					
Comprehensive psychosocial evaluation	√[2]	√[3]	√	√	√
Internal medicine evaluation	√	---	√	---	√
Surgical evaluation	√	---	√	---	---
Nutrition evaluation	---	---	√	---	√
Weight Loss Program					
Required	√	√ (physician-supervised *or* multi-disciplinary surgical prep regimen)	√ (physician- or registered dietician-supervised)	√ (physician-supervised)	√
Timing	Within 180 days of surgery	Within 2 years of surgery (physician-supervised) Within 6 months of surgery (surgical prep regimen)	Within 1 year of surgery	Within 2 years of surgery	Within 2 years of surgery
Duration	≥ 6 months	Cumulative total ≥ 6 months, one program ≥ 3 months (physician-supervised) ≥ 3 months (surgical prep regimen)	≥ 3 months	≥ 6 months	≥ 6 months
Required weight loss	5% of initial body weight	No net weight gain during program	---	----	5% of initial body weight over 6 months

Coverage criteria	Payer				
	Washington Medicaid	Aetna[1]	Cigna[4]	Regence BCBS	Moda
Program Components	Supervised by licensed provider; monthly provider visits; 2x/month counseling by a registered dietitian; patient journal of participation	Physician-supervised: medical record documentation with program compliance record; supervised nutrition and exercise program must have face-to-face component Surgical Prep Regimen: Behavior modification program; dietician or nutritionist consultation; medical record documentation; supervised exercise regimen; substantial face-to-face component; reduced-calorie diet supervised by a dietitian or nutritionist	---	Three visits for medical supervision (no more than 4 months apart); provided by MD, DO, NP, PA, or RD under supervision of MD, DO, NP or PA; assessment and counseling on weight, diet, exercise and behavior modification; clinical documentation of willingness to comply with pre- and post-operative treatment plan	Hypocaloric diet changes, nutritional education, physical activity, behavior change strategies; three or more primary care visits; completion of a 8-week health education, weight management program

Key: √ – required; --- – not in policy description

Abbreviations: DO – doctor of osteopathy; MD – medical doctor; NP – nurse practitioner; PA – physician assistant; RD – registered dietician

Notes:

1. Specific to open or laparoscopic Roun-en-Y gastric bypass (RYGB), laparoscopic adjustable silicone gastric banding (LASGB), open or laparoscopic sleeve gastrectomy, open or laparoscopic biliopancreatic diversion (BPD), and duodenal switch (DS)
2. Provider must be a psychiatrist, licensed psychiatric ARNP, or licensed independent social worker with a minimum of two years postmasters' experience in a mental health setting
3. For members who have a history of severe psychiatric disturbance (schizophrenia, borderline personality disorder, suicidal ideation, severe depression) or who are currently under the care of a psychologist/psychiatrist or who are on psychotropic medications
4. Specific to open or laparoscopic Roux-en-Y gastric bypass, open or laparoscopic adjustable silicone gastric banding (LAP-BAND®, REALIZE™), open or laparoscopic biliopancreatic diversity with duodenal switch

(BPD/DS) for individuals with a BMI >50, open or laparoscopic sleeve gastrectomy, open or laparoscopic vertical banded gastroplasty

Table E4. Facility Requirements

Approved Facility Requirements	Payers Washington Medicaid
Minimum number of bariatric surgical procedures performed	100
Direction	Experience board-certified surgeon
Time in operation	≥ 5 years
Mortality rate	≤ 2%
Morbidity rate	≤ 15%
Patient follow-up	≥ 5 years
Average patient weight loss at 5 years	≥ 50%
Reoperation/revision rate	≤ 5%

Table E5. Repeat Surgery Coverage

Circumstances	Payers		
	Aetna	Cigna	Regence BCBS
Adjustment of silicone gastric band	---	√	---
Removal of gastric band	√	---	---
Correct complications	√	√	√
Conversion to sleeve gastrectomy, RYGB or BPD/DS	√[1, 2, 3]	√[2]	√
Failed dilation of gastric pouch after primary surgery	√[1] (if primary surgery was successful in inducing weight loss)	√	---
Replacement of adjustable band	√ (for complications)	---	---

Key: √ – covered; --- – not in policy description

Abbreviations: BPD – biliopancreatic diversion; DS – duodenal switch RYGB – Roux-en-Y gastric bypass;

Notes:

1. If patient has been compliant with a prescribed nutrition and exercise program following the procedure
2. For members who have not lost > 50% of body weight 2 years following primary surgery
3. Conversion from adjustable band to sleeve gastrectomy, RYGB or BPD/DS, for complications that cannot be corrected with band manipulation, adjustments or replacement

Table E6. Non-Covered Conditions and Procedures

	Payers		
	Aetna	**Cigna**	**Regence BCBS**
Conditions			
Idiopathic intracranial hypertension	X	---	---
Infertility	X	---	---
DM2 w/BMI <35	X	X[1]	
Gastroesophageal reflux in non-obese persons	X	---	X
Gastroparesis	X	---	---
Procedures			
Band over bypass	X	---	X
Band over sleeve	X	---	X
Roux-en-Y gastric bypass combined with simultaneous BPD without DS	---	X	---
Gastrointestinal liners (EndoBarrier™)	X	X	---
Gastroplasty ("stomach stapling")	X	X	X
Intragastric balloon	X	X	
Laparoscopic gastric plication	X	X	X
Loop gastric bypass	X	X	
Mini gastric bypass	X	X	X
Sclerotherapy for the treatment of dilated gastrojejunostomy following bariatric surgery	X	---	X
Silastic ring vertical gastric bypass (Fobi pouch)	X	X	---
Transoral endoscopic surgery (OverStitch suturing device or StomaphyX™ device)	X	X (including TOGA®)	X
Vagus nerve blocking	X	X	---
Gastric electrical stimulation or gastric pacing	---	X	---
Intestinal bypass (jejunoileal bypass)	---	X	X
restorative obesity surgery, endoluminal (ROSE)	---	X	X
Vagus nerve stimulation	---	X	---

Distal gastric bypass (long limb gastric bypass, >150 cm)	---	---	X
Biliopancreatic bypass (Scopinaro procedure)	---	---	X
Biliopancreatic bypass with duodenal switch	---	---	X
Two-stage procedures	---	---	X
Vertical banded gastroplasty	---	---	X
EndoCinch™	---	---	X

Key: √ – covered; X – not covered; --- – not in policy description

Notes:

1. Not covered when performed solely for treatment of diabetes mellitus
2. Specific requirements for vertical banded gastroplasty (members who are at increased risk of adverse consequences from Roux-en-Y Gastric bypass due to the presence of:
    - Demonstrated complications from extensive adhesions involving the intestines from prior major abdominal surgery, multiple minor surgeries, or major trauma
    - Hepatic cirrhosis with elevated liver function tests
    - Inflammatory bowel disease (Crohn's disease or ulcerative colitis)
    - Poorly controlled systemic disease
    - Radiation enteritis.

APPENDIX F. APPLICABLE CODES

CODES	DESCRIPTION
ICD-10	
E11.0 – E11.9	Diabetes, type 2
E66.01-E66.9	Overweight, Obesity and Morbid Obesity
G47.30 – G47.39	Sleep apnea
I10	Essential hypertension
ICD-9-CM Volume I Codes	
250.00, 250.02; 250.10, 250.12, 250.20, 250.22, 250.30, 250.32, 250.40, 250.42, 250.50, 250.52, 250.60, 250.62, 250.70, 250.72, 250.80, 250.82, 250.90, 250.92	Diabetes, Type II
278.00 – 278.03	Overweight, Obesity, and Morbid Obesity
327.20 – 327.29; 780.57	Sleep apnea
401.0 – 401.9	Hypertension
ICD-9-CM Volume III Codes	
43.82	Laparoscopic vertical (sleeve) gastrectomy
43.89	Open and other partial gastrectomy
44.31	High gastric bypass
44.38	Laparoscopic gastroenterostomy
44.5	Revision of gastric anastomosis
44.68	Laparoscopic gastroplasty
44.69	Other repair of stomach
44.95	Laparoscopic gastric restrictive procedure
44.96	Laparoscopic revision of gastric restrictive procedure
44.97	Laparoscopic removal of gastric restrictive device(s)
44.98	Laparoscopic) adjustment of size of adjustable gastric restrictive device

45.51	Isolation of segment of small intestine
45.91	Small-to-small intestinal anastomosis
CPT Codes	
43644	Laparoscopy, surgical, gastric restrictive procedure; with gastric bypass and Roux-en-Y gastroenterostomy (roux limb 150 cm or less)
43645	Laparoscopy, surgical, gastric restrictive procedure; with gastric bypass and small intestine reconstruction to limit absorption
43770	Laparoscopy, surgical, gastric restrictive procedure; placement of adjustable gastric restrictive device (e.g., gastric band and subcutaneous port components)
43771	Laparoscopy, surgical, gastric restrictive procedure; revision of adjustable gastric restrictive device component only
43772	Laparoscopy, surgical, gastric restrictive procedure; removal of adjustable gastric restrictive device component only
43773	Laparoscopy, surgical, gastric restrictive procedure; removal and replacement of adjustable gastric restrictive device component only
43774	Laparoscopy, surgical, gastric restrictive procedure; removal of adjustable gastric restrictive device and subcutaneous port components
43775	Laparoscopy, surgical, gastric restrictive procedure; longitudinal gastrectomy (i.e., sleeve gastrectomy)
43842	Gastric restrictive procedure, without gastric bypass, for morbid obesity; vertical-banded gastroplasty
43843	Gastric restrictive procedure, without gastric bypass, for morbid obesity; other than vertical-banded gastroplasty
43845	Gastric restrictive procedure with partial gastrectomy, pylorus-preserving duodenoileostomy and ileoileostomy (50 to 100 cm common channel) to limit absorption (biliopancreatic diversion with duodenal switch)
43846	Gastric restrictive procedure, with gastric bypass for morbid obesity; with short limb (150 cm or less) Roux-en-Y gastroenterostomy
43847	Gastric restrictive procedure, with gastric bypass for morbid obesity; with small intestine reconstruction to limit absorption
43848	Revision, open, of gastric restrictive procedure for morbid obesity, other than adjustable gastric restrictive device (separate procedure)
43886	Gastric restrictive procedure, open; revision of subcutaneous port component only
43887	Gastric restrictive procedure, open; removal of subcutaneous port component only
43888	Gastric restrictive procedure, open; removal and replacement of subcutaneous port component only

Note: Inclusion on this list does not guarantee coverage

HCPCS Level II Codes	
S2083	Adjustment of gastric band diameter via subcutaneous port by injection or aspiration of saline

APPENDIX G. OUTCOMES BY BASELINE MEAN BMI FROM THE WA HTA REPORT (P. 64-65)

Baseline Mean BMI Category									
		30-34.99		35-39.99		40-49.99		>50	
		Median	Range	Median	Range	Median	Range	Median	Range
% Decrease BMI	RYGB	25.4	(19.6-34.3)	26.0	(24.1-33.1)	32.2	(7.5-52.3)	34	(10.1-46.7)
	VSG	21.3	(21.3-21.3)	22.0	(19.1-22.5)	28.4	(15.0-37.1)	30.1	(11.0-39.4)
	LAGB	16.8	(11.8-21.7)	16.8	(13.0-17.5)	20.4	(6.0-46.8)	17.7	(1.0-31.8)
	BPD/DS	31.8	(17.3-46.3)			32.6	(15.9-50.8)	43.4	(39.2-47.7)
	Follow-up (months)	12.0	(3.0-45.2)	15.3	(12.0-60.0)	12.0	(0.5-120.0)	22.6	(1.2-84.0)
	No. Studies	7		6		79		22	
	Good/Fair/Poor	2/3/2		3/1/2		9/34/36		4/10/8	
% EWL	RYGB	70.0		77.0	(61.0-92.9)	67.0	(27.1-88.0)	61.8	(43.8-72.3)
	VSG			58.5	(51.0-66.0)	59.2	(30.7-83.0)	47.5	(25.4-75.0)
	LAGB	87.2		50.1	(34.0-62.5)	43.5	(18.2-78.8)	45.9	(31.0-73.0)
	BPD/DS					52.7	(34.9-70.4)	73.4	63.0-84.0)
	Follow-up (months)	18.0	(12.0-24.0)	30.0	(18.7-60.0)	24.0	(0.47-120)	24.0	(12.0-84.0)
	No. Studies	2		4		57		15	
	Good/Fair/Poor	1/0/1		1/1/2		6/27/24		1/8/6	
% Improvement Hypertension	RYGB			90.0		71.0	(22.0-100.0)	62.6	(60.7-69.2)
	VSG					64.3	(23.5-100.0)		
	LAGB			40.0		57.5	(18.0-100.0)	54.3	(33.3-66.7)
	BPD/DS	67.0				81.4	(68.6-87.0)	68.3	(66.7-69.9)
	Follow-up (months)	36.0		60.0		21.0	(3.5-84.0)	24.0	(12.0-50.4)
	No. Studies	1		1		29		5	
	Good/Fair/Poor	0/1/0		0/0/1		4/12/13		1/3/1	

Baseline Mean BMI Category									
		30-34.99		35-39.99		40-49.99		>50	
		Median	Range	Median	Range	Median	Range	Median	Range
% Improvement T2DM	RYGB	51.1	(33.0-92.3)	73.4	(66.7-80.0)	79.0	(33.0-100.0)	77.1	(40.0-100.0)
	VSG	50.0	(50.0-50.0)			77.3	(36.0-100.0)	88.9	(88.9-88.9)
	LAGB	33.0	(21.1-100.0)	50.0	(25.0-73.0)	50.0	(17.0-100.0)	52.3	(36.4-66.7)
	BPD/DS	84.8	(83.0-84.8)			87.1	(81.5-92.7)	91.4	(82.7-100.0)
	Follow-up (months)	12.0	(3.0-45.2)	24.0	(12.0-60.0)	16.0	(1.0-62.7)	24.0	(1.5-50.4)
	No. Studies	6		3		35		7	
	Good/Fair/Poor	0/3/3		2/0/1		3/14/18		1/4/2	
% Improvement Sleep Apnea	RYGB	89.0				70.5	(10.0-100.0)	56.7	(49.3-88.0)
	VSG					62.0	(6.0-99.0)		
	LAGB					29.0	(3.0-55.0)	46.2	(39.3-66.7)
	BPD/DS	90.0						79.5	(78.9-80.0)
	Follow-up (months)	45.15				21.6	(12.0-36.0)	20.1	(12.0-20.1)
	No. Studies	1		0		11		4	
	Good/Fair/Poor	0/0/1				2/5/4		1/3/0	
% Improvement Dyslipidemia	RYGB			100.0		64.5	(6.0-100.0)	52.9	(27.3-58.8)
	VSG					67.5	(35.0-67.5)		
	LAGB			38.0		36.5	(0.0-36.5)	34.4	(23.3-45.5)
	BPD/DS					90.0	(90.0-90.0)		
	Follow-up (months)			60.0		24.0	(12.0-62.7)	16.2	(12.0-50.4)
	No. Studies	0		1		18		3	
	Good/Fair/Poor	0		0/0/1		2/9/7		1/1/1	

APPENDIX H. COST-EFFECTIVENESS ESTIMATES FROM THE WA HTA REPORT (P. 80)

BMI Level/ Procedure	Cost ($)	Effectiveness (QALYs)	Cost-effectiveness ($/QALY gained)	
			Vs. SC	Vs. RYGB
BMI≥30				
Standard care	$34,923	7.5680	NA	NA
RYGB	$54,110	8.0807	$37,423	NA
VSG	$48,702	8.0417	$29,087	Less expensive & less effective
LAGB	$47,668	7.9252	$35,680	Less expensive & less effective
BPD/DS	$65,741	8.2307	$46,508	$77,574
BMI 30-34.9				
Standard care	$27,943	7.9418	NA	NA
RYGB	$49,735	8.3529	$53,021	NA
VSG	$44,298	8.3211	$43,122	Less expensive & less effective
LAGB	$42,738	8.2273	$51,826	Less expensive & less effective
BPD/DS	$61,410	8.4730	$63,011	$97,194
BMI 35-39.9				
Standard care	$32,538	7.6567	NA	NA
RYGB	$52,886	8.1351	$42,534	NA
VSG	$47,468	8.0986	$33,789	Less expensive & less effective
LAGB	$46,217	7.9898	$41,073	Less expensive & less effective
BPD/DS	$64,533	8.2751	$51,743	$83,224
BMI≥40				
Standard care	$40,329	7.2846	NA	NA
RYGB	$58,257	7.8630	$30,995	NA
VSG	$53,047	7.8194	$23,784	Less expensive & less effective
LAGB	$52,255	7.6882	$29,552	Less expensive & less effective
BPD/DS	$69,329	8.0322	$38,790	$65,431

BPD = biliopancreatic diversion; ICER = incremental cost-effectiveness ratio; LAGB = laparoscopic adjustable gastric banding; RYGB = Roux-en-Y gastric bypass; VSG = vertical sleeve gastrectomy.

NOTE: Because of rounding, performing calculations may not produce the exact results shown.

[i] Reported as crude event rates

[ii] Reported as crude event rates

[iii] Reported after unadjusted Cox regression; after adjustment for covariates, the HR was 0.80 (95% CI 0.63 to 0.995). An analysis of propensity matched patients resulted in a HR of 0.83 (95% CI 0.61 to 1.14).

[iv] Reported as adjusted Cox proportional hazards

[v] Reported as Cox proportional hazards

[vi] Primary outcome in Sjostrom was not mortality but incidence of CV events (included here because of its analysis by comorbidity)

Bariatric/Metabolic Surgery for Obesity

Issue: The HERC is reviewing treatments for obesity as part of its biennial review. The Health Technology Assessment Subcommittee (HTAS) has performed a detailed assessment of the evidence and developed a Draft Coverage Guidance on bariatric surgery for obesity. The Obesity Task Force can review the Draft Coverage Guidance recommendations and assist in discussing how this best should be implemented as part of the Prioritized List of Health Services.

Current Prioritized List Status:

Line: 30

Condition:	TYPE 2 DIABETES MELLITUS (See Coding Specification Below) (See Guideline Notes 8,62,64,65)
Treatment:	MEDICAL THERAPY, BARIATRIC SURGERY WITH BMI >= 35
ICD-10:	E08.00-E08.29,E08.311-E08.9,E09.00-E09.29,E09.311-E09.9,E11.00-E11.29,E11.311-E11.9,E13.00-E13.29,E13.311-E13.9,E16.1,Z46.51
CPT:	43644,43645,43770-43775,43846-43848,48155,64505-64530,90935-90947,90989-90997,92002-92014,92227,96150-96154,97605-97608,97802-97804,98960-98969,99051,99060,99070,99078,99184,99201-99239,99281-99285,99291-99404,99408-99416,99429-99449,99468-99480,99487-99498,99605-99607
HCPCS:	G0108,G0109,G0245,G0246,G0270,G0271,G0396,G0397,G0406-G0408,G0425-G0427,G0458,G0463,G0466,G0467,S2083,S9140-S9145,S9353,S9537

CPT codes 43644-43645 and 43846-43848 (Roux-En-Y gastric bypass) and 43770-43775 (laparoscopic adjustable gastric banding and sleeve gastrectomy) are only included on this line as treatment according to the requirements in Guideline Note 8 when paired with:

1) a primary diagnosis of E11 (Type II Diabetes with or without complication);
2) a secondary diagnosis of E66.01, E66.09, E66.2, E66.8 or E66.9 (Obesity); AND,
3) a tertiary diagnosis code of Z68.35-Z68.39 or Z68.4.

Line: 325

Condition:	OBESITY (ADULT BMI ≥ 30, CHILDHOOD BMI ≥ 95 PERCENTILE) (See Guideline Notes 5,64,65)
Treatment:	INTENSIVE NUTRITIONAL/PHYSICAL ACTIVITY COUNSELING AND BEHAVIORAL INTERVENTIONS
ICD-10:	E66.01-E66.9,Z68.30-Z68.45,Z68.54
CPT:	96150-96154,97802-97804,98966-98969,99051,99060,99070,99078,99201-99215,99281-99285,99341-99355,99358-99378,99381-99404,99408-99416,99429-99449,99487-99498
HCPCS:	G0396,G0397,G0447,G0463,G0466,G0467,G0473

Line: 589

Condition:	OBESITY (ADULT BMI ≥ 30, CHILDHOOD BMI ≥ 95 PERCENTILE) (See Guideline Notes 8,64,65)
Treatment:	NON-INTENSIVE NUTRITIONAL/PHYSICAL ACTIVITY COUNSELING AND BEHAVIORAL INTERVENTIONS; BARIATRIC SURGERY FOR OBESITY WITH A SIGNIFICANT COMORBIDITY OTHER THAN TYPE II DIABETES & BMI >=35 OR BMI>=40 WITHOUT A SIGNIFICANT COMORBIDITY
ICD-10:	E66.01-E66.9,Z68.30-Z68.45,Z68.54,Z71.3
CPT:	43644,43645,43770-43775,43846-43848,98966-98969,99051,99060,99070,99078,99201-99215,99281-99285,99341-99355,99358-99378,99381-99404,99408-99416,99429-99449,99487-99498,99605-99607
HCPCS:	G0396,G0397,G0447,G0463,G0466,G0467,G0473

Bariatric/Metabolic Surgery for Obesity

GUIDELINE NOTE 8, BARIATRIC SURGERY

Lines 30,589

Bariatric surgery is included under the following criteria:

A) Age ≥ 18
B) The patient has
   1) a BMI ≥ 35 with co-morbid type II diabetes for inclusion on Line 30 TYPE 2 DIABETES MELLITUS; OR
   2) BMI >=35 with at least one significant co-morbidity other than type II diabetes (e.g., obstructive sleep apnea, hyperlipidemia, hypertension) or BMI >= 40 without a significant co-morbidity for inclusion on Line 589
C) No prior history of Roux-en-Y gastric bypass or laparoscopic adjustable gastric banding, unless they resulted in failure due to complications of the original surgery.
D) Participate in the following four evaluations and meet criteria as described.
   1) Psychosocial evaluation: (Conducted by a licensed mental health professional)
      a) Evaluation to assess potential compliance with post-operative requirements.
      b) Must remain free of abuse of or dependence on alcohol during the six-month period immediately preceding surgery. No current use of nicotine or illicit drugs and must remain abstinent from their use during the six-month observation period. Testing will, at a minimum, be conducted within one month of the surgery to confirm abstinence from nicotine and illicit drugs.
      c) No mental or behavioral disorder that may interfere with postoperative outcomes[1].
      d) Patient with previous psychiatric illness must be stable for at least 6 months.
   2) Medical evaluation: (Conducted by OHP primary care provider)
      a) Pre-operative physical condition and mortality risk assessed with patient found to be an appropriate candidate.
      b) Optimize medical control of diabetes, hypertension, or other co-morbid conditions.
      c) Female patient not currently pregnant with no plans for pregnancy for at least 2 years post-surgery. Contraception methods reviewed with patient agreement to use effective contraception through 2nd year post-surgery.
   3) Surgical evaluation: (Conducted by a licensed bariatric surgeon associated with program[2])
      a) Patient found to be an appropriate candidate for surgery at initial evaluation and throughout period leading to surgery while continuously enrolled on OHP.
      b) Received counseling by a credentialed expert on the team regarding the risks and benefits of the procedure[3] and understands the many potential complications of the surgery (including death) and the realistic expectations of post-surgical outcomes.
   4) Dietician evaluation: (Conducted by licensed dietician)
      a) Evaluation of adequacy of prior dietary efforts to lose weight. If no or inadequate prior dietary effort to lose weight, must undergo six-month medically supervised weight reduction program.
      b) Counseling in dietary lifestyle changes

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

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

[2] All surgical services must be provided by a program with current certification by the Metabolic and Bariatric Surgery Accreditation and Quality Improvement Program (MBSAQIP), or in active pursuit of such certification with all of the following: a dedicated, comprehensive, multidisciplinary, pathway-directed bariatric program in place; hospital to have performed bariatrics > 1 year and > 25 cases the previous 12 months; trained and credentialed bariatric surgeon performing at least 50 cases in past 24 months; qualified bariatric call coverage 24/7/365;appropriate bariatric-grade equipment in outpatient and inpatient facilities; appropriate medical specialty services to complement surgeons' care for patients; and quality improvement program with prospective documentation of surgical outcomes. If the program is still pursuing (MBSAQIP) certification, it must also restrict care to lower-risk OHP patients including: age < 65 years; BMI < 70; no major elective revisional surgery; and, no extreme medical comorbidities (such as wheel-chair bound, severe cardiopulmonary compromise, or other excessive risk). All programs must agree to yearly submission of outcomes data to Division of Medicaid Assistance Programs (DMAP).

[3] Only Roux-en-Y gastric bypass, laparoscopic adjustable gastric banding and sleeve gastrectomy are approved for inclusion.

Evidence summary (GRADE table from HTAS draft Coverage Guidance):

Coverage question: Should bariatric surgery be recommended for coverage in adults?				
Outcomes	**Estimate of Effect for Outcome/ *Confidence in Estimate***	**Resource allocation**	**Values and Preferences**	**Other considerations**
All-cause mortality (*Critical outcome)*	Odds ratio: 0.48 (95% CI 0.35 to 0.64) Crude event rates 3.6% with surgery and 11.4% without surgery Number needed to treat = 13 ●●○○ *(low certainty based on consistent but indirect observational studies)*	Bariatric surgery costs tens of thousands of dollars per surgery, but has been shown to be cost effective across BMI thresholds and surgery types.	Patients would balance surgery and its risks with risks of living with morbid obesity. Many patients who have failed conservative attempts at weight loss may elect	The greatest benefit may be with BMI ≥ 40 but otherwise specific subpopulations which would benefit the most from bariatric surgery are not well characterized.

Bariatric/Metabolic Surgery for Obesity

Coverage question: Should bariatric surgery be recommended for coverage in adults?				
Outcomes	**Estimate of Effect for Outcome/ *Confidence in Estimate***	**Resource allocation**	**Values and Preferences**	**Other considerations**
Major adverse cardiovascular events (*Critical outcome*)	Odds ratio: 0.54 (95% CI 0.41 to 0.70) Crude event rates 2.4% with surgery and 4.0% without surgery Number needed to treat = 62 ●●○○ (*low certainty based on consistent but indirect observational studies)*		surgery. The benefits of decreased mortality, dramatic weight loss, and regression of diabetes are important outcomes that patients and society would strongly value. However, there would still be moderate variability because of the risks and costs associated with surgery, as well as the intensive peri- and post-operative follow up.	The pre-operative requirements for achieving optimal outcomes are unclear. Given the rate of complications and need for reoperation reported in the summary literature, benefit plans may wish to consider alternative payment methodologies like bundled payments or a pay-for-outcomes approach. Surgeon case volume, and to a lesser extent hospital case volume, appear to affect outcomes for patients undergoing bariatric surgery and requirements regarding surgeon or facility volume may be reasonable.
Type 2 DM remission/resolution (*Important outcome*)	Odds ratio: 3.6 to 52.4 (favoring surgery) Number needed to treat: 1 to 5 ●●●○ *(moderate certainty based on a mix of RCTs and observational studies with consistent but imprecise effects)*			
Hypertension remission/ resolution (*Important outcome*)	Odds ratio: 2.99 to 3.12 (favoring surgery) Number needed to treat: 4 ●●●○ *(moderate certainty based on a mix of RCTs and observational studies with consistent but imprecise effects)*			
Change in BMI (*Important outcome*)	Mean difference at 1 year: -5.5 to -33.35 kg/m^2 (favoring surgery) Pooled mean difference: -7.4 kg/m^2 (favoring surgery) ●●●○ *(moderate certainty based on a mix of RCTs and observational studies with consistent but imprecise effects)*			

Bariatric/Metabolic Surgery for Obesity

Coverage question: Should bariatric surgery be recommended for coverage in adults?				
Outcomes	**Estimate of Effect for Outcome/ *Confidence in Estimate***	**Resource allocation**	**Values and Preferences**	**Other considerations**
Rationale: Bariatric surgery appears to lower all-cause mortality and major adverse cardiovascular events in obese adults (low certainty), and significantly reduces BMI, and results in resolution of type 2 diabetes and hypertension. The greatest benefit appears to be with BMI ≥ 40. Though bariatric surgery is costly and carries significant perioperative risks, the clear long-term positive health benefits leads to a recommendation for coverage. The strength of the recommendation is based on the fact that there is a strong benefit on critical outcomes (particularly in diabetics), and patients desiring surgery would strongly prefer this intervention. For those without diabetes, and other comorbidities are present, the evidence is less clear, leading to a weak recommendation.				

Recommendation:
Coverage of metabolic and bariatric surgery (including Roux-en-Y gastric bypass, gastric banding, and sleeve gastrectomy) is recommended for:
• Adult obese patients (BMI ≥ 35 and <40) with:
  ○ Type 2 diabetes *(strong recommendation)* OR
  ○ at least two of the following other serious obesity-related comorbidities: hypertension, coronary heart disease, mechanical arthropathy in major weight bearing joint, sleep apnea *(weak recommendation)*
• Adult obese patients (BMI ≥ 40) *(strong recommendation)*
 	
Metabolic and bariatric surgery is recommended for coverage in these populations only when provided in a facility accredited by the Metabolic and Bariatric Surgery Accreditation and Quality Improvement Program *(weak recommendation).*
Metabolic and bariatric surgery is not recommended for coverage in:
• Patients with BMI <35, or 35-40 without the defined comorbid conditions above *(weak recommendation)*				

Note: GRADE framework elements are described in Appendix B. A GRADE evidence profile is provided in Appendix C.

Coverage question: Should bariatric surgery be recommended for coverage in children and adolescents?				
Outcomes	**Estimate of Effect for Outcome/ *Confidence in Estimate***	**Resource allocation**	**Values and Preferences**	**Other considerations**
All-cause mortality (*Critical outcome*)	Insufficient evidence in this population *Insufficient evidence*	High cost (tens of thousands of dollars) but may be cost effective especially given the long	High variability. If conservative treatments have failed, children, adolescents and their	Parental involvement in weight management plans is likely necessary to assist the

Bariatric/Metabolic Surgery for Obesity

Coverage question: Should bariatric surgery be recommended for coverage in children and adolescents?				
Major adverse cardiovascular events (*Critical outcome*)	Insufficient evidence in this population *Insufficient evidence*	time horizon if weight loss is maintained. However, uncertainty about the long-term balance of benefits and harms could significantly alter estimates of cost-effectiveness.	parents would be highly motivated to find an effective alternative intervention. Children may have a significant fear of surgery, but the profound social and emotional impact of obesity may override their concerns. Parents are likely to be more concerned about the long term health impacts of obesity than children, and may be concerned about the uncertainty about the long term benefits.	effectiveness of obesity treatments (based on expert opinion). Pediatric bariatric surgery is likely to be available at only a few highly specialized centers. The American Academy of Pediatrics has 10 criteria that pediatric bariatric surgery programs should meet.
Type 2 DM remission/resolution (*Important outcome*)	Rates of remission of T2DM ranged from 50 to 100% ●○○○ *(very low certainty based on mostly small observational trials with imprecise effects)*			
Hypertension remission/ resolution (*Important outcome*)	Rates of remission of hypertension ranged from 50 to 100% ●○○○ (*very low certainty based on mostly small observational trials with imprecise effects)*			
Change in BMI (*Important outcome*)	Mean weighted difference in BMI at 1 year (from baseline): -10.5 to -17.2 kg/m^2 ●●○○ *(low certainty based on mostly small observational trials)*			
Rationale: Bariatric surgery likely results in significant reductions in BMI (low certainty) and is associated with remission of type 2 diabetes and hypertension (very low certainty). However, coverage is not recommended because of the limited evidence about overall long-term benefits and harms of bariatric surgery in this population as well as the high variability in values and preferences.				
Recommendation: Bariatric surgery is not recommended for coverage in children and adolescents *(weak recommendation).*				

Note: GRADE framework elements are described in Appendix B. A GRADE evidence profile is provided in Appendix C.

Bariatric/Metabolic Surgery for Obesity

Coverage question: Should reoperative bariatric surgery for inadequate weight loss be recommended for coverage?					
Outcomes		**Estimate of Effect for Outcome** **Confidence in Estimate of Effect**	**Resource allocation**	**Values and Preferences**	**Other considerations**
Critical outcomes	All-cause mortality	Insufficient evidence in this population *Insufficient evidence*	A second high cost procedure (tens of thousands of dollars), with a history of prior failure may be more costly in total and less effective, however, the cost – effectiveness in this group is unknown.	There would be high variability in patient preferences. With a prior failure of a bariatric procedure, some patients would be hesitant to try an additional procedure given the burdens of surgery and prior ineffectiveness. Others would be motivated to try a different procedure in hopes that it would work better. Patients seeking reoperation have likely no other good potential option given failure of multiple previous alternatives (e.g. clinical, pharmacological, nutritional, physical activity, and surgical).	There is evidence of greater complications rates with reoperation. There is insufficient evidence in the reoperation group to know if their outcomes would be substantially different that those undergoing their first operation. A significant proportion of these patients would be going from a band to a RYGB (from a procedure with a higher failure rate to a lower failure rate).
	Major adverse cardiovascular events	Insufficient evidence in this population *Insufficient evidence*			
Important outcomes	Type 2 DM remission / resolution	Insufficient evidence in this population *Insufficient evidence*			
	Hypertension remission/ resolution	Insufficient evidence in this population *Insufficient evidence*			
	Change in BMI	Mean change in BMI (from baseline): +2.4 kg/m^2 to -17.2 kg/m^2 (follow-up ranging from 8 to 48 months) ●○○○ *(very low certainty based on small case series)*			
Rationale: Reoperation is associated with higher complication rates but also effective weight loss (based on very low quality evidence). While there are not long term health outcomes available, there is no reason to believe that significant weight loss in the reoperation group would be associated with less future health benefits. Therefore, the subcommittee makes no recommendation that the coverage criteria should be different between reoperation and primary surgery. Surgeons will also evaluate their patients and consider reasons for failure when deciding if the patient is a good candidate for reoperation.					
Recommendation: No recommendation that coverage criteria for re-operation should be different than for primary surgery.					

Note: GRADE framework elements are described in Appendix B GRADE evidence profile is provided in Appendix C

Bariatric/metabolic surgery for obesity

HTAS Coverage Recommendations

Coverage of metabolic and bariatric surgery (including Roux-en-Y gastric bypass, gastric banding, and sleeve gastrectomy) is recommended for:

- Adult obese patients (BMI ≥ 35) with
  - Type 2 diabetes *(strong recommendation)* OR
  - at least two of the following other serious obesity-related comorbidities: hypertension, coronary heart disease, mechanical arthropathy in major weight bearing joint, sleep apnea *(weak recommendation)*
- Adult obese patients (BMI ≥ 40) *(strong recommendation)*

Metabolic and bariatric surgery is recommended for coverage in these populations only when provided in a facility accredited by the Metabolic and Bariatric Surgery Accreditation and Quality Improvement Program *(weak recommendation).*

Metabolic and bariatric surgery is not recommended for coverage in:

- Patients with BMI <35, or 35-40 without the defined comorbid conditions above *(weak recommendation)*

Children and adolescents *(weak recommendation)*

HERC Staff Assessment:

Currently, bariatric surgery only pairs in the funded region of the Prioritized List with type 2 diabetes. The Coverage Guidance suggests that coverage should be expanded to include those with comorbidities other than diabetes. Therefore, changing the primary indication for bariatric surgery on the List to be for obesity rather than diabetes makes sense and consolidating the bariatric surgery codes to the Obesity line is indicated. Having bariatric surgery codes on the lower obesity line (589) is confusing because of the comorbidity rule, when there are clearly defined comorbidities in the new proposed guideline note language.

HERC Staff Recommendations Pending Input from Obesity Task Force:

1) Add bariatric surgery to Line 325
   a. Change the Treatment title
   b. Add bariatric surgery codes (see Code Movement Table)
   c. Add reference to Guideline Note 8
2) Remove bariatric surgery from Line 30, Type 2 Diabetes
   a. Change title of the Treatment to not include bariatric surgery
   b. Remove bariatric surgery codes from line 30 (see Code Movement Table)
   c. Remove coding specification about bariatric surgery
   d. Remove reference to Guideline Note 8
3) If Line 589 is not deleted, remove bariatric surgery from Line 589
   a. Change the Treatment title

b. Remove bariatric surgery codes from Line 589 (see Code Movement Table)

4) Revise Guideline Note 8
   a. Discuss whether to remove the language that excludes reoperations (C)
   b. Discuss whether the preoperative and postoperative requirements should be modified

Line: 30
Condition: TYPE 2 DIABETES MELLITUS (See Coding Specification Below) (See Guideline Notes ~~8~~,62,64,65)
Treatment: MEDICAL THERAPY~~, BARIATRIC SURGERY WITH BMI >= 35~~
ICD-10: E08.00-E08.29,E08.311-E08.9,E09.00-E09.29,E09.311-E09.9,E11.00-E11.29,E11.311-E11.9,E13.00-E13.29, E13.311-E13.9,E16.1,Z46.51
CPT: ~~43644,43645,43770-43775,43846-43848,48155,~~64505-64530,90935-90947,90989-90997,92002-92014,92227, 96150-96154,97605-97608,97802-97804,98960-98969,99051,99060,99070,99078,99184,99201-99239,99281-99285,99291-99404,99408-99416,99429-99449,99468-99480,99487-99498,99605-99607
HCPCS: G0108,G0109,G0245,G0246,G0270,G0271,G0396,G0397,G0406-G0408,G0425-G0427,G0458,G0463,G0466, G0467,S2083,S9140-S9145,S9353,S9537

~~CPT codes 43644-43645 and 43846-43848 (Roux-En-Y gastric bypass) and 43770-43775 (laparoscopic adjustable gastric banding and sleeve gastrectomy) are only included on this line as treatment according to the requirements in Guideline Note 8 when paired with:~~
~~1) a primary diagnosis of E11 (Type II Diabetes with or without complication);~~
~~2) a secondary diagnosis of E66.01, E66.09, E66.2, E66.8 or E66.9 (Obesity); AND,~~
~~3) a tertiary diagnosis code of Z68.35-Z68.39 or Z68.4.~~

Line: 325
Condition: OBESITY (ADULT BMI ≥ 30, CHILDHOOD BMI ≥ 95 PERCENTILE) (See Guideline Notes 5,8,64,65)
Treatment: INTENSIVE NUTRITIONAL/PHYSICAL ACTIVITY COUNSELING AND BEHAVIORAL INTERVENTIONS, BARIATRIC SURGERY
ICD-10: E66.01-E66.9, Z68.30-Z68.45,Z68.54
CPT: 43644,43645,43770-43775,43846-43848,96150-96154,97802-97804,98966-98969,99051,99060,99070,99078, 99201-99215,99281-99285,99341-99355,99358-99378,99381-99404,99408-99416,99429-99449,99487-99498
HCPCS: G0396,G0397,G0447,G0463,G0466,G0467,G0473

Line: 589
Condition: OBESITY (ADULT BMI ≥ 30, CHILDHOOD BMI ≥ 95 PERCENTILE) (See Guideline Notes 8,64,65)
Treatment: NON-INTENSIVE NUTRITIONAL/PHYSICAL ACTIVITY COUNSELING AND BEHAVIORAL INTERVENTIONS~~; BARIATRIC SURGERY FOR OBESITY WITH A SIGNIFICANT COMORBIDITY OTHER THAN TYPE II DIABETES & BMI >=35 OR BMI>=40 WITHOUT A SIGNIFICANT COMORBIDITY~~
ICD-10: E66.01-E66.9,Z68.30-Z68.45,Z68.54,Z71.3
CPT: ~~43644,43645,43770-43775,43846-43848,~~98966-98969,99051,99060,99070,99078,99201-99215,99281-99285, 99341-99355,99358-99378,99381-99404,99408-99416,99429-99449,99487-99498,99605-99607
HCPCS: G0396,G0397,G0447,G0463,G0466,G0467,G0473

GUIDELINE NOTE 8, BARIATRIC SURGERY

Line~~s 30,589~~ 325

Bariatric/metabolic surgery (limited to Roux-en-Y gastric bypass, laparoscopic adjustable gastric banding, and sleeve gastrectomy) is included on Line 325~~under~~ when the following criteria are met:

A) Age ≥ 18
B) The patient has obesity with a:
   1) BMI ≥ 40 OR
   2) BMI ≥ 35 with:
      a) Type 2 diabetes, OR

b) at least two of the following other serious obesity-related comorbidities: hypertension, coronary heart disease, mechanical arthropathy in major weight bearing joint, sleep apnea

~~3) a BMI ≥ 35 with co-morbid type II diabetes for inclusion on Line 30 TYPE 2 DIABETES MELLITUS; OR~~

~~4) BMI >=35 with at least one significant co-morbidity other than type II diabetes (e.g., obstructive sleep apnea, hyperlipidemia, hypertension) or BMI >= 40 without a significant co-morbidity for inclusion on Line 589~~

~~C) No prior history of Roux-en-Y gastric bypass or laparoscopic adjustable gastric banding, unless they resulted in failure due to complications of the original surgery.~~

D) Participate in the following four evaluations and meet criteria as described.

1) Psychosocial evaluation: (Conducted by a licensed mental health professional)
   a) Evaluation to assess potential compliance with post-operative requirements.
   b) Must remain free of abuse of or dependence on alcohol during the six-month period immediately preceding surgery. No current use of nicotine or illicit drugs and must remain abstinent from their use during the six-month observation period. Testing will, at a minimum, be conducted within one month of the surgery to confirm abstinence from nicotine and illicit drugs.
   c) No mental or behavioral disorder that may interfere with postoperative outcomes[1].
   d) Patient with previous psychiatric illness must be stable for at least 6 months.
2) Medical evaluation: (Conducted by OHP primary care provider)
   a) Pre-operative physical condition and mortality risk assessed with patient found to be an appropriate candidate.
   b) Optimize medical control of diabetes, hypertension, or other co-morbid conditions.
   c) Female patient not currently pregnant with no plans for pregnancy for at least 2 years post-surgery. Contraception methods reviewed with patient agreement to use effective contraception through 2nd year post-surgery.
3) Surgical evaluation: (Conducted by a licensed bariatric surgeon associated with program[2])
   a) Patient found to be an appropriate candidate for surgery at initial evaluation and throughout period leading to surgery while continuously enrolled on OHP.
   b) Received counseling by a credentialed expert on the team regarding the risks and benefits of the procedure~~3~~ and understands the many potential complications of the surgery (including death) and the realistic expectations of post-surgical outcomes.
4) Dietician evaluation: (Conducted by licensed dietician)
   a) Evaluation of adequacy of prior dietary efforts to lose weight. If no or inadequate prior dietary effort to lose weight, must undergo six-month medically supervised weight reduction program.
   b) Counseling in dietary lifestyle changes

E) Participate in additional evaluations:

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

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

[2] All surgical services must be provided by a program with current certification by the Metabolic and Bariatric Surgery Accreditation and Quality Improvement Program (MBSAQIP). ~~, or in active pursuit of such certification with all of the following: a dedicated, comprehensive, multidisciplinary, pathway-directed bariatric program in place; hospital to have performed bariatrics > 1 year and > 25 cases the previous 12 months; trained and credentialed bariatric surgeon performing at least 50 cases in past 24 months; qualified bariatric call coverage 24/7/365;appropriate bariatric-grade equipment in outpatient and inpatient facilities; appropriate medical specialty services to complement surgeons' care for patients; and quality improvement program with prospective documentation of surgical outcomes. If the program is still pursuing (MBSAQIP) certification, it must also restrict care to lower-risk OHP patients including: age < 65 years; BMI < 70; no major elective revisional surgery; and, no extreme medical comorbidities (such as wheel-chair bound, severe cardiopulmonary compromise, or other excessive risk). All programs must agree to yearly submission of outcomes data to Division of Medicaid Assistance Programs (DMAP).~~

[3] ~~Only Roux-en-Y gastric bypass, laparoscopic adjustable gastric banding and sleeve gastrectomy are approved for inclusion.~~

Code Movement Table

Code	Code Description	Staff Recommendation
Z46.51	Encounter for fitting and adjustment of gastric lap band	Remove from Line 30, and place on Line 325 only
43644	Laparoscopy, surgical, gastric restrictive procedure; with gastric bypass and Roux-en-Y gastroenterostomy (roux limb 150 cm or less)	Remove from Line 30 and 589, and place on Line 325 only
43645	Laparoscopy, surgical, gastric restrictive procedure; with gastric bypass and small intestine reconstruction to limit absorption	Remove from Line 30 and 589, and place on Line 325 only
43770	Laparoscopy, surgical, gastric restrictive procedure; placement of adjustable gastric restrictive device (eg, gastric band and subcutaneous port components)	Remove from Line 30 and 589, and place on Line 325 only
43771	Laparoscopy, surgical, gastric restrictive procedure; revision of adjustable gastric restrictive device component only	Remove from Line 30 and 589, and place on Line 325 only
43772	Laparoscopy, surgical, gastric restrictive procedure; removal of adjustable gastric restrictive device component only	Remove from Line 30 and 589, and place on Line 325 only
43773	Laparoscopy, surgical, gastric restrictive procedure; removal and replacement of adjustable gastric restrictive device component only	Remove from Line 30 and 589, and place on Line 325 only
43774	Laparoscopy, surgical, gastric restrictive procedure; removal of adjustable gastric restrictive device and subcutaneous port components	Remove from Line 30 and 589, and place on Line 325 only
43775	Laparoscopy, surgical, gastric restrictive procedure; longitudinal gastrectomy (ie, sleeve gastrectomy)	Remove from Line 30 and 589, and place on Line 325 only
43846	Gastric restrictive procedure, with gastric bypass for morbid obesity; with short limb (150 cm or less) Roux-en-Y gastroenterostomy	Remove from Line 30 and 589, and place on Line 325 only
43847	Gastric restrictive procedure, with gastric bypass for morbid obesity; with small intestine reconstruction to limit absorption	Remove from Line 30 and 589, and place on Line 325 only

Bariatric/metabolic surgery for obesity

Code	Code Description	Staff Recommendation
43848	Revision, open, of gastric restrictive procedure for morbid obesity, other than adjustable gastric restrictive device (separate procedure)	Remove from Line 30 and 589, and place on Line 325 only
S2083	Adjustment of gastric band diameter via subcutaneous port by injection or aspiration of saline	Remove from Line 30, place on Line 325

Bariatric Surgery

Draft Coverage Guidance for HERC Consideration

March 10, 2016

Oregon Health Authority

Oregon Health & Science University

Center For Evidence-based Policy

Background – Obesity

- Obesity is defined as:
  - Adult: body mass index (BMI) >30 kg/m^2 in adults
    - Class I BMI 30-34.9 (obese)
    - Class II BMI 35-39.9 (severely obese)
    - Class III BMI 40-49.9 (morbidly obese)
    - Super obesity BMI>50 (super obese)
  - Children and adolescents: > 95^{th} percentile of age- and sex-specific BMI

Background – Obesity

- Obesity is common in the US
  - 35% of adults
  - 17% of 2 to 19 year olds
  - 8.1% of infants and toddlers
- Obesity is a risk factor for many conditions including heart disease, type 2 diabetes (T2DM), stroke, cancer, sleep apnea, and arthritis
- Obesity is costly
  - $147 to $210 billion in annual medical spending attributable to obesity

Background – Obesity

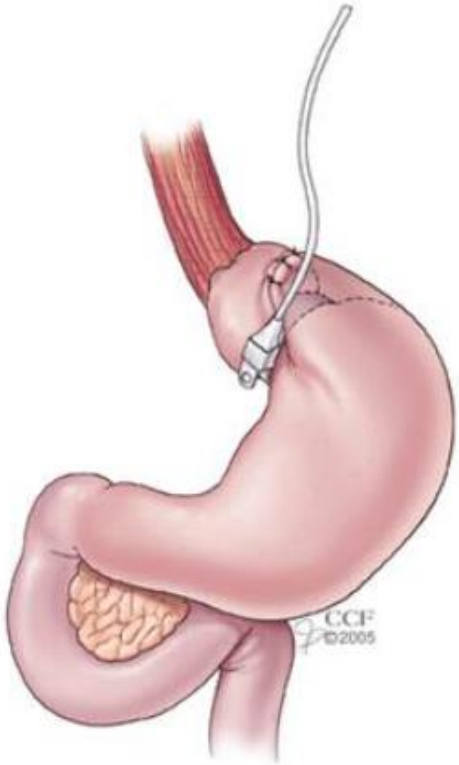
- In Oregon:
  - 24% of adults are obese
  - 38% of OHP-covered adults are obese
  - Approximately 11% of 8th graders are obese
  - Medicaid costs attributable to obesity were estimated at $333 million annually

Background – Treatments

- Structured programs to improve nutrition and physical activity
- Intensive behavioral counseling
- Medications (orlistat, lorcaserin, phentermine, liraglutide, naltrexone, topiramate)
- Devices (vagal nerve blockers, gastric balloons, endoliners)
- Bariatric surgery

Background – Surgery

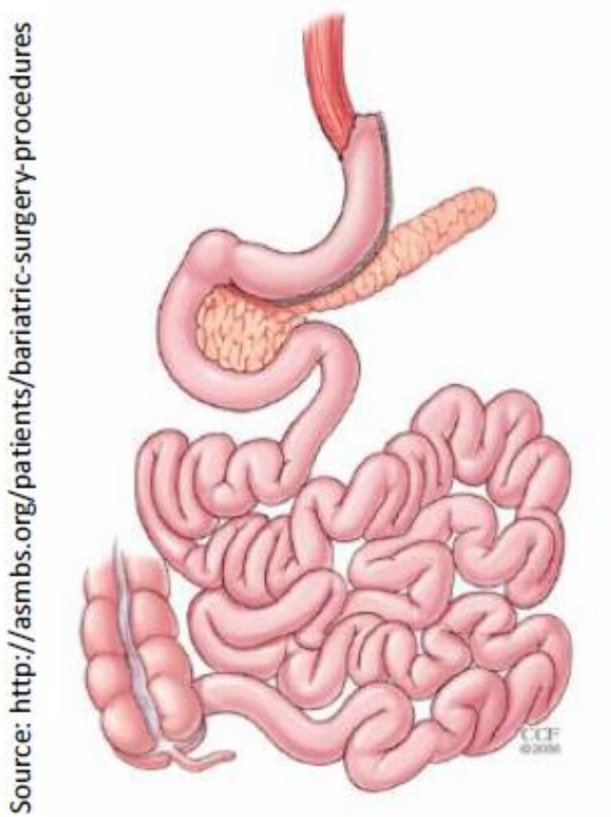
Adjustable gastric banding (AGB or LAGB)



Source: http://asmbs.org/patients/bariatric-surgery-procedures

Background – Surgery

Vertical sleeve gastrectomy (VSG)



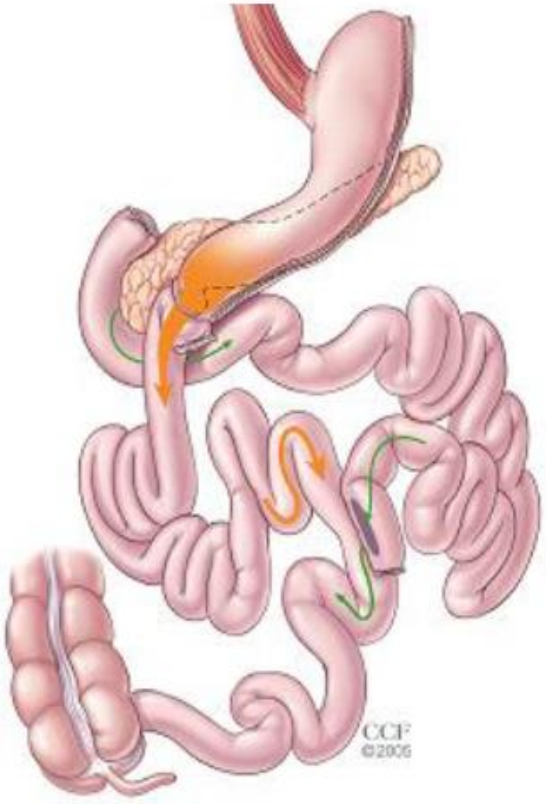
Source: http://asmbs.org/patients/bariatric-surgery-procedures

Background – Surgery

Roux-en-Y gastric bypass (RYGB)

Background – Surgery

- Biliopancreatic diversion/duodenal switch (BPD/DS)



Source: http://asmbs.org/patients/bariatric-surgery-procedures

Background – Surgery

	2011	2012	2013
RYGB	36.7%	37.5%	34.2%
Gastric band	35.4%	20.2%	14.0%
Sleeve gastrectomy	17.8%	33.0%	42.1%
BPD/DS	0.9%	1.0%	1.0%
Revisions	6.0%	6.0%	6.0%
Other	3.2%	2.3%	2.7%
TOTAL	100%	100%	100%
Total number of surgeries	158,000	173,000	179,000

Background – Surgery

	2011	2012	2013
RYGB	36.7%	37.5%	34.2%
Gastric band	**35.4%**	**20.2%**	**14.0%**
Sleeve gastrectomy	**17.8%**	**33.0%**	**42.1%**
BPD/DS	0.9%	1.0%	1.0%
Revisions	6.0%	6.0%	6.0%
Other	3.2%	2.3%	2.7%
TOTAL	100%	100%	100%
Total number of surgeries	158,000	173,000	179,000

PICO Statement

- Population: Obese adults and children
- Intervention: Bariatric or metabolic surgery
- Comparator: Non-surgical treatment
- Outcomes:
  - All-cause mortality (critical)
  - Major adverse cardiovascular events (critical)
  - Resolution of T2DM (important)
  - Resolution of hypertension (important)
  - Weight loss (important)

Key Questions

1. Should coverage be recommended for bariatric surgery in each of the scenarios in the table below?
2. What is the appropriate minimum age for bariatric surgery?
3. What components and systems of care are associated with improved health outcomes? (e.g., centers of excellence, surgeon's experience, etc.)
4. What preoperative assessments or requirements for preoperative weight loss should be recommended in patients being considered for bariatric surgery?

	BMI 30-34.9	BMI 35-39.9	BMI>=40
With DM2	Scenario 1	Scenario 2	Scenario 3
W/o DM2 nor other comorbidities	Scenario 4	Scenario 5	Scenario 6
W/o DM2 but with other comorbidities	Scenario 7	Scenario 8	Scenario 9

Sources

- Full search of core sources
  - Washington HTA report (2015) identified as the most recent and comprehensive review
- Medline search
  - Search dates: January 2014 – July 2015
  - Corresponding to end search date for WA HTA report
  - 13 additional systematic reviews met quality and inclusion criteria
- Clinical practice guideline search (last 5 years)
- Payer policy search

Evidence Strengths and Limitations

- Voluminous evidence base
  - More than 20 SRs published in the last 1.5 years spanning over 600 individual studies
  - Poor agreement on inclusion for individual SRs
- Of 179 studies in the WA HTA report
  - 26 (15%) were good quality
  - 74 (41%) were fair quality
  - 49 (44%) were poor quality

Evidence Strengths and Limitations

- Major limitations include:
  - Many non-comparative studies
  - Baseline differences in study groups
  - Differences in duration of follow-up between groups
  - Limited duration of follow-up and high rates of attrition
  - Inconsistent definitions of harms and outcomes
  - Specific bariatric procedures were variable

Evidence Review – Adults

- WA HTA (2015)
  - 179 comparative trials
    - 21 good or fair quality trials (14 RCTs, 7 cohort) compared bariatric surgery with non-surgical management
    - 13 RYGB, 6 AGB, 4 VSG, 3 BPD/DS
  - Meta-analytic results
    - Weight loss: Pooled mean difference in BMI 7.4 kg/m^2 (95% CI 6.2 to 8.6) favoring surgery
    - Resolution of T2DM: Odds ratio of 3.62 (95% CI 2.49 to 4.73) favoring surgery
- Similar results from other SRs: Chang (2014), Colquitt (2014), Hayes (2014), Kwok (2014), Muller-Stich (2014), Puzziferri (2014)

Evidence Summary – Adults

- Bariatric surgery is associated with lower rates of all-cause mortality, despite a short-term increased risk of perioperative mortality and complications (based on low certainty evidence from cohort studies).
- Bariatric surgery is associated with significant reductions in BMI in adults (based on moderate certainty evidence from a mix of observational and randomized trials).
  - The effects on weight loss appear to be greatest in patients with baseline BMI ≥40.

Evidence Summary – Adults

- Bariatric surgery is associated with remission or resolution of T2DM and hypertension in adults with BMI ≥ 35 (based on moderate certainty evidence from a mix of observational and randomized trials).
  - The effects on remission of T2DM appear to be greatest in patients with baseline BMI ≥40
  - Preliminary evidence suggests that adults with BMI < 35 may also achieve significant reductions in BMI and improvement in comorbid T2DM and hypertension, though the long term effects are not yet clear.

Evidence Summary – Adults

- Harms of bariatric surgery
  - Perioperative mortality rate that probably ranges from 0.1 to 2%
  - Overall complication rate that is probably 8 to 25%
  - Estimated reoperation rate is likely between 2 and 13%.
  - Limited evidence from a single study that comorbid congestive heart failure, cardiac arrhythmias, and peripheral vascular disease are associated with higher rates of complications after bariatric surgery.

Evidence Summary – Patient Selection

- Low certainty conflicting evidence on the effects of preoperative weight loss requirements from one SR.
- Evidence from one SR indicates that the obesity surgery mortality risk score (OR-MRS) is a validated preoperative assessment of perioperative mortality risk and may be useful in selecting patients for surgery or counseling them on surgical risks.

Evidence Summary – Reoperation

- Most studies included in the six SRs were not methodologically rigorous and there are concerns about publication bias in this literature.
- Very low certainty evidence that revisional or conversion procedures may achieve additional weight loss (particularly conversion of AGB to RYGB or BPD/DS)
- Reoperations have a higher rate of complications
- No evidence that bariatric reoperation improved co-morbidity resolution.

Evidence Summary – Systems of Care

- Zevin (2012) – 24 observational studies examining the effects of surgeon and facility volume on outcomes
- Low certainty evidence that surgeon experience is associated with improved outcomes
- Very low certainty evidence that hospital bariatric surgical volume is associated with improved outcomes.

Evidence Review – Children

- General limitations
  - Primarily small, low quality observational studies (only a single RCT of AGB); largest trial included in the SRs was 81 patients
  - Shorter follow-up durations than adult studies (mostly 6 months to 3 years)
- Systematic reviews: Aikenhead (2011), Black (2013), Treadwell (2008)

Evidence Summary – Children

- Bariatric surgery is associated with significant reductions in BMI in children and adolescents (based on low certainty evidence primarily from small, non-comparative observational trials).
- Bariatric surgery is associated with remission or resolution of T2DM and hypertension in children or adolescents (based on very low certainty evidence from a small number of trials).
- There is no evidence-based minimum age recommendation for pediatric bariatric surgery. Patients as young as five years old were included in the studies.

Public Comment

- One public comment, from Oregon Chapter of the American Society for Metabolic and Bariatric Surgery:
  - "We agree the information in the areas of adolescent surgery and surgical treatment of BMI less than 35 is incomplete and rapidly evolving. We believe these two areas should be reassessed in two years."

HERC Coverage Guidance – Metabolic and Bariatric Surgery
Disposition of Public Comments

Table of Contents

Commenters

Identification	Stakeholder
A	Oregon Chapter of the American Society for Metabolic and Bariatric Surgery *[Submitted January 18, 2016]*

Public Comments

ID/#	Comment	Disposition
A1	"[W]e would like to applaud the efforts to update the current policy on metabolic and bariatric surgery. We agreed with standardizing the indications for surgery to come in line with current clinical practice throughout the United States. We agree the information in the areas of adolescent surgery and surgical treatment of BMI less than 35 is incomplete and rapidly evolving. We believe these two areas should be reassessed in two years."	Thank you for your comment. The Oregon HERC assesses any new evidence every two years to determine if a new coverage guidance is needed.