Health Evidence Review Commission's Value-based Benefits Subcommittee

May 18, 2023

8:00 AM - 1:00 PM

Online Meeting

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Section 1.0

Call to Order

Agenda
Value-based Benefits Subcommittee (VbBS)
May 18, 2023

8:00 am–1:00pm

Online meeting

All agenda items are subject to change and times listed are approximate.

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

Plain language summaries of topics and recommendations follow the agenda.

	Time	Topic
I.	8:00 AM	**Call to Order, Roll Call, Approval of Minutes**
II.	8:05 AM	**Staff report**
III.	8:20 AM	**Straightforward/Consent Agenda** *(Routine changes that may be approved without discussion)* A. Straightforward guideline note changes i. Wireless capsule endoscopy ii. Septoplasty iii. Electronic tumor treatment fields iv. Inflammatory skin disease guideline edits v. Solid organ transplant guideline update
IV	8:30 AM	**Pediatric ENT items** 1) Tonsillectomy for recurrent infection (*Removal of tonsils for infections that keep happening*) 2) Cochlear implants for unilateral deafness in children *(Deafness in one ear)*
V.	9:30 AM	**New codes** A. PLA code review *(Laboratory billing codes that can only be used for one company's trademarked laboratory tests)*
VI.	10:00 AM	**Previous discussion items** A. Prostatic urethral lift: *(A procedure to widen the urethra and place a hollow tube that lets urine leave the body)*
	10:15	**BREAK**

	Time	Topic
VII.	10:30 AM	**New discussion items** A. Circadian rhythm disorders *(Problems with timing of falling asleep and waking up*) B. Second bone marrow transplants *(A procedure that delivers healthy stem cells to replace a person's own bone marrow to treat cancer)* C. Magnetic esophageal sphincter augmentation device *(A ring of magnetic beads placed around the outside of the food pipe for serious heartburn)* *D.* Radiation therapy for Dupuytren's contracture and plantar fibromatosis *(Tightening of the tissue of the hand)* E. SPECT for spinal indications *(A type of advanced scan (imaging) of the spine)* F. Two level cervical artificial disc May 2023 review *(Replacing diseased tissue between the spine bones)* G. YAG laser for treatment of hidradenitis suppurativa *(A laser treatment for a condition causing long lasting skin irritation and pain)*
VIII.	11:30 PM	**Coverage Guidances** A. Bariatric surgery (*Weight loss surgery)*
XI.	12:25 PM	**Public comment on topics not on the agenda**
XII.	1:00 PM	**Adjournment**

Plain Language Summary of VbBS Agenda Topics

This plain language summary provides a very short and non-technical explanation of the topics that will be discussed at the meeting, along with the staff's recommendation. Decisions are not final unless approved by the Health Evidence Review Commission and implemented on the Oregon Health Plan. The Commission may modify staff recommendations or decide not to approve them.

Straightforward Guideline Note Changes May 2023

Coverage question: Routine changes that may be approved without discussion.

Inflammatory Skin Disease Guideline Edits May 2023

Coverage question: Should the guideline for a disease affecting the skin be updated?

Should OHP cover this treatment? Yes. The Pharmacy & Therapeutics Committee and experts agree the guideline should be updated to the guideline. The current guideline states you must use treatments that are not widely used today before you can use the more effective and more available treatments.

Solid Organ Transplant Guideline May 2023 Revisions

Background: Clarifying when more than one organ can be transplanted together.

Should OHP cover this treatment? Staff recommends changing the guideline to have general reasons why more than one organ should be transplanted at the same time.

Tonsillectomy for Recurrent Throat Infection

Coverage question: Should we change the guideline for the removal of tonsils for infections that keep happening?

Should OHP cover this treatment? Yes. The definition of an "attack" should be changed to allow for more coverage.

Treatment of Single-sided Deafness

Coverage question: Should treatment of deafness in one ear be covered for adults? Should a surgically placed device that helps a person with deafness in one ear hear sound (cochlear implants) be covered for adults or children?

Should OHP cover this treatment? Yes for children but not for adults. Treatment of adults for deafness in one ear has some limited benefit in certain situations, there is no evidence treatment improves quality of life. Treatment of children with deafness in one ear with cochlear implants may provide developmental benefits and should be covered.

PLA Code Review

Coverage question: There are several hundred unreviewed private and exclusive laboratory analysis (PLA) codes for trademarked laboratory tests that must be used rather than a more genetic CPT code. The top 12 billed codes are reviewed below.

Should OHP cover this treatment? In most cases, yes.

Prostate Procedure Guideline Modifications

Coverage question: Should the requirement to try medication before having a procedure on a prostate to help urine leave the body be removed? Should any changes be made to the requirements for a procedure to help urine leave the body?

Should OHP cover this treatment? The guideline on prostate procedures should be changed to no longer require medications. This is done to agree with expert guidelines. The age range for the procedure should be lowered to 45 years old because the FDA has approved it for younger patients.

Circadian Rhythm Disorders

Coverage question: Should problems with timing of falling asleep and waking up be covered for more than general advice and office visits?

Should OHP cover this treatment? No. Medical studies show that neither medications nor a light box are very effective.

Second Bone Marrow Transplant

Coverage question: Should OHP cover more than one operation (transplant) that delivers healthy stem cells to replace a person's own stem cells?

Should OHP cover this treatment? Yes, when appropriate for the patient. A second transplant is rarely needed but may be required in some situations.

Esophageal Sphincter Augmentation Device for GERD

Coverage question: Should coverage be added for a ring of magnetic beads placed around the outside of the food pipe, just above the stomach, to keep the food pipe closed in patients with severe heartburn?

Should OHP cover this treatment? No, Medicare and other insurers consider this experimental and other effective treatments exist.

Radiation Therapy for Dupuytren's Contracture

Coverage question: Should OHP cover radiation treatment for a tightening of the tissue of the hand?

Should OHP cover this treatment? No. Radiation treatment has not been studied well and there are other treatments (shots, surgery) available.

SPECT for Back Pain

Coverage question: Should OHP cover a pre-surgery advance spine scan of the neck and back called SPECT?

Should OHP cover this treatment? No, not for standard use. It may be useful when there is a reason why a patient cannot have an MRI or to show breaks in the bones of the spine. Individual review should determine which test to use.

Two Level Cervical Artificial Discs

Coverage question: Should we cover an operation for a two-disc replacement between neck bones?

Should OHP cover this treatment? Yes, new medical studies show this operation to be as safe and effective as an operation where the spinal bones are joined together.

YAG Laser Therapy for Hidradenitis Suppurativa

Coverage question: Should a laser treatment for a condition causing long lasting skin irritation and pain be covered?

Should OHP cover this treatment? Yes, though it is more costly than medications it appears to be more effective.

Bariatric procedures – Weight loss surgery

Should certain types of weight loss surgery be covered for people over a certain weight for height (also known as Body Mass Index or BMI)?

Yes, for adults with a BMI of 35 and over.

Yes, for adults with a BMI of 30.0 to 34.9:
Who have type 2 diabetes, and
Do not have well-controlled blood sugar (glucose) despite having tried two diabetes medications

Yes, for people aged of 13-18 when:
BMI is 35 to 39.9 (or the expected height and weight for the person's age, based on the growth curve, is very high)
AND the person has a serious medical condition

BMI is over 40 (or the expected height and weight for the person's age, based on the growth curve, is very high) regardless of other health conditions

People also must:
Have an evaluation by a specialized team of doctors
Not have a drug use problem
Not smoke
Not be pregnant
Agree to follow lifelong lifestyle requirements

Why should we cover this surgery?

Weight loss surgery significantly reduces body weight and can cure type 2 diabetes for many people. It can lower the death rate and risk of heart attacks in adults over certain BMI levels.

We recommend covering this surgery for people 13-18 years old with a certain BMI which aligns with the American Academy of Pediatrics guidelines and expert input.

Why shouldn't balloons and adjustable gastric bands be covered too?

Adjustable gastric bands (lap bands) don't help people lose as much weight as other surgeries and can have complications.

Inserting balloons into the stomach has only been shown to cause short-term weight loss. We chose to recommend coverage for surgeries that help people for longer time periods.

Value-based Benefits Subcommittee (VbBS) Summary

For Presentation to:
Health Evidence Review Commission on March 9, 2023

For specific coding recommendations and guideline wording, please see the text of the March 9, 2023 VbBS minutes.

Recommended Code Movement (Changes to the 10/1/2023 Prioritized List unless otherwise noted):

- Merge the three funded lines for liver transplant into a single line (effective 1/1/2024)
- Add "store and forward" codes to the ancillary file so they will be covered
- Add trigger finger and trigger thumb to a funded line for adults and children
- Add codes for several genetic tests to the diagnostic procedures file (this recommendation was not approved by HERC).
- Make various straightforward coding changes

Item Considered but No Recommendations for Changes Made:

- Vagus nerve stimulators for treat resistant depression

Recommended Guideline Changes (Changes to the 10/1/2023 Prioritized List unless otherwise noted):

- Delete the guideline relating to smoking cessation requirements before elective surgery and add a new statement of intent regarding smoking prior to elective surgery
- Edit the ancillary guideline regarding telehealth to indicate when "store and forward" codes are covered
- Edit the biliary colic guideline to only require one imaging test
- Edit the trigger thumb guideline to include treatment of adults for trigger thumb and treatment of trigger finger for adults and children
- Edit the back surgery guideline to clarify when foraminal stenosis is funded
- Remove a code related to a gene expression test from the guideline note for services not covered for any condition. Remove another code from the excluded file. Add a new guideline regarding cancer genetic testing and delete the previous guideline on biomarker tests of cancer tissue. (These changes were NOT approved by HERC.)
- Add code for vagus nerve stimulators to the line for services that will not be covered for any condition.
- Edit the guideline note related to prostatic urethral life (this change was not approved by the HERC)
- Edit the guideline for spinal fusion surgery.
- Recommend straightforward guideline note changes

Item Tabled for a future meeting:

- Breast reduction for macromastia
- Single sided-deafness coverage for adults; cochlear implants for adults and children with single-sided deafness

Minutes
Value-based Benefits Subcommittee (VbBS)

Online meeting
March 9, 2023

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

Members Absent: Mike Collins; Kathryn Schabel, MD.

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

Also Attending: Val King, MD, MPH & Rita Shiau (Center for Evidence-based Policy); Chris DeMars, Mina Colon & Kristen Darmody (Oregon Health Authority); Carl Stevens; Chris DeMars (Oregon Health Authority); Chris Potters (MCCFL); Cristyn Lauer; Deb Brugman; Jacob Gigliotti; Joan Sunderland; Joanna Roquel Wilson; Joel Stegen; Justin; Laura Briggs; Michelle Bach; Noel S; rebeccagale; Renee Doan (Care Oregon); Richard Bruno; sayj; Scott Haanstad; Sheila Robertson; Shimi Sharief; Siobhan Hess; Steven; Tim Barr.

Call to Order, Minutes Approval, Staff Report

The meeting was called to order at 8:35 am and roll was called. A quorum of members was present at the meeting. Minutes from the January 19, 2023 VbBS meeting were reviewed and approved with no modifications.

Jason Gingerich gave the staff report. He updated members on OHA leadership changes, gave an update on membership, and gave a legislative update. He also updated members on retreat plans.

Straightforward/Consent Agenda

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

Recommended Actions:

1) Modify GN118 as shown in Appendix A
2) Remove CPT 22858 Total disc arthroplasty (artificial disc), anterior approach, including discectomy with end plate preparation (includes osteophytectomy for nerve root or spinal cord decompression and microdissection); second level, cervical (List separately in addition to code for primary procedure) from lines 346 CONDITIONS OF THE BACK AND SPINE WITH URGENT SURGICAL INDICATIONS, 530 CONDITIONS OF THE BACK AND SPINE WITHOUT URGENT SURGICAL INDICATIONS
3) Add CPT 22858 to line 662 CONDITIONS FOR WHICH CERTAIN INTERVENTIONS ARE UNPROVEN, HAVE NO CLINICALLY IMPORTANT BENEFIT OR HAVE HARMS THAT OUTWEIGH BENEFITS
4) Modify the GN173 entry on second artificial disc as shown in Appendix A
5) Place HCPCS S9563 (Home injectable therapy, immunotherapy, including administrative services, professional pharmacy services, care coordination, and all necessary supplies and equipment (drugs and nursing visits coded separately), per diem) on all lines with E&M codes
6) Place CPT 0380U (Drug metabolism (adverse drug reactions and drug response), targeted sequence analysis, 20 gene variants and cyp2d6 deletion or duplication analysis with reported genotype and phenotype) on the DIAGNOSTIC PROCEDURES file
7) Modify Diagnostic Guideline D1 as shown in Appendix A

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

Cancer genetic workgroup report

Discussion: Smits presented the meeting materials.

Public testimony:

Deb Brugman (a genetic counselor with Foundation Medicine) testified. She noted that covering this test will reduce health disparities between Medicaid and privately insured patients. She also noted that the liquid biopsy test PLA 0239U and the tissue test 0037U are different tests and have different clinical indications. The liquid test is used when biopsy is not possible due to the location of the cancer or patient comorbidities. However, at times the liquid test does not find the mutation. The tissue test is the gold standard test. There are Medicare NCDs (National Coverage Determinations) on both of these tests. It was clarified that both of these tests will be on the fee schedule and both would be governed by the proposed new guideline.

Discussion:
Pinzon noted that CLIA approval is not necessarily evidence based. Staff replied that this is at least a low bar and that some tests are not even CLIA approved. The group discussed whether 3 tests are sufficient, as limited in the guideline. Staff noted that additional tests can be approved if medically necessary. Olson noted that 3 tests is within the usual covered amount in current practice.

Hodges requested that the cancer genetic group and the GAP meet more frequently as these tests are coming out more frequently and CCOs need more expert support and input. Staff also expressed a need for regular meetings of these groups. Gingerich also informed the subcommittee that HERC staff is monitoring genetic testing codes for frequency of billing and bringing high use ones to HERC for discussion.

Recommended Actions:

1) Make code placement changes as shown in the table below

Code	Code Description	Current Placement	Recommended Placement
81210	BRAF (B-Raf proto-oncogene, serine/threonine kinase) (eg, colon cancer, melanoma), gene analysis, V600 variant(s)	229 MALIGNANT MELANOMA OF SKIN	DIAGNOSTIC PROCEDURES
81235	EGFR (epidermal growth factor receptor) (eg, non-small cell lung cancer) gene analysis, common variants (eg, exon 19 LREA deletion, L858R, T790M, G719A, G719S, L861Q)	262 CANCER OF LUNG, BRONCHUS, PLEURA, TRACHEA, MEDIASTINUM AND OTHER RESPIRATORY ORGANS	DIAGNOSTIC PROCEDURES
81275	KRAS (Kirsten rat sarcoma viral oncogene homolog) (eg, carcinoma) gene analysis; variants in exon 2 (eg, codons 12 and 13)	157 CANCER OF COLON, RECTUM, SMALL INTESTINE AND ANUS	DIAGNOSTIC PROCEDURES
81518-81523	Oncology (breast), mRNA gene expression profiling	191 CANCER OF BREAST; AT HIGH RISK OF BREAST CANCER	DIAGNOSTIC PROCEDURES
0008M	Oncology (breast), mrna analysis of 58 genes using hybrid capture, on formalin-fixed paraffin-embedded (ffpe) tissue, prognostic algorithm reported as a risk score	191	DIAGNOSTIC PROCEDURES

S3854	Gene expression profiling panel for use in the management of breast cancer treatment	191 and 662	DIAGNOSTIC PROCEDURES

2) Modify the GN173 entry for HCPCS S3854 as shown in Appendix A
3) Advise HSD to remove CPT 0037U (Targeted genomic sequence analysis, solid organ neoplasm, DNA analysis of 324 genes, interrogation for sequence variants, gene copy number amplifications, gene rearrangements, microsatellite instability and tumor mutational burden) from the EXCLUDED FILE and add to the DIAGNOSTIC PROCEDURES file
4) Add a new guideline regarding cancer genetic testing as shown in Appendix B
5) Delete GUIDELINE NOTE 148, BIOMARKER TESTS OF CANCER TISSUE

MOTION: To approve the recommendations as presented. CARRIES 6-0.

NOTE: The above recommendations were not approved at the March 2023 HERC meeting

Smoking cessation and elective surgery

Discussion: Smits reviewed the summary document.

Public testimony:

1) Richard Bruno, MD (family doctor at Central City Concern in Portland, a clinic with many homeless patients). The current policy unfairly affects low income/homeless/communities of color/patients with serious mental illness as these groups have a higher smoking rates. Their patients are being denied needed surgeries. Many surgical groups are requiring smoking cessation for more than 4 weeks, or no nicotine, which goes beyond the current OHP requirement. Pre-surgery smoking cessation should be voluntary rather than mandatory. If policy is continued, add further types of surgery to the non-elective list. Supports option 1 or 2.
2) Shimi Sharief, MD (medical director at CareOregon, CCO). Dr. Sharief is responsible for applying this guideline to CareOregon patients. Objective testing is not readily available and is another barrier. This guideline is unique to Oregon Medicaid. Structural racism and predatory marketing make lower income people more likely to smoke. This guideline has racist impacts. Impacts communities of color disproportionately. Supports option 1. She also stressed the importance of communication of any changes to providers across the state.
3) Joel Stegan (PA at Central City Concern). Mr. Stegan gave story of patient affecting this surgery: this patient cannot get colostomy reversal due to this policy. The impacts of not having surgery is not being taking into consideration. Patients are using illicit drugs due to chronic pain. Patients not able to work, etc. He is seeing the high costs of patients not getting care. Incidence of smoking much higher in the population served by this clinic and smoking cessation is harder for patients with unmet shelter needs or in

unsafe situations. Commercially insured or Medicare patients are not affected by this policy, which is unfair.

Discussion:
Saenger asked for data on the relative impact of smoking vs other conditions like diabetes on adverse surgical outcomes. Staff could not provide this specific information. He noted that there are also synergistic effects of multiple risk factors, like people with diabetes who smoke, on surgical outcomes. Smoking affects the outcomes of cardiac procedures that he performs. This type of guideline can help push patients to quit smoking.

The group discussed the evolution of HERC staff and CCO thinking regarding this guideline.

Hodges spoke as the CCO representative to the group. She felt that the current policy expressly allowed surgical consultation without smoking cessation. The current practice by provider groups denying this is unfortunate and unexpected. She noted that this policy was implemented due to evidence. She also noted that there is an exceptions process to allow people who cannot quit smoking to have surgery approved. She said many surgeons like this policy as it takes the onus off of them to require smoking cessation. Her CCO puts patients into case management when they are having trouble stopping smoking. This policy was never intended to create inequities or access issues.

Olson expressed concern that coverage of elective surgery for smokers would increase cost and expose patients to surgical complications. Access issues may be variable across the state and among different populations.

Pinzon raised concerns that the studies did not include houseless or mentally ill or other groups that are having a greater negative impact from this policy

Recommended Actions:

1) Change Ancillary Guideline A4 into a statement of intent as shown in Appendix B

MOTION: To approve the recommendations as presented. CARRIES 4-1 (Hodges voted Nay, Duty absent)

Single sided deafness coverage

Discussion: Smits reviewed the summary document.

Public testimony:

Scott Haanstad introduced himself as a person with single sided deafness and an OHP member. He provided written testimony as well. He has been appealing lack of coverage of single sided deafness by a CCO. He is an adult who needs cochlear implant to restore hearing in right ear, after being shot in the head. His quality of life has dramatically reduced. He has been hit by electric cars on multiple occasions due to not hearing them. There is a huge quality of life impact to restore bilateral hearing. He said he is an auditory learner and that bilateral hearing aids auditory learners and aids learning for people of all ages. Many private insurers pay for cochlear implants for unilateral deafness. He would like to see coverage for cochlear implants for single sided deafness.

The discussion among the subcommittee was that the members would like expert input on this topic. Staff were directed to reach out to experts and bring this topic back to a future meeting when an expert is able to attend.

Recommended Actions:

1) Tabled to a future meeting

Merging liver transplant lines

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

Recommended Actions:

1) Merge the following lines. The new line should contain all the ICD-10-CM codes contained in these lines and all the CPT/HCPCS codes on these lines.
    a. 162 BILIARY ATRESIA
    b. 241 ACUTE AND SUBACUTE NECROSIS OF LIVER; SPECIFIED INBORN ERRORS OF METABOLISM
    c. 263 CANCER OF LIVER OTHER THAN ANGIOSARCOMA
    d. 307 CIRRHOSIS OF LIVER OR BILIARY TRACT; BUDD-CHIARI SYNDROME; HEPATIC VEIN THROMBOSIS; INTRAHEPATIC VASCULAR MALFORMATIONS; CAROLI'S DISEASE
2) Title the new line: “CONDITIONS REQUIRING LIVER TRANSPLANT” Treatment: LIVER TRANSPLANT
3) Prioritize the new line as shown below

Line scoring:
Line XXX CONDITIONS REQUIRING LIVER TRANSPLANT
Scores in parentheses are for lines 162, 241, 263, 307
Category 6 (all lines are 6)
Impact on healthy life: 7 (7, 9, 7, 5)
Pain/Suffering: 4 (all lines are 4)

Population effects: 0
Vulnerable population: 0
Tertiary Prevention: 0 (1, 0, 0, 0)
Effectiveness: 3 (4, 3, 3, 3)
Need for services: 1.0 (all lines are 1.0)
Cost: 0.5 (1, 0, 1, 0)
Score: 1320
Line: 253

MOTION: To approve the recommendations as presented. CARRIES 6-0.

Store and forward codes

Discussion: Smits reviewed the summary document. Pinzon advocated for using these codes to improve access to SUD treatment and for chronic illness management. Olson noted that this type of care improves access, and is a low cost buffer for the added practice expenses from this type of care. The group approved staff option 2.

Recommended Actions:

1) Remove HCPCS G2010 and G2250 from line 662 and delete the GN173 entry for these codes
    a. Advise HSD to add G2010 and G2250 to the Ancillary file
2) Modify Ancillary guideline A5 as shown in appendix A

MOTION: To approve the recommendations as presented. CARRIES 6-0.

Vagus nerve stimulator for treatment resistant depression

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

Recommended Actions:

1) Add HCPCS K1020 (Non-invasive vagus nerve stimulator) to line 662 CONDITIONS FOR WHICH CERTAIN INTERVENTIONS ARE UNPROVEN, HAVE NO CLINICALLY IMPORTANT BENEFIT OR HAVE HARMS THAT OUTWEIGH BENEFITS
2) Modify GN173 as shown in Appendix A

MOTION: To approve the recommendations as presented. CARRIES 6-0.

Biliary colic guideline revision

Discussion: Smits reviewed the summary document. There was minimal discussion.

Recommended Actions:

1) Modify GN167 as shown in Appendix A

MOTION: To approve the recommendations as presented. CARRIES 6-0.

Trigger finger and trigger thumb

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

Recommended Actions:

1) Add ICD-10-CM M65.30 (Trigger finger, unspecified finger) and M65.33, M65.34 and M65.35 families (Trigger finger, specified fingers) to line 376 DISRUPTIONS OF THE LIGAMENTS AND TENDONS OF THE ARMS AND LEGS, EXCLUDING THE KNEE, RESULTING IN SIGNIFICANT INJURY/IMPAIRMENT and keep on line 590 SYNOVITIS AND TENOSYNOVITIS
2) Modify GN120 as shown in appendix A

MOTION: To approve the recommendations as presented. CARRIES 6-0.

Prostatic urethral lift guideline edits

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

Recommended Actions:

1) Modify GN145 as shown in Appendix A

MOTION: To approve the recommendations as presented. CARRIES 6-0.

NOTE: The above recommendations were not approved at the March 2023 HERC meeting

Breast reduction for macromastia

Discussion: Smits reviewed the summary document. It was noted that this is a commonly-requested surgery. The subcommittee felt that experts should be consulted before a decision is made. The topic was tabled until staff can contact experts to attend a future meeting for input and to answer questions.

Recommended Actions:

1) Tabled until a future meeting

Foraminal stenosis and spinal fusion

Discussion: Smits reviewed the summary document. Members generally supported staff option #2. Hodges raised concerns about some of the requirements in staff option #2. The guideline changes were modified to remove disc height loss and expectation that decompression alone would not be sufficient, as these criteria are not normally found in clinical notes.

Recommended Actions:

1) Modify GN37 as shown in Appendix A

MOTION: To approve the recommendations as modified. CARRIES 6-0.

Public Comment

No additional public comment was received.

Issues for next meeting

- Single sided deafness coverage for adults; cochlear implants for adults and children with single sided deafness
- Breast reduction for macromastia
- Note: due to lack of approval at the March 2023 HERC meeting, the following topics will be brought back to the next VBBS meeting:
    - Genetic testing for malignancies
    - Prostatic urethral lift guideline modifications

Next meeting

May 18, 2023, online.

Adjournment

The meeting adjourned at 12:45 PM.

Appendix A
Revised Guideline Notes

~~**ANCILLARY GUIDELINE A4, SMOKING CESSATION AND ELECTIVE SURGICAL PROCEDURES**~~

~~Surgical consultation is covered for patients who actively smoke and who are referred for surgical consultations; if elective surgery is recommended based on a consultation, the requirements of this guideline note apply.~~

~~Smoking cessation is required prior to elective surgical procedures for active tobacco users. Cessation is required for at least 4 weeks prior to the procedure and requires objective evidence of abstinence from smoking prior to the procedure.~~

~~Elective surgical procedures in this guideline are defined as surgical procedures which are flexible in their scheduling because they do not pose an imminent threat nor require immediate attention within 1 month. Procedures for contraceptive/sterilization purposes, procedures targeted to active cancers (i.e. when a delay in the procedure could lead to cancer progression), diagnostic procedures, and bloodless surgery (e.g., cataract surgery) are not subject to the limitations in this guideline note. This guideline applies regardless of procedure location and anesthesia type.~~

~~The well-studied tests for confirmation of smoking cessation include cotinine levels and exhaled carbon monoxide testing. However, cotinine levels may be positive in nicotine replacement therapy (NRT) users, smokeless tobacco and e-cigarette users (which are not contraindications to elective surgery coverage). In patients using nicotine products aside from combustible cigarettes the following alternatives to urine cotinine to demonstrate smoking cessation may be considered:~~

- ~~Exhaled carbon monoxide testing~~
- ~~Anabasine or anatabine testing (NRT or vaping)~~

~~Certain procedures, such as lung volume reduction surgery, bariatric surgery, erectile dysfunction surgery, and spinal fusion have 6 month tobacco abstinence requirements. See Guideline Notes 8, 100, 112 and 159.~~

ANCILLARY GUIDELINE A5, TELEHEALTH, TELECONSULTATIONS AND ONLINE/TELEPHONIC SERVICES

Telehealth services include a variety of health services provided by synchronous or asynchronous electronic communications, including secure electronic health portal, audio, or audio and video and clinician-to-clinician virtual consultations.

Criteria for coverage

The clinical value of the telehealth service delivered must reasonably approximate the clinical value of the equivalent services delivered in-person.

Coverage of telehealth services requires the same level of documentation, medical necessity, and coverage determinations as in-person visits.

Examples of covered telephone or online services include but are not limited to:

A) Extended counseling when person-to-person contact would involve an unwise delay or exposure to infectious disease.
B) Treatment of relapses that require significant investment of provider time and judgment.

C) Counseling and education for patients with complex chronic conditions.

Examples of non-covered telehealth services include but are not limited to:

A) Prescription renewal.
B) Scheduling a test.
C) Reporting normal test results.
D) Requesting a referral.
E) Services which are part of care plan oversight or anticoagulation management (CPT codes 99339-99340, 99374-99380 or 99363-99364).
F) Services which relate to or take place within the postoperative period of a procedure provided by the physician are not separately covered. (Such a service is considered part of the procedure and is not be billed separately.)

Codes eligible for telehealth delivery include 90785, 90791, 90792, 90832-90834, 90836, 90837-90840, 90846, 90847, 90951, 90952, 90954, 90955, 90957, 90958, 90960, 90961, 90963, 90964-90970, 96116, 96156-96171, 96160, 96161, 97802-97804, 99201-99205, 99211-99215, 99231-99233, 99307-99310, 99354-99357, 99406-99407, 99495-99498, G0108-G0109, G0270, G0296, G0396, G0397, G0406-G0408, G0420, G0421, G0425-G0427, G0438-G0439, G0442-G0447, G0459, G0506, G0508, G0509, G0513, G0514, G2086-G2088. Additional codes are covered when otherwise appropriate according to this guideline note and other applicable coverage criteria.

The originating site code Q3014 is covered only when the patient is present in an appropriate health care setting and receiving services from a provider in another location.

Clinician to Patient Services billed using specified codes indicating telephone or online service delivery

Covered telephonic and online services include services related to evaluation, assessment and management as well as other technology-based services (CPT 98966-98968, 99441-99443, 99421-99423, 98970-98972, G2012, G2061-G2063, G2251-G2252).

Covered telephone and online services billed using these codes do not include either of the following:

A) Services related to a service performed and billed by the physician or qualified health professional within the previous seven days, regardless of whether it is the result of patient-initiated or physician-requested follow-up.
B) Services which result in the patient being seen within 24 hours or the next available appointment.

Clinician-to-Clinician Consultations (telephonic, online or using electronic health record)

Covered interprofessional consultations include consultations delivered online, through electronic health records or by telephone (CPT 99446-99449, 99451-99452).

Store and Forward

Store and forward codes (HCPCS G2010, G2250) are only covered when billed concurrently with a code that includes medical decision making and communication with the patient (for example, HCPCS G2012).

Appendix A
Revised Guideline Notes

DIAGNOSTIC GUIDELINE D1, NON-PRENATAL GENETIC TESTING GUIDELINE

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

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

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

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

E) Related to preconception testing/carrier screening:

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

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

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

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

identified, duplication/deletion testing (CPT 81222) is covered. These tests may be ordered as reflex testing on the same specimen.

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

d) CPT 81225-81227, 81230-81231, 81418, 0380U (cytochrome P450). Covered only for determining eligibility for medication therapy if required or recommended in the FDA labelling for that medication. These tests have unproven clinical utility for decisions regarding medications when not required in the FDA labeling (e.g. psychiatric, anticoagulant, opioids).

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

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

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

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

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

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

k) CPT 81332, SERPINA1 (serpin peptidase inhibitor, clade A, alpha-1 antiproteinase, antitrypsin, member 1) (eg, alpha-1-antitrypsin deficiency), gene analysis, common variants (eg, *S and *Z): The alpha-1-antitrypsin protein level should be the first line test for a suspected diagnosis of AAT deficiency in symptomatic individuals with unexplained liver disease or obstructive lung disease that is not asthma or in a middle age individual

with unexplained dyspnea. Genetic testing of the anpha-1 phenotype test is appropriate if the protein test is abnormal or borderline. The genetic test is appropriate for siblings of people with AAT deficiency regardless of the AAT protein test results.

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

m) CPT 81430-81431, Hearing loss (eg, nonsyndromic hearing loss, Usher syndrome, Pendred syndrome); genomic sequence analysis panel: Testing for mutations in GJB2 and GJB6 need to be done first and be negative in non-syndromic patients prior to panel testing.

n) CPT 81440, 81460, 81465, mitochondrial genome testing: A genetic counseling/geneticist or metabolic consultation is required prior to ordering test.

o) CPT 81425-81427, whole genome sequencing: testing is only covered when
   i) The testing is for a critically ill infant up to one year of age admitted to an inpatient intensive care unit (NICU/PICU) with a complex illness of unknown etiology; AND
   ii) Whole genome sequencing is recommended by a medical geneticist or other physician sub-specialist, including but not limited to a neonatologist or pediatric intensivist with expertise in the conditions and/or genetic disorder for which testing is being considered.

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

GUIDELINE NOTE 37, SURGICAL INTERVENTIONS FOR CONDITIONS OF THE BACK AND SPINE OTHER THAN SCOLIOSIS

Lines 346,530

Spine surgery is included on Line 346 only in the following circumstances:

A) Decompressive surgery is included on Line 346 to treat debilitating symptoms due to central or foraminal spinal stenosis, and only when the patient meets the following criteria:
   1) Has MRI evidence of moderate or severe central or foraminal spinal stenosis AND either
      a) Has neurogenic claudication OR
      b) Has objective neurologic impairment consistent with the MRI findings. Neurologic impairment is defined as objective evidence of one or more of the following:
         i) Markedly abnormal reflexes
         ii) Segmental muscle weakness
         iii) Segmental sensory loss
         iv) EMG or NCV evidence of nerve root impingement
         v) Cauda equina syndrome
         vi) Neurogenic bowel or bladder
         vii) Long tract abnormalities

   Foraminal or central spinal stenosis causing only radiating pain (e.g. radiculopathic pain) is included only on Line 530.

B) Spinal fusion procedures are included on Line 346 for patients with MRI evidence of moderate or severe central or foraminal spinal stenosis only when one of the following conditions are met:
   1) spinal stenosis in the cervical spine (with or without spondylolisthesis) which results in objective neurologic impairment as defined above OR
   2) spinal stenosis in the thoracic or lumbar spine caused by spondylolisthesis resulting in signs and symptoms of neurogenic claudication and which correlate with xray flexion/extension films showing at least a 5 mm translation OR
   3) pre-existing or expected post-surgical spinal instability (e.g. degenerative scoliosis >10 deg, >50% of facet joints per level expected to be resected)
   4) Note: for foraminal stenosis, there must be MRI evidence of moderate or severe foraminal stenosis of the nerve root that correlates with the objective findings above

For all other indications, spine surgery is included on Line 530.

The following interventions are not included on these lines due to lack of evidence of effectiveness for the treatment of conditions on these lines, including cervical, thoracic, lumbar, and sacral conditions:

- local injections (including ozone therapy injections)
- botulinum toxin injection
- intradiscal electrothermal therapy
- therapeutic medial branch block
- coblation nucleoplasty
- percutaneous intradiscal radiofrequency thermocoagulation
- percutaneous laser disc decompression
- radiofrequency denervation
- corticosteroid injections for cervical pain
- intradiscal injections, including platelet rich plasma, stem cells, methylene blue, or ozone

Corticosteroid injections for low back pain with or without radiculopathy are only included on Line 530. Diagnostic anesthetic injections for selective nerve root blocks are included on Line 530 for lumbar or sacral symptoms.

The development of this guideline note was informed by HERC coverage guidances on Percutaneous Interventions for Low Back Pain, Percutaneous Interventions for Cervical Spine Pain, Low Back Pain: Corticosteroid Injections and Low Back Pain: Minimally Invasive and Non-Cordicosteroid Percutaneous Interventions. See https://www.oregon.gov/oha/HPA/DSI-HERC/Pages/Evidence-based-Reports.aspx

GUIDELINE NOTE 118, SEPTOPLASTY

Lines 42,119,202,246,287,466,506,525,577

Septoplasty is included on these lines when

A) The septoplasty is done to address symptomatic septal deviation or deformity which
   1) Fails to respond to a minimum 6 week trial of conservative management (e.g. nasal corticosteroids, decongestants, antibiotics); AND
   2) Results in one or more of the following:

a. Persistent or recurrent epistaxis, OR
b. Documented recurrent sinusitis felt to be due to a deviated septum and the patient meets criteria for sinus surgery in Guideline Note 35, SINUS SURGERY; OR
c. Nasal obstruction with documented absence of other causes of obstruction likely to be responsible for the symptoms (for example, nasal polyps, tumor, etc.) [note: this indication is included only on Line 577; OR

B) Septoplasty is performed in association with cleft lip or cleft palate repair or repair of other congenital craniofacial anomalies; OR

C) Septoplasty is performed as part of a surgery for a neoplasm or facial trauma involving the nose.

Septoplasty is not covered for treatment of obstructive sleep apnea.

GUIDELINE NOTE 120, ~~PEDIATRIC~~ TRIGGER THUMB AND TRIGGER FINGER

Line 376,590

Trigger finger and trigger thumb (ICD-10-CM M65.3 family) are included on line 376 only when there is documented interference with function of the hand. Up to 3 steroid injections are covered per digit.

Surgery is limited to

1) open surgical procedures under local anesthesia; AND
2) only after at least one steroid injection or a minimum of 3 weeks of splinting has been tried and the triggering persists or recurs; OR
3) the patient is diabetic; OR
4) the finger is permanently locked in the palm; OR
5) the patient is a child up to age 21 who has a trigger thumb that does not spontaneously resolve within 48 months of diagnosis. Immediate surgery may be considered for bilateral trigger thumb or trigger thumb with locking symptoms in children.

Otherwise trigger finger and trigger thumb are included on line 590.

NOTE: The guideline note changes below were not approved at the March 2023 HERC meeting

GUIDELINE NOTE 145, TREATMENTS FOR BENIGN PROSTATE ENLARGEMENT WITH LOWER URINARY TRACT SYMPTOMS

Line 327

For men with lower urinary tract symptoms (LUTS) due to benign prostate hyperplasia (BPH), surgical procedures are included on this line for patients with one of the following:

A) Refractory urinary retention; OR
B) Recurrent urinary tract infections due to BPH; OR
C) Recurrent bladder stones or gross hematuria due to BPH; OR
D) Severe symptoms (International Prostate Symptom Score (IPSS) of 20-35) in patients who are not candidates for drug treatment due to intolerable side effects or have failed ~~combination~~

~~therapy with an alpha-blocker and 5-alpha reductase inhibitor~~ a minimum of a 3-month trial of at least one standard BPH medication therapy ~~for at least 3 months~~.

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

- Age 45 ~~50~~ or older
- Estimated prostate volume < 100 ~~80~~ cc
- IPSS ≥ 13
- ~~No obstructive median lobe of the prostate identified on cystoscopy at the time of the procedure~~
- Not a candidate for drug treatment due to intolerable side effects or have failed a minimum of a 3-month trial of at least one standard BPH medication therapy.

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

- Botulinum toxin
- HIFU (High Intensity Focused Ultrasound)
- TEAP (Transurethral Ethanol Ablation of the Prostate)
- Laser coagulation (for example, VLAP/ILC)
- Prostatic artery embolization

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

NOTE: The guideline note changes below were not approved at the March 2023 HERC meeting

~~GUIDELINE NOTE 148, BIOMARKER TESTS OF CANCER TISSUE~~

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

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

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

- ~~Oncotype DX Breast Recurrence Score (CPT 81519) for breast tumors that are estrogen receptor positive, HER2 negative, and either lymph node negative, or lymph node positive with 1-3 involved nodes.~~
- ~~EndoPredict (CPT 81522) and Prosigna (CPT 81520 or PLA 0008M) for breast tumors that are estrogen receptor positive, HER2 negative, and lymph node negative.~~
- ~~MammaPrint (using CPT 81521, 81523 or HCPCS S3854) for breast tumors that are estrogen receptor or progesterone receptor positive, HER2 negative, lymph node negative, and only in those cases categorized as high clinical risk.~~

Appendix A
Revised Guideline Notes

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

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

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

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

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

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

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

~~For prostate cancer, Oncotype DX Genomic Prostate Score and Prolaris Score Assay (CPT 81541) are included on Line 662 CONDITIONS FOR WHICH CERTAIN INTERVENTIONS ARE UNPROVEN, HAVE NO CLINICALLY IMPORTANT BENEFIT OR HAVE HARMS THAT OUTWEIGH BENEFITS.~~

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

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

GUIDELINE NOTE 167, CHOLECYSTECTOMY FOR CHOLECYSTITIS AND BILIARY COLIC

Lines 55,641

Cholecystectomy for cholecystitis and biliary colic are including on Line 55 when meeting the following criteria:

A) For cholecystitis, with either:
   1) The presence of right upper quadrant abdominal pain, mass, tenderness or a positive Murphy's sign, AND

2) Evidence of inflammation (e.g. fever, elevated white blood cell count, elevated C reactive protein) OR
3) Ultrasound findings characteristic of acute cholecystitis or non-visualization of the gall bladder on oral cholecystegram or HIDA scan, or gallbladder ejection fraction of < 35%.

B) For biliary colic ~~(i.e. documented clinical encounter for right upper quadrant or epigastric pain with gallstones seen on imaging during each episode)~~ without evidence of cholecystitis or other complications ~~is included on Line 55~~ only when
1) Recurrent (i.e. 2 or more ~~episodes~~ documented clinical encounters with an exam consistent with gallstone induced pain in a one year period with at least one imaging study demonstrating gallstones) OR
2) A single episode in a patient at high risk for complications with emergent cholecystitis (e.g. immunocompromised patients, morbidly obese patients, diabetic patients) OR
3) When any of the following are present: elevated pancreatic enzymes, elevated liver enzymes or dilated common bile duct on ultrasound.

Otherwise, biliary colic is included on Line 641.

ICD-10-CM K82.8 (Other specified diseases of gallbladder) is included on Line 55 when the patient has porcelain gallbladder or gallbladder dyskinesia with a gallbladder ejection fraction <35%. Otherwise, K82.8 is included on Line 641

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

Line 662

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

Procedure Code	Intervention Description	Rationale	Last Review
~~G2010, G2250~~	~~Remote assessment of recorded video and/or images~~	~~Clinical value not established~~	~~January 2021~~
K1020	Non-invasive vagus nerve stimulator	Insufficient evidence of effectiveness	March 2023
22858, 22860	Total disc arthroplasty (artificial disc), anterior approach, including discectomy to prepare interspace (other than for decompression); second interspace, cervical/lumbar	Insufficient evidence of effectiveness	November 2022

Appendix A
Revised Guideline Notes

Procedure Code	Intervention Description	Rationale	Last Review
Breast Cancer Gene Expression tests billed with nonspecific codes (e.g. 81479, 81599, 84999~~,~~ ~~S3854~~)	Mammostrat Oncotype DX Breast DCIS Score IHC4 **NOTE:** This guideline note entry change was not approved at the March 2023 HERC meeting	Insufficient evidence of effectiveness	May, 2018 Coverage guidance

Appendix B
NEW GUIDELINE NOTES

NOTE: The guideline note below was not approved at the March 2023 HERC meeting

DIAGNOSTIC GUIDELINE DX, GENETIC TESTING OF MALIGNANCIES

A) Genetic tests on tumor tissue are covered as diagnostic, unless they are listed in guideline note 173 INTERVENTIONS THAT ARE UNPROVEN, HAVE NO CLINICALLY IMPORTANT BENEFIT OR HAVE HARMS THAT OUTWEIGH BENEFITS FOR CERTAIN CONDITIONS. To be covered, cancer genetic tests must be a CLIA-approved test or panel of tests that will affect clinical decision making after a biopsy proven diagnosis of malignancy. Examples of covered genetic panels include Foundation Medicine FoundationOneCDX (PLA 0037U), Knight Diagnostic Laboratories GeneTrails (CPT 81455) and Caris Life Sciences Molecular Intelligence (CPT 81479). A single CPT or HCPCS code is covered for each multigene panel performed on tumor tissue. Additional codes for individual genes and for molecular pathology procedures CPT 81400-81408 are excluded from coverage when the multigene panel is covered under the appropriate CPT or HCPCS code.

B) Such tests should have one of the following impacts on medical decision making:
   1) find a mutation for which there is an available therapy that is effective in slowing the growth of the cancer, OR
   2) exclude the use of ineffective therapies, OR
   3) select alternative treatment modalities, OR
   4) determine suitability for directing patients toward promising investigational therapies, OR
   5) establish a definitive diagnosis when other diagnostic approaches yield ambiguous results, OR
   6) find a mutation that indicates prognosis AND influences treatment unrelated to targeted therapies, such as decisions around bone marrow transplantation, high-intensity or low-intensity chemotherapy or radiation therapy, surgery, or palliation

C) Repeat testing may be required in the setting of patients who have clinically progressed per standardized professional guidelines after therapy. Coverage in this situation is limited to 3 times per primary malignancy unless there is indication for additional testing after individualized review of medical necessity.

STATEMENT OF INTENT X: SMOKING CESSATION AND ELECTIVE SURGERGICAL PROCEDURES

Tobacco smoking has been shown to increase the risk of surgical complications. It is the intent of the Commission that current tobacco smokers should be given access to appropriate smoking cessation therapy prior to elective surgical procedures. Pharmacotherapy (including varenicline, buproprion and all five FDA-approved forms of nicotine-replacement therapy) and behavioral counseling are included on line 5 TOBACCO DEPENDENCE.

Section 2.0

Staff Report

Section 3.0

Consent Agenda-

Straightforward Items

Straightforward Guideline Note Changes May 2023

Plain Language Summary:

Coverage question: Routine changes that may be approved without discussion.

Issue 1

1) The diagnostic guideline for wireless capsule endoscopy needs clarification. The current guideline was last reviewed in January 2016. The current guideline refers to "these lines" when it is a diagnostic guideline, which needs to be corrected. Additionally, 3 of the 4 CPT codes for wireless capsule endoscopy are on line 662/GN 173 as they do not meet the criteria of the guideline. The limitation of coverage to CPT 91110 (Gastrointestinal tract imaging, intraluminal (eg, capsule endoscopy), esophagus through ileum, with interpretation and report) should be clarified.
    a. HERC staff recommendation:
        i. Modify Diagnostic Guideline D9 as shown below

DIAGNOSTIC GUIDELINE D9, WIRELESS CAPSULE ENDOSCOPY

A) Wireless capsule endoscopy (CPT 91110 only) is covered ~~included on these lines~~ for diagnosis of:
1) Obscure GI bleeding suspected to be of small bowel origin with iron deficiency anemia or documented GI blood loss
2) Suspected Crohn's disease with prior negative work up

B) Wireless capsule endoscopy is not covered ~~included on these lines~~ for:
1) Colorectal cancer screening
2) Confirmation of lesions of pathology normally within the reach of upper or lower endoscopes (lesions proximal to the ligament of Treitz or distal to the ileum)

C) Wireless capsule endoscopy is only covered ~~included on these lines~~ when the following conditions have been met:
1) Prior studies must have been performed and been non-diagnostic
    a) GI bleeding: upper and lower endoscopy
    b) Suspected Crohn's disease: upper and lower endoscopy, small bowel follow through
2) Radiological evidence of lack of stricture
3) Only covered once during any episode of illness
4) FDA-approved devices must be used
5) Patency capsule should not be used prior to procedure

Other types of wireless capsule endoscopy (i.e. CPT 91111-91113) are included in Guideline Note 173 INTERVENTIONS THAT ARE UNPROVEN, HAVE NO CLINICALLY IMPORTANT BENEFIT OR HAVE HARMS THAT OUTWEIGH BENEFITS FOR CERTAIN CONDITIONS.

Straightforward Guideline Note Changes May 2023

Issue 2

2. The septoplasty guideline needs to be linked to line 202 SLEEP APNEA, NARCOLEPSY AND REM BEHAVIORAL DISORDER, as it has a clause related to sleep apnea.

a. HERC staff recommendation:

i. Modify GN118 as shown below and add to line 202

GUIDELINE NOTE 118, SEPTOPLASTY

Lines 42,119,202,246,287,466,506,525,577

Septoplasty is included on these lines when

A) The septoplasty is done to address symptomatic septal deviation or deformity which
   1) Fails to respond to a minimum 6 week trial of conservative management (e.g. nasal corticosteroids, decongestants, antibiotics); AND
   2) Results in one or more of the following:
      a. Persistent or recurrent epistaxis, OR
      b. Documented recurrent sinusitis felt to be due to a deviated septum and the patient meets criteria for sinus surgery in Guideline Note 35, SINUS SURGERY; OR
      c. Nasal obstruction with documented absence of other causes of obstruction likely to be responsible for the symptoms (for example, nasal polyps, tumor, etc.) [note: this indication is included only on Line 577; OR

B) Septoplasty is performed in association with cleft lip or cleft palate repair or repair of other congenital craniofacial anomalies; OR

C) Septoplasty is performed as part of a surgery for a neoplasm or facial trauma involving the nose.

Septoplasty is not covered for obstructive sleep apnea and not included on line 202 SLEEP APNEA, NARCOLEPSY AND REM BEHAVIORAL DISORDER.

Issue 3

3. GN155 contains a reference to a code that is no longer allowed for electronic tumor fields (HCPCS A4555 electrode/transducer for use with electrical stimulation device used for cancer treatment, replacement only). The electrodes are now bundled into the global rental fee is HCPCS E0766. HERC staff reviewed the current NCCN guidelines for treatment of glioblastoma, and there is no change from the recommendation reviewed in 2016 to create GN155. Additionally, the Optune device is only FDA approved for patients aged 22 years and older (adults).

a) HERC staff recommendation:

i. Modify GN 155 as shown below

GUIDELINE NOTE 155, ELECTRIC TUMOR TREATMENT FIELDS FOR GLIOBLASTOMA

Line 294

Electric tumor treatment fields (~~codes~~ HCPCS ~~A4555 and~~ E0766) are included on this line only when

A) Used for the initial treatment of supratentorial glioblastoma
B) Used in combination with temozolomide

C) The patient is age 22 or older

Premarket Approval (PMA)

New Search[22] Back to Search Results

Note: This medical device record is a PMA supplement. A supplement may have changed the device description/function or indication from that approved in the original PMA. Be sure to look at the original PMA[23] record for more information.

Device	OPTUNE (FORMERLY THE NOVOTTF-100A SYSTEM)
Generic Name	Stimulator, Low Electric Field, Tumor Treatment
Applicant	Novocure GmbH Park 6 Ch-6039 Root D4
PMA Number	P100034
Supplement Number	S013
Date Received	04/10/2015
Decision Date	10/05/2015
Product Code	NZK[24]
Docket Number	15M-4015
Notice Date	11/02/2015
Advisory Committee	Neurology
Clinical Trials	NCT00916409[25]
Supplement Type	Panel Track
Supplement Reason	Labeling Change - Indications/Instructions/Shelf Life/Tradename
Expedited Review Granted?	No
Combination Product	No

Approval Order Statement

APPROVAL FOR THE OPTUNE (FORMERLY THE NOVOTTF-100A SYSTEM). THIS DEVICE IS INDICATED AS A TREATMENT FOR ADULT PATIENTS (22 YEARS OF AGE OR OLDER) WITH HISTOLOGICALLY-CONFIRMED GLIOBLASTOMA MULTIFORME (GBM). OPTUNE WITH TEMOZOLOMIDE IS INDICATED FOR THE TREATMENT OF ADULT PATIENTS WITH NEWLY DIAGNOSED, SUPRATENTORIAL GLIOBLASTOMA FOLLOWING MAXIMAL DEBULKING SURGERY AND COMPLETION OF RADIATION THERAPY TOGETHER WITH CONCOMITANT STANDARD OF CARE CHEMOTHERAPY. OPTUNE WAS PREVIOUSLY APPROVED IN 2011 FOR THE TREATMENT OF RECURRENT GBM WITH THE FOLLOWING INDICATIONS FOR USE (IFU): OPTUNE IS INDICATED FOLLOWING HISTOLOGICALLY-OR RADIOLOGICALLY-CONFIRMED RECURRENCE IN THE SUPRA-TENTORIAL REGION OF THE BRAIN AFTER RECEIVING CHEMOTHERAPY. THE DEVICE IS INTENDED TO BE USED AS A MONOTHERAPY, AND IS INTENDED AS AN ALTERNATIVE TO STANDARD MEDICAL THERAPY FOR GBM AFTER SURGICAL AND RADIATION OPTIONS HAVE BEEN EXHAUSTED.

Approval Order	Approval Order[26]
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25. http://www.clinicaltrials.gov/ct2/results?term=NCT00916409
26. https://www.accessdata.fda.gov/cdrh_docs/pdf10/P100034S013A.pdf

27. https://www.accessdata.fda.gov/cdrh_docs/pdf10/P100034S013B.pdf
28. https://www.accessdata.fda.gov/cdrh_docs/pdf10/P100034S013C.pdf
29. https://www.accessdata.fda.gov/cdrh_docs/pdf10/P100034S013D.pdf

Inflammatory Skin Disease Guideline Edits May 2023

Plain Language Summary:

Coverage question: Should the guideline for a disease affecting the skin be updated?

Should OHP cover this treatment? Yes. The Pharmacy & Therapeutics Committee and experts agree the guideline should be updated to the guideline. The current guideline states you must use treatments that are not widely used today before you can use the more effective and more available treatments.

Coverage Question: How should the inflammatory skin disease guideline be modified?

Question source: Pharmacy and Therapeutics Committee (P&T)

Background: P&T staff have noted some issues with the current severe inflammatory skin disease guideline that need to be addressed:

1) Phototherapy is difficult to include in prior authorization (PA) requirements, and has little utilization for atopic dermatitis (eczema). P&T staff are requesting that HERC consider removing this requirement from the atopic dermatitis section of the guideline
2) Crisaborole and pimecrolimus are only FDA approved for mild to moderate AD. They are required prior to other treatments for AD in the current guideline. P&T staff recommend removing mention of these medications from the guideline.

Current Prioritized List/Coverage status:

GUIDELINE NOTE 21, SEVERE INFLAMMATORY SKIN DISEASE

Lines 426,482,504,533,542,555,656

Inflammatory skin conditions included in this guideline are:

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

Inflammatory Skin Disease Guideline Edits May 2023

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

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

Otherwise, these conditions above are included on Lines 482, 504, 533, 542, 555 and 656.

For severe psoriasis, treatments included on this line are topical agents, phototherapy, targeted immune modulator medications and other systemic medications.

For severe atopic dermatitis/eczema, treatments included on this line are topical moderate- to high-potency corticosteroids, topical calcineurin inhibitors (for example, pimecrolimus, tacrolimus), narrowband UVB, topical phosphodiesterase (PDE)-4 inhibitors, and oral immunomodulatory therapy (e.g. cyclosporine, methotrexate, or oral corticosteroids). Targeted immune modulators (for example, dupilumab) are included on this line when:

A) Prescribed in consultation with a dermatologist or allergist or immunologist, AND
B) The patient has failed (defined as inadequate efficacy, intolerable side effects, or side effects that pose a health risk) either
    1) a 4 week trial of a combination of topical moderate to high potency topical steroids and a topical non-steroidal agent OR
        an oral immunomodulator, OR
    2) 12 weeks of phototherapy.

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

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

Other payer policies:

1) **Aetna 2023**, prior authorization criteria for dupilumab
    a) Atopic dermatitis
        i) The member (12 years of age or older) has a documented diagnosis of moderate to severe atopic dermatitis; **and**
        ii) The member has an Investigator's Global Assessment (IGA) score of 3 or 4 (see *Appendix*); **and**
        iii) Exacerbating factors that may contribute to atopic dermatitis have been evaluated and addressed (e.g., non-adherence with therapy, environmental triggers, patch testing); **and**
        iv) The member has recent history (within 6 months of the screening visit) of failure* [Failure is defined as the member being refractory to daily treatment for at least 1 month for topical corticosteroids and 6 weeks for topical calcineurin inhibitor or the

maximum duration recommended by the product's prescribing information], intolerance, or contraindication to both of the following:
(a) Treatment with one medium to very high potency topical corticosteroid (e.g., betamethasone dipropionate [Diprolene AF], mometasone furoate [Elocon], clobetasol propionate [Temovate] – see *Appendix* for complete list); **and**
(b) Treatment with one topical calcineurin inhibitor (e.g., pimecrolimus [Elidel], tacrolimus [Protopic]); **and**

v) The member does not have a parasitic infection; **and**
vi) Dupilumab (Dupixent) will not be used concomitantly with other biologics, such as benralizumab (Fasenra), etanercept (Enbrel), infliximab (Remicade), mepolizumab (Nucala), omalizumab (Xolair), or reslizumab (Cinqair).

2) **Cigna 2023**, prior authorization criteria for dupilumab
a) Atopic dermatitis
i) Individual is ≥ 6 months of age; AND
ii) Individual has atopic dermatitis involvement estimated to be ≥ 10% of the body surface area according to the prescriber; AND
iii) Individual meets ALL of the following criteria (a, b, and c):
(a) Individual has tried at least one medium-, medium-high, high-, and/or super-high-potency prescription topical corticosteroid; AND
(b) This topical corticosteroid was applied daily for at least 28 consecutive days; AND
(c) Inadequate efficacy was demonstrated with this topical corticosteroid therapy, according to the prescriber; AND
iv) The medication is prescribed by or in consultation with an allergist, immunologist, or dermatologist.

Expert input:

Sabra Leitenberger, OHSU pediatric dermatology

I agree with taking out phototherapy requirement, pimecrolimus, and crisaborole. Agree also with topical corticosteroids and topical tacrolimus (we do use them concurrently) or oral immunomodulator failure. Four weeks is plenty for trial of topicals.

Julie Dhossche, OHSU pediatric dermatology

I think overall this would streamline the guidelines to reflect the current FDA indication for dupilumab: for the treatment of adult and pediatric patients aged 6 months and older with moderate-to-severe atopic dermatitis whose disease is not adequately controlled with topical prescription therapies or when those therapies are not advisable.

I agree phototherapy has generally fallen out of favor given our newer therapies and it may be time to remove this. We often will use maximum topical therapy for severe eczema—which means both steroidal and non-steroidal options, so yes we use them concurrently all the time. For pediatrics especially, I want to allow for use of only topicals for a month before moving to dupilumab if not adequately controlled after that-- since I would not use cyclosporine or methotrexate in say, an 8 month old, given side effect profiles.

Inflammatory Skin Disease Guideline Edits May 2023

HERC staff summary:

Several edits need to be made to the atopic dermatitis section of the severe inflammatory skin disease guideline. These edits are recommended by both P&T staff and experts.

HERC staff recommendation:

1) Modify GN21 as shown below

GUIDELINE NOTE 21, SEVERE INFLAMMATORY SKIN DISEASE

Lines 426,482,504,533,542,555,656

Inflammatory skin conditions included in this guideline are:

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

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

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

Otherwise, these conditions above are included on Lines 482, 504, 533, 542, 555 and 656.

For severe psoriasis, treatments included on this line are topical agents, phototherapy, targeted immune modulator medications and other systemic medications.

For severe atopic dermatitis/eczema, treatments included on this line are topical moderate- to high-potency corticosteroids, topical calcineurin inhibitors (for example, ~~pimecrolimus,~~ tacrolimus), narrowband UVB, ~~topical phosphodiesterase (PDE)-4 inhibitors,~~ and oral immunomodulatory therapy (e.g. cyclosporine, methotrexate, or oral corticosteroids). Targeted immune modulators (for example, dupilumab) are included on this line when:

A) Prescribed in consultation with a dermatologist or allergist or immunologist, AND
B) The patient has failed (defined as inadequate efficacy, intolerable side effects, or side effects that pose a health risk) ~~either~~

~~1)~~ a 4 week trial of a combination of topical moderate to high potency topical steroids and a topical non-steroidal agent OR

an oral immunomodulator~~, OR~~

~~2) 12 weeks of phototherapy.~~

Inflammatory Skin Disease Guideline Edits May 2023

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

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

Solid Organ Transplant Guideline May 2023 Revisions

Plain Language Summary:
Background: Clarifying when more than one organ can be transplanted together.

Should OHP cover this treatment? Staff recommends changing the guideline to have general reasons why more than one organ should be transplanted at the same time.

Questions:
Should the solid organ transplant guideline be modified to be more inclusive of multi-organ transplant?

Question source: Providence CCO

Issue: In January, 2023 a new comprehensive solid organ transplant guideline was adopted. This guideline will be used for the Rules Advisory Committee (RAC) that OHA is convening to update the OARs around organ transplant. Providence CCO reached out to HERC staff requesting clarification of coverage of liver/kidney dual transplants. The current guideline only mentions heart/lung and heart/kidney transplants. The intent of the HERC was to have dual organ transplants covered if the patient qualifies for each organ individually and only the dual transplant will be effective at improving the patient's condition.

HERC staff recommendation:
1) Modify the new solid organ transplant guideline as shown below

GUIDELINE NOTE 42 SOLID ORGAN TRANSPLANTS
Lines 83,99,162,239,240,241,263,264,307,310,563

Solid organ transplants are included on these lines only when BOTH the general criteria AND the organ specific criteria below are met:

GENERAL TRANSPLANT CRITERIA
1) The patient must have irreversible end-stage organ disease or failure and must have medical therapy optimized; AND
2) The patient is a suitable surgical candidate for transplant surgery, indicated by ALL of the following:
    a. No significant uncontrolled co-morbidities such as (not an all-inclusive list):
        i. End-stage cardiac, renal, hepatic or other organ dysfunction unrelated to the primary indication for transplant
        ii. Uncontrolled HIV infection
        iii. Multiple organ compromise secondary to infection, malignancy, or condition with no known cure
        iv. Ongoing or recurrent active infections that are not effectively treated
        v. Psychiatric instability severe enough to jeopardize adherence to medical regimen
        vi. Active alcohol or illicit drug dependency; AND
    b. No tobacco smoking for at least 6 months unless the transplant is done on an emergent basis (other than for corneal transplants); AND

c. Demonstrated compliance with medical treatments and ability to understand and comply with the post-transplant immunosuppressive regimen

It is the intent of the Commission that transplant should be covered if the specific ICD-10-CM code is not included on the same lines as the transplant procedure codes, if it is determined to be the medically appropriate treatment for that particular patient's clinical situation.

HEART TRANSPLANT

Adults must have New York Heart Association (NYHA) Class III or IV cardiac disease or malignant ventricular arrhythmias unresponsive to medical and/or surgical therapy. Children must have intractable heart failure or a congenital abnormality not amenable to surgical correction.

LUNG TRANSPLANT

Patients must have symptoms at rest directed related to chronic pulmonary disease and resultant severe functional limitations.

~~COMBINED HEART/LUNG TRANSPLANTATIONS~~

~~The patent must meet criteria for both heart and lung transplantation and neither a heart transplant or lung transplant alone would be expected to improve the individual's condition and chances of survival.~~

KIDNEY TRANSPLANT

The patient must have one of the following:

1) End-stage renal disease requiring hemodialysis or continuous ambulatory peritoneal dialysis; OR
2) End-stage renal disease, evidence by a creatinine clearance below 20 ml/min or development of symptoms of uremia; OR
3) Chronic renal failure with anticipated deterioration to end-stage renal disease requiring dialysis

~~HEART-KIDNEY TRANSPLANTS~~

~~Patients under consideration for heart/kidney transplant must qualify for each individual type of transplant with the exception of any exclusions due to heart and/or kidney disease.~~

LIVER TRANSPLANT

The patient must have irreversible, end stage, liver damage with no other available treatment options.

PANCREAS TRANSPLANTS

Pancreas transplant alone are not included on any transplant line. Simultaneous pancreas kidney transplant (SPT) is only included on this line for type I diabetes mellitus with end stage renal disease (E10.2). Pancreas after kidney transplant (PAK) is only included on this line for other type I diabetes mellitus with secondary diagnosis of Z94.0 (Kidney transplant status).

ISLET CELL AUTOTRANSPLANT

Islet cell autotransplant (TP IAT) is only included on line 250 when done with total pancreatectomy AND when the patient meets ALL of the following criteria:

A) Has acquired intractable chronic pancreatitis
B) Has intractable abdominal pain despite optimal medical therapy
C) Has not responded to more conservative surgery including endoscopic pancreatic decompression or in whom such surgery is not clinically indicated

D) Has not responded to nerve block procedures or in whom these interventions are not clinically indicated
E) Has been assessed by the multidisciplinary team and determined to have pain of an organic nature and are thought likely to achieve significant pain reduction from TP IAT
F) Is an appropriate candidate for major surgery
G) Is able to adhere to the complex medical management required following TP IAT
H) Does not have type 1 diabetes, known pancreatic cancer or any other condition that would prevent isolation of islet cells for autotransplant
I) Does not have a condition (e.g. portal vein thrombosis or significant parenchymal liver disease such as cirrhosis of the liver) which increases the risks associated with islet cell transplant
J) Does not have any other contraindications such as active alcohol abuse

INTESTINE TRANSPLANT

Intestine transplant is included on this line only for patients with failure of total parenteral nutrition (TPN) as indicated by one of the following, and no contraindications to transplant:

A) Impending or overt liver failure due to TPN, indicated by elevated serum bilirubin and/or liver enzymes, splenomegaly, thrombocytopenia, gastro-esophageal varices, coagulopathy, peristomal bleeding, or hepatic fibrosis/cirrhosis;
B) Thrombosis of ≥ 2 central veins, including jugular, subclavian, and femoral veins;
C) Two or more episodes of systemic sepsis due to line infection, per year, or one episode of septic shock, acute respiratory distress syndrome, and/or line related fungemia;
D) Frequent episodes of dehydration despite IV fluid supplementation;
E) Other complications leading to loss of vascular access

COMBINED ORGAN TRANSPLANTATIONS

The patent must meet criteria for both organs being considered for transplant and neither single organ transplant nor non-simultaneous transplant would be expected to improve the individual's condition and chances of survival.

Section 4.0

Pediatric ENT topics

Tonsillectomy for Recurrent Throat Infection

Plain Language Summary:

Coverage question: Should we change the guideline for the removal of tonsils for infections that keep happening?

Should OHP cover this treatment? Yes. The definition of an "attack" should be changed to allow for more coverage.

Coverage Question: Should the current guideline regarding tonsillectomy be modified to change the definition of "episode" to include sore throat with another factor, not just documented positive streptococcal screens/cultures to agree with the updated AAO guideline?

Question source: Holly Jo Hodges, CCO medical director

Background: The current tonsillectomy guideline requires a certain number of "attacks of strep tonsillitis" in a certain time period "where an attack is considered a positive culture/screen and where an appropriate course of antibiotic therapy has been completed." This wording is based on previous American Academy of Otolaryngology guidelines. In 2019, The AAO published new guidelines regarding tonsillectomy indications. The 2019 AAO guidelines now define an "attack" as a sore throat plus the presence of ≥1 additional factor [fever, cervical adenopathy, tonsillar exudate, positive strep culture].

In the 2019 guidelines, tonsillectomy has been downgraded from a "recommendation" to an "option" while watchful waiting has been upgraded from a "recommendation" to a "strong recommendation."

The 2019 AAO guideline notes that:

1) Controversy persists regarding the actual benefits of tonsillectomy as compared with observation and medical treatment of throat infections. A comparative effectiveness review from the Agency for Healthcare Research and Quality (AHRQ) reported that in children with recurrent throat infections undergoing tonsillectomy, the number of throat infections (moderate strength of evidence) and associated health care utilization and work/school absences (low strength of evidence) improved in the first postsurgical year. These benefits did not persist, and long-term results were lacking

Dr. Hodges is requesting a review of our current guideline for tonsillectomy based on provider requests.

Tonsillectomy for Recurrent Throat Infection

Previous HSC/HERC reviews:

The last review of tonsillectomy for recurrent strep infections occurred in March, 2019. At that time the AAO 2019 guidelines were reviewed, and the current guideline was used as the basis for modifying the guideline. Stricter criteria were adopted such as increasing the number of required "attacks", but no change was made to the definition of "attack."

Current Prioritized List/Coverage status:

Line: 368

Condition:	STREPTOCOCCAL SORE THROAT AND SCARLET FEVER; VINCENT'S DISEASE; ULCER OF TONSIL; UNILATERAL HYPERTROPHY OF TONSIL (See Guideline Note 36)
Treatment:	MEDICAL THERAPY, TONSILLECTOMY/ADENOIDECTOMY
ICD-10:	A38.0-A38.9,A69.0-A69.1,J02.0,J03.00-J03.01,J35.1,J35.3-J35.8
CPT:	42820-42826,98966-98972,99051,99060,99070,99078,99184,99202-99239,99281-99285, 99291-99404,99411-99449,99451,99452,99468-99472,99475-99480,99487-99491,99495-99498,99605-99607
HCPCS:	G0068,G0071,G0088-G0090,G0248-G0250,G0406-G0408,G0425-G0427,G0463,G0466, G0467,G0490,G0508-G0511,G2012,G2211,G2212,G2214,G2251,G2252

GUIDELINE NOTE 36, ADENOTONSILLECTOMY FOR INDICATIONS OTHER THAN OBSTRUCTIVE SLEEP APNEA

Lines 42,47,368,551

Tonsillectomy/adenotonsillectomy is an appropriate treatment for patients with:

A) Seven or more documented attacks of strep tonsillitis in a year or 5 or more documented attacks of strep tonsillitis in each of two consecutive years or 3 or more documented attacks of strep tonsillitis per year in each of the three consecutive years where an attack is considered a positive culture/screen and where an appropriate course of antibiotic therapy has been completed; or,

B) A history of two or more peritonsillar abscesses OR when general anesthesia is required for the surgical drainage of a peritonsillar abscess and tonsillectomy is performed at the time of the surgical drainage; or,

C) Unilateral tonsillar hypertrophy in adults; unilateral tonsillar hypertrophy in children with other symptoms suggestive of malignancy.

ICD-10-CM J35.1 and J35.3 are included on Line 368 only for 1) unilateral tonsillar hypertrophy in adults and 2) unilateral tonsillar hypertrophy in children with other symptoms suggestive of malignancy. Bilateral tonsillar hypertrophy and unilateral tonsillar hypertrophy in children without other symptoms suggestive of malignancy are included only on Line 551.

See Guideline Notes D8 and 27 for diagnosis and treatment of obstructive sleep apnea in children.

Tonsillectomy for Recurrent Throat Infection

Expert guidelines:

Mitchell 2019, AAO guidelines on tonsillectomy

1) Controversy persists regarding the actual benefits of tonsillectomy as compared with observation and medical treatment of throat infections. A comparative effectiveness review from the Agency for Healthcare Research and Quality (AHRQ) reported that in children with recurrent throat infections undergoing tonsillectomy, the number of throat infections (moderate strength of evidence) and associated health care utilization and work/school absences (low strength of evidence) improved in the first postsurgical year. These benefits did not persist, and long-term results were lacking
2) STATEMENT 1. WATCHFUL WAITING FOR RECURRENT THROAT INFECTION: Clinicians should recommend watchful waiting for recurrent throat infection if there have been >7 episodes in the past year, >5 episodes per year in the past 2 years, or \3 episodes per year in the past 3 years. Strong recommendation based on systematic reviews of randomized controlled trials with limitations and observational studies with a preponderance of benefit over harm
    a) Level of evidence: high
    b) aggregate quality evidence: A (systematic reviews of randomized controlled trials that fail to show clinically important advantages of surgery over observation alone)
3) STATEMENT 2. RECURRENT THROAT INFECTION WITH DOCUMENTATION: Clinicians may recommend tonsillectomy for recurrent throat infection with a frequency of at least 7 episodes in the past year, at least 5 episodes per year for 2 years, or at least 3 episodes per year for 3 years with documentation in the medical record for each episode of sore throat and ≥ 1 of the following: temperature >38.3 C (101 F), cervical adenopathy, tonsillar exudate, or positive test for group A beta-hemolytic streptococcus. Option based on systematic reviews of randomized controlled trials, with a balance between benefit and harm
        i) Sore throat plus the presence of ≥1 additional factor [fever, cervical adenopathy, tonsillar exudate OR positive strep culture] qualifies as a counting episode.
        ii) Antibiotics had been administered in conventional dosage for proved or suspected streptococcal episodes
        iii) Documentation
            (a) Each episode and its qualifying features had been substantiated by contemporaneous notation in a clinical record, OR
            (b) If not fully documented, subsequent observance by the clinician of 2 episodes of throat infection with patterns of frequency and clinical features consistent with the initial history
                1. This last statement allows children who meet all other criteria for tonsillectomy except documentation to nonetheless qualify for surgery if the same pattern of reported illness is observed and documented by the clinician in 2 subsequent episodes. Because of this tendency to improve with time, a 12-month period of observation is usually recommended prior to consideration of tonsillectomy as an intervention.
    a) Aggregate evidence quality: Grace B, systematic review of randomized controlled trials with limitations in the consistency with the randomization process regarding recruitment and follow-up
    b) Level of confidence in evidence: Medium

c) Benefits: Patients who proceed with the option of tonsillectomy will achieve a modest reduction in the frequency and severity of recurrent throat infection for 1 year after surgery and a modest reduction in frequency of group A streptococcal infection for 1 year after surgery
d) Risks, harms, costs: Risk and morbidity of tonsillectomy, including but not limited to persistence of throat infection, pain and missed activity after surgery, bleeding, dehydration, injury, and anesthetic complications; direct cost of tonsillectomy, direct nonsurgical costs (antibiotics, clinician visit), and indirect costs (caregiver time, time missed from school) associated with recurrent infections
e) Benefits-harm assessment: Balance between benefit and harm

Other payer policies:

1) **Aetna 2022**
    a. [Tonsillectomy for current throat infection] is considered **medically necessary** for individuals less than 18.0 years of age who meet one or more of the criteria below:
        i. A history of recurrent throat infection with a frequency of at least:
            1. Seven episodes in the past year; **or**
            2. Five episodes per year for 2 years; **or**
            3. Three episodes per year for 3 years;
            and
        ii. Documentation in the medical record for each episode of sore throat which includes at least one of the following:
            1. Temperature greater than 38.3 °C (100.9 °F); **or**
            2. Cervical adenopathy; **or**
            3. Tonsillar exudates or erythema; **or**
            4. Positive test for Group A β-hemolytic streptococcus (GABHS).
2) **Anthem BCBS 2022**
    a. Exactly the same criteria as listed for Aetna above

Expert input:

Dr. Peggy Kelley, pediatric ENT:

I have read your document and it does now reflect my understanding of the intent of the AAO Guidelines 2019.

Tonsillectomy for Recurrent Throat Infection

HERC staff summary:

The AAO 2019 guideline regarding tonsillectomy modified the definition of an "attack." Staff recommends modifying our current guideline to agree with the AAO guideline.

The modifications outlined below will reduce the need for documented strep rapid tests and/or cultures. It would also remove the requirement for a course of antibiotic therapy. Instead, an "attack" can simply be a sore throat with documentation of a fever or abnormal clinical exam.

HERC staff recommendation:

1) Modify GN36 as shown below

GUIDELINE NOTE 36, ADENOTONSILLECTOMY FOR INDICATIONS OTHER THAN OBSTRUCTIVE SLEEP APNEA

Lines 42,47,368,551

Tonsillectomy/adenotonsillectomy is an appropriate treatment for patients with:

~~A) Seven or more documented attacks of strep tonsillitis in a year or 5 or more documented attacks of strep tonsillitis in each of two consecutive years or 3 or more documented attacks of strep tonsillitis per year in each of the three consecutive years where an attack is considered a positive culture/screen and where an appropriate course of antibiotic therapy has been completed; or,~~

A) ~~B)~~Individuals less than 18 years of age with a history of recurrent throat infection
   1) Throat infections must occur with a frequency of at least:
      i) Seven episodes in the past year; **or**
      ii) Five episodes per year for 2 years; **or**
      iii) Three episodes per year for 3 years;
      and
   b) Documentation in the medical record for each episode of sore throat which includes at least one of the following:
      i) Temperature greater than 38.3 °C (100.9 °F); **or**
      ii) Cervical adenopathy; **or**
      iii) Tonsillar exudates or erythema; **or**
      iv) Positive test for Group A β-hemolytic streptococcus (GABHS); OR

B) A history of two or more peritonsillar abscesses OR when general anesthesia is required for the surgical drainage of a peritonsillar abscess and tonsillectomy is performed at the time of the surgical drainage; or,

C) Unilateral tonsillar hypertrophy in adults; unilateral tonsillar hypertrophy in children with other symptoms suggestive of malignancy.

ICD-10-CM J35.1 and J35.3 are included on Line 368 only for 1) unilateral tonsillar hypertrophy in adults and 2) unilateral tonsillar hypertrophy in children with other symptoms suggestive of malignancy. Bilateral tonsillar hypertrophy and unilateral tonsillar hypertrophy in children without other symptoms suggestive of malignancy are included only on Line 551.

Tonsillectomy for Recurrent Throat Infection

See Guideline Notes D8 and 27 for diagnosis and treatment of obstructive sleep apnea in children.

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Clinical Practice Guideline: Tonsillectomy in Children (Update)

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

Abstract

Objective. This update of a 2011 guideline developed by the American Academy of Otolaryngology–Head and Neck Surgery Foundation provides evidence-based recommendations on the pre-, intra-, and postoperative care and management of children 1 to 18 years of age under consideration for tonsillectomy. Tonsillectomy is defined as a surgical procedure performed with or without adenoidectomy that completely removes the tonsil, including its capsule, by dissecting the peritonsillar space between the tonsil capsule and the muscular wall. Tonsillectomy is one of the most common surgical procedures in the United States, with 289,000 ambulatory procedures performed annually in children <15 years of age based on the most recent published data. This guideline is intended for all clinicians in any setting who interact with children who may be candidates for tonsillectomy.

Purpose. The purpose of this multidisciplinary guideline is to identify quality improvement opportunities in managing children under consideration for tonsillectomy and to create explicit and actionable recommendations to implement these opportunities in clinical practice. Specifically, the goals are to educate clinicians, patients, and/or caregivers regarding the indications for tonsillectomy and the natural history of recurrent throat infections. Additional goals include the following: optimizing the perioperative management of children undergoing tonsillectomy, emphasizing the need for evaluation and intervention in special populations, improving the counseling and education of families who are considering tonsillectomy for their children, highlighting the management options for patients with modifying factors, and reducing inappropriate or unnecessary variations in care. Children aged 1 to 18 years under consideration for tonsillectomy are the target patient for the guideline.

For this guideline update, the American Academy of Otolaryngology–Head and Neck Surgery Foundation selected a panel representing the fields of nursing, anesthesiology, consumers, family medicine, infectious disease, otolaryngology–head and neck surgery, pediatrics, and sleep medicine.

Key Action Statements. The guideline update group made *strong recommendations* for the following key action statements (KASs): (1) Clinicians should recommend watchful waiting for recurrent throat infection if there have been <7 episodes in the past year, <5 episodes per year in the past 2 years, or <3 episodes per year in the past 3 years. (2) Clinicians should administer a single intraoperative dose of intravenous dexamethasone to children undergoing tonsillectomy. (3) Clinicians should recommend ibuprofen, acetaminophen, or both for pain control after tonsillectomy.

The guideline update group made *recommendations* for the following KASs: (1) Clinicians should assess the child with recurrent throat infection who does not meet criteria in KAS 2 for modifying factors that may nonetheless favor tonsillectomy, which may include but are not limited to multiple antibiotic allergies/intolerance, PFAPA (periodic fever, aphthous stomatitis, pharyngitis, and adenitis), or history of >1 peritonsillar abscess. (2) Clinicians should ask caregivers of children with obstructive sleep-disordered breathing and tonsillar hypertrophy about comorbid conditions that may improve after tonsillectomy, including growth retardation, poor school performance, enuresis, asthma, and behavioral problems. (3) Before performing tonsillectomy, the clinician should refer children with obstructive sleep-disordered breathing for polysomnography if they are <2 years of age or if they exhibit any of the following: obesity, Down syndrome, craniofacial abnormalities, neuromuscular disorders, sickle cell disease, or mucopolysaccharidoses. (4) The clinician should advocate for polysomnography prior to tonsillectomy for obstructive

sleep-disordered breathing in children without any of the comorbidities listed in KAS 5 for whom the need for tonsillectomy is uncertain or when there is discordance between the physical examination and the reported severity of oSDB. (5) Clinicians should recommend tonsillectomy for children with obstructive sleep apnea documented by overnight polysomnography. (6) Clinicians should counsel patients and caregivers and explain that obstructive sleep-disordered breathing may persist or recur after tonsillectomy and may require further management. (7) The clinician should counsel patients and caregivers regarding the importance of managing posttonsillectomy pain as part of the perioperative education process and should reinforce this counseling at the time of surgery with reminders about the need to anticipate, reassess, and adequately treat pain after surgery. (8) Clinicians should arrange for overnight, inpatient monitoring of children after tonsillectomy if they are <3 years old or have severe obstructive sleep apnea (apnea-hypopnea index ≥ 10 obstructive events/hour, oxygen saturation nadir $<80\%$, or both). (9) Clinicians should follow up with patients and/or caregivers after tonsillectomy and document in the medical record the presence or absence of bleeding within 24 hours of surgery (primary bleeding) and bleeding occurring later than 24 hours after surgery (secondary bleeding). (10) Clinicians should determine their rate of primary and secondary posttonsillectomy bleeding at least annually.

The guideline update group made a *strong recommendation against* 2 actions: (1) Clinicians should not administer or prescribe perioperative antibiotics to children undergoing tonsillectomy. (2) Clinicians must not administer or prescribe codeine, or any medication containing codeine, after tonsillectomy in children younger than 12 years.

The policy level for the recommendation about documenting recurrent throat infection was an *option:* (1) Clinicians may recommend tonsillectomy for recurrent throat infection with a frequency of at least 7 episodes in the past year, at least 5 episodes per year for 2 years, or at least 3 episodes per year for 3 years with documentation in the medical record for each episode of sore throat and ≥ 1 of the following: temperature $>38.3°C$ (101°F), cervical adenopathy, tonsillar exudate, or positive test for group A beta-hemolytic streptococcus.

Differences from Prior Guideline

(1) Incorporating new evidence profiles to include the role of patient preferences, confidence in the evidence, differences of opinion, quality improvement opportunities, and any exclusion to which the action statement does not apply.
(2) There were 1 new clinical practice guideline, 26 new systematic reviews, and 13 new randomized controlled trials included in the current guideline update.
(3) Inclusion of 2 consumer advocates on the guideline update group.
(4) Changes to 5 KASs from the original guideline: KAS 1 (Watchful waiting for recurrent throat infection), KAS 3 (Tonsillectomy for recurrent infection with modifying factors), KAS 4 (Tonsillectomy for obstructive sleep-disordered breathing), KAS 9 (Perioperative pain counseling), and KAS 10 (Perioperative antibiotics).
(5) Seven new KASs: KAS 5 (Indications for polysomnography), KAS 6 (Additional recommendations for polysomnography), KAS 7 (Tonsillectomy for obstructive sleep apnea), KAS 12 (Inpatient monitoring for children after tonsillectomy), KAS 13 (Postoperative ibuprofen and acetaminophen), KAS 14 (Postoperative codeine), and KAS 15a (Outcome assessment for bleeding).
(6) Addition of an algorithm outlining KASs.
(7) Enhanced emphasis on patient and/or caregiver education and shared decision making.

Keywords

tonsillectomy, adenotonsillectomy, child, tonsillitis, sleep-disordered breathing, obstructive sleep apnea, polysomnography

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Tonsillectomy is one of the most common surgical procedures in the United States, with 289,000 ambulatory procedures performed annually in children

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Treatment of Single-sided Deafness

Plain Language Summary:

Coverage question: Should treatment of deafness in one ear be covered for adults? Should a surgically placed device that helps a person with deafness in one ear hear sound (cochlear implants) be covered for adults or children?

Should OHP cover this treatment? No, for adults. Treatment of adults for deafness in one ear has some limited benefit in certain situations, there is no evidence treatment improves quality of life. Treatment of children with deafness in one ear with cochlear implants may provide developmental benefits and should be covered.

Coverage Questions: Should treatment of single-sided deafness be expanded to adults? Should additional treatment modalities be added for single-sided deafness?

Question source: VBBS

Background: At the January 2023 VBBS meeting, the cochlear implant guideline was revised. As part of that discussion, Dr. Yael Raz from OHSU ear, nose and throat doctor (ENT) asked for a review of treatment modalities for single-sided deafness. Dr. Raz noted that sudden single-sided hearing loss is much more treatable than long standing single-sided hearing loss. She also noted that cochlear implants are being used for the treatment of single-sided hearing loss, although the current Prioritized List guideline restricts cochlear implants to bilateral severe hearing impairment. Dr. Raz also recommended looking at coverage for contralateral routing of signal systems (CROS) and bone-anchored hearing aids (BAHA) for adults (current coverage for both of these is limited to children up to age 21). VBBS members were interested in an updated review of coverage of single-sided deafness, with quality of life being included as a coverage factor. The last review of coverage of single-sided deafness by HERC was in 2014.

Single-sided deafness (SSD), also called unilateral hearing loss, is defined as normal or near-normal hearing in one ear and a severe-to-profound hearing loss in the other ear. Common causes of SSD in adulthood include acoustic neuroma (a type of benign tumor on the nerve leading from the inner ear to the brain), inner ear infections like labyrinthitis, and Ménière's disease (a disorder of the inner ear). In some cases, the cause is not known, for example in sudden onset sensorineural hearing loss. Difficulties in daily life as a result of SSD vary considerably from person to person. They may include difficulties in understanding speech in noisy environments and knowing which direction sounds are coming from.

Treatments for single-sided deafness include conventional hearing aids, bone anchored hearing aids (BAHA) and contralateral routing of signal (CROS) system. BAHAs are surgically implanted devices that conduct sound to the inner ear and are used when a patient has conductive hearing loss (outer or middle ears that do not conduct sound, but the cochlea and inner ear function normally). CROS hearing aids are a nonsurgical management option consisting of a hearing aid worn on the impaired ear containing a microphone and transmitter. This hearing aid transmits the acoustical signal to a receiver in a hearing aid worn on the better hearing ear.

Treatment of Single-sided Deafness

In recent years, there has been increased interest and research into unilateral cochlear implants as a treatment for SSD.

At the March, 2023 VBBS meeting, this topic was discussed. Testimony was heard from an OHP member with single sided deafness regarding how his condition has dramatically reduced his quality of life. Evidence was reviewed showing limited benefit on quality of life with treatment. HERC staff were directed to reach out to experts for input.

The prevalence of single sided deafness in children has been postulated to be 3.6 out of 1000 children (0.36%) [Dewyer et al 2022]. Single sided deafness is adults has a prevalence of 0.1-0.15% of the US population.

Previous HSC/HERC reviews:

Coverage of single-sided deafness was last reviewed in 2014. At that time, coverage was added for children with a new guideline. Current coverage of single-sided deafness remains limited to persons under the age of 21, and includes conventional hearing aids, contralateral routing of signal (CROS) systems, and bone anchored hearing aids (BAHA). The restriction for children only was based on the evidence that treatment aids in language development and school success. Indications for BAHA and for cochlear implants have been reviewed by HERC in the past few years.

Current Prioritized List/Coverage status:

Line:311 HEARING LOSS - AGE 5 OR UNDER
Treatment: includes hearing aids, BAHA, CROS

Line:326 SENSORINEURAL HEARING LOSS
Treatment: COCHLEAR IMPLANT

Line:446 HEARING LOSS - OVER AGE OF FIVE (See Guideline Notes 103,51,143 and 154)
Treatment: includes hearing aids, BAHA, CROS

GUIDELINE NOTE 31, COCHLEAR IMPLANTATION

Line 326

Patients will be considered candidates for cochlear implants if the following criteria are met:

A) Children who are either
   1) Any age with severe to profound sensorineural hearing loss in both ears (defined as 4-frequency PTA > 80 dB HL or 2-frequency PTA > 85); OR
   2) Aged 12 months an older with between 65 and 85 dB hearing loss in both ears whose early aided auditory skill development and speech and language progress indicate a persistent, or widening, gap in age appropriate auditory and language skills
B) Adults with bilateral severe to profound sensorineural hearing impairment (defined as >71 dB hearing loss in both ears) with limited benefit from appropriate hearing (or vibrotactile) aids.

Limited benefit from amplification is defined by test scores of less than or equal to 60% correct in the best-aided listening condition on recorded tests of open-set sentence cognition

C) No medical contraindications
D) High motivation and appropriate expectations (both patient and family, when appropriate)

Bilateral cochlear implants are included on this line. Simultaneous implantation appears to be more cost-effective than sequential implantation.

GUIDELINE NOTE 103, BONE ANCHORED HEARING AIDS

Lines 311,446

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

A) The patient is aged 5-20 years for initial implanted bone anchored hearing aids or headband mounted BAHA devices; headband mounted BAHA devices may be used for children under age 5; AND
B) The patient has one of the following:
    1) Permanent bilateral conductive or mixed hearing loss (for example, congenital malformation of the middle/external ear, microtia, or ossicular disease) unable to be aided by conventional air conducting devices; OR
    2) Unilateral conductive hearing loss with ear canal stenosis or ear canal atresia that is unlikely to benefit from surgery; OR
    3) Profound unilateral sensorineural hearing loss when the contralateral ear has normal hearing with or without a hearing aid; OR
    4) Temporary bilateral conductive hearing loss in patients with cleft palate and middle ear effusions until their palate is repaired and tympanostomy tubes can be placed (for BAHA headband only)

Continuation and maintenance (including repair/replacement) of these devices is included on these lines. This includes patients over the age of 20 who received these devices in childhood or adolescence.

Use of BAHA for treatment of tinnitus is not covered.

GUIDELINE NOTE 143, TREATMENT OF UNILATERAL HEARING LOSS

Lines 311,446

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

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

Treatment of Single-sided Deafness

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

Treatment of Single-sided Deafness

Evidence:

Treatment of adult SSD with CROS or BAHA

1) **Hampton 2021**, systematic review and meta-analysis of bone conduction devices for single-sided sensorineural deafness with quality of life
    a. N=11 studies (203 patients)
        i. participants with SSD (defined as pure tone average >70 dB hearing loss in the worse hearing ear and <30 dB in the better hearing ear)
        ii. Small before-after studies (N=12-25)
        iii. Intervention was BAHA
    b. General quality of life measure
        i. Data on the mean changes measured by HUI-3 comprehensive status were available from 3 studies with 45 patients. No significant change was detected in mean scores (overall mean change, 0.03; 95% CI, −0.04 to 0.10). The smallest difference in HUI-3 scores considered to have clinical significance is 0.05.
    c. Conclusion: This systematic review and meta-analysis found that BCDs are associated with significant improvements in hearing-related QOL as measured by APHAB and SSQ scores in adult patients, whereas no difference was found in the measures of generic QOL.
2) **Kitterick 2016**, systematic review and meta-analysis of hearing instruments for unilateral severe to profound sensorineural hearing loss in adults
    a. N=27 studies
        i. Bone conduction hearing aids, CROS, cochlear implant (CI)
        ii. Most studies were before-after comparisons. 3 studies with matched controls (case-control or cohort studies)
        iii. Low to moderate quality studies
    b. Meta-analyses of two studies evaluating air conduction devices (ACD) effects (Niparko et al. 2003; Wazen et al. 2003) and three studies evaluating bone conduction devices (BCD) effects (Niparko et al. 2003; Wazen et al. 2003; Dumper et al. 2009) identified no significant change in speech-reception thresholds (SRT) following use of either type of device [BAHA or CROS]
    c. Two studies reported a statistically significant improvement in speech perception in quiet after cochlear implantation. However, in both cases, speech perception was assessed when participants listened using only their implanted ear. Neither study reported equivalent outcomes when participants also had the use of their nonimplanted ear
    d. The available evidence suggests that rerouting devices (e.g. BAHA, CROS) provide benefits to speech perception in noise when the signal to noise ratio (SNR) is more favorable at the impaired ear (IE) but degrade speech perception when the SNR is less favorable at the IE. There is an absence of evidence for any effect of rerouting signals on speech perception when the SNR is similar at both ears. There is also a lack of evidence for the effects of cochlear implant use on speech perception in noise due to variations in testing methodologies across studies. The evidence for additional benefits from one device type over another is limited and inconclusive.
    e. The evidence suggests that rerouting signals to the normal ear does not improve the ability to determine the location of a sound. There is currently a lack of evidence to indicate whether CI can restore the ability to localize sounds and meta-analysis of the available evidence is limited by the use of inconsistent testing methodologies.

f. There is a lack of evidence for the effects of any intervention on health-related quality of life
g. Conclusions: Devices that reroute sounds from an ear with a severe to profound hearing loss to an ear with minimal hearing loss may improve speech perception in noise when signals of interest are located toward the impaired ear. However, the same device may also degrade speech perception as all signals are rerouted indiscriminately, including noise. Although the restoration of functional hearing in both ears through cochlear implantation could be expected to provide benefits to speech perception, the inability to synthesize evidence across existing studies means that such a conclusion cannot yet be made. For the same reason, it remains unclear whether cochlear implantation can improve the ability to localize sounds despite restoring bilateral input

Treatment of pediatric or adult SSD with unilateral cochlear implants

1) **Peters 2021**, CINGLE-trial of cochlear implants compared to BAHA and CROS
   a) N=120 adult patients
   b) CI (n = 28), BCD (n = 25), CROS (n = 34), and No treatment (n = 26)
   c) Speech perception in noise:
      i) For the CI group, there was a statistically significant improvement in speech perception in noise (with speech and noise coming from the front) at 3 and 6 months follow-up compared to baseline. Also the BCD group had a significant improvement compared to baseline, but only at 6 months follow-up. There were no significant changes for the CROS and No treatment groups
   d) Quality of life scores
      i) Speech, Spatial and Qualities of hearing (SSQ) scale: There was a significant improvement (higher score) for all treatment groups at 3 and 6 months follow-up compared to baseline (Fig 10). There was no significant change compared to baseline for the No treatment group
      ii) APHAD questionnaire: All treatment groups scored significantly better than the No treatment group at 3 and 6 months follow-up. The CI group had significantly better scores than the CROS group at 3 and 6 months follow-up, and also significantly better scores than the BCD group at 6 months follow-up.
      iii) Glasgow Benefit Inventory (GBI): On the general subscale, the scores improved (i.e. >0) in all treatment groups. The CI group had a significantly better score than the CROS group at 3 months follow-up.
   e) Conclusion: In this RCT, we compared CI, BCD, CROS, and No treatment for patients with SSD. Speech perception in noise improved in all configurations for the CI group, whereas speech perception in noise improved or deteriorated for the BCD and CROS groups depending on the configuration. Sound localization improved in the CI group only.
2) **Assouly 2020**, systematic review of the use of cochlear implants for tinnitus
   a) N=7 prospective cohort studies (105 patients, children and adults)
      i) Pts had SSD and tinnitus
      ii) Risk of bias moderate in 2 studies, serious in 5 studies
   b) We found a clinically relevant tinnitus reduction in all included studies for every reported follow-up moment from 3 months and beyond
   c) Conclusion: Our systematic review reveals that electrical stimulation by cochlear implants in patients with a primary complaint of tinnitus has a positive impact on

tinnitus distress. Nevertheless, only small sample sizes were found and studies showed considerable risks of bias

3) **Levy 2020**, systematic review and meta-analysis of cochlear implantation for treatment of tinnitus in SSD
   a) N=17 studies (247 patients)
      i) 4 studies at high risk of bias, 2 studies at low to high risk, 1 study at low risk
   b) Tinnitus Handicap Inventory (THI)
      i) According to six studies, CI resulted in a mean THI difference of –35.4 [–55.8 to –15.0] with significant overall effect ($p < 0.001$)
   c) Conclusion: patients experienced significant reduction in their scores, representing an overall improvement in tinnitus severity that likely translates to improvement in patient quality of life
4) **Marx 2020**: Prospective cohort study on treatment of SSD
   a) N=155 patients
      i) Patients self-selected to received CROS, bone conduction device (BCD), or cochlear implants or no treatment
   b) CROS was chosen by 75 subjects, followed by cochlear implantation (n = 51), BCD (n = 18) and abstention (n = 11). Patients who opted for cochlear implantation had a poorer quality of life (P = .03)

Treatment of unilateral deafness in children with cochlear implants

1) **Benchetrit 2020**, systematic review and meta-analysis of cochlear implantation in children with single sided deafness
   a. N=12 observational cohort studies (119 children total, studies ranged from 3 to 23 patients)
      i. 6 studies included in the meta-analysis
   b. Speech perception in noise
      i. N=8 studies (49 children)
      ii. Thirty-nine of 49 children (79.6%) experienced improved speech perception in noise after cochlear implantation
      iii. Overall, 5 of the 8 studies (with 30 of 49 children [61.2%]) that assessed speech perception in noise reported a clinically meaningful improvement with the implant among all patients
      iv. Long duration of deafness (>4 years in congenital SSD and >7 years in perilingual SSD) was the most commonly proposed reason for lack of improvement.
   c. Speech perception in quiet
      i. N=6 studies (42 children)
      ii. Overall, 34 children (81.0%) experienced improvement from the cochlear implantation, and their mean scores ranged from 56% to 100%
   d. Sound localization
      i. N=6 studies
      ii. Device use was associated with decreased root-mean-square (RMS) error and improved sound localization (MD, –24.78°; 95% CI, –34.16° to –15.40°)
      iii. Most children in these studies (n = 55 of 62 [88.7%]) showed improvement in sound localization 1 to 2 years after cochlear implantation, with mean reduction

of 24.78° in localization error. All studies reported clinical improvement of sound localization at most angles.

e. Patients with acquired SSD and shorter duration of deafness compared with those with congenital SSD reported greater improvements in speech (MD, 2.27; 95% CI, 1.89-2.65 vs 1.58; 95% CI, 1.00-2.16) and spatial (MD, 2.95; 95% CI, 2.66-3.24 vs 1.68; 95% CI, 0.96-2.39) hearing qualities.
f. The duration of deafness among device nonusers was statistically significantly longer than the duration of deafness among regular device users (median difference, 6.84; 95% CI, 4.02-9.58).
g. CONCLUSIONS AND RELEVANCE This systematic review and meta-analysis found that cochlear implantation for children with SSD was associated with clinically meaningful improvements in audiological and patient-reported outcomes; shorter duration of deafness may lead to better outcomes.

2) **Brown 2021**, CUHL trial of cochlear implantation for childhood unilateral hearing loss
   a. N=20 children, cohort study
      i. Moderate to profound sensorineural hearing loss in one ear and normal hearing in the other ear
      ii. Subjects were required to be between 3.5 and 6.5 years of age at the time of cochlear implantation
   b. word score perception in quiet significantly improved (1% to 50%, P < .0001) by 12 months after activation.
   c. Speech perception in noise by BKB-SIN significantly improved in all three noise configurations; there was a 3.6 dB advantage in head shadow (P < .0001), a 1.6 dB advantage in summation (P = .003), and a 2.5 dB advantage in squelch (P = .0001).
   d. Localization improved by 26 degrees at 9 months (P < .0001).
   e. Speech, Spatial, and Qualities (SSQ) demonstrated significant improvements in speech (5.2 to 7.4, P = .0012), qualities of hearing (5.9 to 7.5, P = .0056), and spatial hearing (2.7 to 6.6, P < .0001). SSQ subscales associated with binaural hearing were significantly improved, as was listening effort (P = .0082). Subjects demonstrated a non-significant improvement in fatigue.
   f. Conclusions: This study demonstrates that children with UHL significantly benefit from cochlear implantation

Expert guidelines

1) **Park 2022**, American cochlear implant alliance task force guidelines for clinical assessment and management of cochlear implantation in children with single-sided deafness
   a. Cochlear implantation to address SSD in an ear with cochlear nerve deficiency is contraindicated. Accurate diagnosis of nerve deficiency is important because it is present in almost half of children with SSD. Therefore, high resolution 3D MRI of the internal auditory canals is recommended rather than computer tomography alone
   b. Cochlear implantation should be considered a priority for children at risk of hearing loss progression in the better hearing ear. Children with SSD due to bacterial meningitis should be implanted promptly
   c. Younger age at implantation is expected to be advantageous in children with SSD. Children with longer lengths of deafness may experience fewer benefits and should be

counseled as such. The impact of age and length of deafness is not yet fully understood in this population.

d. A CI evaluation is recommended for children with a unilateral three frequency pure tone average (3FPTA) of >60 dB HL and/or an aided SII < 0.65 because these children are unlikely to receive adequate benefit from traditional amplification.
e. Trials with re-routing devices are not recommended for children seeking binaural hearing as these devices are not able to provide the brain with bilateral input and the trial could delay a time-sensitive procedure.

Other payer policies:

CROS and BAHA

Most private payers appear to be paying for BAHA or CROS for any age person with single-sided deafness

Cochlear implants for single-sided deafness

1) **Anthem BCBS 2022**: cochlear implants for unilateral deafness is not medically necessary
2) **Premara BCBS 2022**: cochlear implantation as a treatment for patients with unilateral hearing loss, with or without tinnitus, is considered investigational
3) **Cigna 2022**:
    a. Unilateral Sensorineural Hearing Loss. A traditional cochlear implant is considered medically necessary for the treatment of profound sensorineural hearing loss when an individual meets ALL of the following criteria:
        i. age ≥ five years
        ii. obtains limited benefit from an appropriately fitted unilateral hearing aid in the ear to be implanted
        iii. EITHER of the following
            1. profound sensorineural hearing loss in one ear and normal hearing or mild sensorineural hearing loss in the other ear (i.e., single-sided deafness [SSD])
            2. profound sensorineural hearing loss in one ear and mild to moderately severe sensorineural hearing loss in the other ear, with a difference of at least 15 dB in pure tone averages (PTAs) between ears (i.e., asymmetric hearing loss [AHL])
        iv. NOTE: • For an individual ≥ age 18 years and above, limited benefit from unilateral amplification is defined by test scores of five percent correct or less on monosyllabic consonant-nucleus-consonant (CNC) words in quiet when tested in the ear to be implanted alone. • For an individual age 5–18 years, insufficient functional access to sound in the ear to be implanted determined by aided speech perception test scores of five percent or less on developmentally appropriate monosyllabic word lists when tested in the ear to be implanted alone. • Profound hearing loss is defined as having a PTA of 90 dB HL or greater at 500 Hz, 1000 Hz, 2000 Hz and 4000 Hz. • Normal hearing is defined as having a PTA of up to 15 dB HL at 500 Hz, 1000 Hz, 2000 Hz and 4000 Hz. Mild hearing loss is defined as having a PTA of up to 30 dB HL at 500 Hz, 1000 Hz, 2000 Hz and 4000 Hz. • Mild to moderately severe hearing loss is defined as having a PTA ranging from 31 to up to 55 dB HL at 500 Hz, 1000 Hz, 2000 Hz and 4000 Hz.

Treatment of Single-sided Deafness

4) Aetna 2023

1. Aetna considers uniaural (monaural) cochlear implantation medically necessary for individuals aged 1 year and older with single-sided deafness (SSD) or asymmetric hearing loss (AHL) who meet the following criteria:
   a. Persons with single-sided deafness (SSD) who have profound sensorineural hearing loss in one ear and normal hearing or mild sensorineural hearing loss in the other ear, who have obtained limited benefit from a one-month or longer trial of an appropriately fitted unilateral hearing aid in the ear to be implanted; *or*
   b. Persons with asymmetric hearing loss (AHL) who have profound sensorineural hearing loss in one ear and mild to moderately severe sensorineural hearing loss in the other ear who have obtained limited benefit from a one-month or longer trial of an appropriately fitted unilateral hearing aid in the ear to be implanted.

   For adults 18 years of age or older with SSD or AHL, limited benefit from unilateral amplification is defined by aided speech perception test scores of 5 % correct or less on monosyllabic consonant-nucleus-consonant (CNC) words in quiet when tested in the ear to be implanted alone. For children and adolescents with SSD or AHL, insufficient functional access to sound in the ear to be implanted must be determined by aided speech perception test scores of 5% or less on developmentally appropriate monosyllabic word lists when tested in the ear to be implanted alone.

   Before implantation with a cochlear implant, individuals with SSD or AHL must have at least one month of experience wearing a hearing aid, a CROS hearing aid or other relevant device and not show any subjective benefit.

   For SSD and AHL indications, profound hearing loss is defined as having a PTA of 90 dB HL or greater at 500 Hz, 1000 Hz, 2000 Hz and 4000 Hz. Normal hearing is defined as having a PTA of up to 15 dB HL at 500 Hz, 1000 Hz, 2000 Hz and 4000 Hz. Mild hearing loss is defined as having a PTA of up to 30 dB HL at 500 Hz, 1000 Hz, 2000 Hz and 4000 Hz. Mild to moderately severe hearing loss is defined as having a PTA ranging from 31 to up to 55 dB HL at 500 Hz, 1000 Hz, 2000 Hz and 4000 Hz.

Expert input:

Dr. Peggy Kelley, pediatric ENT

> If the hearing loss is identified early it is possible to significantly improve the child's language development and other developmental factors, and in this way reduce future costs for extra educational resources… We already have screened and found the children with hearing loss so it would make sense to me to treat aggressively without harm (see info on hearing aid and CROS aid below). On big hurdle is the speed with which the field is progressing.

From her contact Jennifer Drohosky, audiologist at Children's Hospital Colorado

> CROS does not provide binaural stimulation. Technically, the criterion states a month trial with some sort of a device. Not a hearing aid AND a CROS, but rather, a trial of one (CROS, BCHD, or HA). The HA might provide some input, but it is often distorted at those levels of a severe to profound SNHL. So we have really shied away from hearing aids when it's a no response or

profound loss. It has the potential to do more harm than good. The CROS and BCHD are known to be detrimental in noisy situations, and the CROS is not appropriate for young children typically. In no way does it simulate potential benefit from a CI. It's a not very invasive trial, but kind of a waste of time. Other children's hospitals are not recommended a trial with any device, but we understand that insurance may not get that.

Treatment of Single-sided Deafness

HERC staff summary: Treatment of single-sided deafness in adults with BAHA or CROS appears to have some limited benefit in terms of specific hearing situations. However, these devices do not appear to have benefits for overall quality of life based on two recent systematic reviews/meta-analyses.

Treatment of single-sided deafness in adults with or without tinnitus with cochlear implants is an area of active study. The published literature mainly consists of small studies at high risk of bias. There does appear to be some improvement in sound perception in nose and sound localization. There also appears to be improvement in some patients for tinnitus severity, but this improvement appears to vary widely between patients. Quality of life outcomes are not consistent across studies. Major insurers are variable in coverage of cochlear implants for single-sided deafness.

Use of cochlear implants for single-sided deafness appears in children to have evidence of benefit in speech perception and sound localization based on small cohort studies. Expert input supports use of cochlear implants for children. This group may have developmental benefits from cochlear implantation in terms of stimulation of the auditory cortex and may have additional benefits in terms of ability to participate in school.

HERC staff recommendations:

1) Do not add coverage for BAHA, CROS, or cochlear implants for single-sided deafness in adults
2) Discuss adding cochlear implants for single-sided deafness in children
    a. If coverage for cochlear implants is added for children, modifications to GN 31 and GN 143 are suggested below

GUIDELINE NOTE 31, COCHLEAR IMPLANTATION

Line 326

Patients will be considered candidates for bilateral cochlear implants if the following criteria are met:

A) Children who are either
    1) Any age with severe to profound sensorineural hearing loss in both ears (defined as 4-frequency PTA > 80 dB HL or 2-frequency PTA > 85); OR
    2) Aged 12 months an older with between 65 and 85 dB hearing loss in both ears whose early aided auditory skill development and speech and language progress indicate a persistent, or widening, gap in age appropriate auditory and language skills
B) Adults with bilateral severe to profound sensorineural hearing impairment (defined as >71 dB hearing loss in both ears) with limited benefit from appropriate hearing (or vibrotactile) aids. Limited benefit from amplification is defined by test scores of less than or equal to 60% correct in the best-aided listening condition on recorded tests of open-set sentence cognition
C) No medical contraindications
D) High motivation and appropriate expectations (both patient and family, when appropriate)

Patients will be considered candidates for unilateral cochlear implants if the following criteria are met:

A) The patient is a child under age 21; AND
B) Has severe to profound sensorineural hearing loss in one ear (defined as 4-frequency PTA > 90 dB HL) and normal hearing or mild hearing loss in the other ear; AND
C) Has obtained limited benefit from a one-month or longer trial of an appropriately fitted unilateral hearing aid, CROS hearing aid or other relevant assistive device in the ear to be implanted . Limited benefit as determined by aided speech perception test scores of 5% or less

on developmentally appropriate monosyllabic word lists when tested in the ear to be implanted alone.

D) No medical contraindications, including imaging showing no cochlear nerve deficiency in the deaf ear

E) High motivation and appropriate expectations (both patient and family, when appropriate)

~~Bilateral cochlear implants are included on this line. Simultaneous implantation appears to be more cost-effective than sequential implantation.~~

GUIDELINE NOTE 143, TREATMENT OF UNILATERAL HEARING LOSS

Lines 311,446

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

1. For mild to moderate sensorineural unilateral hearing loss (defined as 26-70 dB hearing loss at 500, 1000 and 2000 Hz), first line intervention should be a conventional hearing aid, with second line therapy being contralateral routing of signal (CROS) system
2. For severe to profound unilateral sensorineural hearing loss (defined as 71 dB hearing loss or greater at 500, 1000 and 2000 Hz), first line therapy should be a contralateral routing of signal (CROS) system with second line therapy being a bone anchored hearing aid (BAHA). BAHA SoftBand therapy may be first line therapy for children under age 5 or patients with severe ear deformities (e.g. microstia, severe canal atresia). Unilateral cochlear implants may be considered per Guideline Note 31 COCHLEAR IMPLANTATION.

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

Original Article

Pediatric Single-Sided Deafness: A Review of Prevalence, Radiologic Findings, and Cochlear Implant Candidacy

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Nicholas A. Dewyer, MD[1], Sullivan Smith, MD[2], Barbara Herrmann, PhD, CCC-A[3], Katherine L. Reinshagen, MD[4], and Daniel J. Lee, MD, FACS[5,6]

Abstract

Objective: To characterize the prevalence, imaging characteristics, and cochlear implant candidacy of pediatric patients with single-sided deafness (SSD).

Methods: An audiometric database of patients evaluated at a large tertiary academic medical center was retrospectively queried to identify pediatric patients (<18 years old) with SSD, defined as severe to profound sensorineural hearing loss in one ear and normal hearing in the other. Medical records of identified patients were reviewed to characterize the prevalence, etiology, and cochlear implant candidacy of pediatric patients with SSD.

Results: We reviewed audiometric data obtained from 1993 to 2018 for 52,878 children at our institution. 191 (0.36%) had the diagnosis of SSD. Cochlear nerve deficiency (either hypoplasia or aplasia) diagnosed on MRI and/or CT was the most common etiology of SSD and was present in 22 of 88 (25%) pediatric SSD patients with available imaging data. 70 of 106 (66%) pediatric SSD patients with available imaging had anatomy amenable to cochlear implantation.

Conclusions: Pediatric SSD is a rare condition and the most common etiology based on radiology is cochlear nerve deficiency. High resolution imaging of the temporal bone is essential to determine cochlear nerve morphology prior to consideration of cochlear implantation.

Keywords

cochlear implant, otology, otolaryngology, single sided deaf, pediatric hearing loss, sensorineural hearing loss, asymmetry

Introduction

Unilateral sensorineural hearing loss (SNHL) is the most common type of mild SNHL in children, with an estimated prevalence of 3.0%,[1] In contrast, single-sided deafness (SSD), defined as severe to profound SNHL in one ear and normal hearing in the other, is rare in the pediatric population. Historically, unilateral hearing loss has often been undertreated as the "good" ear was felt to be adequate for overall language development, but there is mounting evidence that congenital SSD (or unilateral conductive hearing loss) can hinder binaural processing and speech and language development in children.[2-4] Patients with SSD can function well when communicating face-to-face in quiet environments, but they struggle with understanding speech in background noise and with sound localization. The most common management options for these children include behavioral modifications and listening strategies as well as contralateral routing of sound via air- or bone-conduction devices. However, none of these interventions directly restore hearing in the deaf ear or provide substantial gains in binaural hearing.

The number of reports of cochlear implantation (CI) for SSD has been growing rapidly. It is now well-established

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JAMA Otolaryngology–Head & Neck Surgery | Original Investigation

Association of Bone Conduction Devices for Single-Sided Sensorineural Deafness With Quality of Life
A Systematic Review and Meta-analysis

Thomas Hampton, MA; Kristijonas Milinis, MPhil; Emma Whitehall, MBChB; Sunil Sharma, MBBS

IMPORTANCE Although bone conduction devices (BCDs) have been shown to improve audiological outcomes of patients with single-sided sensorineural deafness (SSD), their effects on the patients' quality of life (QOL) are unclear.

OBJECTIVE To investigate the association of BCDs on QOL in patients with SSD.

DATA SOURCES Literature search of databases (Medline, Embase, Cochrane Library, and ClinicalTrials.gov) from January 1, 1978, to June 24, 2021, was performed.

STUDY SELECTION Prospective interventional studies with 10 or more participants with SSD (defined as pure tone average >70 dB hearing loss in the worse hearing ear and ≤30 dB in the better hearing ear) who underwent unilateral BCD implantation and assessment of QOL before and after the intervention using a validated tool were eligible for inclusion. Studies on adults and children were eligible for inclusion. Patients with only conductive, mixed, or bilateral hearing loss were excluded.

DATA EXTRACTION AND SYNTHESIS Data were extracted by 2 independent reviewers. Study clinical and demographic characteristics were obtained. Meta-analysis of mean differences in QOL scores before and after the intervention was performed. Study bias was assessed using Joanna Briggs Institute risk of bias tool.

MAIN OUTCOMES AND MEASURES The main study outcome was mean change in QOL scores at 6 months after insertion of BCDs. The 3 QOL instruments used in the studies included the Abbreviated Profile of Hearing Aid Benefit (APHAB), the Health Utilities Index–3 (HUI-3), and the Speech, Spatial and Qualities of Hearing Scale (SSQ). The APHAB and the SSQ are the hearing-related QOL measures, whereas the HUI-3 is a generic QOL measure.

RESULTS A total of 486 articles were identified, and 11 studies with 203 patients met the inclusion criteria. Only adult studies met inclusion criteria. Ten of 11 studies were nonrandomized cohort studies. The BCDs assessed were heterogeneous. There was a significant statistical and clinically meaningful improvement in the global APHAB scores (mean change, 15.50; 95% CI, 12.63-18.36; I^2 = 0) and the SSQ hearing qualities (mean change, 1.19; 95% CI, 0.46-1.92; I^2 = 78.4%), speech (mean change, 2.03; 95% CI, 1.68-2.37; I^2 = 0), and spatial hearing (mean change, 1.51; 95% CI, 0.57-2.44; I^2 = 81.1%) subscales. There was no significant change detected in the mean HUI-3 scores (mean change, 0.03; 95% CI, −0.04 to 0.10; I^2 = 0). The risk of bias was assessed to be low to moderate.

CONCLUSIONS AND RELEVANCE These findings suggest that adult patients who receive BCDs may experience improvements in hearing-specific QOL measures but not in generic QOL measures. Prospective QOL studies should be considered in this cohort, particularly for children with SSD.

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Supplemental content

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OPEN

Hearing Instruments for Unilateral Severe-to-Profound Sensorineural Hearing Loss in Adults: A Systematic Review and Meta-Analysis

Pádraig Thomas Kitterick,[1,2] Sandra Nelson Smith,[1,2] and Laura Lucas[1,2]

Objectives: A systematic review of the literature and meta-analysis was conducted to assess the nature and quality of the evidence for the use of hearing instruments in adults with a unilateral severe to profound sensorineural hearing loss.

Design: The PubMed, EMBASE, MEDLINE, Cochrane, CINAHL, and DARE databases were searched with no restrictions on language. The search included articles from the start of each database until February 11, 2015. Studies were included that (a) assessed the impact of any form of hearing instrument, including devices that reroute signals between the ears or restore aspects of hearing to a deaf ear, in adults with a sensorineural severe to profound loss in one ear and normal or near-normal hearing in the other ear; (b) compared different devices or compared a device with placebo or the unaided condition; (c) measured outcomes in terms of speech perception, spatial listening, or quality of life; (d) were prospective controlled or observational studies. Studies that met prospectively defined criteria were subjected to random effects meta-analyses.

Results: Twenty-seven studies reported in 30 articles were included. The evidence was graded as low-to-moderate quality having been obtained primarily from observational before-after comparisons. The meta-analysis identified statistically significant benefits to speech perception in noise for devices that rerouted the speech signals of interest from the worse ear to the better ear using either air or bone conduction (mean benefit, 2.5 dB). However, these devices also degraded speech understanding significantly and to a similar extent (mean deficit, 3.1 dB) when noise was rerouted to the better ear. Data on the effects of cochlear implantation on speech perception could not be pooled as the prospectively defined criteria for meta-analysis were not met. Inconsistency in the assessment of outcomes relating to sound localization also precluded the synthesis of evidence across studies. Evidence for the relative efficacy of different devices was sparse but a statistically significant advantage was observed for rerouting speech signals using abutment-mounted bone conduction devices when compared with outcomes after preoperative trials of air conduction devices when speech and noise were colocated (mean benefit, 1.5 dB). Patients reported significant improvements in hearing-related quality of life with both rerouting devices and following cochlear implantation. Only two studies measured health-related quality of life and findings were inconclusive.

Conclusions: Devices that reroute sounds from an ear with a severe to profound hearing loss to an ear with minimal hearing loss may improve speech perception in noise when signals of interest are located toward the impaired ear. However, the same device may also degrade speech perception as all signals are rerouted indiscriminately, including noise. Although the restoration of functional hearing in both ears through cochlear implantation could be expected to provide benefits to speech perception, the inability to synthesize evidence across existing studies means that such a conclusion cannot yet be made. For the same reason, it remains unclear whether cochlear implantation can improve the ability to localize sounds despite restoring bilateral input. Prospective controlled studies that measure outcomes consistently and control for selection and observation biases are required to improve the quality of the evidence for the provision of hearing instruments to patients with unilateral deafness and to support any future recommendations for the clinical management of these patients.

Key words: Air conduction, Bone conduction, Cochlear implantation, Contralateral routing of signals, Localization, Meta-analysis, Quality of life, Re-routing devices, Restorative devices, Single-sided deafness, Speech perception, Systematic review, Unilateral deafness, Unilateral hearing loss.

(Ear & Hearing 2016;37;495–507)

INTRODUCTION

The onset of unilateral deafness in adulthood is often sudden and idiopathic (Baguley et al. 2006). Even a small asymmetry between the ears has the potential to impose an audiological handicap, particularly in situations with multiple people speaking at the same time (Noble & Gatehouse 2004). Consequently, the near or total loss of hearing in one ear gives rise to substantial difficulties with listening in most everyday situations (Dwyer et al. 2014). Unilateral deafness impairs the ability to understand speech in noise and to localize sounds and also limits awareness of sounds that are located on the side of the impaired ear (IE; McLeod et al. 2008). These difficulties and their consequences for social and vocational activities can lead to feelings of annoyance, embarrassment, and helplessness (Giolas & Wark 1967).

One approach to improve the awareness of sounds on the side of the IE is to reroute signals to the contralateral, nonimpaired ear. This contralateral routing of signals was first achieved by connecting a hearing aid microphone on the side of the IE to a hearing aid on the non-IE (Harford & Barry 1965; Harford & Dodds 1966). A similar result is now achieved via wireless communication between two behind-the-ear devices (Valente 1995). Due to limitations in the frequency response of early rerouting devices, an alternative approach was to fit a high-powered in-the-ear-canal hearing aid in the IE to stimulate the nonimpaired cochlea via conduction through the cranial bones (Valente et al. 1995). Candidacy for bone-anchored hearing devices that were originally developed for conductive or mixed losses has also been extended to include unilateral sensorineural deafness (Niparko et al. 2003). Recently, cochlear implantation (CI) has been considered for unilateral deafness, initially for suppressing tinnitus (Van de Heyning et al. 2008) but subsequently for

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PLOS ONE

RESEARCH ARTICLE

Short-term outcomes of cochlear implantation for single-sided deafness compared to bone conduction devices and contralateral routing of sound hearing aids—Results of a Randomised controlled trial (*CINGLE-trial*)

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Abstract

Single-sided deafness (SSD) leads to difficulties with speech perception in noise, sound localisation, and sometimes tinnitus. Current treatments (Contralateral Routing of Sound hearing aids (CROS) and Bone Conduction Devices (BCD)) do not sufficiently overcome these problems. Cochlear implants (CIs) may help. Our aim was to evaluate these treatments in a Randomised Controlled Trial (RCT). Adult SSD patients were randomised using a web-based randomisation tool into one of three groups: CI; trial period of 'first BCD, then CROS'; trial period of 'first CROS, then BCD'. After these trial periods, patients opted for BCD, CROS, or No treatment. The primary outcome was speech perception in noise (directed from the front (S_0N_0)). Secondary outcomes were speech perception in noise with speech directed to the poor ear and noise to the better ear ($S_{pe}N_{be}$) and vice versa ($S_{be}N_{pe}$), sound localisation, tinnitus burden, and disease-specific quality of life (QoL). We described results at baseline (unaided situation) and 3 and 6 months after device activation. 120 patients were randomised. Seven patients did not receive the allocated intervention. The number of patients per group after allocation was: CI (n = 28), BCD (n = 25), CROS (n = 34), and No treatment (n = 26). In S_0N_0, the CI group performed significantly better when compared to baseline, and when compared to the other groups. In $S_{pe}N_{be}$, there was an advantage for all treatment groups compared to baseline. However, in $S_{be}N_{pe}$, BCD and CROS groups performed worse compared to baseline, whereas the CI group improved. Only in the CI group sound localisation improved and tinnitus burden decreased. In general, all treatment groups improved on disease-specific QoL compared to baseline. This RCT demonstrates that cochlear implantation for SSD leads to improved speech perception in noise,

CHAPTER

Cochlear implantation for patients with tinnitus – A systematic review

2

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Abstract

Background: Cochlear implantation (CI) is used in patients with severe-to-profound hearing loss when hearing aids provide limited or no benefit for speech perception. Studies on this topic reported tinnitus reduction as a common side effect of the electrical activation after cochlear implantation. So far, it is unclear what the effect is when patients do receive their implant primarily because of tinnitus complaints. *Objectives*: To assess the effectiveness of the electrical stimulation with a cochlear implant in patients with tinnitus as a primary complaint, by systematically reviewing the literature. *Methods*: Two independent authors identified studies, extracted data and assessed risk of bias of included studies. Original studies reporting outcomes of electrical stimulation by cochlear implantation for primarily tinnitus (defined as severe or incapacitating distress levels) were included, if they reported a follow-up of at least three months. The pre- and post-implantation tinnitus distress scores on single and/or multi-item questionnaires of the included studies were extracted. *Results*: In total, 4091 unique articles were retrieved. After screening titles, abstracts and full texts, we included seven prospective cohort studies (105 subjects in total, range: 10–26). All studies had considerable risks of bias. All tinnitus patients in the included studies had asymmetrical hearing loss or single-sided deafness. A statistically significant tinnitus distress improvement based on tinnitus questionnaire scores was found in every study. *Conclusion*: Our systematic review reveals that electrical stimulation by cochlear implants in patients with a primary complaint of tinnitus has a positive impact on tinnitus distress. Nevertheless, only small sample sizes were found and studies showed considerable risks of bias.[a]

[†]Both authors contributed equally to first authorship

[a]Systematic review registration: PROSPERO CRD42020146773.

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The Laryngoscope

Benefits of Cochlear Implantation in Childhood Unilateral Hearing Loss (CUHL Trial)

Kevin D. Brown, MD, PhD; Margaret T. Dillon, AuD; Lisa R. Park, AuD

Objectives/Hypotheses: Children with unilateral sensory hearing loss (UHL) struggle to understand speech in noise and locate the origin of sound and have reduced quality of hearing. This clinical trial will determine the benefits of cochlear implantation in children with UHL.

Study Design: Prospective clinical trial.

Methods: Twenty children with at least moderate to profound sensory hearing loss and poor speech perception (word score <30%) in one ear and normal hearing in the contralateral ear participated in a Food and Drug Administration-approved clinical trial. Subjects were evaluated for speech perception in quiet, speech perception in noise, sound localization, and subjective benefits after implantation.

Results: CNC word score perception in quiet significantly improved (1% to 50%, $P < .0001$) by 12 months after activation. Speech perception in noise by BKB-SIN significantly improved in all three noise configurations; there was a 3.6 dB advantage in head shadow ($P < .0001$), a 1.6 dB advantage in summation ($P = .003$), and a 2.5 dB advantage in squelch ($P = .0001$). Localization improved by 26° at 9 months ($P < .0001$). Speech, Spatial, and Qualities (SSQ) demonstrated significant improvements in speech (5.2 to 7.4, $P = .0012$), qualities of hearing (5.9 to 7.5, $P = .0056$), and spatial hearing (2.7 to 6.6, $P < .0001$). SSQ subscales associated with binaural hearing were significantly improved, as was listening effort ($P = .0082$). Subjects demonstrated a non-significant improvement in fatigue.

Conclusions: This study demonstrates that children with UHL significantly benefit from cochlear implantation.

Key Words: Unilateral hearing loss, single sided deafness, pediatrics, cochlear implantation.

Level of Evidence: Level 3

***Laryngoscope*, 132:S1–S18, 2022**

INTRODUCTION

Unilateral sensory hearing loss (UHL) is thought to affect approximately 1 in 1,000 newborns with congenital loss and up to 3% to 6% of school-aged children.[1–6] It has become well-established that there are significant ramifications for multiple aspects of child development, education, and well-being when UHL is present.[7,8] As such, efforts have been focused on identifying children with UHL, providing educational accommodations (speech and language services) necessary to optimize their outcomes, and fitting appropriate hearing technology.[8–10] Many of these children have or will develop a degree of hearing loss that is inadequately rehabilitated with a traditional hearing aid,[9] and as such are unable to take advantage of the critical benefits of binaural hearing. These patients with substantial UHL, or single-sided deafness (SSD), can be defined as having moderate-to-profound sensorineural hearing loss with limited speech perception in one ear and normal to near-normal hearing in the contralateral ear.

Improved binaural auditory function occurs when people with normal hearing listen with both ears, and when those with hearing loss utilize bilateral hearing aids or cochlear implants (CI).[11,12] Conversely, amplification or implantation of only one side in patients with bilateral hearing loss is associated with reduced auditory function as compared with bilateral input.[12–15] Three primary effects on auditory perception have been identified in binaural hearing: the head shadow effect, the binaural squelch effect, and the binaural summation effect.[16,17]

The head shadow effect occurs when the target speech and masker are spatially separated. For example, a masker on the right side of the listener would interfere with the right ear, but the head would block the masker (create an acoustic shadow) for the left ear. Thus, the head shadow effect would result in a better target-to-masker ratio in the left ear. A listener is able to selectively attend to the ear with the better target-to-masker ratio for improved speech intelligibility.[18]

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JAMA Otolaryngology–Head & Neck Surgery | Original Investigation

Cochlear Implantation in Children With Single-Sided Deafness
A Systematic Review and Meta-analysis

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IMPORTANCE In 2019, the US Food and Drug Administration approved cochlear implantation for children with single-sided deafness (SSD). The absence of robust clinical data specific to pediatric patients to guide shared decision-making and to identify potential advantages is a challenge in family counseling.

OBJECTIVE To evaluate the audiological and patient-reported outcomes in children who underwent cochlear implantation for SSD and to assess the association between time of implantation, subjective outcomes, and cochlear implant device use rates.

DATA SOURCE MEDLINE, Embase, Scopus, Cochrane, and PubMed were searched for English-language articles that were published in a peer-reviewed journal from database inception to February 18, 2020.

STUDY SELECTION Inclusion criteria were designed to capture studies that evaluated pediatric patients (1) younger than 18 years, (2) with a diagnosis of SSD for which they underwent a cochlear implantation, and (3) with at least 1 outcome of interest measured numerically: speech perception, sound localization, device use, and patient-reported outcomes. Of the 526 articles reviewed, 12 (2.3%) met the selection criteria.

DATA EXTRACTION AND SYNTHESIS The Meta-analyses Of Observational Studies in Epidemiology (MOOSE) reporting guidelines were followed. Data were pooled using fixed-effect and random-effect models. The following information was obtained from each article: study characteristics, patient characteristics, hearing loss and intervention characteristics, and outcomes.

MAIN OUTCOMES AND MEASURES Outcomes were (1) postoperative changes in speech perception (in quiet was measured as a proportion of correct responses, and in noise was measured as decibel signal to noise ratio for speech reception threshold) and sound localization (measured in degree of localization error), (2) patient-reported audiological outcomes (measured by the speech, spatial, and qualities of hearing scale), and (3) device use rates among children who received cochlear implantation for SSD.

RESULTS Twelve observational studies that evaluated 119 children (mean [SD] age, 6.6 [4.0] years) with SSD who received a cochlear implant were included. Most children showed clinically meaningful improvement in speech perception in noise (39 of 49 children [79.6%]) and in quiet (34 of 42 children [81.0%]). Long duration of deafness (>4 years in congenital SSD and >7 years in perilingual SSD) was the most commonly proposed reason for lack of improvement. Sound localization as measured by degrees of error from true location (mean difference [MD], −24.78°; 95% CI, −34.16° to −15.40°; I^2 = 10%) improved statistically significantly after cochlear implantation. Patients with acquired SSD and shorter duration of deafness compared with those with congenital SSD reported greater improvements in speech (MD, 2.27; 95% CI, 1.89-2.65 vs 1.58; 95% CI, 1.00-2.16) and spatial (MD, 2.95; 95% CI, 2.66-3.24 vs 1.68; 95% CI, 0.96-2.39) hearing qualities. The duration of deafness among device nonusers was statistically significantly longer than the duration of deafness among regular device users (median difference, 6.84; 95% CI, 4.02-9.58).

CONCLUSIONS AND RELEVANCE This systematic review and meta-analysis found that cochlear implantation for children with SSD was associated with clinically meaningful improvements in audiological and patient-reported outcomes; shorter duration of deafness may lead to better outcomes. These findings can guide future research efforts, refine cochlear implantation candidacy criteria, and aid in family counseling and shared decision-making.

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Supplemental content

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Cochlear Implantation for Treatment of Tinnitus in Single-sided Deafness: A Systematic Review and Meta-analysis

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Objective: Quantify the benefit of cochlear implantation (CI) for tinnitus relief among individuals with single-sided deafness (SSD).

Data Sources: PubMed, Scopus, and Cochrane databases were searched through July 10, 2019. Search strategies used a combination of subject headings (e.g., MeSH in PubMed) and keywords for the following three concepts: single-sided deafness, cochlear implantation, and tinnitus.

Study Selection: English articles that reported the preintervention (baseline) tinnitus-related patient-reported outcome measures (e.g., Tinnitus Handicap Inventory [THI] and Visual Analog Scale [VAS] for loudness) in patients with SSD that underwent CI were included.

Data Extraction: Number of patients, mean age, etiology of hearing loss, duration of deafness, baseline and follow-up THI and VAS scores.

Data Synthesis: A total of 17 studies met inclusion criteria encompassing 247 patients with SSD receiving a cochlear implant (mean age 50.2 yr, range 23–71). For THI, CI resulted in a mean difference of −35.4 points [95% CI −55.8 to −15.0, $p < 0.001$]. VAS decreased by −4.6 points [CI −6.0 to −3.3, $p < 0.001$]. A weighted proportion of 14.9% [CI 6.4–26.1] of patients experienced complete resolution of tinnitus, while 74.5% [CI 63.1–84.5] experienced partial improvement; 7.6% [CI 4.1–12.6] of patients had no change in severity, and 3.0% [CI 1.0–6.7] experienced worsening of their tinnitus.

Conclusions: On both THI and VAS, patients reported significant reduction in their scores, representing an overall improvement in tinnitus severity while wearing the cochlear implant. Most patients with SSD will experience partial improvement or complete resolution of tinnitus with a cochlear implant. **Key Words:** Asymmetric hearing loss—Cochlear implant—Patient-reported outcome measures—Ringing—Single-sided deafness—Tinnitus—Unilateral deafness.

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Single-sided deafness (SSD) is a debilitating condition resulting in reduced sound localization, poor speech comprehension (in both quiet and noise), and a decreased quality of life (QoL) (1). SSD is also associated with severe tinnitus in many patients which can further diminish QoL (1). Although the exact cause of tinnitus remains elusive, one hypothesis posits that reduced or absent auditory input leads to changes in neural activity (2).

A variety of interventions exist for SSD, which generally send sound from the poor-hearing ear to the better hearing ear. With the exception of a cochlear implant, these interventions do not improve hearing or tinnitus in the poor-hearing ear. Although approaches such as contralateral routing of sound (CROS) and bone conduction devices can recuperate some measures of speech understanding under various listening situations, they fail to effectively ameliorate other critical domains such as sound localization and tinnitus (3,4). Rather than rerouting sound to the normal ear as with CROS and bone conduction devices, cochlear implantation (CI) directly stimulates the acoustic nerve of the poor-hearing ear, thus providing binaural information to the patient's auditory system. The resulting stimulation provides a more robust therapeutic effect compared with other options (5,6). Previous research has shown that in patients with SSD, CI improves not only hearing, speech recognition, and QoL (1,7–9), but substantially reduces the severity of tinnitus (1,5,7,8,10). Unfortunately, most of these investigations are limited to small sample sizes from international locations. This prevents generalizability of published data and restricts any meaningful cross-study comparisons. Up until now, narrow indications for CI in the United States can account for the paucity of studies on this subject. However, the US Food and Drug Administration recently approved the MED-EL CI for patients with SSD age 5 and older (11).

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American Cochlear Implant Alliance Task Force Guidelines for Clinical Assessment and Management of Cochlear Implantation in Children With Single-Sided Deafness

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More children with single-sided deafness (SSD) are receiving cochlear implants (CIs) due to the expansion of CI indications. This unique group of pediatric patients has different needs than the typical recipient with bilateral deafness and requires special consideration and care. The goal of cochlear implantation in these children is to provide bilateral input to encourage the development of binaural hearing. Considerations for candidacy and follow-up care should reflect and measure these goals. The purpose of this document is to review the current evidence and provide guidance for CI candidacy, evaluation, and management in children with SSD.

Key words: Candidacy, Children, Cochlear implant, Guidelines, Single-sided deafness, Test battery, Unilateral hearing loss.

(Ear & Hearing 2022;43;255–267)

PURPOSE

When cochlear implants (CIs) were first approved for children, the initial goal was unilateral sound awareness. With multichannel CIs, speech perception became an achievable and expected goal. Outcome measures moved from detection of speech to closed set word recognition, to open-set word recognition, to sentences in quiet, and ultimately sentence perception in noise. With bilateral cochlear implantation becoming standard of care for children in the US with bilateral severe to profound hearing loss, clinicians began to describe outcomes in terms of individual ear word recognition and bilateral performance on speech perception tasks (Uhler et al. 2017). Now children with hearing loss in only one ear are receiving CIs and clinicians are challenged with programming, testing, and evaluating performance in children who have hearing thresholds within the normal range on the contralateral side. This is a considerable challenge as so much of the groundwork for evaluation of CI patients has been laid by working with patients who have bilateral hearing loss. Children who seek cochlear implantation for unilateral hearing loss (UHL) or single-sided deafness (SSD) are seeking implantation not solely for better speech understanding, but in the hopes of achieving binaural hearing. Candidacy considerations, counseling, habilitation, and evaluation postactivation must look beyond simple speech perception and move toward evaluation that encompasses tasks associated with binaural hearing. The aim of this review is to summarize the current literature regarding CI outcomes for children with SSD and provide guidance for candidacy, outcome measures, and mapping of children with SSD + CI. The following recommendations were developed based on published research and experience of clinicians managing children and adults with SSD + CI. While many of these principles may be applicable to children who have asymmetric hearing loss (AHL) wherein there is a mild-to-moderate hearing loss in the better ear, these recommendations focus on children with SSD who have thresholds falling within the normal to near normal range in the better ear (Vincent et al. 2015).

BACKGROUND

UHL is known to occur in approximately 0.6 to 0.7 per 1000 live births in the U.S. (Centers for Disease Control Early Hearing Detection and Intervention [CDC] Database). By school-age, the number of children with UHL is estimated to be 2.5 to 6% (Bess 1998; Ross et al. 2010; Shargorodsky 2010). The impact of UHL includes difficulty understanding speech in noise (Bess & Tharpe 1984; Bess et al. 1986; Sangen et al. 2017; Corbin et al. 2021) and localizing on the horizontal plane (Bess & Tharpe 1984; Bess et al. 1986; Johnstone et al. 2010; Sangen et al. 2017; Corbin et al. 2021), resulting in an increased risk for problems with speech and language (Bess & Tharpe 1984; Fischer & Lieu 2014; Anne et al. 2017; Sangen et al. 2017), cognition (Bess & Tharpe 1984; Ead et al. 2013; Fischer & Lieu 2014), behavior (Bess & Tharpe 1984; Culbertson & Gilbert 1986), and quality of life (QoL) (Umansky et al. 2011; Roland et al. 2016).

Although a hearing aid (HA) may be beneficial for children with mild-to-moderate UHL, it is contra-indicated in those with more significant degrees of UHL, often referred to as SSD (Bagatto et al. 2019). Traditionally, hearing technologies available for school-age children with SSD have included re-routing devices such as contralateral-routing-of-signal (CROS) HAs and bone conduction devices (BCD). Each re-routing device has advantages and disadvantages, although they are typically contraindicated in young children with SSD (McKay et al. 2008; Bagatto et al. 2019). The auditory deprivation associated with SSD causes irreversible changes in the auditory cortex (Kral et al. 2013a, 2013b; Gordon et al. 2015), which re-routing devices

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Section 5.0

New Codes

PLA Code Review

May 2023

Plain Language Summary:

Coverage question: There are several hundred unreviewed private and exclusive laboratory analysis (PLA) codes for trademarked laboratory tests that must be used rather than a more genetic CPT code. The top 12 billed codes are reviewed below.

Should OHP cover this treatment? In most cases, yes.

Issue: there are several hundred proprietary laboratory analysis (PLA) codes. These codes are designated for a trademarked laboratory test and must be used rather than a more genetic CPT code when a PLA code is available. These codes have never been reviewed. HERC staff undertook an initial analysis of the most highly billed PLA codes. This analysis included all paid claims in 2022. The top 11 currently valid billed codes are reviewed below.

1) **0241U** – Infectious disease (viral respiratory tract infection), pathogen-specific RNA, 4 targets (Severe Acute Respiratory Syndrome Coronavirus 2 [SARS-CoV-2], influenza A, influenza B, respiratory syncytial virus [RSV]), upper respiratory specimen, each pathogen reported as detected or not detected
    a. Used for Xpert Xpress SARS-Cov2/Flu/RSV (all targets)
    b. FDA EUA issued October 2021
        i. The Xpert Xpress CoV-2/Flu/RSV plus test is a rapid, multiplexed real-time RT-PCR test intended for the simultaneous qualitative detection and differentiation of RNA from SARSCoV-2, influenza A, influenza B, and/or respiratory syncytial virus (RSV) in either nasopharyngeal swab, anterior nasal swab or nasal wash/ aspirate specimens collected from individuals suspected of respiratory viral infection, consistent with COVID-19, by their healthcare provider
        ii. FDA EUA is for point of care or CLIA approved lab use
    c. Paid claims: 15,935
    d. Similar codes are all on the Diagnostic Procedures file:
        i. 87635 Infectious agent detection by nucleic acid (DNA or RNA); severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) (coronavirus disease [COVID-19]), amplified probe technique
        ii. 87636 Infectious agent detection by nucleic acid (DNA or RNA); severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) (coronavirus disease [COVID-19]) and influenza virus types A and B, multiplex amplified probe technique
        iii. U0003 Infectious agent detection by nucleic acid (dna or rna); severe acute respiratory syndrome coronavirus 2 (sars-cov-2) (coronavirus disease [covid-19]), amplified probe technique, making use of high throughput technologies as described by cms-2020-01-r

iv. U0004 2019-ncov coronavirus, sars-cov-2/2019-ncov (covid-19), any technique, multiple types or subtypes (includes all targets), non-cdc, making use of high throughput technologies as described by cms-2020-01-r
v. U0005 Infectious agent detection by nucleic acid (dna or rna); severe acute respiratory syndrome coronavirus 2 (sars-cov-2) (coronavirus disease [covid-19]), amplified probe technique, cdc or non-cdc, making use of high throughput technologies, completed within 2 calendar days from date of specimen collection (list separately in addition to either hcpcs code u0003 or u0004) as described by cms-2020-01-r2

e. HERC staff summary: commonly used test which can differentiate etiology of a viral illness to assist with anti-viral medication selection or other treatments
f. HERC staff recommendation:
    i. Advise HSD to place 0241U on the Diagnostic Procedures File

2) **0202U** – Infectious disease (bacterial or viral respiratory tract infection), pathogen specific nucleic acid (DNA or RNA), 22 targets including Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2), qualitative RT-PCR, nasopharyngeal swab, each pathogen reported as detected or not detected
    a. Used for: Biofire Respiratory Panel 2.1
    b. FDA EUA issued October 2020
        i. The BioFire RP2.1-EZ is a multiplexed polymerase chain reaction (PCR) test authorized for use with nasopharyngeal swab specimens collected from individuals suspected of COVID-19 by their healthcare provider.
    c. Paid claims: 1,430
    d. Similar codes (see 0241U above) are all on the Diagnostic Procedures file
    e. HERC staff summary: commonly used test for COVID-19 infection
    f. HERC staff recommendation:
        i. Advise HSD to place 0202U on the Diagnostic Procedures File

3) **0240U** Infectious disease (viral respiratory tract infection), pathogen-specific RNA, 3 targets (Severe Acute Respiratory Syndrome Coronavirus 2 [SARS-CoV-2], influenza A, influenza B), upper respiratory specimen, each pathogen reported as detected or not detected
    a. Used for: Xpert Xpress SARS-CoV2/Flu/RSV (SARS-Cov-2 & Flu targets only)
    b. FDA EUA issued January 2021
        i. The Xpert Xpress SARS-CoV-2/Flu/RSV test is a rapid, multiplexed real-time RT-PCR test intended for the simultaneous qualitative detection and differentiation of SARS-CoV-2, influenza A, influenza B, and respiratory syncytial virus (RSV) viral RNA in either nasopharyngeal swab, nasal swab or nasal wash/ aspirate specimens collected from individuals suspected of respiratory viral infection consistent with COVID-19 by their healthcare provider
    c. Paid claims: 906
    d. Similar codes (see 0241U above) are all on the Diagnostic Procedures file

e. HERC staff summary: commonly used test which can differentiate etiology of a viral illness to assist with anti-viral medication selection or other treatments
f. HERC staff recommendation:
    i. Advise HSD to place 0240U on the Diagnostic Procedures File

4) **0077U** Immunoglobulin paraprotein (M-protein), qualitative, immunoprecipitation and mass spectrometry, blood or urine, including isotype
    a. Paid claims: 24
    b. Per CMS, 0077U must be billed with one of the following ICD-10-CM codes:
        i. C88.0 (Waldenstrom macroglobulinemia) on line 260 MULTIPLE MYELOMA Treatment: BONE MARROW TRANSPLANT
        ii. C90.0 family (Multiple myeloma) on lines 234 ACUTE LYMPHOCYTIC LEUKEMIAS (ADULT) AND MULTIPLE MYELOMA, 260
        iii. D47.2 (Monoclonal gammopathy) on lines 234 and 260
        iv. E85.81 (Light chain (AL) amyloidosis) on lines 234 and 260
    c. Expert recommendation
        i. **Murray 2021** Mass spectrometry for the evaluation of monoclonal proteins in multiple myeloma and related disorders: an International Myeloma Working Group Mass Spectrometry Committee Report
            1. Serum protein electrophoresis (SPEP) enables the detection and relative quantitation of the M-protein, whereas serum immunofixation electrophoresis (IFE) enables establishment of M-protein isotype. Another widely utilized assay is the serum free light chain (sFLC) assay that utilizes specific antibodies for quantitation of circulating free kappa (κ) and lambda (λ) light chains (LCs)
            2. Two mass spectrometry (MS) methods have emerged in the literature. Both methods start with immune-enrichment of patient immunoglobulins (Igs) but differ on the analytical target used to detect the M-protein. One method utilizes Ig trypsin digestion and detection of peptides specific to the M-protein CDR. This method has been termed the “clonotypic peptide” approach. The second method utilizes total LC mass distributions from Igs which have been chemically reduced and denatured into heavy and light chain components. This method will be termed intact LC mass measurements
            3. We conclude that MS has the advantage of increased accuracy, documented clinical and analytic sensitivity, and the intact LC MALDI-TOF method is easier on laboratory work flow for the detection of M-proteins. The IMWG Mass Spectrometry Committee endorses detection of M-proteins by MS (intact MALDI-TOF method) as an alternative to IFE for clinical practice and clinical trials. The group also endorses MS for distinguishing residual M-protein from therapeutic monoclonal antibodies for clinical practice, and for accurate interpretation and determination of complete response in clinical trials. We recognize that

using mass spectrometric methods instead of conventional IFE may lead to lower rates of complete response (CR), and therefore cross-comparisons of CR rates in trials done in different time periods is not recommended. We hope, with further data, that mass spectrometric methods (MALDI-TOF, miRAMM, or clonotypic peptide approach) may provide the ability to test for measurable disease in the peripheral blood and help guide timing of bone marrow tests for next-generation flow cytometry and NGS studies

d. HERC staff summary: mass spectrometry for the diagnosis of multiple myeloma is recommended by experts and appears to have increased accuracy over existing testing modalities
e. <u>HERC staff recommendation:</u>
    i. Advise HSD to place 0077U on the Diagnostic Procedures File

5) **0219U** Infectious agent (human immunodeficiency virus), targeted viral next-generation sequence analysis (ie, protease [PR], reverse transcriptase [RT], integrase [INT]), algorithm reported as prediction of antiviral drug susceptibility
    a. Paid claims: 7
    b. Used for the Sentosa SQ HIV-1 genotyping assay by Vela Diagnostics
        i. Received FDA approval in November 2019
        ii. The Sentosa® SQ HIV-1 Genotyping Assay is a next generation sequencing (NGS) - based in vitro diagnostic (IVD) test intended for use in detecting HIV-1 genomic mutations (in the protease, reverse transcriptase and integrase regions of the pol gene) as an aid in monitoring and treating HIV-1 infection. This test is used in adjunct to the therapeutic management of patients diagnosed with HIV-1 Group M infection with viral loads of at least 1,000 RNA copies per mL in EDTA plasma specimens
    c. ICD-10 B20 (Human immunodeficiency virus [HIV] disease) is on line 12 HIV DISEASE (INCLUDING ACQUIRED IMMUNODEFICIENCY SYNDROME) AND RELATED OPPORTUNISTIC INFECTIONS
    d. Evidence
        i. **Bonifacio 2022**, analytical assessment of Vela Diagnostic HIV resistance testing
            1. Accuracy testing done with 5 reference samples
                a. 3 of the 5 samples obtained a 100% match with expected variants
            2. Intra-assay reproducibility assessment done with 9 clinical samples
                a. 3 mismatches reported
            3. Assessment of 420 patient samples comparing Sentosa SQ to Sanger sequencing [gold standard]
                a. Comparing NGS and Sanger sequencing systems, the results agreement reached 97.2%
    e. Other payer policies

i. Aetna 2022: Aetna considers the Sentosa SQ HIV-1 genotyping assay experimental and investigational for use in drug susceptibility phenotype prediction because its clinical value has not been established.
ii. Premara BCBS 2023
1. Lists 0219U as experimental/investigational

f. HERC staff summary: the Sentosa SQ HIV genotyping assay appears to be experimental. The commonly used resistance testing via the Sanger method is covered.
g. HERC staff recommendation:
i. Place 0219U on Line 662 CONDITIONS FOR WHICH CERTAIN INTERVENTIONS ARE UNPROVEN, HAVE NO CLINICALLY IMPORTANT BENEFIT OR HAVE HARMS THAT OUTWEIGH BENEFITS
ii. Add an entry to GN173 as shown below

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

Line 662

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

Procedure Code	Intervention Description	Rationale	Last Review
0219U	Infectious agent (human immunodeficiency virus), targeted viral next-generation sequence analysis (ie, protease [PR], reverse transcriptase [RT], integrase [INT]), algorithm reported as prediction of antiviral drug susceptibility	Insufficient evidence of effectiveness	May 2023

6) **0027U** JAK2 (Janus kinase 2) (eg, myeloproliferative disorder) gene analysis, targeted sequence analysis exons 12-15
a. Paid claims: 7
b. Similar code: CPT 81270 (JAK2 (Janus kinase 2) (eg, myeloproliferative disorder) gene analysis, p.Val617Phe (V617F) variant) and 81279 (JAK2 (Janus kinase 2) (eg, myeloproliferative disorder) targeted sequence analysis (eg, exons 12 and 13)) are Diagnostic and not included in any of the genetic testing guidelines
c. Used in the evaluation of and treatment decisions for chromic myeloproliferative diseases, such as polycythemia vera (PV), essential thrombocythemia (ET), idiopathic myelofibrosis (IMF), and chronic myeloid leukemia (CML)
i. D45 Polycythemia vera on line 397 MYELOID DISORDERS

ii. D47.1 (Chronic myeloproliferative disease) on lines 158 NON-HODGKIN'S LYMPHOMAS, 179 ACUTE LEUKEMIA, MYELODYSPLASTIC SYNDROME treatment: BONE MARROW TRANSPLANT
iii. D47.3 (Essential (hemorrhagic) thrombocythemia) is on lines 158, 179

d. Other payer policies
   i. Cigna 2023: covers for the evaluation of myeloproliferative and myelodysplastic disease
   ii. Aetna 2023: covered similarly to CPT 81270 and 81279
e. HERC staff recommendation:
   i. Advise HSD to place 0027U on the Diagnostic Procedures File

7) **0035U** Neurology (prion disease), cerebrospinal fluid, detection of prion protein by quaking-induced conformational conversion, qualitative
   a. Paid claims: 3
   b. Information: real–time quaking–induced conversion for prion detection (RT–QuIC) test from the National Prion Disease Pathology Surveillance Center, which is an ultrasensitive diagnostic test on cerebrospinal fluid to detect abnormal CSF 14–3–3 protein, a marker for human prion disease
   c. Evidence
      i. **Franceschini 2017**, High diagnostic value of second generation CSF RT-QuIC across the wide spectrum of CJD prions
         1. N=239 patients with definite or probable prion disease
            a. Control: 100 patients with a definite alternative diagnosis
         2. we compared the performance of the first (PQ-CSF) and second generation (IQ-CSF) RT-QuIC assays, and investigated the diagnostic value of IQ-CSF across the broad spectrum of human prions. Our results confirm the high sensitivity of IQ-CSF for detecting human prions with a sub-optimal sensitivity for the sporadic CJD subtypes MM2C and MM2T, and a low sensitivity limited to variant CJD, Gerstmann-Sträussler-Scheinker syndrome and fatal familial insomnia. While we found no difference in specificity between PQ-CSF and IQ-CSF, the latter showed a significant improvement in sensitivity, allowing prion detection in about 80% of PQ-CSF negative CJD samples. Our results strongly support the implementation of IQ-CSF in clinical practice.
   d. Other payer policies
      i. Medi-Cal 2020:
         1. Documentation of the following criteria:
            a. Rapidly progressive dementia AND
            b. At least 2 of the following 4 clinical features:
               i. Myoclonus
               ii. Visual or cerebellar signs
               iii. Pyramid/extrapyramidal signs
               iv. Akinetic mutism

c. A positive result on at least one of the following tests:
    i. Atypical EEG (periodic sharp wave complexes) during an illness of any duration
    ii. High signal in caudate/putamen in MRI brain scan or at least two cortical regions (temporal, parietal, occipital) either on diffusion-weighted imaging or fluid attenuated inversion recovery (FLAIR)
d. No routine investigations indicating an alternative diagnosis
e. Allowed once per lifetime

ii. United Healthcare 2023: non-covered

e. HERC staff summary: This appears to be a developing technology. However, this is a test for a very rare disease and therefore large studies may be difficult to perform. Other payer coverage is varied. Given the rarity of the disease and low numbers of claims, staff recommends coverage with monitoring of the evidence base and utilization.
f. HERC staff recommendations:
    i. Advise HSD to 0035U place on Diagnostic Procedures File
    ii. Monitor for utilization and consider guideline if utilization increases

8) **0034U** TPMT (thiopurine S-methyltransferase), NUDT15 (nudix hydroxylase 15) (eg, thiopurine metabolism) gene analysis, common variants (ie, TPMT *2, *3A, *3B, *3C, *4, *5, *6, *8, *12; NUDT15 *3, *4, *5)
    a. Paid claims: 2
    b. Similar codes
        i. 81335 (TPMT (thiopurine S-methyltransferase) (eg, drug metabolism), gene analysis, common variants (eg, *2, *3)) is Diagnostic
        ii. 81306 (NUDT15 (nudix hydrolase 15) (eg, drug metabolism) gene analysis, common variant(s) (eg, *2, *3, *4, *5, *6)) is on line 662/GN173
    c. Past HERC review:
        i. 81335 was reviewed by GAP and by HERC in November 2022. TPMT testing was removed from line 662/GN173 as added to the Diagnostic Procedures file for testing prior to use of azathioprine and 6MP per FDA labeling requirements
            1. Note: the FDA labeling for azathioprine does not mention NUDT15 testing
        ii. 81306 reviewed by GAP Oct 2018 "There is no evidence that genetic analysis leads to clinical decision changes or improves patient outcomes; data to date is only that positive tests are correlated with higher risk of adverse outcomes. There is no evidence that testing will prevent overall adverse outcomes. The test is not listed in NCCN guidelines as recommended prior to use of thiopurines in oncology"
    d. **FDA 2020** labeling for purinethol
        i. Evaluate thiopurine S-methyltransferase (TPMT) and nucleotide diphosphatase (NUDT15) status in patients with severe myelosuppression or repeated episodes or myelosuppression

ii. Patients with homozygous deficiency of either enzyme typically require 10% or less of the recommended dosage. Reduce the recommended starting dosage of PURINETHOL in patients who are known to have homozygous TPMT or NUDT15 deficiency

e. HERC staff summary: testing for NUDT15 mutation status is included in the FDA labeling as a test that should be considered prior to use of purinethol and mutation status affects the starting dosage of this medication. TPMT testing is already covered.

f. HERC staff recommendations:
   i. Advise HSD to place 0034U on the Diagnostic Procedures File
   ii. Remove the GN173 entry for CPT 81306 as shown below
      1. Advise HSD to place CPT 81306 on the Diagnostic Procedures File

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

Line 660

The following Interventions are prioritized on Line 660 CONDITIONS FOR WHICH CERTAIN INTERVENTIONS ARE UNPROVEN, HAVE NO CLINICALLY IMPORTANT BENEFIT OR HAVE HARMS THAT OUTWEIGH BENEFITS:

Procedure Code	Intervention Description	Rationale	Last Review
~~81306~~	~~NUDT15 (nudix hydrolase 15) (eg, drug metabolism) gene analysis~~	~~Insufficient evidence of effectiveness~~	~~November 2018~~

9) **0001U** Red blood cell antigen typing, DNA, human erythrocyte antigen gene analysis of 35 antigens from 11 blood groups, utilizing whole blood, common RBC alleles reported

a. Paid claims: 2

b. Code 0001U describes the Immucor, Inc. PreciseType® HEA Test, which is a multiplexed molecular assay on a whole blood specimen that identifies 24 polymorphisms associated with 35 human erythrocyte antigens from 11 blood groups and report of the common RBC alleles.

c. Organ Procurement and Transplantation Network/HRSA guidance for addressing blood type determination 2020
   i. https://optn.transplant.hrsa.gov/professionals/by-topic/guidance/guidance-for-addressing-blood-type-determination/
   ii. Accessed April 3, 2023
   iii. Since the early 1900s, blood typing has been performed by serological methodology. This has consisted of a forward and reverse typing which together are evaluated and must agree to give a valid blood type phenotype. However, when patients have been transfused out of their own blood type, or discrepancies between the forward and reverse typing or mixed field typing is seen, DNA based testing may be considered.

d. HERC staff summary: DNA based blood typing is rarely used, but may be necessary in certain clinical scenarios

e. HERC staff recommendation:
    i. Advise HSD to place 0001U on the Diagnostic Procedures File

10) **0279U** Hematology (von Willebrand disease [VWD]), von Willebrand factor (VWF) and collagen III binding by enzyme-linked immunosorbent assays (ELISA), plasma, report of collagen III binding
    a. Paid claims: 1
    b. From Quest Diagnostics: von Willebrand Factor Collagen Binding Assay - The Collagen Binding Activity is a surrogate assay for the measurement of von Willebrand Factor (VWF) mediated Platelet adhesion. Decreased activity (collagen bound to the A3 domain of the VWF protein) relative to the VWF antigen level, is observed with qualitative defects of VWF (type 2 disorders). The CBA assay may assist in the discrimination of type 2 disorders. In addition, there have been reports of isolated defects of CBA as a cause for a variant form of von Willebrand disease.
    c. Similar codes for von Willibrand factor testing (e.g. 85246, 85247) are Diagnostic
    d. HERC staff summary: collagen binding assay may help in the diagnosis of von Willebrand disease. This test appears to be rarely used
    e. HERC staff recommendation:
        i. Advise HSD to place 0279U on the Diagnostic Procedures File

11) **0058U** Oncology (Merkel cell carcinoma), detection of antibodies to the Merkel cell polyoma virus oncoprotein (small T antigen), serum, quantitative
    a. Paid claims: 1
    b. ICD-10-CM C4A family (Merkel cell carcinoma) is on line 276 CANCER OF SKIN, EXCLUDING MALIGNANT MELANOMA
    c. Merkel cell carcinoma is a very rare and aggressive skin cancer often caused by the Merkel cell polyomavirus
    d. Evidence
        i. **Paulson 2017** Viral oncoprotein antibodies as a marker for recurrence of Merkel cell carcinoma: a prospective validation study
            1. N=465 patients in prospective cohort study of natural history of Merkel cell carcinoma
                a. N=219 patients with blood test for viral oncoprotein antibodies
            2. MCPyV antibody seropositive status was independently associated with a 42% decreased risk of recurrence (hazard ratio = 0.58, 95% confidence interval 0.36-0.97) in the multivariate model adjusting for known prognostic factors
            3. a majority of patients with a rising titer were found to have recurrence/progression within 45 days of the rising titer
            4. Conclusion: Merkel cell carcinoma (MCC) is an aggressive cutaneous malignancy with a recurrence rate of >40%. Here we report in a large prospective validation cohort a clinically available virus directed assay that can identify two populations of patients at diagnosis: a MCPyV-

oncoprotein seronegative group at higher risk of recurrence who may benefit from closer imaging surveillance and a MCPyV oncoprotein seropositive group for whom serial MCPyV antibody titer assessment may assist in ongoing surveillance.

e. Other payer policies
    i. MediCal: covers with an ICD-10-CM code in the C4A family
f. HERC staff summary: antibodies to the Merkel cell polyoma virus oncoprotein may be useful in management of Merkel cell carcinoma. This is a very rare cancer, making studies difficult. Given the rarity of the disease and low numbers of claims, staff recommends coverage with monitoring of the evidence base.
g. HERC staff recommendation:
    i. Add 0058U to line 276 CANCER OF SKIN, EXCLUDING MALIGNANT MELANOMA

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Blood Cancer Journal

ARTICLE Open Access

Mass spectrometry for the evaluation of monoclonal proteins in multiple myeloma and related disorders: an International Myeloma Working Group Mass Spectrometry Committee Report

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Abstract

Plasma cell disorders (PCDs) are identified in the clinical lab by detecting the monoclonal immunoglobulin (M-protein) which they produce. Traditionally, serum protein electrophoresis methods have been utilized to detect and isotype M-proteins. Increasing demands to detect low-level disease and new therapeutic monoclonal immunoglobulin treatments have stretched the electrophoretic methods to their analytical limits. Newer techniques based on mass spectrometry (MS) are emerging which have improved clinical and analytical performance. MS is gaining traction into clinical laboratories, and has replaced immunofixation electrophoresis (IFE) in routine practice at one institution. The International Myeloma Working Group (IMWG) Mass Spectrometry Committee reviewed the literature in order to summarize current data and to make recommendations regarding the role of mass spectrometric methods in diagnosing and monitoring patients with myeloma and related disorders. Current literature demonstrates that immune-enrichment of immunoglobulins coupled to intact light chain MALDI-TOF MS has clinical characteristics equivalent in performance to IFE with added benefits of detecting additional risk factors for PCDs, differentiating M-protein from therapeutic antibodies, and is a suitable replacement for IFE for diagnosing and monitoring multiple myeloma and related PCDs. In this paper we discuss the IMWG recommendations for the use of MS in PCDs.

Background

Plasma cell disorders (PCDs) are a group of diseases characterized by clonal expansion of plasma cells[1]. Central to the diagnosis and monitoring of most PCDs is detection of the monoclonal immunoglobulin components which are generally overproduced by the expanding plasma cell clone. This overproduced monoclonal immunoglobulin (often referred to as an M-protein or paraprotein) typically is an intact immunoglobulin, and also can be either the free light chain (LC) component alone or the heavy chain component alone in rare instances[2].

While the M-protein is homogeneous and typically constant in any particular patient, the heterogeneity of M-proteins from patient to patient is significant and thus a diverse set of methods are employed to characterize and

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MDPI

Article

Analytical Assessment of the Vela Diagnostics NGS Assay for HIV Genotyping and Resistance Testing: The Apulian Experience

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Abstract: Drug-resistance monitoring is one of the hardest challenges in HIV management. Next-generation sequencing (NGS) technologies speed up the detection of drug resistance, allowing the adjustment of antiretroviral therapy and enhancing the quality of life of people living with HIV. Recently, the NGS Sentosa® SQ HIV Genotyping Assay (Vela Diagnostics) received approval for in vitro diagnostics use. This work is the first Italian evaluation of the performance of the Vela Diagnostics NGS platform, assessed with 420 HIV-1 clinical samples. A comparison with Sanger sequencing performance is also reported, highlighting the advantages and disadvantages of the Sentosa® NGS assay. The precision of the technology was studied with reference specimens, while intra- and inter-assay reproducibility were evaluated for selected clinical samples. Vela Diagnostics' NGS assay reached an 87% success rate through 30 runs of analysis in a real-world clinical context. The concordance with Sanger sequencing outcomes was equal to 97.2%. Several detected mismatches were due to NGS's superior sensitivity to low-frequency variants. A high accuracy was observed in testing reference samples. Repeatability and reproducibility assays highlighted the good performance of the NGS platform. Beyond a few technical issues that call for further optimization, the key improvement will be a better balance between costs and processing speed. Once these issues have been solved, the Sentosa® SQ HIV Genotyping Assay will be the way forward for HIV resistance testing.

Keywords: next-generation sequencing (NGS); human immunodeficiency virus (HIV); genotyping; Vela Diagnostics; Sanger sequencing (SS); resistance-associated mutations (RAM); protease inhibitors (PIs); integrase strand transfer inhibitors (INSTIs); nucleoside reverse transcriptase inhibitors (NRTIs); non-nucleoside reverse transcriptase inhibitors (NNRTIs)

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1. Introduction

More than 40 million people all over the world are currently living with HIV, the retrovirus responsible for the HIV/AIDS pandemic [1]. After almost 40 years from the isolation of HIV, this retrovirus is still a world health threat. Indeed, in 2020, HIV claimed the life of 680,000 people [2].

Combined antiretroviral therapy (cART) suppresses HIV replication, preventing the development of AIDS syndrome and replacing it with a manageable chronic disease [3]. However, a cure with which to eradicate HIV is currently unavailable, partly because of the intrinsic genetic variability of this infectious agent [4]. cART triggers the emergence of HIV-resistant variants, selected under drug pressure [5]. Several studies have explored the impact of low-frequency resistance-associated mutations (RAMs) on virological failure [6,7].

SCIENTIFIC REPORTS

OPEN

High diagnostic value of second generation CSF RT-QuIC across the wide spectrum of CJD prions

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An early and accurate *in vivo* diagnosis of rapidly progressive dementia remains challenging, despite its critical importance for the outcome of treatable forms, and the formulation of prognosis. Real-Time Quaking-Induced Conversion (RT-QuIC) is an *in vitro* assay that, for the first time, specifically discriminates patients with prion disease. Here, using cerebrospinal fluid (CSF) samples from 239 patients with definite or probable prion disease and 100 patients with a definite alternative diagnosis, we compared the performance of the first (PQ-CSF) and second generation (IQ-CSF) RT-QuIC assays, and investigated the diagnostic value of IQ-CSF across the broad spectrum of human prions. Our results confirm the high sensitivity of IQ-CSF for detecting human prions with a sub-optimal sensitivity for the sporadic CJD subtypes MM2C and MM2T, and a low sensitivity limited to variant CJD, Gerstmann-Sträussler-Scheinker syndrome and fatal familial insomnia. While we found no difference in specificity between PQ-CSF and IQ-CSF, the latter showed a significant improvement in sensitivity, allowing prion detection in about 80% of PQ-CSF negative CJD samples. Our results strongly support the implementation of IQ-CSF in clinical practice. By rapidly confirming or excluding CJD with high accuracy the assay is expected to improve the outcome for patients and their enrollment in therapeutic trials.

Human transmissible spongiform encephalopathies (TSEs) or prion diseases are neurodegenerative disorders characterized by the conversion of a constitutively expressed cellular glycoprotein, the prion protein (PrP^{C}), into an abnormally folded, beta-sheet enriched, isoform (PrP^{Sc})[1]. While the mechanism of initial PrP^{Sc} formation remains largely unexplained, compelling evidence indicates that disease propagation involves the templated misfolding of PrP^{C} by PrP^{Sc}[2,3].

Human prion diseases are highly heterogeneous disorders including four major disease groups, namely Creutzfeldt-Jakob disease (CJD), fatal insomnia, Gerstmann-Sträussler-Scheinker (GSS) syndrome, and variably protease-sensitive prionopathy (VPSPr)[4–7]. Disease subtypes with distinctive molecular and phenotypic features can also be found within these four groups, as it is exemplified by the current recognition of six clinico-pathological subtypes of sporadic CJD (sCJD) correlating at molecular level with the genotype at the polymorphic codon 129 (methionine, M or valine, V) in the gene encoding the prion protein (*PRNP*) and the type (1 or 2) of PrP^{Sc} accumulating in the brain[8,9]. This phenotypic diversity mostly relates to the biology of prions, which exist in different strains, thought to be enciphered in distinct PrP^{Sc} conformations, that are able to transmit distinctive phenotypic traits, including incubation time, clinical signs, progression rate, type and patterns of PrP^{Sc} deposition, and neuropathological lesions[10,11]. Specifically, current evidence indicate that five out of six sCJD subtypes (MM1, MM2C, MM2T, VV1 and VV2) behave as distinct prion strains after serial transmission into animal models. As the only exception, the VV2 and MV2K variants showed the same transmission properties, indicating a host-genotype (codon 129) effect[12–15].

Due to of the significant phenotypic overlap with a number of other medical conditions which present with a rapidly progressive neurological syndrome, the clinical diagnosis of prion disease is often challenging. The introduction of diagnostic investigations such as brain diffusion weighted-MRI (DW-MRI) and surrogate CSF

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HIGHLIGHTS OF PRESCRIBING INFORMATION

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

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

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

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

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

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

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

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

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

Tablets: 50 mg (3)

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

None.

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

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

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

The most common adverse reaction (>20%) is myelosuppression, including anemia, leukopenia and thrombocytopenia. Adverse reactions occurring in 5% to 20% of patients include anorexia, nausea, vomiting, diarrhea, malaise and rash. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Stason Pharmaceuticals at (888) 598-7707 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

----------DRUG INTERACTIONS----------

- Allopurinol: Reduce the dose of PURINETHOL when co-administered with allopurinol. (2.4, 7.1)
- Warfarin: PURINETHOL may decrease the anticoagulant effect. (7.2)

----------USE IN SPECIFIC POPULATIONS----------

- Lactation: Advise not to breastfeed. (8.2)
- Infertility: Can impair fertility. (8.3)

See 17 for PATIENT COUNSELING INFORMATION

Revised: 12/2020

FULL PRESCRIBING INFORMATION: CONTENTS*

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

FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

1.1 Acute Lymphoblastic Leukemia

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

2 DOSAGE AND ADMINISTRATION

2.1 Recommended Dosage

The recommended starting dosage of PURINETHOL is 1.5 mg/kg to 2.5 mg/kg orally once daily as part of combination chemotherapy maintenance regimen. A recommended dosage for patients less than 17 kg is not achievable, because the only available strength is 50 mg. Take PURINETHOL either consistently with or without food.

After initiating PURINETHOL, monitor complete blood count (CBC) and adjust the dose to maintain absolute neutrophil count (ANC) at a desirable level and for excessive myelosuppression. Evaluate the bone marrow in patients with prolonged myelosuppression or repeated episodes of myelosuppression to assess leukemia status and marrow cellularity.

Evaluate thiopurine S-methyltransferase (TPMT) and nucleotide diphosphatase (NUDT15) status in patients with severe myelosuppression or repeated episodes or myelosuppression *[see Dosage and Administration (2.2)]*.

Do not administer to patients who are unable to swallow tablets.

If a patient misses a dose, instruct the patient to continue with the next scheduled dose.

PURINETHOL is a cytotoxic drug. Follow special handling and disposal procedures.

2.2 Dosage Modifications in Patients with TPMT and NUDT15 Deficiency

Consider testing for TPMT and NUDT15 deficiency in patients who experience severe myelosuppression or repeated episodes of myelosuppression *[see Warnings and Precautions (5.1), Clinical Pharmacology (12.5)]*.

Homozygous Deficiency in either TPMT or NUDT15

Patients with homozygous deficiency of either enzyme typically require 10% or less of the recommended dosage. Reduce the recommended starting dosage of PURINETHOL in patients who are known to have homozygous TPMT or NUDT15 deficiency.

Heterozygous Deficiency in TPMT and/or NUDT15

Reduce the PURINETHOL dose based on tolerability. Most patients with heterozygous TPMT or NUDT15 deficiency tolerate the recommended dosage, but some require a dose reduction based on adverse reactions. Patients who are heterozygous for both TPMT and NUDT15 may require more substantial dose reductions.

2.3 Dosage Modifications in Renal and Hepatic Impairment

Renal Impairment

Use the lowest recommended starting dosage for PURINETHOL in patients with renal impairment (CLcr less than 50 mL/min). Adjust the dosage to maintain absolute neutrophil count (ANC) at a desirable level and for adverse reactions *[see Uses in Specific Populations (8.6)]*.

Hepatic Impairment

Use the lowest recommended starting dosage for PURINETHOL in patients with hepatic impairment. Adjust the dosage to maintain absolute neutrophil count (ANC) at a desirable level and for adverse reactions *[see Uses in Specific Populations (8.7)]*.

2.4 Dosage Modification with Concomitant Use of Allopurinol

Reduce the dose of PURINETHOL to one-third to one-quarter of the current dosage when coadministered with allopurinol *[see Drug Interactions (7.1)]*.

3 DOSAGE FORMS AND STRENGTHS

Tablets: 50 mg, biconvex, round, pale yellow to buff, scored tablets imprinted with “9|3”

4 CONTRAINDICATIONS

None.

5 WARNINGS AND PRECAUTIONS

5.1 Myelosuppression

The most consistent, dose-related adverse reaction is myelosuppression, manifested by anemia, leukopenia, thrombocytopenia, or any combination of these. Monitor CBC and adjust the dosage of PURINETHOL for excessive myelosuppression *[see Dosage and Administration (2.1)]*.

Consider testing for TPMT or NUDT15 deficiency in patients with severe myelosuppression or repeated episodes of myelosuppression. TPMT genotyping or phenotyping (red blood cell TPMT activity) and NUDT15 genotyping can identify patients who have reduced activity of these enzymes. Patients with heterozygous or homozygous TPMT or NUDT15 deficiency may require a dose reduction *[see Dosage and Administration (2.2), Clinical Pharmacology (12.5)]*.

Myelosuppression can be exacerbated by coadministration with allopurinol, aminosalicylates or other products that cause myelosuppression *[see Drug Interactions (7.1, 7.3, 7.4)]*. Reduce the dose of PURINETHOL when coadministered with allopurinol *[see Dosage and Administration (2.4)]*.

5.2 Hepatotoxicity

Mercaptopurine is hepatotoxic. There are reports of deaths attributed to hepatic necrosis associated with the administration of mercaptopurine. Hepatic injury can occur with any dosage but seems to occur with greater frequency when the recommended dosage is exceeded. In some patients, jaundice has cleared following withdrawal of mercaptopurine and reappeared with rechallenge.

Usually, clinically detectable jaundice appears early in the course of treatment (1 to 2 months); however, jaundice has been reported as early as 1 week and as late as 8 years after the starting mercaptopurine. The hepatotoxicity has been associated in some cases with anorexia, diarrhea, jaundice and ascites. Hepatic encephalopathy has occurred.

Monitor serum transaminase levels, alkaline phosphatase, and bilirubin levels at weekly intervals when first beginning therapy and at monthly intervals thereafter. Monitor liver tests more frequently in patients who are receiving PURINETHOL with other hepatotoxic products *[see Drug Interactions (7.5)]* or with known pre-existing liver disease. Withhold PURINETHOL at onset of hepatotoxicity.

5.3 Immunosuppression

Mercaptopurine is immunosuppressive and may impair the immune response to infectious agents or vaccines. Due to the immunosuppression associated with maintenance chemotherapy for ALL, response to all vaccines may be diminished and there is a risk of infection with live virus vaccines. Consult immunization guidelines for immunocompromised patients.

5.4 Treatment Related Malignancies

Hepatosplenic T-cell lymphoma has been reported in patients treated with mercaptopurine for inflammatory bowel disease (IBD), an unapproved use. Mercaptopurine is mutagenic in animals and humans, carcinogenic in animals, and may increase the risk of secondary malignancies.

Patients receiving immunosuppressive therapy, including mercaptopurine, are at an increased risk of developing lymphoproliferative disorders and other malignancies, notably skin cancers (melanoma and non-melanoma), sarcomas (Kaposi's and non-Kaposi's) and uterine cervical cancer in situ. The increased risk appears to be related to the degree and duration of immunosuppression. It has been reported that discontinuation of immunosuppression may provide partial regression of the lymphoproliferative disorder.

A treatment regimen containing multiple immunosuppressants (including thiopurines) should therefore be used with caution as this could lead to lymphoproliferative disorders, some with reported fatalities. A combination of multiple

immunosuppressants, given concomitantly increases the risk of Epstein-Barr virus (EBV)-associated lymphoproliferative disorders.

5.5 Macrophage Activation Syndrome

Macrophage activation syndrome (MAS) (hemophagocytic lymphohistiocytosis) is a known, life-threatening disorder that may develop in patients with autoimmune conditions, in particular with inflammatory bowel disease (IBD), and there could potentially be an increased susceptibility for developing the condition with the use of mercaptopurine (an unapproved use). If MAS occurs, or is suspected, discontinue PURINETHOL. Monitor for and promptly treat infections such as EBV and cytomegalovirus (CMV), as these are known triggers for MAS.

5.6 Embryo-Fetal Toxicity

PURINETHOL can cause fetal harm when administered to a pregnant woman. An increased incidence of miscarriage has been reported in women who received mercaptopurine in the first trimester of pregnancy. Adverse embryo-fetal findings, including miscarriage and stillbirth, have been reported in women who received mercaptopurine after the first trimester of pregnancy. Advise pregnant women of the potential risk to a fetus. Advise females of reproductive potential to use effective contraception during treatment with PURINETHOL and for 6 months after the last dose. Advise males with female partners of reproductive potential to use effective contraception during treatment with PURINETHOL and for 3 months after the last dose *[see Use in Specific Populations (8.1, 8.3)]*.

6 ADVERSE REACTIONS

The following clinically significant adverse reactions are described elsewhere in the labeling:

- Myelosuppression *[see Warnings and Precautions (5.1)]*
- Hepatotoxicity *[see Warnings and Precautions (5.2)]*
- Immunosuppression *[see Warnings and Precautions (5.3)]*
- Treatment related malignancies *[see Warnings and Precautions (5.4)]*
- Macrophage activation syndrome *[see Warnings and Precautions (5.5)]*

6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

Based on multicenter cooperative group ALL trials, the most common adverse reaction occurring in > 20% of patients was myelosuppression, including anemia, neutropenia, lymphopenia and thrombocytopenia. Adverse reactions occurring in 5% to 20% of patients included anorexia, nausea, vomiting, diarrhea, malaise and rash. Adverse reactions occurring in < 5 % of patients included urticaria, hyperuricemia, oral lesions, increased transaminases, hyperbilirubinemia, hyperpigmentation, infections, and pancreatitis. Oral lesions resemble thrush rather than antifolic ulcerations. Delayed or late adverse reactions include hepatic fibrosis, hyperbilirubinemia, alopecia, pulmonary fibrosis, oligospermia and secondary malignancies *[see Warnings and Precautions (5.1, 5.2)]*.

Drug fever has been reported with mercaptopurine.

Additional adverse reactions that have been reported in patients who have received mercaptopurine include photosensitivity, hypoglycemia, and portal hypertension.

7 DRUG INTERACTIONS

7.1 Allopurinol

Allopurinol can inhibit the first-pass oxidative metabolism of mercaptopurine by xanthine oxidase, which can lead to an increased risk of mercaptopurine adverse reactions (i.e., myelosuppression, nausea, and vomiting) *[see Warnings and Precautions (5.1), Adverse Reactions (6.1)]*. Reduce the dose of PURINETHOL when coadministered with allopurinol *[see Dosage and Administration (2.4)]*.

7.2 Warfarin

The concomitant administration of PURINETHOL and warfarin may decrease the anticoagulant effectiveness of warfarin. Monitor the international normalized ratio (INR) in patients receiving warfarin and adjust the warfarin dosage as appropriate.

7.3 Myelosuppressive Products

PURINETHOL can cause myelosuppression. Myelosuppression may be increased when PURINETHOL is coadministered with other products that cause myelosuppression. Enhanced myelosuppression has been noted in some patients also receiving trimethoprim-sulfamethoxazole. Monitor the CBC and adjust the dose of PURINETHOL for excessive myelosuppression *[see Dosage and Administration (2.1), Warnings and Precautions (5.1)]*.

7.4 Aminosalicylates

Aminosalicylates (e.g., mesalamine, olsalazine or sulfasalazine) may inhibit the TPMT enzyme, which may increase the risk of myelosuppression when coadministered with PURINETHOL. When aminosalicylates and PURINETHOL are coadministered, use the lowest possible doses for each drug and monitor more frequently for myelosuppression *[see Warnings and Precautions (5.1)]*.

7.5 Hepatotoxic Products

PURINETHOL can cause hepatotoxicity. Hepatotoxicity may be increased when PURINETHOL is coadministered with other products that cause hepatotoxicity. Monitor liver tests more frequently in patients who are receiving PURINETHOL with other hepatotoxic products *[see Warnings and Precautions (5.2)]*.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

PURINETHOL can cause fetal harm when administered to a pregnant woman *[see Clinical Pharmacology (12.1)]*. Pregnant women who receive mercaptopurine have an increased incidence of miscarriage and stillbirth *(see Data)*. Advise pregnant women of the potential risk to a fetus.

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

Data

Human Data

Women receiving mercaptopurine in the first trimester of pregnancy have an increased incidence of miscarriage; the risk of malformation in offspring surviving first trimester exposure is not known. In a series of 28 women receiving mercaptopurine after the first trimester of pregnancy, 3 mothers died prior to delivery, 1 delivered a stillborn child, and 1 aborted; there were no cases of macroscopically abnormal fetuses.

Animal Data

Mercaptopurine was embryo-lethal and teratogenic in several animal species (rat, mouse, rabbit, and hamster) at doses less than the recommended human dose.

8.2 Lactation

Risk Summary

There are no data on the presence of mercaptopurine or its metabolites in human milk, the effects on the breastfed child, or the effects on milk production. Because of the potential for serious adverse reactions in the breastfed child, advise women not to breastfeed during treatment with PURINETHOL and for 1 week after the last dose.

8.3 Females and Males of Reproductive Potential

PURINETHOL can cause fetal harm when administered to pregnant women *[see Use in Specific Populations (8.1)]*.

Pregnancy Testing

Verify the pregnancy status in females of reproductive potential prior to initiating PURINETHOL *[see Use in Specific Populations (8.1)]*.

Contraception

Females

Advise females of reproductive potential to use effective contraception during treatment with PURINETHOL and for 6 months after the last dose.

Males

Based on genotoxicity findings, advise males with female partners of reproductive potential to use effective contraception during treatment with PURINETHOL and for 3 months after the last dose *[see Nonclinical Toxicology (13.1)]*.

Infertility

Females and Males

Based on findings from animal studies, PURINETHOL can impair female and male fertility *[see Nonclinical Toxicology (13.1)]*. The long-term effects of mercaptopurine on female and male fertility, including the reversibility have not been studied.

8.4 Pediatric Use

Safety and effectiveness of PURINETHOL has been established in pediatric patients. Use of PURINETHOL in pediatrics is supported by evidence from the published literature and clinical experience. Symptomatic hypoglycemia has been reported in pediatric patients with ALL receiving mercaptopurine. Reported cases were in pediatrics less than 6 years of age or with a low body mass index.

8.5 Geriatric Use

Clinical studies of mercaptopurine did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects. Other reported clinical experience has not identified differences in responses between the elderly and younger patients. In general, dose selection for an elderly patient should be cautious, usually starting at the low end of the dosing range, reflecting the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or another drug therapy.

8.6 Renal Impairment

Use the lowest recommended starting dosage for PURINETHOL or increase the dosing interval to every 36-48 hours in patients with renal impairment (CLcr less than 50 mL/min). Adjust the dose to maintain absolute neutrophil count (ANC) at a desirable level and for adverse reactions *[see Dosage and Administration (2.3)]*.

8.7 Hepatic Impairment

Use the lowest recommended starting dosage for PURINETHOL in patients with hepatic impairment. Adjust the dose to maintain absolute neutrophil count (ANC) at a desirable level and for adverse reactions *[see Dosage and Administration (2.3)]*.

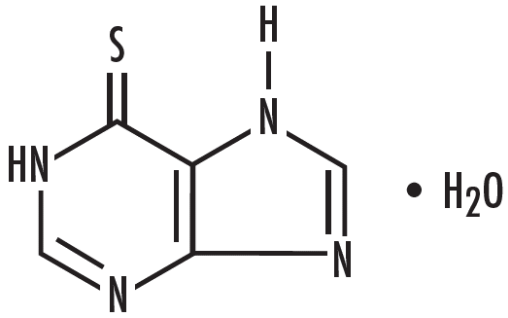
10 OVERDOSAGE

Signs and symptoms of mercaptopurine overdosage may be immediate (anorexia, nausea, vomiting, and diarrhea); or delayed (myelosuppression, liver dysfunction, and gastroenteritis). Dialysis cannot be expected to clear mercaptopurine. Hemodialysis is thought to be of marginal use due to the rapid intracellular incorporation of mercaptopurine into active metabolites with long persistence.

Withhold PURINETHOL immediately for severe or life-threatening adverse reactions occur during treatment. If a patient is seen immediately following an accidental overdosage, it may be useful to induce emesis.

11 DESCRIPTION

Mercaptopurine is a nucleoside metabolic inhibitor, the chemical name is 6*H*-purine-6-thione, 1,7-dihydro-, monohydrate. The molecular formula is $C_5H_4N_4S \cdot H_2O$ and the molecular weight is 170.20. Its structural formula is:



Mercaptopurine is a yellow, crystalline powder. Mercaptopurine is practically insoluble in water and in ether. It has a pKa of 7.8, an average tapped density of 1.0 g/mL and average bulk density of 0.85 g/mL. It dissolves in solutions of alkali hydroxides.

PURINETHOL is available for oral use. Each scored tablet contains 50 mg mercaptopurine and the following inactive ingredients: corn starch, pregelatinized, potato starch, lactose, magnesium stearate and stearic acid.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Mercaptopurine is a purine analog that undergoes intracellular transport and activation to form metabolites including thioguanine nucleotides (TGNs). Incorporation of TGNs into DNA or RNA results in cell-cycle arrest and cell death. TGNs and other mercaptopurine metabolites are also inhibitors of de novo purine synthesis and purine nucleotide interconversions. Mercaptopurine was cytotoxic to proliferating cancer cells in vitro and had antitumor activity in mouse tumor models. It is not known which of the biochemical effects of mercaptopurine and its metabolites are directly or predominantly responsible for cell death.

12.2 Pharmacodynamics

Exposure-Response Relationships

Mercaptopurine exposure-response relationships and the time course of pharmacodynamics response are unknown.

12.3 Pharmacokinetics

Following a single oral dose of mercaptopurine 50 mg under fasted conditions to adult healthy subjects, the mean $AUC_{0\text{-}INF}$ was 129 h·ng/mL and C_{max} was 69 ng/mL.

Absorption

Food Effect

Food has been shown to decrease the exposure of mercaptopurine.

Distribution

The volume of distribution usually exceeded that of the total body water. There is negligible entry of mercaptopurine into cerebrospinal fluid.

Plasma protein binding averages 19% over the concentration range 10 to 50 mcg/mL (a concentration only achieved by intravenous administration of mercaptopurine at doses exceeding 5 to 10 mg/kg).

Elimination

The elimination half-life is less than 2 hours following a single oral dose.

Metabolism

Mercaptopurine is inactivated via two major pathways. One is thiol methylation, which is catalyzed by the polymorphic enzyme thiopurine S-methyltransferase (TPMT), to form the inactive metabolite methyl-mercaptopurine. The second inactivation pathway is oxidation, which is catalyzed by xanthine oxidase. The product of oxidation is the inactive metabolite 6-thiouric acid.

Excretion

Following the oral administration of radiolabeled mercaptopurine, 46% of the dose was recovered in the urine (as parent drug and metabolites) in the first 24 hours.

12.5 Pharmacogenomics

Several published studies indicate that patients with reduced TPMT or NUDT15 activity receiving usual doses of mercaptopurine, accumulate excessive cellular concentrations of active 6-TGNs, and are at higher risk for severe myelosuppression. In a study of 1028 children with ALL, the approximate tolerated mercaptopurine dosage for patients with TPMT and/or NUDT15 deficiency on mercaptopurine maintenance therapy (as a percentage of the planned dosage) was as follows: heterozygous for either TPMT or NUDT15, 50-90%; heterozygous for both TPMT and NUDT15, 30-50%; homozygous for either TPMT or NUDT15, 5-10%.

Approximately 0.3% (1:300) of patients of European or African ancestry have two loss-of-function alleles of the TPMT gene and have little or no TPMT activity (homozygous deficient or poor metabolizers), and approximately 10% of patients have one loss-of-function TPMT allele leading to intermediate TPMT activity (heterozygous deficient or intermediate metabolizers). The TPMT*2, TPMT*3A, and TPMT*3C alleles account for about 95% of individuals with reduced levels of TPMT activity.

NUDT15 deficiency is detected in <1% of patients of European or African ancestry. Among patients of East Asian ancestry (i.e., Chinese, Japanese, Vietnamese), 2% have two loss-of-function alleles of the NUDT15 gene, and approximately 21% have one loss-of-function allele. The p.R139C variant of NUDT15 (present on the *2 and *3 alleles) is the most commonly observed, but other less common loss-of-function NUDT15 alleles have been observed.

Consider all clinical information when interpreting results from phenotypic testing used to determine the level of thiopurine nucleotides or TPMT activity in erythrocytes, since some coadministered drugs can influence measurement of TPMT activity in blood and blood from recent transfusions will misrepresent a patient's actual TPMT activity *[see Dosage and Administration (2.2), Warnings and Precautions (5.1)]*.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Mercaptopurine is carcinogenic in animals.

Mercaptopurine causes chromosomal aberrations in cells derived from animals and humans and induces dominant-lethal mutations in the germ cells of male mice.

Mercaptopurine can impair fertility. In mice, surviving female offspring of mothers who received chronic low doses of mercaptopurine during pregnancy were found sterile, or if they became pregnant, had smaller litters and more dead fetuses as compared to control animals

15 REFERENCES

1. OSHA Hazardous Drugs. OSHA. http://www.osha.gov/SLTC/hazardousdrugs/index.html

16 HOW SUPPLIED/STORAGE AND HANDLING

PURINETHOL is supplied as biconvex, round, pale yellow to buff, scored tablets containing 50 mg mercaptopurine, imprinted with "9|3" available in:

- bottles of 25 NDC 62033-601-12

Store at 20°C to 25°C (68°F to 77°F); excursions permitted to 15°C to 30°C (59°F to 86°F) [see USP Controlled Room Temperature]. Store in a dry place. Dispense in tight container as defined in the USP.

PURINETHOL is a cytotoxic drug. Follow special handling and disposal procedures[1].

17 PATIENT COUNSELING INFORMATION

Major Adverse Reactions

Advise patients and caregivers that PURINETHOL can cause myelosuppression, hepatotoxicity, and gastrointestinal toxicity. Advise patients to contact their healthcare provider if they experience fever, sore throat, jaundice, nausea, vomiting, signs of local infection, bleeding from any site, or symptoms suggestive of anemia *[see Warnings and Precautions (5.1, 5.2, 5.3)]*.

Embryo-Fetal Toxicity

- Advise pregnant women of the potential risk to a fetus. Advise females of reproductive potential to inform their healthcare provider of a known or suspected pregnancy *[see Warnings and Precautions (5.6), Use in Specific Populations (8.1)]*.
- Advise females of reproductive potential to use effective contraception during treatment with PURINETHOL and for 6 months after the last dose *[see Use in Specific Populations (8.3)]*.
- Advise males with female partners of reproductive potential to use effective contraception during treatment with PURINETHOL and for 3 months after the last dose *[see Use in Specific Populations (8.3), Nonclinical Toxicology (13.1)]*.

Lactation

Advise women not to breastfeed during treatment with PURINETHOL and for 1 week after the last dose *[see Use in Specific Populations (8.2)]*.

Infertility

Advise males and females of reproductive potential that PURINETHOL can impair fertility *[see Use in Specific Populations (8.3)]*.

Other Adverse Reactions

Instruct patients to minimize sun exposure due to risk of photosensitivity *[see Adverse Reactions (6.1)]*.

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Viral oncoprotein antibodies as a marker for recurrence of Merkel cell carcinoma: a prospective validation study

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Abstract

Background—Merkel cell carcinoma (MCC) is an aggressive skin cancer with a recurrence rate of >40%. Of the 2000 MCC cases/year in the USA, most are caused by the Merkel cell polyomavirus (MCPyV). Antibodies to MCPyV-oncoprotein (T-antigens) have been correlated with MCC tumor burden. We prospectively validated the clinical utility of MCPyV oncoprotein antibody titers for MCC prognostication and surveillance.

Methods—MCPyV-oncoprotein antibody detection was optimized in a clinical laboratory. A cohort of 219 patients with newly-diagnosed MCC were followed prospectively (median follow-up 1.9 years). Among seropositive patients, antibody titer and disease status were serially tracked.

Results—Antibodies to MCPyV-oncoproteins were rare among healthy individuals (1%) but present in most MCC patients (114 of 219, 52%, $p<0.01$). Seropositivity at diagnosis independently predicted decreased recurrence risk (HR=0.58; $p=0.04$) in multivariate analyses adjusted for age, sex, stage, and immunosuppression. Following initial treatment, seropositive patients whose disease did not recur had rapidly falling titers that became negative by a median of 8.4 months. Among seropositive patients who underwent serial evaluation (71 patients; 282 timepoints), an increasing oncoprotein titer had a positive predictive value of 66% for clinically evident recurrence while a decreasing titer had a negative predictive value of 97%.

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Conflicts of interest: None

Conclusions—Determination of oncoprotein antibody titer assists in the clinical management of newly diagnosed MCC patients by stratifying them into a higher risk seronegative cohort in whom radiologic imaging may play a more prominent role, and into a lower-risk seropositive cohort whose disease status can be tracked in part via oncoprotein antibody titer.

Introduction

Merkel cell carcinoma (MCC) is a neuroendocrine skin cancer with an incidence of 0.6 per 100,000,[1] corresponding to approximately 2,000 new cases annually in the United States based on 2015 census data.[2] Age, sun exposure, and male sex are risk factors for MCC,[3] and immunosuppression portends poorer outcome.[4, 5] MCC has a recurrence rate of >40%.[6] This high recurrence rate indicates a need for data-driven surveillance approaches.

In 2008, a causative polyomavirus (Merkel cell polyomavirus/MCPyV) was identified in 80% of MCCs[7] (Fig 1A). MCPyV is common worldwide, with 60% of adults demonstrating serologic evidence of prior infection.[8-11] Infection often occurs in childhood and is typically self-limited.[11-13] However, among patients who develop MCC, MCPyV integrates into the human genome and undergoes tumor-specific truncating mutations and thus can no longer replicate (Fig 1B).[7, 14] Instead, viral oncoproteins (T-antigens) are persistently expressed in MCC tumors and help to promote cell cycle progression and tumorigenesis through multiple mechanisms,[15] including inhibition of the tumor-suppressor pRb,[16] stabilization of the oncoprotein c-Myc,[17] and evasion of innate immunity.[18, 19] These oncoproteins are detectable by immunohistochemistry in 70-100% of MCCs.[16, 17]

90% of persons with MCC produce antibodies to the MCPyV capsid proteins.[8] High titers of anti-capsid antibodies at presentation have been reported to be a favorable prognostic factor. [20, 21] However, these antibodies (which mark previous exposure) are also detectable in >60% of healthy adults.[8, 10] Furthermore, titers of antibodies to the MCPyV capsid protein do not vary with MCC tumor burden[21, 22] and thus could not serve as a biomarker for recurrence. Given limitations of anti-capsid antibodies, we instead focused on antibodies against MCPyV-oncoprotein. These antibodies are rarely detectable in healthy individuals, but are prevalent among MCC patients.[21, 22] In a discovery case series of 20 patients, we observed that titers increased with rising MCC burden and fell after tumor excision.[22] Similarly, others have shown that patients with blood draws at the time of recurrence are more likely to have detectable antibodies than those with draws at the time of remission, although longitudinal patient-specific data was not presented.[21]

In this study, using a large, prospective validation cohort of 219 newly diagnosed patients followed over a 5-year period, we tested the clinical utility of MCPyV-oncoprotein antibodies in MCC management. To maximize clinical applicability, the assay was first established in a hospital-based laboratory. We tested two clinical roles for oncoprotein antibody quantitation: initial MCC prognostication and as a marker for disease recurrence following definitive therapy (Fig 1C). Our results suggest that MCPyV-oncoprotein antibody titer is a biomarker that can assist in optimizing MCC management.

Section 6.0

Previously Discussed Items

Prostate Procedure Guideline Modifications

Plain Language Summary:

Coverage question: Should the requirement to try medication before having a procedure on a prostate to help urine leave the body be removed? Should any changes be made to the requirements for a procedure to help urine leave the body?

Should OHP cover this treatment? The guideline on prostate procedures should be changed to no longer require medications. This is done to agree with expert guidelines. The age range for the procedure should be lowered to 45 years old because the FDA has approved it for younger patients.

Coverage Question: How should the guideline regarding prostatic lift procedures be updated to reflect new FDA approval criteria for the devices?

Question source: Max Kaiser, CCO medical director

Background: Coverage for prostatic urethral lift procedures was added with a 2016 coverage guidance. This coverage guidance included the then-current FDA approval criteria for Urolift. The FDA has modified the criteria to lower the age of eligibility to 45 (from 50) and for a slightly more liberal prostatic volume (≤100 cc vs the prior ≤80 cc). The FDA has also removed the restriction that this procedure should not be done with median lobe hyperplasia.

Dr. Kaiser is requesting that guideline note 145 be updated to reflect the current FDA approval criteria. He is also requesting that the guideline be clarified to include that medication failure is required for urethral lift procedures.

From Dr. Kaiser:

> When reviewing an appeal I noticed there was a FDA Section 510(k) pre market approval for an updated version of the UroLift that lowers the approved age to 45 (the original product was 50 per the GN) and increases the prostate volume to <100 cc (the original product was <80 cc per the GN) - https://www.accessdata.fda.gov/cdrh_docs/pdf20/K201837.pdf. I don't know if in practice this replaced the old product. If it has it would be appropriate to update the GN.
>
> I would also request to update the GN to clarify medication failure is required for urethral lift procedures by re-stating the requirements per part D). Medication failure was part of the original guidance approved in 2018. As written, it's confusing if medication failure is required, as per part D), as part D) also requires a higher IPSS than is required in the urethral lift section.

Prostate Procedure Guideline Modifications

This topic was discussed at the March 2023 VBBS and HERC meetings. VBBS approved the staff recommended changes; however, HERC members were concerned that the suggested changes did not align with the current American Urology Association (AUA) guideline on management of BPH. Specifically, there were concerns that the AUA guideline still required a trial and failure of two medications together prior to proceeding to an invasive treatment.

HERC staff were directed to review the current AUA guideline and seek expert input and opinion.

The 2021 AUA guideline recommends prostatic urethral lift only for men with prostates less than or equal to 80 ccs and only without median lobe hypertrophy based on lack of high quality studies of the procedure in men with larger prostates or with median lobe hypertrophy.

The 2021 AUA guidelines do not recommend trial and failure of two medications prior to invasive treatment. The AUA guideline only recommends medication as an option.

Current Prioritized List/Coverage status:

GUIDELINE NOTE 145, TREATMENTS FOR BENIGN PROSTATE ENLARGEMENT WITH LOWER URINARY TRACT SYMPTOMS

Line 327

For men with lower urinary tract symptoms (LUTS) due to benign prostate hyperplasia (BPH), surgical procedures are included on this line for patients with one of the following:

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

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

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

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

- Botulinum toxin
- HIFU (High Intensity Focused Ultrasound)
- TEAP (Transurethral Ethanol Ablation of the Prostate)
- Laser coagulation (for example, VLAP/ILC)

Prostate Procedure Guideline Modifications

- Prostatic artery embolization

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

Submitted literature:

1) **Eure 2023**, Prostatic Urethral Lift (PUL) for Obstructive Median Lobes (OML): Consistent Results Across Controlled Trial and Real-World Settings
    a. N= 4 studies
        i. BPH6: RCT of TURP vs PUL, N=35 men randomized to TURP
        ii. L.I.F.T.: RCT of sham vs PUL, in subjects with lateral lobe obstruction (66 subjects randomized to sham)
        iii. MedLift, an U.S. Food and Drug Administration-approved Investigational Device Exemption (IDE) extension of the L.I.F.T. trial (45 men with OML)
        iv. RWR: retrospective database (N=180 mend with OML)
    b. Analysis compared the MedLift group (N=45) and the RWR group (N=180) with the control groups from BPH6 and LIFT (N=35 and 66 respectively)
    c. At 3 months, MedLift subjects experienced 170% greater IPSS improvement than sham control subjects and significantly better QoL, Qmax, and benign prostatic hyperplasia impact index (BPHII) outcomes. MedLift IPSS and QoL were significantly improved compared with TURP controls at 1 and 3 months post-procedure and were equivalent at 6 and 12 month
    d. PUL outcomes for treating OML were equivalent to those for treating lateral lobe hypertrophy in the RWR study
    e. Conclusion: Controlled and real-world outcomes confirm PUL is a safe and effective treatment for BPH patients with and without OML
    f. HERC staff comment: comparing the treatment group in one study with the control group in another study is a non-standard way of evaluating evidence

Expert guidelines:

1) **AUA 2021**, management of lower urinary tract symptoms attributed to benign prostatic hyperplasia: AUA guideline
    a. An initial trial of medical management over 4 weeks with an alpha blocker or PDE5, and over 6-12 months with a 5-ARI is reasonable in men with bothersome LUTS.
    b. Medications
        i. Clinicians should offer one of the following alpha blockers as a treatment option for patients with bothersome, moderate to severe LUTS/BPH: alfuzosin, doxazosin, silodosin, tamsulosin, or terazosin. (Moderate Recommendation; Evidence Level: Grade A)
        ii. For the purpose of symptom improvement, 5-ARI monotherapy should be used as a treatment option in patients with LUTS/BPH with prostatic enlargement as judged by a prostate volume of > 30cc on imaging, a prostate specific antigen (PSA) > 1.5ng/dL, or palpable prostate enlargement on digital rectal exam (DRE). (Moderate Recommendation; Evidence Level: Grade B)

iii. 5-ARIs alone or in combination with alpha blockers are recommended as a treatment option to prevent progression of LUTS/BPH and/or reduce the risks of urinary retention and need for future prostate-related surgery. (Strong Recommendation; Evidence Level: Grade A)
iv. For patients with LUTS/BPH irrespective of comorbid erectile dysfunction (ED), 5mg daily tadalafil should be discussed as a treatment option. (Moderate Recommendation; Evidence Level: Grade B)
v. 5-ARI in combination with an alpha blocker should be offered as a treatment option only to patients with LUTS associated with demonstrable prostatic enlargement as judged by a prostate volume of > 30cc on imaging, a PSA >1.5ng/dL, or palpable prostate enlargement on DRE. (Strong Recommendation; Evidence Level: Grade A)
vi. Anticholinergic agents, alone or in combination with an alpha blocker, may be offered as a treatment option to patients with moderate to severe predominant storage LUTS. (Conditional Recommendation; Evidence Level: Grade C)
vii. Beta-3-agonists in combination with an alpha blocker may be offered as a treatment option to patients with moderate to severe predominate storage LUTS. (Conditional Recommendation; Evidence Level: Grade C)
viii. Clinicians should not offer the combination of low-dose daily 5mg tadalafil with alpha blockers for the treatment of LUTS/BPH as it offers no advantages in symptom improvement over either agent alone. (Moderate Recommendation; Evidence Level: Grade C)

c. Surgery is recommended for patients who have renal insufficiency secondary to BPH, refractory urinary retention secondary to BPH, recurrent urinary tract infections (UTIs), recurrent bladder stones or gross hematuria due to BPH, and/or with LUTS/BPH refractory to or unwilling to use other therapies. (Clinical Principle)
d. Prostatic Urethral Lift (PUL)
    i. PUL should be considered as a treatment option for patients with LUTS/BPH provided prostate volume 30-80cc and verified absence of an obstructive middle lobe. (Moderate Recommendation; Evidence Level: Grade C)
        1. The L.I.F.T study compared PUL to SHAM55 in 206 patients. It excluded patients with a prostate 80g or an obstructive middle lobe. The primary outcome was urinary symptom score. The mean change from baseline IPSS (MD: -5.2; 95%CI: -7.45, -2.95) and improvement in IPSS-QoL (MD: 1.2; 95%CI: 1.7, - 0.7) favored PUL.
        2. Since the last amendment, there have been retrospective chart reviews evaluating a small number of patients with prostate sizes between 81-100mL. The Panel recognizes that many devices do not necessarily lack efficacy in prostates below or above the size ranges stipulated in the Statements, but there is insufficient evidence to make formal recommendations beyond those sizes identified.
        3. The Panel limited this guideline statement to include patients with a prostate lacking an obstructive middle lobe, consistent with the L.I.F.T. study criteria. The Panel identified an observational cohort study (n=45 patients) observing improvements in urinary and sexual health outcomes from baseline in patients with an obstructive middle lobe following PUL. This study was excluded from formal efficacy analysis

because it was a nonrandomized cohort study utilizing historic controls rather than an RCT.

ii. PUL may be offered as a treatment option to eligible patients who desire preservation of erectile and ejaculatory function. (Conditional Recommendation; Evidence Level: Grade C)

2) **Knight 2022**, UroLift for Treating Lower Urinary Tract Symptoms of Benign Prostatic Hyperplasia: A NICE Medical Technology Guidance Update
   a. Scoping
      i. Population—Adults with LUTS caused by BPH, aged 45 years or over, with prostate volumes ≤ 100 mL
      ii. Indication—Prostatic urethral lift using the UroLift system
      iii. Comparators: – Monopolar or bipolar transurethral resection of the prostate (TURP) – Holmium laser enucleation of the prostate (HoLEP) – Transurethral water vapor therapy using Rezum (Boston Scientific)
      iv. Outcomes—Length of hospital stay, changes in ejaculatory or sexual function, need for and duration of post-operative catheterization, symptoms of BPH, quality of life (QoL) and procedure time
   b. N=10 studies (2 RCTs and 8 non-randomized studies)
      i. Moderate to high quality
      ii. Studies were sought for use of additional implants for obstructive median lobe
   c. Since the publication of NICE MTG26, a larger body of clinical evidence has emerged, with 5-year follow-up, and with direct comparisons with TURP and other surgical procedures. The clinical benefits of UroLift are sustained; it is not as efficacious as TURP but is recommended by NICE as a less invasive option with fewer complications for people of age over 50 years with prostate volume of 30–80 mL.
   d. Cost savings are uncertain when UroLift is used for treating an obstructive median lobe.
   e. Consultees [public comment] suggested that the evidence for using the UroLift System in men with prostate volume between 80 and 100 mL is limited. The committee agreed and amended recommendations to include the use of the UroLift System for treating lower urinary tract symptoms of benign prostatic hyperplasia in those with a prostate volume between 30 and 80 mL.

Other payer policies:

Private payers cover prostatic urethral lifts and generally do not have specific criteria. Presumably, they require the FDA approval criteria for the devices.

Medicare LCD requires that “The beneficiary has had an adequate trial of, but is refractory to or intolerant of, usual BPH medication” prior to coverage of prostatic urethral lifts.

Regulatory guidance:

FDA 2020 approval: The UroLift 2 System is indicated for the treatment of symptoms due to urinary outflow obstruction secondary to benign prostatic hyperplasia (BHP), including lateral and median lobe hyperplasia, in men 45 years of age or older.

Prostate Procedure Guideline Modifications

Expert input:

Dr. Kamran Sajadi, OHSU urology:

1. The document is frankly incorrect in stating the AUA guidelines call for medical management before surgical therapy. From the AUA guidelines directly: “There also exist clinical scenarios in which conservative management—including lifestyle changes (e.g., fluid restriction, avoidance of substances with diuretic properties)—or pharmacological management are either inadequate or inappropriate. More recently, long-term use of medications for LUTS/BPH have been implicated in cognitive issues and depression.21 These situations merit consideration of one of the many invasive procedures available for the treatment of LUTS/BPH. Indications for these procedures include a desire by the patient to avoid taking a daily medication, failure of medical therapy to sufficiently ameliorate bothersome LUTS, intolerable pharmaceutical side effects, and/or the following conditions resulting from BPH and for which medical therapy is insufficient: acute and/or chronic renal insufficiency, refractory urinary retention, recurrent UTIs, recurrent bladder stones, and recalcitrant gross hematuria. Acute and chronic adverse events are associated with each class of medical therapy and can include cardiovascular and sexual effects.”
2. The AUA Guidelines also state “Before starting a 5-ARI [e.g., finasteride], clinicians should inform patients of the risks of sexual side effects, certain uncommon physical side effects, and the low riks of prostate cancer.” In addition, it should only be offered to those with objectively demonstrated prostatic enlargement >30cc (and other studies have shown >40cc) – statement 18.
3. My recommendation would be that patients should be OFFERED medical therapy but may decline.
4. To be consistent with the AUA guidelines, if keeping the cutoff for UroLift to 80cc, then the statement should read limited to prostates <= 80cc instead of <80cc.

Prostate Procedure Guideline Modifications

HERC staff summary:

The FDA approval criteria has changed for prostatic urethral lift (age 45, prostate volume <100 cc, approved for median lobe hypertrophy). However, the American Urology Association (AUA) continues to recommend use only in men with prostate volume between 30 and 80 cc, and without median lobe hypertrophy. The AUA states that use of prostatic urethral lifts in prostates larger than 80 cc or in median lobe hypertrophy is not supported by high quality studies. A recent NICE technology review came to the same conclusions that evidence is poor for larger prostate volumes and that other procedures are more efficacious for treatment in the setting of median lobe hypertrophy. Based on these evidence based guidelines, HERC staff is no longer recommending expanding coverage for the prostatic urethral lift procedure for larger prostates or with median lobe hypertrophy, although such expansion was initially recommended by experts.

Expert input heard at the March 2023 meeting recommended removing the requirement for two medications to be tried and failed prior to invasive interventions. HERC staff have reviewed the 2021 AUA guideline, and there is no recommendation for a requirement to try and fail two medications prior to a prostate procedure. The AUA recommendations for combination therapy are "should be offered" or "may be offered" recommendations. Tadalafil "should not [be offered]" in combination with other medications. The AUA recommends surgery for patients "with LUTS/BPH refractory to or unwilling to use other therapies." The NICE guideline does not have any information or recommendations regarding medications prior to PUL.

Based on the AUA guideline, the surgical indications should be updated to reflect lack of need to try several drugs prior to procedures. The prostatic lift procedure requirements should only be updated to reflect a younger age to qualify.

HERC staff recommendation:

1) Modify GN145 as shown below

GUIDELINE NOTE 145, TREATMENTS FOR BENIGN PROSTATE ENLARGEMENT WITH LOWER URINARY TRACT SYMPTOMS

Line 327

For men with lower urinary tract symptoms (LUTS) due to benign prostate hyperplasia (BPH), surgical procedures are included on this line for patients with one of the following:

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

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

- Age 45 ~~50~~ or older

Prostate Procedure Guideline Modifications

- Estimated prostate volume ~~<~~ ≤ 80 cc
- IPSS ≥ 13
- No obstructive median lobe of the prostate identified on cystoscopy at the time of the procedure

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

- Botulinum toxin
- HIFU (High Intensity Focused Ultrasound)
- TEAP (Transurethral Ethanol Ablation of the Prostate)
- Laser coagulation (for example, VLAP/ILC)
- Prostatic artery embolization

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

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Prostatic Urethral Lift for Obstructive Median Lobes: Consistent Results Across Controlled Trial and Real-World Settings

Gregg Eure, MD,[1] Daniel Rukstalis, MD,[2] and Claus Roehrborn, MD[3]

Abstract

Introduction: The evidence for prostatic urethral lift (PUL), in treating lower urinary tract symptoms/benign prostatic hyperplasia (BPH) in men with obstructive median lobes (OMLs), has grown. In this study, we present the first detailed comparison of outcomes between OML patients treated with PUL in controlled and real-world settings to relevant comparators (subjects treated with transurethral resection of the prostate [TURP] and sham in randomized controlled trials [RCTs]) to demonstrate similar symptom, safety, and patient experience outcomes.
Materials and Methods: Symptom and safety outcomes and patient satisfaction were compared through 12 months among controlled PUL studies: BPH6 RCT (35 men randomized to TURP); L.I.F.T. pivotal RCT in subjects with lateral lobe obstruction (66 subjects randomized to sham) and MedLift, an U.S. Food and Drug Administration-approved Investigational Device Exemption (IDE) extension of the L.I.F.T. trial (45 men with OML). Symptom improvement, catheterization, and adverse event rates were compared between MedLift subjects and OML patients ($n = 187$) from the large real-world retrospective (RWR) study of PUL filtered on baseline characteristics to approximate the MedLift population.
Results: Posttreatment, International Prostate Symptoms Score (IPSS) improvement for MedLift subjects was 170% greater compared with sham at 3 months with significantly better quality of life (QoL), Qmax, and benign prostatic hyperplasia impact index (BPHII). Compared with TURP, MedLift IPSS and QoL improved significantly better at 1 and 3 months and with superior ejaculatory function scores at all time points after PUL. IPSS, QoL, postvoid residual (PVR), and Qmax outcomes were equivalent between MedLift and RWR OML groups at 3, 6, and 12 months. RWR OML patients did not experience higher rates of overall adverse events compared with MedLift.
Conclusion: Controlled and real-world outcomes confirm PUL is a safe and effective treatment for BPH patients with and without OML.

Keywords: lower urinary tract symptoms, retrospective study, real world, prostatic urethral lift, benign prostatic hyperplasia, randomized controlled trials, clinically controlled trials, CCT, minimally invasive surgical therapy, transurethral resection of the prostate, symptom score, IPSS

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Approved by the AUA Board of Directors

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

American Urological Association (AUA)

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

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EXECUTIVE SUMMARY

Purpose

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

Methodology

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

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

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

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REVIEW ARTICLE

UroLift for Treating Lower Urinary Tract Symptoms of Benign Prostatic Hyperplasia: A NICE Medical Technology Guidance Update

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Accepted: 11 April 2022 / Published online: 18 July 2022

Abstract

Lower urinary tract symptoms (LUTS) commonly occur as a consequence of benign prostatic hyperplasia (BPH), also known as prostate enlargement. Treatments for this can involve electrosurgical removal of a section of the prostate via transurethral resection of the prostate (TURP), Holmium laser enucleation of the prostate (HoLEP), or prostatic urethral lift using the UroLift system. The UroLift system implants to pull excess prostatic tissue away so that it does not narrow or block the urethra. In this way, the device is designed to relieve symptoms of urinary outflow obstruction without cutting or removing tissue. National guidance recommending the use of UroLift in the UK NHS was first issued in 2015 by the National Institute for Health and Care Excellence (NICE MTG26). We now report on the process to update the economic evaluation of UroLift, leading to updated NICE guidance published in May 2021 (NICE MTG58). The conclusions of the available clinical evidence were mixed and suggested that whilst UroLift improves symptoms over time, this improvement is smaller than that of TURP for symptom severity (IPSS) and urological outcomes. However, UroLift appears to be superior to Rezum for symptom severity and measures of erectile dysfunction and ejaculatory dysfunction. The updated economic model estimated that using UroLift as a day-case procedure for people with prostate of volume 30–80 mL creates a saving of £981 per person compared with bipolar TURP, £1242 compared with monopolar TURP, and £1230 compared with HoLEP.

Key Points for Decision Makers

Since the publication of NICE MTG26, a larger body of clinical evidence has emerged, with 5-year follow-up, and with direct comparisons with TURP and other surgical procedures. The clinical benefits of UroLift are sustained; it is not as efficacious as TURP but is recommended by NICE as a less invasive option with fewer complications for people of age over 50 years with prostate volume of 30–80 mL.

The cost saving arising from UroLift is also sustained, under most circumstances. UroLift as a day-case procedure remains cost saving relative to TURP and HoLEP. Cost savings are uncertain when UroLift is used for treating an obstructive median lobe.

Transurethral water vapour therapy using Rezum has emerged as a comparator therapy to UroLift. It is uncertain whether UroLift is cost saving compared to Rezum.

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Section 7.0

New Discussion Items

Circadian Rhythm Disorders

Plain Language Summary:

Coverage question: Should problems with timing of falling asleep and waking up be covered for more than general advice and office visits?

Should OHP cover this treatment? No. Medical studies show that neither medications nor a light box are very effective.

Coverage Question: Should the diagnoses for various circadian rhythm disorders be moved to the covered portion of the Prioritized List?

Question source: P&T

Background: P&T is conducting a class review of medications for treatment of circadian rhythm disorders. Currently, all of these disorders are on a non-funded line. P&T is requesting HERC review to determine if any of these disorders need to be moved to a covered line.

Circadian rhythm sleep-wake disorders are defined as sleep disruption caused by misalignment of a person's internal circadian rhythm and the external environment.2 The internal (or intrinsic) circadian sleep rhythm is typically slightly longer than 24 hours for most people and is synchronized (or entrained) to a 24 hour period by the 24-hour dark-light cycle and secretion of melatonin, a pineal hormone. Circadian rhythm sleep-wake disorders are classified based whether on the primary driver of the disorder is internal (intrinsic) or external (environmentally-influenced).2 For example, shift work disorder and jet lag are common circadian rhythm sleep-wake disorders that are classified as extrinsic disorders. Common intrinsic disorders include advanced sleep phase disorder, delayed sleep phase disorder, irregular sleep-wake rhythm disorder, or non-24 hour sleep-wake syndrome. These are most commonly diagnosed based on clinical history, sleep logs and actigraphy.

Types of Circadian Rhythm Sleep Disorders [AASM 2008, available at https://aasm.org/resources/factsheets/crsd.pdf]

1) Delayed sleep phase disorder (DSP): DSP occurs when a person regularly goes to sleep and wakes up more than two hours later than is considered normal. People with DSP tend to be "evening types" who typically stay awake until 1 a.m. or later and wake-up in the late morning or afternoon. If able to go to bed at the preferred late time on a regular basis, a person with DSP will have a very stable sleep pattern. DPS is more common among adolescents and young adults with a reported prevalence of 7-16%. It is estimated that DPS is seen in approximately 10% of patients with chronic insomnia in sleep clinics. A positive family history may be present in approximately 40% of individuals with DPS.
2) Advanced sleep phase disorder (ASP): ASP occurs when a person regularly goes to sleep and wakes up several hours earlier than most people. People with ASP tend to be "morning types"

who typically wake up between 2 a.m. and 5 a.m. and go to sleep between 6 p.m. and 9 p.m. If able to go to bed at the preferred early time on a regular basis, a person with ASP will have a very stable sleep pattern. ASP affects approximately 1% in middle-aged and older adults and increases with age.

3) Jet lag disorder: Jet lag occurs when long travel by airplane quickly puts a person in another time zone. In this new location the person must sleep and wake at times that are misaligned with his or her body clock. The severity of the problem increases with the number of time zones that are crossed. The body tends to have more trouble adjusting to eastward travel than to westward travel. Jet lag affects all age groups. However, in the elderly, symptoms may be more pronounced and the rate of recovery may be more prolonged than in younger adults. Sleep deprivation, prolonged uncomfortable sitting positions, air quality and pressure, stress and excessive caffeine and alcohol use may increase the severity of insomnia and impaired alertness and function associated with transmeridian travel. Jet lag is a temporary condition with symptoms that begin approximately one to two days after air travel across at least two time zones. Exposure to light at inappropriate times may prolong the time of adjustment by shifting the circadian rhythms in the opposite direction.
4) Shift work disorder: Shift work disorder occurs when a person's work hours are scheduled during the normal sleep period. Sleepiness during the work shift is common, and trying to sleep during the time of day when most others are awake can be a struggle. Shiftwork schedules include night shifts, early-morning shifts and rotating shifts. Depending on the type of shift, diurnal or circadian preferences may influence the ability to adjust to shift work. For example, individuals described as morning types appear to obtain shorter daytime sleep after a night shift. Persons with comorbid medical, psychiatric and other sleep disorders such as sleep apnea and individuals with a strong need for stable hours of sleep may be at particular risk.
5) Irregular sleep-wake rhythm: This disorder occurs when a person has a sleep-wake cycle that is undefined. The person's sleep is fragmented into a series of naps that occur throughout a 24-hour period. Sufferers complain of chronic insomnia, excessive sleepiness or both. A low-amplitude or irregular circadian rhythm of sleep-wake pattern may be seen in association with neurological disorders such as dementia and in children with mental retardation.
6) Free-running (nonentrained) type: This disorder occurs when a person has a variable sleep-wake cycle that shifts later every day. It results most often when the brain receives no lighting cues from the surrounding environment. Occasionally, the disorder is associated with [intellectual disability] or dementia. It has also been suggested that there may be an overlap between circadian rhythm sleep disorder, delayed sleep phase type, and circadian rhythm sleep disorder, free-running type
7) Non-24-hour sleep-wake disorder (N24) is a circadian rhythm sleep disorder in which an individual's biological clock fails to synchronize to a 24-hour day. Instead of sleeping at roughly the same time every day, someone with N24 will typically find their sleep time gradually delaying by minutes to hours every day. N24 affects mainly blind people. It is estimated that 55-70% of all people who are totally blind have N24. Tasimelteon (Hetlioz) was FDA-approved in 2014 for N24. The treatment of non-24 hour sleep wake disorder in sighted persons is use of phototherapy/light exposure. Light therapy is ineffective for people who are blind. The hormone melatonin may be used to stabilize the sleep-wake cycle. While melatonin is often effective in blind patients with N24, it is rarely successful as the sole treatment in sighted patients.

Circadian Rhythm Disorders

Previous HSC/HERC reviews: none

Current Prioritized List/Coverage status:

The following ICD-10-CM codes are on line 606 DISORDERS OF SLEEP WITHOUT SLEEP APNEA.

- G47.20 Circadian rhythm sleep disorder, unspecified type
- G47.21 Circadian rhythm sleep disorder, delayed sleep phase type
- G47.22 Circadian rhythm sleep disorder, delayed sleep phase type
- G47.23 Circadian rhythm sleep disorder, irregular sleep wake type
- G47.24 Circadian rhythm sleep disorder, free running type—used for non-24 hour sleep wake disorder
- G47.25 Circadian rhythm sleep disorder, jet lag type
- G47.26 Circadian rhythm sleep disorder, shift work type
- G47.27 Circadian rhythm sleep disorder in conditions classified elsewhere
- G47.29 Other circadian rhythm sleep disorder

Evidence:

1) **Drug Effectiveness Review Project (DERP) drug class review 2023**: circadian rhythm disorders
    a. There is insufficient direct evidence to evaluate comparative efficacy or safety of stimulants or sedatives for circadian rhythm sleep-wake disorders.
    b. There is insufficient evidence to support use of sedative hypnotics (e.g., zolpidem, eszopiclone, zaleplon, orexin receptor antagonists, or benzodiazepines) in people with circadian rhythm sleep-wake disorders.
    c. Stimulants which have been studied for circadian rhythm sleep-wake disorders include modafinil, armodafinil, and caffeine. There is no evidence to support use of other stimulants for treatment of circadian rhythm sleep-wake disorders.
    d. There are no drugs currently approved by the Food and Drug Administration (FDA) for treatment of jet lag. A recent systematic review found insufficient evidence for use of pharmacologic treatments (including stimulants, sedative hypnotics, melatonin or melatonin agonists) for athletes with jet lag.
    e. In patients with shift work disorder, melatonin and stimulants have the most evidence for use. In people with shift work disorder, there is insufficient evidence comparing efficacy or safety of melatonin, modafinil, armodafinil, and caffeine.
        i. Evidence supporting efficacy of melatonin for shift work disorder is mixed. There is low quality evidence that melatonin may increase self-reported total sleep time by less than 30 minutes within 24 hours after administration in people with shift work disorder, but the clinical significance of this difference is unclear. The only study which evaluated objective sleep time did not identify any differences between melatonin and placebo, and there is low quality evidence of no difference in sleep latency or sleep quality compared to placebo.
        ii. In adults with shift work disorder and symptoms of moderate to severe excessive sleepiness, modafinil and armodafinil decreased sleepiness during the night shift (mean difference of about one point on the 9-point Karolinska Sleepiness Scale [KSS]), but was associated with more serious adverse events (9.7% vs 2.4%; relative risk [RR] 3.97; 95% Confidence Interval [CI] 1.15 to

13.71). Latency to persistent sleep during the work shift was improved by an average of 1-3 minutes compared to placebo, and remained less than 6 minutes for most patients indicating continued moderate to severe sleepiness.

iii. In shift work disorder, a 2010 Cochrane review found low quality evidence that caffeine may reduce errors at work, but there was insufficient evidence for the prevention of injuries during work.

f. Systematic reviews evaluating use of melatonin for sleep disorders in people who are blind have found insufficient evidence for efficacy and safety of melatonin.

g. Recommendations:
   i. Medicaid Open Card will pay for caffeine tablets when prescribed by a provider without prior authorization. Medicaid Open Card will pay for melatonin without prior authorization when prescribed for children. Melatonin is not covered for adults.
   ii. We recommend Medicaid continue to pay for medicines for circadian rhythm sleep-wake disorders only when necessary, on a case-by-case basis.

Expert guidelines:

1) **American Society of Sleep Medicine 2015**, Clinical Practice Guideline for the Treatment of Intrinsic Circadian Rhythm Sleep-Wake Disorders
   a. Expert consensus recommendations
   b. Advanced sleep-wake phase disorder (ASWPD):
      i. The TF suggests that clinicians treat adult ASWPD patients with evening light therapy (versus no treatment). [WEAK FOR]
      ii. cumulative level of evidence for light therapy was VERY LOW
      iii. No recommendation for any medications
   c. Delayed sleep-wake phase disorder (DSWPD):
      i. The TF suggests that clinicians treat DSWPD in adults with and without depression with strategically timed melatonin (versus no treatment). [WEAK FOR] LOW quality of evidence
      ii. The TF suggests that clinicians treat children and adolescents with DSWPD (and no comorbidities) with strategically timed melatonin (versus no treatment). [WEAK FOR] Moderate quality of evidence
      iii. The TF suggests that clinicians treat children and adolescents with DSWPD comorbid with psychiatric conditions with strategically timed melatonin (versus no treatment). [WEAK FOR] LOW quality of evidence
      iv. The TF suggests that clinicians treat children and adolescents with DSWPD with post-awakening light therapy in conjunction with behavioral treatments (versus no treatment). [WEAK FOR] LOW quality of evidence
   d. Non-24 hour sleep wake disorder (N24SWD)
      i. The TF suggests that clinicians use strategically timed melatonin for the treatment of N24SWD in blind adults (versus no treatment). [WEAK FOR] LOW quality of evidence
      ii. There is insufficient evidence to support the use of melatonin among sighted patients with N24SWD (versus no treatment). No recommendation.

iii. There is insufficient evidence to support the use of light therapy in patients with N24SWD (versus no treatment). No recommendation
iv. There is no evidence to support the use of sleep-promoting or wakefulness-promoting medications in patients with N24SWD. No recommendation

e. Irregular sleep-wake rhythm disorder (ISWRD)
   i. The TF suggests that clinicians treat ISWRD in elderly patients with dementia with light therapy (versus no treatment). [WEAK FOR] VERY LOW quality of evidence
   ii. The TF recommends that clinicians avoid the use of sleep-promoting medications to treat demented elderly patients with ISWRD (versus no treatment). [STRONG AGAINST]
   iii. The TF suggests that clinicians avoid the use of melatonin as a treatment for ISWRD in older people with dementia (versus no treatment). [WEAK AGAINST] LOW quality of evidence
   iv. The TF suggests that clinicians use strategically timed melatonin as a treatment for ISWRD in children/ adolescents with neurologic disorders (versus no treatment). [WEAK FOR] MODERATE quality of evidence
   v. The TF suggests that clinicians avoid the use of combined treatments consisting of light therapy in combination with melatonin in demented, elderly patients with ISWRD (versus no treatment). [WEAK AGAINST] VERY LOW quality of evidence

f. **British Association of Psychopharmacology 2019**: consensus statement on evidence-based treatment of circadian rhythm disorders (CRDs)
   i. Melatonin agonists may be promising in the treatment of CRDs, e.g. non-24-hour non-24 hour sleep wake rhythm disorder (SWRD), but there remains a need for RCTs in well-characterized CRD populations
   ii. No other treatments recommended for SWRD

HERC staff summary: No change recommended due to low effectiveness of treatment. Expert guidelines either do not recommend or have a weak recommendation for use of light box therapy based on no to low level of evidence for treatment of any type of circadian rhythm disorder. A DURP drug class review found limited, if any, evidence of benefit from medications for circadian-rhythm disorders. P&T staff indicate that there is a pathway to coverage for medications through individualized review.

HERC staff recommendation:

1) Keep ICD-10-CM G47.2 family (Circadian rhythm sleep disorder) on line 606 DISORDERS OF SLEEP WITHOUT SLEEP APNEA.

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Drug Class Review: Circadian Rhythm Sleep Disorders

Date of Review: April 2023 **End Date of Literature Search:** 1/1/2007-01/03/2023

Purpose for Class Review:
To evaluate efficacy and safety of medications, including stimulants and sedating drugs, for circadian rhythm sleep disorders.

Plain Language Summary:

- People have difficulty sleeping during the night and staying awake during the day when their body's internal sleep cycle does not match their usual sleep schedule. These specific types of sleep problems are called circadian rhythm sleep-wake disorders. Examples include shift work disorder and jet lag.
- Evidence shows 2 types of medicines may help people with these types of sleep disorders:
    - Sedative medicines that help people sleep better during the night or
    - Stimulant medicines like armodafinil, modafinil, and caffeine that help people stay awake longer during the day.
- Researchers have not studied other stimulants in people with circadian rhythm sleep disorders.
- Changes in lifestyle may improve sleep problems for people with these conditions. For example, people may be more alert during the day and get better sleep when they:
    - change their exposure to bright light,
    - change the time of day that they exercise,
    - change their bedtime, or
    - plan naps during the day.
- To improve sleep, the American Academy of Sleep Medicine recommends melatonin and medicines that act like melatonin in the body for:
    - adults who are blind,
    - people who have difficulty falling asleep at night, and
    - children with conditions affecting their brain development.
- In people who have trouble staying awake at work, armodafinil and modafinil may help people avoid error during work, but they also have serious side effects including risk for heart problems, thoughts of suicide, and skin damage.
- In people who have trouble falling asleep after working a night shift, melatonin may help people sleep about 15 to 30 minutes longer compared to no treatment.
- Evidence does not show that any one medicine is better than another, or that medicine is better than lifestyle changes.
- Providers must explain to the Oregon Health Authority why someone needs a sedative or stimulant before Medicaid will pay for it. This process is called prior authorization.

Author: Sarah Servid, PharmD

- Medicaid Open Card will pay for caffeine tablets when prescribed by a provider without prior authorization. Medicaid Open Card will pay for melatonin without prior authorization when prescribed for children. Melatonin is not covered for adults.
- We recommend Medicaid continue to pay for medicines for circadian rhythm sleep-wake disorders only when necessary, on a case-by-case basis.

Research Questions:

1. What is the comparative efficacy or effectiveness of drugs (e.g., sedative hypnotics, melatonin, melatonin agonists, benzodiazepines, or stimulants) for treatment of circadian rhythm sleep-wake disorders?
2. What is the comparative safety of drugs for treatment of circadian rhythm sleep-wake disorders?
3. Are there any subpopulations who would receive more benefit or suffer more harm from drugs for treatment of circadian rhythm sleep-wake disorders (e.g., based on disease severity markers, specific types of circadian rhythm sleep-wake disorders, or comorbid conditions)?

Conclusions:

- There is insufficient direct evidence to evaluate comparative efficacy or safety of stimulants or sedatives for circadian rhythm sleep-wake disorders.
- There is insufficient evidence to support use of sedative hypnotics (e.g., zolpidem, eszopiclone, zaleplon, orexin receptor antagonists, or benzodiazepines) in people with circadian rhythm sleep-wake disorders.[1,2]
- Stimulants which have been studied for circadian rhythm sleep-wake disorders include modafinil, armodafinil, and caffeine. There is no evidence to support use of other stimulants for treatment of circadian rhythm sleep-wake disorders.
- There are no drugs currently approved by the Food and Drug Administration (FDA) for treatment of jet lag. A recent systematic review found insufficient evidence for use of pharmacologic treatments (including stimulants, sedative hypnotics, melatonin or melatonin agonists) for athletes with jet lag.[3]
- In patients with shift work disorder, melatonin and stimulants have the most evidence for use. In people with shift work disorder, there is insufficient evidence comparing efficacy or safety of melatonin, modafinil, armodafinil, and caffeine.
    - Evidence supporting efficacy of melatonin for shift work disorder is mixed. There is low quality evidence that melatonin may increase self-reported total sleep time by less than 30 minutes within 24 hours after administration in people with shift work disorder, but the clinical significance of this difference is unclear.[1] The only study which evaluated objective sleep time did not identify any differences between melatonin and placebo, and there is low quality evidence of no difference in sleep latency or sleep quality compared to placebo. [1]
    - In adults with shift work disorder and symptoms of moderate to severe excessive sleepiness, modafinil and armodafinil decreased sleepiness during the night shift (mean difference of about one point on the 9-point Karolinska Sleepiness Scale [KSS]), but was associated with more serious adverse events (9.7% vs 2.4%; relative risk [RR] 3.97; 95% Confidence Interval [CI] 1.15 to 13.71).[1] Latency to persistent sleep during the work shift was improved by an average of 1-3 minutes compared to placebo, and remained less than 6 minutes for most patients indicating continued moderate to severe sleepiness.[4,5]
    - In shift work disorder, a 2010 Cochrane review found low quality evidence that caffeine may reduce errors at work, but there was insufficient evidence for the prevention of injuries during work.[6]
- Systematic reviews evaluating use of melatonin for sleep disorders in people who are blind have found insufficient evidence for efficacy and safety of melatonin.[7,8]
- Guidelines from the American Academy of Sleep Medicine (2015) recommend melatonin or a melatonin agonist for the following intrinsic circadian rhythm sleep-wake disorders: [2]
    - Adults, adolescents, and children with delayed sleep-wake phase disorder (low to moderate quality evidence).

- Adults who are blind and have non-24 hour sleep-wake disorder (low quality evidence).
- Children and adolescents with neurologic disorders and irregular sleep-wake rhythm disorder (moderate quality evidence).
- There was insufficient evidence to inform recommendations for other treatments or other subpopulations of people with intrinsic circadian rhythm sleep-wake disorders.

Recommendations:

- Due to limited evidence of benefit for circadian rhythm sleep-wake disorders, continue to limit prescription drug use to FDA-labeled and funded indications.
- If drug treatment is medically necessary for funded circadian rhythm sleep-wake disorders or circadian rhythm sleep-wake disorders covered under EPSDT, consider coverage of melatonin or a melatonin agonist before trial of stimulants or other sedating drugs (**Appendix 4**).

Previous Reviews and Current Policy

- In 2020, a systematic review evaluated evidence for sleep disturbances in patients with dementia.[9] Irregular sleep-wake rhythm disorder is common in patients with neurodegenerative and neurodevelopmental disorders, though this study did not specify the specific types of sleep disorders diagnosed in this review. They identified low quality evidence that trazodone 50 mg may improve sleep efficiency and total sleep time (mean difference [MD] 42.46 minutes, 95% CI 0.9 to 84.0) with short-term treatment (2 weeks).[9] Trazodone was not included in this updated literature search for Orexin antagonists (suvorexant or lemborexant) may improve total sleep time (MD 28.2 minutes, 95% CI 11.1 to 45.3) and wake after sleep onset times (MD –15.7 minutes, 95% CI –28.1 to –3.3) compared to placebo over 4 weeks of treatment (based on moderate quality evidence).[9] Other sleep outcomes demonstrated no difference from placebo. Ramelteon and melatonin did not demonstrate any change in sleep outcomes based on low quality evidence.[9] No studies evaluated other commonly prescribed therapies such as benzodiazepines or benzodiazepine receptor agonists (e.g., eszopiclone, zolpidem, zaleplon).
- A systematic review evaluating use of melatonin for sleep disorders in adults who are blind found insufficient evidence for efficacy and safety of melatonin.[7]
- Tasimelteon oral suspension was FDA approved in December 2020 for nighttime sleep disturbances in Smith-Magenis Syndrome in patients at least 16 years of age based on results from one small, crossover, placebo-controlled trial (n=25) evaluating treatment over 4 weeks.[10] Smith-Magenis Syndrome is a funded condition on the prioritized list. The primary outcomes were subjective total sleep time and nighttime sleep quality (reported by the patient's parent/guardian) for the 50% of nights with the worst sleep.[10] Sleep quality was rated on a 5 point scale from excellent (5) to poor (1). Compared to placebo, tasimelteon treatment resulted in improved sleep quality for the 50% of nights with the worst sleep quality though magnitude of benefit was small (2.8 vs. 2.4; least square mean difference 0.4 [95% CI 0.1 to 0.7]).[10] The difference from placebo in total sleep time for the 50% of nights with the worst sleep was not statistically improved with tasimelteon (7 vs. 6.7 hours; least square mean difference 0.3 [95% CI -0.0 to 0.6]).[10]
- In Fee for Service (FFS), all sedative drugs require prior authorization (PA). For treatment of chronic insomnia, the Health Evidence Review Commission (HERC) has recommended coverage of sedative hypnotics not exceeding 30 days every year. Melatonin is currently covered for people up to 18 years of age without PA, but is not covered for adults.
- Armodafinil and modafinil are carved-out of coordinated care organizations (CCOs) and require PA which limits use to funded conditions with documented evidence of benefit. Caffeine tablets (available over the counter) can be covered by FFS when prescribed by a provider.

Background:

Circadian rhythm sleep-wake disorders are defined as sleep disruption caused by misalignment of a person's internal circadian rhythm and the external environment.[2] The internal (or intrinsic) circadian sleep rhythm is typically slightly longer than 24 hours for most people and is synchronized (or entrained) to a

24 hour period by the 24-hour dark-light cycle and secretion of melatonin, a pineal hormone.[2] Food and exercise have a more modest effect on the circadian rhythm. Failure to synchronize to this 24-hour period can lead to circadian rhythm sleep-wake disorders.[2]

Circadian rhythm sleep-wake disorders are classified based whether on the primary driver of the disorder is internal (intrinsic) or external (environmentally-influenced).[2] For example, shift work disorder and jet lag are common circadian rhythm sleep-wake disorders that are classified as extrinsic disorders. Common intrinsic disorders include advanced sleep phase disorder, delayed sleep phase disorder, irregular sleep-wake rhythm disorder, or non-24 hour sleep-wake syndrome. These are most commonly diagnosed based on clinical history, sleep logs and actigraphy. The diagnostic criteria for circadian rhythm sleep-wake disorders includes recurrent symptoms of insomnia, sleepiness or both caused by misalignment of the endogenous circadian rhythm and the individual's external environment or schedule. Polysomnography may be used to rule out other related sleep conditions, but is not usually recommended to diagnose circadian rhythm sleep-wake disorders.

Extrinsic circadian rhythm sleep-wake disorders are defined based on their external cause. Jet lag disorder is categorized as a temporary disorder related to travel across time zones creating misalignment between the desired sleep time in the new time zone and the endogenous circadian sleep-wake cycle. Symptoms typically worsen when traveling in an eastward direction and across multiple time zones. Shift work disorder occurs when a person's work schedule overlaps with usual sleep time. It is estimated that about 15% of salaried workers in the United States work on shifts including nights.[1] Shift work is generally common in younger people and prevalence varies based on the job. Some of the most common jobs that rely on shift work include healthcare and transportation industries. In people with shift work disorder, symptoms are usually present for at least 1 month and associated with functional impairment or significant distress. It is estimated that people working night shifts are more likely to fall asleep at work or experience insomnia symptoms compared to people working during the day (10% vs. 7%).[1]

Intrinsic circadian rhythm sleep-wake disorders are typically defined based on the timing of sleep and wake symptoms. Delayed sleep-wake phase disorder is characterized by a delay in the major sleep episode compared to the desired sleep schedule.[2] This results in excessive sleepiness when waking at the desired time and insomnia symptoms when trying to sleep at the desired time, but quality of sleep is typically reported as normal if sleeping on the delayed schedule. Advanced sleep-wake disorder is characterized by the opposite sleep pattern with excessive sleepiness in the evening before the individual's usual bedtime and insomnia symptoms in the early morning before the individual would normally be awake.[2] Non-24 hour sleep-wake disorder is diagnosed when an individual fails to entrain to a 24-hour cycle resulting in a gradually shifting sleep-wake pattern over time. As the internal circadian rhythm shifts, individuals experience hypersomnolence during the day and insomnia symptoms at night.[2] This is most common in individuals who are totally blind and lack external input from the 24-hour light-dark cycle. However, non-24 hour sleep-wake disorder has been documented in individuals who are sighted.[2] Irregular sleep-wake rhythm disorder does not have a clearly defined sleep-wake pattern. Symptoms typically include prolonged periods of wakefulness during the night and excessive sleepiness during the day with fragmented sleep. Irregular sleep-wake rhythm disorder is most commonly diagnosed in people with neurodevelopmental or neurodegenerative disorders.[2] For all intrinsic disorders, diagnosis typically requires documentation of sleep and insomnia symptoms for at least 7-14 days by actigraphy or sleep diary.[2]

The goal of treatment for circadian rhythm sleep-wake disorders is to realign the endogenous sleep-wake cycle with the desired external schedule to improve daytime functioning. Common outcomes evaluated in clinical trials include changes in biologic markers of circadian rhythm, total sleep time, sleep latency (or the time it takes to fall asleep), sleep quality, and sleep onset and offset times. There are no well-established standards for minimum clinically important differences in these outcomes for people with circadian rhythm sleep-wake disorders.[2] In 2015, the American Academy of Sleep Medicine defined significance

thresholds based on expert consensus that were critical for evaluating and making recommendations for intrinsic circadian rhythm sleep-wake disorders (**Table 1**).[2]

Table 1. AASM-defined clinical significance thresholds for outcomes that were critical for guideline recommendations[2]

Disorder	Change in circadian phase or total sleep time	Change in sleep onset, offset or sleep latency	Entrainment status
Advanced sleep-wake disorder Delayed sleep-wake disorder Irregular sleep rhythm disorder	30 minutes	15 minutes	N/A
Non-24 hour sleep-wake disorder	N/A	N/A	Yes/No

Abbreviation: AASM = American Academy of Sleep Medicine; N/A = not applicable

For some people total sleep time may be unchanged, but patients experience excessive sleepiness when they want to be awake, and experience insomnia symptoms when they want to sleep. In these circumstances, sleep latency and sleep onset/offset times may be a better marker of symptoms than total sleep times. Sleep quality, wakefulness, and excessive sleepiness can also be evaluated using a wide variety of tools and scales. One of the more common scales used to evaluate excessive sleepiness in circadian rhythm disorders is the Karolinska Sleepiness Scale (KSS). The KSS ranges from 1 (extremely alert) to 5 (neither alert nor sleepy) to 9 (very sleepy, great effort keeping awake).[11] There is no well-established minimum clinically important difference referenced in literature for KSS. In many clinical trials, the circadian rhythm can be evaluated using excretion of urinary or salivary melatonin concentrations (referred to as the dim light melatonin onset or the start of endogenous melatonin production during dim light conditions). However, it is not clear whether endogenous secretion of melatonin correlates well with symptoms of insomnia or function in all conditions. Several studies have evaluated dim light melatonin onset but results do not consistently correlate with improvement in symptoms of insomnia, alertness, sleep quality, or daytime function.[12] Historically, the FDA has not accepted biomarkers of urinary melatonin excretion as relevant outcomes for FDA approval of drug treatment for circadian rhythm sleep-wake disorders.[10]

Treatments for circadian rhythm sleep-wake disorders fall broadly into 4 categories including:[2]

- Prescribed timing of the sleep-wake schedule or timed physical activity/exercise
- Strategic avoidance or receipt of light
- Use of medications or supplements to shift the sleep-wake cycle or promote alertness
- Somatic interventions to alter bodily functions and impact sleep-wake behaviors

Timed administration of bright light can help to prevent symptoms of excessive sleepiness. A variety of factors can influence efficacy of light exposure including timing and duration of exposure, prior light exposure or "light history", and light intensity and light wavelength.[2] Sedating drugs (most commonly melatonin) have also been used prior to the desired sleep time to prevent insomnia symptoms. The optimal dose of melatonin has not been determined, and some studies suggest that the timing of melatonin administration may be more important than the dose.[2] In some types of circadian rhythm sleep-wake disorders, stimulants such as modafinil, armodafinil or caffeine have also been used to improve alertness after waking. Drugs that are FDA-approved for circadian rhythm sleep-wake disorders include stimulants (e.g., modafinil, armodafinil) indicated to improve wakefulness in for shift work disorder and tasimelteon indicated for non-24 hour sleep-wake disorder. **Table 2** describes studies evaluated for FDA approval of these drugs**.** Other stimulants and sedating drugs are indicated for related conditions to improve excessive sleepiness associated with narcolepsy or decrease symptoms of insomnia, but are not specifically FDA-approved for circadian rhythm sleep-wake disorders. Randomized controlled trials (RCTs) have also been completed which evaluate use of stimulants or melatonin receptor agonists in

patients with jet lag disorder and irregular sleep-wake rhythm disorder,[12-15] but these agents have not yet been FDA approved for these conditions. In Europe, regulatory approval of modafinil and armodafinil for shift work disorder was withdrawn in 2010 as a result of serious adverse events including neuropsychiatric disorders and fatal skin reactions associated with treatment.[1] European regulatory agencies concluded that benefits of modafinil and armodafinil only outweigh risks when used in patients with narcolepsy.

Historically, insomnia and circadian rhythm sleep-wake disorders have been unfunded on the HERC prioritized list of health services. In 2022, HERC recommended changes to expand non-pharmacological coverage for insomnia and limit duration of drug coverage for insomnia. These changes limit drug coverage of sedative hypnotics to 30 days for treatment of insomnia. In FFS Medicaid, melatonin is covered for people up to 18 years of age, but is not covered for adults due to lack of documented benefit for common sleep disorders like insomnia. Prior authorization is required for all sedatives and stimulants with indications for sleep disorders (e.g., modafinil and armodafinil). These drugs can be covered for unfunded sleep conditions if the sleep disorder is related to a comorbid funded condition and standard treatments for the funded condition were inadequate to control symptoms.

Table 2. Summary of Studies Evaluated for FDA-Approval of Common Circadian Rhythm Sleep-Wake Disorders

<table>
<tr><th>Study</th><th>Comparison</th><th>Population</th><th>Primary Outcome</th><th>Results</th><th>Notes/Limitations</th></tr>
<tr>
<td>Lockey, et al. 2015.[16]

MC, DB, PC, RCT

Duration: SET: 26 weeks
RESET: 11 weeks</td>
<td>SET
1. Tasimelteon 20 mg 1 hour before bedtime (n=42)
2. Placebo (n=42)

RESET: Withdrawal Study
1. Continue tasimelteon 20 mg (n=10)
2. Withdraw to placebo (n=10)</td>
<td>Adults who were blind with non-24H sleep-wake disorder

27 sites in the US and 6 sites in Germany</td>
<td><u>Primary Outcome</u>
Proportion of patients entrained (SET) or who maintain entrainment (RESET)

<u>Relevant Secondary Outcomes Evaluated for FDA approval</u>[10]
Change in total sleep time during the day or night on most symptomatic days/nights</td>
<td>Entrainment
<table>
<tr><th></th><th>SET</th><th>RESET</th></tr>
<tr><td>1.</td><td>8/40 (20%)</td><td>9/10 (90%)</td></tr>
<tr><td>2.</td><td>1/38 (3%)</td><td>2/10 (20%)</td></tr>
<tr><td></td><td>Difference 17%
95% CI 3.2-31.6;
p=0.0171</td><td>Difference 70%
95% CI 26.4-100;
p=0.0026</td></tr>
</table>
Change from baseline in sleep time on 25% most symptomatic days/nights (minutes)
<table>
<tr><th>SET</th><th>Nighttime</th><th>Daytime</th></tr>
<tr><td>1.</td><td>50</td><td>-49</td></tr>
<tr><td>2.</td><td>22</td><td>-22</td></tr>
</table>
<table>
<tr><th>RESET</th><th>Nighttime</th><th>Daytime</th></tr>
<tr><td>1.</td><td>-7</td><td>-9</td></tr>
<tr><td>2.</td><td>-74</td><td>50</td></tr>
</table>
</td>
<td>Randomized via interactive voice response system. Baseline characteristics balanced. Blinded with matching placebo. High attrition 24% and 28% in treatment and placebo groups, respectively. Outcomes reported as specified, but a secondary, post-hoc outcome was used for FDA approval. Industry funded.

Ethnicities other than white (81-86%) were underrepresented. Patients with any significant medical or psychiatric disorders were excluded. Of 391 patients evaluated, 136 (35%) were enrolled in the screening period and 84 (62% of enrolled) were randomized.</td>
</tr>
<tr>
<td>Czeisler 2005. [5]

MC, DB, PC, RCT</td>
<td>1. Modafinil 200 mg taken 30-60 minutes before the</td>
<td>Adults with SWD and moderate to severe excessive sleepiness</td>
<td><u>Primary</u>
CGI-C (range 1-7)
MSLT

<u>Secondary</u></td>
<td>CGI-C at least minimally improved
1. 74%
2. 36%
P<0.001
Change in MSLT from baseline</td>
<td>Randomization method unspecified. Baseline characteristics balanced. Blinded with matching placebo. Per protocol analysis used with attrition</td>
</tr>
</table>

N=209 Duration: 3 months	night shift (n=110) 2. Placebo (n=99)	during the night shift for at least 3 months, mean sleep latency ≤6 minutes, and insomnia symptoms during the day (sleep efficiency ≤ 87.5%) 39 centers in the US between December 2001 and September 2002	Psychomotor vigilance test KSS (range 1-9)	1. 1.7±0.4 minutes; P<0.001 2. 0.3±0.3 minutes; P=0.24 Psychomotor vigilance test (change from baseline in number of lapses of attention in 20 minutes) 1. -2.6 lapses 2. 3.8 lapses P=0.005 for difference at final visit Change in KSS from baseline 1. -1.5±0.2 2. -0.4±0.2 P<0.001 Patients with accidents or near accidents (reported in patient diary) 1. 46 (29%) 2. 58 (54%) Severe adverse events 1. 6 (5%) 2. 5 (5%)	of 25% over 3 months. Industry funded. Of 609 patients screened, 209 (34%) were randomized. Most common reasons for exclusion were failure to meet disease severity markers for polysomnography or sleep latency (n=160, 40%). Average sleep latency was about 2 minutes at baseline. Despite some improvement with modafinil, sleep latency remained below 6 minutes, which indicates excessive sleepiness even with treatment.
Czeisler, et al. 2009.[4] MC, DB, PC, RCT N=254 Duration: 12 weeks	1. Armodafinil 150 mg taken 30-60 minutes before the night shift (n=123) 2. Placebo (n=122)	Night shift workers with moderate-severe SWD, ≥3 months of excessive sleepiness during their shift, mean sleep latency ≤6 minutes, and insomnia symptoms during the day (sleep efficiency ≤ 87.5%)	<u>Primary</u> CGI-C (range 1-7) MSLT	CGI-C at least minimally improved 1. 89 (79%) 2. 61 (59%) P=0.001 Change in MSLT from baseline 1. 3.1 minutes (SD 4.5) 2. 0.4 minutes (SD 2.9) Severe Adverse Events 1. 12 (10%) 2. 3 (2%)	Randomization method unspecified. Baseline characteristics balanced Blinded with matching placebo. Assessment of MSLT blinded. Attrition of 31% in placebo and 24% in armodafinil group. Per protocol analysis included only patients with baseline and at least one outcome assessment. Industry funded. Patients were excluded if there was a history of substance abuse, psychiatric disorders, caffeine consumption more than 600mg/day (~6 cups). Of 747 patients screened, 254 (34%) were randomized.

		42 centers in US and Canada from April to December 2004			Severe adverse events were determined by site investigator and included diarrhea, low back pain, and suicidal ideation.

Abbreviations: CGI-C = clinical global impression of change; CI = confidence interval; DB = double blind; FDA = Food and Drug Administration; H = hour; KSS = Karolinska Sleepiness Scale, MC = multi-center; MSLT = mean sleep latency test; PC = placebo-controlled; RCT =randomized controlled trial; SWD = shift work disorder; US = United States

Methods:
A Medline literature search for new systematic reviews and RCTs assessing clinically relevant outcomes to active controls, or placebo if needed, was conducted. The Medline search strategy used for this review is available in **Appendix 2**, which includes dates, search terms and limits used. The OHSU Drug Effectiveness Review Project, Agency for Healthcare Research and Quality (AHRQ), National Institute for Health and Clinical Excellence (NICE), Department of Veterans Affairs, and the Canadian Agency for Drugs and Technologies in Health (CADTH) resources were manually searched for high quality and relevant systematic reviews. When necessary, systematic reviews are critically appraised for quality using the AMSTAR tool and clinical practice guidelines using the AGREE tool. The FDA website was searched for new drug approvals, indications, and pertinent safety alerts.

The primary focus of the evidence is on high quality systematic reviews and evidence-based guidelines. Randomized controlled trials will be emphasized if evidence is lacking or insufficient from those preferred sources.

Systematic Reviews:
Non-24 Hour Disorder
An evidence review was developed by NICE 2021 evaluating use of melatonin for treatment of sleep disorders in adults who are blind.[7] Three studies were identified and included in the review (one RCT and 2 crossover studies).[7] The single RCT did not have adequately reported randomization methods which may increase risk of bias.[7] All studies were small (with the largest enrolling 13 participants) and were likely underpowered to determine differences between groups.[7] All identified studies were of short duration (maximum 12 weeks) with long-term efficacy and safety unknown.[7] Overall, 2 studies (n=20) found no significant improvement in total sleep time with 2 mg or 10 mg of melatonin. One study reported a statistically significant improvement in total sleep time of 0.65 hours (about 40 minutes) with use of melatonin 0.5 mg compared to placebo.[7] Two studies reported melatonin decreased the time spent awake after sleep onset by 0.56 hours with melatonin 0.5 mg and 1.3 hours with melatonin 10 mg.[7] No studies identified a difference with melatonin compared to placebo for sleep latency or quality of life. Overall, authors concluded that evidence is insufficient to determine efficacy and safety for use of melatonin in adults who are blind.[7]

A 2011 Cochrane review evaluated efficacy and safety of melatonin for treatment of sleep disorders in children who are visually impaired.[8] Searches were conducted through July 2011 and failed to identify any RCTs evaluating use of melatonin in this population.[8] Identified literature included non-randomized case series studies, studies in adults who were blind, or studies that included mixed populations where results for the visually impaired cohort could not be independently evaluated.[8] Authors concluded that there was insufficient evidence to support or refute the use of melatonin for sleep disorders in visually impaired children.[8]

Shift Work Disorder - Cochrane

A 2014 Cochrane review evaluated pharmacological interventions for symptoms caused by shift work disorder.[1] Fifteen RCTs were included in the review, and pharmacologic interventions included melatonin (n=9), sedative hypnotics (n=2), modafinil (n=1), armodafinil (n=2), and caffeine combined with pre-shift naps (n=1).[1] Data from these trials was limited by lack of methodological reporting on blinding methods and allocation concealment. Five RCTs had high discontinuation rates (>30%), and there was high risk for selective outcome reporting in multiple trials.[1] When multiple measures were used to evaluate sleepiness or alertness, results for a specific measure were rarely reported when the outcome did not differ from placebo.[1] All included trials were limited by short durations (<7 days) and the long-term efficacy and safety of these treatments for shift work disorder is unclear.

In 7 of the 9 RCTs evaluating melatonin, participants had no reported sleeping problems at enrollment which limits applicability of these results.[1] Doses of melatonin ranged between 1 and 10 mg, and were typically administered after the work shift before going to sleep. Eight trials utilized a cross-over study design, and all RCTs evaluated efficacy of melatonin after one or several consecutive night shifts.[1] Outcomes of total sleep time and sleep onset latency were most commonly reported via patient diaries. There was low quality evidence that melatonin may increase self-reported total sleep time by an average of 24 minutes (95% CI 9.8 to 38.9; 7 RCTs; n=263) during the day after administration and 17 minutes (95% CI 3.71 to 30.22; 3 RCTs; n=234) the night after administration, but did not improve sleep latency or sleep quality compared to placebo.[1] Only one RCT evaluated objective sleep time via actigraphy with no difference in duration of sleep.[1]

RCTs of modafinil and armodafinil enrolled shift workers with SWD and moderate to severe excessive sleepiness (mean sleepiness score of 6 to 6.7 points in the placebo group on the 1 to 9 point KSS scale).[1] Most participants (87-93%) had permanent shift work (vs. rotating shifts). The effect of armodafinil (up to 150 mg) and modafinil (200mg) was evaluated over 3-4 days for outcomes of sleepiness (evaluated via KSS or mean sleep latency test [MSLT]) and alertness (evaluated by reaction time).[1] There was moderate quality evidence that armodafinil and modafinil decreased sleepiness during the night shift evaluating using the KSS scale (MD -0.89, 95% CI -1.37 to -0.4 for armodafinil; MD -0.90, 95% CI -1.45 to -0.35 for modafinil).[1] Serious adverse events were more common with armodafinil than placebo (9.7% vs 2.4%; RR 3.97; 95% CI 1.15 to 13.71). Common adverse events included headache and nausea for both stimulants and insomnia for modafinil. In a long-term extension study of armodafinil, about 11% of patients discontinued treatment due to adverse events.[1] Cardiovascular adverse events and clinically relevant increases in blood pressure were also observed in 6% and 18% of patients prescribed armodafinil, respectively.[1] Serious skin reactions, some of which were fatal, and development of psychiatric disorders including suicidal ideation were also documented in post-marketing studies of modafinil[17] and armodafinil[18] resulting in withdrawal of licensing for the indication of shift work disorder in Europe.[1]

Two small studies (n=88) evaluated the impact of hypnotics (zopiclone and lorazepam) on duration of sleep after a work shift in people with sleeping problems.[1] Outcomes were evaluated after 3 or 7 consecutive days for zopiclone and lorazepam, respectively.[1] There was low quality evidence that zopiclone does not improve total sleep time compared to placebo.[1] Patients prescribed lorazepam may be more likely to have a normal sleep pattern than placebo (89% vs. 64%), but statistical differences were not reported between groups.[1]

A 2010 Cochrane review evaluated caffeine for the prevention of injuries and errors caused by impaired alertness in people with jet lag or shift work disorder.[6] The most common dose administered was 200-400 mg, but doses varied across trials and some trials included weight based dosing.[6] Thirteen RCTs were included, though injuries were not reported as an outcome. Only 2 trials evaluated errors and others assessed cognitive performance using a variety of tests. Data were limited by unclear methods for randomization (6 RCTs), allocation concealment (9 RCTs), inadequate information to assess missing data (11 RCTs), and selective outcome reporting (5 RCTs).[6] Most trials were conducted under simulated conditions limiting applicability to real world settings. Compared to placebo, caffeine improved memory (SMD -1.08; 95% CI -2.07 to -0.09, P = 0.03) and orientation and attention (SMD -0.55; 95% CI -0.83 to -0.27, P0.0001), but did not demonstrate improvement in concept formation and reasoning, verbal functioning and language skills, or perception.[6] Two trials assessed errors with night-time

driving and flight simulation with less errors made if people were administered caffeine compared to placebo. Only one RCT was identified comparing caffeine to each of the following other interventions: naps, bright light, and modafinil.[6] These limited studies did not identify any differences in cognitive performance between treatments.[6] Adverse effects associated with caffeine which were more common than placebo included disruption of subsequent sleep and risk for dependence. Authors conclude that caffeine may improve performance but the degree to which this might reduce injury risk is unknown.[6]

Jet Lag

A 2020 systematic review evaluated pharmacologic and non-pharmacologic treatments for travel fatigue and jet lag in athletes.[3] If the initial literature search failed to identify targeted studies in athletes, then the scope of the search was expanded to healthy populations and evidence was downgraded for applicability. Fourteen RCTs and 8 observational studies evaluated management of jet lag and were included in the review.[3] Eleven studies focused on pharmacological interventions conducted under simulated (n=3) or actual (n=9) travel conditions.[3] Pharmacologic treatments included melatonin (n=2), sedatives (n=1), stimulants (n=4), and melatonin agonists (n=4).[3] There were no studies identified which evaluated travel fatigue. Because of heterogeneous study design, populations, flight direction, outcomes measured and statistical parameters, results were summarized descriptively and a meta-analysis was not conducted. The majority of studies enrolled healthy populations, and only a few studies (n=3) evaluated pharmacologic treatments specifically in athletes.[3] RCTs and observational studies of non-pharmacological interventions had high risk of bias and concerns identified with directness, consistency, precision and publication bias. Most RCTs of pharmacologic interventions were evaluated as having low to moderate risk of bias, and methodologic quality of all observational studies was poor. Major evidence limitations included concerns for consistency, precision, and publication bias.[3]

- There was insufficient evidence for use of melatonin in jet lag symptoms in athletes. Evidence was based on 2 single-arm studies with small sample sizes and no comparator group that had mixed results for management of jet lag.[3]
- There was insufficient evidence for use of sedatives in management of jet lag in athletes. A single observational study was identified that evaluated temazepam for travel symptoms.[3]
- No studies evaluated stimulants or melatonin analogues in athletes. In healthy populations, there was moderate quality evidence from 4 RCTs that stimulants (e.g., armodafinil or caffeine) increased alertness and improve resynchronization of the circadian rhythm.[3]
- There were mixed results for use of melatonin agonists to improve jet lag symptoms following travel in healthy populations. Results from 2 RCTs in tasimelteon showed improved sleep symptoms compared to placebo.[3] There were mixed results in 2 studies of ramelteon for jet lag symptoms. In one study of ramelteon, sleep onset was improved with low doses (1 mg) but not high doses (4-8 mg), alertness was improved with 4mg dose but not low (1 mg) or high (8 mg) doses, and all doses decreased scores on the immediate memory recall test.[3] In the second RCT, there was an observed phase shift in the circadian rhythm with 1-4 mg ramelteon compared to placebo, but no difference in jet lag symptoms.[3]

Authors generally concluded that available evidence for management of jet lag in athletes was of low quality and additional studies were required to draw valid conclusions.

After review, 12 systematic reviews were excluded due to poor methodologic quality (e.g., network meta-analyses),[19-30] wrong study design of included trials (e.g., observational), comparator (e.g., no control or placebo-controlled), or outcome studied (e.g., non-clinical).

Guidelines:

High Quality Guidelines:

Practice guidelines from the American Academy of Sleep Medicine for the treatment of intrinsic circadian rhythm sleep-wake disorders were updated in 2015.[2] Recommendations were graded as strong or weak recommendations based on degree of clinical certainty regarding net health benefits or harms. For many interventions, there was insufficient evidence to support a recommendation for therapy. There was evidence to support interventions in these populations:

- In adults with advanced sleep-wake phase disorder, evening light therapy is weakly recommended (very low quality evidence).[2]
- In adults, adolescents, and children with delayed sleep-wake phase disorder, strategically timed melatonin or melatonin agonists are weakly recommended (low quality evidence for adults; low-moderate quality evidence for children and adolescents). In children or adolescents, post-awakening light therapy is also weakly recommended (low quality evidence).[2]
- In adults who are blind and have non-24 hour sleep-wake disorder, there is a weak recommendation for strategically timed melatonin or melatonin agonists (low quality evidence).[2]
- In elderly adults with irregular sleep-wake rhythm disorder and dementia, light therapy is weakly recommended (very low quality evidence). There are recommendations against the use of sleep-promoting medications (strong recommendation), melatonin or melatonin agonists (weak recommendation), and combined light therapy and melatonin (weak recommendation) in this population (low to very low quality evidence).[2]
- In children and adolescents with neurologic disorders and irregular sleep-wake rhythm disorder, melatonin or melatonin agonists are weakly recommended (moderate quality evidence).[2]

Additional Guidelines for Clinical Context:
Recommendations for extrinsic circadian rhythm sleep-wake disorders were included in practice parameters published by the American Academy of Sleep Medicine in 2007.[31] Because recommendations for intrinsic sleep-wake disorders were updated in 2015,[2] this summary focuses on recommendations for extrinsic disorders (e.g., shift work disorder and jet lag). Recommendations were based on a systematic review of the literature and graded based on evidence. Recommendations were categorized based on certainty of evidence (**Table 3**).[31] This summary will focus on "standard" or "guideline" recommendations.

Table 3. Evidence grades and levels of evidence for Guideline Recommendations[31]

Strength of Recommendation	Degree of Clinical Certainty	Supporting Level of Evidence
Standard	High	High quality RCTs on well-characterized patients or overwhelming evidence from multiple flawed RCTs and/or cohort studies
Guideline	Moderate	Evidence from a cohort study or flawed clinical trial, or consensus from multiple case control studies
Option	Uncertain	Inconclusive or conflicting evidence or conflicting expert opinion. Clinical benefits or risks in this population are uncertain.

Two treatment recommendations were supported by standard recommendations with high quality evidence from well-designed RCTs:
- Planned sleep schedules are recommended in people with shift work disorder.[31] Several lab simulation and observational studies have demonstrated that napping prior to a work night shift will improve alertness, reaction time, and work accidents without affecting post-shift daytime sleep.
- Timed melatonin administration is recommended for people with jet lag disorder.[31] In several studies, melatonin has demonstrated improvements in duration of sleep and sleep quality compared to placebo, with mixed results for improvement of jet lag symptoms. The most effective dose of melatonin is unclear and one study demonstrated decreased efficacy after more than 3 days of use post-travel.

Several treatment recommendations were supported by guideline recommendations with moderate quality evidence from flawed RCTs or observational studies
- Timed light exposure is recommended in people with shift work disorder.[31] In shift work disorder, several studies utilizing a variety of light intensities and durations have demonstrated that administration of bright light for during the work shift demonstrate improvements in timed work performance tasks,

alertness, and mood compared to ordinary light exposure. There is mixed evidence for improvements in daytime sleep in patients with shift work disorder.

- Timed melatonin is recommended in people with shift work disorder.[31] In shift work disorder, several studies have shown that melatonin administered prior to sleep after a work shift improved daytime sleep quality and duration, but failed to improve alertness during the work shift.
- Hypnotics (for insomnia symptoms) or alerting agents like modafinil are recommended in people with shift work disorder.[31] Hypnotics evaluated for shift work disorder included triazolam, temazepam, and zolpicone and generally demonstrated improvements in duration of sleep and sleep quality with inconsistent effects on alertness during the work shift. Authors caution that risks of hypnotics should be weighed against benefits as hypnotics could worsen comorbid conditions. Stimulants like modafinil have shown improved psychomotor performance and alertness during night shifts, but are not a substitute for adequate sleep and have the potential to impair daytime sleep periods.

Randomized Controlled Trials:

A total of 127 citations were manually reviewed from the initial literature search. After further review, all citations were excluded because of wrong study design (eg, observational), comparator (eg, no control or placebo-controlled), outcome studied (eg, non-clinical), or inclusion in systematic reviews and guidelines.

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Appendix 1: Preferred Drug List

Sedatives

Generic	Brand	Form	PDL
melatonin	MELATONIN	TABLET	Y
zolpidem tartrate	AMBIEN	TABLET	Y
zolpidem tartrate	ZOLPIDEM TARTRATE	TABLET	Y
daridorexant HCl	QUVIVIQ	TABLET	N
diphenhydramine HCl	NIGHTTIME SLEEP AID	CAPSULE	N
diphenhydramine HCl	SLEEP AID	CAPSULE	N
diphenhydramine HCl	SLEEP TIME	CAPSULE	N
diphenhydramine HCl	SLEEP AID	LIQUID	N
diphenhydramine HCl	SLEEP TIME	LIQUID	N
diphenhydramine HCl	NIGHTTIME SLEEP AID	TABLET	N
diphenhydramine HCl	SLEEP AID	TABLET	N
diphenhydramine HCl	SLEEP TABS	TABLET	N
doxepin HCl	DOXEPIN HCL	TABLET	N
doxepin HCl	SILENOR	TABLET	N
doxylamine succinate	SLEEP AID	TABLET	N
estazolam	ESTAZOLAM	TABLET	N
eszopiclone	ESZOPICLONE	TABLET	N
eszopiclone	LUNESTA	TABLET	N
flurazepam HCl	FLURAZEPAM HCL	CAPSULE	N
lemborexant	DAYVIGO	TABLET	N
midazolam HCl	MIDAZOLAM HCL	SYRUP	N
ramelteon	RAMELTEON	TABLET	N
ramelteon	ROZEREM	TABLET	N
suvorexant	BELSOMRA	TABLET	N

tasimelteon	HETLIOZ	CAPSULE	N
tasimelteon	HETLIOZ LQ	ORAL SUSP	N
temazepam	RESTORIL	CAPSULE	N
temazepam	TEMAZEPAM	CAPSULE	N
triazolam	HALCION	TABLET	N
triazolam	TRIAZOLAM	TABLET	N
zaleplon	ZALEPLON	CAPSULE	N
zolpidem tartrate	AMBIEN CR	TAB MPHASE	N
zolpidem tartrate	ZOLPIDEM TARTRATE ER	TAB MPHASE	N
zolpidem tartrate	EDLUAR	TAB SUBL	N
zolpidem tartrate	ZOLPIDEM TARTRATE	TAB SUBL	N
chloral hydrate	CHLORAL HYDRATE	SYRUP	
dexmedetomidine HCl	IGALMI	FILM	
melatonin/pyridoxine HCl (B6)	MELATONIN-VITAMIN B6	TABLET	

Other Stimulants

Generic	Brand	Form	PDL	Carveout
armodafinil	ARMODAFINIL	TABLET	Y	Y
armodafinil	NUVIGIL	TABLET	Y	Y
modafinil	MODAFINIL	TABLET	Y	Y
modafinil	PROVIGIL	TABLET	Y	Y
solriamfetol HCl	SUNOSI	TABLET	V	Y
pitolisant HCl	WAKIX	TABLET	N	

ADHD Drugs

Generic	Brand	Form	PDL	Carveout
atomoxetine HCl	ATOMOXETINE HCL	CAPSULE	Y	Y
atomoxetine HCl	STRATTERA	CAPSULE	Y	Y
dexmethylphenidate HCl	DEXMETHYLPHENIDATE HCL ER	CPBP 50-50	Y	
dexmethylphenidate HCl	FOCALIN XR	CPBP 50-50	Y	
dexmethylphenidate HCl	DEXMETHYLPHENIDATE HCL	TABLET	Y	
dexmethylphenidate HCl	FOCALIN	TABLET	Y	
dextroamphetamine/amphetamine	ADDERALL XR	CAP ER 24H	Y	
dextroamphetamine/amphetamine	DEXTROAMPHETAMINE-AMPHET ER	CAP ER 24H	Y	
dextroamphetamine/amphetamine	ADDERALL	TABLET	Y	
dextroamphetamine/amphetamine	DEXTROAMPHETAMINE-AMPHETAMINE	TABLET	Y	
lisdexamfetamine dimesylate	VYVANSE	CAPSULE	Y	
lisdexamfetamine dimesylate	VYVANSE	TAB CHEW	Y	

methylphenidate	DAYTRANA	PATCH TD24	Y	
methylphenidate	METHYLPHENIDATE	PATCH TD24	Y	
methylphenidate HCl	METHYLPHENIDATE HCL CD	CPBP 30-70	Y	
methylphenidate HCl	METHYLPHENIDATE HCL ER (CD)	CPBP 30-70	Y	
methylphenidate HCl	CONCERTA	TAB ER 24	Y	
methylphenidate HCl	METHYLPHENIDATE ER	TAB ER 24	Y	
methylphenidate HCl	METHYLPHENIDATE HCL	TABLET	Y	
methylphenidate HCl	RITALIN	TABLET	Y	
clonidine HCl	CLONIDINE HCL ER	TAB ER 12H	V	Y
guanfacine HCl	GUANFACINE HCL ER	TAB ER 24H	V	Y
guanfacine HCl	INTUNIV	TAB ER 24H	V	Y
viloxazine HCl	QELBREE	CAP ER 24H	V	Y
amphetamine	DYANAVEL XR	SUS BP 24H	N	
amphetamine	DYANAVEL XR	TAB BP 24H	N	
amphetamine	ADZENYS XR-ODT	TAB RAP BP	N	
amphetamine sulfate	EVEKEO ODT	TAB RAPDIS	N	
amphetamine sulfate	AMPHETAMINE SULFATE	TABLET	N	
amphetamine sulfate	EVEKEO	TABLET	N	
dextroamphetamine	XELSTRYM	PATCH TD24	N	
dextroamphetamine sulfate	DEXEDRINE	CAPSULE ER	N	
dextroamphetamine sulfate	DEXTROAMPHETAMINE SULFATE ER	CAPSULE ER	N	
dextroamphetamine sulfate	DEXTROAMPHETAMINE SULFATE	SOLUTION	N	
dextroamphetamine sulfate	PROCENTRA	SOLUTION	N	
dextroamphetamine sulfate	DEXTROAMPHETAMINE SULFATE	TABLET	N	
dextroamphetamine sulfate	ZENZEDI	TABLET	N	
dextroamphetamine/amphetamine	MYDAYIS	CPTP 24HR	N	
methamphetamine HCl	DESOXYN	TABLET	N	
methamphetamine HCl	METHAMPHETAMINE HCL	TABLET	N	
methylphenidate	COTEMPLA XR-ODT	TAB RAP BP	N	
methylphenidate HCl	ADHANSIA XR	CPBP 20-80	N	
methylphenidate HCl	METHYLPHENIDATE ER (LA)	CPBP 50-50	N	
methylphenidate HCl	METHYLPHENIDATE LA	CPBP 50-50	N	
methylphenidate HCl	RITALIN LA	CPBP 50-50	N	
methylphenidate HCl	JORNAY PM	CPDR ER SP	N	
methylphenidate HCl	APTENSIO XR	CSBP 40-60	N	
methylphenidate HCl	METHYLPHENIDATE ER	CSBP 40-60	N	
methylphenidate HCl	METHYLIN	SOLUTION	N	
methylphenidate HCl	METHYLPHENIDATE HCL	SOLUTION	N	

methylphenidate HCl	QUILLIVANT XR	SU ER RC24	N	
methylphenidate HCl	QUILLICHEW ER	TAB CBP24H	N	
methylphenidate HCl	METHYLPHENIDATE HCL	TAB CHEW	N	
methylphenidate HCl	METHYLPHENIDATE ER	TAB ER 24	N	
methylphenidate HCl	RELEXXII	TAB ER 24	N	
methylphenidate HCl	METHYLPHENIDATE ER	TABLET ER	N	
serdexmethylphen/dexmethylphen	AZSTARYS	CAPSULE	N	

Appendix 2: Medline Search Strategy

Ovid MEDLINE(R) ALL 1946 to January 03, 2023

1	exp "Hypnotics and Sedatives"/	129148
2	exp Melatonin/	22605
3	exp Doxylamine/	397
4	exp Estazolam/	112
5	ramelteon.mp.	493
6	suvorexant.mp.	347
7	exp Triazolam/	1241
8	zaleplon.mp.	437
9	exp Diphenhydramine/	4516
10	exp Doxepin/	847
11	exp Eszopiclone/	134
12	exp Flurazepam/	781
13	exp Midazolam/	9610
14	exp Zolpidem/	1735
15	exp Dexmedetomidine/	5093
16	daridorexant.mp.	47
17	exp Benzodiazepines/	68872
18	exp central nervous system stimulants/ or exp amphetamine/ or exp dexmethylphenidate hydrochloride/ or exp dextroamphetamine/ or exp methylphenidate/ or exp modafinil/	101793
19	exp Atomoxetine Hydrochloride/	1337
20	exp Clonidine/	13470

Author: Servid April 2023

21	exp Guanfacine/	751
22	exp Viloxazine/	242
23	serdexmethylphenidate.mp.	5
24	armodafinil.mp.	225
25	solriamfetol.mp.	83
26	pitolisant.mp.	171
27	1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24 or 25 or 26	289392
28	exp Sleep Disorders, Circadian Rhythm/	2685
29	delayed sleep-wake phase disorder.mp.	88
30	advanced sleep-wake phase disorder.mp.	11
31	irregular sleep-wake rhythm disorder.mp.	18
32	non-24 hour sleep-wake rhythm disorder.mp.	18
33	shift work disorder.mp.	153
34	exp Jet Lag Syndrome/	584
35	28 or 29 or 30 or 31 or 32 or 33 or 34	2805
36	27 and 35	632
37	limit 36 to (english language and humans)	537
38	limit 37 to (clinical study or clinical trial, all or clinical trial, phase iii or clinical trial, phase iv or clinical trial or comparative study or controlled clinical trial or equivalence trial or meta analysis or multicenter study or practice guideline or pragmatic clinical trial or randomized controlled trial or "systematic review")	127

Appendix 3: Key Inclusion Criteria

Population	Circadian Rhythm Sleep Disorders (e.g., delayed or advanced sleep-wake phase disorder, irregular sleep-wake rhythm disorder, non-24 hour sleep-wake rhythm disorder, shift work disorder, jet lag) in adults and children.
Intervention	Stimulants (**Appendix 1**) Sedatives (**Appendix 1**)
Comparator	Active medication comparators listed in **Appendix 1** or placebo
Outcomes	Symptoms (e.g., excessive daytime sleepiness, amount and quality of sleep) Quality of life Function (e.g., impacts on driving, work, school)
Setting	Outpatient

Appendix 4: Proposed Prior Authorization Criteria

Sedatives

Goals:

- Restrict use of sedatives to OHP-funded conditions. Long-term treatment of insomnia with sedatives is not funded.
- Encourage use of cognitive behavioral therapy for insomnia.
- Prevent concomitant use of sedatives, including concomitant use with benzodiazepines or opioids.
- Limit daily zolpidem dose to the maximum recommended daily dose by the FDA.
- Permit use of melatonin in children and adolescents 18 years of age or younger.

Length of Authorization:

- Up to 12 months or lifetime (criteria-specific)

Requires PA:

- All sedatives (e.g., sedative hypnotics, hypnotics-melatonin agonists) except melatonin in children and adolescents. Melatonin is not covered for adults over 18 years of age.

Covered Alternatives:

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

Zolpidem Daily Quantity Limits

Generic	Brand	Max Daily Dose
Zolpidem	Ambien	10 mg
Zolpidem ER	Ambien CR	12.5 mg

Approval Criteria		
1. What diagnosis is being treated?	Record ICD10 code.	
2. Is the request for melatonin in an adult over 18 years of age?	**Yes:** Pass to RPh. Deny; medical appropriateness.	**No:** Go to #3
3. Is the request for zolpidem at a higher dose than listed in the quantity limit chart?	**Yes:** Pass to RPh. Deny; medical appropriateness.	**No:** Go to #4
4. Is the request for a non-preferred product and will the prescriber consider a change to a preferred product? Message: Preferred products are evidence-based and reviewed for comparative effectiveness and safety by the P&T Committee.	**Yes:** Inform prescriber of preferred alternatives in class. Go to #5	**No:** Go to #5
5. Is the patient being treated under palliative care services (ICD10 Z51.5) with a life-threatening illness or severe advanced illness expected to progress toward dying?	**Yes:** Approve for lifetime.	**No:** Go to #6
6. Has the patient been treated with a different non-benzodiazepine sedative, benzodiazepine, or opioid within the past 30 days?	**Yes:** Go to #7	**No:** Go to #9

Approval Criteria		
7. Is this a switch in sedative therapy due to intolerance, allergy or ineffectiveness?	**Yes:** Go to #9 Document reason for switch.	**No:** Go to #8
8. Is concurrent sedative therapy part of a plan to switch and taper off a long-acting benzodiazepine (such as diazepam, clonazepam, or chlordiazepoxide) AND has the provider included a detailed strategy to taper? Note: a documented taper strategy should include planned dose reductions and length of time between each dose modification for at least the next few weeks. It should also include a documented follow-up plan to monitor progress and manage withdrawal symptoms (regular check-ins are essential for a successful taper). Triazolam may be discontinued without a taper in most cases (2-hour half-life prevents physical dependence).	**Yes:** Approve duplicate benzodiazepine therapy for the duration specified in the taper plan (not to exceed 6 months).	**No:** Pass to RPh. Deny; medical appropriateness.
9. Does the patient have a diagnosis of insomnia with obstructive sleep apnea?	**Yes:** Go to #10	**No:** Go to #11
10. Is the patient on CPAP?	**Yes:** Go to # 11	**No:** Pass to RPh. Deny; medical appropriateness. Sedative/hypnotics are contraindicated due to depressant effect.
11. Is the request for treatment of insomnia?	**Yes:** Go to #12	**No:** Go to #13

Approval Criteria		
12. Is the patient currently engaged in cognitive behavioral therapy focused on insomnia treatment (CBT-I), failed to have benefit in symptoms after 5-6 CBT interventions, OR have inability to access CBT-I?	**First request:** Sedative treatment can be approved for 30 days. Long-term treatment must document that benefits outweigh risks. **Subsequent request:** Go to **Renewal Criteria**	**No:** Pass to RPh. Deny; medical appropriateness.
13. RPh only: Is diagnosis being treated a funded condition and is there medical evidence of benefit for the prescribed sedative?	**Funded:** Document supporting literature and approve 30 days with subsequent approvals dependent on follow-up and documented response.	**Not Funded:** Current age ≥ 21 years: Deny; not funded by OHP. Current age < 21 years: Go to #14
14. Is there documentation that the condition is of sufficient severity that it impacts the patient's health (e.g., quality of life, function, growth, development, ability to participate in school, perform activities of daily living, etc)?	**Yes:** Go to #15 Document baseline	**No:** Pass to RPh. Deny; medical necessity.
15. Is the request for a melatonin agonist (e.g., melatonin, ramelteon, tasimelteon) for treatment of one of the following circadian rhythm sleep-wake disorders: • People with delayed sleep-wake phase disorder • Adults with non-24 hour sleep-wake disorder • Children and adolescents with neurologic disorders and irregular sleep-wake rhythm disorder?	**Yes:** Approve for approve 30 days with subsequent approvals dependent on follow-up and documented response.	**No:** Pass to RPh. Deny; medical appropriateness.

Renewal Criteria		
1. Is the request for a slow taper plan?	**Yes:** Approve for duration of taper (not to exceed 3 months). Subsequent requests should document progress toward discontinuation	**No:** Go to #2
2. Is the request for treatment of an unfunded condition previously approved by FFS?	**Yes:** Go to #3	**No:** Go to #4
3. Is there documentation of improvement (e.g., of symptoms, function, quality of life, etc) since treatment was started?	**Yes:** Go to #4	**No:** Pass to RPh. Deny; medical appropriateness.
~~3.~~4. Is there documentation that benefits of ongoing benefits (hospitalizations, function, quality of life), outweigh risks (memory problems, dementia, cognitive impairment, daytime sedation, falls, fractures, dependence, and reduced long-term efficacy)?	**Yes:** Approve for 3 months	**No:** Pass to RPh. Deny; medical appropriateness.

P&T/DUR Review: *12/22 (SS); 8/22; 12/20; 7/18; 3/17; 11/14, 3/14, 5/06, 2/06, 11/05, 9/05, 2/04, 2/02, 9/01*
Implementation: *1/1/23; 10/1/22; 1/1/21; 8/15/18; 1/1/15, 7/1/14; 1/1/07, 7/1/06, 11/15/05*

Sleep-Wake Medications

Goal(s):

- To promote safe use of drugs for obstructive sleep apnea and narcolepsy.
- Limit use to diagnoses where there is sufficient evidence of benefit and uses that are funded by OHP. Excessive daytime sleepiness related to shift-work is not funded by OHP.
- Limit use to safe doses.

Length of Authorization:

- Initial approval of 90 days if criteria met; approval of up to 12 months with documented benefit

Requires PA:

- Modafinil or armodafinil without previous claims evidence of narcolepsy or obstructive sleep apnea
- Solriamfetol
- Pitolisant

Covered Alternatives:

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

Table 1. Funded Indications.

Indication	Modafinil (Provigil™)	Armodafinil (Nuvigil™)	Solriamfetol (Sunosi™)	Pitolisant (Wakix™)
• Excessive daytime sleepiness in narcolepsy	FDA approved for Adults 18 and older	FDA approved for Adults 18 and older	FDA approved for Adults 18 and older	FDA approved for Adults 18 and older
• Residual excessive daytime sleepiness in obstructive sleep apnea patients treated with CPAP.	FDA approved for Adults 18 and older	FDA approved for Adults 18 and older	FDA approved for Adults 18 and older	Not FDA approved; insufficient evidence
• Depression augmentation (unipolar or bipolar I or II acute or maintenance phase) • Cancer-related fatigue • Multiple sclerosis-related fatigue	Not FDA approved; Low level evidence of inconsistent benefit	Not FDA approved; insufficient evidence	Not FDA approved; insufficient evidence	Not FDA approved; insufficient evidence
• Drug-related fatigue • Excessive daytime sleepiness or fatigue related to other neurological disorders (e.g. Parkinson's Disease, traumatic brain injury, post-polio syndrome) • ADHD	Not FDA approved; insufficient evidence	Not FDA approved; insufficient evidence	Not FDA approved; insufficient evidence	Not FDA approved; insufficient evidence

• Cognition enhancement for any condition				

Table 2. Maximum Recommended Dose (consistent evidence of benefit with lower doses).

Generic Name	Minimum Age	Maximum FDA-Approved Daily Dose
Armodafinil	18 years	250 mg
Modafinil	18 years	200 mg
Solriamfetol	18 years	150 mg
Pitolisant	18 years	17.8 mg (poor CYP2D6 metabolizers)

Approval Criteria		
1. What diagnosis is being treated?	Record ICD10 code.	
2. Is the patient 18 years of age or older?	**Yes:** Go to #3	**No:** Pass to RPh. Deny; medical appropriateness. Providers for patients 7 to 17 years of age may also submit a request for sodium oxybate as it is FDA-approved for narcolepsy in this age group.
3. Is the request for continuation of therapy at maintenance dosage previously approved by the FFS program?	**Yes:** Go to **Renewal Criteria**	**No:** Go to #4
4. Is this a funded diagnosis? Non-funded diagnoses: • Shift work disorder (ICD10 G4720-4729; G4750-4769; G478) • Unspecified hypersomnia (ICD10 G4710)	**Yes:** Go to #5	**No:** For current age ≥ 21 years: Pass to RPh. Deny; not funded by the OHP For current age < 21 years: Go to #5

Approval Criteria		
5. Is there documentation that the condition is of sufficient severity that it impacts the patient's health (quality of life, function, growth, development, ability to participate in school, perform activities of daily living, etc) despite lifestyle modifications (e.g., strategic bright light receipt or avoidance, sleep hygiene, dietary changes, etc)?	**Yes:** Document symptom severity. Go to #6 Evidence supports modafinil and armodafinil in moderate-severe shift work disorder (e.g., sleep latency ≤ 6 minutes) and risks likely outweigh benefits in patients with mild symptoms.	**No:** Pass to RPh. Deny; medical necessity.
~~5.~~6. Is the drug prescribed by or in consultation with an appropriate specialist for the condition (e.g., sleep specialist, neurologist, or pulmonologist)?	**Yes:** Go to #~~7~~6	**No:** Pass to RPh. Deny; medical appropriateness
~~6.~~7. Will prescriber consider a preferred alternative?	**Yes:** Inform prescriber of preferred alternatives (e.g., preferred methylphenidate)	**No:** Go to #~~8~~7
~~7.~~8. Is the prescribed daily dose higher than recommended in Table 2?	**Yes:** Go to #~~9~~8	**No:** Go to #10~~9~~
~~8.~~9. Is the request for pitolisant in a patient with documentation of all the following: • CYP2D6 testing which indicates the patient is not a poor metabolizer • Chart notes or provider attestation indicating lack of hepatic or renal impairment	**Yes:** Go to #10~~9~~ Max dose for pitolisant is 35.6 mg daily.	**No:** Pass to RPh. Deny; medical appropriateness.
~~9.~~10. Is there baseline documentation of fatigue severity using a validated measure (e.g., Epworth score, Brief Fatigue Inventory, or other validated measure)?	**Yes:** Go to #11~~0~~ Document baseline scale and score	**No:** Pass to RPh. Deny; medical appropriateness

Approval Criteria		
~~10.~~11. Is the request for solriamfetol or pitolisant?	**Yes:** Go to #121~~1~~	**No:** Go to #165~~5~~
~~11.~~12. Does the patient have a diagnosis of end stage renal disease?	**Yes:** Pass to RPh. Deny; medical appropriateness	**No:** Go to #132~~2~~
~~12.~~13. Is the request for solriamfetol?	**Yes:** Go to #143~~3~~	**No:** Go to #165~~5~~
~~13.~~14. Is the request for concurrent use with a monoamine oxidase inhibitor?	**Yes:** Pass to RPh. Deny; medical appropriateness	**No:** Go to #154~~4~~
~~14.~~15. Is there documentation of a recent cardiovascular risk assessment (including blood pressure) with physician attestation that benefits of therapy outweigh risks?	**Yes:** Go to #198~~8~~ Document recent blood pressure within the last 3 months and physician attestation of cardiovascular risk assessment	**No:** Pass to RPh. Deny; medical appropriateness Use of solriamfetol is not recommended in patients with uncontrolled hypertension or serious heart problems.
~~15.~~16. Is the patient of childbearing potential?	**Yes:** Go to #16	**No:** Go to #198~~8~~
~~16.~~17. Is the patient pregnant or actively trying to conceive?	**Yes:** Pass to RPh. Deny; medical appropriateness	**No:** Go to #167~~7~~
~~17.~~18. Is there documentation that the provider and patient have discussed the teratogenic risks of the drug if the patient were to become pregnant?	**Yes:** Go to #198~~8~~	**No:** Pass to RPh. Deny; medical appropriateness.
~~18.~~19. Is the request for treatment of narcolepsy for a drug FDA-approved for the condition (Table 1)?	**Yes:** Approve for 90 days and inform prescriber further approval will require documented evidence of clinical benefit.	**No:** Go to #2019~~19~~

Approval Criteria		
~~19.~~20. Is the request for treatment of obstructive sleep apnea (OSA) (without narcolepsy) for a drug FDA-approved for the condition (see Table 1)?	**Yes:** Go to #2~~1~~0	**No:** Go to #22~~1~~
~~20.~~21. Is the patient compliant with recommended first-line treatments (e.g., CPAP or other primary therapy)?	**Yes:** Approve for 90 days and inform prescriber further approval will require documented evidence of clinical benefit.	**No:** Pass to RPh; Deny; medical appropriateness
~~21.~~22. Is the request for off-label use of armodafinil, solriamfetol, or pitolisant (see Table 1)?	**Yes:** Pass to RPh. Deny; medical appropriateness. There is insufficient evidence for off-label use.	**No:** Go to #23~~2~~
~~22.~~23. Is the primary diagnostic indication for modafinil fatigue secondary to major depression (MDD), MS or cancer-related fatigue? Note: Methylphenidate is recommended first-line for cancer.	**Yes:** Inform prescriber of first-line options available without PA. May approve for 90 days and inform prescriber further approval will require documented evidence of clinical benefit and assessment of adverse effects.	**No:** Go to #24~~3~~

23. All other diagnoses must be evaluated as to the OHP-funding level and evidence for clinical benefit.

- Evidence supporting treatment for excessive daytime sleepiness (EDS) or fatigue as a result of other conditions is currently insufficient and should be denied for “medical appropriateness”.
- Evidence to support cognition enhancement is insufficient and should be denied for “medical appropriateness”.

If new evidence is provided by the prescriber, please forward request to Oregon DMAP for consideration and potential modification of current PA criteria.

Renewal Criteria		
1. Is the request for solriamfetol?	**Yes:** Go to #2	**No:** Go to #3
2. Is there documentation of a recent blood pressure evaluation (within the last 3 months)?	**Yes:** Go to #3	**No:** Pass to RPh. Deny; medical appropriateness
3. Is the request for treatment of obstructive sleep apnea?	**Yes:** Go to #4	**No:** Go to #5
4. Is the patient adherent to primary OSA treatment (e.g.,CPAP) based on chart notes?	**Yes:** Go to #5	**No:** Pass to RPh. Deny; medical appropriateness
5. Is there documentation of clinical benefit and tolerability from baseline? The same clinical measure used to diagnose excessive daytime sleepiness (EDS), fatigue secondary to MS and/or cancer, major depressive disorder (MDD) is recommended to document clinical benefit. For Epworth Sleepiness Scale, and improvement of at least 3 points is considered clinically significant.	**Yes:** Approve for up to 12 months	**No:** Pass to RPh. Deny; medical appropriateness

P&T Review: 10/1/2020 (DE); 2/2020; 7/19; 03/16; 09/15
Implementation: 11/1/20; 3/1/2020; 8/19/19; 8/16, 1/1/16

SPECIAL ARTICLES

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Journal of Clinical Sleep Medicine

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Clinical Practice Guideline for the Treatment of Intrinsic Circadian Rhythm Sleep-Wake Disorders: Advanced Sleep-Wake Phase Disorder (ASWPD), Delayed Sleep-Wake Phase Disorder (DSWPD), Non-24-Hour Sleep-Wake Rhythm Disorder (N24SWD), and Irregular Sleep-Wake Rhythm Disorder (ISWRD). An Update for 2015

An American Academy of Sleep Medicine Clinical Practice Guideline

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A systematic literature review and meta-analyses (where appropriate) were performed and the GRADE approach was used to update the previous American Academy of Sleep Medicine Practice Parameters on the treatment of intrinsic circadian rhythm sleep-wake disorders. Available data allowed for positive endorsement (at a second-tier degree of confidence) of strategically timed melatonin (for the treatment of DSWPD, blind adults with N24SWD, and children/adolescents with ISWRD and comorbid neurological disorders), and light therapy with or without accompanying behavioral interventions (adults with ASWPD, children/adolescents with DSWPD, and elderly with dementia). Recommendations against the use of melatonin and discrete sleep-promoting medications are provided for demented elderly patients, at a second- and first-tier degree of confidence, respectively. No recommendations were provided for remaining treatments/populations, due to either insufficient or absent data. Areas where further research is needed are discussed.

Keywords: circadian rhythms, DSWPD, ASWPD, N24SWD, ISWRD

Citation: Auger RR, Burgess HJ, Emens JS, Deriy LV, Thomas SM, Sharkey KM. Clinical practice guideline for the treatment of intrinsic circadian rhythm sleep-wake disorders: advanced sleep-wake phase disorder (ASWPD), delayed sleep-wake phase disorder (DSWPD), non-24-hour sleep-wake rhythm disorder (N24SWD), and irregular sleep-wake rhythm disorder (ISWRD). An update for 2015. *J Clin Sleep Med* 2015;11(10):1199–1236.

SUMMARY

Purpose

The present document replaces/updates the previous American Academy of Sleep Medicine (AASM) Practice Parameters pertaining to the intrinsic CRSWDs (i.e., ASWPD, DSWPD, N24SWD, and ISWRD). The treatment of remaining CRSWDs is not addressed.

Methodology

The AASM commissioned a Task Force (TF) of 4 members with expertise in the field of CRSWDs, appointed a Board of Directors (BOD) liaison, and assigned a Science and Research Department staff member to manage the project. PICO (Patient, Population or Problem, Intervention, Comparison, and Outcomes) questions were developed by the TF and approved by the BOD. Extensive literature searches were performed to identify articles of interest, and relevant data were extracted by the TF. The TF developed consensus-based relevant outcomes, rated their relative importance, and determined clinical significance thresholds. Extracted data were pooled across studies for each outcome measure in accordance with PICO questions, and based upon CRSWD diagnosis, study design, patient population, outcome of interest, and method of derivation. Statistical analyses were performed using dedicated software, and meta-analyses were completed when applicable. The GRADE (Grading of Recommendations Assessment, Development, and Evaluation) approach was used to develop recommendation statements and to determine the direction and strengths of these recommendations based upon a composite assessment of evidence quality, benefits versus harms analyses, and patient values and preferences.

Findings

Available data allowed for positive endorsement (at a second-tier degree of confidence) of strategically timed melatonin (for the treatment of DSWPD, blind adults with N24SWD, and

children/adolescents with ISWRD and comorbid neurological disorders), and light therapy with or without accompanying behavioral interventions (adults with ASWPD, children/adolescents with DSWPD, and elderly with dementia and ISWRD). Recommendations against the use of melatonin and discrete sleep-promoting medications are provided for demented elderly patients, at a second- and first-tier degree of confidence, respectively. No recommendations were provided for remaining treatments/populations, due to either insufficient or absent data.

Recommendations are as Follows

ASWPD

5.1.4a The TF suggests that clinicians treat adult ASWPD patients with evening light therapy (versus no treatment). [WEAK FOR]

DSWPD

5.2.6.1a The TF suggests that clinicians treat DSWPD in adults with and without depression with strategically timed melatonin (versus no treatment). [WEAK FOR]

5.2.6.2.1a The TF suggests that clinicians treat children and adolescents with DSWPD (and no comorbidities) with strategically timed melatonin (versus no treatment). [WEAK FOR]

5.2.6.2.2a The TF suggests that clinicians treat children and adolescents with DSWPD comorbid with psychiatric conditions with strategically timed melatonin (versus no treatment). [WEAK FOR]

5.2.9.2a The TF suggests that clinicians treat children and adolescents with DSWPD with post-awakening light therapy in conjunction with behavioral treatments (versus no treatment). [WEAK FOR]

N24SWD

5.3.6.1a The TF suggests that clinicians use strategically timed melatonin for the treatment of N24SWD in blind adults (versus no treatment). [WEAK FOR]

ISWRD

5.4.4a The TF suggests that clinicians treat ISWRD in elderly patients with dementia with light therapy (versus no treatment). [WEAK FOR]

5.4.5a The TF recommends that clinicians avoid the use of sleep-promoting medications to treat demented elderly patients with ISWRD (versus no treatment). [STRONG AGAINST]

5.4.6.1a The TF suggests that clinicians avoid the use of melatonin as a treatment for ISWRD in older people with dementia (versus no treatment). [WEAK AGAINST]

5.4.6.2a The TF suggests that clinicians use strategically timed melatonin as a treatment for ISWRD in children/adolescents with neurologic disorders (versus no treatment). [WEAK FOR]

5.4.9.1a The TF suggests that clinicians avoid the use of combined treatments consisting of light therapy in combination with melatonin in demented, elderly patients with ISWRD (versus no treatment). [WEAK AGAINST]

Conclusion

Use of the GRADE system for this updated Clinical Practice Guideline represents a major change. This update should provide clinicians with heightened confidence with respect to prescribing select treatments and, equally importantly, should serve as a roadmap for future studies that will propel higher quality, more sophisticated therapies for the intrinsic CRSWDs.

Second Bone Marrow Transplant

Plain Language Summary:

Coverage question: Should OHP cover more than one operation (transplant) that delivers healthy stem cells to replace a person's own stem cells?

Should OHP cover this treatment? Yes, when appropriate for the patient. A second transplant is rarely needed but may be required in some situations.

Coverage Question: Should the limitation to a single bone marrow transplant be removed from the Prioritized List?

Question source: HSD medical management committee

Background: Guideline note 14 currently limits bone marrow transplant coverage to a single transplant except in multiple myeloma. HSD recently reviewed a case of a young patient with Hodgkin's lymphoma who had relapsed and was being considered for a second bone marrow transplant. HSD is requesting a review of the current policy limitation.

Bone marrow transplant (hematopoietic cell transplantation or HCT) involves the harvesting of bone marrow, stem cells, or umbilical cord stem cells from a patient (autologous) or a donor (allogeneic) and infusing them into a patient after the patient's bone marrow has been eliminated through chemotherapy, immunotherapy and/or radiation therapy. The majority of HCT is done for treatment of bone marrow malignancies, such as leukemia and lymphoma. There are some cases in which HCT is done for treatment of a non-bone marrow malignancy, such as germ cell testicular tumors.

Previous HSC/HERC reviews:

The last review of second HCT was conducted in 2003/2004. At that time, only one systematic review on second HCT was identified (for acute leukemia) with all trials being uncontrolled. Results showed minimal increase in survival. From the December 2003 HOSC minutes: "It was agreed that second bone marrow transplants currently do not meet the criteria of greater than 5% 5-year survival and technically would not be covered at this time." Note: in 2003 there was a flow chart for transplants that required a minimum 5 year survival for coverage. From the March 2004 HOSC minutes: "all the studies listed except for the French study on tandem autologous transplant for multiple myeloma were case series, none were controlled trials. It was agreed that second bone marrow transplants would be approved only for myeloma, and only as planned tandem transplants."

Second Bone Marrow Transplant

Current Prioritized List/Coverage status:

Bone marrow transplant is included on 11 covered lines and no non-covered lines

GUIDELINE NOTE 14, SECOND BONE MARROW TRANSPLANTS

Lines 94,113,115,130,163,179,217,260,288

Second bone marrow transplants are not covered except for tandem autologous transplants for multiple myeloma.

Evidence:

1) **NHS 2017**, Clinical Commissioning Policy: Second allogeneic haematopoietic stem cell transplant for relapsed disease (all ages)
    a. Published evidence of clinical effectiveness is limited to retrospective case series and two controlled studies. These are mostly single centre and report outcomes on patients treated over periods of more than twenty years, during which time approaches to treatment and options available may have varied. Risks of bias and confounding are inherent in the study design. The patients reported in these studies are heterogeneous with respect to disease, disease stage, previous treatment, conditioning regimes as well as demographic factors (age, gender, etc.). The outcomes reported from these studies indicate a 5-year overall survival from Allo-HSCT as a second transplant of 16% to 28%
    b. The review found one study of the comparative effectiveness of Allo-HSCT compared to other management strategies in patients who have relapsed following an initial transplant for haematological malignancy. It reported no significant difference in oneyear survival rates between people with acute myeloid leukaemia and myelodysplastic syndrome treated with supportive care, palliative or intensive chemotherapy, a second Allo-HSCT or other treatments. The only factor influencing overall survival was time to relapse after first Allo-HSCT
    c. Coverage decision: When patients relapse following their first Allo-HSCT, a multi-disciplinary team consisting of a haematology specialist, specialist nurse and transplant physicians is called to assess clinical options. These include: further chemotherapy; withdrawal of immunosuppressive treatment (given to reduce graft-versus-host disease); infusion of donor lymphocytes; treatment with cytokines; or a second Allo-HSCT. Where relapse has occurred >12 months after procedure, a decision whether the patient is clinically fit to undergo a second Allo-HSCT is taken.

Expert guidelines:

1) **NCCN** 2.2022 Hematopoietic cell transplantation (HCT)
    a. Second HCT is not mentioned

Other payer policies:

1) Anthem BCBS 2023

a. For acute myeloid leukemia, acute lymphoblastic leukemia, chronic myeloid leukemia, chronic lymphocytic leukemia, myelodysplastic syndromes, and myelofibrosis:

Second Bone Marrow Transplant

i. A *second or repeat allogeneic (ablative or non-myeloablative) stem cell transplantation* due to relapsed disease is considered **medically necessary.**

HERC staff summary:

Second bone marrow transplant is rarely required, but has reasonable survival rates when necessary for a variety of bone marrow cancers. The current 20-year-old policy was based on expected survival rates, which is not allowed under the ACA. The existing guideline should be deleted and medical appropriateness should be applied for coverage decisions.

HERC staff recommendation:

1) Delete guideline note 14

~~GUIDELINE NOTE 14, SECOND BONE MARROW TRANSPLANTS~~

~~*Lines 94,113,115,130,163,179,217,260,288*~~

~~Second bone marrow transplants are not covered except for tandem autologous transplants for multiple myeloma.~~

Esophageal Sphincter Augmentation Device for GERD

Plain Language Summary:

Coverage question: Should coverage be added for a ring of magnetic beads placed around the outside of the food pipe, just above the stomach, to keep the food pipe closed in patients with severe heartburn?

Should OHP cover this treatment? No, Medicare and other insurers consider this experimental and other effective treatments exist.

Coverage Question: Should coverage be added for the LINX magnetic esophageal sphincter augmentation device as a treatment for GERD?

Question source: Dr. Derek Rogalsky, general surgeon, as part of his public comment on the bariatric surgery coverage guidance

Background: Gastroesophageal reflux disease (GERD) is a common condition in which stomach acid enters the esophagus. This can cause pain, coughing, and damage to the esophagus. Standard therapies for GERD include lifestyle modifications, antacids, proton pump inhibitor medications (PPIs), and fundoplication surgery. One minimally invasive procedure that can be done to treat GERD is the placement of a series of magnets for esophageal sphincter augmentation. This procedure is the LINX Reflux Management System. Using laparoscopic surgery, a ring of beads is placed around the outside of the esophagus, just above the stomach. Magnets inside the beads hold them together to keep the esophagus closed but move apart to allow food or liquid to be swallowed.

Currently, the CPT code for the placement of the LINX device (CPT Laparoscopy, surgical, esophageal sphincter augmentation procedure, placement of sphincter augmentation device (ie, magnetic band), including cruroplasty when performed) is on line 662/GN173. As part of the public comment for the bariatric surgery coverage guidance, a bariatric surgeon indicated that de novo or worsening GERD after sleeve gastrectomy cannot be treated with fundoplication as the sleeve procedure removes the fundus of the stomach. The only surgical treatment options after sleep gastrectomy for the treatment of GERD is conversion to gastric bypass or placement of the LINX device.

From the public comment: “OHP should cover…placement of a LINX device for GERD in either the presence of biopsy proven intestinal metaplasia (Barretts), reflux esophagitis, or bravo pH probe with DeMeester score greater than or equal to 14. Without this coverage patients will be left to suffer with GERD, with no recourse except long term high dose PPIs, which often are not as effective in symptom control due to altered stomach anatomy.”

Esophageal Sphincter Augmentation Device for GERD

Previous HSC/HERC reviews:

The insertion of the LINX device was first reviewed as a new code in November 2016. That review consisted of a 2012 NICE evidence review on insertion of a magnetic bead band for GERD that found it to be experimental, as well as a 2013 AHRQ emerging technologies review that found lack of long-term data on safety and efficacy. Based on these two evidence reviews, the procedure was deemed experimental and made non-covered.

The most recent review of magnetic sphincter augmentation was done as part of the coverage guidance on newer interventions for GERD, approved in January 2019. "Magnetic sphincter augmentation for treatment of GERD is not recommended for coverage *(weak recommendation)*." That coverage guidance review found no data on the effect of magnetic sphincter augmentation for prevention of Barrett's esophagus, stricture, or other complications of GERD. There was no statistically significant difference in GERD health-related qualify of life scores or with PPI cessation with magnetic sphincter augmentation compared to fundoplication at 6 and 12 months. From the coverage guidance: "Although magnetic sphincter augmentation (MSA) appears to have similar effectiveness and similar adverse events and complications compared to laparoscopic fundoplication, we have very low confidence in the evidence." "Based on observational studies and one poor-quality RCT, the level of evidence is insufficient at present to establish the comparative effectiveness of MSA. Some additional costs would be likely with the addition of MSA coverage, and there are no strong values or preferences that would favor MSA over other available GERD treatment options. Our recommendation for non-coverage is weak because future studies may better establish the benefits of the MSA procedure."

Current Prioritized List/Coverage status:

43284 (Laparoscopy, surgical, esophageal sphincter augmentation procedure, placement of sphincter augmentation device (ie, magnetic band), including cruroplasty when performed) is on line 662 CONDITIONS FOR WHICH CERTAIN INTERVENTIONS ARE UNPROVEN, HAVE NO CLINICALLY IMPORTANT BENEFIT OR HAVE HARMS THAT OUTWEIGH BENEFITS

43285 (Removal of esophageal sphincter augmentation device) is on line 424 COMPLICATIONS OF A PROCEDURE USUALLY REQUIRING TREATMENT

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

Line 660

The following Interventions are prioritized on Line 660 CONDITIONS FOR WHICH CERTAIN INTERVENTIONS ARE UNPROVEN, HAVE NO CLINICALLY IMPORTANT BENEFIT OR HAVE HARMS THAT OUTWEIGH BENEFITS:

Procedure Code	**Intervention Description**	**Rationale**	**Last Review**
43284	Laproscopy, surgical, esophageal sphincter augmentation procedure, placement of sphincter augmentation device (ie, magnetic band)	Insufficient evidence of effectiveness	January, 2019

Esophageal Sphincter Augmentation Device for GERD

Evidence:

1) **NICE 2022**, rapid evidence review, "Interventional procedure overview of laparoscopic insertion of a magnetic ring for gastro-oesophageal reflux disease"
    a. Outcome measures:
        i. The DeMeester score is a composite score of the acid exposure during a prolonged ambulatory pH monitoring. A score more than 14.7 is considered abnormal acid reflux, scores between 14.7 and 100 are regarded as mild-to-moderate GORD, and a score greater than 100 is regarded as severe GORD.
        ii. The GORD health-related quality of life (HRQL) scale measures symptomatic outcomes and therapeutic effects in patients with GORD. The scale has 10 items, and each item is scored from 0 to 5, with 0 indicating no symptoms and 5 presenting symptoms being incapacitating (unable to do daily activities).
    b. Included studies
        i. Systematic review and meta-analysis of 15 studies (N=1,138 patients)
            1. **Zhuang 2021**
                a. 10 single arm cohort studies
                b. 1 RCT
                c. 3 comparative cohorts with fundoplication
        ii. Systematic review and meta-analysis of 19 studies (N=12,697 patients)
            1. **Guidozzi 2019**
                a. 6 comparative cohort studies of magnetic sphincter augmentation (MSA) vs fundoplication (1099 patients; 632 MSA vs 467 fundoplication)
                b. 12 single-cohort studies (11,598 patients)
        iii. Systematic review and meta-analysis of 7 studies (N=1,211 patients)
            1. Aiolfi 2018
            2. Included in coverage guidance review
        iv. RCT of 134 patients (magnetic ring vs PPI), Bell 2020
            1. Comparison of magnetic sphincter augmentation to PPI therapy
        v. Non randomized comparative study of 631 patients (Bonavina 2020)
        vi. Case series, N=553 patients (Ayazi 2020a)
        vii. Case series, N=124 patients (Ferrari 2020)
        viii. Non randomized comparative study, N=336 patients (Ferrari 2021)
        ix. randomized comparative study, N=350 patients (Ayazi 2020b)
    c. Efficacy
        i. Zhuang 2021:
            1. the pooled rate of GORD-HRQL improvement (at least 50% reduction) was 88% (95% confidence interval [CI] 83% to 93%, Cochrane Q P=0.11, I2= 55%; 3 studies) within 1 year, and 85% (95% CI 78% to 91%, Cochrane Q P=0.52, I2=0%; 2 studies) within 5 years. The total pooled rate was 88% (95% CI 84% to 92%; Cochrane Q P=0.17, I2=40%; 4 studies). When comparing laparoscopic insertion of a magnetic ring with laparoscopic Nissen fundoplication (LNF), the weighted mean difference

(WMD) in GORD-HRQL score was 0.20 (95% CI -1.60 to 2.00, p=0.83; Cochrane Q P=0.79, I2=0%; 3 studies)

2. the pooled rate of postoperative PPI use was 13% (95% CI 9.9% to 17.4%; Cochrane Q P =0.12, I 2=43%; 6 studies) within 1 year, 14% (95% CI 8.3% to 20.6%; Cochrane Q P=0.89, I2=0%; 2 studies) within 2 years, and 19% (95% CI 9.9% to 35.9%; Cochrane Q P=0.13, I2=55%; 2 studies) within 5 years. When comparing laparoscopic insertion of a magnetic ring with LNF, there was no statistically significant difference in postoperative PPI use (risk ratio [RR] 1.55, 95% CI 0.49 to 4.94, p=0.46, Cochrane Q P=0.27, I2=19%; 2 studies

ii. Guidozzi 2019

1. comparing laparoscopic insertion of a magnetic ring with fundoplication, the WMD in postoperative GORD-HRQL score was 0.34 (95% CI −0.70 to 1.37, p=0.525, I 2=70.6%; 3 studies)
2. analysis of 13 single cohort studies showed that the proportion of patients who needed postoperative PPI therapy was 13% (138/1,043). When comparing laparoscopic insertion of a magnetic ring with fundoplication, there was no statistically significant difference in postoperative PPI therapy (pooled odds ratio [OR] 1.08, 95% CI 0.40 to 2.95, p=0.877, I 2=72%; 5 studies)

iii. Safety

1. Overall postoperative morbidity ranged from 0% to 3% of patients who had laparoscopic insertion of a magnetic ring and from 0% to 7% of patients who had fundoplication in the systematic review and meta-analysis of 7 studies (Aiolfi 2018).
2. The intraoperative complication rate was 2% in the laparoscopic insertion of a magnetic ring group and 1% in the fundoplication group, and the procedure-related complication rate was about 2% in each group in the non-randomised comparative study of 631 patients (Bonavina 2020).
3. Major complications were reported in 2 patients in the case series of 553 patients. These complications included CO2 retention needing reintubation (n=1) and mediastinal abscess needing drainage and intravenous antibiotic (n=1; Ayazi 2020a). Minor complications were described in 9% (49/553) of patients in the case series of 553 patients.
4. Analysis of 13 single-arm cohort studies revealed that the overall rate of oesophageal erosion was less than 1% (31/11,530)
5. Device removal was reported in 15 patients (5 studies) at 5-year follow up

d. Coverage recommendation

i. Evidence on the safety and efficacy of laparoscopic insertion of a magnetic ring for gastro-oesophageal reflux disease (GORD) is adequate to support using this procedure

Esophageal Sphincter Augmentation Device for GERD

Expert guidelines:

1) **American Gastroenterological Association (AGA) 2022**, *Clinical Practice Update on the Personalized Approach to the Evaluation and Management of GERD: Expert Review*
    a. Expert consensus
    b. In patients with proven GERD, laparoscopic fundoplication and magnetic sphincter augmentation are effective surgical options
    c. Laparoscopic fundoplication is recommended, with the statement "Magnetic sphincter augmentation is another option, often combined with a crural repair in the setting of known hiatal hernia"
    d. Further research into risks/benefits, durability, effectiveness, and treatment outcomes will enhance optimal utilization of these newer endoscopic and surgical options.
    e. Candidacy for invasive antireflux procedures includes confirmatory evidence of pathologic GERD, exclusion of achalasia, and assessment of esophageal peristaltic function

Other payer policies:

1) Aetna 2022:
    a. Aetna considers the LINX Reflux Management System (a sphincter augmentation device) experimental and investigational for the management of GERD
2) United Health Care 2023
    a. Currently, these procedures [including LINX® Reflux Management System] other than TIF are considered non-covered due to the fact that current peer-reviewed literature does not support the long-term efficacy and long-term safety of the services.
3) Anthem BCBS 2022
    a. Lower esophageal sphincter augmentation devices are considered **investigational and not medically necessary** for the treatment of gastroesophageal reflux disease (GERD) and for all other indications**.**
4) Regence BCBS 2022
    a. An implantable magnetic esophageal ring is considered investigational as a treatment of gastroesophageal reflux disease (GERD).
5) Medicare NCD 2021
    a. Coverage is not available for LINX® Reflux Management System, which is not a true endoluminal treatment but is also not considered reasonable and necessary for the diagnosis or treatment of an injury or disease
    b. LINX® Reflux Management system and/or similar treatments are promising for treatment of patients in whom proton pump inhibitor therapy fails. Clinical data from various studies are emerging. At this time, open-label studies or patient registries with short term follow-ups are the dominant source of data. The overwhelming preponderance of reviewers remain equivocal in their support and have called for randomized controlled trials with long-term follow-ups. In the absence of evidence from such studies, and in the absence of wide acceptance, endoscopic treatments for GERD are not proven effective.
    c. Randomized controlled studies are lacking, including head-to-head comparisons with other modes of treatment.

Esophageal Sphincter Augmentation Device for GERD

FDA Approval Documentation/Labeling 2012

1) LINX Reflux Management System states that this system is indicated for patients diagnosed with Gastroesophageal Reflux Disease (GERD) as defined by abnormal pH testing, and who continue to have chronic GERD symptoms despite maximum medical therapy for the treatment of reflux.
2) The LINX device has not been evaluated in patients with a hiatal hernia larger than 3 cm. Use of LINX device in patients with a hiatal hernia larger than 3cm should be considered on the basis of each patient's medical history and severity of symptoms.
3) The safety and effectiveness of the LINX device has not been evaluated in patients with Barrett's esophagus or Grade C or D (LA classification) esophagitis.
4) The safety and effectiveness of the LINX device has not been evaluated in patients with major motility disorders
5) The safety and effectiveness of the LINX Reflux Management System has not been established for the following conditions [partial list]:
    a. prior esophageal or gastric surgery or endoscopic intervention
    b. esophageal stricture or gross esophageal anatomic abnormalities (Schatzki's ring, obstructive lesions, etc.)
    c. morbid obesity (BMI > 35)

Esophageal Sphincter Augmentation Device for GERD

HERC staff summary:

Esophageal magnetic sphincter augmentation has been shown to have similar outcomes to fundoplication for improvement in quality of life and reduction in PPI utilization in a recent trusted source evidence review (NICE). The literature on the efficacy and safety of esophageal sphincter augmentation remains short term comparative cohorts or registry studies. RCTs of esophageal sphincter augmentation compared to established surgical treatments such as fundoplication are lacking. The American Gastroenterological Association expert guidelines state this procedure is efficacious and safe as well. However, all major insurers surveyed in the US still consider this procedure experimental.

Expert input indicates that patients who have undergone gastric sleeve surgery cannot have fundoplication, leaving PPI therapy and esophageal sphincter augmentation as available treatment options. However, the device is not FDA approved in patients with prior bariatric surgery, BMI>35, or esophageal anatomic abnormalities. The ADA recommends excluding achalasia and other esophageal motility disorders prior to this procedure. Given the FDA and ADA recommendations and restrictions, the population eligible for magnetic sphincter augmentation would be very small (non-obese persons with symptomatic GERD but no esophageal damage and no motility disorders who had no previous esophageal or gastric procedures who choose to not continue/not adequately controlled by PPI therapy and choose not to have more established procedures such as fundoplication).

Currently, PPI and other medication therapy is covered for GERD, as well as the gold-standard surgery (fundoplication). Given the lack of RCT data comparing GERD to other established surgical interventions and the lack of long term follow-up studies, as well as the lack of CMS or any other US insurer coverage, HERC staff recommends continued non-coverage of this device. This procedure should be revisited with comparative trial data is available.

HERC staff recommendation:

1) Update the entry for CPT 43284 in GN173 as shown below

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

Line 660

The following Interventions are prioritized on Line 660 CONDITIONS FOR WHICH CERTAIN INTERVENTIONS ARE UNPROVEN, HAVE NO CLINICALLY IMPORTANT BENEFIT OR HAVE HARMS THAT OUTWEIGH BENEFITS:

Procedure Code	**Intervention Description**	**Rationale**	**Last Review**
43284	Laproscopy, surgical, esophageal sphincter augmentation procedure, placement of sphincter augmentation device (ie, magnetic band)	Insufficient evidence of effectiveness	~~January, 2019~~ May 2023

REFLUX MANAGEMENT SYSTEM

INSTRUCTIONS FOR USE

Caution: Federal (USA) Law restricts this device to sale by or on the order of a physician.

1. SYSTEM DESCRIPTION

The LINX® Reflux Management System is comprised of the following components:

- LINX® Reflux Management System Implant
- LINX® Reflux Management System Esophagus Sizing Tool (packaged separately)

  The Esophagus Sizing tool is a single use disposable device provided non-sterile, that must be cleaned and sterilized prior to use (Refer to the LINX® Reflux Management System Esophagus Sizing Tool Instructions for Use.

The LINX® Reflux Management System Implant consists of a series of titanium beads with magnetic cores that are connected with independent titanium wires to form an annular shape. The attractive force of the magnetic beads is designed to provide additional strength to keep a weak LES closed (Figure 1). During swallowing, the magnetic beads slide away from each other on the independent titanium wire "links" to allow esophageal distention as the bolus passes by (Figure 2).

The implant device is offered in multiple sizes to accommodate variation in esophagus size. The sizes are denoted by the model number (e.g., LS12 = 12 Bead Implant). The LINX® Reflux Management System Esophagus Sizing Tool, packaged separately, is utilized to associate the esophagus size to an appropriate LINX® implant device. An illustration of a "12 Bead" size LINX® implant is provided in Figures 1 and 2.

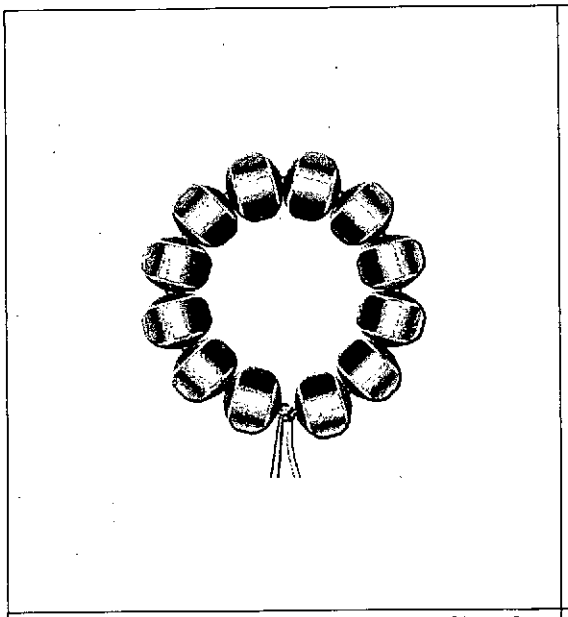

Figure 1 – Illustration of Implant, Closed

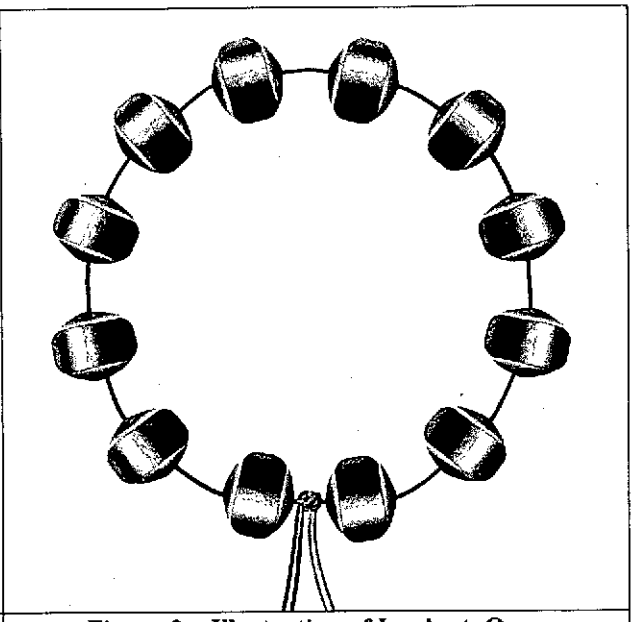

Figure 2 – Illustration of Implant, Open

2. INDICATION FOR USE

The LINX™ Reflux Management System is indicated for patients diagnosed with Gastroesophageal Reflux Disease (GERD) as defined by abnormal pH testing, and who continue to have chronic GERD symptoms despite maximum medical therapy for the treatment of reflux.

3. CONTRAINDICATIONS

3.1. Do not implant the LINX® Reflux Management System in patients with suspected or known allergies to titanium, stainless steel, nickel, or ferrous materials.

4. WARNINGS

4.1. The device is to be placed around the esophagus including the anterior and excluding the posterior vagus nerve bundle. The device should never be placed outside both vagus nerve bundles.

4.2. The LINX® Implant is considered MR Unsafe. After implantation, the patient should not be exposed to an MRI environment. The MRI environment could cause serious injury to the patient and/or interfere with the magnetic strength and the function of the device. A recommendation should be made to patients receiving the LINX® device to register their implant with the MedicAlert Foundation (www.medicalert.org) or equivalent organization. In the event alternative diagnostic procedures can not be used and MRI is required, the LINX device can be safely removed utilizing a laparoscopic technique that does not compromise the option for traditional anti-reflux procedures.

4.3. Failure to secure the LINX® device properly may result in its subsequent displacement and necessitate a second operation.

4.4. Laparoscopic placement of the LINX® Reflux Management System is major surgery and death can occur.

4.5. The device should not be exposed to temperatures above 100°C (212°F) as this could adversely affect the magnets and the function of the device.

5. PRECAUTIONS

5.1. Implantation of the device should only be performed by a surgeon who has experience in laparoscopic anti-reflux procedures and has received product specific training.

5.2. It is the responsibility of the surgeon to advise the patient of the known risks and complications associated with the surgical procedure and implant.

5.3. The sterile package and device should be inspected prior to use. If sterility or performance of the device is suspect or compromised, it should not be used.

5.4. The device is intended for single use only. Do NOT re-sterilize the device. Functionality and sterility of the device can not be assured if re-used.

5.5. The device is magnetic and will be attracted to ferrous objects in the surgical field and other surgical instruments that are ferromagnetic.

5.6. The LINX® device has not been evaluated in patients with a hiatal hernia larger than 3 cm. Use of LINX® device in patients with a hiatal hernia larger than 3cm should be considered on the basis of each patient's medical history and severity of symptoms.

5.7. Patients should be advised that the LINX® Reflux Management System is a long-term implant. Explant (removal) and replacement surgery may be indicated at any time. Medical management of adverse reactions may include explantation and/or replacement.

5.8. The safety and effectiveness of the LINX® device has not been evaluated in patients with Barrett's esophagus or Grade C or D (LA classification) esophagitis.

5.9. The safety and effectiveness of the LINX® device has not been evaluated in patients with electrical implants such as pacemakers and defibrillators, or other metallic, abdominal implants.

5.10. The safety and effectiveness of the LINX® device has not been evaluated in patients with major motility disorders.

5.11. The safety and effectiveness of the LINX® Reflux Management System has not been established for the following conditions:

- Scleroderma
- Suspected or confirmed esophageal or gastric cancer
- Prior esophageal or gastric surgery or endoscopic intervention
- Distal esophageal motility less than 35 mmHg peristaltic amplitude on wet swallows or <70% (propulsive) peristaltic sequences or a known motility disorder such as Achalasia, Nutcracker Esophagus, and Diffuse Esophageal Spasm or Hypertensive LES.
- Symptoms of dysphagia more than once per week within the last 3 months.
- Esophageal stricture or gross esophageal anatomic abnormalities (Schatzki's ring, obstructive lesions, etc.).
- Esophageal or gastric varices.
- Lactating, pregnant or plan to become pregnant.
- Morbid obesity (BMI >35).
- Age < 21

6. ADVERSE EVENTS

6.1. Adverse events that may result from use of the LINX® Reflux Management System are both those commonly associated with general surgical procedures as well as those associated with the device specifically.

6.2. Potential adverse events associated with laparoscopic surgery and anesthesia include adverse reaction to anesthesia (headache, muscle pain, nausea), anaphylaxis, cardiac arrest, death, diarrhea, fever, hypotension, hypoxemia, infection, myocardial infarction, perforation, pneumonia, pulmonary embolism, respiratory distress, and thrombophlebitis. Other risks reported after anti-reflux surgery procedures include bloating, nausea, dysphagia, odynophagia, retching, and vomiting.

6.3. Potential risks associated specifically with the LINX® Reflux Management System include achalasia, bleeding, death, decreased appetite, device erosion, device explant/re-operation, device failure, device migration (device does not appear to be at implant site), diarrhea, dysphagia, early satiety, esophageal spasms, flatulence, food impaction, hiccups, inability to belch or vomit, increased belching, infection, impaired gastric motility, injury to the esophagus, spleen, or stomach, nausea, odynophagia, organ damage caused by device migration, pain, peritonitis, pneumothorax, regurgitation, stomach bloating, vomiting, weight loss, and worsening of preoperative symptoms (including but not limited to dysphagia or heartburn).

6.4. The LINX® Reflux Management System is intended to be a long-term implant, and may need to be either explanted or replaced.

6.5. Following are summary safety results from the pivotal clinical study:

The analysis of safety in the clinical study was based on 100 subjects.

There were no cases of esophageal erosion or device migration as assessed by upper endoscopy and chest x-rays in any of the subjects that were evaluated up to the 24 month time point. The majority of subjects evaluated with barium esophagram had normal swallow function; there were three subjects with abnormal function, one of whom required dilation.

Manometry was performed at baseline and 12 months. At 12 months, 31 out of the 32 subjects who had a hypotensive LES at baseline were evaluated and three remained hypotensive. Fifteen of 93 subjects had <70% effective swallows, and four had distal esophageal amplitude <35 mmHg. One subject was reported to have ongoing complaints

of dysphagia and abnormal motility. No other significant differences were seen in measures between baseline and 12 months.

Seventy-six (76) of the 100 subjects (76.0%) implanted with the LINX® device experienced a total of 162 adverse events related to the device and/or procedure, as shown in Table 1.

Table 1: Adverse Events Related to or Relationship to Device or Procedure Unknown

	Related or Unknown		Mild		Moderate		Severe	
Adverse Event	**AEs (n)**	**Subj. % (n)**	**AEs (n)**	**Subj. % (n)**	**AEs (n)**	**Subj. % (n)**	**AEs (n)**	**Subj. % (n)**
Total	162	76% (76)	108	65% (65)	42	28% (28)	12	10% (10)
Dysphagia	76	68% (68)	54	49% (49)	17	16% (16)	5	5% (5)
Pain	25	24% (24)	8	8% (8)	13	13% (13)	4	4% (4)
Stomach Bloating	15	14% (14)	13	12% (12)	2	2% (2)	0	0%
Nausea	8	7% (7)	4	3% (3)	2	2% (2)	2	2% (2)
Odynophagia	8	8% (8)	4	4% (4)	3	3% (3)	1	1% (1)
Other: Hiccups	8	8% (8)	7	7% (7)	1	1% (1)	0	0%
Inability to belch or vomit	6	6% (6)	5	5% (5)	1	1% (1)	0	0%
Decreased Appetite	4	4% (4)	4	4% (4)	0	0%	0	0%
Belching	2	2% (2)	2	2% (2)	0	0%	0	0%
Flatulence	2	2% (2)	2	2% (2)	0	0%	0	0%
Weight Loss	2	2% (2)	2	2% (2)	0	0%	0	0%
Food Impaction	1	1% (1)	0	0%	1	1% (1)	0	0%
Globus Sensation	1	1% (1)	1	1% (1)	0	0%	0	0%
IBS/Dyspepsia	1	1% (1)	1	1% (1)	0	0%	0	0%
Regurgitation of Sticky Mucus	1	1% (1)	0	0%	1	1% (1)	0	0%
Uncomfortable Feeling in Chest	1	1% (1)	1	1% (1)	0	0%	0	0%
Vomiting	1	1% (1)	0	0%	1	1% (1)	0	0%

The most common adverse event experienced by subjects was dysphagia (76 events in 68 subjects). Eighteen (18) subjects at seven sites underwent esophageal dilation for dysphagia, odynophagia, regurgitation or burning sensation in throat. Twelve (12) of these subjects had at least two dilations and 10 of these subjects continued to have symptoms. The second most common event experienced by subjects was pain (25 events in 24 subjects). Unanticipated adverse events included hiccups, belching, food impaction, and pain.

There were nine serious device-or procedure-related adverse events reported in six subjects (Table 2).

Table 2: Serious Adverse Events – Related or Unknown (as determined by either the Investigator or CEC)

Serious Adverse Event	Events (n)	Subjects % (n)
Total	9	6% (6)
Dysphagia	3	3% (3)
Nausea	2	2% (1)
Vomiting	2	2% (2)
Odynophagia	1	1% (1)
Pain[1]	1	1% (1)

[1]Adjudicated with a relationship of Unknown to device and/or procedure

Regarding the time to onset, of the adverse events, there were 149 device or procedure related adverse events that occurred between 0 and 180 days. After 180 days, there were 13 events considered related to the device/procedure or of unknown relationship; one of these events was considered serious. This subject experienced chest pain, nausea, and symptoms of indigestion (day 235 post implant). This is shown in Table 3.

Table 3: Days to Onset of Adverse Event

Adverse Event Type	0 – 90 Days	90-180 Days	>180 Days
All Adverse Events	70% (218/310)	10% (32/310)	19% (60/310)
Related to device/procedure or unknown relationship	84% (136/162)	8% (13/162)	8% (13/162)
Serious	41% (7/17)	35.3% (6/17)	24% (4/17)
Serious related to device/procedure or unknown relationship	78% (7/9)	11% (1/9)	11% (1/9)

There were five subjects who had the device explanted. Three subjects had the device explanted for dysphagia. Two subjects elected to have a Nissen fundoplication following device removal. Details of the five explants are given below:

- One subject with history of severe heartburn, severe regurgitation, and frequent and prolonged nausea, experienced nausea coupled with dysphagia within two weeks of device implantation. The subject underwent balloon dilation in the region of the gastroesophageal junction without resolution of symptoms and the subject requested to have the device removed at thirty days post-implant. The subject underwent a Nisssen fundoplication at a later date.

- One subject with history of GERD started with dysphagia within five days of device implantation. The subject underwent esophageal dilation without resolution of symptoms. Subsequent manometry/motility testing was performed and showed loss of esophageal motility. The device was removed on post-operative day 21.

- One subject started with dysphagia within five days post-implant and odynophagia within seven days post-implant. Esophageal dilations of the gastroesophageal junction (GEJ) were performed without resolution of symptoms and the device was removed 93 days post implant.

- One subject with recurrent GERD symptoms elected to have the device removed so a Nissen fundoplication could be performed. This occurred 489 days post-implant.

- One subject started with intermittent vomiting within three months of device implantation. The subject was subsequently diagnosed with a Helicobacter pylori infection and started on medication. The vomiting episodes continued and the device was explanted at 357 days post-implant.

Side effects associated with antireflux surgery were minimal after the LINX® implant. Additionally, other GERD-related outcomes as assessed by the unvalidated Foregut questionnaire, (bloating, regurgitation, extra-esophageal symptoms) showed long-term improvement (Table 4).

Table 4: Side Effects and Additional Clinical Outcomes

Parameter	Baseline[1]	12 Months[1]	24 Months[1]
Inability to Belch	0%	1%	0%
Inability to Vomit	0%	0%	1%
Bloating Frequency – Frequently/Continuously	40%	5%	7%

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Parameter	Baseline[1]	12 Months[1]	24 Months[1]
Heartburn – Severe or Moderate	89%	3%	6%
Heartburn – Mean frequency/week	79	2	2
Regurgitation – Severe or Moderate	57%	2%	1%
Regurgitation – Mean frequency/week	28	1%	1%
Absence of Extra-Esophageal Symptoms	49%	86%	88%
Chest Pain	69%	20%	16%
Difficulty Swallowing	23%	44%	46%
Difficulty Swallowing – requiring liquids for clearing	4%	7%	12%
Difficulty Swallowing – Mean frequency/week	1	2	1
Patient Satisfied with Present Condition Off PPI On PPI	 0% 13%	 95% NA	 90% NA

[1]Assessments completed off PPI therapy, unless noted

7. CLINICAL STUDIES

The LINX System has been evaluated in two prospective, single-arm, multicenter clinical trials with a combined enrollment of 144 subjects.

Feasibility Study

The first study enrolled 44 subjects at four clinical sites (2 US and 2 OUS) as part of a feasibility IDE trial. Performance outcomes for symptom improvement, reduction of PPI dependence and esophageal acid reduction have been reported through three years (Table 5).

Table 5: Long-Term Feasibility IDE Trial Performance Outcomes

Performance Outcomes[1]	12 Months % (n/N)	24 Months % (n/N)	36 Months % (n/N)
Improvement in GERD-HRQL scores by ≥50%	97.4% (38/39)	88.6% (31/35)	96.3% (26/27)
Reduction in PPI therapy by ≥50%	89.7% (35/39)	82.9% (29/35)	87.5% (28/32)
pH normalization or ≥50% reduction in distal acid exposure[2]	79.5% (31/39)	90.0% (18/20)	85.0% (17/20)

[1]Compared to the subject's baseline data and assessed while off proton pump inhibitors
[2] pH monitoring is not performed in US subjects beyond the 12-month follow-up.

A total of 24/44 (54.5%) subjects experienced adverse events related to the device and/or procedure. The most common adverse event experienced by subjects was dysphagia (22 events in 20 subjects). Although most cases resolved within approximately three months, two subjects required dilation in the area of the GEJ, and one subject had the device removed. Other common adverse events included pain, nausea and vomiting. No intra-operative complications, deaths, life-threatening events, device erosions, device migrations or infections were reported. Two subjects had serious adverse events related to the device and procedure that included one device removal for dysphagia and one hospitalization for chest pain <30 days following the device implant procedure. Both events resolved without clinical sequelae.

There were three subjects who had the device explanted. Reasons for explant included ongoing dysphagia (serious adverse event reported above) and elective removal due to recurrent heartburn and need for an MRI study.

- One subject experienced neurological and vascular symptoms unrelated to the device and procedure. The study subject requested removal of the device in order to undergo this MRI procedure. The Investigator complied with this request and removed the device 468 post-implant without incident.

- Another subject continued to experience recurrent heartburn. A decision was made to remove the device and perform a Nissen fundoplication. The device was removed 1302 days post-implant without incident.

Pivotal Study

The second study, a pivotal IDE trial, enrolled a total of 100 subjects at 14 clinical sites (13 US and 1 OUS). All 100 subjects were implanted with the LINX device during a laparoscopic procedure with a mean duration of 39 minutes (range 7 to 125 minutes). Half the subjects (50/100) were discharged the same day as surgery, and the other half (50/100) were discharged the next day. Follow-up data is available for 12 and 24 months.

The average age of subjects implanted was 50.4 years. Fifty-two percent (52%) were male and 48% female. Fifty-five percent (55%) were overweight (BMI 25-30) and 26% were obese (BMI > 30). Baseline summary statistics for selected demographics and Body Mass Index (BMI) are shown in Table 6.

Table 6: Baseline Demographics

Characteristic	N	Mean±SD (Median)	Range
Age (years)	100	50.4±12.4 (53.0)	18.3, 74.7
Body Mass Index (BMI)	100	27.9±3.4 (27.9)	19.8, 34.7
Characteristic	**% (n/N)**		
Gender			
Male	52% (52/100)		
Female	48% (48/100)		
Race			
Caucasian/Non-Hispanic	96% (96/100)		
Black	0% (0/100)		
Hispanic	3% (3/100)		
Other	1% (1/100)		
BMI Class			
Normal (<25)	19% (19/100)		
Overweight (≥25 and <30)	55% (55/100)		
Obese (≥30)	26% (26/100)		

In the pivotal IDE trial, a subject met the primary endpoint at 12 months if either of the following criteria were met:

- there was normalization of pH, with normalization defined as pH < 4 for ≤ 4.5% of monitoring time, or
- there was a reduction of at least 50% in total time that pH <4, relative to baseline.

This endpoint would be met if the lower bound of a 97.5% confidence interval for the success rate was at least 60%.

At 12 months, 64% of subjects had pH normalization or a ≥50% reduction in distal esophageal acid exposure, and the mean total acid exposure (percent time pH<4) was reduced from 11.9% at baseline to 5.4%. Since the lower limit of the 97.5% confidence interval fell below the 60% success threshold (53.8%), the primary endpoint of the study was not met. See Table 7.

Table 7: Primary Effectiveness Endpoint: Bravo pH Normalization or ≥ 50% Reduction at 12 months

Primary Efficacy Endpoint	% Successful (Number of Subjects/Total)	Lower 97.5% Exact Binomial Confidence Limit	p-value[1]
Bravo pH • Normalization (≤4.5%) OR • ≥ 50% reduction from baseline	64.0% (64/100)	53.8%	0.24

In obtaining the primary endpoint of pH testing, other components of the DeMeester Score as well as the composite score were also able to be examined. It is the composite score, which is made up of these individual components pertaining to acid exposure time, frequency, and duration, that has been reported to be the most reliable measurement of a therapeutic acid suppression regimen or an effective antireflux operation, with sensitivity and specificity for GERD at 96%. There was improvement in the composite DeMeester score in 93% of subjects that had pH testing at 12 months, and 52% had a normalized DeMeester score. This is shown in the Table 8.

Table 8: pH Parameters of Esophageal Acid Exposure

DeMeester Components	Normal Values	Baseline	12 Months
Total time pH <4 (%)	5.3	11.6 ± 4.7 (10.9)N=100	5.1 ± 4.8 (3.3) N=96
Upright time pH <4 (%)	6.9	14.0±7.2 (12.7) N=100	6.5 ± 5.8 (4.3) N=96
Supine Time pH <4 (%)	6.7	7.8±7.2 (6.0) N=98	2.9 ± 5.8 (0.4) N=95
# of Episodes pH <4	36.8	175.0±81.7 (161.0) N=100	82.8 ± 67.6 (67.0) N=96
# of Episodes > 5 min	1.2	12.4±6.7 (12.0) N=99	6.1 ± 6.8 (4.0) N=96
Longest Episode (min)	N/A	37.4±24.4 (29.0) N=99	19.7 ± 20.9 (13.0) N=96
DeMeester Score	<14.72	41 .0±16.3 (36.6) N=97	18.7 ± 17.3 (13.5) N=95
Percentage of subjects with normal DeMeester score		0%	52%

Elimination of daily PPIs was achieved in 91% and 92% of subjects at 12 and 24 months, respectively. The proportion of subjects achieving at least a 50% reduction in daily use of PPIs from baseline was 93% (93/100) at 12 months and 86%(86/100) at 24 months based on the entire treatment group and 96% (86/90) based on evaluable subjects at 24 months. See Table 9.

Table 9: Secondary Efficacy Endpoint: ≥ 50% Reduction in Daily PPI Use from Baseline

Parameter	Follow-up Time	Success Rate	95% CI
≥50% reduction in daily PPI use (secondary endpoint)	12 months	93% (93/100)	86%, 97%
	24 months (treatment group)	86% (86/100)	78%, 92%
	24 Months (evaluable subjects)	96% (86/90)	89%, 98%
Elimination of daily PPI use	12 months (evaluable subjects)	91% (88/97)	83%, 96%
	24 Months (evaluable subjects)	92% (83/90)	85%, 97%

A validated questionnaire called the GERD-HRQL Questionnaire was one method used to assess improvement in GERD-related symptoms. The questionnaire consists of a total of 10 questions that include 6 heartburn questions, 2 swallowing questions, 1 bloating/gas question and one question about GERD medications. Each question is scored on a scale of 0 (no symptoms) to 5 (incapacitating). The best possible score is 0 and the worst score is 50. The mean total GERD-HRQL score at baseline was 26.6 assessed off PPIs and 12.0 assessed on PPIs. At 12 and 24 months, the mean GERD-HRQL scores assessed off PPIs improved to 3.8 and 4.3, respectively.

The proportion of subjects achieving at least a 50% reduction compared to baseline score was 92% (92/100) at 12 months and 84% at 24 months (treatment group) and 93% (84/90) at 24 months based on evaluable subjects. See Table 10.

Table 10: ≥ 50% Reduction in GERD-HRQL Total Score from Baseline (Off PPI)

Follow-up Time	Success Rate	95% CI
12 months	92% (92/100)	85%, 97%
24 months (treatment group)	84% (84/100)	78%. 92%
24 Months (evaluable subjects)	93% (84/90)	86%, 98%

The percentage of subjects with no esophagitis increased from 60.0% at baseline to 87.6% at 12 months and 88.7 % at 24 months. Grade B esophagitis decreased from 18% at baseline to 3.4 % at 24 months. Twenty-two subjects had Grade A at baseline while ten had Grade A at 12 months, and 7 at 24 months. One subject developed Grade D esophagitis at 12 months, which was resolved at 24 months. Esophagitis grade by study visit is provided in Table 11.

Table 11: Esophagitis Grade by Visit

Esophagitis Grade	Baseline % (n/N)	Month 12 % (n/N)	Month 24 % (n/N)
None	60.0% (60/100)	87.6% (85/97)	88.7% (79/89)
Grade A	22.0% (22/100)	10.3% (10/97)	7.9% (7/89)
Grade B	18.0% (18/100)	1.0% (1/97)	3.4% (3/89)
Grade C	0.0% (0/100)	0.0% (0/97)	0.0% (0/89)
Grade D	0.0% (0/100)	1.0% (1/97)	0.0% (0/89)

Adverse event and safety information for the clinical study is presented above in Section 6.

8. DIRECTIONS FOR USE

8.1. Surgical Access

8.2. Gain surgical access through a laparoscopic port to the esophagus at the region of the gastroesophageal junction.

8.3. Dissect the soft tissues away from the outside of the esophagus at the location of the gastroesophageal junction. Tissue should be removed to expose the outer muscle of the esophagus. Create a tunnel under the posterior vagus nerve through the peri-neural tissue. The anterior vagus nerve will be included within the implant. Care should be taken to avoid injuring the vagus nerve bundles.

8.4. Sizing of the Esophagus

Refer to the LINX® Reflux Management System Esophagus Sizing Tool Instructions for Use.

The Esophagus Sizing tool is a single use disposable device provided non-sterile, that must be cleaned and sterilized prior to use.

8.5. Placement of the LINX® Implant

8.5.1. Bring the chosen LINX® implant into the surgical field through a laparoscopic port of minimum internal diameter of 10 mm.

8.5.2. Place the device around the esophagus in the same location that was measured, reference Figure 3.

8.5.3. Using the suture provided, secure the ends of the device with a hand tied knot or a Top-Knot® device such that the eyelets of the device are touching or overlapping. Complete this method of securement for each set of white and green sutures for a total of two secured knots. Once secured, trim sutures, reference Figure 4.

8.5.4. If a hiatal hernia is observed intra-operatively, repair of the hernia should be considered in conjunction with the LINX® implant procedure.

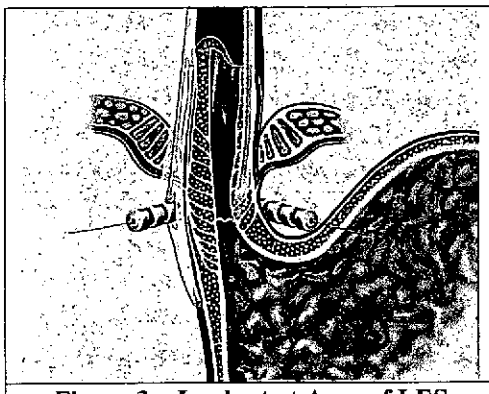

Figure 3 – Implant at Area of LES

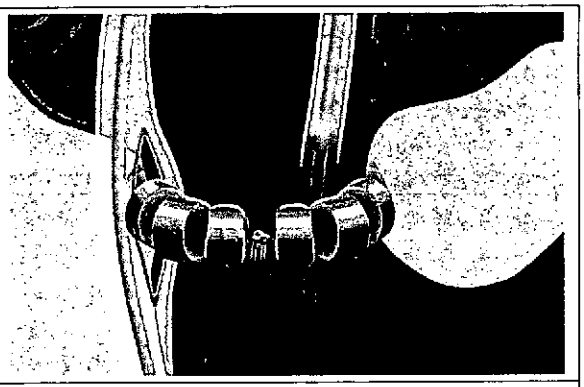

Figure 4 – Completed Implant

9. PACKAGING/STORAGE

The LINX® device is provided sterile and designed to remain sterile unless the primary product pouch has been opened or damaged. Store in a cool, dry place. If opened and not used, discard device or return device to Torax Medical Inc. Do Not Resterilize.

10. LIMITED WARRANTY

(a) Torax warrants that the product shall be free from material defects in materials and/or workmanship, and shall perform substantially in accordance with the written specifications, through the earlier of (i) the expiration of the shelf-life as specified on the applicable product labeling or (ii) the date on which the products are used or implanted.

(b) This limited warranty does not extend to damage caused by (i) abuse or misuse of any product, (ii) accident or neglect by you or a third party; (iii) use of the product other than in accordance with Torax's instructions or specifications; or (iv) any alterations made to the product after shipment.

(c) Torax's entire liability and your exclusive remedies under this limited warranty are, at Torax's option, for Torax to use commercially reasonable efforts to fix or replace the defective product.

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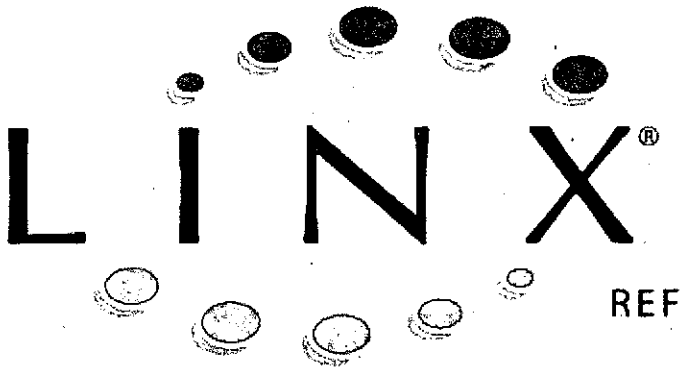

REFLUX MANAGEMENT SYSTEM

ESOPHAGUS SIZING TOOL

INSTRUCTIONS FOR USE

Caution: Federal (USA) Law restricts this device to sale by or on the order of a physician.

1. SYSTEM DESCRIPTION

The LINX® Reflux Management System Esophagus Sizing Tool is an accessory to the LINX® Reflux Management System (packaged separately). See the Instructions for Use provided with the LINX® Reflux Management System

The Esophagus Sizing tool is a single use disposable device provided non-sterile, that must be cleaned and sterilized prior to use.

The device consists of a series of titanium beads with magnetic cores that are connected on a continuous stainless steel cable so that it can form an annular shape. The beads of the device are color coded to correspond with the size range of the LINX® Reflux Management System Implants. An illustration of the LINX® Reflux Management System Esophagus Sizing Tool is provided in Figure 1.

Figure 1 – Illustration of Sizing Tool

2. DIRECTIONS FOR USE

2.1 Clean and Sterilize Before Use

2.1.1 Every sizing tool must be cleaned and sterilized before it is used. The Esophagus Sizing Tool was developed for sterilization by autoclave.

2.2 Cleaning Before Use

2.2.1 Every sizing tool must be disinfected and thoroughly cleaned before use. Clean and inspect the sizing tool carefully. Sterilize the sizing tool before surgery. Clean the instrument as follows:

2.2.2 Do not use corrosive cleaning agents. Cleaning solutions and rinses at or near a neutral pH (7.0) are best. Use of an enzymatic cleaning solution intended specifically for surgical instruments is recommended.

2.2.3 Do not use abrasive cleaners.

2.2.4 Rinse thoroughly with tap water or equivalent (distilled water, etc.).

2.2.5 Only a soft brush should be used.

2.2.6 Rinse the sizing tool with tap water for two minutes while brushing with a soft bristled cleaning brush to remove most or all of the visible gross debris.

2.2.7 Place the sizing tool into an enzymatic bath for five (5) minutes following the enzymatic cleaner manufacturer's directions. Scrub the sizing tool with a soft bristled cleaning brush to remove any remaining debris from the instrument.

2.2.8 Rinse the sizing tool for two minutes using tap water.

2.2.9 Visually inspect the sizing tool under normal lighting to verify cleanliness. Thoroughly dry the sizing tool carefully with compressed air, or allow the sizing tool to air dry.

2.3 Sterilization Before Use

2.3.1 Steam autoclave sterilization is recommended. Do not sterilize in hot air.

2.3.2 Standard **gravity** autoclave steam cycle 132°C - 135°C for 30 minutes.

2.3.3 Standard **pre-vacuum** autoclave steam cycle 132°C - 135°C for 4 minutes.

2.4 Inspection and Functional Check

2.4.1 It is very important to carefully examine each sizing tool for breaks, cracks, loose or faded color coding, corrosion, broken wires, or other malfunctions before use. **DO NOT USE DAMAGED INSTRUMENTS. DO NOT REPLACE COLOR CODING.**

2.5 Surgical Access

2.5.1 Gain surgical access through a laparoscopic port to the esophagus at the region of the gastroesophageal junction.

2.5.2 Dissect the soft tissues away from the outside of the esophagus at the location of the gastroesophageal junction. Tissue should be removed to expose the outer muscle of the esophagus. Create a tunnel under the posterior vagus nerve through the peri-neural tissue. The anterior vagus nerve will be included within the implant. Care should be taken to avoid injuring the vagus nerve bundles.

2.6 Sizing of the Esophagus

2.6.1 Use the LINX® Esophagus Sizing Tool to determine the LINX® Implant size. The LINX® implant sizes are denoted by the model number (e.g., LS12 = 12 Bead Implant).

2.6.2 Bring the LINX® Esophagus Sizing Tool into the surgical field through a laparoscopic port of a minimum internal diameter of 10 mm.

2.6.3 Place the sizing tool around the esophagus in the dissected space around the exposed outer muscle and through the tunnel created under the posterior vagus nerve bundle, reference Figure 2.

2.6.4 Hold opposite ends of the sizing tool and wrap the sizing tool into a circular shape around the esophagus, reference Figure 3.

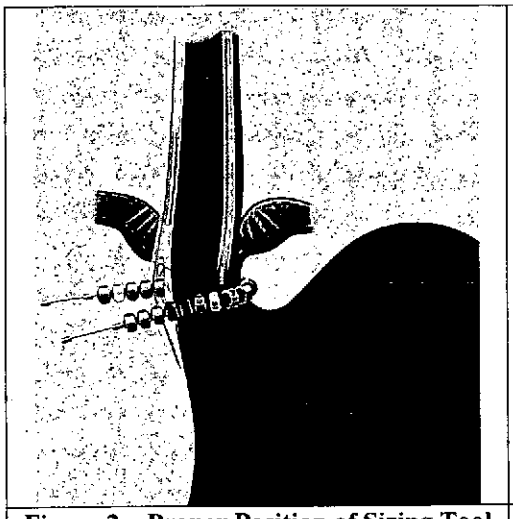

Figure 2 – Proper Position of Sizing Tool

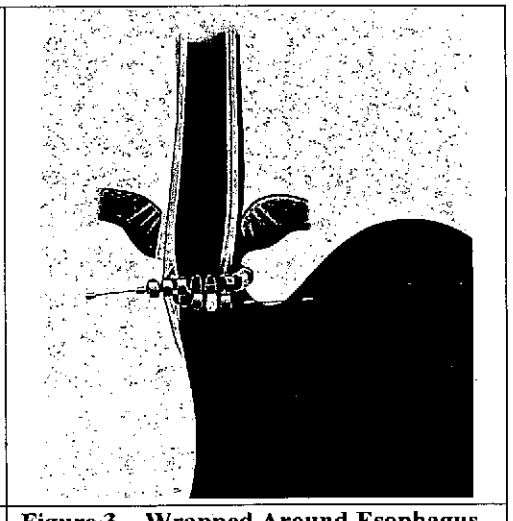

Figure 3 – Wrapped Around Esophagus

2.6.5 There is a white bead near the end of the sizing tool. With the sizing tool wrapped around the esophagus, align the white bead with the remaining colored beads of the sizing tool, reference Figure 4.

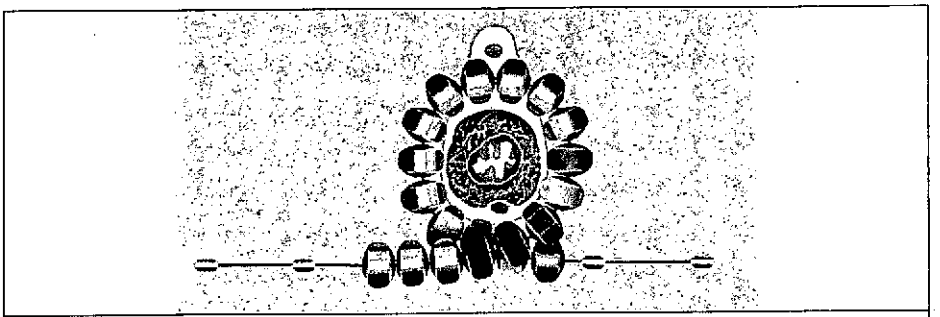

Figure 4 – Colored Bead Aligned with White Bead

2.6.6 Determine the color that aligns with the white bead and referring to the sizing chart in Table 1, select the appropriate device for implantation.

Table 1 – Sizing Chart

Bead Color	Associated LINX® Implant Device
1st Bead Pre-Orange	10-Bead
Orange	11-Bead
Yellow	12-Bead
Green	13-Bead
Blue	14-Bead
Purple	15-Bead
1st Bead Post-Purple	16-Bead
2nd Bead Post-Purple	17-Bead
3rd Bead Post-Purple	18-Bead

2.6.7 Should the white bead align between two colors, choose the device with the higher number of beads.

1. PACKAGING/STORAGE

The LINX® Sizing Tool is provided non-sterile. Store in a cool, dry place. If opened and not used, discard device or return device to Torax Medical Inc.

2. LIMITED WARRANTY

(a) Torax warrants that the product shall be free from material defects in materials and/or workmanship, and shall perform substantially in accordance with the written specifications, through the earlier of (i) the expiration of the shelf-life as specified on the applicable product labeling or (ii) the date on which the products are used or implanted.

(b) This limited warranty does not extend to damage caused by (i) abuse or misuse of any product, (ii) accident or neglect by you or a third party; (iii) use of the product other than in accordance with Torax's instructions or specifications; or (iv) any alterations made to the product after shipment.

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LINX® Reflux Management System

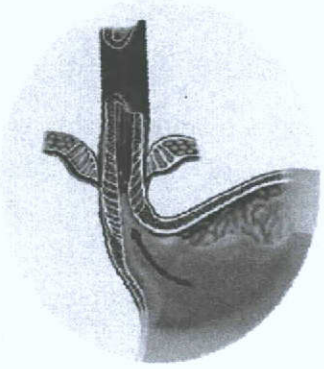
Patient Information

Caution: Federal (USA) Law restricts this device to sale by or on the order of a physician.

Table of Contents

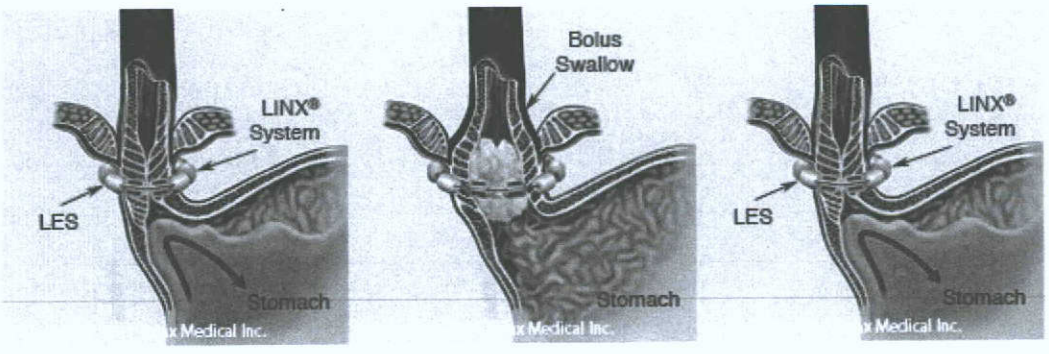
What is the LINX Reflux Management System?

The LINX Reflux Management System is a medical device for patients 21 years and older who have been diagnosed with GERD and continue to have heartburn or regurgitation, despite taking medication to treat GERD.



GERD occurs when the sphincter (valve) between the stomach and esophagus is weak or opens abnormally. Stomach juices reflux into the esophagus and may injure the esophagus and cause symptoms of heartburn or regurgitation.

The LINX System is designed to help the sphincter stay closed to stop the reflux. It uses a small, flexible band of beads. Each bead has a magnet inside. When placed around the outside of the esophagus, the magnetic attraction between the beads helps the sphincter stay closed to prevent reflux. Swallowing food will overcome the magnetic attraction and allow the beads to separate, allowing food and liquid to pass normally into the stomach.



Why doctors use it

The LINX Reflux Management System is used for treating GERD when medication no longer provides adequate symptom control. The LINX System is another option to the standard surgery for GERD, such as Nissen fundoplication. The LINX System is:

- **Less invasive.** Placement of the LINX System does not involve significant alterations to anatomy that may limit future treatment options. With the Nissen fundoplication, the top part of the stomach is wrapped around the lower esophagus to improve the reflux barrier.

- **Removable.** If needed, the LINX System can be removed during a laparoscopic procedure similar to the implant procedure. Removal of the device generally leaves the esophagus the same as before the implant.

- **Well-tolerated.** After surgery, patients usually go home the same day or the next day. Patients are able to eat a normal diet after surgery. With Nissen fundoplication, patients are restricted to a liquid diet that is slowly advanced over weeks to normal food.

Contraindications: Who cannot have the LINX System

Patients with suspected or known allergies to titanium, stainless steel, nickel, or ferrous materials should never be implanted with the LINX System. If you have an allergy to titanium, stainless steel, nickel or ferrous materials, tell your doctor.

Warnings: Things you must do to avoid serious harm

- The LINX System is not considered safe for magnetic resonance imaging (MRI). You must avoid having a MRI test if you are treated with the LINX System. The MRI could cause serious injury to you and/or interfere with the magnetic strength and the function of the device. It is recommended that anyone implanted with the LINX System register the device with the MedicAlert Foundation (www.medicalert.org) or a similar organization.
- The LINX System should not be used with electrical implants (pacemakers or implantable defibrillators, for example) or metallic implants in the abdomen.

Risks of having this done

A clinical study of 100 patients showed that difficulty swallowing, pain, and stomach bloating were the most common risks associated with the LINX System (summarized below). If you are planning to have the LINX System, your doctor will review these risks with you.

Risk	% of Patients	Clinical Experience
Difficulty swallowing	68%	Treatment included dilation (stretching lower esophagus with a balloon) or removal of device in 3% of patients. Difficulty swallowing resolved when the device was removed. After dilation, the difficulty swallowing improved but sometimes returned and required having the dilation repeated. See below for more information about difficulty swallowing.
Pain	24%	Most cases were mild and resolved by 3 months after the procedure. Treatment included pain medications.
Stomach Bloating	14 %	Stomach bloating was mild to moderate and resolved in nearly all patients.

More information about difficulty swallowing

Before and after treatment, patients completed a questionnaire that included a question about difficulty swallowing. Before treatment, 69% of patients reported no symptoms related to difficulty swallowing compared to 55% at 6 months, 64% at 1 year and 59% at 2 years. Before treatment, difficulty swallowing that bothered patients every day or worse was 5% compared to 7% at 6 months, 5% at 1 year and 4% at 2 years. The average number of times per week that a patient had difficulty swallowing was 1 to 2 times per week after treatment. Data about difficulty swallowing is reported below.

Do you have difficulty swallowing?*

	Before Treatment	After Treatment		
		6 Months	1 Year	2 Years
0 = No Symptoms	69%	55%	64%	59%
1 = Symptoms noticeable, but not bothersome	11%	15%	18%	15%
2 = Symptoms bothersome, but not everyday	15%	22%	14%	22%
3 = Symptoms bothersome everyday	2%	7%	5%	4%
4 = Symptoms affect daily activities	3%	0%	0%	0%
5 = Symptoms are incapacitating, unable to do activities	0%	0%	0%	0%
Average number of times per week with difficulty swallowing*	1	2	2	1

*Questionnaire completed while off GERD medications

Other risks of the LINX System reported less frequently included:

- Painful swallowing – 8%
- Hiccups – 8%
- Nausea – 7%
- Inability to belch or vomit – 6%
- Decreased Appetite – 4%
- Increased belching – 2%
- Flatulence – 2%
- Weight loss – 2%
- Vomiting – 1%
- Food impaction – 1%
- Lump in throat – 1%
- Upset stomach or indigestion – 1%
- Regurgitation of sticky mucus – 1%
- Uncomfortable feeling in chest – 1%
- Vomiting – 1%

Other possible risks related to the LINX System may include, but are not limited to:

- Achalasia (muscles of the esophagus fail to relax during swallowing)
- Bleeding
- Death
- Device erosion (device passes through esophagus wall)
- Device failure
- Device migration (device does not appear to be at implant site)
- Device removal or re-operation
- Esophageal spasm
- Diarrhea
- Infection
- Impaired gastric motility (ability to move food/liquid through your system)
- Injury to the esophagus, spleen, or stomach
- Organ damage caused by device migration
- Peritonitis (inflammation of the thin tissue that lines the inner wall of the abdomen)
- Pneumothorax (collapsed lung)
- Perforation
- Regurgitation
- Retching
- Worsening of pre-operative symptoms (including but limited to difficulty swallowing or heartburn)

Risks of general surgery and anesthesia

Additionally, general surgery and anesthesia carries risk. These risks may include, but are not limited to the following:

- Adverse reaction to anaesthesia (headache, muscle pain, nausea)
- Anaphylaxis (Life threatening allergic reaction)
- Cardiac arrest (Blood circulation stops)
- Death
- Diarrhea
- Fever
- Hypotension (Low blood pressure)
- Hypoxemia (Inadequate oxygen in blood)
- Infection
- Myocardial infarction (heart attack)
- Nausea
- Odynophagia (pain or discomfort with swallowing)

(Risks of general surgery and anesthesia – continued)

- Pneumonia (Lung infection)
- Pulmonary embolism (Blocked artery in lungs)
- Respiratory distress (breathing trouble)
- Thrombophlebitis (Blood clot causing inflammation)
- Vomiting

Benefits of having this done

Benefits of treatment with the LINX System may include:

- Reduction in acid exposure to your esophagus
- Improvement in heartburn and regurgitation symptoms
- Reduction or elimination of GERD medications
- Less invasive surgery compared to the standard surgical treatment for GERD
- Ability to resume a normal diet following surgery
- Discharge the same day or the next day after surgery
- Minimal side effects, such as being unable to belch or vomit

How to decide about this treatment

When considering the LINX System, it is important to understand the following:

- The device is a permanent implant, and limited long-term experience is available. Sustainability of effect, as assessed by quality of life scores, has not been studied past 2 years. It is possible that the device may need to be removed or replaced at a later time (for example, in 10 years). If the device fails or breaks, your GERD symptoms may return or you may experience unusual pain.

(How to decide about this treatment – continued)

- 90% of patients reported improvement in GERD symptoms or elimination of GERD medications in a clinical study at 1 and 2 years after treatment. Every patient is different. There are no guarantees you will have the same results. It is possible you may need to continue GERD medications after treatment.

- MRI is not allowed while the device is implanted as it may cause serious injury to you and/or the device. This may be an issue if you currently have or may develop a disease or condition where MRI is the appropriate diagnostic test. You should discuss the MRI restriction with your doctor prior to deciding on treatment with the LINX System.

- The LINX System has not been studied in patients with hiatal hernias greater than 3 cm in size, Barrett's esophagus, advanced esophagitis (inflammation of the esophagus), swallowing difficulties, or motility disorders. Please discuss your medical history with your doctor to determine if you have any conditions for which the LINX System is not recommended.

- The LINX System is not the only option available. The standard surgical treatment for GERD is the Nissen fundoplication. Your doctor will discuss this option and other options available to you, which may include treatments performed by endoscopy such as radiofrequency applications to the sphincter area and endoscopic sewing devices that sew part of the stomach to the esophagus.

- Other treatments performed in the area of lower esophagus may not be possible or will need careful consideration if the LINX System is present. These treatments may include surgical or endoscopic interventions for weight loss, Barrett's esophagus or GERD.

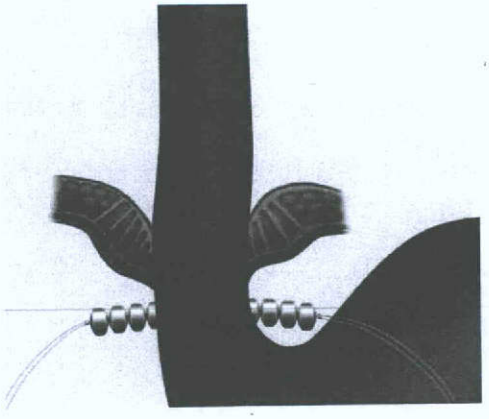
What happens before the treatment?

You will need to have several tests to make sure you are healthy enough for the surgery and to assess your esophagus. Your doctor will explain these tests to you. These tests will likely include:

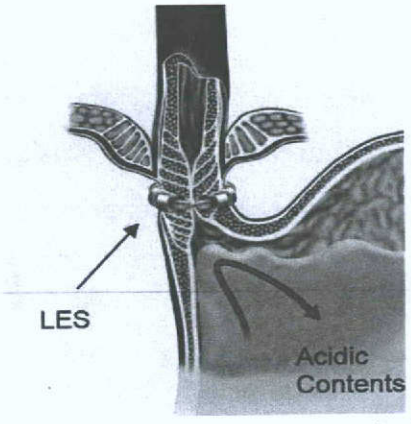
- Esophageal pH testing (tests for acid in the esophagus)
- Manometry/Motility (measures pressures in the esophagus and how many swallows are effective)
- Endoscopy (a visual examination of your esophagus using an endoscope)
- Barium esophagram (x-ray to examine the esophagus. The x-ray is performed while you drink chalky substance called contrast.)

What happens during the treatment?

Under general anesthesia, a surgeon who has experience in laparoscopic anti-reflux procedures and has received specific training in the use of the LINX device, will access the esophagus using a laparoscopic approach (through several small incisions made in the abdomen). The LINX System is placed around the esophagus and the ends of the device are attached to each other. The procedure usually takes less than one hour to perform. It is unlikely that the LINX System will move from the place where it was implanted since it becomes encapsulated (covered) with tissue during the healing process.



LINX is placed around the esophagus at the sphincter



LINX in place with ends attached

What happens after the treatment?

Return to normal diet

You should return to a normal diet as soon as tolerated after the surgery. This is important to ensure proper healing at the implant site of the LINX System.

You may have difficulty swallowing

You may feel like you are having difficulty or pain with swallowing after the surgery. This is normal and expected. If you experience difficulty swallowing, follow these steps:

- Drink a few sips of water before taking your first bite of food and between bites as necessary.
- Take small bites of foods that can easily pass down your esophagus and into your stomach.
- Chew food well before swallowing.
- Foods like bread, pasta, rice, and meat are more likely to cause problems.

Implant Card

You will receive a LINX Implant Card following your surgery. Carry your LINX Implant Card with you as notification to care providers that you have received a LINX System. If you lose this card, please contact your doctor's office to receive a replacement card.

When to call your doctor

After the procedure, your doctor will provide you with instructions about when to call. In general, you should contact your doctor if you have:

- Fever over 100.4 degrees or signs of infection
- Difficulty swallowing or inability to swallow
- Painful swallowing
- Increased abdominal pain
- Nausea or vomiting
- Cough or difficulty breathing

(When to call your doctor – continued)

You should call your doctor if:

- You are told that you need to have an MRI procedure. You should not be exposed to an MRI environment. The MRI could cause injury to you and/or damage to the LINX System.
- You are told you need other surgical procedures or endoscopic treatments of your esophagus. These may be contraindicated because of the presence of the LINX System.

Travel

You may travel as soon as advised by your doctor. The LINX System should not interfere with airport security. You should carry your implant card when traveling so others will know you have an implanted device in case of an emergency.

What studies showed

The LINX System has been evaluated in two clinical studies enrolling a total of 144 patients. The largest clinical study enrolled 100 patients. Patients have been followed for at least 2 years and as long as 5 years.

Safety

No deaths or intra-operative complications occurred. None of the reported risks discussed earlier resulted in permanent disabilities or impairment. If needed, the device was safely removed without complications.

Effectiveness

Many assessments were used to evaluate how well the LINX System improved the reflux barrier to prevent reflux and improve symptoms.

- **Testing for Acid in the Esophagus**

Evidence of an improved reflux barrier was evaluated by testing the percentage of time that stomach acid refluxed into the lower esophagus. Before treatment, the average time significant acid was detected in the esophagus was 11.6% of the time. After treatment, the average time decreased to 5.1% of the time. Normal acid exposure time in the esophagus was 4.5% or less for the study. All patients had abnormal acid exposure time before treatment, and after treatment, the majority of patients had normal acid exposure time in the esophagus. After treatment, the likelihood of achieving any reduction in acid exposure time in the esophagus was 90%.

- **Symptoms**

Questionnaires were used to assess the frequency and severity of GERD-related symptom before and after treatment. The table below compares GERD symptoms before treatment and 2 years after treatment with the LINX System.

% of patients with symptom before LINX	GERD Symptom	% of patients with symptom 2 years after LINX
70%	Reflux affecting sleep on a daily basis	2%
76%	Reflux affecting what food they could eat every day	2%
57%	Moderate or severe regurgitation including aspirations (breathing liquid into the lungs)	1%
55%	Severe heartburn affecting their daily life	1%
40%	Esophagitis	11%

- **GERD Medications**

Patients in the study had been taking proton-pump inhibitors (Prilosec or Nexium, for example) for an average of 6 years before treatment and all patients were taking GERD medications on a daily basis. After treatment, about 90% no longer required daily GERD medication at 1 and 2 years.

More about your condition

You can find additional information on GERD at the National Institutes of Health's website:

http://www.nlm.nih.gov/medlineplus/gerd.html

Where you can find out more

Additional information about the LINX system can be found at: www. toraxmedical.com

Glossary

Esophagus is the tube that carries food, liquids and saliva from your mouth to the stomach.

Nissen fundoplication is a surgical procedure which involves tightening the lower esophageal sphincter to prevent reflux by wrapping the very top of the stomach around the outside of the lower esophagus.

Lower esophageal sphincter (LES) is a ring of muscle that forms a valve at the lower end of the esophagus, where it joins the stomach.

Gastroesophageal reflux disease (GERD) is a condition in which the stomach contents (food or liquid) leak backwards from the stomach into the esophagus (the tube from the mouth to the stomach). This action can irritate the esophagus, causing heartburn and other symptoms.

Barrett's esophagus is a disorder in which the lining of the esophagus (the tube that carries food from the throat to the stomach) is damaged by stomach acid and changed to a lining similar to that of the stomach.

(Glossary – continued)

Hiatal hernia is the protrusion (bulging) of the upper part of the stomach into the chest through a tear or weakness in the diaphragm.

Magnetic resonance imaging (MRI) is a test that uses a magnetic field and pulses of radio wave energy to make pictures of organs and structures inside the body. In many cases MRI gives different information about structures in the body than can be seen with an x-ray, ultrasound, or computed tomography (CT) scan. MRI also may show problems that cannot be seen with other imaging methods.

Proton-pump inhibitors (PPIs) are a group of drugs whose main action is to stop production of stomach acid. They are the most potent inhibitors of acid secretion available today.

Esophageal pH monitoring is a test that measures how often and for how long stomach acid enters the tube that leads from the mouth to the stomach (esophagus).

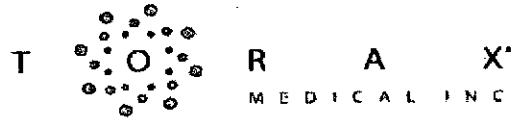
Endoscopy is a procedure where a doctor is able to see the inside lining of your digestive tract. This examination is performed using an endoscope (a flexible fiberoptic tube with a tiny TV camera at the end). The camera is connected to either an eyepiece for direct viewing or a video screen that displays the images on a color TV. The endoscope not only allows diagnosis of gastrointestinal (GI) disease but treatment as well.

Barium esophagram or swallow is used as an initial diagnostic test for several esophageal conditions such as Barrett's esophagus, dysphagia (difficulty swallowing) as well as complications such as stricture, obstruction, narrowing, ulcers and tumors. During this procedure, the patient swallows barium, a white, chalky substance, which can then be viewed via x-ray. Using this procedure the physician can view many abnormalities associated with the esophagus.

(Glossary – continued)

Esophageal manometry is a test to measure the pressure inside the lower part of the esophagus. During the test, a thin, pressure-sensitive tube is passed through your mouth or nose and into your stomach. Once in place, the tube is pulled slowly back into your esophagus.

Laparoscopic surgery is a minimally invasive surgery , is a modern surgical technique in which operations in the abdomen are performed through small incisions (usually 0.5–1.5 cm) as opposed to the larger incisions needed in laparotomy (surgery where a large incision is made).



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INTERVENTIONAL PROCEDURES PROGRAMME

Interventional procedure overview of laparoscopic insertion of a magnetic ring for gastro-oesophageal reflux disease

Gastro-oesophageal reflux disease can occur when the ring of muscle between the food pipe (oesophagus) and the stomach does not close properly. Stomach acid can then travel up towards the throat (reflux), causing symptoms such as heartburn and nausea. This procedure is done under general anaesthesia. Using keyhole (laparoscopic) surgery, a ring of beads is placed around the outside of the food pipe, just above the stomach. Magnets inside the beads hold them together to keep the food pipe closed but are weak enough to move apart to allow food or liquid to be swallowed. The aim is to prevent acid reflux.

Contents

Professional societies

- Association of Upper Gastrointestinal Surgeons for Great Britain and Ireland (AUGIS)
- British Society of Gastroenterology (BSG)
- British Obesity and Metabolic Surgery Society (BOMSS)

Description of the procedure

Indications and current treatment

Gastro-oesophageal reflux disease (GORD) is a common condition in which acid from the stomach flows back up into the oesophagus. It is usually caused by the sphincter at the lower end of the oesophagus becoming weakened. Symptoms of GORD can be directly related to reflux episodes (such as heartburn, regurgitation, chest pain and nausea) or be caused by complications of the disease (such as dysphagia and respiratory difficulties). Repeated episodes of GORD can damage the lining of the oesophagus and lead to oesophageal ulceration, oesophageal stricture and Barrett's oesophagus.

NICE's guideline on GORD and dyspepsia in adults: investigation and management describes managing GORD in adults. The standard treatments for symptomatic GORD are lifestyle modification and drug therapy. People may be offered antireflux surgery (usually laparoscopic fundoplication) if their symptoms do not improve, or they develop complications despite medication or an intolerance to medication. Endoscopic interventions (such as endoscopic radiofrequency ablation at the gastro-oesophageal junction) and electrical stimulation of the lower oesophageal sphincter (LOS) can also be used.

What the procedure involves

The aim of laparoscopic insertion of a magnetic ring for GORD is to relieve reflux-related symptoms (such as heartburn or regurgitation) without impeding the ability to swallow, belch or vomit.

The procedure is done under general anaesthesia. Using a laparoscopic approach, a specially designed sizing tool is placed around the distal oesophagus to assess the size of implant needed. The sizing tool is then removed, and the implant is placed at the gastro-oesophageal junction, with the posterior vagus nerve trunk located outside the magnetic ring. The ends of the implant are secured together to hold it in place. Intraoperative endoscopy may be

used to help identify the anatomic gastro-oesophageal junction and to assess device position.

The implant consists of a ring of interlinked beads, each with a weak magnetic force that holds the beads together and reduces reflux. When the person swallows, the magnetic force is overcome, allowing the ring to open. After swallowing, magnetic attraction brings the beads together and the distal oesophagus is again closed.

Outcome measures

The DeMeester score is a composite score of the acid exposure during a prolonged ambulatory pH monitoring to categorise patients as GORD + or GORD -. The parameters that constitute the score are number of reflux episodes, number of episodes longer than 5 minutes, longest reflux duration, total percentage of monitoring time with pH below 4, and the percentage of time with pH below 4 in an upright position and supine position, respectively. The DeMeester score is the sum of the scores calculated for each of the 6 parameters. A score more than 14.7 is considered abnormal acid reflux, scores between 14.7 and 100 are regarded as mild-to-moderate GORD, and a score greater than 100 is regarded as severe GORD.

The GORD health-related quality of life (HRQL) scale measures symptomatic outcomes and therapeutic effects in patients with GORD. The scale has 10 items, and each item is scored from 0 to 5, with 0 indicating no symptoms and 5 presenting symptoms being incapacitating (unable to do daily activities).

Efficacy summary

GORD-HRQL

In a systematic review and meta-analysis of 15 studies (n=1,138), the pooled rate of GORD-HRQL improvement (at least 50% reduction) was 88% (95% confidence interval [CI] 83% to 93%, Cochrane Q P=0.11, I^2= 55%; 3 studies) within 1 year, and 85% (95% CI 78% to 91%, Cochrane Q P=0.52, I^2=0%; 2 studies) within 5 years. The total pooled rate was 88% (95% CI 84% to 92%; Cochrane Q P=0.17, I^2=40%; 4 studies). When comparing laparoscopic insertion of a magnetic ring with laparoscopic Nissen fundoplication (LNF), the weighted mean difference (WMD) in GORD-HRQL score was 0.20 (95% CI -1.60 to 2.00, p=0.83; Cochrane Q P=0.79, I^2=0%; 3 studies; Zhuang 2021).

In a systematic review and meta-analysis of 19 studies (n=12,697), when comparing laparoscopic insertion of a magnetic ring with fundoplication, the WMD in postoperative GORD-HRQL score was 0.34 (95% CI −0.70 to 1.37, p=0.525, I^2=70.6%; 3 studies; Guidozzi 2019).

In a systematic review and meta-analysis of 7 studies (n=1,211), the estimated pooled mean difference in postoperative GORD-HRQL score was −0.48 (95% CI -1.05 to 0.09, p=0.101, I^2=0.0%; 6 studies) between laparoscopic insertion of a magnetic ring and fundoplication (Aiolfi 2018).

In a randomised controlled trial (RCT) of 134 patients, the proportion of patients who had an at least 50% reduction in GORD-HRQL score was 81% (38/47) in the laparoscopic insertion of a magnetic ring group and 8% (7/87) in the twice-daily proton pump inhibitor (PPI) group (p<0.001) at 6-month follow up (Bell 2019). For all patients who had laparoscopic insertion of a magnetic ring (both primary and crossover groups) the mean GORD-HRQL score was 30±10 off PPIs and 24±10 on daily PPIs at baseline, and statistically significantly improved to 6 at 6 months and to 5 at 12 months (p<0.001). The proportion of patients who had an at least 50% reduction in GORD-HRQL score on PPIs was 81% (61/75). For the group who had medical treatment, no improvement in GORD-HRQL score was seen at study completion (exact data was not reported; Bell 2020).

In a non-randomised comparative study of 631 patients with GORD, there was a statistically significantly improvement in mean GORD-HRQL score at 3 years after treatment in both laparoscopic insertion of a magnetic ring (baseline, 22.0±9.1; 3 years, 4.6±6.0; mean change, -16.6±10.2, p<0.001) and fundoplication groups (baseline, 23.6±9.8; 3 years, 4.9±7.1; mean change, -17.8±10.6, p<0.001; Bonavina 2020).

In a case series of 553 patients with GORD, the mean GORD-HRQL total score statistically significantly improved from 33.8±18.7 at baseline to 7.2±9.0 (p<0.001) at a mean follow up of 10.3 months. The proportion of patients who had an at least 50% improvement in their GORD-HRQL total score was 84% (Ayazi 2020a).

In a case series of 124 patients with GORD who were followed up for 6 to 12 years after laparoscopic insertion of a magnetic ring, the mean total GORD-HRQL score statistically significantly improved from 19.9 at baseline to 4.01 (p<0.001) at a median follow up of 9 years. Clinically significant improvement in GORD-HRQL (>50% improvement) occurred in 93% of patients (Ferrari 2020).

In a non-randomised comparative study of 336 patients, the mean GORD-HRQL score statistically significantly improved from 19.2±7.7 at baseline to 3.8±5.7 at a mean follow up of 50.8 months in the non-severe GORD group and from 21.0±7.5 to 3.9±4.8 in the severe GORD group (all p<0.05). Comparison between groups showed that the mean score was statistically significantly higher in the severe GORD group than the non-severe GORD group at baseline (p=0.0479) but not at the final follow up (p=0.8870; Ferrari 2021).

In a non-randomised comparative study of 350 patients with GORD, the proportion of patients who had an at least 50% reduction in GORD-HRQL total score was 79% in the no hiatal hernia group, 78% in the small hiatal hernia group, 82% in the large hiatal hernia group, and 88% in the paraesophageal hernia group (p=0.77). The overall rate of clinical improvement in GORD-HRQL total score was 79% at a mean follow up of 13.6 months (Ayazi 2020b).

PPI use

In the systematic review and meta-analysis of 15 studies, the pooled rate of postoperative PPI use was 13% (95% CI 9.9% to 17.4%; Cochrane Q P =0.12, I^2=43%; 6 studies) within 1 year, 14% (95% CI 8.3% to 20.6%; Cochrane Q P=0.89, I^2=0%; 2 studies) within 2 years, and 19% (95% CI 9.9% to 35.9%; Cochrane Q P=0.13, I^2=55%; 2 studies) within 5 years. When comparing laparoscopic insertion of a magnetic ring with LNF, there was no statistically significant difference in postoperative PPI use (risk ratio [RR] 1.55, 95% CI 0.49 to 4.94, p=0.46, Cochrane Q P=0.27, I^2=19%; 2 studies; Zhuang 2021).

In the systematic review and meta-analysis of 19 studies, analysis of 13 single-cohort studies showed that the proportion of patients who needed postoperative PPI therapy was 13% (138/1,043). When comparing laparoscopic insertion of a magnetic ring with fundoplication, there was no statistically significant difference in postoperative PPI therapy (pooled odds ratio [OR] 1.08, 95% CI 0.40 to 2.95, p=0.877, I^2=72%; 5 studies; Guidozzi 2019).

In the systematic review and meta-analysis of 7 studies, there was no statistically significant difference in PPI suspension (pooled OR 0.81, 95% CI 0.42 to 1.58, p=0.548, I^2=63.9%; 6 studies) between the laparoscopic insertion of a magnetic ring group and the fundoplication group (Aiolfi 2018).

In the RCT of 134 patients, 91% (43/47) of patients in the laparoscopic insertion of a magnetic ring group discontinued PPIs at 6-month follow up (Bell 2019). At study completion (12 months), 91% (68/75) of patients who had laparoscopic insertion of a magnetic ring (both primary and crossover groups) stopped PPIs (Bell 2020).

In the non-randomised comparative study of 631 patients, the proportion of patients who used PPIs reduced from 98% (453/463) at baseline to 24% (76/314) at 3 years after laparoscopic insertion of a magnetic ring group and from 96% (158/165) to 20% (17/87) after fundoplication (Bonavina 2020).

In the case series of 553 patients, the proportion of patients who were free from PPI use was 93% at a mean follow up of 10.3 months (Ayazi 2020a).

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DISEASES OF THE ESOPHAGUS

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Review

Laparoscopic magnetic sphincter augmentation versus fundoplication for gastroesophageal reflux disease: systematic review and pooled analysis

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SUMMARY. **Magnetic sphincter augmentation (MSA) has been proposed as a less invasive, more appealing alternative intervention to fundoplication for the treatment of gastroesophageal reflux disease (GERD). The aim of this study was to evaluate clinical outcomes following MSA for GERD control in comparison with laparoscopic fundoplication. A systematic electronic search for articles was performed in Medline, Embase, Web of Science, and Cochrane Library for single-arm cohort studies or comparative studies (with fundoplication) evaluating the use of MSA. A random-effects meta-analysis for postoperative proton pump inhibitor (PPI) use, GERD-health-related quality of life (GERD-HRQOL), gas bloating, ability to belch, dysphagia, and reoperation was performed. The systematic review identified 6 comparative studies of MSA versus fundoplication and 13 single-cohort studies. Following MSA, only 13.2% required postoperative PPI therapy, 7.8% dilatation, 3.3% device removal or reoperation, and esophageal erosion was seen in 0.3%. There was no significant difference between the groups in requirement for postoperative PPI therapy (pooled odds ratio, POR = 1.08; 95%CI 0.40–2.95), GERD-HRQOL score (weighted mean difference, WMD = 0.34; 95%CI −0.70–1.37), dysphagia (POR = 0.94; 95%CI 0.57–1.55), and reoperation (POR = 1.23; 95%CI 0.26–5.8). However, when compared to fundoplication MSA was associated with significantly less gas bloating (POR = 0.34; 95%CI 0.16–0.71) and a greater ability to belch (POR = 12.34; 95%CI 6.43–23.7). In conclusion, magnetic sphincter augmentation achieves good GERD symptomatic control similar to that of fundoplication, with the benefit of less gas bloating. The safety of MSA also appears acceptable with only 3.3% of patients requiring device removal. There is an urgent need for randomized data directly comparing fundoplication with MSA for the treatment of GERD to truly evaluate the efficacy of this treatment approach.**

KEY WORDS: **fundoplication, gastroesophageal reflux disease, magnetic sphincter augmentation.**

INTRODUCTION

Gastroesophageal reflux disease (GERD) represents a significant burden on the Western health-care system, affecting up to 20% of adults, with the incidence on the increase.[1,2] Not only does this have a negative impact on a patient's health-related quality of life, but GERD has also been associated with a significant increase in risk of developing esophageal adenocarcinoma.[3] Traditional management of GERD incorporates lifestyle and dietary modification, followed by antireflux medication (proton pump inhibitors, PPIs, or histamine antagonists) and culminates in surgery for incessant symptoms or pathological complications.[4] The REFLUX randomized clinical trial suggested that surgery offers the most effective symptom control at five years of follow-up, as well as being the most cost-effective treatment strategy.[4–5] Recent evidence has also emerged that suggests that the long-term use of antireflux medication may be associated with dementia, renal pathology, and fractures.[6]

Laparoscopic fundoplication is currently the gold standard of surgical treatment for managing GERD, which can be performed either as a 360° (Nissen) or a partial (Toupet or anterior) fundoplication. According to guidelines from the Society of American Gastrointestinal and Endoscopic Surgeons and the European Association of Endoscopic Surgery, there is no convincing evidence at present to suggest one surgical procedure is superior to the

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META ANALYSIS

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Magnetic sphincter augmentation in treating refractory gastroesophageal reflux disease: A systematic review and meta-analysis

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Objective: In this systematic review and meta-analysis we aimed to determine the efficacy and safety of magnetic sphincter augmentation (MSA) in the management of refractory gastroesophageal reflux disease (rGERD).

Methods: Literature search was conducted in PubMed, the Cochrane Library, EMBASE, Web of Science, OpenGrey and ClincalTrials.gov for single-arm studies evaluating the efficacy and safety of MSA in rGERD or comparative studies with proton pump inhibitor (PPI) or laparoscopic Nissen fundoplication (LNF) serving as the control published until April 2020. Primary outcome was the rate of postoperative PPI use, and secondary outcomes included postoperative GERD-health-related quality of life (GERD-HRQL), normalization of acid exposure time (AET) and incidence of procedure-related adverse events (AE).

Results: Ten single-arm studies, one randomized controlled trial and three cohort studies involving 1138 participants were included. Post-MSA PPI withdrawal, significant GERD-HRQL improvement and AET normalization were achieved in 87.0%, 88.0% and 75.0% of the patients, respectively. The incidence of postoperative dysphagia was 29% and endoscopic dilation was required in 7.4% of patients undergoing MSA. MSA showed a better efficacy in symptom control than PPI (PPI cessation: 91% vs 0%; GERD-HRQL improvement: 81% vs 8%) and similar effectiveness but a lower risk of gas-bloat syndrome (risk ratio [RR] 0.69, 95% confidence interval [CI] 0.51-0.93, $P = 0.01$) and better reserved ability to belch (RR 1.48, 95% CI 0.76-2.86, $P = 0.25$) compared with LNF.

Conclusions: MSA was an effective and safe therapy for rGERD. Well-designed randomized trials that compare the efficacy of MSA with other therapies are needed.

KEYWORDS
gastroesophageal reflux disease, laparoscopic anti-reflux surgery, magnetic sphincter augmentation, refractory gastroesophageal reflux disease

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AGA Clinical Practice Update on the Personalized Approach to the Evaluation and Management of GERD: Expert Review

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Abstract

BACKGROUND & AIMS: As many as one-half of all patients with suspected gastroesophageal reflux disease (GERD) do not derive benefit from acid suppression. This review outlines a personalized diagnostic and therapeutic approach to GERD symptoms.

METHODS: The Best Practice Advice statements presented here were developed from expert review of existing literature combined with extensive discussion and expert opinion to provide practical advice. Formal rating of the quality of evidence or strength of recommendations was not the intent of this clinical practice update.

BEST PRACTICE ADVICE 1: Clinicians should develop a care plan for investigation of symptoms suggestive of GERD, selection of therapy (with explanation of potential risks and benefits), and long-term management, including possible de-escalation, in a shared-decision making model with the patient.

BEST PRACTICE ADVICE 2: Clinicians should provide standardized educational material on GERD mechanisms, weight management, lifestyle and dietary behaviors, relaxation strategies, and awareness about the brain-gut axis relationship to patients with reflux symptoms.

BEST PRACTICE ADVICE 3: Clinicians should emphasize safety of proton pump inhibitors (PPIs) for the treatment of GERD.

BEST PRACTICE ADVICE 4: Clinicians should provide patients presenting with troublesome heartburn, regurgitation, and/ or non-cardiac chest pain without alarm symptoms a 4- to 8-week

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Supplementary Material

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trial of single-dose PPI therapy. With inadequate response, dosing can be increased to twice a day or switched to a more effective acid suppressive agent once a day. When there is adequate response, PPI should be tapered to the lowest effective dose.

BEST PRACTICE ADVICE 5: If PPI therapy is continued in a patient with unproven GERD, clinicians should evaluate the appropriateness and dosing within 12 months after initiation, and offer endoscopy with prolonged wireless reflux monitoring off PPI therapy to establish appropriateness of long-term PPI therapy.

BEST PRACTICE ADVICE 6: If troublesome heartburn, regurgitation, and/or non-cardiac chest pain do not respond adequately to a PPI trial or when alarm symptoms exist, clinicians should investigate with endoscopy and, in the absence of erosive reflux disease (Los Angeles B or greater) or long-segment (≥3 cm) Barrett's esophagus, perform prolonged wireless pH monitoring off medication (96-hour preferred if available) to confirm and phenotype GERD or to rule out GERD.

BEST PRACTICE ADVICE 7: Complete endoscopic evaluation of GERD symptoms includes inspection for erosive esophagitis (graded according to the Los Angeles classification when present), diaphragmatic hiatus (Hill grade of flap valve), axial hiatus hernia length, and inspection for Barrett's esophagus (graded according to the Prague classification and biopsied when present).

BEST PRACTICE ADVICE 8: Clinicians should perform upfront objective reflux testing off medication (rather than an empiric PPI trial) in patients with isolated extra-esophageal symptoms and suspicion for reflux etiology.

BEST PRACTICE ADVICE 9: In symptomatic patients with proven GERD, clinicians should consider ambulatory 24-hour pHimpedance monitoring on PPI as an option to determine the mechanism of persisting esophageal symptoms despite therapy (if adequate expertise exists for interpretation).

BEST PRACTICE ADVICE 10: Clinicians should personalize adjunctive pharmacotherapy to the GERD phenotype, in contrast to empiric use of these agents. Adjunctive agents include alginate antacids for breakthrough symptoms, nighttime H2 receptor antagonists for nocturnal symptoms, baclofen for regurgitation or belch predominant symptoms, and prokinetics for coexistent gastroparesis.

BEST PRACTICE ADVICE 11: Clinicians should provide pharmacologic neuromodulation, and/or referral to a behavioral therapist for hypnotherapy, cognitive behavioral therapy, diaphragmatic breathing, and relaxation strategies in patients with functional heartburn or reflux disease associated with esophageal hypervigilance reflux hypersensitivity and/or behavioral disorders.

BEST PRACTICE ADVICE 12: In patients with proven GERD, laparoscopic fundoplication and magnetic sphincter augmentation are effective surgical options, and transoral incisionless fundoplication is an effective endoscopic option in carefully selected patients.

BEST PRACTICE ADVICE 13: In patients with proven GERD, Roux-en-Y gastric bypass is an effective primary anti-reflux intervention in obese patients, and a salvage option in non-obese patients, whereas sleeve gastrectomy has potential to worsen GERD.

BEST PRACTICE ADVICE 14: Candidacy for invasive anti-reflux procedures includes confirmatory evidence of pathologic GERD, exclusion of achalasia, and assessment of esophageal peristaltic function.

Keywords

Ambulatory Reflux Monitoring; Gastroesophageal Reflux Disease; Proton Pump Inhibitors

The prevalence of symptomatic gastro-esophageal reflux disease (GERD) is rising, with more than 30% of United States adults reporting at least weekly symptoms.[1,2] Symptoms of GERD encompass heartburn or regurgitation (typical esophageal symptoms), non-cardiac chest pain (atypical esophageal symptom), and a myriad of extra-esophageal symptoms which include cough, dysphonia, sore throat, and globus.[3] Further, symptoms can arise from coexisting or confounding pathophysiology such as mechanical defects, physiologic abnormalities, heightened nociception, and hypervigilance. Despite heterogeneous presentations and pathogeneses, patients with GERD have historically been managed in a similar catch-all fashion, often in the absence of objective abnormalities. Up to 50% of patients, however, do not derive adequate relief with empirical proton pump inhibitor (PPI) therapy.[4–6] Drivers of inadequate response include absence of pathologic GERD to begin with or symptom pathophysiology that is insufficiently targeted with acid suppression.[7] In recognition of this problem, the current care paradigm has shifted towards a personalized approach to the evaluation and management of GERD symptoms.[8] This Clinical Practice Update (CPU) provides best practice advice for a personalized diagnostic and therapeutic approach to GERD.

Methods

This expert review was commissioned jointly by the American Gastroenterological Association (AGA) Institute Clinical Practice Updates Committee, the AGA Center for GI Innovation and Technology (CGIT), and the AGA Governing Board to provide timely guidance on a topic of high clinical importance to the AGA membership. The AGA CGIT Consensus Conferences bring together content experts, stakeholders (industry, regulatory, and payor), along with a patient advocate to discuss current needs and gaps in innovation relevant to the topic. This is an exhaustive, comprehensive didactic and discussion session created to provide a novel interactive environment to foster the AGA CGIT mission. The topic of this CPU was thoroughly discussed by expert faculty contributors selected by AGA CGIT, industry representatives and patient advocates at the conference organized and hosted by AGA CGIT. The content of this expert review was generated, discussed, and voted upon by the expert faculty contributors at a closed-door meeting during the AGA CGIT conference. All faculty contributors provided up-to-date declaration of conflicts of interest to ensure credibility of this document, and signed off on the final manuscript, which underwent internal peer review by the AGA Institute Clinical Practice Updates Committee as well as external peer review through standard procedures of *Clinical Gastroenterology and Hepatology*.

LCD - Select Minimally Invasive GERD Procedures (L35080)

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Removed hyperlink for U.S. Food and Drug Administration (FDA) in the Bibliography section.

CMS National Coverage Policy

Language quoted from Centers for Medicare and Medicaid Services (CMS), National Coverage Determinations (NCDs) and coverage provisions in interpretive manuals is italicized throughout the policy. NCDs and coverage provisions in interpretive manuals are not subject to the Local Coverage Determination (LCD) Review Process (42 CFR 405.860[b] and 42 CFR 426 [Subpart D]). In addition, an administrative law judge may not review an NCD. See Section 1869(f)(1)(A)(i) of the Social Security Act.

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Title XVIII of the Social Security Act (SSA):
Section 1862(a)(1)(A) excludes expenses incurred for items or services which are not reasonable and necessary for the diagnosis or treatment of illness or injury or to improve the functioning of a malformed body member.

Section 1833(e) prohibits Medicare payment for any claim which lacks the necessary information to process the claim.

Section 1862(a)(7) excludes routine physical examinations, unless otherwise covered by statute.

Code of Federal Regulations:
42 CFR, Section 410.32, indicates that diagnostic tests may only be ordered by the treating physician (or other treating practitioner acting within the scope of his or her license and Medicare requirements) who furnishes a consultation or treats a beneficiary for a specific medical problem and who uses the results in the management of the beneficiary's specific medical problem. Tests not ordered by the physician (or other qualified non-physician provider) who is treating the beneficiary are not reasonable and necessary (see Sec. 411.15(k)(1) of this chapter).

Coverage Guidance

Coverage Indications, Limitations, and/or Medical Necessity

Indications:

EsophyX™ is a device for performing transoral incisionless fundoplication surgery (TIF) for treating gastroesophageal reflux disease. This procedure reconstructs the valve at the top of the stomach that helps prevent acid reflux.

Benefits are not available for endoluminal treatment for Gastroesophageal Reflux Disease (GERD) using the Stretta® procedure, the Bard EndoCinch™ Suturing System, Plicator™, Enteryx® or similar treatments as these procedures are not considered reasonable and necessary for the diagnosis or treatment of an injury or disease. Coverage is not available for LINX® Reflux Management System, which is not a true endoluminal treatment but is also not

considered reasonable and necessary for the diagnosis or treatment of an injury or disease.

Currently, these procedures other than TIF are considered non-covered due to the fact that current peer-reviewed literature does not support the long-term efficacy and long-term safety of the services. Claims will be denied as "not proven effective."

Limitations:

For TIF, Coverage is not extended to:

1. any patient who has recurrent symptoms or other evidence of failure following a prior TIF. These procedures (repeat TIF) would be considered investigational at this time.
2. any patient with a hiatal hernia greater than 2 cm, except where the hernia has been reduced to 2 cm or less by a successful laparoscopic hernia reduction procedure prior to the TIF procedure. (Based on (FDA) approval).
3. any GERD patients with BMI > 35, esophagitis LA grade >B, Barrett's esophagus > 2 cm, and presence of achalasia or esophageal ulcer or has not been on an appropriate trial of proton pump inhibitors.

Summary of Evidence

Summary of evidence for TIF:

As noted above, transoral incisionless fundoplication surgery is a method for treating gastroesophageal reflux disease. This procedure reconstructs the valve at the top of the stomach that helps prevents acid reflux.

1. Anti-Reflux Surgery Supplement to Endogastric Solutions TIF ESOPHYX Reconsideration Request NGS MAC, April 2017. This is not a peer-reviewed publication but a summary of what the procedure is and a summary of selective publications. Thus, this is not a peer-reviewed publication indexed in the U.S. National Library of Medicine of the National Institutes of Health and thus not valid as supportive literature.

2. Hakansson B., Montgomery M., Cadiere G, et al. Randomised clinical trial: transoral incisionless fundoplication vs. sham intervention to control chronic GERD. Alimentary Pharmacology and Therapeutics. 2015 John Wiley & Sons Ltd. This publication is indexed in the U.S. National Library of Medicine of the National Institutes. The study was blinded and divided equally into TIF and sham procedures. While the follow up period was only six (6) months, the time (average days) in remission offered by the TIF procedure (197) was significantly longer compared to those submitted to the sham intervention (107), $P < 0.001$. After 6 months 13/22 (59%) of the chronic GERD patients remained in clinical remission after the active intervention. Likewise, the secondary outcome measures were all in the TIF2 procedure. No safety issues were raised.

3. Stefanidis G, Viazis N, Kotsikoros N. Long-term benefit of transoral incisionless fundoplication using the esophyx device for the management of gastroesophageal reflux disease responsive to medical therapy. Diseases of the Esophagus (2017) 30, 1–8. This publication is indexed in the U.S. National Library of Medicine of the National Institutes of Health. The study initially had 45 patients who had the TIF procedure and were followed for a mean of 59 months (range 36–75). Only one patient had a complication during surgery and thus was excluded. The 44 patients all had follow-up upper endoscopy at 6 months, 1 year, and 3–5 years postoperatively. Seventy-two point seven percent that completed the study follow up reported elimination of their main symptom, without the need for PPI administration (none PPI usage). Six more patients (13.6%), five with heartburn, and one with regurgitation reported half PPI dose taken for <50% of the preceding follow up period (occasional PPI usage), while six more patients (four with heartburn, one with regurgitation, and one with chest pain) reported full or half PPI dose taken for more than 50% of the preceding follow up period (daily PPI usage). This paper supports the procedure.

4. Technology Coverage Statement on Minimally Invasive Surgical Options for Gastroesophageal Reflux Disease April 2016. This is a position paper from the American Gastrological Association based on its reviews of TIF publications. It is strongly supportive.

5. Clinical Spotlight Review: Endoluminal Treatments for Gastroesophageal Reflux Disease (GERD)sages.org/publications/guidelines/endoluminal-treatments-for-gastroesophageal-reflux-disease-gerd. This is a statement from the Board of Governors of the Society of American Gastrointestinal and Endoscopic Surgeons (SAGES) on Mar 2017. Its recommendation is: Based on existing evidence, TIF can be performed with an acceptable safety risk in appropriately selected patients. The procedure leads to better control of GERD symptoms compared with PPI treatment in the short term (6 months), but appears to lose effectiveness during longer term follow-up and is associated with moderate patient satisfaction scores. Objective: GERD measures improve similarly after TIF 2.0 compared with PPI. No comparative, controlled trials exist between TIF and surgical fundoplication, but preliminary evidence suggests that the latter can be used safely after TIF failure. (Per SAGES, this is level of evidence +++, strong recommendation)

6. Vaezi M, Bril J, Mills M, et al. An Episode Payment Framework for Gastroesophageal Reflux Disease. Gastroenterology 2016;150:1019–1025. This is an economic and coding paper and not a clinical paper. It is not supportive.

7. Hunter JG, Kahrilas PJ, Bell RCW, et al. Gastroenterology. 2015 Feb;148(2):324-333. The largest RCT with the lowest risk of bias is an industry-sponsored double-blind sham controlled multicenter study (RESPECT) that evaluated transoral fundoplication in patients whose symptoms were not well-controlled on proton pump inhibitors (PPIs). Out of 696 patients screened, 129 met inclusion and exclusion criteria and were randomized in a 2:1 ratio; 87 patients received transoral fundoplication combined with six months of placebo and 42 patients received sham surgery with six months of daily PPI therapy (sham/PPI). Control of esophageal pH improved after TIF (mean 9.3% before and 6.3% after; P < .001), but not after sham surgery (mean 8.6% before and 8.9% after). This is supportive.

8. Bell RCW, Barnes WE, Carter BJ, et al. Transoral incisionless fundoplication: 2-year results from the prospective multicenter U.S. study. AM Surg. 2014 Nov;80(11);1093-1105. This 24-month follow-up has been reported from a prospective multicenter registry of patients with chronic GERD who received transoral fundoplication using the EsophyX2 system with SerosaFuse fasteners. For the 100 consecutive patients who were treated in this community-based study, the median GERD symptom duration was nine years (range, one to 35 years), the median duration of PPI use was seven years (range, one to 20 years), and 92 percent of patients had incomplete symptom control despite maximal medical therapy. This three-year study provides evidence to demonstrate sustainable improvement in health outcomes, symptom relief, decrease in PPI utilization and improvement in esophageal pH with transoral fundoplication. This is supportive.

Summary of evidence for Stretta®:

The Stretta® procedure is an endoluminal treatment for GERD in which radiofrequency energy is delivered to smooth muscle of the lower esophageal sphincter (LES). A flexible catheter equipped with special needle electrodes for precise energy delivery is placed by mouth into the esophagus and carefully controlled radiofrequency energy is then delivered to the LES and gastric cardia, creating thermal lesions. The manufacturer maintains that the changes that occur immediately, and over time, result in a "tighter" LES and a less compliant gastric cardia. Additionally, the interruption of nerve pathways in the LES area is believed to reduce the incidence of inappropriate LES "relaxations," leading to an improvement in GERD symptoms.

Evidence reviewed based on reconsideration request received October 17, 2019

Gregory et al (2016) This is an economic paper, not a clinical paper. Medicare does not use cost as a reason to cover

or deny a treatment. This does not support changing the LCD.

Funk et al (2015) This is an economic paper, not a clinical paper. Medicare does not use cost as a reason to cover or deny a treatment. This has been previously reviewed by this contractor and this does not support changing the LCD.

Noar et al (2014) has previously been reviewed by this contractor and this does not support changing the LCD.

Dughera et al (2014) has been previously reviewed by this contractor and thus not any new support.

Dughera et al (2011) This old study involved 69 patients but only 56 of them reached a 48 month follow up. It excludes patients with large hiatal hernias, severe grade C-D erosive esophagitis despite medical treatment, Barrett esophagus, or primarily extraesophageal manifestations of GERD (e.g., asthma). There was no control group. The mean age was only 42+/- 14 years. Thus, these patients were much younger than typical Medicare beneficiaries. The radiofrequency treatment significantly improved heartburn scores, GERD-specific quality of life scores, and general quality of life scores at 24 months and 48 months in 52 out of 56 patients (92.8%) and substantially reduced the use of proton pump inhibitors. The authors stated there was no conflict of interest. This paper reflects a small uncontrolled study and gives minimal support to Stretta.

Noar et al (2007) This old study reported on 96 (out of 109) consecutive patients who were followed for four years. The mean age was only 51 which is much younger than typical Medicare beneficiaries. All patients had the diagnosis of GERD confirmed by finding erosive esophagitis at upper endoscopy (Los Angeles grade A or higher) or abnormal acid contact time detected at ambulatory esophageal pH testing. Patients with erosive esophagitis were maintained on medical therapy until all erosions had healed. Esophageal motility was performed in all patients to exclude those patients with achalasia. Patients with metaplasia were treated and followed according to standard Barrett's protocol with EGD and 4-quadrant biopsy at each follow-up. Gastric emptying scans (GES) were performed on all patients and 31 of 109 demonstrated abnormal emptying. The fact that 1/3rd of the patients had this concurrent problem is a concern. Patients with stenosis, stricture, or ulceration of the pyloric valve were excluded. Medication usage decreased significantly from 100% of patients on twice daily PPI therapy at baseline to 75% of patients showing elimination of medications or only as-needed use of antacids/over-the-counter PPIs at 48 months.

DISCLOSURE: Noar M.D. has served in the capacity as a member of the clinical advisory board and has received honoraria for speaking and training for Curon Medical, Inc, and has no other conflicts of interest to disclose. Lotfi-Emran S. has no conflicts of interest to disclose. This paper suffers from patients not being the typical age for Medicare beneficiaries and being uncontrolled. Thus, it gives minimal support for Stretta.

Reymunde et al (2007) This is another old paper with the authors following 83 consecutive patients with persistent GERD symptoms for 48 months. It was a nonrandomized study, lacked a control arm, and lacked data of 24-hour pH. These patients experience a partial response to daily PPI or other antisecretory medications. All patients underwent a careful evaluation to document the diagnosis of GERD by ambulatory esophageal pH testing, demonstrating abnormal esophageal acid exposure time or the presence of erosive esophagitis at endoscopy. Barium radiography or endoscopy were used to exclude patients with a hiatal hernia larger than 3 cm. Endoscopy was also used to exclude patients with severe erosive esophagitis (greater than Los Angeles grade B) or long-segment Barrett's esophagus. Esophageal manometry was performed in most patients to exclude those patients with very poor lower esophageal sphincter (LES) function (LES pressure <5 mm Hg) or aperistalsis. The authors did not mention the ages of the participants. None of the authors hold any significant financial interest in the product being discussed that would represent a conflict of interest. This paper suffers from the age of the patients not being described and being uncontrolled. This gives minimal support for Stretta.

Torquati et al (2004) This very old uncontrolled paper reported on 82 patients, and 41 of them (50%) had a follow-

up period longer than 18 months. The authors note, "Follow-up surveys were completed by 36 patients (88%) during a mean follow-up period of 27.1 ± 3.7 months." Thus, there really were only 36 patients not 82 followed and the period was quite short. The mean age of the 82 patients was 46.8 +/- 18.3 years. The authors do not explain if the age of the 36 patients followed were of the same age. Thus, these patients were much younger than typical Medicare beneficiaries. Only eleven patients returned for 24-h pH testing at a mean of 27.4 ± 4.1 months. Acknowledgments: Dr. Alfonso Torquati is the recipient of a Master of Science in Clinical Investigation grant from Vanderbilt University School of Medicine. Dr. William Richards is a member of the Curon Medical Scientific Advisory Board and has received grant support from Curon Medical. Thus, gives very minimal support for Stretta.

Herman et al (2014) This is not a human study. It does not pertain to the esophagus. This is not supportive medical literature.

Perry et al (2012) This is a meta analysis English literature, indexed in PubMed and Medline databases (1966 to 2010). Sixty-eight articles were originally identified but 48 were rejected. Thus, there were only 20 articles and only two of them were random sham-controlled trials. The mean age was 47.5±7.2 years which is not typical of Medicare beneficiaries. The mean follow-up interval was 17.1±15.5 months: thus only 1.5 years. The included studies were published between 2000 and 2010 and contained 1441 patients with a mean follow up interval of 15 months. Radiofrequency energy delivery to the LES produced significant improvements in GERD symptoms and both disease-specific and global QOL. Esophageal acid exposure was improved, but not normalized after treatment; and the Stretta procedure did not significantly increase LES pressure. They noted, "The Stretta procedure has demonstrated the ability to reduce, but not consistently normalize esophageal acid exposure." They also noted the "definition of the appropriate patient populations for Stretta therapy remains controversial." The authors noted that their meta-analysis was limited by differences in methodology and definition of criteria for some variables between studies, and absence of blindness in most of the included studies. The authors did not include a formal assessment of methodologic quality. The beneficial effects of Stretta were based on single-arm, pre–post design studies, which are prone to regression to the mean, making the efficacy of Stretta susceptible to a high risk of bias. Regression to the mean is a statistical phenomenon that affects all pre-experimental designs that include, or analyze data from, participants selected on the basis of an extreme, usually low or high, pre-intervention condition. Although there is well-recognized value to using single-group studies to identify and quantify the occurrence of adverse events, the role of these studies in evaluating efficacy and safety is not well developed. Therefore, the nearly unanimous efficacy of Stretta for the management of GERD observed in single-arm studies is not appropriate for informed decision making. Another drawback is that they did not assess the quality of study methodologies, which is key to any systematic review. The heterogeneity of the study population across these reports may also have influenced the interpretation of the pooled results. We agree with their conclusion that "Larger and longer-term studies are required to establish the durability of the treatment effect, and to identify the patient populations that gain the greatest benefit from this treatment." There is no mention of disclaimers.

Fass et al (2017) All potentially relevant articles were examined to determine their eligibility using the following inclusion criteria: (1) at least 3 months follow-up, (2) study design was controlled trial or cohort study and (3) sufficient data for at least one of the six selected outcome variables (defined below). Exclusion criteria included patients from special populations (e.g. obese, pediatric or gastroparesis patients), (2) patients undergoing combined treatment modalities, (3) letters, editorials, review articles and animal studies and (4) non-English publications. Overall, 28 studies met the selection criteria, and each was crosschecked with studies included in previous Stretta meta-analyses to ensure that all relevant studies had been captured. The authors identified three self-reported symptom variables and three physiological markers that appear with sufficient frequency in the studies to enable meta-analysis: (1) PPI use, (2) GERD/HRQL (Health Related Quality of Life), (3) heartburn score, (4) presence of erosive esophagitis, (5) esophageal acid exposure and (6) LES basal pressure. Data from the HRQL instrument—a validated scale for GERD symptom relief that ranges from 0 (asymptomatic) to 50 (incapacitating symptoms) [10, 11]—were reported in only 11 studies. Heartburn score was reported in 13 studies but different scales were used. Erosive esophagitis data were extracted from the 12 studies that performed upper endoscopy at baseline and follow-up. Eleven studies reported esophageal acid exposure time. Nine studies reported LES basal pressure (mmHg). There

were four randomized controlled trials. This is a bit confusing since on Clinicaltrials.gov there currently are only five registered trials with "Stretta" in their titles. One is from India and its status is "Unknown." A second was "Terminated" but was for Management of Reflux After Sleeve [Gastrectomy] Using Stretta. This is not a typical use anyway. The third is from China and its status is "Recruiting." The fourth is "Completed." It is from France and entitled "Stretta In Reflux Uncontrolled by IPP (SIRUP)." There is no mention of the results being published. The fifth (also from France) is "Completed (in 2007)" and entitled Evaluation of the Efficiency of Radiofrequency in the Treatment of Gastroesophageal Reflux Disease. There is no mention of the results being published. The sixth and final registered clinical trial is from China and entitled "A New System for GERD Diagnosis and Treatment (EAISMLP)". It is not yet recruiting. Thus, it is difficult to understand the discovered randomized clinical trials or their significance. Collectively at baseline, 97.1% (1743) of patients in the Stretta group were using PPI. After Stretta treatment, 49% (850) of these patients were using PPI. Thus, this seems to negate some of the advantages of the procedure. Concerning HRQL effects, the sham procedure had 1/3rd the effect of the true treatment. Concerning heartburn scores, treatment effect was not found for either the Stretta subgroup or the control subgroup. However, when pooled, the Stretta arm of the RCT studies with the cohort subgroup, Stretta treatment reduced (thus improved) the heartburn standardized score significantly. For the random effects model, Stretta treatment marginally reduced the pooled estimate of frequency of erosive esophagitis at follow-up in all Stretta subgroups. Stretta treatment reduced (thus improved) the pooled estimate of esophageal acid exposure. In the RCT subgroups, the pooled estimate of Stretta treatment effect compared to the sham treatment effect was not significantly different. However, in the cohort subgroup, the treatment effect in the cohort subgroup, the treatment effect was significant. For the effects on lower esophageal sphincter basal pressure. In the RCT subgroups, the pooled estimate of treatment effect for Stretta was not significantly different than sham group. Comparing Stretta procedures, sham procedures and laparoscopic fundoplication procedures the reported adverse event rate for the Stretta procedure was 0.93% and 7.18% for the LF procedure. For Stretta, small erosions and mucosal lacerations was the most frequent AE at less than 1%, while for LF procedures, subcutaneous emphysema was the most frequent AE at approximately 3%. The authors noted as a limitation of their study include the lack of contemporaneous control groups in most of the studies. The four RCTs considered alone have limitations: they enrolled a total of 92 Stretta-treated patients, whereas the cohort trials and registry enrolled 2376 Stretta-treated patients. Only one of the outcome measures (erosive esophagitis) was measured in all four RCTs. Three of the outcome measures (HRQL, heartburn, PPI use) were measured in only two RCTs. Furthermore, the longest follow-up time in the RCTs was 12 months, whereas cohort studies included data up to 120 months (average 23 months). They concluded that their meta-analysis demonstrated that the Stretta procedure reduced the use of PPIs while improving esophageal acid exposure time, heartburn symptoms, and HRQL. The reduction in erosive esophagitis incidence was not statistical significance under the random effects but did reach statistical significance under fixed effects. There was no significant effect on LES basal pressure. Disclosures: Dennis J. Scotti is a part-time consultant with Baker Tilly Virchow Krause, LLC. Baker Tilly Virchow Krause, LLC is a Business Advisor to Mederi Therapeutics, Inc. David A. Gregory is a principal with Baker Tilly, a business advisor to Mederi Therapeutics. Frederick Cahn is a principal with BioMedical Strategies, a business advisor to Baker Tilly. Ronnie Fass is an advisor to Ironwood and Mederi Therapeutics, Speaker for AstraZeneca, Dr. Reddy, Mederi Therapeutics and Takeda and receives research grant from Ironwood. This paper gives minimal support for Stretta.

CareFirst Medical Policy Reference Manual Medical Policy

HIGHMARK Commercial Medical Policy – Delaware – S-145-010

HIGHMARK Commercial Medical Policy – Pennsylvania – S-145-020

HIGHMARK Commercial Medical Policy – West Virginia – S-145-018

Blue Cross Blue Shield of North Dakota

None of these commercial insurance decisions are in anyway relevant to Medicare coverage. Of note, other companies such as CIGNA do not cover Stretta ("Each of the following endoscopic anti-reflux procedures for gastroesophageal reflux disease (GERD), or any other indication, is considered experimental, investigational or unproven:

- radiofrequency energy to the gastroesophageal junction (e.g., Stretta® System)"

Commercial insurance decisions include contract language as part of their decision process while Medicare uses evidence based methods. The Novitas Local Coverage Determination (LCD): Upper Gastrointestinal Endoscopy (Diagnostic and Therapeutic) (L35350) does not seem to mention Stretta. Of note, none of the other six Medicare contractors cover Stretta.

A review article entitled Stretta Radiofrequency Treatment for GERD: A Safe and Effective Modality without any date of publication, journal name or any information appears to be an unpublished draft and does not support Stretta.

UpToDate. This mentions Stretta but not does not give any actual support or recommendation. However, this is not peer-reviewed published literature. This also erroneously states "The Stretta system was approved by the Food and Drug Administration (FDA) in the United States in 2000." We find no evidence that the FDA approved this device, although it was merely cleared. If we are incorrect, we would appreciate knowing the FDA premarketing number. However we note that the Mederi Stretta Catheter and Accessory Kit, Sterile (K152317) was subject to a recall in 2017 but apparently this has been terminated. Thus, this is not supportive.

Triadafilopoulos (2016) This review paper states for Stretta, "Despite the aforementioned favorable results with Stretta in open, uncontrolled trials, the assessment of controlled data has questioned the value of the procedure. Using the standards of the Cochrane collaboration, a systematic meta-analysis of trials evaluated the efficacy of Stretta for the management of GERD. They analyzed normalization of esophageal pH, augmentation of lower esophageal sphincter pressure (LESP), health-related quality of life (HRQL), and PPI use. The pooled data from four trials and 153 analyzed patients showed no differences between Stretta and sham or PPI therapy for the outcomes of mean esophageal acid exposure LESP, ability to stop PPIs, or HRQL." Conflict of Interest: George Triadafilopoulos reports that he has an equity position with Mederi Therapeutics, C2 Therapeutics, and EndoStim. This article does not support coverage of Stretta.

Nabi and Reddy (2016) The authors note, "recently published systemic review and meta-analyses, which included four RCTs, showed no difference between Stretta versus sham or PPIs in patients with GERD for the outcomes of EAET, LES pressure, ability to stop PPIs, or HRQL.[22] However, one of the criteria for efficacy in this review was normalization of pH (pH <4 exposure time <4%), which is rather stringent and not achieved even in patients who respond successfully to PPIs.[23] Moreover, the authors agree that the overall quality of evidence from RCTs on the efficacy of the Stretta procedure was extremely low." Conflicts of Interest: The authors have no financial conflicts of interest. This article does not support coverage of Stretta.

Chang (2015) This is not a medical article in a peer reviewed medical journal indexed in PubMed of the US National Library of Medicine National Institutes of Health. It is really an OpEd and does not support changing the LCD.

Subramanian and Triadafilopoulos (2015) This is a short review and offers minimal support for Stretta.

de Souza et al (2018) This really is a case report of three patients who underwent Stretta in Sept 2017. The follow up period is not apparent, but since this was published in 2018, the follow up has to be extremely short. Declared conflict of interest of all authors: none. This three person "series" without follow up is not supportive of changing the current LCD.

Sandhu and Fass (2019) This is a very limited review of the literature concerning Stretta. Conflict of Interest: R Fass was a speaker for Mederi Therapeutics. DS Sandhu has no conflicts of interest to declare. This offers minimal support for Stretta.

Triadafilopoulos (2014) previously reviewed by this contractor and thus does not add any new support for changing the Stretta LCD.

Viswanath et al (2018) This paper was not found indexed in PubMed of the US National Library of Medicine National Institutes of Health. Thus, it is not supportive.

Subramanian and Triadafilopoulos (2014) previously reviewed by this contractor and thus does not add any new support for changing the Stretta LCD.

Ayman et al (2010) previously reviewed by this contractor and thus does not add any new support for changing the Stretta LCD.

Corley et al (2003) previously reviewed by this contractor and thus does not add any new support for changing the Stretta LCD. The associated editorial on page 970 was noted.

Coron et al (2008) Forty-three (43) patients (30 men, mean age: 48 years) with PPI-dependent typical reflux symptoms were randomized to either RF (n = 23) or maintenance PPI therapy alone (n = 20). After randomization, seven patients were lost to follow-up or withdrew their consent to participate, leaving 36 patients available for PP analysis at 6 months. Between the 6th and 12th months, two patients in the control group were excluded from the study, leaving 34 patients available for the PP analysis at 12 months (fourteen in the control arm and 20 in the RA treatment arm). The mean age of participants was only 48 years old. At 12 months, ITT (intention-to-treat) analysis showed that 13 /23(56%) patients in the RF group were able to stop or decrease their PPI use vs. seven of 20 (35%) in the control group (P = 0.16). PP analysis confirmed these results with 13 /20 (65%) patients in the RF group being able to stop or decrease their PPI use vs. six of 16 (38%) in the control group (P = 0.10). Thus, this is not statistically significant. At 6 months, 16 /20 (80%) patients had <3 symptomatic episodes of GERD occurring per week in the RF group vs. six of 16 (40%) in the control group (P = 0.01) but no significant difference was noted at 12 months between both groups. Global REFLUX-QUAL and SF-36 scores were not significantly different between both groups at 6 and 12 months. However, two items of the REFLUX-QUAL, namely well-being and fears, were significantly better in the RF group compared with the PPI group at 6 months (P = 0.05 and P = 0.03), but this statistical difference remained at 12 months only for fears. Monitoring of PPI needs showed that the mean daily dose of PPI was significantly lower in the RF group compared with the control group at 6 and 12 months (12 _ 11 vs. 30 _ 19 mg /day; P = 0.01 and 16 _ 14 vs. 37 _ 30 mg/ day; P = 0.05 respectively). A 24 hour pH study performed at 6 months (off PPI therapy) showed that OAE was not significantly different between the RF and control groups. The absolute change in OAE from baseline to the 6-month assessment was not significantly different between the RF and the control group. In addition, upper GI endoscopy revealed that an esophagitis was noted in 10 (four grade A and six grade B) and seven patients (five grade A, one grade B and one grade C) of the RF and the control groups, respectively (P = 0.946). Declaration of personal interests: J. P. Galmiche has served as a speaker, a consultant and an advisory board member for AstraZeneca, Given Imaging, Pentax, Janssen-Cilag, Sanofi, Nycomed and has received research funding from AstraZeneca, Given Imaging, Janssen-Cilag France and Negma-Gild. F. Zerbib has served as a speaker and a consultant for AstraZeneca, Janssen-Cilag, Sanofi and has received research funding from

AstraZeneca, Janssen-Cilag France, Sandhill, Addex and Nycomed. P. Ducrotte´ has served as a speaker for AstraZeneca and Janssen-Cilag and has received research funding from Beaufour Ipsen Pharma and Sanofi. F. Ducrot has worked on the development of Janssen Pharmaceutical gastrointestinal drugs up to 1985, and has occasionally served as a speaker for AstraZeneca since. S. Bruley des Varannes has served as a speaker and a consultant for AstraZeneca, Janssen-Cilag, Sanofi, and has received research funding from AstraZeneca, Janssen-Cilag France, Medtronic and Danone. Declaration of funding interests: This work was supported in part by the Société Nationale Francaise de Gastro-Entérologie (SNFGE), INSERM and CHU of Nantes. The study was conducted independently of Curon Ltd with no interference of this company in the trial design or analysis of results. This study was old, short and small. The patients' mean age of 48 is far less than the typical Medicare beneficiary. The results were not impressive. This does not support the change in the LCD coverage.

Kalapala et al (2017) The study was registered at ClinicalTrials.gov (Identifier number: NCT02935881). Twenty (20) patients, followed for three months. Ten (10) underwent the Stretta procedure and 10 were controls (all were treated with standard dose of PPIs once daily. The mean age of the treated patients was 38.89 and the controls were 34.00. The primary outcome measure was the proportion of patients showing improvement in the quality of life and improvement in the frequency and severity of GERD symptoms (heartburn, regurgitation, chest pain, and cough). Secondary outcomes included LES pressure at esophageal manometry, reduction in medication use, and patient satisfaction. Data on these measures were collected through a questionnaire consisting of two questions: (1) Are you completely independent of PPIs? and (2) Are you satisfied with the treatment? Responses were graded on 6-point Likert scale. At baseline, only 20% (Stretta 20%; control 20%) of patients overall reported that they were satisfied with their quality of life. Three months after Stretta treatment, 80% reported satisfaction compared with only 30% in the control group. This is also reflected in the patient satisfaction response. Three months after treatment, an increase in lower esophageal sphincter pressure was observed in both Stretta treated as well as the control group. However, the difference between the groups was not significant. Conflict of interest: RK, HS, ZN, SD, RT, and DNR declare that they have no conflict of interest. This paper has too small of a treated number, too short of a follow up period, and too young of a populations (mean age of the treated patients 38.89 and controls 34.00) to support any change in the LCD.

Arts et al (2011) previously reviewed by this contractor and thus does support any change to the LCD.

SAGES. (2015) This review paper briefly mentions Stretta and notes, "However, although the esophageal acid exposure, as measured by the DeMeester score, was significantly reduced after treatment (44.4 vs 28.5, P Z .007), it did not normalize. In addition, no significant increase in lower esophageal sphincter pressure was observed. Adverse events were infrequent and typically minor. The technique appears to durably relieve GERD symptoms for up to 10 years in the majority of patients." This is a bit premature to state this since literature does not support this follow up. This paper gives very minimal support for Stretta.

Stefanidis (2017) Statement from the Board of Governors of the Society of American Gastrointestinal and Endoscopic Surgeons (SAGES) on Mar 2017. This paper has been previously reviewed by this contractor and thus does support any change to the LCD.

Auyang et al (2013) and the SAGES Guidelines Committee. These results were not based on the findings of a systematic review and have serious methodology issues in study conduct and analysis. For example, the systematic review did not perform a meta-analysis despite the availability of data from 2 randomized controlled trials. In addition, most of the studies were single-arm case series and did not involve a control or comparator, making it impossible to deduce the effect of the Stretta procedure. A key purpose of the systematic review and meta-analysis is to determine whether results are observed because of the intervention or because of bias, owing to poor study design. Therefore, assessment of the methodologic quality of included studies is an important requirement for a systematic review and is recommended by the Cochrane Collaboration. This paper has been previously reviewed by this contractor and thus does support any change to the LCD.

McClusky III et al (2007) previously reviewed by this contractor and thus does support any change to the LCD.

Mattar et al (2006) previously reviewed by this contractor and thus does support any change to the LCD.

Richards et al (2003) previously reviewed by this contractor and thus does not support any change to the LCD.

Noar et al (2016) The authors "prospectively assessed and compared patient reported outcomes in 18 refractory LNF patients and 81 standard refractory GERD patients that all underwent Stretta during 10-year follow-up. Patient-reported outcomes measured were GERD-HRQL (health-related quality of life), patient satisfaction scores, and daily medication requirements." Originally there were 149 patients who reached the 10 year follow up evaluation cutoff. However, 36 could not be contacted, 11 were deceased, and three declined. The mean age was 50 which is not the typical Medicare beneficiary age. This was a non-randomized open-label prospective comparative trial study which was conducted at a single center. There was inclusion of long-term pH or motility data. While the study was to compare the results of laparoscopic Nissen fundoplication patients who underwent Stretta and standard refractory GERD patients who underwent Stretta, the number of refractory LNF patients were only 18. This not a true clinical study of Stretta that was randomized. It is a comparative of treating poor results of a laparoscopic Nissen fundoplication. Disclosure: Dr. Mark D. Noar has received honoraria for speaking and training for Mederi Therapeutics Inc., and has no other conflicts of interest or financial ties to disclose. Patrick J. Squires and Sulman R. Khan have no conflicts of interest or financial ties to disclose. This paper is not supportive to changing the current policy.

Mederi (2018) This is an unpublished (does not appear on PubMed) proprietary evaluation of Stretta. Unpublished works are not acceptable as support for any Medicare review.

Lipka et al (2015). The authors searched MEDLINE and the Cochrane Central Register of Controlled Trials (The Cochrane Library) from inception until February 28, 2014, along with other databases, for randomized controlled trials of Stretta in patients with GERD. Primary outcomes were physiologic parameters of GERD, including normalization of esophageal pH values and augmentation of lower esophageal sphincter pressure (LESP). Secondary outcomes were health-related quality of life (HRQOL) and ability to stop the use of proton pump inhibitors (PPIs). For quality assurance purposes, two investigators were involved throughout the study. Data were pooled under a random-effects model. The systematic review was performed as per the standards of the Cochrane collaboration. They then collected data from 4 trials and a total of 165 patients (153 patients were analyzed). Three trials compared Stretta vs sham, and 1 trial compared Stretta with PPI therapy. The overall quality of evidence was very low. The pooled results showed no difference between Stretta and sham or management with PPI in patients with GERD for the outcomes of mean (%) time the pH was less than 4 over a 24-hour time course, LESP, ability to stop PPIs, or HRQOL. The authors concluded that in a meta-analysis of trials, Stretta for patients with GERD does not produce significant changes, compared with sham therapy, in physiologic parameters, including time spent at a pH less than 4, LESP, ability to stop PPIs, or HRQOL. The initial electronic search retrieved 136 references that were screened by title and abstract But after the final screening, 4 published studies met the predetermined inclusion criteria. The study by Arts et al was a single-center, randomized, controlled trial comparing Stretta with sham therapy in 22 patients (11 in each group). The study by Aziz et al was a multi-arm randomized trial comparing sham treatment vs single - and double dose Stretta. The randomized, multicenter, national, single-arm, cross-over study by Corley et al studied 64 patients assigned to Stretta (n = 35) or sham therapy (n = 29). Coron et al performed a multicenter international randomized controlled trial, with a parallel design, comparing Stretta and PPI therapy. Forty-three patients were assigned randomly to sham (n = 20) or Stretta (n = 23). The authors noted that the overall methodologic quality of the included studies was very low as determined by GRADE methodology and prone to high risk of bias. None of the included studies provided details on randomization sequence generation, blinding of patients, or outcome assessors. Only a fourth of studies provided details on allocation concealment and three fourths of studies had complete reporting of outcomes data. All included studies were prone to outcome reporting bias because none reported how many patients actually had complete alleviation of symptoms, normalization of pH, or

LES pressure. All included studies provided details on random error (ie, sample size calculations, a and b error, and expected difference). Conflicts of interest: Joel E. Richter is a consultant for Endostim, Inc and Givens Imaging. This paper does not support the use of Stretta.

Summary of evidence for EndoCinch™ Suturing System and the Plicator™:

The Bard EndoCinch™ Suturing System and the Plicator™ are intended for use in endoscopic placement of suture(s) in the soft tissue of the esophagus and stomach and for approximation of tissue for treatment of symptomatic gastroesophageal reflux disease. Substantial peer-reviewed evidence to fully support these assumptions needs to be published.

Summary of evidence for Enteryx®:

Enteryx® is an endoscopic, minimally-invasive procedure in which an ethylene vinyl alcohol polymer solution is injected into one's lower esophageal sphincter muscle using a small needle. This product was recalled by the FDA in September 2005 due to adverse patient events.

Summary of evidence for LINX® Reflux Management System:

LINX® Reflux Management System - a sphincter augmentation device designed to prevent reflux due to abnormal opening of the lower esophageal sphincter (LES). The system is comprised of a small flexible band of 10 to 18 interlinked titanium beads with magnetic cores. Using standard laparoscopic techniques, the band is placed around the esophagus at the level of the gastroesophageal junction. The magnetic attraction between the beads is intended to augment the lower esophageal sphincter to prevent gastric reflux into the esophagus without compressing the esophageal wall. Unlike the other procedures mentioned, this is extraluminal, not intraluminal.

1. Saino et al (2015) reported five-year results on the 44 implant procedures of the magnetic sphincter augmentation (MAS) first performed in the world. Safety and efficacy were evaluated in a prospective, multicenter study with patients serving as their own controls. Thirty-three of the 44 patients (75%) were followed-up at five years. Enrolled patients had an abnormal esophageal pH on ambulatory monitoring, typical GERD symptoms, had been taking daily PPIs, and were between 18 and 75 years of age. Patients were excluded if they had a large hiatal hernia (> 3 cm), Grade B or higher esophagitis (Los Angeles scale), a body mass index (BMI) > 35 kg/m2, Barrett's esophagus, motility disorders, gross esophageal anatomic abnormalities, or an allergy to titanium, stainless steel, nickel, or ferrous materials. Mean total of time the esophageal pH was < 4 was 11.9% at baseline and 4.6% at five years (P<.001), with 85% (28) of patients achieving a normal pH or a 50% reduction. Mean total GERD-HRQL scores improved from 25.7 to 2.9 (P<.001). Complete discontinuation of PPIs was achieved by 87.8% of patients. Most patients (90.9%) were satisfied with their condition at five years versus none at baseline. Side effects such as gas bloat and difficulty swallowing were no worse after the procedure. There were no long-term complications but there were three of the 44 patients (86.8%) that had a serious adverse event which resolved. Three devices were removed. Limitations of the study were noted as lack of a comparison group, loss of patients during the five-year follow-up, and lack of pH monitoring at all sites after the first year.
2. Ganz et al (2015) (in press) performed a prospective study of MAS safety and efficacy in the 100 adults who had GERD for six months or more, were partially responsive to daily proton pump inhibitors (PPIs), and had evidence of pathologic esophageal acid exposure. Exclusion criteria included a hiatal hernia > 3 cm, grade C or D esophagitis (Los Angeles scale), BMI > 35, Barrett's esophagus, or motility disorder. Eighty-five patients in 14 centers in the United States and The Netherlands were followed for five years serving as their own controls. The GERD-HRQL questionnaire was performed at baseline on and off PPIs and after the placement of the device. A 50% or greater reduction occurred in 83% at five years and a 50% or greater reduction of PPI use

occurred in 89.4%. Daily use of PPIs was 100% at baseline and 15.3% at five years with 75.3% reporting no use. All patients reported the ability to belch and vomit with no change in dysphagia. Symptoms of bloating/gas decreased from 52% to 8.3%. No device erosions occurred; seven percent (7%) were removed. Limitations of the study were stated as lack of esophageal pH testing and manometry beyond one year and no comparison group.

3. Warren et al (2015) performed a retrospective cohort study of patients with GERD undergoing placement of the MAS or a Nissen fundoplication (NF) at three high-volume esopohageal centers. Inclusion criteria included age of 18 – 85 years, a documented history of GERD at least partially responsive to PPIs, and positive pH testing. Excluded were those with a prior history of gastric or esophageal surgery, a hiatal hernia > 3cm, esophageal dysmotility and/or distal esophageal amplitude of < 35 mm Hg, and the visible presence of Barrett's or esophageal stricture. There were a total of 415 patients (201 MSA and 214 NF) compared at one year post-procedure. Although the patients were similar in age and gender, the NF patients had higher BMIs (40 vs. 32), dysphagia (39 vs. 27) DeMeester scores (39 vs. 34), microscopic Barrett's (31% vs 18%) and hiatal hernia (69% vs. 55%). At a one-year follow-up 354 patients (169 MSA and 185 NF) had significant improvement in GERD-HRQL scores. MSA patients had a greater ability to belch and vomit with less gas bloat. Propensity matched cases (144) showed similar GERD-HRQL scores. The differences in ability to belch or vomit and gas bloat persisted in favor of MSA but mild dysphagia was higher for MSA as was resumption of daily PPIs (24 vs. 12, p = 0.02). Satisfaction rates were similar. There were no deaths and no significant differences in postoperative minor and major morbidities. Two patients had the MSA device removed and two had an NF revision. Study limitations included its retrospective nature and being performed in high-volume esophageal centers may limit its application to other centers.
4. Reynolds et al (2015) retrospectively compared charges, complications, and outcomes at one year for 119 patients undergoing MSA (54) or NF (67). Follow-up data were available for 48/52 (92%) of the MSA patients and 59/67 (88%) of the NF patients. There were no significant differences between charges, mean GERD-HRQL, or freedom from PPIs. MSA patients had a shorter operating room time and length of stay, reported less gas bloat symptoms and inability to belch or vomit. Two 30-day complications occurred in the NF group but were resolved. Noted limitations were that the study was not powered to detect a difference in PPI use and charges versus costs were compared. It was concluded that MSA might be an alternative for "gap" patients who are those having residual symptoms on PPIs but not having complicated GERD or complete lower esophageal sphincter (LES) failure.

Evidence reviewed based on reconsideration request received March 12, 2019

On 03/15/2018 the FDA approval for updating the precautions statement to state that use of the LINX Reflux Management System in patients with a hiatal hernia larger than 3 cm should include hiatal hernia repair to reduce the hernia to less than 3 cm and that the LINX Reflux Management System has not been evaluated in patients with an unrepaired hiatal hernia greater than 3 cm, added a hiatal hernia clinical data summary in the instructions for use, updated the instructions for use section to highlight the recommendation to repair a hiatal hernia, if present, at the time of the LINX Reflux Management System implantation, and updated the patient information booklet to align with the instructions for use and include 5 year clinical study results.

1. Aiolfi et al (2018) reported a systematic review and meta-analysis comparing early outcomes of laparoscopic Nissen and Toupet fundoplication (LF) and Magnetic Sphincter Augmentation (MSA). After identifying all possible studies, seven were determined to be appropriately performed (Louie 2014, Reynold 2015, Sheu 2015, Riegler 2015, Warren 2016, Reynolds 2016, and Asti 2016). There is concern that the two Reynolds papers and the Warren paper had overlapping patients. They concluded that: "Patients with GERD may benefit from both LF and MSA in terms of, safety, risk of dysphagia, postoperative disease-related quality of life, and PPI suspension rate at one-year follow-up. MSA appears to induce less bloating and flatulence, and to facilitate belch and vomiting. Whether MSA should be considered a first-line surgical option in appropriately selected patients remains to be determined." A concern is that the mean age of the patients ranged from 39.3 to 54 years of age (geometric mean 48.8), which is far below the age of the typical Medicare beneficiary. MSA was

associated with a significantly lower incidence of gas/bloat symptoms (OR=0.39 [95% CI, 0.25-0.61]; P<0.001) and a greater incidence in the ability to vomit (OR=10.10 [95% CI, 5.33-19.15]; P<0.001) and belch (OR=5.53 [95% CI, 3.73-8.19]; P<0.001). However, dysphagia requiring endoscopic dilation occurred equally in the 2 groups (9.3% versus 6.6%, respectively; OR=1.56 [95% CI, 0.61-3.95]; P=0.119). The incidence of endoscopic dilation and the incidence of reoperation were similar between groups (P>0.1). This does offer support to the LINX. "Funding disclosure: None. Conflicts of interest: None."

2. Alicuben et al (2018) reported on data obtained from the device manufacturer Torax Medical, Inc., as well as the Manufacturer and User Facility Device Experience (MAUDE) database. The study period was from February 2007 through July 2017 and included all devices placed worldwide. According to the authors, 9453 devices were placed during this study period with only 29 reported cases of erosions. The risk of erosion was 0.05% at one year and 0.3% at four years. The authors noted the 12-bead device, which was responsible for 18/29 (62%) of erosions, is no longer available for implantation. This relies on the self-reporting by physicians which can underestimate the numbers. Grant Support: There was no financial assistance. This does offer support to the LINX but since this only looked at erosion, the support is limited to safety, not to effectiveness.
3. American Society of General Surgeons. LINX Statement of Support from ASGS. 2014. https://theasgs.org/position-statements/linx-statement-of-support-from-asgs/. This gives an opinion with limited basis of evidence to support this. This does give some support but it must be noted that no matter what categorization or scale is used, testimonials, opinions of respected authorities, and reports of expert committees are the lowest level of evidence. There is no statement related to financial conflict although it is apparent that this organization represents surgeons who perform this procedure.
4. Ayazi et al (2019) published a "retrospective review of prospectively collected data" on 350 patients who underwent magnetic sphincter augmentation and their hiatal hernia (HH) status (none, small [<cm], large [≥3cm], paraesophageal). There were 65 patients (18.6%) with no HH, 205 (58.6%) with small HH (< 3 cm), 58 (16.6%) with large HH (≥ 3 cm) and 22 (6.2%) with paraesophageal HH. Preoperative esophagogastroduodenoscopy (EGD) with biopsy was performed to assess the presence of esophagitis, Barrett's esophagus and the presence and size of a hiatal hernia. The average age was only 53.5 which is not typical for the Medicare population. At a mean follow-up of 13.6 (10.4) months, the rate of outcome satisfaction was high and similar between the four groups (p = 0.72). The authors do not explain 13.6 verses 10.4. A total of 19 patients required readmission within 90 days after surgery. The study suffers from several issues. First, the patients were not typical Medicare age patients. Second, the short follow up period. Third, it was not a randomized controlled study. Fourth, related to #3, there was no comparison to the Laparoscopic Nissen fundoplication. Disclosures: Dr. Blair A. Jobe is on the scientific advisory board of Johnson and Johnson and Medtronic and receives a consulting fee. Drs. Shahin Ayazi, Nobel Chowdhury, Ali H. Zaidi, Kristy Chovanec, Yoshihiro Komatsu, Ashten N. Omstead, Ping Zheng and Toshitaka Hoppo have no conflicts of interest or financial ties to disclose.
5. Ayazi et al (2019) compared the costs of laparoscopic magnetic sphincter augmentation (MSA) and laparoscopic Nissen fundoplication (LNF) in a large healthcare system. Of note, the article starts off with, "Magnetic sphincter augmentation (MSA) is a promising antireflux surgical treatment." It then notes, "Laparoscopic Nissen fundoplication is a safe, effective, and durable treatment." This is an economic study and costs cannot be used by Medicare as a reason for denying coverage. Disclosure: Dr. Jobe is on the scientific advisory board of Johnson and Johnson and Medtronic and receives a consulting fee. Drs. Ayazi, Zaidi, Zheng, Chovanec, Chowdhury, Salvitti, Newhams, Levy, and Hoppo have no conflicts of interest or financial ties to disclose. This work was completed with assistance of VITAL, Highmark Health.
6. Bell et al (2019) reported on 152 patients with moderate to severe regurgitation symptoms while they were being treated with once-day proton-pump inhibitors. "Enrolled patients were randomly assigned 2:1 to the following treatment arms: Twice-daily PPI (BID PPI) therapy with omeprazole 20 mg (N Z 102) or laparoscopic MSA (N Z 50). Primary endpoint efficacy and safety assessments were performed at 6 months and are the subject of this report." The range of patients was 21-76 with a mean of only 46; again not in the typical Medicare age. Also, only 134 were analyzed. "Per protocol, 89% (42/47) of MSA patients achieved resolution of moderate-to-severe regurgitation at the 6-month primary endpoint. In stark contrast, only 10% (10/101) of patients in the medical therapy arm reported relief from moderate-to-severe regurgitation at the 6-month endpoint." However, these numbers do not add up to the 134 who were subsequently analyzed. Additional

concerns are the short follow up, and the above noted age of the patients. While the authors noted, "This is the first prospective, randomized, controlled study comparing MSA with BID PPI therapy in a population of patients with GERD with moderate-to-severe regurgitation despite once-daily PPI therapy." There are several problems with this study. First, all the improvement is subjective rather than some objective measurements. Second, this was not a blinded study. Of course it is difficult to perform a sham abdominal procedure. The short follow up period and the atypical ages of the patients compared to the typical Medicare age are additional concerns. This gives minimal support. "DISCLOSURE: All authors are grant recipients from Torax Medical; A. Park, research grant support from Stryker Endoscopy."

7. Buckley et al (2018) reported on 200 patients in a multicenter prospective study treated with magnetic sphincter augmentation (MSA) and a concurrent hiatal hernia repair of greater than 3 centimeters. In fact, 78% of patients had axial hiatal hernias greater or equal to 5 cm or large paraesophageal component. Twenty-nine percent presented with an intrathoracic stomach. Seventeen had undergone a prior hiatal hernia repair with fundoplication. The mean age was 59.5. Non-permanent mesh reinforcement of the hiatal repair was performed in 85% of the patients. One hundred and fifty-six were followed at a median of 8.6 months. While twenty percent of patients had Barrett's metaplasia, and 40% had esophagitis, there was no mention of these conditions on follow up. The amount of various antacid medication was not quantified. Again, the improvements were subjective. The fact that all the patients had large hiatal hernia repairs concurrently makes it difficult to interpret what improvement was from the MSA and what was from the hiatal hernia repair. Funding: This study received no funding. Compliance with ethical standards. Disclosures: Dr. F.P. ''Tripp'' Buckley III is on the speakers' bureau for Torax Medical. Dr. Reginald C.W. Bell is on the speakers' bureau for Torax Medical. Stephanie Doggett PA-C is on the speakers' bureau for Torax Medical. Katherine Freeman N.P. and Rachel Heidrick R.N have no conflicts of interest or financial ties to disclose. This paper gives very minimal support to LINX.
8. Chen M et al (2017) performed a meta-analysis of four clinical trials which involve 624 patients. Three of the publications (Louise, Reynolds, and Warren) have been previously reviewed by this contractor. The Sheu article had not. If trials were included in the meta-analysis, the criteria had to be fulfilled as follows: (1) Compare the original outcomes of MSA (Magnetic Sphincter Augmentation) and NF (Nissen fundoplication) for the treatment of GERD; (2) report on at least incidence of adverse events, complications, and proton-pump inhibitor use. There were similar outcomes in the number of adverse events and complication between two groups were shown. The authors noted, "There are still many unanswered questions whether MSA is still appropriate for hiatal hernias which are more than 3 cm, whether the long-term outcomes of MSA are the same as the short-time outcomes, whether the incidence of LINX device removed and erosion will increase as time goes on, and so on. Therefore, it is very important and necessary to perform randomized controlled trials to describe the efficacy of MSA compared to NF in short term and long term." The authors "have no conflicts of interest or financial ties to disclose." This gives minimal support to LINX.
9. Skubleny D et al (2016) performed a meta-analysis of laparoscopic Nissen fundoplications with magnetic sphincter augmentation. However, the three primary studies were Riegler et al, Warren et al, and Sheu et al. Thus, it is incorrect to accept this as new evidence since the original articles and meta-analysis have already been evaluated. Disclosures: Daniel Skubleny, Noah J. Switzer, Jerry Dang, Richdeep S. Gill, Xinzhe Shi, Christopher de Gara, Daniel W. Birch, Clarence Wong, Matthew M. Hutter and Shahzeer Karmali have no conflicts of interest or financial ties to disclose.
10. Smith C et al (2014) reported on the post-operative course of 66 patients who received the magnetic sphincter augmentation. The average follow-up was only 5.8 months (range 1 to 18.6 months). Forty-four of the 66 patients had hiatal hernia. The average age was 53.7 which is below the typical Medicare age. There was no control group. They concluded,... "This is a promising new offering for patients with GERD." They did specifically comment on the learning curve for surgeons performing this surgery. Disclosure Information: "Drs. Smith and DeVault received pay as consultants to Torax Medical during the final review of the results of their Pivotal Trial. Dr. Smith presented outcomes data to the FDA advisory panel and continues to advise the company on how to deploy Linx in clinical practice. Mauricia Buchanan has nothing to declare."
11. Smith C et al (2017) reported on data obtained from the device manufacturer Torax Medical, Inc., as well as the Manufacturer and User Facility Device Experience (MAUDE) database. The study period was from March 22, 2012 (FDA approval) through May 31, 2016, and unlike the Alicuben paper, included only events occurring in

the United States. An estimated 3283 patients underwent magnetic sphincter augmentation (165 surgeons at 191 institutions). The median implant duration was 1.4 years, with 1016 patients implanted for at least 2 years. No deaths, life-threatening events, or device malfunctions were reported. The overall rate of device removal was 2.7% (89/3283). Disclosure Statement: Drs. C.D.S., J.C.L., and R.C.B. received consulting and research funding from Torax Medical. This does offer support to the LINX as being not dangerous, but no support for it being effective.

12. Telem D et al (2017) authored a SAGES Committee Paper on SAGES technology and value assessment committee (TAVAC) safety and effectiveness analysis: LINX_ reflux management system. This is a SAGES Committee Paper. Except for Asti et al who reported the results of a retrospective review of prospectively collected data examining the outcomes of 164 patients undergoing LINX implantation with median follow-up of 48 months, all the papers reviewed by SAGES have been evaluated by this contractor. As this SAGES paper notes about the articles reviewed: Limitations of currently published data.
    - Patients used repeatedly in some publications.
    - There may be a publication bias in favor of LINX, as several studies were either funded by the manufacturer or were performed by investigators affiliated with the manufacturer.
    - Most studies were performed in high volume centers in highly selected patients and may not reflect broader clinical practice, which may lead to underreporting of complications.
    - Current studies lack randomization and blinding.

Expert panel recommendation

This expert panel convened by the SAGES Technology and Value Assessment Committee finds that:

With regards to safety:

- Safety analyses suggest the LINX procedure was associated with few serious adverse events and no reported mortality.
- The most common anticipated side effect was acute dysphagia.
- The reported rate of erosion is in the range of 0.1–0.2%. The published literature on erosions suggests that the device can be safely removed endoscopically or laparoscopically without serious adverse outcomes.
- Some devices require removal, most often for recurrent GERD or persistent and/or severe dysphagia.
- No new patterns of failure or complications have been reported in long-term follow-up.
- Longer-term follow-up supports the FDA conclusion that the device is safe.

With regards to efficacy, the panel concludes:

- LINX implant results in pH normalization, improved quality of life, and complete cessation of regular PPI use on a consistent basis. The ability to belch and vomit is maintained following implantation of LINX, and de novo moderate-severe gas bloat is uncommon.
- When compared to laparoscopic fundoplication, rates of success in alleviating GERD symptoms and dysphagia are similar following LINX. Bloating side effects may be lower.
- Longer-term follow-up data demonstrates that the LINX Reflux Management System is effective in the management of GERD.

Conclusions

- Longer-term (3–5 years) experience with the LINX Reflux Management System confirms the initial safety profile that led to FDA approval of the device.
- The LINX device has been demonstrated to result in long-term GERD control based on symptomatic outcomes,

PPI utilization, and pH studies.
- LINX is a reasonable treatment option for appropriately selected patients with GERD who meet indications for antireflux surgery. The LINX procedure is part of the armamentarium in the treatment of GERD. As such, it should be performed by surgeons familiar with the workup and different management alternatives of GERD and not offered in isolation.
- Implantation of the LINX device should be covered and reimbursed by insurance for appropriate patients who meet the selection criteria as described above.

Disclosures Dana Telem, MD: Research funding at Cook, Consulting Fees at Ethicon and Medtronic, Honoraria at Gore. Andrew Wright, MD: Honoraria at Medtronic. Paresh Shah, MD: Consultant at Stryker, Zmicro, Olympus, Endoevolution. Matthew Hutter, MD: Reimbursed to attend Masters in MIS Forum by Olympus. This document underwent prescreening review prior to submission to SAGES Board of Governors for approval by SD Schwaitzberg, MD and Patricia Sylla, MD.

Again, as noted above, it must be noted that no matter what categorization or scale is used, testimonials, opinions of respected authorities, and reports of expert committees are the lowest level of evidence.

1. Trad K et al (2018) studied transoral incisionless fundoplication (TIF). Clinical outcomes were evaluated at 5 years post-TIF 2.0. A total of 63 chronic gastroesophageal reflux disease (GERD) sufferers with troublesome symptoms refractory to proton pump inhibitor (PPI) therapy, absent or ≤2 cm hiatal hernia, and abnormal esophageal acid exposure were randomized to the TIF group or PPI group. This study has nothing to do with magnetic sphincter augmentation and thus does not support LINX. In summary, it does however support TIF.
2. Yadlapati R (2018) convened an expert panel and gave their evaluations of nine patients with GERD. The treatment options were laparoscopic fundoplication, magnetic sphincter augmentation, transoral incisionless fundoplication, and radiofrequency energy delivery. Of note, radiofrequency energy delivery such as the Stretta procedure is not covered by National Government Services. Financial support: RY and JEP supported by NIH R01 DK092217 (JEP). Potential competing interests: MFV, MFV, SJS, JR, DK, POK, PJK, CPG, LG, RF, DOC, JC, LH: None. RY: Consultant for Ironwood. CPG: Research: Medtronic; Consultant: Ironwood, Torax, Quintiles; and Teaching: Medtronic, Sandhill. NJS: Research funding: Boston Scientific, CSA Medical, C2 Therapeutics, CDx Medical, Interpace Diagnostics, and Medtronic. Consultant for Shire and Cook Medical. BEL: Scientific advisory board member for Ironwood, Salix. JEP: Consultant for Crospon, Ironwood, Torax, Astra Zeneca, Takeda, Impleo, Medtronic, and Sandhill. Expert panels are the lowest category of medical evidence. Thus, this is very minimal support for LINX.

Analysis of Evidence (Rationale for Determination)

Gastroesophageal reflux disease (GERD) is mostly treated by medical management. As outlined in the ACG Practice Guidelines (updated in 2005) many patients are treated by empirical therapy, without the use of endoscopy. However some patients require additional diagnostic studies and interventions. The Practice Guidelines discusses the historical controversy of medical vs. surgical intervention but did establish the following two treatment guidelines:

- Antireflux surgery, performed by an experienced surgeon, is a maintenance option for the patient with well-documented GERD.
- Endoscopic therapy controls symptoms in selected patients with well-documented GERD.

These guidelines note anti-reflux surgery, performed by an experienced surgeon, is a maintenance option for the patient with well documented GERD. In these guidelines endoscopic therapy for GERD was discussed, pointing out there are three broad categories of endoscopic therapy: ‘radiofrequency application to the LES area, techniques designed to decrease reflux using endoscopic sewing devices, and techniques using an injection into the LES region.’

The guidelines also raised remaining issues, including: long-term durability, efficacy in atypical presentation of GERD patients, and efficacy of these procedures performed outside of clinical trials.

Transoral Incisionless Fundoplication (TIF):

Since these guidelines were updated in 2005, a newer endoscopic suturing technique has emerged in the literature. Transoral Incisionless Fundoplication (TIF) is an endoscopic technique. At present, the only such device currently on the market is the ExophyX™. The FDA cleared this device. The FDA clearance is for those patients with chronic GERD, with continued responsiveness to PPIs, and a hiatal hernia greater than 2 cm, when a laparoscopic hiatal hernia repair reduces the hernia to 2 cm or less. The TIF procedure is described as:

During transoral fundoplication, a General Surgeon constructs an anterior partial fundoplication of 270-300 degrees by attaching the fundus to the anterior and left lateral wall of the distal esophagus slightly above the esophagogastric junction through full thickness placation using multiple fasteners around the gastroesophageal junction. The TIF procedure has had different versions (TIF 1.0 vs. 2.0) depending on the circumferential amount of reestablishment of the valve, i.e. 220 degrees vs. 240 degrees.

As noted above, the evidence supports limited coverage for Transoral Incisionless Fundoplication (TIF).

Stretta® procedure:

At this time, open-label studies or patient registries with short term follow-ups are the dominant source of data. The overwhelming preponderance of reviewers remain equivocal in their support and have called for randomized controlled trials with long-term follow-ups. In the absence of evidence from such studies, and in the absence of wide acceptance, endoscopic treatments for GERD are not proven effective.

Thus, the evidence is not sufficient and/or robust to support any change in coverage.

Analysis based on reconsideration request received October 17, 2019

Forty three (43) papers were submitted with this reconsideration request.

- Thirteen of them had previously been evaluated by National Government Services and had already been included in the bibliography. These did not add any new support for Stretta.
- Eight "positive coverage" documents were included. None of these are from Medicare contractors but rather commercial insurance plans which use contract language as part of their decision process rather than evidence based methods that Medicare requires. These did not add any support to Stretta.
- Many of the remaining twenty-two (22) articles were old.
- Others were small studies or had short follow up procedures.
- Many pertained to patients not reflective of typical Medicare beneficiaries.
- The methodologic quality and design of the study of most were poor.
- Some were unpublished and/or not found in PubMed of the National Library of Medicine of the National Center for Biotechnology Information.
- A forty-fourth article (a review one based on the Cochrane Data Base) was mentioned in one of the submitted articles. This was obtained, reviewed and added.

In summary, there was not sufficient, robust evidence submitted to change the current non-coverage of Stretta. Stretta will remain non-covered.

Enteryx® Procedure:

Based on the evidence and FDA recall of this product, change in coverage is not warranted.

LINX® Reflux Management system:

LINX® Reflux Management system and/or similar treatments are promising for treatment of patients in whom proton pump inhibitor therapy fails. Clinical data from various studies are emerging. At this time, open-label studies or patient registries with short term follow-ups are the dominant source of data. The overwhelming preponderance of reviewers remain equivocal in their support and have called for randomized controlled trials with long-term follow-ups. In the absence of evidence from such studies, and in the absence of wide acceptance, endoscopic treatments for GERD are not proven effective.

NGS finds the MAS literature to have small numbers of patients with only short follow-up periods with the exception of Saino et al and Ganz with 44 and 100 patients respectively, noting data were available for 33/44 and 85/100. Randomized controlled studies are lacking, including head-to-head comparisons with other modes of treatment. NGS will review future literature as it becomes available and is provided.

Thus, the evidence is not sufficient and/or robust to support any change in coverage.

Analysis based on reconsideration request received March 12, 2019

The number of submitted literature was small and that included one paper that was not related to the LINX procedure. There were also eight other papers submitted with the current reconsideration that had previously been reviewed by this contractor (Bonavina J 2013, Ganz 2016, Lipham 2015, Louie BE 2014, Reynolds 2016, Riegler 2015, Saino 2015, and Warren 2016) and thus not reviewed again. In addition, some of the current papers appear to contain overlapping patients. While the SAGES Technology and Value Assessment Committee paper was reviewed and noted, expert and/or consensus statements are the lowest form of recognized levels of evidence. The follow up periods for the studies were short and most patients were not of the typical Medicare age. There is concern about conflict of interest but this is difficult to avoid. In summary, there were concerns about the quality of the evidence including randomization, the above mentioned likely patient overlap between 3 studies, and concern of long-term efficacy and safety assessments. The first Ayazi (2019) gives very limited support for LINX since the mean age of patients were not in the typical Medicare population, the follow up period was short, it was not a randomized controlled study, and there was no comparison to the Laparoscopic Nissen fundoplication. The second Ayazi (2019) gives no support for LINX. It is an economic study and cost savings are not acceptable for determining Medicare coverage. In addition, it notes, “Magnetic sphincter augmentation (MSA) is a promising antireflux surgical treatment” as well as “Laparoscopic Nissen fundoplication is a safe, effective, and durable treatment.”

Thus, the submitted medical evidence does not reach a level to support the changing of this contractor’s non-coverage policy.

General Information

Associated Information

N/A

Sources of Information

Sources added for reconsideration request received October 17, 2019

CareFirst Medical Policy Reference Manual - Endoscopic Therapies for Gastroesophageal

Reflux (GERD). Last reviewed: 2/21/2017

Highmark Commercial Medical Policy – Delaware – S-145-010 - Transesophageal Endoscopic Therapies for Gastroesophageal Reflux Disease (GERD). Last review: January 2019

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Highmark Commercial Medical Policy – West Virginia – S-145-018 - Transesophageal Endoscopic Therapies for Gastroesophageal Reflux Disease (GERD). Last review: January 2019

Blue Cross Blue Shield of North Dakota - Transesophageal Endoscopic Therapies for Gastroesophageal Reflux Disease (GERD). Last reviewed May: 15, 2019

Novitas Solutions, Inc. LCD L35350 - Upper Gastrointestinal Endoscopy (Diagnostic and Therapeutic). Revision date: 10/01/2018

PriorityHealth Medical Policy No. 91483-R9 - GASTROESOPHAGEAL REFLUX DISEASE (GERD) AND BARRETT'S ESOPHAGUS. Review date: 11/16

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Revision History Information

REVISION HISTORY DATE	REVISION HISTORY NUMBER	REVISION HISTORY EXPLANATION	REASONS FOR CHANGE
02/10/2022	R12	Removed hyperlink for U.S. Food and Drug Administration (FDA) in the Bibliography section.	• Other (Removed hyperlink)
04/15/2021	R11	Based on a reconsideration request for the Stretta® procedure, the "Summary of Evidence" and "Analysis of Evidence" sections have been revised and sources have been added to the "Bibliography" section of the LCD. No changes were made in coverage.	• Provider Education/Guidance • Reconsideration Request
04/01/2020	R10	Based on a reconsideration request for the LINX® Reflux Management System, the "Summary of Evidence" and "Analysis of Evidence" sections have been revised and sources have been added to the "Bibliography" section of the LCD. No changes were made in coverage.	• Provider Education/Guidance • Reconsideration Request
10/17/2019	R9	This LCD was converted to the new "no-codes" format. There has been no change in coverage with this LCD revision.	• Revisions Due To Code Removal

REVISION HISTORY DATE	REVISION HISTORY NUMBER	REVISION HISTORY EXPLANATION	REASONS FOR CHANGE
08/15/2019	R8	Consistent with Change Request 10901, all coding information, National coverage provisions, and Associated Information (Documentation Requirements, Utilization Guidelines) have been removed from the LCD and placed in the related Billing and Coding Article, A56863. There has been no change in coverage with this LCD revision.	• Provider Education/Guidance
12/01/2017	R7	Based on a provider/practitioner request, the "Limitations" section has been revised to remove the following: "any patient in which a staged procedure is being done, as described as a laparoscopic esophageal or paraesophageal diaphragmatic hernia / opening closure followed by a TIF endoscopically."	• Provider Education/Guidance
12/01/2017	R6	Based on a reconsideration request, information has been added to the "Limitations" and "Analysis of Evidence (Rationale for Determination)" sections of the LCD to reflect revised FDA guidelines.	• Reconsideration Request
12/01/2017	R5	The LCD was submitted to Jurisdiction 6 and Jurisdiction K for public and CAC comment from 06/19/2017 through 08/02/2017. Based on the comments and peer-reviewed literature received, the changes shown below were made: The title of the LCD has changed from "Endoscopic Treatment of GERD" to "Select Minimally Invasive GERD Procedures." Non coverage information for the LINX® Reflux Management System has been added to the LCD. Based on a reconsideration request coincident with the CAC draft comment cycle, limited coverage has been added for TIF. Bill Type codes 13X and 83X have been added.	• Provider Education/Guidance • Reconsideration Request

REVISION HISTORY DATE	REVISION HISTORY NUMBER	REVISION HISTORY EXPLANATION	REASONS FOR CHANGE
		CPT codes 43257, 43284, 43499, 43999 and 49999 have been moved to Group 2 of the "CPT/HCPCS Codes" section as not medically necessary. The "ICD-10 Codes that Support Medical Necessity" section has been updated to add payable ICD-10-CM codes for CPT code 43210. Additional references were included in the "Bibliography" section.	
12/01/2016	R4	Based on a reconsideration request for Stretta®, sources have been added to the "Sources of Information" section of the LCD. No changes were made in coverage. *DATE (08/01/2017): At this time 21st Century Cures Act will apply to new and revised LCDs that restrict coverage which requires comment and notice. This revision is not a restriction to the coverage determination; and, therefore not all the fields included on the LCD are applicable as noted in this policy.*	• Reconsideration Request
12/01/2016	R3	In the "Indications" section of the LCD, the last sentence in the paragraph for the Stretta® procedure has been changed from: Substantial peer-reviewed evidence to fully support these assumptions remains to be published To: Substantial peer-reviewed evidence to fully support these assumptions needs to be published. This same sentence been added to the end of the paragraphs for the Bard EndoCinch™ Suturing System and the Plicator™ and the EsophyX™ device. The language in the paragraph for Enteryx® has been changed from: Enteryx® is an endoscopic, minimally-invasive procedure in which an ethylene vinyl alcohol	• Provider Education/Guidance

REVISION HISTORY DATE	REVISION HISTORY NUMBER	REVISION HISTORY EXPLANATION	REASONS FOR CHANGE
		polymer solution is injected into your lower esophageal sphincter muscle using a small needle. To: Enteryx® is an endoscopic, minimally-invasive procedure in which an ethylene vinyl alcohol polymer solution is injected into one's lower esophageal sphincter muscle using a small needle. The following reference has been added to the "Sources of Information and Basis for Decision" section of the LCD: Trad KS, Fox MA, Simoni G, et al. Transoral fundoplication offers durable symptom control for chronic GERD; 3-year report from the TEMPO randomized trial with a crossover arm. *Surg Endosc.* 2016 Sep 21. [Epub ahead of print]	
01/01/2016	R2	Based on the annual 2016 HCPCS update, HCPC code C9724 has been deleted and replaced with CPT code 43210.	• Revisions Due To CPT/HCPCS Code Changes
10/01/2015	R1	The Sources of Information section has been revised to add additional sources for Stretta and transoral incisionless fundoplication (TIF) based on updates made to the ICD-9-CM version.	• Provider Education/Guidance

Associated Documents

Attachments

N/A

Related Local Coverage Documents

Articles

A56863 - Billing and Coding: Select Minimally Invasive GERD Procedures

A58614 - Response to Comments: Select Minimally Invasive GERD Procedures

Related National Coverage Documents

N/A

Public Versions

UPDATED ON	EFFECTIVE DATES	STATUS
02/04/2022	02/10/2022 - N/A	Currently in Effect (This Version)
Some older versions have been archived. Please visit the MCD Archive Site to retrieve them.		

Keywords

N/A

Radiation Therapy for Dupuytren's Contracture

Plain Language Summary:

Coverage question: Should OHP cover radiation treatment for a tightening of the tissue of the hand?

Should OHP cover this treatment? No. Radiation treatment has not been studied well and there are other treatments (shots, surgery) available.

Coverage Question: Should radiation therapy be added as a treatment for Dupuytren's disease (palmar fibromatosis) or plantar fibromatosis?

Question source: Medical Management Committee

Background: Dupuytren's contracture is an abnormal thickening of tissues in the palm of the hand. The thickened tissues may develop into a hard lump and may cause one or more fingers to contract inward toward the palm. Standard treatments for this condition are Botox injections, steroid injections, and surgical fasciectomy, which releases the thick, tight tissue. There was a recent case discussed at the Medical Management Committee (MMC) of HSD requesting coverage of radiation therapy for Dupuytren's disease.

The same case as above also requested radiation therapy for treatment of plantar fibromatosis (also known as morbus Ledderhose). This condition is a rare benign hyperproliferative disorder of the planar fascia of unknown etiology. This condition creates slow grown nodules in the medial and central bands of the plantar fascia with may become painful and affect ambulation. This condition is associated with Dupuytren's disease. Current therapies include orthotics, extracorporeal shock wave therapy, steroid ingestions, topical verapamil, and surgical treatment.

Previous HSC/HERC reviews:

No previous reviews of this pairing have been done

Current Prioritized List/Coverage status:

ICD-10-CM M72.0 (Palmar fascial fibromatosis [Dupuytren]) is on lines 359 DEFORMITY/CLOSED DISLOCATION OF JOINT AND RECURRENT JOINT DISLOCATIONS and 416 PERIPHERAL NERVE ENTRAPMENT; PALMAR FASCIAL FIBROMATOSIS

ICD-10-CM M72.2 (Plantar fascial fibromatosis) is on line 540 LESION OF PLANTAR NERVE; PLANTAR FASCIAL FIBROMATOSIS

Radiation Therapy for Dupuytren's Contracture

Radiation therapy (various codes) are on multiple lines, but not on line 346, 416, or 540

Evidence:

1) **Kadhum 2017,** Systematic review of radiotherapy for Dupuytren's disease
    a. N=6 articles (770 irradiated hands in 698 patients)
        i. 5 retrospective cohort studies (Damietz et al., 2001; Betz et al., 2010; Keilholz et al., 1996; Herbst and Regler, 1986; Zirbs et al., 2015)
        ii. 1 RCT (Seegenschmiedt et al 2001)
    b. Disease regression ranged from 0%–56%, stability from 14%–98% and progression from 2%–86%
    c. Four studies measured short-term complications, which occurred in 20% to 43% of patients and included erythema, drying of the skin and desquamation
    d. Conclusion: On balance, radiotherapy should be considered an unproven treatment for early Dupuytren's disease due to a scarce evidence base and unknown long-term adverse effects. Well-designed randomized controlled studies are required to confirm the benefits of radiotherapy treatment
2) **Carroll 2018**, evidence based review of plantar fibromatosis
    a. There exist very little published data on the use of radiation on plantar fibromas

Other payer policies:

1) **NICE 2016,** radiation therapy for early dupuytren's disease https://www.nice.org.uk/guidance/ipg573/resources/radiation-therapy-for-early-dupuytrens-disease-pdf-1899872106511813
    a. The evidence on radiation therapy for early Dupuytren's disease raises no major safety concerns. Current evidence on its efficacy is inadequate in quantity and quality, and is difficult to interpret because of uncertainty about the natural history of Dupuytren's disease. Therefore, this procedure should only be used with special arrangements

2) **Aetna 2022**
    a. Aetna considers ortho-voltage radiation medically necessary for the treatment of early-stage Dupuytren's contracture (stage N, N/I). (Note: stage N: nodules/cords, no extension deficit = flexion deformity; stage N/I: less than or equal to 10 degrees deficit).

Expert input:

1) **American Academy of Orthopaedic Surgeons**
    a. https://orthoinfo.aaos.org/en/diseases--conditions/dupuytrens-disease/
        i. Accessed April 19, 2023
    b. Recommended treatments are splinting, steroid injection, enzyme injection, needle aponeurotomy, fasciotomy and subtotal palmar fasciectomy. Radiation therapy is not mentioned as a treatment

Radiation Therapy for Dupuytren's Contracture

HERC staff summary:

Radiation therapy for Dupuytren's contracture has not been well studied. Multiple effective treatments for this condition are currently paired on the Prioritized List, including injections and surgery. Radiation therapy for plantar fibromatosis is even less well studied, and this condition falls below the funding line

HERC staff recommendation:

1) Make no change in the non-pairing of Dupuytren's contracture and plantar fibromatosis and radiation therapy
    a. Line 416 PERIPHERAL NERVE ENTRAPMENT; PALMAR FASCIAL FIBROMATOSIS contains procedure codes for injections and fasciectomy
2) Consider reprioritization of plantar fibromatosis as a biennial review item
    a. Current non-funded line specifically calls out this condition [540 LESION OF PLANTAR NERVE; PLANTAR FASCIAL FIBROMATOSIS]
    b. May have impact on ambulation and function
    c. An in-depth review of effectiveness of various treatments will be required with podiatry input

Review Article

JHS(E)

The Journal of Hand Surgery
(European Volume)
2017, Vol. 42E(7) 689–692

DOI: 10.1177/1753193417695996
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SAGE

Radiotherapy in Dupuytren's disease: a systematic review of the evidence

M. Kadhum[1], E. Smock[2], A. Khan[2] and A. Fleming[2]

Abstract

Radiotherapy has been advocated as an alternative treatment in early Dupuytren's disease. We have systematically reviewed the evidence on the use of radiotherapy in Dupuytren's disease. Only six articles met a minimum set standard, five of which were retrospective cohort studies and one a randomized controlled study. A total of 770 Dupuytren's hands, nearly all with Tubiana stage 0–1 disease, were irradiated with an average 30 Gy. Disease regression ranged from 0%–56%, stability from 14%–98% and progression from 2%–86%. Salvage surgery was successful in all cases of disease progression post-radiotherapy. There were no reports of adverse wound healing problems associated with such surgery or radiotherapy-associated malignancy. On balance, radiotherapy should be considered an unproven treatment for early Dupuytren's disease due to a scarce evidence base and unknown long-term adverse effects. Well-designed randomized controlled studies are required to confirm the benefits of radiotherapy treatment.

Level of evidence: II

Keywords

Systematic review, Dupuytren's disease, Dupuytren's contracture, radiotherapy, radiation therapy, surgery

Date received: 1st June 2016; revised: 29th January 2017; accepted: 6th February 2017

Introduction

Radiotherapy is sometimes used as an adjunct in the treatment of benign conditions, such as keloid scars, which are characterized by increased proliferative cellular activity. In Dupuytren's disease, it has been proposed that low dose irradiation may inhibit fibroblast proliferation and induce an anti-inflammatory effect mediated by inhibition of the innate immune response and activation of nitric oxide synthetase pathways (Arenas et al., 2012; Seegenschmiedt et al., 2001). A dosage of 30–32 Gy is widely used in the treatment of benign diseases and similar doses have been used to treat Dupuytren's disease (Royal College of Radiologists, 2015). The only prospective study of radiotherapy in Dupuytren's disease advocates its use in early stage disease only, as 'the radiobiological potential of ionizing radiation is limited to early stages, as long as proliferating fibroblasts exist as the predominant radiosensitive target' (Seegenschmiedt et al., 2001).

Radiation fibrosis is a well-characterized late effect of radiotherapy (Barker et al., 2015) and the use of a fibrosis-inducing modality of therapy to treat a fibrosing condition may, perhaps, seem counter-intuitive. Hence, the use of radiotherapy in Dupuytren's disease remains both limited and controversial among hand surgeons. Specifically, the efficacy of radiotherapy in managing Dupuytren's disease remains uncertain, the longer-term risks unclear and whether irradiation may complicate subsequent surgery remains a concern. In the UK, current National Institute for Health and Care Excellence (NICE) guidance permits the use of radiotherapy in early Dupuytren's disease and there are a small number of NHS and private clinics that offer this service. The aim of this study was to review the available evidence for the treatment of Dupuytren's disease with radiotherapy.

Methods

An advanced search was performed on PubMed, Google Scholar and the Cochrane Library. Specific vocabulary terms, keywords and synonyms were entered as part of a systematic search strategy.

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Review

Plantar Fibromatosis: Pathophysiology, Surgical and Nonsurgical Therapies

An Evidence-Based Review

Paul Carroll, DPM, Robert M. Henshaw, MD, Caitlin Garwood, DPM, Katherine Raspovic, DPM, and Dhruv Kumar, MD

Abstract: *Plantar fibromatosis (morbus Ledderhose), an extra-abdominal desmoid tumor of the plantar foot, is a rare benign hyperproliferative disorder of the plantar fascia with an unknown etiology. The main clinical characteristics include slow growing nodules on the medial and central bands of the plantar fascia, which may become painful and negatively affect ambulation. Most established conservative therapies today target symptomatic relief. As symptoms progress, therapies such as injections, shockwave ablation, radiation, and/or surgery may be required. This review aims to provide insight into the pathophysiology of this condition in addition to detailing current and investigational therapies for this disorder. Many therapies have been proven in similar conditions, which could lead to promising treatment options for plantar fibromatosis.*

Levels of Evidence: *Level V: Expert opinion*

Keywords: fasciectomy; hyperproliferative; myofibroblasts; nodule; plantar fascia; verapamil topical

Plantar fibromatosis or morbus Ledderhose disease was first described in 1897 by Georg Ledderhose.[1] It is characterized by slow growing benign extra-abdominal desmoid nodules on the plantar aponeurosis (Figure 1). It has been hypothesized that these nodules form as a result of hyperactivity of mature fibroblasts.[2-4] However, the exact etiology is unknown.[3,5] Ledderhose disease has been associated with several other conditions such as Dupuytren's, Peyronies's, frozen shoulder, alcohol addiction, diabetes, epilepsy, smoking, repeated trauma, long-term phenobarbital use and possible genetic inheritance.[2,3,6,7] Men are twice as likely to be affected as females most common seen between the ages of 20 and 40 years.[2-4,6,8] In roughly 25% of the cases, it occurs bilaterally.[3,8] The aim of this study is to review the current literature regarding the pathophysiology, presentation, as well conservative and surgical treatment options for plantar fibromatosis.

> "Plantar fibromatosis is most commonly seen on the medial and central bands of the plantar apeuneurosis."

Presentation

Plantar fibromas are well encapsulated and firm (Figure 2). Symptoms include painful ambulation, large nodules on the plantar foot as well as toe flexure

DOI: 10.1177/1938640017751184. From the Division of Podiatric Surgery, Center for Wound Healing, MedStar Georgetown University Hospital, Washington, DC (PC); MedStar Washington Hospital Center, MedStar Georgetown Orthopedic Institute, Georgetown University School of Medicine, Washington, DC (RMH); Children's National Medical Center, National Cancer Institute, Washington, DC (RMH); Department of Plastic Surgery, Division of Podiatric Surgery, MedStar Washington Hospital Center, MedStar Georgetown University Hospital, Washington, DC (CG, KR); and Department of Pathology, MedStar Washington Hospital Center, Washington, DC (DK). Address correspondence to: Paul Carroll, DPM, Plastic Surgery, Center for Wound Healing, MedStar Georgetown University Hospital, 3800 Reservoir Road Northwest, Washington, DC 20007; email: paul.carroll011@gmail.com.

SPECT for Back Pain

Plain Language Summary:

Coverage question: Should OHP cover a pre-surgery advance spine scan of the neck and back called SPECT?

Should OHP cover this treatment? No, not for standard use. It may be useful when there is a reason why a patient cannot have an MRI or to show breaks in the bones of the spine. Individual review should determine which test to use.

Coverage Question: Should the advanced imaging in back pain guideline be clarified as to when SPECT is covered for spinal imaging?

Question source: Doug Luther, CCO medical director

Background:

Single photon emission computed tomography (SPECT) is a nuclear medicine technique that uses a radioactive tracer and a CT scan to produce image slices of various parts of the body. SPECT images are functional in nature rather than being purely anatomical such as ultrasound, computed tomography (CT), and magnetic resonance imaging (MRI).

SPECT is primarily used in cancer work up and to detect altered blood flow in organs such as the brain to help diagnose certain vascular disorders. SPECT can also detect stress fractures in bones.

Dr. Luther has had several requests recently for SPECT-CT to identify an area of pain focus prior to spinal fusion surgery. The main use of SPECT in the spine is to diagnose stress fractures of the vertebra, infections such as osteomyelitis, and tumors of the spine.

Previous HSC/HERC reviews:

CPT 78830 and 78832 (SPECT-CT) were last reviewed as new codes in November 2019. It was noted that these codes were more generic than their predecessors, which were organ specific codes. The old codes were all on the diagnostic file. The new codes were placed on the Diagnostic Procedures File without further review. The code that might have been used prior to 2020 for spine SPECT was CPT 78320 (Bone and/or joint imaging; tomographic (SPECT)) which was diagnostic.

Current Prioritized List/Coverage status:

The following codes are on the Diagnostic Procedures File:

SPECT for Back Pain

78830 Radiopharmaceutical localization of tumor, inflammatory process or distribution of radiopharmaceutical agent(s) (includes vascular flow and blood pool imaging, when performed); tomographic (SPECT) with concurrently acquired computed tomography (CT) transmission scan for anatomical review, localization and determination/detection of pathology, single area (eg, head, neck, chest, pelvis), single day imaging

78832 Radiopharmaceutical localization of tumor, inflammatory process or distribution of radiopharmaceutical agent(s) (includes vascular flow and blood pool imaging, when performed); tomographic (SPECT) with concurrently acquired computed tomography (CT) transmission scan for anatomical review, localization and determination/detection of pathology, minimum 2 areas (eg, pelvis and knees, abdomen and pelvis), single day imaging, or single area imaging over 2 or more days

DIAGNOSTIC GUIDELINE D4, ADVANCED IMAGING FOR LOW BACK PAIN

In patients with non-specific low back pain and no "red flag" conditions [see Table D4], imaging is not a covered service; otherwise work up is covered as shown in the table. Repeat imaging is only covered when there is a substantial clinical change (e.g. progressive neurological deficit) or new clinical indication for imaging (i.e. development of a new red flag condition). Repeat imaging for acute exacerbations of chronic radiculopathic pain is not covered.

Electromyelography (CPT 96002-4) is not covered for non-specific low back pain.

Table D4

Low Back Pain - Potentially Serious Conditions ("Red Flags") and Recommendations for Initial Diagnostic Work-up

Possible cause	**Key features on history or physical examination**	**Imaging[1]**	**Additional studies[1]**
Cancer	• History of cancer with new onset of LBP	MRI	ESR
	• Unexplained weight loss • Failure to improve after 1 month • Age >50 years • Symptoms such as painless neurologic deficit, night pain or pain increased in supine position	Lumbosacral plain radiography	
	• Multiple risk factors for cancer present	Plain radiography or MRI	
Spinal column infection	• Fever • Intravenous drug use • Recent infection	MRI	ESR and/or CRP

SPECT for Back Pain

Possible cause	Key features on history or physical examination	Imaging[1]	Additional studies[1]
Cauda equina syndrome	• Urinary retention • Motor deficits at multiple levels • Fecal incontinence • Saddle anesthesia	MRI	None
Vertebral compression fracture	• History of osteoporosis • Use of corticosteroids • Older age	Lumbosacral plain radiography	None
Ankylosing spondylitis	• Morning stiffness • Improvement with exercise • Alternating buttock pain • Awakening due to back pain during the second part of the night • Younger age	Anterior-posterior pelvis plain radiography	ESR and/or CRP, HLA-B27
Nerve compression/ disorders (e.g. herniated disc with radiculopathy)	• Back pain with leg pain in an L4, L5, or S1 nerve root distribution present < 1 month • Positive straight-leg-raise test or crossed straight-leg-raise test	None	None
	• Radiculopathic signs[2] present >1 month • Severe/progressive neurologic deficits (such as foot drop), progressive motor weakness	MRI[3]	Consider EMG/NCV
Spinal stenosis	• Radiating leg pain • Older age • Pain usually relieved with sitting (Pseudoclaudication a weak predictor)	None	None

SPECT for Back Pain

Possible cause	Key features on history or physical examination	Imaging[1]	Additional studies[1]
	• Spinal stenosis symptoms present >1 month	MRI[3]	Consider EMG/NCV

[1]Level of evidence for diagnostic evaluation is variable
[2]Radiculopathic signs are defined for the purposes of this guideline as the presence of any of the following:

A) Markedly abnormal reflexes
B) Segmental muscle weakness
C) Segmental sensory loss
D) EMG or NCV evidence of nerve root impingement
E) Cauda equina syndrome,
F) Neurogenic bowel or bladder
G) Long tract abnormalities

[3]Only if patient is a potential candidate for surgery

Red Flag: Red flags are findings from the history and physical examination that may be associated with a higher risk of serious disorders.

CRP = C-reactive protein; EMG = electromyography; ESR = erythrocyte sedimentation rate; MRI = magnetic resonance imaging; NCV = nerve conduction velocity.

Extracted and modified from Chou R, Qaseem A, Snow V, et al: Diagnosis and Treatment of Low Back Pain: A Joint Clinical Practice Guideline from the American College of Physicians and the American Pain Society. Ann Intern Med. 2007; 147:478-491.

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

Evidence:

1) **Brusko 2019**, case series of preoperative SPECT imaging for surgical planning in patients with neck and back pain
    a. N=23 patients
        i. Had SPECT or SPECT/CT done for non-reported indications (not necessarily pre-operative assessment alone)
        ii. Patients had spinal surgery for various clinical indications (not necessarily related to SPECT imaging findings alone)
        iii. No comparison group. Outcomes not reported for patients with hypermetabolic SPECT finding who did not have subsequent surgery or patients who underwent spinal surgery without SPECT
    b. Retrospective record review
    c. All patients underwent fusion surgery, either lumbar (n = 14), with interbody fusion most commonly used (64.2%); or cervical (n = 9), with anterior cervical discectomy and fusion (66.6%) being the most common. At the 3-month follow-

up, 18 patients (78.3%) reported clinical improvement in pain. Eleven patients (47.8%) reported complete symptom resolution at the 6-month follow-up. At 1 year postoperatively, 19 patients (82.6%) reported significant relief of their symptoms following surgery

   d. Conclusion: The results demonstrate that SPECT imaging may be a useful adjunct to guide surgical planning, resulting in substantial clinical improvement following surgery.

2) **Tender 2019**, case series of CT-SPECT for preoperative evaluation in degenerative spinal disease
   a. N=48 patients
   b. The overall axial spinal pain, as assessed through self-reporting of visual analog scale scores at 6 months postoperatively, improved from 9.04 ± 1.4 to 4.34 ± 2.3 ($p = 0.026$), with cervical fusion patients improving from 8.8 ± 1.8 to 3.92 ± 2.2 ($p = 0.019$) and lumbar fusion patients improving from 9.35 ± 0.7 to 4.87 ± 2.3 ($p = 0.008$).
   c. Conclusion: CT-SPECT may offer a diagnostic advantage over current imaging modalities in identifying the primary pain generator in patients with axial spinal pain.

Expert guidelines:

1) **American College of Radiology 2021**: Appropriateness Criteria for imaging in low back pain
   a. SPECT or SPECT CT is usually not appropriate for acute, subacute or chronic low back pain with or without radiculopathy with or without a history of prior lumbar surgery when no red flags are present
   b. SPECT or SPECT CT may be appropriate for subacute or chronic low back pain when surgery or intervention is being considered for persistent or progressive symptoms during or following 6 weeks of optimal medical management.
      i. MRI is listed as the most appropriate imaging
   c. SPECT or SPECT CT is usually not appropriate for initial imaging for low back pain with suspicion of cancer, infection or immunosuppression

Other payer policies:

1) Aetna 2023
   a. Aetna considers single photon emission computed tomography (SPECT) medically necessary for *any* of the following indications:
      i. Assessment of osteomyelitis, to distinguish bone from soft tissue infection; *or*
      ii. Detection of spondylolysis and stress fractures not visible from x-ray

b. The following procedures are considered experimental and investigational because the effectiveness of these approaches has not been established:
    i. Work-up of individuals undergoing non-cardiac surgery.

2) **CMS 2002** national coverage determination (NCD) for single photon emission computed tomography (SPECT)
    a. SPECT covered for the diagnosis of
        i. stress fracture
        ii. spondylosis
        iii. infection (e.g., discitis)
        iv. tumor (e.g., osteoid osteoma)
        v. analyze blood flow to an organ, as in the case of myocardial viability
        vi. differentiate ischemic heart disease from dilated cardiomyopathy.

SPECT for Back Pain

HERC staff summary:

The use of SPECT for pre-operative evaluation of back pain has very limited evidence of effectiveness, consisting of a few small case-series. American College of Radiology (ACR) appropriateness criteria list this indication as "may be appropriate" but list MRI as the most appropriate imaging modality. SPECT involves radiation and therefore is somewhat higher risk than MRI. Preoperative SPECT imaging of the spine is not covered by CMS or other major insurers. Based on the limited evidence of effectiveness and higher risk that other available imaging, staff is recommending against coverage of SPECT for pre-operative evaluation of neck or back pain.

The main use of SPECT in the spine is to diagnose stress fractures of the vertebra, infections such as osteomyelitis, and tumors of the spine. However, ACR appropriateness criteria read "SPECT or SPECT CT is usually not appropriate for initial imaging for low back pain with suspicion of cancer, infection…"

HERC staff recommendation:

1) Modify Diagnostic Guideline D4 as shown below
    a. Do not put in covered indications; these can be determined by medical appropriateness review

DIAGNOSTIC GUIDELINE D4, ADVANCED IMAGING FOR LOW BACK PAIN

In patients with non-specific low back pain and no "red flag" conditions [see Table D4], imaging is not a covered service; otherwise work up is covered as shown in the table. Repeat imaging is only covered when there is a substantial clinical change (e.g. progressive neurological deficit) or new clinical indication for imaging (i.e. development of a new red flag condition). Repeat imaging for acute exacerbations of chronic radiculopathic pain is not covered.

Electromyelography (CPT 96002-4) is not covered for non-specific low back pain.

Single photon emission computed tomography (SPECT) (CPT 78830-78832) is not covered for routine pre-operative evaluation of neck or back pain. SPECT of the spine may be covered in certain clinical situations (for example, evaluation for possible spinal infection when MRI is contraindicated or for evaluation of spinal stress fractures not visualized on x-ray in adolescents).

SPECT for Back Pain

Table D4

Low Back Pain - Potentially Serious Conditions ("Red Flags") and Recommendations for Initial Diagnostic Work-up

Possible cause	Key features on history or physical examination	Imaging[1]	Additional studies[1]
Cancer	• History of cancer with new onset of LBP	MRI	ESR
	• Unexplained weight loss • Failure to improve after 1 month • Age >50 years • Symptoms such as painless neurologic deficit, night pain or pain increased in supine position	Lumbosacral plain radiography	
	• Multiple risk factors for cancer present	Plain radiography or MRI	
Spinal column infection	• Fever • Intravenous drug use • Recent infection	MRI	ESR and/or CRP
Cauda equina syndrome	• Urinary retention • Motor deficits at multiple levels • Fecal incontinence • Saddle anesthesia	MRI	None
Vertebral compression fracture	• History of osteoporosis • Use of corticosteroids • Older age	Lumbosacral plain radiography	None
Ankylosing spondylitis	• Morning stiffness • Improvement with exercise • Alternating buttock pain • Awakening due to back pain during the second part of the night • Younger age	Anterior-posterior pelvis plain radiography	ESR and/or CRP, HLA-B27
Nerve compression/ disorders (e.g. herniated disc with radiculopathy)	• Back pain with leg pain in an L4, L5, or S1 nerve root distribution present < 1 month • Positive straight-leg-raise test or crossed straight-leg-raise test	None	None
	• Radiculopathic signs[2] present >1 month • Severe/progressive neurologic deficits (such as foot drop), progressive motor weakness	MRI[3]	Consider EMG/NCV
Spinal stenosis	• Radiating leg pain • Older age	None	None

SPECT for Back Pain

Possible cause	Key features on history or physical examination	Imaging[1]	Additional studies[1]
	• Pain usually relieved with sitting (Pseudoclaudication a weak predictor)		
	• Spinal stenosis symptoms present >1 month	MRI[3]	Consider EMG/NCV

[1]Level of evidence for diagnostic evaluation is variable

[2]Radiculopathic signs are defined for the purposes of this guideline as the presence of any of the following:

H) Markedly abnormal reflexes
I) Segmental muscle weakness
J) Segmental sensory loss
K) EMG or NCV evidence of nerve root impingement
L) Cauda equina syndrome,
M) Neurogenic bowel or bladder
N) Long tract abnormalities

[3]Only if patient is a potential candidate for surgery

Red Flag: Red flags are findings from the history and physical examination that may be associated with a higher risk of serious disorders.

CRP = C-reactive protein; EMG = electromyography; ESR = erythrocyte sedimentation rate; MRI = magnetic resonance imaging; NCV = nerve conduction velocity.

Extracted and modified from Chou R, Qaseem A, Snow V, et al: Diagnosis and Treatment of Low Back Pain: A Joint Clinical Practice Guideline from the American College of Physicians and the American Pain Society. Ann Intern Med. 2007; 147:478-491.

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

NEUROSURGICAL FOCUS

Neurosurg Focus 47 (6):E19, 2019

Preoperative SPECT imaging as a tool for surgical planning in patients with axial neck and back pain

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OBJECTIVE Hybrid SPECT with CT imaging has been used to help elucidate pain generators in patients with axial neck and back pain, identifying potential sites for treatment. Few studies have examined its role in spine surgery and most literature focuses on its use postoperatively. The authors describe the largest series to date of patients with symptomatic spondylosis who underwent preoperative SPECT imaging for surgical planning.

METHODS A retrospective medical and imaging record review was conducted to identify patients who underwent SPECT or SPECT/CT studies between January 2014 and May 2018. Patients who underwent spine surgical intervention for spondylosis with primary symptoms of axial neck or back pain and who had evidence of hypermetabolic foci on spinal SPECT imaging were included. Only those patients who subsequently underwent surgery on a spinal level associated with increased radiotracer uptake were included in the analysis. Patient baseline and demographic information, and data pertaining to SPECT imaging, surgical planning, and postoperative care were collected and analyzed.

RESULTS A total of 23 patients with an average age at surgery of 60.0 ± 11.0 years were included. Fifteen patients (65.2%) were male. A total of 53 spinal levels were treated, with an average of 2.30 levels treated per patient. All patients underwent fusion surgery, either lumbar (n = 14), with interbody fusion most commonly used (64.2%); or cervical (n = 9), with anterior cervical discectomy and fusion (66.6%) being the most common. The average length of hospital stay was 3.45 ± 2.32 days. One patient developed a wound infection postoperatively, requiring readmission. At the 3-month follow-up, 18 patients (78.3%) reported clinical improvement in pain. Eleven patients (47.8%) reported complete symptom resolution at the 6-month follow-up. At 1 year postoperatively, 19 patients (82.6%) reported significant relief of their symptoms following surgery.

CONCLUSIONS This is the largest series to date describing patients with axial neck and back pain who underwent preoperative SPECT imaging and subsequent surgical intervention on the affected spinal levels. The results demonstrate that SPECT imaging may be a useful adjunct to guide surgical planning, resulting in substantial clinical improvement following surgery.

https://thejns.org/doi/abs/10.3171/2019.9.FOCUS19648

KEYWORDS axial pain; imaging; preoperative planning; single-photon emission computed tomography; SPECT; spine surgery

High-resolution SPECT or hybrid SPECT/CT imaging has been increasingly used as a spinal imaging modality. When other imaging studies appear inconclusive, SPECT can be used to highlight sites of mechanical stress and degeneration, especially when combined with CT.[9] However, use of SPECT imaging in the perioperative period has not been well described in the existing literature.

Few studies have examined SPECT or hybrid SPECT/CT imaging to evaluate persistent or recurrent pain following spine surgery when conventional imaging modalities such as CT or MRI were inconclusive.[2,3] However, the utility of postoperative SPECT imaging, particularly in the early postoperative period, is limited because increased osteoblastic activity related to bony fusion results in a high degree of radiotracer uptake on SPECT imaging.

Thus, a more clinically impactful use for SPECT imaging may be during the preoperative period. SPECT and hybrid SPECT/CT imaging have recently aided identification of pain generators in patients with axial neck and

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NEUROSURGICAL FOCUS

Neurosurg Focus 47 (6):E18, 2019

Primary pain generator identification by CT-SPECT in patients with degenerative spinal disease

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OBJECTIVE Axial spinal pain generators are difficult to identify using current diagnostic modalities. Merging CT with SPECT (CT-SPECT) scans allows for accurate identification of areas with increased osteoblastic activity, which may reflect pain generators. In this study, the authors aimed to evaluate the degree of pain improvement in patients who underwent surgery, addressing primary pain generators identified by CT-SPECT.

METHODS The authors retrospectively reviewed all patients with chronic axial spine pain who underwent diagnostic CT-SPECT at their institution and analyzed pain improvement in those who underwent surgical treatment in order to determine whether CT-SPECT correctly identified the primary pain generator.

RESULTS A total of 315 patients underwent diagnostic CT-SPECT between January 2014 and August 2018. Forty-eight patients underwent either cervical or lumbar fusion; there were 26 women (16 cervical, 10 lumbar) and 22 men (9 cervical, 13 lumbar). The overall axial spinal pain, as assessed through self-reporting of visual analog scale scores at 6 months postoperatively, improved from 9.04 ± 1.4 to 4.34 ± 2.3 ($p = 0.026$), with cervical fusion patients improving from 8.8 ± 1.8 to 3.92 ± 2.2 ($p = 0.019$) and lumbar fusion patients improving from 9.35 ± 0.7 to 4.87 ± 2.3 ($p = 0.008$).

CONCLUSIONS CT-SPECT may offer a diagnostic advantage over current imaging modalities in identifying the primary pain generator in patients with axial spinal pain.

https://thejns.org/doi/abs/10.3171/2019.9.FOCUS19608

KEYWORDS CT-SPECT; spinal fusion; spine; pain

Chronic pain of spinal origin due to degenerative disease is common. The AANS/CNS guidelines on intractable low-back pain recommend a fusion procedure for axial pain due to 1- or 2-level degenerative disease that is refractory to conservative management.[5] However, identifying the primary pain generator in these patients is notoriously difficult. Many imaging techniques and invasive tests have been tried to reliably identify pain generators in these challenging cases but with little success.

SPECT uses detection of ^{99m}technetium bound to osteoblasts to gain information on the amount of bone remodeling activity in the spinal axis.[21] Using image-merging software between the SPECT and CT (CT-SPECT), we can thus identify, with a high degree of anatomical precision, which parts of the spine exhibit increased osteoblastic activity. If this activity is increased around a joint (e.g., disc or facet joint), it may be indicative of a primary pain generator. Previous reports regarding the reliability of this imaging modality in identifying the pain generator have shown positive results.[20] In the present study, we evaluated the degree of pain improvement in patients who underwent fusion surgery, addressing primary pain generators identified by CT-SPECT.

Methods

This is a retrospective study of all patients who underwent CT-SPECT at our institution between January 2014 (when we began using CT-SPECT as a diagnostic tool for

ABBREVIATIONS MI = minimally invasive; TLIF = transforaminal lumbar interbody fusion; VAS = visual analog scale.

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Two Level Cervical Artificial Discs

Plain Language Summary:

Coverage question: Should we cover an operation for a two-disc replacement between neck bones?

Should OHP cover this treatment? Yes, studies show this operation to be as safe and effective as an operation where the spinal bones are joined together.

Coverage Question: Should two levels of artificial discs be covered for cervical spine indications?

Question source: Max Kaiser, CCO medical director and HERC member

Background: Artificial discs are an alternative to spinal fusion for patients with back or neck pain who fail non-operative management (medications, physical therapy, etc.). Artificial discs can be used at one spinal level, or at two adjacent levels.

In November 2022, the evidence for lumbar second artificial discs was reviewed as part of the 2023 CPT code review. Insufficient evidence of effectiveness was found, and the CPT code for the second artificial disc was placed on line 662/GN173. There is a guideline regarding artificial discs that specifies that only a single level is covered for both lumbar and cervical levels. Based on the above, HERC staff recommended in March 2023 that the CPT code for cervical second artificial disc placement be removed from the covered and uncovered spine surgery lines and placed on line 662/GN173. This recommendation was approved by HERC.

Dr. Kaiser is requesting a review specific to cervical artificial discs, as the evidence supporting use at a second level is much better than the evidence supporting use in the lumbar spine at a second level.

On review, the decision in March 2023 to remove the second artificial disc placement code from coverage was partially based on FDA approval data from 2020, which indicated that these discs only had FDA approval for a single level. There are now two types of artificial disc which have FDA approval for 2 cervical levels.

Previous HSC/HERC reviews:

Cervical artificial discs were last reviewed as part of a coverage guideline in 2012 and reaffirmed in 2014. The coverage guidance concluded "Cervical artificial disc replacement appears to be comparable or superior to anterior cervical discectomy with fusion in effectiveness, and superior in safety." The 2014 review included the FDA contraindication to use cervical artificial discs at more than one level. The current artificial disc guideline was based on the 2012/2014 coverage guidance.

Two Level Cervical Artificial Discs

Two level cervical artificial discs were reviewed in August 2020. During that review, the 2016 Washington HTA report was reviewed, as well as three systematic reviews and meta-analyses on 1 vs two level cervical artificial discs (Kuang 2016, Jiang 2016, Zhao 2015). The staff conclusion was "Based on new meta-analyses and high-quality systematic reviews, there appears to be moderate evidence that two-level cervical artificial disc replacement is as effective or more effective than fusion surgery and appears to be safer and more cost-effective." The VBBS/HERC decision was to make no change in the coverage of only one level cervical artificial discs. The data was felt to be old and not compelling enough to make a change.

Current Prioritized List/Coverage status:

Placement prior to the March 2023 HERC meeting:

22858 Total disc arthroplasty (artificial disc), anterior approach, including discectomy with end plate preparation (includes osteophytectomy for nerve root or spinal cord decompression and microdissection); second level, cervical (List separately in addition to code for primary procedure) is on line 346 CONDITIONS OF THE BACK AND SPINE WITH URGENT SURGICAL INDICATIONS, 530 CONDITIONS OF THE BACK AND SPINE WITHOUT URGENT SURGICAL INDICATIONS

Placement after the March 2023 HERC meeting:

22858 is on line 662 CONDITIONS FOR WHICH CERTAIN INTERVENTIONS ARE UNPROVEN, HAVE NO CLINICALLY IMPORTANT BENEFIT OR HAVE HARMS THAT OUTWEIGH BENEFITS

GUIDELINE NOTE 101, ARTIFICIAL DISC REPLACEMENT

Lines 346,530

Artificial disc replacement (CPT 22856-22865) is included on Line 346 as an alternative to fusion for patients who meet criteria for spinal fusion procedures as defined in Guideline Note 37 only when all of the following criteria are met:

Lumbar artificial disc replacement

A) Patients must first complete a structured, intensive, multi-disciplinary program for management of pain, if covered by the agency;
B) Patients must be 60 years or under;
C) Patients must meet FDA approved indications for use and not have any contraindications. FDA approval is device specific but includes:
    - Failure of at least six months of conservative treatment
    - Skeletally mature patient
    - Replacement of a single disc for degenerative disc disease at one level confirmed by patient history and imaging

Cervical artificial disc replacement

A) Patients must meet FDA approved indications for use and not have any contraindications. FDA approval is device specific but includes:
    - Skeletally mature patient

Two Level Cervical Artificial Discs

- Reconstruction of a single disc following single level discectomy for intractable symptomatic cervical disc disease (radiculopathy or myelopathy) confirmed by patient findings and imaging.

Otherwise, artificial disc replacement is included on Line 530.

Artificial disc replacement combined with fusion in a single procedure (hybrid procedure) is not covered.

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

Guideline note 173 after the March 2023 HERC meeting:

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

Line 662

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

Procedure Code	Intervention Description	Rationale	Last Review
22858, 22860	Total disc arthroplasty (artificial disc), anterior approach, including discectomy to prepare interspace (other than for decompression); second interspace, cervical/lumbar	Insufficient evidence of effectiveness	November 2022

Evidence:

1) **CDATH 2019,** Health Technology Assessment: cervical artificial disc replacement vs fusion for cervical degenerative disc disease
    a. Included studies
        i. Mobi-C
            1. Davis et al 2013, RCT of 330 patients with 2 level cervical disc replacement [outcomes reported in Davis et al 2013, Davis et al 2015, Radcliff et al 2015]
                a. Cervical total disc replacement (TDR)=225 patients
                b. Anterior cervical discectomy and fusion (ACDF)=105 patients
        ii. Prestige-LP
            1. Gomet et al 2017, RCT of 456 patients with 2 level cervical disc replacement

a. Cervical total disc replacement (TDR)=226 patients
b. Anterior cervical discectomy and fusion (ACDF)=230 patients

b. Overall treatment success
    i. Moderate quality evidence
c. Health related quality of life
    i. High quality evidence
d. Conclusions:
    i. C-ADR might be preferable to fusion for cervical degenerative disc disease given outcomes that are statistically superior to fusion: quicker recovery and return to work (GRADE moderate), higher technical success and lower rate of re-operation at the index site (GRADE moderate), maintenance of more normal spinal segment kinetics (GRADE moderate), and higher overall treatment success for two-level cervical degenerative disc disease (GRADE moderate)
    ii. We are uncertain if adjacent-level surgery rates differ between C-ADR and fusion for one-level and two-level cervical degenerative disc disease (GRADE low). Evidence was also insufficient to determine the long-term durability of C-ADR devices

2) **Washington HTA 2016**, Artificial Disc Replacement-Rereview https://www.hca.wa.gov/assets/program/adr-rr-final-report-20161219.pdf
    a. Cervical Artificial Disc Replacement (C-ADR), 2 level
        i. N=2 RCTs and 2 comparative observational studies
            a. Comparing cervical artificial disc to fusion
        ii. Effectiveness at 24-60 months: Moderate quality evidence suggests that 2-level C-ADR is superior to ACDF in terms of overall success and NDI success; while low quality evidence suggests that C-ADR is as good as or better than ACDF in terms of arm and neck pain scores. However, the groups are comparable in terms of neurological success (low quality evidence). (Arm and neck pain success were not reported.)
            a. Based on 1 RCT of 320 patients (ST IDE trial)
        iii. Safety: Low quality evidence suggests that 2-level C-ADR is superior to ACDF in terms of the incidence of secondary surgery at the index level, serious/major adverse events, and device-related adverse events.
        iv. Safety: Low quality evidence suggests that 2-level C-ADR is superior to ACDF in terms of the incidence of secondary surgery at the index level, serious/major adverse events, and device-related adverse events up to 60 months
3) **NICE 2016**, Innovation briefing on Mobi-C for cervical disc replacement https://www.nice.org.uk/advice/mib70/resources/mobic-for-cervical-disc-replacement-pdf-63499340741317
    a. The evidence from 1 systematic review and 3 additional studies of mixed quality (N=1,675 patients)
    b. In 1 randomised controlled trial of 2-level Mobi-C included in the systematic review (n=330), the subsequent 4-year follow-up found that 66% of the Mobi-C group and 36% of the ACDF group achieved a composite end point of overall success.
        i. Davis et al 2013
4) **Zou 2017**, meta-analysis of RCTs on cervical discectomy and fusion vs artificial disc for two contiguous levels
    a. N=6 RCTs

Two Level Cervical Artificial Discs

i. N=650 patients (317 in the artificial disc group, 333 in the fusion group)
ii. Davis 2015 [included in studies above], Hou 2013, Cheng 2011, Jawahar 2010, Grob 2009, Kim 2009
iii. Multiple products

b. The results of the meta-analysis indicated that the artificial disc patients had significant superiorities in mean blood loss (P < 0.00001, standard mean differences (SMD) = −0.85, 95 % confidence interval (CI) = −1.22 to −0.48); reoperation (P = 0.0009, risk ratio (RR) = 0.28, 95 % confidence interval (CI) = 0.13– 0.59), adjacent segment degeneration (P < 0.00001, risk ratio (RR) = 0.48, 95 % confidence interval (CI) = 0.40– 0.58) and Neck Disability Index (P = 0.002, SMD = 0.31, 95 % CI = 0.12–0.50)
c. No significant difference was identified between the two groups regarding mean surgical time (P = 0.84, SMD = −0.04, 95 % CI = −0.40 to 0.32), neck and arm pain scores (P = 0.52, SMD = 0.06, 95 % CI = −0.13 to 0.25) reported on a visual analog scale and rate of postoperative complications [risk ratio (RR) = 0.79; 95 % CI = 0.50–1.25; P = 0.31].
d. Conclusion We can learn from this meta-analysis that the cervical disc arthroplasty (CDA) group is equivalent and in some aspects has more significant clinical outcomes than the ACDF group at two contiguous levels cervical degenerative disc disease.

Regulatory guidelines

1) **Bydon 2021**, Review of FDA approved cervical artificial discs
   a) ne artificial discs have been approved by the US Food and Drug Administration (FDA) for single-level cervical total disc replacement (CTDR): PRESTIGE ST, PRODISC-C, BRYAN, SECURE-C, PCM, Mobi-C, PRESTIGE LP, M6-C, and Simplify
   b) Mobi-C and PRESTIGE LP have been approved for 2-level CTDR

Other payer policies:

1) **Aetna 2023**
   a) Aetna considers the following Food and Drug Administration (FDA)-approved prosthetic intervertebral discs medically necessary for the treatment of skeletally mature persons with symptomatic cervical degenerative disc disease or herniated disc at 2 contiguous levels:
      i) MOBI-C
      ii) Prestige LP Cervical Disc
      iii) Simplify Cervical Artificial Disc
2) **CMS LCD 2019**
   a) Two-level procedures performed simultaneously may be considered reasonable and necessary if there is objective clinical evidence of radiculopathy, myelopathy or spinal cord compression at two corresponding contiguous levels. A CDR device FDA-approved for 2 levels is required.
3) **United Health Care 2023**
   a) Cervical artificial total disc replacement with an FDA-approved prosthetic intervertebral disc is proven and medically necessary for treating one-level or two contiguous levels of cervical Degenerative Disc Disease (C3 to C7), in a Skeletally Mature individual with symptomatic radiculopathy and/or myelopathy.

Two Level Cervical Artificial Discs

b) Cervical artificial disc replacement with an FDA-approved prosthetic intervertebral disc is proven and medically necessary for treating one level or two contiguous levels of cervical Degenerative Disc Disease, in a Skeletally Mature individual with a history of cervical spinal fusion at another level (adjacent or non-adjacent).

4) **Premara BCBS 2022**

a) Cervical artificial intervertebral disc implantation may be considered medically necessary when ALL of the following criteria are met:

i) The device is approved by Food and Drug Administration (FDA): For two contiguous levels: ♣ Mobi-C® Cervical Disc (Zimmer Biomet) ♣ Prestige™ LP Cervical Disc (Medtronic) ♣ Simplify®Cervical Artificial Disc (NuVasive)

ii) The patient is skeletally mature

iii) The patient has intractable cervical radicular pain or myelopathy

(a) Which has failed at least 6 weeks of conservative nonoperative treatment including physical therapy and at least one of the following: Acupuncture, Cervical collar, Corticosteroids, Exercise program, Medical treatment with NSAIDs or other analgesics OR

(b) The patient has severe or rapidly progressive symptoms of nerve root or spinal cord compression requiring hospitalization or immediate surgical treatment

iv) Degeneration is documented by imaging within the prior 12 months (magnetic resonance imaging, computed tomography or myelography)

v) Cervical degenerative disc disease is from C3 through C7

vi) The patient is free from contraindication to artificial cervical intervertebral disc implantation

Expert input:

Dr. Josiah Orina, OHSU neurosurgery:

As a surgeon who performs cervical disc replacements, I fully support this change to OHP coverage guidelines. There are three devices that are FDA approved for 2 contiguous levels, and data is increasingly showing cervical disc replacement to be at least non-inferior to ACDF. Several commercial insurers already cover 2-level cervical disc replacements in indicated patients.

Dr. Jung Yoo and I are also in the midst of writing up our study examining the outcomes of 1 and 2 level cervical disc replacement compared to ACDF using a national, population database of 160 million people. This preliminary data is favorable for cervical disc replacement as well.

Two Level Cervical Artificial Discs

HERC staff summary:

Based on trusted source technology reviews (Washington HTA and CDATH), there is moderate evidence that two-level cervical artificial disc replacement is as effective or more effective than fusion surgery and appears to be safer and more cost-effective. These findings are based on the same 2 RCTs with a total of 786 patients. A third trusted source technology review (NICE) reached the same conclusion for one brand of cervical artificial disc, based on one RCT included in the WHTA and CDATH reviews. An expert submitted meta-analysis that included 650 patients found that two level artificial disc replacement had similar outcomes to two level fusion.

All private payers surveyed cover two level cervical disc disease.

HERC staff recommend reversing the March 2023 decision and covering two level cervical artificial disc replacement.

HERC staff recommendations:

1) Reverse the March 2023 decision and return two level artificial disc replacement to the covered and uncovered surgical back lines
    a. Return CPT 22858 (Total disc arthroplasty (artificial disc), anterior approach, including discectomy with end plate preparation (includes osteophytectomy for nerve root or spinal cord decompression and microdissection); second level, cervical (List separately in addition to code for primary procedure)) to lines 346 CONDITIONS OF THE BACK AND SPINE WITH URGENT SURGICAL INDICATIONS and 530 CONDITIONS OF THE BACK AND SPINE WITHOUT URGENT SURGICAL INDICATIONS
    b. Remove CPT 22858 from line 662 CONDITIONS FOR WHICH CERTAIN INTERVENTIONS ARE UNPROVEN, HAVE NO CLINICALLY IMPORTANT BENEFIT OR HAVE HARMS THAT OUTWEIGH BENEFITS
2) Reverse the March 2023 decision and remove the CPT code for two level artificial disc replacement from GN173
3) Modify GN101 as shown below

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

Line 662

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

Procedure Code	Intervention Description	Rationale	Last Review
~~22858,~~ 22860	Total disc arthroplasty (artificial disc), anterior approach, including discectomy to prepare interspace (other than for decompression); second interspace, ~~cervical/~~lumbar	Insufficient evidence of effectiveness	November 2022

Two Level Cervical Artificial Discs

GUIDELINE NOTE 101, ARTIFICIAL DISC REPLACEMENT

Lines 346,530

Artificial disc replacement (CPT 22856-22865) is included on Line 346 as an alternative to fusion for patients who meet criteria for spinal fusion procedures as defined in Guideline Note 37 only when all of the following criteria are met:

Lumbar artificial disc replacement

D) Patients must first complete a structured, intensive, multi-disciplinary program for management of pain, if covered by the agency;
E) Patients must be 60 years or under;
F) Patients must meet FDA approved indications for use and not have any contraindications. FDA approval is device specific but includes:
   - Failure of at least six months of conservative treatment
   - Skeletally mature patient
   - Replacement of a single disc for degenerative disc disease at one level confirmed by patient history and imaging

Cervical artificial disc replacement

B) Patients must meet FDA approved indications for use and not have any contraindications. FDA approval is device specific but includes:
   - Skeletally mature patient
   - Reconstruction of a single or 2 level disc following single or 2 level discectomy for intractable symptomatic cervical disc disease (radiculopathy or myelopathy) confirmed by patient findings and imaging.

Otherwise, artificial disc replacement is included on Line 530.

Artificial disc replacement combined with fusion in a single procedure (hybrid procedure) is not covered.

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

Health Quality Ontario

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ONTARIO HEALTH TECHNOLOGY ASSESSMENT SERIES

Cervical Artificial Disc Replacement Versus Fusion for Cervical Degenerative Disc Disease: A Health Technology Assessment

KEY MESSAGES

What Is This Health Technology Assessment About?

Cervical degenerative disc disease occurs in the cervical spine (the part of the spine in the neck) when the discs between the vertebrae (the bones of the spine) start to deteriorate. It causes painful and disabling symptoms that impact people's quality of life and ability to function.

When treatments such as medication and physical therapy are insufficient, surgery is an option. The most common surgery is anterior cervical discectomy and fusion (often simply called "fusion"). However, this surgery sometimes has a negative effect on the discs next to the one being treated. Another surgical option is cervical artificial disc replacement (C-ADR).

This health technology assessment looked at the effectiveness, safety, durability, and cost-effectiveness of C-ADR compared with fusion for treating cervical degenerative disc disease. We also looked at the budget impact of publicly funding C-ADR and the preferences, values, and experiences of people with cervical degenerative disc disease.

What Did This Health Technology Assessment Find?

C-ADR and fusion are relatively safe, and both decrease pain and improve symptom-related disability and health-related quality of life. Clinical trials show that C-ADR is an effective and safe alternative to fusion. Unlike fusion, C-ADR also allows the neck to move more normally and likely results in better outcomes in terms of recovery, return to work, technical failures, and need for re-operation at the original surgery site. Although further surgeries for degeneration at other spinal levels might be needed later for people having either type of surgery, we don't yet know if the need for additional surgeries differs between C-ADR and fusion.

C-ADR appears to be cost-effective for both one-level and two-level cervical disc degeneration. In Ontario, publicly funding C-ADR could result in extra costs of about $900,000 for one-level procedures and about $700,000 for two-level procedures over the next 5 years.

People who had undergone C-ADR reported positively on its effect on their symptoms, their quality of life, and their ability to move their neck following surgery. Limited access to C-ADR in Ontario was viewed as a barrier to receiving this treatment.

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Ontario
Health Quality Ontario

ABSTRACT

Background

Cervical degenerative disc disease is a multifactorial condition that begins with deterioration of the intervertebral disc and results in further degeneration within the spine involving the facet joints and ligaments. This health technology assessment examined the effectiveness, safety, durability, and cost-effectiveness of cervical artificial disc replacement (C-ADR) versus fusion for treating cervical degenerative disc disease.

Methods

We performed a systematic literature search of the clinical evidence comparing C-ADR with fusion. We assessed the risk of bias in each study and the quality of the body of evidence according to the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) Working Group criteria. We performed a systematic review of the economic literature and assessed the cost-effectiveness of C-ADR compared with fusion. We also estimated the budget impact of publicly funding C-ADR in Ontario over the next 5 years. To contextualize the potential value of C-ADR, we spoke with people with cervical degenerative disc disease.

Results

Eight studies of C-ADR for one-level cervical degenerative disc disease and two studies of C-ADR for two-level disease satisfied the criterion of statistical noninferiority compared with fusion on the primary outcome of 2-year overall treatment success (GRADE: Moderate). In two studies of C-ADR for two-level disease, C-ADR was statistically superior to fusion surgery for the same primary outcome (GRADE: Moderate). C-ADR was also noninferior to fusion for perioperative outcomes (e.g., operative time, blood loss), patient satisfaction, and health-related quality of life (GRADE: Moderate). C-ADR was superior to fusion for recovery and return to work, had higher technical success, and had lower rates of re-operation at the index site (GRADE: Moderate). C-ADR also maintained motion at the index-treated cervical level (GRADE: Moderate), but evidence was insufficient to determine if adjacent-level surgery rates differed between C-ADR and fusion. Current evidence is also insufficient to determine the long-term durability of C-ADR.

The primary economic analysis shows that C-ADR is likely to be cost-effective compared with fusion for both one-level ($11,607/quality-adjusted life-year [QALY]) and two-level ($16,782/QALY) degeneration. Various sensitivity and scenario analyses confirm the robustness of the results. The current uptake for one-level and two-level C-ADR in Ontario is about 8% of the total eligible. For one-level involvement, the estimated net budget impact increases from $7,243 (18 procedures) in the first year to $395,623 (196 procedures) in the fifth year following public funding, for a total budget impact over 5 years of $916,326. For two-level involvement, the corresponding values are $5,460 (7 procedures) in the first year and $283,689 (76 procedures) in the fifth year, for an estimated total budget impact of $705,628 over 5 years.

People with cervical degenerative disc disease reported that symptoms of pain and numbness can have a negative impact on their quality of life. People with whom we spoke had tried a variety of treatments with minor success; surgery was perceived as the most effective and permanent solution. Those who had undergone C-ADR spoke positively of its impact on their quality of life and ability to move their neck after surgery. The limited availability of C-ADR in Ontario was viewed as a barrier to receiving this treatment.

Conclusions

For carefully selected patients with cervical degenerative disc disease, C-ADR provides patient-important and statistically significant reductions in pain and disability. Further, unlike fusion, C-ADR allows people to maintain relatively normal cervical spine motion.

Compared with fusion, C-ADR appears to represent good value for money for adults with one-level cervical degenerative disc disease ($11,607/QALY) and for adults with two-level disease ($16,782/QALY). In Ontario, publicly funding C-ADR could result in total additional costs of $916,326 for one-level procedures and $705,628 for two-level procedures over the next 5 years.

People with whom we spoke who had undergone C-ADR surgery spoke positively of its impact on their quality of life and ability to move their neck after surgery. The limited availability of C-ADR in Ontario was viewed as a barrier to receiving this treatment.

Cervical Total Disc Replacement

Food and Drug Administration–Approved Devices

Mohamad Bydon, MD[a,b,c,*], Giorgos D. Michalopoulos, MD[a,b,c], Mohammed Ali Alvi, MBBS, MS[a,b,c], Anshit Goyal, MBBS, MS[a,b,c], Kingsley Abode-Iyamah, MD[d]

KEYWORDS

• FDA-approved artificial discs • Single-level CTDR • Two-level CTDR

KEY POINTS

- Nine artificial discs have been approved by the US Food and Drug Administration (FDA) for single-level cervical total disc replacement (CTDR):PRESTIGE ST, PRODISC-C, BRYAN, SECURE-C, PCM, Mobi-C, PRESTIGE LP, M6-C, and Simplify.
- Mobi-C and PRESTIGE LP have been approved for 2-level CTDR.
- FDA Investigational Device Exemption trials have shown noninferiority of CTDR compared with anterior cervical decompression and fusion.

INTRODUCTION

The gold-standard surgical treatment of patients with cervical radiculopathy or myelopathy caused by disc herniation or spondylosis has traditionally been anterior cervical decompression and fusion (ACDF); however, restricted mobility and concerns related to adjacent segment disease (ASD) led to the development of a motion-preserving alternative. Cervical total disc replacement (CTDR) offers a suitable alternative for carefully selected patients, which allows resolution of compressive disorder while preserving segmental motion.

At present, the Food and Drug Administration (FDA) in the United States has approved the commercial distribution of 9 CTDR devices (**Table 1**), arranged here in chronologic order of FDA approval:

- PRESTIGE ST (Medtronic Sofamor Danek, Memphis, TN)[a]
- PRODISC-C (Centinel Spine, West Chester, PA)
- BRYAN (Medtronic Sofamor Danek, Memphis, TN)[a]
- SECURE-C (Globus Medical, Audubon, PA)
- PCM (NuVasive Inc, San Diego, CA)
- Mobi-C (LDR, Sainte-Savine, France)
- PRESTIGE LP (Medtronic Sofamor Danek, Memphis, TN)
- M6-C (Spinal Kinetics, Sunnyvale, CA)
- Simplify (Simplify Medical, Sunnyvale, CA)

This article describes the path to FDA approval for CTDR, discusses the salient features of approved CTDR devices, and presents a comparison of clinically relevant parameters among these approved devices.

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[a]No longer manufactured for distribution.

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Table 1
US Food and Drug Administration–approved artificial discs for 1-level cervical total disc replacement until October 2020

Device	Material	Characteristics
PRESTIGE ST	Stainless steel	Ball in trough, Large prevertebral fixation system
PRODISC-C[a]	CoCrMo endplates, UHMWPE core	Ball and socket, fixed center of rotation
BRYAN	Ti endplates, PU nucleus and shell	Shock-absorbing potential, unconstrained
SECURE-C	CoCrMo endplates, UHMWPE core	Ball in trough, semiconstrained, translation enabled
PCM	CoCrMo endplates, UHMWPE core	Ball and socket, unconstrained
Mobi-C	CoCrMo endplates, UHMWPE core	Ball in trough, unconstrained, translation in 2 planes. Also, 2-level approved
PRESTIGE LP	Ti ceramic	Ball in trough, semiconstrained, translation enabled. Also, 2-level approved
M6-C	Ti endplates, PU nucleus, UHMWPE annulus	Shock-absorbing properties, 6° of freedom
Simplify	PEEK endplates, ceramic core	Translation in 2 planes

Abbreviations: CoCrMo, cobalt, chromium, molybdenum; PEEK, polyether ether ketone; PU, polyurethane; Ti, titanium; UHMWPE, ultrahigh-molecular-weight polyethylene.
[a] The original PRODISC-C device.

FOOD AND DRUG ADMINISTRATION APPROVAL PROCESS

CTDR devices are considered class III devices by the FDA; that is, "those that support or sustain human life, are of substantial importance in preventing impairment of human health, or which present a potential, unreasonable risk of illness or injury."[1] Thus, these devices are subject to stringent evaluation before they are made available, a process designed to obtain premarket approval (PMA).

Most devices are initially implanted in cadaveric models and tested on mechanical parameters, such as range of motion and alignment. This testing is usually followed by some single-arm feasibility clinical studies with a brief follow-up period of no more than 2 years, which provides a vague measure of efficacy for a small number of eligible patients, while concomitantly providing a first impression of the risks and adverse events. Most of the aforementioned devices went through the latter phase in Europe.

A critical step for PMA is a multicenter FDA Investigational Device Exemption (IDE) randomized clinical trial (RCT). In such a trial, the FDA allows the use of the device in limited centers and sets the regulations under which CTDR with the investigated device will be compared with ACDF, the existing gold standard. The primary aim of these trials is usually to establish safety and efficacy with a noninferiority statistical design. The patients are randomized to either procedure type, are not blinded because of the nature of the intervention, and are generally followed for 10 years. The primary outcome is overall success (defined later), whereas common secondary outcomes include Neck Disability Index (NDI), visual analog scale pain score, and rates of ASD and reoperation. Noninferiority results compared with ACDF at the end of 2-year follow-up are usually sufficient to grant PMA.

FDA-approved devices are then allowed to be manufactured and marketed; however, the IDE study sponsor is required to follow the study cohort for 7 to 10 years in total and report to the FDA long-term outcomes annually, even following PMA. So far, only the PRESTIGE and BRYAN devices have gone through the entire 10-year post-approval process.

The overall success of both ACDF and CTDR, which is the primary end point of the FDA IDE trials so far, is defined as the fulfillment of a composite measure, typically consisting of the following criteria:

1. Improvement of more than 15 points in the NDI scale compared with preoperative status.

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REVIEW ARTICLE

Anterior cervical discectomy and fusion (ACDF) versus cervical disc arthroplasty (CDA) for two contiguous levels cervical disc degenerative disease: a meta-analysis of randomized controlled trials

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Abstract

Background Anterior cervical discectomy and fusion (ACDF) has been considered as a gold standard for symptomatic cervical disc degeneration (CDD), which may result in progressive degeneration of the adjacent segments. The artificial cervical disc was designed to reduce the number of lesions in the adjacent segments. Clinical studies have demonstrated equivalence of cervical disc arthroplasty (CDA) for anterior cervical discectomy and fusion in single segment cervical disc degeneration. But for two contiguous levels cervical disc degeneration (CDD), which kind of treatment method is better is controversial.

Purpose To evaluate the clinical effects requiring surgical intervention between anterior cervical discectomy and fusion (ACDF) and cervical disc arthroplasty (CDA) at two contiguous levels cervical disc degeneration.

Methods We conducted a comprehensive search in multiple databases, including PubMed, Cochrane Central Register of Controlled Trials, EBSCO and EMBASE. We identified that six reports meet inclusion criteria. Two independent reviewers performed the data extraction from archives. Data analysis was conducted with RevMan 5.3.

Results After applying inclusion and exclusion criteria, six papers were included in meta-analyses. The overall sample size at baseline was 650 patients (317 in the TDR group and 333 in the ACDF group). The results of the meta-analysis indicated that the CDA patients had significant superiorities in mean blood loss ($P < 0.00001$, standard mean differences (SMD) = −0.85, 95 % confidence interval (CI) = −1.22 to −0.48); reoperation ($P = 0.0009$, risk ratio (RR) = 0.28, 95 % confidence interval (CI) = 0.13–0.59), adjacent segment degeneration ($P < 0.00001$, risk ratio (RR) = 0.48, 95 % confidence interval (CI) = 0.40–0.58) and Neck Disability Index ($P = 0.002$, SMD = 0.31, 95 % CI = 0.12–0.50). No significant difference was identified between the two groups regarding mean surgical time ($P = 0.84$, SMD = −0.04, 95 % CI = −0.40 to 0.32), neck and arm pain scores ($P = 0.52$, SMD = 0.06, 95 % CI = −0.13 to 0.25) reported on a visual analog scale and rate of postoperative complications [risk ratio (RR) = 0.79; 95 % CI = 0.50–1.25; $P = 0.31$]. The CDA group of sagittal range of motion (ROM) of the operated and adjacent levels, functional segment units (FSU) and C2-7 is superior to ACDF group by radiographic data of peroperation, postoperation and follow-up.

Conclusion We can learn from this meta-analysis that the cervical disc arthroplasty (CDA) group is equivalent and in some aspects has more significant clinical outcomes than the ACDF group at two contiguous levels CDD.

Keywords Cervical disc arthroplasty · Anterior cervical discectomy fusion · Cervical disc degeneration · Two contiguous levels · Meta-analysis

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Introduction

Cervical disc degeneration (CDD) is accounted for neck and arm pain, radiculopathy and myelopathy, which seriously affects our quality of life [1]. Anterior cervical

YAG Laser Therapy for Hidradenitis Suppurativa

Plain Language Summary:

Coverage question: Should a laser treatment for a condition causing long lasting skin irritation and pain be covered?

Should OHP cover this treatment? Yes, though it is more costly than medications, it appears to be more effective.

Coverage Question: Should treatment with YAG laser be added to one or both of the hidradenitis suppurativa lines?

Question source: Holly Jo Hodges, CCO medical director, OHSU dermatology

Background: Hidradenitis suppurativa (HS) is a chronic inflammatory skin condition characterized by recurrent painful boils in flexural sites, such as the axillae and groin, that affects about 1% of the population, with onset in early adulthood. Coverage for more severe forms of this condition (Hurley stages II and III) was added as a biennial review item for 2020. On the new, covered line for HS are skin excision codes. Medications such as antibiotics and immune modulators are covered for the disease.

OHSU dermatology is requesting consideration of use of YAG lasers to treat HS. Laser treatment was not discussed during the 2018 biennial review of this topic. YAG lasers are a type of laser than can reach the deeper layers of the skin. They are used to treat a variety of skin conditions, such as hemagiomas and telangiectasia. They can also be used for tattoo removal and hair removal. They are also used for cosmetic purposes, such as treating age spots or wrinkles. YAG lasers are generally safe, but can cause local irritation and redness and pain.

Previous HSC/HERC reviews:

HS was last reviewed as a biennial review item in 2018. YAG laser therapy was not included in that review.

Current Prioritized List/Coverage status:

ICD-10-CM L73.2 (Hidradenitis suppurativa) is on lines 418 MODERATE TO SEVERE HIDRADENITIS SUPPURATIVA and 514 MILD HIDRADENITIS SUPPURATIVA; DISSECTING CELLULITIS OF THE SCALP.

YAG Laser Therapy for Hidradenitis Suppurativa

GUIDELINE NOTE 198, HIDRADENITIS SUPPURATIVA

Lines 418,514

Hidradenitis suppurativa is included on Line 418 only for moderate to severe disease (e.g. Hurley Stage II or Hurley Stage III); otherwise this condition is included on Line 514.

Initial treatment with adalimumab is limited to adults whose disease has not responded to at least a 90-day trial of conventional therapy (e.g., oral antibiotics), unless such a trial is not tolerated or contraindicated. Treatment with adalimumab after 12 weeks is only included on Line 418 for patients with a clear evidence of response, defined as:

A) a reduction of 25% or more in the total abscess and inflammatory nodule count, AND
B) no increase in abscesses and draining fistulas.

Code placement

YAG laser therapy is represented by CPT 17110-17111 (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/15 or more lesions). These codes are on lines:

137 OPPORTUNISTIC INFECTIONS IN IMMUNOCOMPROMISED HOSTS; CANDIDIASIS OF STOMA; PERSONS RECEIVING CONTINUOUS ANTIBIOTIC THERAPY
312 GENDER DYSPHORIA/TRANSEXUALISM, 387 ANOGENITAL VIRAL WARTS
401 BENIGN CONDITIONS OF BONE AND JOINTS AT HIGH RISK FOR COMPLICATIONS
559 BENIGN NEOPLASM OF BONE AND ARTICULAR CARTILAGE INCLUDING OSTEOID OSTEOMAS; BENIGN NEOPLASM OF CONNECTIVE AND OTHER SOFT TISSUE
589 CORNS AND CALLUSES
613 VIRAL WARTS EXCLUDING VENEREAL WARTS

YAG Laser Therapy for Hidradenitis Suppurativa

Evidence:

1) **Jfri 2020**, Systematic review and meta-analysis of efficacy of non-ablative light-based devices in hidradenitis suppurativa
    a) N=5 RCTs (N=18, 22, 22, 43, 20 patients)
        i) Hurley stage II or III
    b) N=5 case series (N=20, 20, 25, 1, 15 patients)
        i) Hurley stage I, II, III or IV
    c) Meta-analysis done on 3 of the RCTs (53 treatment and 53 control patients). Low certainty evidence
        i) Significant statistical heterogeneity in reporting of HS-LASI existed in these RCTs, where I 2 was measured at 65.37% (P = 0.03, Q = 8.66).
        ii) Meta-analysis revealed that treatment with Nd:YAG laser (58 patients) significantly improved HS-LASI scores compared to the control group with a standardized mean difference (SMD) of 0.99 (95% CI: 0.28 to 1.71, p = 0.006)
    d) Conclusion:
        i) Our meta-analysis of Nd:YAG laser in HS patients suggests significant improvement in HS-LASI scores
        ii) Importantly, given that non-ablative light devices are costly, not covered by most insurance plans in North America, and that multiple sessions are required, confirming their effectiveness in well-designed randomized trials prior to incorporating them into treatment algorithms remains essential.
2) **CADTH 2013**, rapid evidence review of YAG laser for treatment of hidradenitis suppurativa
    a) N=4 articles (1 SR, 3 RCTs)
        i) Hurley stage II and III
        ii) Studies were small: 6, 20, 22 patients
        iii) Control group treated with topical interventions (1% clindamycin, benzoyl peroxide)
        iv) Overall, the quality of the included studies was moderate
    b) 2 month outcomes: In the RCT that presented results for patients after two-months of treatment, statistically significantly lower disease activity was seen lesions treated with the Nd:YAG laser when compared with the control lesions.3 The decrease in the modified HS-LASI rating was 31.6% for all anatomic sites, 24.4% for axillary sites, and 36.8% for inguinal sites
    c) 3 month outcomes: The SR presented the three month RCT outcomes.7 The decrease in HS-LASI rating in Nd:YAG treated areas was 65.3% for all sites, 62% for axillary sites, 73.4% for inguinal sites, and 53.2% for inframammary sites. These changes were significant, whereas changes in control-site lesions were not.
    d) 6 month outcome: The RCT that reported six month outcomes included the same cohort of patients as the SR that reported the three month outcomes. Like the three month results, at the six month follow-up, a decrease in HS-LASI rating was observed after Nd:YAG treatment.
    e) Conclusion: As long-pulsed Nd:YAG laser treatment is non-invasive, and was found to be both well-tolerated and satisfactory to patients, it is likely a reasonable treatment option for patients with HS. Studies with longer follow-up are needed in order to determine its long-term effectiveness and economic studies are needed in order to determine its cost-effectiveness

YAG Laser Therapy for Hidradenitis Suppurativa

Expert guidelines:

3) **Alikhan 2019**, North American clinical management guidelines for hidradenitis suppurativa
    a) Moderate-quality evidence for surgical management of chronic lesions has consisted of uncontrolled, retrospective reports
        i) Wide local excision has been the mainstay of traditional surgery
    b) An Nd:YAG laser is recommended in patients with Hurley stage II or /III disease on the basis RCT and case series data and in patients with Hurley stage I disease on the basis of expert consensus

Other payer policies:

1) **Aetna 2022**: Aetna considers laser treatment experimental and investigational for the following indications because of insufficient evidence in the peer-reviewed literature (not an all-inclusive list):
    - Hidradenitis suppurativa

Expert input:

From Heather Onoday, NP at OHSU dermatology:

YAG laser is a recommended from the North American Clinical Guidelines for clinical management of hidradenitis suppurativa. See below references. I would disagree that YAG laser is 'expensive and not covered by other insurers', as per this report. It is actually covered by many insurers and is significantly less expensive than adalimumab, infliximab, surgical interventions and several other complementary treatment options. Our data in our clinic reflects that reimbursement for this laser procedure approximates $200 paid to the institution.

Compared below, is the current US pricing per Uptodate for adalimumab:
Pen-injector Kit (Humira Pen-CD/UC/HS Starter Subcutaneous)

40 mg/0.8 mL (per each): $3,845.91

80 mg/0.8 mL (per each): $7,691.83
Pen-injector Kit (Humira Pen-Ps/UV/Adol HS Start Subcutaneous)

40 mg/0.8 mL (per each): $3,845.91 ***(EVERY WEEK)***

Because of the difficulty treating this complex disease, patients need an opportunity to utilize various and/or combined therapies, as they often fail monotherapy, never respond (or no longer respond) to combined therapies/treatments, and need options for treating their painful and chronic disease. YAG laser receives the same strength of recommendation (or higher) than all therapies for HS, save adalimumab. This would leave adalimumab as the only "reasonably" recommended treatment for HS, which is obviously unrealistic considering it is only recommended for moderate and severe (refractory) HS, is contraindicated for some patients, and has significantly greater risk to the patient compared to laser, such as serious infections. It is

also very expensive, as above. This would imply that anything other than moderate disease or worse, should not receive treatment-nor would patients receive treatment if they have contraindications adalimumab. If they are not a candidate for adalimumab (the only "A" ranked recommendation)*, the next reasonable treatment option is a "B" ranked treatment, of which YAG is included in the guidelines.* I can state unequivocally, from my experience treating these complex patients with laser for more than 10 years: this treatment can sometimes be the *only* therapy that has ever significantly controlled these patients' disease. There were many patients who, when denied opportunities for their laser appts during the pandemic, had significant flaring of their disease because of that absence of lasering of their skin. Upon clinics reopening and them restarting laser therapy, their disease was again controlled and was clearly attributed to their laser therapy. Many have been able to avoid use of adalimumab because of laser, when they sought laser as an alternative.

We work very hard to offer this treatment for our patients, because we know what a significant impact it can make for the majority of our patients who are afforded the opportunity. Most truly do report that they are very grateful for the treatments and are confident that it improves their disease and quality of life. The lasering helps regardless of quality or quantity of hair. The treatments are used on many affected areas: inframammary, abdominal, flank, groin, buttock, labia, and other areas, regardless of hair presence, quality, color/responsiveness, etc. All areas can demonstrate improvement with the light energy, typically within 4-6 treatments. Depending on their flares, patients will space out their treatments, some returning 3- 4 times per year- some more, some less.

It is not uncommon for us to see these patients after they have failed biologic therapy, many oral antibiotics/anti-androgens, weight loss, surgical intervention/large grafts, intralesional injections, etc, and this is the therapy that finally helps them. This is actually a fairly *inexpensive* modality for treatment, provides a reduced risk of comorbidity due to medication compatibility issues, and is a treatment that can complement any other HS therapy without concern for contraindication.

HERC staff summary:

Use of YAG lasers to treat hidradenitis suppurativa has been shown to be effective is several small RCTs. The literature is composed of small studies, largely due to the rare nature of this condition. Due to the rare nature of this condition, the suffering it causes, and the low side effect profile of this treatment, HERC staff feels that adding coverage is reasonable. Expert guidelines and expert opinion recommend YAG lasers as a treatment option for HS. YAG laser treatment is more expensive that some oral and topical medications, but less expensive that immune modulating medications. Some private payers do not cover this therapy for HS.

HERC staff recommendation:

1) Add CPT 17110-17111 (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/15 or more lesions) to line 418 MODERATE TO SEVERE HIDRADENITIS SUPPURATIVA

frontiers in Medicine

SYSTEMATIC REVIEW
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The Efficacy and Effectiveness of Non-ablative Light-Based Devices in Hidradenitis Suppurativa: A Systematic Review and Meta-Analysis

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Hidradenitis suppurativa (HS) is a chronic inflammatory skin disorder that may be treated with non-ablative light-based devices; however, no systematic reviews on the topic exist to date. We conducted a systematic review and meta-analysis to determine efficacy of non-ablative light-based devices in treating HS. Specifically, a systematic review was conducted using MEDLINE, EMBASE, Web of Science and CINAHL. We analyzed the use of non-ablative light-based devices in the treatment of HS. At least two investigators performed title/abstract review and data extraction. Meta-analysis was conducted using comprehensive meta-analysis software. 5 RCTs and 11 case reports/series were included ($n = 211$ unique patients). No observational studies were found. For Nd:YAG laser, meta-analysis of 3 RCTs reported improvement in modified HS Lesion Area and Severity Index (HS-LASI) when compared to control subjects. In addition, three case reports/series reported HS-LASI, Physician Global Assessment (PGA) scores and number-of-lesion improvements in treated patients. For intense pulsed light (IPL), two RCTs reported HS-LASI and Dermatology Life Quality Index (DLQI) score improvements. For Alexandrite laser, one case report showed lesion improvement. In conclusion, meta-analysis of Nd:YAG laser in HS patients suggests significant improvement in HS-LASI scores. For IPL, evidence is limited, but suggests improvement in HS-LASI and DLQI scores. For Alexandrite laser, evidence precludes conclusions. Given small sample sizes and inconsistent reporting scales, larger RCTs are required to better determine the efficacy of these modalities in treating HS.

Keywords: hidradenitis suppurativa, lasers, hair removal, neodymium-doped yttrium aluminum garnet (Nd:YAG), alexandrite, intense pulse light (IPL), light-based devices

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North American clinical management guidelines for hidradenitis suppurativa: A publication from the United States and Canadian Hidradenitis Suppurativa Foundations:

Part I: Diagnosis, evaluation, and the use of complementary and procedural management

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Disclosure: Dr Sayed reports service as a speaker for AbbVie and Novartis, an advisory board member for AbbVie and InflaRx, a coinvestigator for AbbVie and Novartis, and an investigator for InflaR and UCB. Dr Hamzavi reports service as an investigator for AbbVie, The Microdermis Corporation, Adelphi Values, and Lenicura and a consultant for UCB and Incyte; in addition, he is president of the Hidradenitis Suppurativa Foundation. Dr Hazen reports service as a speaker for AbbVie and an advisory board member for AbbVie. Dr Kimball reports service as a consultant and investigator for Amgen, AbbVie, Janssen, and Novartis and has received fellowship funding from Novarti and AbbVie. Dr Lowes reports service as an advisory board member for AbbVie and Janssen and a consultant for AbbVie, XBiotech, and Incyte. Dr Alavi reports service as a clinical investigator and consultant for AbbVie, Janssen, Novartis, Pfizer, Galderma, Leo, and Valeant and has received grant funding from AbbVie. Dr Naik reports grant funding from AbbVie. Dr Alhusayen reports service for AbbVie as an advisory board member and consulting and has received research funding from the company; he has also served as an advisory board member for Janssen and a consultant for Eli Lilly and Company and Hidramed Solutions. Dr Orgill has served as a consultant and investigator for KCI, Inc, and Integra. Dr Brassard has served as a speaker and advisory board member for AbbVie, Janssen, Celgene, and 3M and as a speaker for Coloplast and Hollister. Dr Miller has served as a consultant for AbbVie and an advisory board member for AbbVie and BSN; in addition, she is employed by the Hidradenitis Suppurativa Foundation and is president and founding director of the Hope for HS support group. Dr Poulin has served as an investigator, advisory board member, and speaker for AbbVie. Dr Kirby has served as an advisory board member and speaker for AbbVie and a consultant for Incyte and Chemocentryx. Dr Gottlieb has served as an investigator for Novartis and a speaker for AbbVie. Dr Jaleel has served as an investigator for Eli Lilly and Company. Dr Alikhan, Dr Micheletti, Dr Eisen, Dr Burkhart, and Dr Crowell have no conflicts of interest to disclose.

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Abstract

Hidradenitis suppurativa is a chronic inflammatory disorder affecting hair follicles, with profoundly negative impact on patient quality of life. Evidence informing ideal evaluation and management of patients with hidradenitis suppurativa is still sparse in many areas, but it has grown substantially in the last decade. Part I of this evidence-based guideline is presented to support health care practitioners as they select optimal management strategies, including diagnostic testing, comorbidity screening, and both complementary and procedural treatment options. Recommendations and evidence grading based on the evidence available at the time of the review are provided.

Keywords

acne inversa; adalimumab; biomarkers; carbon dioxide laser; clindamycin; comorbidities; ertapenem; finasteride; guidelines; hidradenitis suppurativa; infliximab; laser; lifestyle modification; microbiome; Nd:YAG; oral contraceptive pills; rifampin; spironolactone

DISCLAIMER

The purpose of these guidelines is to summarize the available data at the time of preparation. It is possible that certain treatments or procedures are not included, as the primary literature review concluded on March 16, 2017, with only selected updates of high clinical impact through December 1, 2018. Given the difficulty in treating hidradenitis suppurativa (HS), there is no guarantee that following the guidelines will result in successful treatment. Moreover, the guidelines are not meant to set a standard of care. Care of a patient with HS is ultimately guided by the physician and patient, with an emphasis on factors unique to individual patients.

SCOPE

The guidelines address management of patients presenting with HS and discuss various treatments and procedures available at the time of preparation. In Part I of the guidelines

Section 8.0

Coverage Guidances

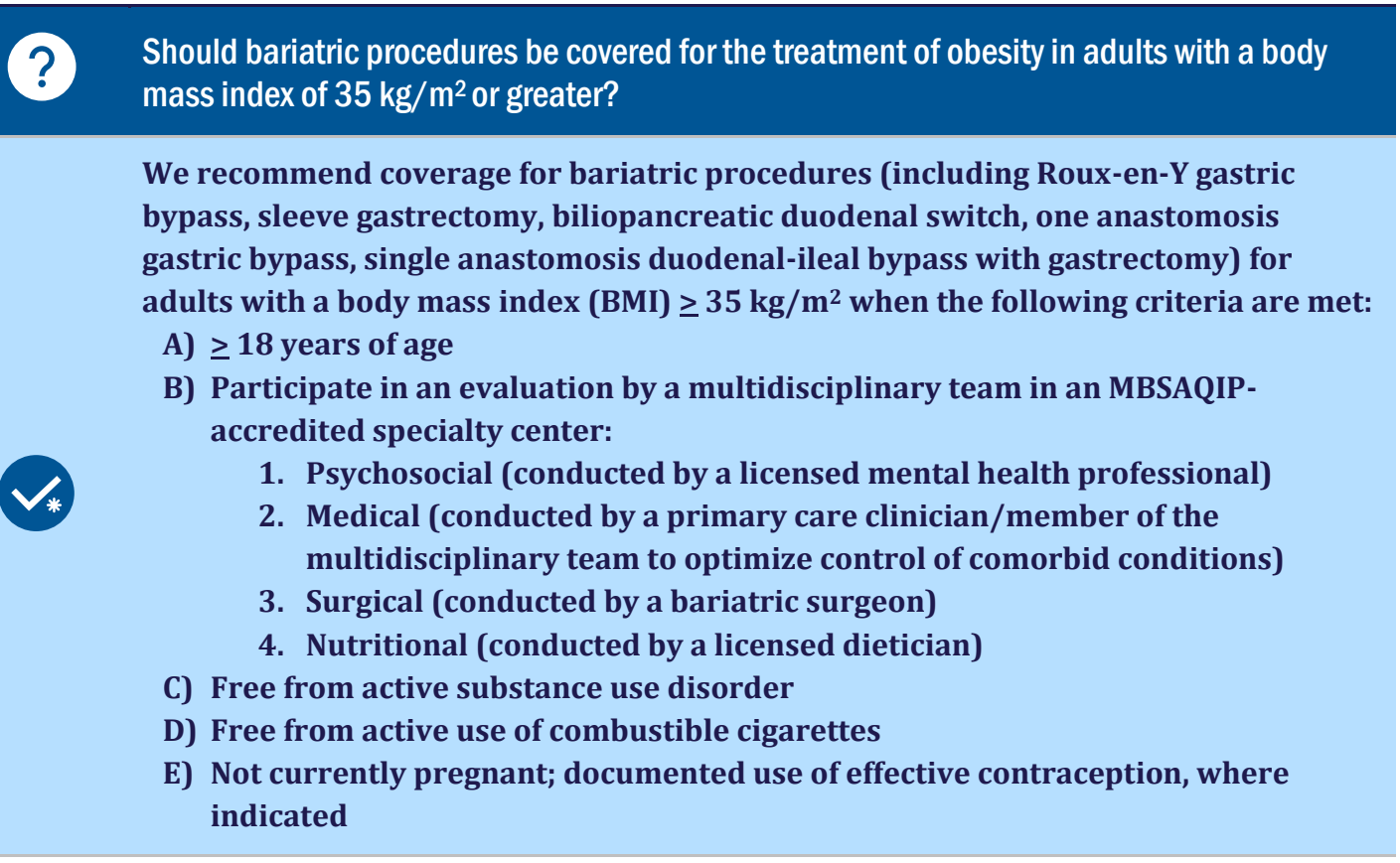
Bariatric procedures

Coverage Question: How should the Coverage Guidance Bariatric Procedures be applied to the Prioritized List?

Question source: EbGS

Issue: EbGS conducted a re-review of the 2016 coverage guidance for bariatric procedures at their September 2022, February 2023 and April 2023 meetings. Based on the evidence review, the initial staff recommendation included expanding coverage for adults with BMI 30-34.9 with type 2 diabetes mellitus (T2DM) but not adolescents due to insufficient evidence of effectiveness and lack of follow up beyond 2 years. The recommendation also included expanding covered bariatric procedure types beyond Roux-en-Y gastric bypass and sleeve gastrectomy.

During subcommittee deliberation, the recommendation was revised to include coverage for adolescents based on a recent release of AAP's clinical practice guideline on obesity, which includes a recommendation to "offer referral for adolescents aged 13 and older with severe obesity for evaluation for metabolic and bariatric surgery." The revised draft coverage guidance was put out for public comment in February 2023. Based on public comments received and additional subcommittee discussion, the blue box was modified to include coverage for adolescents as well adults with BMI 30-34.9 with poorly-controlled T2DM, subject to coverage criteria. The new coverage guidance was referred to HERC at the EbGS April 20, 2023 meeting. The "blue box" wording is shown below:



Bariatric procedures

F) Adhere to post-surgical evaluation and post-operative care recommendations, some of which may require lifelong adherence

Adjustable gastric banding and intragastric balloons are not recommended for coverage.

Rationale

We recommend coverage because evidence shows these procedures significantly improve type 2 diabetes, hypertension, weight loss, and risk of death. These benefits are considerably greater than the low risk of harms. We have added preoperative eligibility requirements based on clinical guideline standards. Due to a lack of evidence of long-term benefit, adjustable gastric banding and intragastric balloons are not recommended for coverage.

Should bariatric procedures be covered for the treatment of obesity in adults with a body mass index range from 30.0 to 34.9 kg/m²?

We recommend coverage for bariatric procedures in adults with BMI 30.0 to 34.9 kg/m² who, in addition to meeting the above coverage requirements, also have a diagnosis of Type 2 Diabetes Mellitus (T2DM) which has not met clinical glycemic targets despite trials of two diabetes medications.

Rationale

We recommend limiting coverage to patients who have been unable to achieve diabetes control (HbA1c above clinical target) despite trials of two diabetes medications, because medication should be sufficient for many patients to achieve diabetes control. Evidence indicates that these procedures significantly improve weight outcomes and rates of diabetes remission for patients with T2DM, which is greater than the low risk of harms. Evidence is less clear regarding hypertension and other health outcomes, with no evidence reported on risk of death. We have added preoperative eligibility requirements based on clinical guideline standards.

Should bariatric procedures be covered for the treatment of obesity in adolescents?

We recommend coverage for bariatric procedures in adolescents when ALL of the following criteria are met:

Bariatric procedures

A) Over the age of 12
B) Participate in an evaluation by a multidisciplinary team in an MBSAQIP-accredited specialty center with Adolescent accreditation:
1. **Psychosocial (conducted by a licensed mental health professional)**
2. **Medical (conducted by a primary care clinician/member of the multidisciplinary team to optimize control of comorbid conditions)**
3. **Surgical (conducted by a bariatric surgeon)**
4. **Nutritional (conducted by a licensed dietician)**

C) When BMI is:
1. **≥35kg/m² or 120% of the 95th percentile for age and sex AND a clinically significant comorbid condition; OR**
2. **≥40kg/m² or 140% of the 95th percentile for age and sex**

D) Adhere to post-surgical evaluation and post-operative care recommendations, some of which may require lifelong adherence.

Rationale
We recommend coverage to align with professional society guidelines and expert input. There are known clinically significant comorbid conditions that are associated with obesity that, if not addressed earlier in the lifecourse, may result in premature morbidity and mortality. We have added preoperative eligibility requirements based on clinical guideline standards.

Previous HSC/HERC reviews: A coverage guidance process for bariatric procedures was last conducted in 2016.

Blue box coverage guidance approved 10/6/2016:

Coverage of metabolic and bariatric surgery (including Roux-en-Y gastric bypass 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:

Bariatric procedures

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

Current Prioritized List status:

CODES	DESCRIPTION		PLACEMENT
CPT		Known as	
43644	Laparoscopy, surgical, gastric restrictive procedure; with gastric bypass and Roux-en-Y gastroenterostomy (roux limb 150 cm or less)	Roux-en-Y gastric bypass	320
43645	Laparoscopy, surgical, gastric restrictive procedure; with gastric bypass and small intestine reconstruction to limit absorption	Roux-en-Y gastric bypass	320
43659	Unlisted laparoscopy procedure, stomach	Unlisted procedure	ANCILLARY PROCEDURES
43770	Laparoscopy, surgical, gastric restrictive procedure; placement of adjustable gastric restrictive device (e.g., gastric band and subcutaneous port components)	Adjustable gastric banding	662
43771	Laparoscopy, surgical, gastric restrictive procedure; revision of adjustable gastric restrictive device component only	Adjustable gastric banding revision	320,424
43772	Laparoscopy, surgical, gastric restrictive procedure; removal of adjustable gastric restrictive device component only	Adjustable gastric banding removal	285,320,424
43773	Laparoscopy, surgical, gastric restrictive procedure; removal and replacement of adjustable gastric restrictive device component only	Adjustable gastric banding removal and replacement	285,320,424
43774	Laparoscopy, surgical, gastric restrictive procedure; removal of adjustable gastric restrictive device and subcutaneous port components	Adjustable gastric banding removal	285,320,424
43775	Laparoscopy, surgical, gastric restrictive procedure; longitudinal gastrectomy (i.e., sleeve gastrectomy)	Sleeve gastrectomy	320
43842	Gastric restrictive procedure, without gastric bypass, for morbid obesity; vertical-banded gastroplasty	Vertical banded gastroplasty	662
43843	Gastric restrictive procedure, without gastric bypass, for morbid obesity; other than vertical-banded gastroplasty	Adjustable banded gastroplasty	662

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CODES	DESCRIPTION		PLACEMENT
CPT		**Known as**	
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)	Biliopancreatic diversion with duodenal switch	662
43846	Gastric restrictive procedure, with gastric bypass for morbid obesity; with short limb (150 cm or less) Roux-en-Y gastroenterostomy	Roux-en-Y gastric bypass	320
43847	Gastric restrictive procedure, with gastric bypass for morbid obesity; with small intestine reconstruction to limit absorption	Roux-en-Y gastric bypass	320
43848	Revision, open, of gastric restrictive procedure for morbid obesity, other than adjustable gastric restrictive device (separate procedure)	Revision	285,320,424
43886	Gastric restrictive procedure, open; revision of subcutaneous port component only	Revision	662
43887	Gastric restrictive procedure, open; removal of subcutaneous port component only	Removal	662
43888	Gastric restrictive procedure, open; removal and replacement of subcutaneous port component only	Removal	662
43999	Unlisted procedure, stomach	Unlisted procedure	NEVER REVIEWED
HCPCS			
S2083	Adjustment of gastric band diameter via subcutaneous port by injection or aspiration of saline	Adjustable gastric banding adjustment	320
ICD-10-CM			
E66.01	Morbid (severe) obesity due to excess calories		320
E66.09	Other obesity due to excess calories		320
E66.1	Drug-induced obesity		320
E66.2	Morbid (severe) obesity with alveolar hypoventilation		320
E66.8	Other obesity		320
E66.9	Obesity, unspecified		320
Z46.51	Encounter for fitting and adjustment of gastric lap band		320
Z68.30	Body mass index [BMI] 30.0-30.9, adult		320
Z68.31	Body mass index [BMI] 31.0-31.9, adult		320
Z68.32	Body mass index [BMI] 32.0-32.9, adult		320
Z68.33	Body mass index [BMI] 33.0-33.9, adult		320
Z68.34	Body mass index [BMI] 34.0-34.9, adult		320
Z68.35	Body mass index [BMI] 35.0-35.9, adult		320

Bariatric procedures

CODES	DESCRIPTION	PLACEMENT
CPT	Known as	
Z68.36	Body mass index [BMI] 36.0-36.9, adult	320
Z68.37	Body mass index [BMI] 37.0-37.9, adult	320
Z68.38	Body mass index [BMI] 38.0-38.9, adult	320
Z68.39	Body mass index [BMI] 39.0-39.9, adult	320
Z68.41	Body mass index [BMI] 40.0-44.9, adult	320
Z68.42	Body mass index [BMI] 45.0-49.9, adult	320
Z68.43	Body mass index [BMI] 50.0-59.9, adult	320
Z68.44	Body mass index [BMI] 60.0-69.9, adult	320
Z68.45	Body mass index [BMI] 70 or greater, adult	320
Z68.53	Body mass index [BMI] pediatric, 85th percentile to less than 95th percentile for age	320
Z68.54	Body mass index [BMI] pediatric, greater than or equal to 95th percentile for age	320

GUIDELINE NOTE 8, BARIATRIC SURGERY

Line 320

Bariatric/metabolic surgery (limited to Roux-en-Y gastric bypass and sleeve gastrectomy) is included on Line 320 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
C) Repeat bariatric surgery is included when it is a conversion from a less intensive (such as gastric band or sleeve gastrectomy) to a more intensive surgery (e.g. Roux-en-Y). Repair of surgical complications (excluding failure to lose sufficient weight) are also included on this and other lines. Reversal of surgical procedures and devices is included on this line when benefits of reversal outweigh harms.
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 any nicotine product or illicit drugs and must remain abstinent from their use during the six-month observation period. Testing will, at a minimum, be conducted within 1 month of the quit date and within 1 month of the surgery to confirm abstinence from illicit drugs. Tobacco and nicotine abstinence to be confirmed in active users by negative cotinine levels at least 6 months apart, with the second test within one month of the surgery date.

c) No mental or behavioral disorder that may interfere with postoperative outcomes[1].
d) Patient with 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.
b) Received counseling by a credentialed expert on the team regarding the risks and benefits of the procedure and understands the many potential complications of the surgery (including death) and the realistic expectations of post-surgical outcomes.

4) Dietitian evaluation: (Conducted by licensed dietitian)
a) Counseling in dietary lifestyle changes
b) Counseling on post-operative dietary change requirements

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 accreditation (as a comprehensive center or low acuity center) by the Metabolic and Bariatric Surgery Accreditation and Quality Improvement Program (MBSAQIP)

Bariatric procedures

HERC staff summary:

The coverage guidance would result in the following changes to the current Guideline Note 8 BARIATRIC SURGERY. Below is a comparison of the current guideline and proposed changes:

Item	Current GN 8	Proposed GN 8
Surgery type	Roux-en-Y, sleeve gastrectomy	Roux-en-Y gastric bypass, sleeve gastrectomy, biliopancreatic duodenal switch, one anastomosis gastric bypass, single anastomosis duodenal-ileal bypass with sleeve gastrectomy (SADI-S)
Age	Adults over 18 years of age	People over 12 years of age
BMI alone	40 kg/m^2	Adults: 35 kg/m^2 Adolescents 13-18: 40 kg/m^2 or 140% of 95th percentile
BMI with comorbidity	35 kg/m^2 with T2DM or two conditions: hypertension, coronary heart disease, mechanical arthropathy in joint, sleep apnea	Adults: 30 kg/m^2 with T2DM that has not been optimized with medical therapy Adolescents 13-18: 35 kg/m^2 or 120% of 95th percentile with a clinically significant comorbid condition
Contraception requirement	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.	Not currently pregnant; documented use of effective contraception, where indicated
Nicotine use	Must remain free of abuse of or dependence on alcohol during the six-month period immediately preceding surgery. No current use of any nicotine product or illicit drugs and must remain abstinent from their use during the six-month observation period. Testing will, at a minimum, be conducted within 1 month of the quit date and within 1 month of the surgery to confirm abstinence from illicit drugs. Tobacco and nicotine abstinence to be confirmed in active users by negative cotinine levels at least 6 months apart, with the second test within one month of the surgery date	Free from active use of combustible cigarettes
Evaluation: Psychosocial	No mental or behavioral disorder that may interfere with postoperative outcomes. Patient with psychiatric illness must be stable for at least 6 months. Evaluation to assess potential compliance with post-operative requirements	Psychosocial (conducted by a licensed mental health professional)
Evaluation: Medical	Pre-operative physical condition and mortality risk assessed with patient found to be an appropriate candidate. Optimize medical control of diabetes, hypertension, or other co-morbid conditions	Medical (conducted by a primary care clinician/member of the multidisciplinary team to optimize control of comorbid conditions)
Evaluation: Surgical	Patient found to be an appropriate candidate for surgery at initial evaluation and throughout period leading to surgery. Received counseling by a credentialed expert on the team regarding the risks and benefits of the procedure and understands the many potential complications of	Surgical (conducted by a bariatric surgeon)

Bariatric procedures

	the surgery (including death) and the realistic expectations of post-surgical outcomes.	
Evaluation: Nutritional	Counseling in dietary lifestyle changes. Counseling on post-operative dietary change requirements	Nutritional (conducted by a licensed dietician)
Evaluation: Post-operative maintenance	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).	Adhere to post-surgical evaluation and post-operative care recommendations, some of which may require lifelong adherence
Center requirements	MBSAQIP-accredited comprehensive center or low acuity center	MBSAQIP-accredited comprehensive center, low acuity center or comprehensive center with Adolescent accreditation
Repeat bariatric surgery	Repeat bariatric surgery is included when it is a conversion from a less intensive (such as gastric band or sleeve gastrectomy) to a more intensive surgery (e.g. Roux-en-Y).	Unchanged
Revision or repair	Repair of surgical complications (excluding failure to lose sufficient weight) are also included on this and other lines. Reversal of surgical procedures and devices is included on this line when benefits of reversal outweigh harms.	Unchanged

HERC staff recommendation:

1) Add the following CPT codes to Line 320 OBESITY IN ADULTS AND CHILDREN; OVERWEIGHT STATUS IN ADULTS WITH CARDIOVASCULAR RISK FACTORS and remove from line 662 CONDITIONS FOR WHICH CERTAIN INTERVENTIONS ARE UNPROVEN, HAVE NO CLINICALLY IMPORTANT BENEFIT OR HAVE HARMS THAT OUTWEIGH BENEFITS:

   a) 43842 Gastric restrictive procedure, without gastric bypass, for morbid obesity; vertical-banded gastroplasty
   b) 43843 Gastric restrictive procedure, without gastric bypass, for morbid obesity; other than vertical-banded gastroplasty
   c) 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)
   d) 43886 Gastric restrictive procedure, open; revision of subcutaneous port component only
   e) 43887 Gastric restrictive procedure, open; removal of subcutaneous port component only
   f) 43888 Gastric restrictive procedure, open; removal and replacement of subcutaneous port component only
   g) 43999 Unlisted procedure, stomach

Bariatric procedures

2) Modify GN173 as shown below

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

Line 660

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

Procedure Code	Intervention Description	Rationale	Last Review
43770~~, 43842-43845, 43886-43888~~	~~Gastric restrictive procedures (gastric band, other)~~ Laparoscopy, surgical, gastric restrictive procedure; placement of adjustable gastric restrictive device (e.g., gastric band and subcutaneous port components)	No evidence of effectiveness	~~October, 2016~~ May 2023

3) Revise Guideline Note 8 BARIATRIC SURGERY to align with coverage guidance recommendation:
   a) Consider specifying clinical glycemic target
   b) Consider parameters regarding active use of combustible cigarettes
   c) Note that the repeat bariatric surgery coverage language has not been changed from prior guideline note

GUIDELINE NOTE 8, BARIATRIC SURGERY

Line 320

Bariatric/metabolic surgery (limited to Roux-en-Y gastric bypass, ~~and~~ sleeve gastrectomy, biliopancreatic duodenal switch, one anastomosis gastric bypass, single anastomosis duodenal-ileal bypass with gastrectomy) is included on Line 320 ~~when the following criteria are met~~ with specific criteria for adults and adolescents:

A) For adults aged ≥ 18 when ALL of the following criteria are met:
   1) The patient has obesity with a:
      a) BMI > 35 kg/m^2; OR
      b) BMI 30-34.9 kg/m^2 with Type 2 Diabetes Mellitus which has not met clinical glycemic targets despite trials of two diabetes medications
   2) Participate in an evaluation by a multidisciplinary team in an MBSAQIP-accredited specialty center[1]:
      a) Psychosocial (conducted by a licensed mental health professional)
      b) Medical (conducted by a primary care clinician/member of the multidisciplinary team to optimize control of comorbid conditions)
      c) Surgical (conducted by a bariatric surgeon)
      d) Nutritional (conducted by a licensed dietician)
   3) Free from active substance use disorder
   4) Free from active use of combustible cigarettes
   5) Not currently pregnant; documented use of effective contraception, where indicated

6) Adhere to post-surgical evaluation and post-operative care recommendations, some of which may require lifelong adherence

B) For adolescents aged 13 and older when ALL of the following criteria are met:
1) The patient has obesity with a:
   a) BMI > 35 kg/m2 or 120% of the 95th percentile for age and sex AND a clinically significant comorbid condition; OR
   b) BMI > 40 kg/m2 or 140% of the 95th percentile for age and sex
2) Participate in an evaluation by a multidisciplinary team in an MBSAQIP-accredited specialty center with Adolescent accreditation1:
   a) Psychosocial (conducted by a licensed mental health professional)
   b) Medical (conducted by a primary care clinician/member of the multidisciplinary team to optimize control of comorbid conditions)
   c) Surgical (conducted by a bariatric surgeon)
   d) Nutritional (conducted by a licensed dietician)
3) Adhere to post-surgical evaluation and post-operative care recommendations, some of which may require lifelong adherence
4) Free from active substance use disorder
5) Free from active use of combustible cigarettes
6) Not currently pregnant; documented use of effective contraception, where indicated

Repeat bariatric surgery is included when it is a conversion from a less intensive (such as gastric band or sleeve gastrectomy) to a more intensive surgery (e.g. Roux-en-Y). Repair of surgical complications (excluding failure to lose sufficient weight) are also included on this and other lines. Reversal of surgical procedures and devices is included on this line when benefits of reversal outweigh harms.

CPT code 43999 (Unlisted procedure, stomach) is only included on this line when used for single anastomosis duodenal-ileal bypass with sleeve (SADI-S). It is not included on this line for gastric balloons.

[1] All surgical services must be provided by a program with current accreditation (as a comprehensive center, low acuity center, or a comprehensive center with Adolescent accreditation) by the Metabolic and Bariatric Surgery Accreditation and Quality Improvement Program (MBSAQIP)

~~A) Age ≥ 18~~
~~B) The patient has obesity with a:~~
~~3) BMI ≥ 40 OR~~
~~4) 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~~
~~C) Repeat bariatric surgery is included when it is a conversion from a less intensive (such as gastric band or sleeve gastrectomy) to a more intensive surgery (e.g. Roux-en-Y). Repair of surgical complications (excluding failure to lose sufficient weight) are also included on this and other lines. Reversal of surgical procedures and devices is included on this line when benefits of reversal outweigh harms.~~

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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 any nicotine product or illicit drugs and must remain abstinent from their use during the six-month observation period. Testing will, at a minimum, be conducted within 1 month of the quit date and within 1 month of the surgery to confirm abstinence from illicit drugs. Tobacco and nicotine abstinence to be confirmed in active users by negative cotinine levels at least 6 months apart, with the second test within one month of the surgery date.
      c) No mental or behavioral disorder that may interfere with postoperative outcomes[1].
      d) Patient with 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.
      b) Received counseling by a credentialed expert on the team regarding the risks and benefits of the procedure and understands the many potential complications of the surgery (including death) and the realistic expectations of post-surgical outcomes.
   4) Dietitian evaluation: (Conducted by licensed dietitian)
      a) Counseling in dietary lifestyle changes
      b) Counseling on post-operative dietary change requirements

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 accreditation (as a comprehensive center or low acuity center) by the Metabolic and Bariatric Surgery Accreditation and Quality Improvement Program (MBSAQIP)

HEALTH EVIDENCE REVIEW COMMISSION (HERC)
COVERAGE GUIDANCE PLAIN LANGUAGE SUMMARY

For complete details, please see the coverage guidance document, "Bariatric Procedures" that follows this summary.

WEIGHT LOSS SURGERY (Bariatric Procedures)

5/18/2023

Should certain types of weight loss surgery be covered for people over a certain weight for height (also known as Body Mass Index or BMI)?

Yes, for adults with a BMI of 35 and over.

Yes, for adults with a BMI of 30.0 to 34.9:

- Who have type 2 diabetes, and
- Do not have well-controlled blood sugar (glucose) despite having tried two diabetes medications

Yes, for people aged of 13-18 when:

- BMI is 35 to 39.9 (or the expected height and weight for the person's age, based on the growth curve, is very high) AND the person has a serious medical condition
- BMI is over 40 (or the expected height and weight for the person's age, based on the growth curve, is very high) regardless of other health conditions

People also must:

- Have an evaluation by a specialized team of doctors
- Not have a drug use problem
- Not smoke
- Not be pregnant
- Agree to follow lifelong lifestyle requirements

Why should we cover this surgery?

Weight loss surgery significantly reduces body weight and can cure type 2 diabetes for many people. It can lower the death rate and risk of heart attacks in adults over certain BMI levels.

We recommend covering this surgery for people 13-18 years old with a certain BMI which aligns with the American Academy of Pediatrics guidelines and expert input.

Why shouldn't balloons and adjustable gastric bands be covered too?

Adjustable gastric bands (lap bands) don't help people lose as much weight as other surgeries and can have complications.

Inserting balloons into the stomach has only been shown to cause short-term weight loss. We chose to recommend coverage for surgeries that help people for longer time periods.

HEALTH EVIDENCE REVIEW COMMISSION (HERC) COVERAGE GUIDANCE

BARIATRIC PROCEDURES

DRAFT for HERC & VbBS Meetings May 18, 2023

QUESTION ONE

Should bariatric procedures be covered for the treatment of obesity in adults with a body mass index of 35 kg/m^2 or greater?

We recommend coverage for bariatric procedures (including Roux-en-Y gastric bypass, sleeve gastrectomy, biliopancreatic duodenal switch, one anastomosis gastric bypass, single anastomosis duodenal-ileal bypass with gastrectomy) for adults with a body mass index (BMI) ≥ 35 kg/m^2 when the following criteria are met:

- **A) ≥ 18 years of age**
- **B) Participate in an evaluation by a multidisciplinary team in an MBSAQIP-accredited specialty center:**
  1. **Psychosocial (conducted by a licensed mental health professional)**
  2. **Medical (conducted by a primary care clinician/member of the multidisciplinary team to optimize control of comorbid conditions)**
  3. **Surgical (conducted by a bariatric surgeon)**
  4. **Nutritional (conducted by a licensed dietician)**
- **C) Free from active substance use disorder**
- **D) Free from active use of combustible cigarettes**
- **E) Not currently pregnant; documented use of effective contraception, where indicated**
- **F) Adhere to post-surgical evaluation and post-operative care recommendations, some of which may require lifelong adherence**

Adjustable gastric banding and intragastric balloons are not recommended for coverage.

Rationale

We recommend coverage because evidence shows these procedures significantly improve type 2 diabetes, hypertension, weight loss, and risk of death. These benefits are considerably greater than the low risk of harms. We have added preoperative eligibility requirements based on clinical guideline standards. Due to a lack of evidence of long-term benefit, adjustable gastric banding and intragastric balloons are not recommended for coverage.

QUESTION TWO

Should bariatric procedures be covered for the treatment of obesity in adults with a body mass index range from 30.0 to 34.9 kg/m²?

We recommend coverage for bariatric procedures in adults with BMI 30.0 to 34.9 kg/m² who, in addition to meeting the above coverage requirements, also have a diagnosis of Type 2 Diabetes Mellitus (T2DM) which has not met clinical glycemic targets despite trials of two diabetes medications.

Rationale

We recommend limiting coverage to patients who have been unable to achieve diabetes control (HbA1c above clinical target) despite trials of two diabetes medications, because medication should be sufficient for many patients to achieve diabetes control. Evidence indicates that these procedures significantly improve weight outcomes and rates of diabetes remission for patients with T2DM, which is greater than the low risk of harms. Evidence is less clear regarding hypertension and other health outcomes, with no evidence reported on risk of death. We have added preoperative eligibility requirements based on clinical guideline standards.

QUESTION THREE

Should bariatric procedures be covered for the treatment of obesity in adolescents?

We recommend coverage for bariatric procedures in adolescents when ALL of the following criteria are met:

A) Over the age of 12

B) Participate in an evaluation by a multidisciplinary team in an MBSAQIP-accredited specialty center with Adolescent accreditation:

1. **Psychosocial (conducted by a licensed mental health professional)**
2. **Medical (conducted by a primary care clinician/member of the multidisciplinary team to optimize control of comorbid conditions)**
3. **Surgical (conducted by a bariatric surgeon)**
4. **Nutritional (conducted by a licensed dietician)**

C) When BMI is:

1. **≥35kg/m² or 120% of the 95th percentile for age and sex AND a clinically significant comorbid condition; OR**
2. **≥40kg/m² or 140% of the 95th percentile for age and sex**

D) Adhere to post-surgical evaluation and post-operative care recommendations, some of which may require lifelong adherence.

Rationale

We recommend coverage to align with professional society guidelines and expert input. There are known clinically significant comorbid conditions that are associated with obesity that, if not addressed earlier in the lifecourse, may result in premature morbidity and mortality. We have added preoperative eligibility requirements based on clinical guideline standards.

TABLE OF CONTENTS

RATIONALE FOR DEVELOPMENT OF COVERAGE GUIDANCES AND MULTISECTOR INTERVENTION REPORTS

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

The Health Evidence Review Commission (HERC) uses the following principles in selecting topics for its reports to guide public and private payers:

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

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

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

GRADE Tables

HERC develops recommendations by using the concepts of the GRADE system. GRADE is a transparent and structured process for developing and presenting evidence and for performing the steps involved in developing recommendations. The tables below list the elements that determine the strength of a recommendation. HERC reviews the evidence and assesses each element, which in turn is used to develop the recommendations presented in the coverage guidance box. Estimates of effect are derived from the evidence presented in this document. Assessments of confidence are from the published systematic reviews and meta-analyses, where available and judged to be reliable. The level of confidence in the estimate is determined by HERC based on the assessment of 2 independent reviewers from the Center for Evidence-based Policy (Center; Figure 1).

In some cases, no systematic reviews or meta-analyses encompass the most current literature. In those cases, HERC may describe the additional evidence or alter the assessments of confidence in light of all

available information. Such assessments are informed by clinical epidemiologists from the Center. Unless otherwise noted, statements regarding resource allocation, values and preferences, and other considerations are the assessments of HERC, as informed by the evidence reviewed, public testimony, and subcommittee discussion.

GRADE Table Key

Outcomes	Table Key					
	Confidence in Estimate:	NO DATA	VERY LOW	LOW	MODERATE	HIGH
		○○○○	●○○○	●●○○	●●●○	●●●●
	Direction of Effect:	NO DATA, UNCLEAR, NO EFFECT, BENEFIT, HARM, MIXED				

Notes. Recommendations for coverage are based on the balance of benefit and harms, resource allocation, values and preferences, and other considerations. See Appendix A for more details about the factors that constitute the GRADE table.
Abbreviation. GRADE: Grading of Recommendations, Assessment, Development, and Evaluations.

GRADE TABLES

POPULATION: Adults with BMI ≥ 35 kg/m^2

CRITICAL OUTCOMES

All-cause mortality

●●●○

BENEFIT

Bariatric procedures resulted in a statistically significant reduction in all-cause mortality compared with medical therapy in adults with or without T2DM (3.5 to 8.7 year follow up; range of risk reduction 49% to 71%). Stratified analyses demonstrated a statistically significantly greater effect in mortality for adults with T2DM versus without (59% vs. 30% risk reduction).

3 reviews including 19 comparative cohort studies
Moderate confidence based on consistent direction and magnitude of effect; downgraded due to lack of nonobservational data

IMPORTANT OUTCOMES

Weight change

●●●●

BENEFIT

Bariatric procedures were associated with statistically significant weight loss in adults with or without T2DM compared with medical therapy. Meta-analyses of 1- to 10-year follow-up data from a review of 19 RCTs found that treatment with surgery resulted in an additional 18.5 kg of weight loss and a BMI reduction of almost 5 kg/m^2 beyond that experienced by the control group.

Patients in trials with higher BMI enrollment requirements and those who received gastric bypass procedures (i.e., RYGB, BPD-DS) vs. non-bypass procedures (e.g., AGB, SG) exhibited greater weight loss compared with nonsurgical obesity interventions.

5 reviews including 36 RCTs and 5 observational studies
High confidence based on consistent magnitude, direction, and significance of effect from high-quality study designs with low risk of bias

Improvement or resolution of chronic disease

Diabetes

●●●○

BENEFIT

Statistically significant differences in rates of T2DM remission[a] were observed in adults undergoing bariatric procedures versus medical therapy interventions over 1 to 5 years follow-up (rate of remission 21% to 53% vs. 0 to 16%). In meta-analyses, bariatric surgery was associated with statistically significantly higher 5-year rates of T2DM remission compared with medical therapy (RR range, 6.0 to 16.9; $P < .001$).

POPULATION: Adults with BMI ≥ 35 kg/m^2

All bariatric procedure types were associated with increased T2DM remission. At 3 to 5 years follow-up, BPD alone exhibited the greatest differential rate of T2DM remission compared with medical therapy controls (RR, 31.8 [95% CI, 5.0 to 201.8]) followed by RYGB and BPD/DS (RR, 7.5 for both [95% CI, 1.9 to 29.5]) and SG (RR, 6.7 [95% CI, 1.8 to 25.6]).

5 reviews with 28 unique RCTs
Moderate confidence based on consisent direction, magnitude, and significance of effect from pooled results in low risk of bias systematic reviews; downgraded due to varying remission definitions across studies

Hypertension

MIXED EFFECTS

The comparative effect of bariatric procedures versus medical therapy on hypertension was mixed. One meta-analysis demonstrated a statistically significant reduction in systolic blood pressure and diastolic blood pressure versus medical therapy (MD, -3.94 mmHg and -2.69 mmHg, respectively). However, subgroup analyses showed no differential effect on blood pressure among individuals younger than 45 years, individuals with baseline BMI less than 40, individuals with baseline HbA1c less than 7.0 percent, and among those who received AGB or BPD/DS.

Reviews limited to adults with T2DM with follow-up of 5 to 10 years demonstrated no between-group difference in systolic blood pressure and an increase in diastolic blood pressure with bariatric procedures.

3 reviews with 20 unique RCTs and 2 comparative cohort studies
Low confidence based on mixed results across blood pressure outcomes and between timepoints and use of a network meta-analyses for primary results

Coronary artery disease

BENEFIT

Meta-analyses of RCTs and comparative cohort studies showed statistically significant reductions in the risk of coronary artery disease-related outcomes for bariatric procedures versus medical therapy, including risk of macrovascular complications over 2 to 20 years follow-up (RR range, 0.43 to 0.50 [95% CI, 0.27 to 0.73]); any cardiovascular event (HR, 0.52 [95% CI, 0.39 to 0.71]); and myocardial infarction (RR, 0.46 [95% CI, 0.38 to 0.55]).

2 reviews of 7 RCTs and 6 comparative cohort studies
Low confidence based on risk of bias concerns from contributing systematic reviews, including insufficient search strategies and inclusion of low-quality study designs, and use of results based on some composite outcomes

POPULATION: Adults with BMI ≥ 35 kg/m^2

Obstructive sleep apnea NO DATA	No studies met inclusion criteria.
Joint arthropathy NO DATA	No studies met inclusion criteria.
Intracranial hypertension NO DATA	No studies met inclusion criteria.
Quality of life BENEFIT	There was greater improvement in overall and gastrointestinal QoL in the long-term (i.e., ≥ 3 years) with bariatric procedures compared with medical therapy. Results from network meta-analyses showed that bariatric surgery groups had higher mean scores on the Gastrointestinal QoL Index (scoring range, 0 to 144 points) compared with non surgical controls at 3 years (MD range, 17.4 to 25.8 points) and 5 years (MD range, 11.8 to 17.5 points). Additionally, the between-group mean differences exceeded the clinically significant threshold of 5 points for all procedure types. In another review, 3 studies observed higher overall QoL among bariatric surgery groups compared with nonsurgical groups at 5 years, as measured by the SF-36 scale. 2 reviews including 8 RCTs and 6 observational studies Low confidence based on concerns from regarding lack of control for confounding from individual studies in the contributing systematic reviews and use of a composite QoL scale using scores converted from multiple surveys
Harms MIXED EFFECTS	There was no significant difference over 1 to 10 years between bariatric procedures and medical therapy in overall rate of adverse events, nonsurgical serious adverse events, severe hypoglycemia, or death. Evidence on fracture rates was mixed. Bariatric procedures were associated with low rates of perioperative complications (0.1% to 5.1%) such as hernia, internal bleeding, wound

infections, dumping syndrome, and very low rates of perioperative mortality (0.08%).

Five-year revision rates range from 5% to 22% across all assessed bariatric procedure types. Moreover, 10-year estimates (8% to 64%) indicate that need for revision may increase over time.

6 reviews with 40 unique RCTs and 67 observational studies
Low confidence incomplete methods reporting in contributing systematic reviews and a lack of consistent event reporting between reviews and studies

Balance of benefits and harms
The benefits of bariatric procedures in reducing all-cause mortality and T2DM are considerably greater than the risks in adult populations with BMI ≥35 kg/m², with greater benefits for those with pre-existing T2DM.

Resource Allocation
Bariatric procedures are surgically extensive, expensive, and resource intensive. A complete behavioral, physical, and psychological evaluation may help ensure patients meet eligibility criteria and are supported to follow post-operative care recommendations, some of which may require lifelong adherence. Improvement or resolution of comorbid chronic conditions may offset healthcare expenditures in the long term.

Values and Preferences
Patients may value a surgery that could improve important health outcomes and reduce the risk of death. Given the limited evidence on possible harms, as well as a range of benefits associated with bariatric procedures for an individual, a shared decision-making approach may help patients understand the risks, benefits, and alternatives as they apply their values and preferences.

Other considerations
Known complications of surgery should be discussed. All surgical services must be provided by a program with current accreditation (such as a Comprehensive Center or Low Acuity Center) by the Metabolic and Bariatric Surgery Accreditation and Quality Improvement Program (MBSAQIP) to maintain quality and safety standards.

Given gaps in the evidence, clinical guidelines and expert input may inform coverage decisions regarding specific bariatric procedures or specific populations.

Notes. GRADE table elements are described in Appendix A. A corresponding GRADE Evidence Profile is in Appendix B. [a] T2DM remission was most commonly defined as achieving an HbA1c < 6.0% without ongoing glycemic therapy (e.g., metformin, insulin). Other definitions included fasting plasma glucose targets or different HbA1c thresholds.
Abbreviations. AGB: adjustable gastric banding; BMI: body mass index; BPD/DS: biliopancreatic diversion with duodenal switch; CI: confidence interval; GRADE: Grading of Recommendations, Assessment, Development, and Evaluations; HbA1c: glycated hemoglobin; HR: hazard ratio; kg/m^2: kilograms per meters squared; MD: mean difference; mmHg: millimeters of mercury; QoL: quality of life; RCT: randomized controlled trial; RR: relative risk or risk ratio; RYGB: Roux-en-Y gastric bypass; SF-36: short form-36 survey; SG: sleeve gastrectomy; T2DM: type 2 diabetes.

POPULATION: Adults with BMI 30.0 to 34.9 kg/m^2

CRITICAL OUTCOMES

All-cause mortality

NO DATA

No studies met inclusion criteria.

IMPORTANT OUTCOMES

Weight change

BENEFIT

Bariatric surgery groups experienced statistically greater percent total body weight loss (22% to 30% vs. 5% to 9%; $P < .001$) and had lower mean BMIs (25 to 28 kg/m^2 vs. 29 to 32 kg/m^2; $P < .001$) compared with medical therapy groups across 1 to 5 years of follow-up.

5 RCTs; N = 391
Moderate certainty based on consistent direction, magnitude, and statistical significance of effect; downgraded for imbalances in baseline characteristics and high control group attrition

Improvement or resolution of chronic disease

Diabetes

BENEFIT

Across 1 to 5 years of follow-up, bariatric surgery groups experienced better T2DM outcomes compared with medical therapy, as indicated by comparatively higher rates of remission (RR range, 2.7 to 36.4) and statistically significant lower mean HbA1c values (6.0% to 7.2% vs. 7.5% to 9.1%; $P < .007$) at all reported timepoints.

6 RCTs; N = 433
Low certainty based on consistent findings across 5 years of follow-up; downgraded for differential attrition in control groups and variation in remission definitions across studies

Hypertension

UNCLEAR

There were mixed results on the effect of bariatric surgery on hypertension. Pooled analyses of mean systolic and diastolic blood pressure showed inconsistent results across 5 years of follow-up, suggesting that bariatric surgery groups may either have statistically significant lower blood pressure values or no difference compared with medical therapy groups. Both bariatric surgery and medical therapy groups achieved mean blood pressure values at or below the thresholds for hypertension at most follow-up timepoints.

5 RCTs; N = 391

POPULATION: Adults with BMI 30.0 to 34.9 kg/m^2

	Very low certainty based on mixed effects across follow-up timepoints in pooled analyses of mean blood pressure values; downgraded forhigh control group attrition, limited number of observations for some timepoints, and mixed effects across outcomes and timepoints
Coronary artery disease UNCLEAR	Only intermediate measures of coronary artery disease risk (e.g., LDL cholesterol and triglycerides concentrations) were available in the included trials. Findings for LDL cholesterol were mixed, with 2 studies observing comparatively higher mean concentrations in surgical vs. medical groups at the longest follow-up and no between-group differences in 3 studies. In contrast, all surgical groups had significantly lower mean triglycerides concentrations over 1 to 5 years of study follow-up compared with medical therapy groups. There were no differences in the use of medications to treat or prevent progression of heart disease (e.g., beta blockers, ACE inhibitors) between groups. 5 RCTs; N = 391 Very low certainty based on mixed effects for intermediate measures associated with increased risk of cardiovascular disease; downgraded for control group attrition, wide confidence intervals, use of intermediate measures, and mixed results
Obstructive sleep apnea NO DATA	No studies met inclusion criteria.
Joint arthropathy NO DATA	No studies met inclusion criteria.
Intracranial hypertension NO DATA	No studies met inclusion criteria.
Quality of life UNCLEAR	At 2 years of follow-up, participants randomized to bariatric surgery had statistically significant higher quality of life scores (SF-36 scale) in most general health domains, except for mental health, compared to medical therapy controls.

POPULATION: Adults with BMI 30.0 to 34.9 kg/m^2

1 RCT; N = 100
Very low certainty based on consistent direction of effect across most domains; downgraded due to imbalances in baseline characteristics, small sample size, and limited population generalizability (non-US with chronic kidney disease)

Harms

UNCLEAR

Adverse events were more common in bariatric surgery groups primarily because of early surgical complications. Common adverse events included nausea, dehydration, diarrhea, and upper gastrointestinal pain. Few serious adverse events occurred in any study group. When reported, events were generally related to additional surgeries (e.g., cholecystectomy) or hospitalizations for infection. Rates of reoperation or surgical revisions related to the primary bariatric surgery were not reported.

Nutritional abnormalities (only reported in 1 trial) were rare and generally did not differ significantly between study groups, although rates of iron deficiency were higher in the bariatric surgery group at 2 years.

5 RCTs; N = 391
Very low certainty due to control group attrition, low event rates, wide variation in assessed events, and much higher rates of events in 1 trial vs. amost none in other studies

Balance of benefits and harms
The benefits of bariatric procedures for weight reduction and T2DM resolution are greater than the risks in adults with T2DM and BMI 30.0-34.9kg/m^2; there is no evidence in populations without diabetes.

Resource Allocation
Similar resource allocation considerations exist for this population; however, given the low level of evidence to support meaningful clinical outcomes, the limited benefits, including weight reduction and resolution of T2DM, may not be sufficient compared to the potential healthcare costs of these procedures, including post-operative maintenance and lifelong adherence standards.

Values and Preferences
Some patients may prefer a surgical treatment option that improves important health outcomes, such as weight loss and T2DM resolution. Other patients may not place as much value on these benefits compared to the risks of surgery. It is important to use shared decision-making to

review the effectiveness of treatment options for patients and offer resources and referrals as appropriate.

Other considerations

Similar considerations for surgical services exist for this population, including complications of surgery and the requirement for procedures to be provided by an accredited program. Given greater uncertainty and gaps in the evidence, recommendations from clinical guidelines and expert input may inform coverage decisions regarding bariatric procedures for this population.

Note. GRADE table elements are described in Appendix A. A corresponding GRADE Evidence Profile is in Appendix B.
Abbreviations. ACE: angiotensin-converting enzyme; BMI: body mass index; GRADE: Grading of Recommendations, Assessment, Development, and Evaluations; HbA1c: glycated hemoglobin; kg: kilogram; kg/m2: kilograms per meter squared; LDL: low density lipoprotein; RCT: randomized controlled trial; RR: relative risk or risk ratio; SF-36: short form-36 survey; T2DM: type 2 diabetes.

POPULATION: Adolescents

CRITICAL OUTCOMES

All-cause mortality

NO DATA

No studies met inclusion criteria.

IMPORTANT OUTCOMES

Weight change

BENEFIT

Bariatric procedures were associated with statistically significant mean BMI reductions (range, -13 to -17 kg/m^2) over 2 to 12 years of follow-up in adolescent cohorts. Where comparative data were available, groups treated with bariatric surgery experienced statistically greater weight reduction than those treated with medical therapy. In 1 study, the surgical group experienced a 5-year mean BMI reduction of -13.1 kg/m^2 compared with a 3.3 kg/m^2 increase in the nonsurgical control group ($P < .001$).

4 cohort studies; N = 525
Low certainty based on statistically significant weight reduction in surgical groups from baseline across 2 to 12 years of follow-up and greater 2 to 5-year weight loss compared with medical groups; downgraded due to imbalances in key study group characteristics at baseline and use of a comparator group from another trial in 1 study

Improvement or resolution of chronic disease

Diabetes

UNCLEAR

Bariatric procedures were associated with high rates of T2DM resolution (86% to 100%) in all adolescent studies compared with no remission reported with medical therapy; however, differing definitions of remission were used among studies. Bariatric surgery was also associated with reductions in fasting plasma glucose compared with medical therapy controls, but results were mixed for HbA1c.

4 cohort studies; N = 525
Very low confidence based on high rates of observed remission in bariatric surgery groups, but limited ability to draw comparative conclusions due to imbalances in key study group characteristics at baseline, few reported remission events across study groups, variation in remission definitions, and conflicting comparative results for some outcomes

POPULATION: Adolescents

Hypertension

UNCLEAR

Bariatric procedures were associated with high rates of elevated blood pressure resolution (74% to 100%) at 2 to 12 years follow up versus no remission in medical therapy comparator groups. In comparative stuies, between-group results for mean systolic and diastolic blood pressure were mixed.

4 cohort studies; N = 525
Very low confidence based on imbalances in key study group characteristics at baseline limited number of reported remission events across study groups, and conflicting comparative results

Coronary artery disease

UNCLEAR

Only intermediate measures of coronary artery disease risk (e.g., LDL cholesterol and triglycerides concentrations) were available in the included adolescent studies. All bariatric surgery participants with elevated LDL cholesterol and elevated triglycerides (≥ 130 mg/dL) at baseline experienced resolution at 5 years in 1 comparative cohort study, but no control group results were reported for these outcomes. Additionally, 2 comparative studies observed statsitically significant reductions in mean triglycerides in surgical participants compared with medical therapy ($P < .001$), but comparative results for mean LDL cholesterol were mixed.

2 cohort studies; N = 255
Very low confidence based on imbalances in key study group characteristics at baseline, limited number of reported remission events across study groups, use of intermediate measures of cardiovascular disease risk, and conflicting comparative results

Obstructive sleep apnea

NO DATA

No studies met inclusion criteria.

Joint arthropathy

UNCLEAR

Only intermediate measures of joint arthropathy were available in the included adolescent studies. In 1 study, fewer adolescents who received bariatric surgery reported musculoskeletal pain concerns during physical activity assessments at the 1 year and 2 year postsurgical follow-ups compared with baseline (25% at baseline vs. 8% at 1 year and 12% at 2 years; $P < .01$).

1 cohort study; N = 206

POPULATION: Adolescents

	Very low confidence based on low completion rate of follow-up visits, small sample size, and use of a proxy outcome measure for joint arthropathy
Intracranial hypertension NO DATA	No studies met inclusion criteria.
Quality of life UNCLEAR	In 1 noncomparative study, adolescents who received bariatric surgery reported statistically significant improvements in weight-related physical limitations, self-esteem, and interpersonal relationships at 3 years (IWQoL-Kids scale). Similarly, in 1 comparative study, adolescents who underwent bariatric sugery reported statitically significant reductions in weight-related distress during activities such as shopping, swimming, eating at restaurants, and intimate relations at 5 years (OP-14 scale), but did not experience significantly different changes as compared with adolescents who received medical therapy. In the same comparative study, findings for general QoL (SF-36 scale) were mixed. Compared with medical therapy, bariatric surgery significantly improved physical function but there were no comparative differences in reported mental health, pain, and general health perceptions. 2 cohort studies; N = 395 Very low confidence, based on lack of comparator group and imbalances in some baseline characteristics, mixed comparative general QoL outcomes, and wide confidence intervals for some domains
Harms UNCLEAR	Reported harms varied across studies. Most adverse events in the bariatric surgery groups occurred before hospital discharge and were generally known complications of surgery. The most common long-term harms associated with bariatric surgery were additional abdominal operations, mostly for gall bladder removal, and nutritional abnormalities, which occurred in 45% to 80% of surgical participants. Across 12 years of follow-up, mortality was rare (4 deaths) and was not attributed to surgical causes. However, 2 deaths were related to drug overdose, highlighting the need for substance use support.

POPULATION: Adolescents

	4 cohort studies; N = 525 Very low confidence based on based on imbalances in key study group characteristics at baseline, few reported events for some outcomes, and a lack of consistent adverse events definitions and reporting

	Balance of benefits and harms Despite evidence of weight loss among adolescents, the balance of benefits and harms is unclear due to the lack of comparative data for other outcomes, lack of longer-term follow up given the age of this population, and concern for nutritional deficiencies associated with these procedures.
	Resource Allocation Given the low level of evidence to support meaningful clinical outcomes, the potential benefits of bariatric procedures in adolescents may not be sufficient compared to the potential healthcare costs of these procedures.
	Values and Preferences Adolescents with obesity and their caregivers may desire any treatment that could potentially reduce the future risk for obesity-related chronic illnesses. However, other concerns may include potential risks and side effects of undergoing major abdominal surgery in younger populations, issues with adherence and follow-up, and the potential for future nutritional deficiencies.
	Other considerations Current guidance exists for addressing obesity in adolescents that includes comprehensive, intensive behavioral interventions, which have more data supporting their effectiveness in this population compared with bariatric procedures. In adolescents with severe obesity, referral to a multidisciplinary center for comprehensive assessment may be considered.

Note. GRADE table elements are described in Appendix A. A corresponding GRADE Evidence Profile is in Appendix B.
Abbreviations. BMI: body mass index; GRADE: Grading of Recommendations, Assessment, Development, and Evaluations; HbA1c: glycated hemoglobin; IWQoL Kids: Impact of Weight on Quality of Life Scale for Kids; kg: kilogram; kg/m^2: kilograms per meters squared; LDL: low density lipoprotein; OP-14: Obesity-related Problems Scale-14; QoL: quality of life; SF-36: short form-36 survey; T2DM: type 2 diabetes.

BACKGROUND

Obesity is a complex chronic condition characterized by the retention of excess body fat that may increase an individual's risk of long-term health complications and premature mortality.[1,2] Having a body mass index (BMI)–a measure of an individual's weight in kilograms divided by their height in meters squared (i.e., kg/m^2)–greater than 30 is the generally accepted threshold for obesity, which is further stratified as class I (BMI 30.0 to 34.9), class II (BMI 35.0 to 39.9), and class III (BMI ≥ 40) obesity.[3] Common health morbidities that have been independently linked with obesity include[1]:

- Type 2 diabetes mellitus (T2DM)
- Hypertension
- Asthma
- Sleep apnea
- Osteoarthritis
- Some cancers (e.g., endometrial, gallbladder, esophageal, renal)

State surveys indicate that the prevalence of obesity and obesity-related morbidity in Oregon has been increasing. The Oregon Health Authority estimates that prevalence of obesity among Oregon adults aged 18 years and older was 29.0% in 2017 and the prevalence of diagnosed T2DM was 9.4% in 2015.[4,5] These estimates correspond with a more than two-fold increase in obesity and diabetes prevalence from 1990, when about 10% of adults were identified as having obesity and fewer than 5% had diagnosed T2DM.[4,5] In addition, the 2017 prevalence of obesity among Oregon adolescents, while lower than that of adults, has increased by over 50% since 2001 (7.3% vs. 11.4%).[4]

Although obesity has been increasing among adults and adolescents, certain racial and ethnic groups are disproportionately affected. Among Oregon adults, estimated obesity rates are highest among people who identify as Pacific Islander (45.1%) or as American Indian or Alaska Native (40.6%) and lowest among those who identify as Asian (9.5%).[4] Among Oregon adolescents (i.e., 8th graders), the prevalence of obesity is highest for those who identify as Hispanic or Latino (15.5%) and lowest among Whites (9.9%).[4] It should be noted that the unequal prevalence of obesity across racial and ethnic groups may be due to complex factors including social determinants of health.

The cost impact of obesity in Oregon is substantial. Oregon Health Authority (OHA) estimates the costs for health care and lost productivity due to obesity-related T2DM total nearly $3 billion per year.[5] Annual medical expenditures for T2DM are estimated at $2.2 billion while reduced or lost productivity from T2DM is estimated at around $840 million per year.[5] Oregon Medicaid is disproportionately affected by T2DM, with nearly 19% of beneficiaries having diabetes compared with 7% in employer-sponsored health plans.[5] In 2012, the Oregon Health Plan paid an estimated $106 million in T2DM-related claims, including costs for complications such as cardiovascular events, peripheral artery disease, and retinopathy.[5]

Interventions

First-line nonsurgical interventions for obesity (e.g., nutritional counseling, exercise programs) have been found to offer significant short-term weight loss and remission of obesity-related complications, but these effects are rarely maintained in the long-term.[6-8] In patients who fail to maintain weight loss with

nonsurgical interventions (i.e., lifestyle modifications, pharmacotherapy), controlled studies of metabolic or bariatric surgery indicate that these procedures may be effective therapy for the long-term treatment of obesity and common obesity-related morbidities.[1,9-11]

Bariatric procedures may be performed as open surgery or endoscopically, and generally involve restricting the capacity of the stomach or bypassing parts of the small intestine to limit food intake and nutrientabsorption.[2] As shown in Table 1, there are currently 7 primary bariatric procedures endorsed by the American Society for Bariatric and Metabolic Surgeries (ASMBS), including 2 types of US Food and Drug Administration (FDA)-approved devices, the adjustable gastric band and the intragastric balloon.[12]

Table 1. ASMBS-Endorsed Metabolic and Bariatric Procedures

PROCEDURE NAME	STOMACH RESTRICTION	BYPASS PROCEDURE	REVERSIBLE?
Surgical Procedures			
Sleeve Gastrectomy (SG)	80% of the stomach is removed, leaving a banana-shaped "sleeve"	NA	No
Roux-en-Y Gastric Bypass (RYGB)	Stomach is reduced to a pouch the size of an egg or walnut	The stomach pouch is attached to the middle of the small intestine, bypassing about 3-4 feet of small intestine	No
Adjustable Gastric Band (AGB)	Adjustable silicone band[a] is placed around the top of the stomach creating a small pouch; main stomach stays attached	NA	Yes
Biliopancreatic Diversion with Duodenal Switch (BPD/DS)	Similar to SG	The stomach sleeve is attached to the lower small intestine, bypassing 75% of the small intestine	No
Single Anastomosis Duodenal-Ileal Bypass with Sleeve Gastrectomy (SADI-S)	Similar to SG	The stomach sleeve is attached to a loop of small intestine several feet before the end of the small intestine	No
One Anastomosis Gastric Bypass (OAGB)[c]	Similar to SG	The stomach sleeve is attached to a loop from the middle portion of the small intestine	No
Endoscopic Procedures			
Intragastric Balloon (IGB)	Saline-filled silicone balloons[b] temporarily placed in the stomach, limiting amount of food one can eat	NA	Yes

Notes. [a] FDA-approved device: the Lap-Band. [b] FDA-approved devices: Orbera, Reshape, and Obalon. [c] Also known as the mini gastric bypass.
Sources. ASMBS, 2021[13] and ASMBS, 2022.[12]
Abbreviations. AGB: adjustable gastric banding; ASMBS: American Society for Metabolic and Bariatric Surgery; BPD/DS: biliopancreatic diversion with duodenal switch; FDA: United States Food and Drug Administration; IGB: intragastric balloon; NA: not applicable; OAGB: one anastomosis gastric bypass; RYGB: Roux-en-Y gastric bypass; SADI-S: single anastomosis duodenal-ileal bypass with sleeve gastrectomy; SG: sleeve gastrectomy.

According to the ASMBS, approximately 213,000 primary bariatric procedures and 43,000 revisions were performed in the US in 2019, the most recent year for which statistics are available prior to the COVID-19 pandemic.[14] Of the total primary bariatric procedures performed, the majority were sleeve gastrectomy (SG; 71%) or Roux-en-Y gastric bypass procedures (RYGB; 21%).[14] Other procedures made up a

comparatively smaller portion of primary bariatric surgeries, with adjustable gastric banding (AGB), biliopancreatic diversion with duodenal switch (BPD/DS), and intragastric balloons (IGB) each accounting for around 2% of procedures.[14] One anastomosis gastric bypass (OAGB) and single anastomosis duodenal ileal bypass with sleeve gastrectomy (SADI-S) procedures were not yet endorsed by the ASMBS in 2019, but each accounted for less than 1% of primary bariatric procedures performed in 2020.[14]

Eligibility and Standard of Care

The current generally accepted criteria for bariatric surgery eligibility were developed in 1991 by the National Institutes of Health (NIH).[15] The guidelines apply to adults ages 18 to 60 years and specify that bariatric procedures should be offered to patients who have a BMI of at least 35 kg/m^2 with obesity-related morbidities or who have a BMI of 40 kg/m^2 with or without comorbidities.[15] Contraindications for bariatric procedures include severe heart or lung disease, uncontrolled psychiatric or substance use disorders, tobacco use, active cancer, inflammatory bowel diseases (for example, Crohn disease), severely impaired intellectual capacity, and current pregnancy.[15] Although the NIH guidelines reflect consensus decisions based largely on expert opinion, they have been continually endorsed by professional societies in the 30 years since they were published.[2,3,16]

Patients who are referred for bariatric procedures must undergo a comprehensive evaluation by a multidisciplinary team experienced in obesity surgery, which typically includes a bariatric surgeon, dietitian, mental health specialist, social worker, and a primary care practitioner.[2,3] During assessment, the care team and the patient collaboratively select the optimal procedure based on the patient's current health status and treatment goals.[3] In the months immediately following a bariatric procedure, patients must adopt a substantially altered diet and are monitored closely for surgical complications. In the long-term, bariatric surgery patients are expected to participate in regular ongoing follow-up including nutritional counseling, vitamin supplementation, and periodic testing to monitor bones density, lipid levels, blood glucose, and serious nutritional deficiencies (e.g., iron, vitamin B12).[3,17]

Access and Equity

Few patients who meet the NIH criteria undergo bariatric procedures. A 2019 study conducted at a large university-based health care system found that only about 5% of patients who met the criteria for bariatric procedures in primary care settings were referred to surgical clinics, suggesting that lack of referrals may be a factor in the low rate of bariatric surgery utilization.[18] Moreover, a recent systematic review found that bariatric surgery referral rates varied by patient characteristics, with male patients, Hispanic patients, and patients with lower BMI less likely to receive referrals than female and White or Black patients with higher BMI.[19] Patients with T2DM and sleep apnea were also more likely to receive referrals compared with patients who had hypertension, dyslipidemia, or heart disease.[19] Ultimately, the authors of the systematic review identified lack of provider familiarity with bariatric surgery efficacy, safety, and postoperative recovery as the primary barrier to patient referrals.[19]

A number of people who may benefit from bariatric procedures fall outside of the clinical eligibility criteria. For example, recent clinical guidelines recommended adjusting BMI criteria for Asian populations who have been shown to experience obesity-related morbidities at a lower BMI compared to other racial and ethnic groups.[2,20] Similarly, population studies have shown that new obesity staging

scales that consider the burden of a patient's obesity-related physical and psychologic morbidity alongside their BMI (e.g., the Edmonton Obesity Staging System) are better predictors of all-cause mortality than BMI alone.[2,21,22] These findings suggest that people with BMI 30.0 to 34.9 (i.e., class I obesity) who have significant morbidities could experience a mortality benefit with bariatric procedures beyond that expected for a with a lower-stage patient who has a higher BMI but few obesity-related morbidities.[2,21,22] Age requirements pose an additional eligibility barrier. Despite the known downstream health effects resulting from obesity during adolescence and promising evidence of reduced morbidity after bariatric procedures,[23-25] age under 18 years was found to be the most common reason for coverage denials in a large prospective cohort study of adolescents undergoing bariatric surgery.[26] Older adults (i.e., ages 60 years and older), who are considered to be outside of the recommended NIH age range for bariatric surgery, also experience high rates of age-related coverage denials despite evidence supporting similar outcomes after bariatric procedures as younger adult cohorts.[27]

Among patients who undergo bariatric procedures, outcomes may vary by racial and ethnic identity. Retrospective chart reviews of bariatric surgery patients during the perioperative period have shown that patients who identify as Black have significantly longer lengths of hospital stays as well as higher rates of readmissions, reoperations, and 30-day mortality compared with patients who identify as White.[28] Evidence on longer-term outcome disparities is less conclusive; however, analyses from recent systematic reviews suggests that patients who identify as Black may experience less favorable weight loss outcomes after bariatric procedures than patients who identify as Hispanic or White,[29] but may not differ in terms of comorbidity resolution.[29,30] These disparities in short- and long-term outcomes highlight the need for additional research regarding bariatric surgery access and care.

Accreditation of Surgery Centers

Bariatric surgery programs are accredited through the Metabolic and Bariatric Surgery Accreditation and Quality Improvement Program (MBSAQIP), which is a national program that is jointly administered by the American College of Surgeons (ACS) and the ASMBS.[31] There are currently 6 outpatient and 1 inpatient MBSAQIP accreditation designations that vary in terms of the type of allowed procedures, treatment population, and procedural volume requirements (Table 2). As of January 2023, there are 13 MBSAQIP-accredited bariatric surgery centers in Oregon.[32]

Table 2. MBSAQIP Accreditation Designation Descriptions

DESIGNATION TYPES[a]	BARIATRIC PROCEDURES	POPULATIONS	VOLUME REQUIREMENTS	AVAILABLE IN OREGON?
Accredited Inpatient Centers				
Comprehensive Center	All ASMBS-endorsed procedures[b]	Patients aged ≥ 18 years	≥ 50 bariatric stapling procedures annually	Yes
Comprehensive Center with Adolescent Qualifications	All ASMBS-endorsed procedures	Patients of all ages	≥ 50 bariatric stapling procedures annually	Yes
Comprehensive Center with Obesity Medicine Qualifications	All ASMBS-endorsed procedures	Patients aged ≥ 18 years	≥ 50 bariatric stapling procedures annually	Yes
Comprehensive Center with Adolescent and Obesity	All ASMBS-endorsed procedures	Patients of all ages	≥ 50 bariatric stapling procedures annually	No

Management Qualifications				
Low Acuity Center	ASMBS-endorsed primary procedures AGB replacement, positioning, or removal Port revision or removal Emergent revisional procedures[c]	Ambulatory patients aged ≥ 18 to < 65 years BMI < 55 for males and < 60 for females No history of organ failure or current cardiopulmonary impairment	≥ 25 bariatric procedures annually	Yes
Adolescent Center	All ASMBS-endorsed procedures	Patients aged < 18 years	≥ 15 bariatric stapling procedures annually or utilizes a verified co-surgeon	No
Accredited Outpatient Centers				
Ambulatory Surgery Center	ASMBS-endorsed primary procedures AGB replacement, positioning, or removal Port revision or removal Emergent revisional procedures	Ambulatory patients aged ≥ 18 to < 65 years BMI < 55 for males and < 60 for females No history of organ failure or current cardiopulmonary impairment	≥ 25 bariatric procedures annually	Yes

Notes. [a] Regardless of designation type, all centers must demonstrate compliance with MBSAQIP standard, successfully complete site visits, and enter data into the MBSAQIP registry. [b] MBSAQIP-accredited centers must receive approval from an Institutional Review Board to perform primary procedures that are not endorsed by the ASMBS. [c] An emergent case is usually performed within a short interval of time between patient diagnosis or the onset of related preoperative symptomatology. It is understood that the patient's well-being and outcome is potentially threatened by unnecessary delay and the patient's status could deteriorate unpredictably or rapidly.
Source. American College of Surgeons, 2022.[31,32]
Abbreviations. AGB: adjustable gastric banding; ASMBS: American Society for Metabolic and Bariatric Surgeries; BMI: body mass index; MBSAQIP: Metabolic and Bariatric Surgery Accreditation and Quality Improvement Program.

Programs seeking accreditation must demonstrate compliance with MBSAQIP standards regarding facility structures, staff competencies, and data reporting needed to provide quality metabolic and bariatric care. These standards include:

- A dedicated bariatric surgery committee consisting of a director, a coordinator, a clinical reviewer, a pediatric medical advisor (if applicable), an obesity medicine director (if applicable), the clinical staff, and representative from the facility's administration team. The committee is responsible for sharing best practices, discussing adverse events, and conducting quality improvement.[31]
- Multidisciplinary teams capable of providing integrated preoperative, perioperative, and postoperative care for bariatric surgery patients. Programs must be able to provide access or referral to consistent and credentialed surgeons and operating teams, nursing staff, registered dieticians, and mental health professionals. Accredited adolescent centers must also have clinicians specializing in pediatrics for the treatment of pediatric obesity for both medical and behavioral domains.[31]
- Facilities, equipment, and furniture that can accommodate all bariatric surgery candidates. This includes larger beds, wheelchairs, x-ray equipment, and weight-rated or supported toilets.[31]

- Comprehensive patient education and care pathways for patient selection, preoperative behavioral and physical evaluation, nutritional support, and transition plans for pediatric patients to move from a pediatric specialist to an adult program over time.[31]

METHODS

The following sections summarize the overall scope of the evidence review, including Key Questions (KQs) and Contextual Questions (CQs), inclusion and exclusion criteria, and a brief overview of the methods used to conduct the review. Additional information regarding methods can be found in Appendix C.

Key Questions

KQ1. What is the effectiveness of bariatric procedures for the treatment of obesity in adults and adolescents as compared to other treatments?
KQ2. What are the harms of bariatric procedures for the treatment of obesity in adults and adolescents?
KQ3. Is there evidence of differential effectiveness or harms for bariatric procedures by:
   a. Age
   b. Sex
   c. Race/ethnicity
   d. BMI category
   e. Comparator
   f. Whether the patient has received prior bariatric surgery
   g. Comorbidities (e.g., medical or behavioral health, disabilities)
   h. Site of procedure (e.g., inpatient vs. outpatient surgical center, centers of excellence vs. not)
   i. Time since procedure

Contextual Questions

CQ1. What kinds of accreditation standards and center of excellence designations exist in the United States and what are the requirements of each?
CQ2. What is the appropriate minimum age or developmental stage for bariatric surgery?

Study Eligibility Criteria

Table 3 describes the criteria used to inform study selection for the evidence review.

Table 3. Evidence Review Criteria Overview

HEADER	INCLUDE	EXCLUDE
Population	Adults and adolescents with obesity (BMI ≥ 30) who are being considered for bariatric procedures	Adults and adolescents with overweight (BMI < 30)
Interventions	Bariatric procedures (e.g., AGB, RYGB, BPD/DS, SG, OAGB, SADI-S, IGB)	Bariatric devices that are not FDA approved or not available in the United States
Comparators	Nonsurgical treatment of obesity (e.g., medical management, pharmacotherapy, intensive multicomponent behavioral interventions, behavioral counseling, structured weight management programs, other nonsurgical devices or procedures, combinations of these therapies)	Studies comparing bariatric procedures

Outcomes	Critical: all-cause mortality Important: weight change, improvement or resolution of chronic disease, quality of life, harms	Changes in health care utilization
Study Designs	Adults with BMI ≥ 35: systematic reviews of RCTs and cohort studies Adults with BMI 30 to 34.9: RCTs Adolescents: best available prospective literature	Adults with BMI ≥ 35: reviews of small comparative cohort studies (N < 500) or uncontrolled observational studies Adults with BMI 30 to 34.9: nonrandomized studies Adolescents: retrospective studies
Follow-up	Effectiveness: RCTs ≥ 1 year, nonrandomized studies ≥ 3 years Harms: Any time period	--

Abbreviations. AGB: adjustable gastric banding; BMI: body mass index; BPD/DS: biliopancreatic diversion with duodenal switch; FDA: US Food and Drug Administration; IGB: intragastric balloon; OAGB: one anastomosis gastric bypass; RCT: randomized controlled trial; RYGB: Roux-en-Y gastric bypass; SADI-S: single anastomosis duodenal-ileal bypass with sleeve gastrectomy; SG: sleeve gastrectomy.

Methods Overview

To answer the KQs, we searched multiple clinical evidence databases (e.g., Ovid MEDLINE, Cochrane Library) for published systematic reviews and comparative primary studies evaluating the effectiveness and harms of bariatric procedures as compared with nonsurgical medical interventions for obesity. To meet eligibility criteria, primary studies had to be available in English, include follow-up of at least 1 year, and be published in the past 10 years (i.e., 2012 through 2021); systematic reviews had to be published in the past 3 years (i.e., 2019 through 2021), be available in English, and include a majority (i.e., more than half) of studies that met the inclusion criteria for primary literature. Two reviewers independently examined abstracts and full-text articles for inclusion and assessed the risk of bias (RoB) of included studies. Disagreements were resolved through consensus or by a third reviewer.

Pooled analyses of selected outcomes from included primary trials of adults with BMI 30 to 34.9 were conducted using Review Manager 5.4, Cochrane's systematic review software.[33] Outcomes data were pooled when 2 or more studies reported the same outcome using similar criteria for at least 2 follow-up timepoints in order to better visualize the effects of bariatric surgery over time.

CQs were addressed using studies identified in the KQ database searches. Evidence regarding the CQs is summarized in the Background section; specifically, the *Accreditation of Surgery Centers* subsection for CQ1 and in both the *Access and Equity* background subsection as well as in the summary of evidence-based guidelines for CQ2.

EVIDENCE REVIEW

The following results section organizes findings by 3 key population groups:

- Adults with BMI ≥ 35 kg/m^2
- Adults with BMI 30.0 to 34.9 kg/m^2
- Adolescents

Within each population, results are summarized by outcomes.

Adults with BMI of 35 kg/m^2 or Greater

We identified 12 systematic reviews[34-45] that reported meta-analyses (MA) or network meta-analyses (NMA), and 1 narrative review[16,46-48] that addressed the scope of this topic. Of the included systematic reviews, 6 limited their analysis to randomized controlled trials (RCTs),[37,38,40,43,45] 4 analyzed only observational studies,[35,36,39,41] and 3 analyzed RCTs and observational studies.[34,42,44] Although the narrative review included mixed study designs, we limited our discussion of the review to studies within it that met our inclusion criteria and had abstractable estimates for eligible outcomes. Table 4 summarizes key characteristics of each included review; see Appendix D, Tables D1 and D2 for additional study characteristics.

Table 4. Characteristics of Included Reviews of Adults with BMI ≥ 35

AUTHOR, YEAR	RISK OF BIAS	REVIEW POPULATION	NO. OF INCLUDED STUDIES	TOTAL SAMPLE SIZE	FOLLOW-UP RANGE	BARIATRIC SURGERY TYPES	KQS ADDRESSED
SRs of RCTs							
Cresci, 2020[40]	Moderate	Adults with BMI ≥ 35 and T2DM	k = 24	N = 1,351	6 months to 5 years	AGB, BPD/DS, OAGB, RYGB, SG	KQ1, KQ2, KQ3
Cui, 2021[38]	Moderate	Adults with BMI ≥ 35 and T2DM	k = 7	N = 447	1 to 5 years	RYGB	KQ1
Khorgami, 2019[45]	Moderate	Adults with BMI ≥ 35 and T2DM	k = 7	N = 463	2 to 5 years	AGB, BPD/DS, RYGB, SG	KQ1, KQ3
Park, 2019[43]	Low	Adults with BMI ≥ 35	k = 45	N = 4,089	6 months to 5 years	AGB, BPD/DS, OAGB, RYGB, SG, VBG	KQ1, KQ2, KQ3
Wang, 2021[37]	Low	Adults with BMI ≥ 35	k = 19	N = 663	1 to 10 years	AGB, BPD/DS, RYGB, SG	KQ1, KQ2, KQ3
SRs of Mixed Study Designs							
Ablett, 2019[44]	Moderate	Adults with BMI ≥ 35	k = 9	N = 283,405	2 to 8.9 years	AGB, RYGB, SG	KQ1, KQ2
Malczak, 2021[34]	High	Adults with BMI ≥ 35	k = 47	N = 26,629	NR	BPD/DS, OAGB, RYGB, SG	KQ1
Yan, 2019[42]	Moderate	Adults with BMI ≥ 35 and T2DM	k = 10	N = 50,150	5 to 15 years	AGB, BPD/DS, ESG, RYGB, SG	KQ1, KQ3
SRs of Observational Studies							
Hussain, 2021[39]	High	Adults with BMI ≥ 35 and T2DM	k = 5	N = 49,211	1.8 to 18.1 years	AGB, BPD/DS, RYGB	KQ1
Pontiroli, 2020[41]	Moderate	Adults with BMI ≥ 35	k = 9	N = 607,643	4 to 14 years	BPD/DS, RYGB, SG	KQ1, KQ3
Robertson, 2020[35]	High	Adults with BMI ≥ 35	k = 58	N = 3,650,961	In-hospital to 90 days post-surgery	AGB, BPD/DS, OAGB, RYGB, SG	KQ2, KQ3
Syn, 2021[36]	Low	Adults with BMI ≥ 35	k = 17	N = 174,772	2.6 to 24 years	AGB, BPD/DS, OAGB, RYGB, SG	KQ1, KQ3
Narrative Reviews							

AUTHOR, YEAR	RISK OF BIAS	REVIEW POPULATION	NO. OF INCLUDED STUDIES	TOTAL SAMPLE SIZE	FOLLOW-UP RANGE	BARIATRIC SURGERY TYPES	KQS ADDRESSED
Arterburn, 2020[16]	High	Adults with BMI ≥ 35	k = 12 (T2DM only)	N = 874	1 to 5 years	AGB, BPD/DS, RYGB, SG	KQ1

Abbreviations. AGB: adjustable gastric banding; BMI: body mass index; BPD/DS: biliopancreatic diversion with duodenal switch; ESG: endoscopic sleeve gastroplasty; KQ: Key Question; No.: number; NR: not reported; OAGB: one anastomosis gastric bypass; RCT: randomized controlled trials; RYGB: Roux-en-Y gastric bypass; SG: sleeve gastrectomy; SR: systematic review; T2DM: type 2 diabetes mellitus; VBG: vertical banded gastroplasty.

Taken together, these reviews represent 59 unique RCTs and 118 unique observational studies from the rapidly growing field of bariatric research. It should be noted that there is considerable overlap among our included reviews in terms of the primary RCTs they include, with most reviews including some or all of 12 common RCTs comparing bariatric procedures with medical therapy. Conversely, there was almost no overlap among the comparative cohort studies included across our eligible reviews.

We rated 3 systematic reviews as having a low RoB, 7 as moderate RoB, and 3 as high RoB; all narrative reviews were rated as having a high RoB (Table 4; Appendix C). Reviews with moderate and high RoB ratings generally lacked complete methods reporting, did not account for potential publication bias, and did not adequately incorporate RoB of the primary studies into the review conclusions. In addition to RoB considerations, included reviews were inconsistent in reporting sample sizes and time points associated for MA and NMA results, which further limited the overall strength of evidence.

We focused on comparative studies of bariatric procedures versus nonsurgical medical therapy interventions (i.e., medical therapy) for obesity. Included reviews assessed all ASMBS-endorsed bariatric procedures except for intragastric balloons and SADI-S. Medical therapy comparator groups included interventions such as behavioral lifestyle interventions, pharmacotherapy, and combination therapy. Most reviews broadly compared bariatric procedures with any eligible medical therapy. Studies of harms did not require a comparator. Findings from relevant systematic reviews form the core of the evidence review results, with reviews of RCTs receiving priority over reviews with mixed or observational-only study designs; narrative reviews were used to fill gaps in the evidence that were not addressed by systematic reviews.

All-cause Mortality

Three reviews analyzed all-cause mortality reported in at least 19 unique comparative cohort studies, each with over 500 participants (Table 5; Appendix D, Table D3).[36,39,41] Eligible reviews ranged from low- to high-risk of bias and included studies of adults with BMI ≥ 35 with or without T2DM. The primary reported outcome was the comparative risk of all-cause mortality between bariatric surgery participants and controls, which was generally expressed as a cumulative ratio. When possible, ratios were described in the context of differential risk reduction percentages.

Table 5. All-cause Mortality Outcomes from Included Reviews of Adults with BMI ≥ 35

AUTHOR, YEAR ROB	REVIEW POPULATION	OUTCOME TYPE	FOLLOW-UP	NO. OF OBSERVATIONAL STUDIES	EFFECT ESTIMATE[a,b] (95% CI)	*P* VALUE
Hussain, 2021[39] High	Adults with BMI ≥ 35 and T2DM	Risk of all-cause mortality	3.5 to 4.7 years (median)	2	RR, 0.39 (0.30 to 0.50)	*P*< .001
Pontiroli, 2020[41] Moderate	Adults with BMI ≥ 35	Global mortality	8.7 years (mean)	9	OR, 0.29 (0.17 to 0.49)	*P*= .001
Syn, 2021[36] Low	Adults with BMI ≥ 35	Cumulative all-cause mortality	5.8 years (median)	17	HR, 0.51 (0.48 to 0.54)	*P*< .001
		Change in median life expectancy	5.8 years (median)	17	+6.1 years (5.2 to 6.9)	NR

Notes. [a] Unless otherwise noted, effect estimates for systematic reviews represent between-group comparisons for bariatric procedures vs. medical therapy controls. [b] Ratio-based estimates less than 1 may be inverted to estimate the percentage risk reduction with bariatric procedures. For example, (1 – 0.39)*100% = 61% risk reduction with bariatric procedures vs. controls.
Abbreviations. BMI: body mass index; CI: confidence interval; HR: hazard ratio; No.: number; NR: not reported; OR: odds ratio; ROB: risk of bias; RR: relative risk or risk ratio; T2DM: type 2 diabetes mellitus.

Two reviews estimated all-cause mortality from studies of general adult populations with a BMI 35 or greater, with or without comorbidities.[36,41] A 2021 review that included a meta-analysis of 17 comparative observational studies with follow-up ranging from 2.6 to 24 years provided the most robust mortality data.[36] In this analysis, Syn and colleagues estimated that patients who received bariatric procedures had a 49% lower risk of all-cause mortality (i.e., hazard ratio [HR], 0.51), corresponding with an additional 6.1 years of median life expectancy, compared with matched medical controls at 5.8 years of median follow-up ($P < .001$).[36] Another moderate-RoB review and meta-analysis of 9 observational studies estimated that bariatric surgery patients had a 71% reduced risk of all-cause mortality at 8.7 years of mean follow-up ($P = .001$), suggesting a persistent benefit of bariatric surgery over time.[41]

Adults with BMI ≥ 35 and T2DM

Two reviews reported all-cause mortality estimates in adults with BMI 35 or greater and T2DM (Table 5).[36,39] A meta-analysis of 2 large US-based registry studies from a high-RoB systematic review (SR) conducted by Hussain and colleagues found that bariatric procedures reduced the 3 to 5 year risk of all-cause mortality by 61% compared with nonsurgical interventions in adults with obesity and T2DM ($P < .001$).[39] This finding aligns with the differential risk reductions reported for general adult bariatric surgery populations in the prior section. However, subgroup analyses in the review conducted by Syn and colleagues (Appendix D, Table D3) showed that while individuals with and without T2DM who underwent bariatric procedures experienced significantly reduced risk of all-cause mortality compared to controls at 5.8 years of follow-up, the mortality effect of bariatric procedures was significantly greater among adults with T2DM (comparative risk reduction: 59% with T2DM vs. 30% without T2DM; $P < .001$).[36] For that same follow-up period, individuals with T2DM also experienced a greater differential

gain in life expectancy with bariatric procedures (+9.1 years) compared with individuals without T2DM (+ 5.1 years).[36]

Other Subgroup Analyses

All-cause mortality subgroup analyses were also available by age and bariatric procedure type (Appendix D, Table D3). Age-stratified analyses conducted by Pontiroli and colleagues showed that the estimated all-cause mortality treatment effect between individuals treated with bariatric procedures compared with medical therapy was not significant for individuals below the median cohort analysis age for each study (odds ratio [OR], 0.78 [95% confidence interval [CI], 0.57 to 1.06]; $P = .110$), but was significant for individuals above the median cohort age (OR, 0.23 [95% CI, 0.12 to 0.44]; $P < .001$).[41] In contrast, Syn and colleagues found that while all major bariatric procedure types assessed in the included primary studies (i.e., AGB, RYGB, SG) were associated with significant reductions in all-cause mortality risk compared to medical therapy controls (HR range, 0.43 to 0.50; $P < .001$), there was no differential mortality benefit associated with any specific procedure ($P = .36$).[36]

Weight Change

Five reviews[37,40,42-44] analyzed weight change outcomes in adults with BMI of 35 or greater (Table 6). Except for SADI-S, weight change analyses included all ASMBS-endorsed procedures. Currently, there is no standardized measure for assessing weight change, and among the included reviews, weight change was assessed by a range of measures including absolute change in kilograms or BMI units or the proportion of total or excess weight loss during follow-up. Results reported in Table 6 largely reflect overall estimates of between-group (i.e., bariatric procedures vs. medical therapy) outcomes.

Table 6. Weight Change Outcomes from Included Reviews of Adults with BMI ≥ 35

AUTHOR, YEAR ROB	REVIEW POPULATION	OUTCOME TYPE	FOLLOW-UP	NO. OF STUDIES	EFFECT ESTIMATE[a] (95% CI)	*P* VALUE
Ablett, 2019[44] Moderate	Adults with BMI ≥ 35	Mean weight change (kg)	2 years	3 RCTs	MD, -22.2 (-31.6 to -12.8)	*P*< .001
Cresci, 2020[40] Moderate	Adults with BMI ≥ 35 and T2DM	% Total weight loss	1 to 5 years	9 RCTs	MD, -16.83 (-18.03 to -15.62)	*P*< .001
		Mean BMI change (kg/m^2)	1 to 5 years	10 RCTs	MD, -5.74 (-7.05 to -4.43)	*P*< .001
Park, 2019[43] Low	Adults with BMI ≥ 35	% Excess weight loss	1 year	24 RCTs	No overall estimate MD range by procedure type: 26.9% to 70.7%	*P*< .05 for all
			2 years	14 RCTs	No overall estimate MD range by procedure type: 52.8% to 75.0%	*P*< .05 for all
			3 years	9 RCTs	No overall estimate MD range by procedure type: 19.0% to 45.0%	*P*< .05 for all

AUTHOR, YEAR ROB	REVIEW POPULATION	OUTCOME TYPE	FOLLOW-UP	NO. OF STUDIES	EFFECT ESTIMATE[a] (95% CI)	*P*VALUE
Wang, 2021[37] Low	Adults with BMI ≥ 35	Mean weight change (kg)	1 to 10 years	19 RCTs	MD, -18.47 (-22.99 to -13.93)	*P*< .001
		Mean BMI change (kg/m^2)	1 to 10 years	12 RCTs	MD, -4.79 (-7.92 to -1.66)	*P*< .001
Yan, 2019[42] Moderate	Adults with BMI ≥ 40 and T2DM	Mean BMI change (kg/m^2)	5 to 10 years	2 RCTs and 2 OS	MD, -8.49 (-15.01 to -1.98)	NR

Note. [a] Unless otherwise noted, effect estimates for SRs represent between-group comparisons for bariatric procedures vs. medical therapy controls. Effect estimates from NRs are raw estimates as no MAs or NMAs were performed.
Abbreviations. BMI: body mass index; CI: confidence interval; kg: kilogram; m^2: meters squared; MA: meta-analysis; MD: mean difference; NMA: network meta-analysis; No.: number; NR: not reported; OS: observational studies; RCT: randomized controlled trial; ROB: risk of bias; SR: systematic review; T2DM: type 2 diabetes mellitus.

Three low- to moderate-RoB SRs reported weight change outcomes for general adult populations with BMI 35 or greater (Table 6; Appendix D, Table D3).[37,43,44] The most comprehensive direct evidence for this population comes from a 2021 SR of RCTs comparing bariatric procedures with nonsurgical treatment for obesity.[37] Based on meta-analyses of 1- to 10-year follow-up data from 19 RCTs, Wang and colleagues estimated that treatment with bariatric procedures resulted in an additional 18.5 kg of weight loss and a BMI reduction of almost 5 kg/m^2 compared with nonsurgical control group participants.[37] Results from a meta-analysis of 3 RCTs in a 2019 SR were similar, with adults who were randomized to bariatric procedures experiencing an estimated additional 22.2 kg of weight loss compared with medical controls.[44] Indirect evidence from a 2019 network meta-analysis of excess weight loss in 24 RCTs conducted by Park and colleagues support the direct results generated by the previously described meta-analyses.[43] Although no overall network analyses were reported, patients randomized to bariatric procedures experienced proportionally greater excess weight loss with AGB, BPD/DS, RYGB, and SG procedures compared with medical controls at both 1 and 3 years.[43] Differential weight loss was highest at 2 years, with bariatric surgery patients experiencing around 53% to 75% more excess weight reduction than controls.[43]

Adults with BMI ≥ 35 and T2DM

Two moderate-RoB SRs analyzed weight change outcomes from studies of adults with T2DM (Table 6).[40,42] Based on a network meta-analysis of RCTs with 1- to 5-year follow-up, Cresci and colleagues estimated that adults with T2DM who were randomized to bariatric procedures lost around 17% more weight than medical controls, corresponding with a differential BMI reduction of almost 6 kg/m^2.[40] Two SRs indicate that these short-term differential weight reductions observed among T2DM patients with bariatric procedures may be maintained in the long-term. A meta-analysis of RCTs and observational studies conducted by Yan and colleagues estimated that at 5 to 10 years follow-up, T2DM patients treated with bariatric surgery experienced a differential BMI reduction of 8.5 kg/m^2 compared to controls.[42]

Other Subgroup Analyses

Included reviews conducted weight change subgroup analyses by bariatric procedure type, trial BMI criteria, and trial duration (Appendix D, Table D3). Four reviews reported comparative weight change by bariatric procedure type.[37,40,42,43] With rare exceptions, patients who received one of the common bariatric procedures (i.e., AGB, BPD/DS, RYGB, SG) experienced significantly greater weight loss at all follow-up time points compared with medical controls. More recently endorsed ASMBS procedures, such as the OAGB, also exhibited greater short-term weight loss in meta-analyses compared with medical controls. In general, AGB and SG resulted in lower differential weight compared with RYGB and BPD/DS.

In addition to procedure type, Cresci and colleagues conducted subgroup analyses by minimum trial BMI requirements and trial duration as part of a network meta-analysis of RCTs. Although participants who underwent bariatric procedures experienced statistically significant reductions in mean BMI compared with nonsurgical controls, regardless of the trial BMI enrollment threshold, there was a smaller but statistically significant reduction in BMI for intervention groups in trials with BMI enrollment thresholds below 35 kg/m^2.[40] However, there were no differences in BMI reduction by overall trial follow-up duration (i.e., ≤ 2 years vs. > 2 years).[40]

Change in Chronic Disease Status

We assessed the effect of bariatric surgery on improvement or resolution of several obesity-related chronic conditions. The conditions selected for this evidence review include T2DM, hypertension (HTN), coronary artery disease (CAD), obstructive sleep apnea (OSA), joint arthropathy, and intracranial HTN. We prioritized evidence regarding condition resolution and presented evidence regarding improvement when resolution data were not available. No studies meeting inclusion criteria reported on clinical outcomes or joint arthropathy or intracranial HTN.

Diabetes

Five reviews[37,38,40,43,45,48] analyzed improvement or resolution in diabetes in adults with BMI of 35 or greater (Table 7; Appendix D, Table D4). Diabetes data were exclusively focused on T2DM populations, and we did not identify any reviews assessing the effect of bariatric procedures on type 1 diabetes. Most eligible reviews reported on T2DM remission, which was most commonly defined as achieving an HbA1c < 6.0% without ongoing glycemic therapy (e.g., metformin, insulin). Other definitions included fasting plasma glucose (FPG) targets or different HbA1c thresholds.

Table 7. Diabetes Outcomes from Included Reviews of Adults with BMI ≥ 35

AUTHOR, YEAR ROB	REVIEW POPULATION	OUTCOME TYPE	FOLLOW-UP	NO. OF STUDIES	RATE, INTEVENTION VS. CONTROL EFFECT ESTIMATE [a] (95% CI)	*P* VALUE
Cresci, 2020[40] Moderate	Adults with BMI ≥ 35 and T2DM	T2DM remission	1 to 5 years	9 RCTs	34.6% vs. 1.9% OR, 19.26 (5.68 to 65.31)	*P* = .001
Cui, 2021[38] Moderate	Adults with BMI ≥ 35 and T2DM	T2DM remission	1 year	4 RCTs	28.2% vs. 0.6% RR, 18.01 (4.53 to 71.70)	*P* < .001
			2 years	4 RCTs	54.8% vs. 16.4% RR, 12.70 (0.45 to 358.63)	*P* = .14

AUTHOR, YEAR ROB	REVIEW POPULATION	OUTCOME TYPE	FOLLOW-UP	NO. OF STUDIES	RATE, INTEVENTION VS. CONTROL EFFECT ESTIMATE [a] (95% CI)	*P* VALUE
			3 years	3 RCTs	35.1% vs. 0 RR, 29.58 (5.92 to 147.82)	*P*< .001
			5 years	3 RCTs	21.4% vs. 0 RR, 16.92 (4.15 to 69.00)	*P*< .001
Khorgami, 2019[45] Moderate	Adults with BMI ≥ 35 and T2DM	T2DM remission	2 years	7 RCTs	52.5% vs. 3.5% RR, 10.0 (5.5 to 17.9)	*P*< .001
			5 years	4 RCTs	27.5% vs. 4.5% RR, 6.0 (2.7 to 13.0)	*P*< .001
Park, 2019[43] Low	Adults with BMI ≥ 35	T2DM remission	1 to 2 years	15 RCTs	Overall estimates NR RR range across procedure types: 7.6 to 14.3	*P*< .001 for all
			3 to 5 years	11 RCTs	Overall estimates NR RR range across procedure types: 6.7 to 31.8	*P*< .001 for all
Wang, 2021[37] Low	Adults with BMI ≥ 35	Reduced use of metformin	1 to 5 years	IG: 6 RCTs CG: 5 RCTs	IG: RR, 0.46 (0.25 to 0.87) CG: RR, 0.98 (0.81 to 1.19)	*P*= .02 *P*= .83
		Reduced use of insulin	1 to 5 years	IG: 13 RCTs CG: 9 RCTs	IG: RR, 0.35 (0.23 to 0.52) CG: RR, 0.93 (0.75 to 1.16)	*P*< .001 *P*= .54
		Reduced use of other T2DM drugs	1 to 5 years	IG: 9 RCTs CG: 7 RCTs	IG: RR, 0.55 (0.42 to 0.72) CG: RR, 0.89 (0.80 to 0.99)	*P*< .001 *P*= .04

Notes. [a] Unless otherwise noted, effect estimates for SRs represent between-group comparisons for bariatric procedures vs. medical therapy controls. Effect estimates from NRs are raw estimates as no MAs or NMAs were performed. [b] Results for bariatric surgery groups only.
Abbreviations. BMI: body mass index; CG: control group; CI: confidence interval; IG: intervention group; MA: meta-analysis; NMA: network meta-analysis; No.: number; NR: not reported; OR: odds ratio; RCT: randomized controlled trial; ROB: risk of bias; RR: relative risk or risk ratio; SR: systematic review; T2DM: type 2 diabetes mellitus.

Five moderate- to low-RoB reviews assessed diabetes outcomes in adults with BMI of 35 kg/m^2 or greater (Table 7).[37,38,40,43,45] Of these reviews, 4 reported T2DM remission with 1 to 5 years of available follow-up data.[38,40,43,45] Across all follow-up periods, remission rates ranged from 21.4% to 52.5% with bariatric procedures compared with 0 to 16.4% with medical therapy; comparative estimates from meta-analyses showed that the likelihood of remission with bariatric procedures was significantly higher compared with medical therapy (relative risk [RR] range, 6.0 to 16.9; $P < .001$).[38,40,43,45] Rates of remission were generally higher in both intervention and control groups during short-term follow-up (i.e., 1 to 2 years), but the comparative likelihood of remission during this period (RR range, 7.6 to 18.01) was not statistically higher compared with longer-term follow-up (RR range, 6.0 to 31.8).[38,40,43,45] Subgroup analyses by bariatric procedure type from a network meta-analysis showed that all major bariatric procedures were associated with increased likelihood of short- and long-term T2DM remission compared with medical controls, with AGB having the smallest relative effect and gastric bypass procedures having the largest remission effect (Appendix D, Table D4).[43]

One review reported on changes in participants' use of key elements of glycemic therapy for T2DM (Table 7; Appendix D, Table D4).[37] Over 1 to 5 years of follow-up, Wang and colleagues found that groups randomized to bariatric procedures demonstrated a statistically significant reduction in the use of metformin and insulin compared with nonsurgical weight loss groups.[37] In comparison, there were no between-group differences in use of other antidiabetic medications.[37]

Hypertension

Three reviews[37,40,42,47,48] analyzed improvement or resolution of HTN in adults with BMIs of 35 or greater and several key subpopulations (Table 8; Appendix D, Table D4). HTN is defined by the American Heart Association as having a systolic blood pressure of 130 mmHg or higher or a diastolic blood pressure of 80 mmHg or higher[49]; blood pressures above these thresholds have been linked to increased risk for adverse cardiovascular outcomes, including stroke and myocardial infarction.[50] Most reviews reported measures of HTN improvement, including mean and percent change in systolic and diastolic blood pressure. HTN resolution or remission was generally measured by the cessation of antihypertensive medications at follow-up, although some definitions required patients to meet a systolic blood pressure target without the use of medications.

Table 8. Hypertension Outcomes from Included Reviews of Adults with BMI ≥ 35

AUTHOR, YEAR ROB	REVIEW POPULATION	OUTCOME TYPE	FOLLOW-UP	NO. OF STUDIES	IG vs. CG RATE EFFECT ESTIMATE [a] (95% CI)	*P* VALUE
Cresci, 2020[40] Moderate	Adults with BMI ≥ 35 and T2DM	Mean change in SBP (mmHg)	1 to 5 years	9 RCTs	MD, -2.62 mmHg (-4.46 to -0.79)	*P* = .005
		Mean change in DBP (mmHg)	1 to 5 years	9 RCTs	MD, 0.91 mmHg (-1.54 to 3.36)	*P* = .46
		Mean change in % using antiHTN drugs from baseline	2 to 5 years	2 RCTs	IG range: -28 to -48 percentage points CG range: 0 to +10 percentage points	NR
Wang, 2021[37] Low	Adults with BMI ≥ 35	Mean change in SBP (mmHg)	1 to 5 years	19 RCTs	WMD, -3.94 mmHg (-6.00 to -1.88)	*P* < .001
		Mean change in DBP (mmHg)	1 to 5 years	19 RCTs	WMD, -2.69 mmHg (-3.99 to -1.39)	*P* < .001
		Mean change in % using antiHTN drugs	1 to 5 years	IG: 5 RCTs CG: 5 RCTs	Baseline vs. follow-up by group IG: 67.3% vs. 37.3% MD, -0.91 per capita reduction (-1.49 to -0.33) CG: 70.9% vs. 68.4% MD, -0.05 per capita reduction (-0.39 to 0.29)	*P* = .002 *P* = .78

AUTHOR, YEAR ROB	REVIEW POPULATION	OUTCOME TYPE	FOLLOW-UP	NO. OF STUDIES	IG vs. CG RATE EFFECT ESTIMATE [a] (95% CI)	*P* VALUE
Yan, 2019[42] Moderate	Adults with BMI ≥ 40 and T2DM	Mean change in SBP (mmHg)	5 to 10 years	2 RCTs and 2 OS	WMD, 0.00 (-0.11 to 0.11)	NR
		Mean change in DBP (mmHg)	5 to 10 years	2 RCTs and 2 OS	WMD, 0.90 (0.82 to 0.97)	NR

Notes. [a] Unless otherwise noted, effect estimates for SRs represent between-group comparisons for bariatric procedures vs. medical therapy controls. Effect estimates from NRs are raw estimates as no MAs or NMAs were performed. [b] Remission definition: SBP < 130 mmHg at 12 months and without the use of antihypertensive medication.

Abbreviations. BMI: body mass index; CG: control group; CI: confidence interval; DBP: diastolic blood pressure; HTN: hypertension; IG: intervention group; MA: meta-analysis; MD: mean difference; mmHg: millimeters of mercury; NMA: network meta-analysis; No.: number; NR: not reported; OS: observational studies; RCT: randomized controlled trial; ROB: risk of bias; SBP: systolic blood pressure; SR: systematic review; T2DM: type 2 diabetes mellitus; WMD: weighted mean difference.

Three moderate- to low-RoB reviews assessed blood pressure outcomes in adults with BMI of 35 kg/m^2 or greater (Table 8).[37,40,42] A low-RoB 2021 SR of RCTs, conducted by Wang and colleagues, provided the most comprehensive and direct estimates of short- to mid-term (i.e., 1 to 5 years) HTN outcomes in this population. Based on a meta-analysis of 19 RCTs, bariatric surgery was associated with a statistically significant reduction in systolic blood pressure and diastolic blood pressure compared to medical therapy (mean difference [MD], -3.94 mmHg and -2.69 mmHg, respectively). Subgroup analyses showed a statistically significant reduction in systolic blood pressure and diastolic blood pressure among patients with higher age (≥ 45 years), higher baseline BMI (≥ 40 kg/m^2), higher baseline HbA1c (≥ 7.0%), and among those who underwent RYGB. In contrast, there were no between-group differences in mean systolic blood pressure or diastolic blood pressure at follow-up among patients with lower age (< 45 years), lower baseline BMI (< 40 kg/m^2), lower baseline HbA1c (< 7.0%), and those who received AGB or BPD/DS (Appendix D, Table D4). In a meta-analysis of antihypertensive medication use from 5 RCTs, there was a significant within-group reduction from baseline in the use of medications among patients randomized to bariatric procedures (67.3% vs. 37.3%; *P* = .002); in contrast, patients randomized to nonsurgical control groups did not experience a significant reduction in medication use (*P* = .78). These findings suggest that bariatric procedures may result in better blood pressure control and a higher rate of HTN remission than medical therapy for obesity among adult populations with BMI of 35 or greater, with or without comorbidities.

Two reviews assessed HTN outcomes for adults with BMI 35 or greater and T2DM (Table 8) and reported mixed results.[40,42] Results from 1 network meta-analysis of 9 RCTs, conducted by Cresci and colleagues, reported a statistically significant reduction in systolic blood pressure for bariatric procedures versus medical therapy over 1 to 5 years of follow-up (MD, -2.62 mmHg; *P* =.005), but no difference in diastolic blood pressure.[40] However, another meta-analyses of longer-term data (i.e., 5 to 10 years) from RCTs and comparative observational studies of adults with obesity and T2DM, conducted by Yan and colleagues, found no difference in systolic blood pressure with bariatric procedures compared with medical therapy and indicated that bariatric procedures may be associated with increased diastolic blood pressure (MD, 0.90 mmHg).[42]

Coronary Artery Disease

Two moderate- to high-RoB reviews[39,42] analyzed coronary artery disease-related outcomes in adults with BMIs of 35 or greater and several key subpopulations (Table 9; Appendix D, Table D4). Key outcomes for this category ranged from specific events (e.g., myocardial infarction [MI]) to broad categories, such as cardiovascular events. Both reviews assessed macrovascular complications, which is a composite outcome that includes cerebrovascular incidents such as stroke, and coronary artery disease-related incidents such as myocardial infarction.

Table 9. Cardiovascular-Related Outcomes from Included Reviews in Adults with BMI ≥ 35

AUTHOR, YEAR ROB	REVIEW POPULATION	OUTCOME TYPE	FOLLOW-UP	NO. OF STUDIES	IG vs. CG RATE EFFECT ESTIMATE[a] (95% CI)	*P* VALUE
Hussain, 2021[39] High	Adults with BMI ≥ 35 and T2DM	Macrovascular complications	1.8 to 18.1 years	5 OS	RR, 0.50 (0.35 to 0.73) Adj. RR, 0.54 (0.37 to 0.79)	*P*= .003 *P*= .002
Yan, 2019[42] Moderate	Adults with BMI ≥ 40 and T2DM	Macrovascular complications	5 to 20 years	3 RCTs and 6 OS	3.4% vs. 7.2% RR, 0.43 (0.27 to 0.70)	NR
		Cardiovascular events		1 RCT and 2 OS	HR, 0.52 (0.39 to 0.71)	NR
		Myocardial infarction	5 to 20 years	3 RCTs and 4 OS	1.0% vs. 2.2% RR, 0.46 (0.38 to 0.55)	NR

Note. [a] Unless otherwise noted, effect estimates for SRs represent between-group comparisons for bariatric procedures vs. medical therapy controls. Effect estimates from NRs are raw estimates as no MAs or NMAs were performed.

Abbreviations. Adj.: adjusted; BMI: body mass index; CG: control group; CI: confidence interval; HR: hazard ratio; IG: intervention group; MA: meta-analysis; NMA: network meta-analysis; No.: number; NR: not reported; OS: observational studies; RCT: randomized controlled trial; RoB: risk of bias; RR: relative risk; SR: systematic review; T2DM: type 2 diabetes mellitus.

Two reviews assessed coronary artery disease-related outcomes in adults with BMI ≥ 35 and T2DM (Table 9).[39,42] Meta-analyses of RCTs and observational studies conducted for both reviews found that treatment with bariatric procedures reduced the risk of macrovascular complications over a wide range of follow-up (i.e., 1.8 to 20 years) compared with medical therapy (RR range, 0.43 to 0.50; $P < .01$).[39,42] Additional analyses conducted by Yan and colleagues also showed that patients treated with bariatric procedures had a statistically significant reduction in risk for any cardiovascular event (HR, 0.52 [95% CI, 0.39 to 0.71]) or MI (RR, 0.46 [0.38 to 0.55]) at 5 or more years post intervention compared with medical controls.[42]

Subgroup analyses stratified by study design (Appendix D, Table D4) found that the risk reduction in composite macrovascular complications with bariatric procedures observed for the primary analysis in Yan and colleagues (i.e., RR, 0.43) was largely informed by 3 large retrospective cohort studies (RR, 0.31 [95% CI, 0.16 to 0.62]), as between-group analyses for RCTs and prospective cohort studies were not statistically significant.[42] In contrast, all study designs demonstrated significant risk reductions in myocardial infarction with bariatric procedures compared to medical therapy.[42] Risk reduction estimates

were statistically significant across study designs, and were highest in prospective cohort studies (RR, 0.35 [95% CI, 0.22 to 0.55]), followed by retrospective cohort studies (RR, 0.45 [95% CI, 0.36 to 0.56]) and RCTs (RR, 0.63 [95% CI, 0.43 to 0.93]).[42]

Other subgroup analyses by geographic region and bariatric procedure type, conducted by Hussain and colleagues, found that studies conducted in the US had larger differential risk reductions in macrovascular complications compared with non-US studies (59% vs. 29%) and that RYGB resulted in greater risk reductions than other bariatric procedures (61% vs. 45%); all between-group comparisons in subgroup analyses were significant ($P < .001$).[39]

Obstructive Sleep Apnea

We did not identify any eligible reviews of bariatric procedures that assessed improvement or resolution of obstructive sleep apnea.

Joint Arthropathy

We did not identify any eligible reviews of bariatric procedures that assessed improvement or resolution of joint arthropathy.

Intracranial Hypertension

We did not identify any eligible reviews of bariatric procedures that assessed improvement or resolution of intracranial HTN.

Quality of Life

Two SRs (1 moderate- and 1 high-RoB)[34,40] analyzed quality of life (QoL) in adults with BMIs of 35 or greater (Table 10). The reviews assessed QoL broadly in adults with severe obesity and adults with T2DM. Five-year QoL results were available for both reviews. Primary studies included in the reviews used a wide range of measurement scales to assess QoL outcomes, including general functioning scales (e.g., Short Form 36 Health Survey [SF-36]) and condition-specific scales (e.g., Gastrointestinal QoL Index [GIQLI], Impact of Weight on QoL [IWQOL]). Owing to the heterogeneity in QoL reporting, reviews opted to either standardize all QoL outcomes to a single scale (i.e., a standardized mean difference) or report results narratively.

Table 10. Quality of Life Outcomes from Included Reviews of Adults with BMI ≥ 35

AUTHOR, YEAR ROB	REVIEW POPULATION	OUTCOME TYPE	FOLLOW-UP	NO. OF STUDIES	EFFECT ESTIMATE (95% CI)	*P* VALUE
Malczak, 2021[34] High	Adults with BMI ≥ 35	GIQLI scores[a,b]	3 years	4 RCTs, 6 OS	Statistically higher QoL scores for all surgical types compared with medical therapy: ■ AGB: MD, 17.38 (8.87 to 25.92) ■ BPD/DS: MD, 25.8 (9.9 to 41.6) ■ RYGB: MD, 21.4 (14.4 to 28.5) ■ SG: MD, 20.1 (12.9 to 27.3)	NR
		GIQLI scores[a,b]	5 years	4 RCTs, 3 OS	Statistically higher QoL scores for all surgical types compared with medical therapy: ■ BPD/DS: MD, 17.5 (12.9 to 24.2) ■ OAGB: MD, 13.0 (8.1 to 18.0)	NR

AUTHOR, YEAR ROB	REVIEW POPULATION	OUTCOME TYPE	FOLLOW-UP	NO. OF STUDIES	EFFECT ESTIMATE (95% CI)	*P* VALUE
					■ RYGB: MD, 16.4 (12.1 to 20.7) ■ SG: MD, 11.8 (7.5 to 16.2)	
Cresci, 2020[40] Moderate	Patients with BMI ≥ 35 and T2DM	QOL (various scales)	1 year	1 RCT	■ Improvements in overall QOL (EQ5D scale) noted in both groups (RYGB vs. medical controls) ■ No significant between-group difference in scores	NR
			3 years	1 RCT	■ Improvements in overall (SF-36) and diabetes-related QOL (PAID) noted in both groups; no significant between-group difference in scores ■ Superior weight-related QoL scores (IWQoL) among participants with RYGB vs. controls	NR
			5 years	3 RCTs	■ Superior SF-36 scores among participants with surgery (i.e., AGB, BPD/DS, RYGB) vs. controls	NR

Notes. Between-group *P* values not reported for any available QoL analysis. [a] To pool data from different QoL forms, SMDs were used for overall QOL and then converted to GIQLI scale scores. [b] GIQLI score range: 0 to 144; higher scores indicate better GIQLI, with a clinically meaningful difference of > 5 points.

Abbreviations. AGB: adjustable gastric banding; BMI: body mass index; BPD/DS: biliopancreatic diversion with duodenal switch; CI: confidence interval; EQ5D: European QoL questionnaire; GIQLI: Gastrointestinal QoL Index; IWQoL: Impact of Weight on QoL questionnaire; MD: mean difference; No.: number; NR: not reported; OAGB: one anastomosis gastric bypass; OS: observational study; PAID: Problem Areas in Diabetes; QoL: quality of life; RCT: randomized controlled trial; ROB: risk of bias; RYGB: Roux-en-Y gastric bypass; SF-36: short form 36; SG: sleeve gastrectomy; SMD: standardized mean difference; T2DM: type 2 diabetes mellitus.

In their 2021 SR, Malczak and colleagues conducted NMAs of mixed study designs to assess 3-year (4 RCTs and 6 comparative cohort studies) and 5-year (4 RCTs and 3 comparative cohort studies) differences in QoL between patients with severe obesity who underwent bariatric procedures compared with those who received nonsurgical lifestyle interventions.[34] To pool data from different QoL scales, review authors compared standardized mean differences (SMDs) of overall QOL scores between groups and then converted the results into a single GIQLI.[34] After 3 years of follow-up, patients who received AGB, BPD/DS, laparoscopic RYGB, and SG reported significantly greater improvements in overall health-related QoL mean scores (SMD range, 0.78 to 1.16) corresponding with clinically significant differential improvements (i.e., > 5 points on the GIQLI scale) in gastrointestinal QoL (range, 17.4 to 25.8 points) compared with nonsurgical controls (Table 10).[34] Only 1 procedure type included in the 3-year analysis, the banded RYGB, was not associated with comparatively greater QoL.[34] Results at 5 years were similar, with patients who received any bariatric procedure (i.e., BPD/DS, OAGB, RYGB, SG) reporting significantly greater improvements in overall QoL (SMD range, 0.92 to 1.43) and gastrointestinal QoL (range, 11.8 to 17.5 points) compared with nonsurgical controls (Table 10).[34] The clinical implications of these results are unclear given variation in QoL measures, study designs, statistical methodology, and study quality.

Adults with BMI ≥ 35 and T2DM

In a systematic review conducted by Cresci and colleagues comparing the effectiveness of bariatric procedures with nonsurgical management for patients with T2DM, QoL results from 5 RCTs were narratively summarized.[40] In general, studies showed that there were few between-group differences in overall or condition-specific QoL in the short-term (i.e., 1 to 3 years post randomization), whereas patients with T2DM randomized to bariatric procedures reported significantly higher overall QoL scores after 5 years compared with nonsurgical controls (Table 10).[40]

Harms

Six low- to high-RoB reviews[16,35,40,43,44,46,48,51] assessed harms outcomes in adults with BMI of 35 or greater (Table 11; Appendix D, Table D3). Reviews reported a range of harms including deaths, surgical complications, surgical revisions and reoperations, vitamin deficiencies, overall serious adverse events, and specific adverse events, such as fractures. As compared with other outcomes assessed in this evidence review, harms reporting in the primary studies was less robust, particularly for longer-term outcomes, which may have resulted in the underestimation of complications.

Table 11. Harms Outcomes from Included Reviews of Adults with BMI ≥ 35

AUTHOR, YEAR ROB	REVIEW POPULATION	OUTCOME TYPE	FOLLOW-UP	NO. OF STUDIES	EFFECT ESTIMATE[a] (95% CI)	*P* VALUE
Ablett, 2019[44] Moderate	Adults with BMI ≥ 35	Bone fractures (any type)	1 to 2 years	3 RCTs	IG: 8 of 226 CG: 5 of 139 RR, 0.82 (0.29 to 2.35)	*P* = .72
			2.2 to 8.9 years	6 OS	4 studies reported a significantly increased risk of fracture with surgery vs. medical therapy: HR range, 1.21 (1.01 to 1.44) to 2.3 (1.8 to 2.8) 2 studies found no difference in the risk of fracture between groups	NR
Arterburn, 2020[16] High	Adults with BMI ≥ 35	Reoperations	5 years	2 RCTs 5 OS	Overall: 5% to 22.1% RCTs: 8.3% to 22.1% OS: 5% to 22.1%	NR
			10 years	9 studies	Overall: 8% to 64% RYGB (7 studies): 8% to 64% (median 29%) SG (2 studies): 32% to 36%	
Cresci, 2020[40] Moderate	Adults with BMI ≥ 35 and T2DM	Serious adverse events		10 RCTs	IG: 72 of 386 CG: 44 of 337 HR, 1.44 (0.66 to 3.16)	*P* = .36
		Death		10 RCTs	IG: 0 of 386 CG: 3 of 337 HR, 0.21 (0.03 to 1.32)	*P* = .10
		Severe hypoglycemia		10 RCTs	IG: 4 of 386 CG: 4 of 337 HR, 0.69 (0.19 to 2.52)	*P* = .58
		Revisions		10 RCTs	4 of 386	
Park, 2019[43] Low	Adults with BMI ≥ 40	Death	1 to 5 years	45 RCTs	ABG: no deaths BPD/DS: no deaths RYGB: 2 deaths (mortality rate: 0.1%) SG: no deaths VBG: 2 deaths (mortality rate: 2.0%)	NR
		Surgical complications	1 to 5 years	45 RCTs	Hernia: 0.6% to 5.1% Obstruction/stricture: 0.8% to 4.0% GI bleeding: 0.8% to 3.5% Leakage/perforation: 0.7% to 3.5% Wound infection: 0.3% to 1.8% Ulcer: 0.2% to 1.5%	NR

AUTHOR, YEAR ROB	REVIEW POPULATION	OUTCOME TYPE	FOLLOW-UP	NO. OF STUDIES	EFFECT ESTIMATE[a] (95% CI)	*P* VALUE
					Dumping syndrome: 0.2% to 0.7% Hemoperitoneum: 0.1% (RYGB only)	
Robertson, 2020[35] High	Adults with BMI ≥ 35	Surgical complications (perioperative mortality rate)	90 days	58 OS	4,707 of 3,650,961 Rate: 0.08 (0.06 to 0.10)	NR
Wang, 2021[37] Low	Adults with BMI ≥ 35	Adverse events	1 to 10 years	19 RCTs	IG: 603 events (0.28 per person/year) CG: 393 events (0.23 per person/year)	NR
		Deaths	1 to 10 years	19 RCTs	IG: 2 deaths (1 after CABG surgery; 1 cause not reported) CG: 2 deaths (fatal MIs)	NR

Note. [a] Unless otherwise noted, effect estimates for SRs represent between-group comparisons for bariatric procedures vs. medical therapy controls. Effect estimates from NRs are raw estimates as no MAs or NMAs were performed.

Abbreviations. AGB: adjustable gastric banding; BMI: body mass index; BPD/DS: biliopancreatic diversion with duodenal switch; CABG: coronary artery bypass graft; CG: control group; CI: confidence interval; GI: gastrointestinal; HR: hazard ratio; IG: intervention group; MA: meta-analysis; MI: myocardial infarction; NMA: network meta-analysis; No.: number; NR: not reported; OS: observational studies; RCT: randomized controlled trial; ROB: risk of bias; RR: relative risk or risk ratio; RYGB: Roux-en-Y gastric bypass; SG: sleeve gastrectomy; SR: systematic review; T2DM: type 2 diabetes mellitus; VBG: vertical banded gastroplasty.

Six reviews reported on harms in adults with BMI 35 kg/m^2 or greater (Table 11; Appendix D, Table D3).[16,35,40,43,44,51]

Three reviews included at least 22 RCTs and 6 observational studies comparing the rates of adverse events for bariatric procedures versus medical therapy over 1 to 10 years of follow-up.[40,44,51] Across the reviews, no between-group differences were observed in the overall rate of adverse events,[51] serious adverse events,[40] severe hypoglycemia events,[51] or death.[40,51] One review that assessed the risk of bone fractures as a proxy measure for vitamin deficiencies observed no short-term difference in 3 RCTs; however, 4 of 6 observational studies with longer-term follow-up observed a statistically significant higher risk of bone fractures of any type or site with bariatric procedures than medical therapy (HR range, 1.21 to 2.3).[44]

Two reviews assessed complications and mortality in the perioperative period (i.e., 90 days postsurgery). In one review of 45 RCTs, overall rates of reported surgical complications were low, ranging from 0.1% to 5.1%.[43] Common complications included hernia, obstructions or structures, gastrointestinal bleeding, leaking or perforation at the surgical site, wound infections, ulcers, and dumping syndrome.[43] The most common complications for each included procedure were hernias with RYGB (5.1%), obstruction or stricture with SG (1.2%), bleeding or leakage with BPD/DS (3.5%), and obstruction or leakage with AGB (0.8%). In terms of mortality, an analysis of 58 observational studies that included over 3.5 million participants found that the pooled rate of perioperative mortality up to 90 days post-surgery was less than 0.1% (rate, 0.08 [95% CI, 0.06 to 0.10]).[35] Subgroup analyses showed that the rate of perioperative

mortality did not vary significantly by follow-up period (i.e., in-hospital, 30 days, 90 days) or study type, but was significantly higher with BPD/DS (rate, 0.41 [95% CI, 0.25 to 0.60]) compared to other bariatric procedures.

Two reviews reported on rates of surgical revisions or reoperations following bariatric procedures.[16,40] Across 10 RCTs and 1 to 5 years of follow-up, Cresci and colleagues identified 4 instances of surgical revisions (among 386 patients) but did not specify which bariatric procedure types required revisions or give detail about the type or extent of revision required.[40] A narrative review reported rates of reoperations ranging from 5% to 22% at 5 years of follow-up and from 8% to 64% at 10 years of follow-up, suggesting an increasing need for surgical reintervention in the long-term.[16] In cohort studies, rates of reoperations were significantly lower with SG compared to RYBG (HR range, 0.72 to 0.80), but there was no significant difference in rates reported in RCTs.[16]

Ongoing Studies

One recent publication described ongoing RCTs for bariatric procedures worldwide including studies representing populations on 6 continents based on a map of registered trials.[52] The authors identified 62 ongoing RCTs with a combined total of 10,800 planned participants.[52] Most of the studies plan to investigate the effectiveness of bariatric procedures for treating other chronic conditions related to obesity (e.g., type 2 diabetes, HTN), improving QoL, increasing weight loss, and collecting information about surgical complications.[52] More than half of the studies plan to have at least a 12-month follow-up after the procedure, and about a quarter plan to follow up 4 years after the procedure.[52] The most common procedures included in the trials are RYGB and SG, and more recent surgical procedures are included in fewer trials, but are still represented (e.g., SADI-S in 8.1%). [52] Some of the trials include participants with BMI as low as 25 to 30.[52] None of the identified RCTs enrolled participants younger than 18 years of age.[52]

Adults with BMI 30.0 to 34.9 kg/m^2

We identified 6 eligible RCTs (N = 596) that compared bariatric surgery with medical therapy for the treatment of obesity management in adults with BMIs between 30 and 34.9 (Table 12).[53-58] Although not a criterion for inclusion, all eligible trials in this population were only conducted among individuals with T2DM. Study samples sizes ranged from 57 to 150 participants and included study follow-up ranging from 1 to 5 years. A majority of RCTs included US study sites; non-US study sites were located in Brazil, China, and Taiwan. Most studies compared RYGB with a range of medical therapies including both lifestyle interventions and pharmacotherapy. See Appendix D Table D5 for details regarding study inclusion criteria and additional participant characteristics.

Two included trials had populations with mean baseline BMIs that exceeded the upper limit (i.e., BMI 34.9).[54,58] Most participants in the Randomized Trial to Compare Surgical and Medical Treatments for Type 2 Diabetes (TRIABETES) study[54] had BMIs within the target range (i.e., BMI 30 to 34.9), so full study results are reported. In contrast, adults with BMI in the target range accounted for only about a third of participants in the Surgical Treatment and Medications Potentially Eradicate Diabetes Efficiently (STAMPEDE) trial[58]; therefore, we limited results to subgroup analyses of participants with BMI less than 35.

It should also be noted that several otherwise eligible trials comparing surgery to medical therapy in this population were excluded as they solely assessed AGB, which is of limited relevance to current clinical practice.

Table 12. Characteristics of Included Trials of Adults with BMI 30 to 34.9

AUTHOR, YEAR STUDY NAME RISK OF BIAS	STUDY POPULATION	TOTAL SAMPLE MAX FOLLOW-UP COUNTRY	STUDY GROUP	N, GROUP	AGE (YEARS)	BMI (kg/m^2)
Cohen, 2020[53] MOMS Moderate	Adults with BMI 30 to 35, T2DM, and early-stage kidney disease	N = 100 2 years Brazil	RYGB	N = 51	52.5 (7.6)	32.5 (1.9)
			MT	N = 49	50.2 (7.5)	32.6 (2.1)
Courcoulas, 2014[54] TRIABETES Moderate	Adults with Grade I or II obesity and T2DM	N = 61 5 years United States	RYGB	N = 20	46.3 (7.2)	35.5 (2.6)
			MT	N = 20	48.3 (4.7)	35.7 (3.3)
Ikramuddin, 2013[55] DSS Low	Adults with BMI 30.0 to 39.9 and T2DM for at least 6 months	N = 120 5 years United States and Taiwan	RYGB	N = 60	49.0 (9.0)	34.9 (3.0)
			MT	N = 60	49.0 (8.0)	34.3 (3.1)
Liang, 2013[56] Moderate	Obese adults with T2DM and hypertension	N = 108 1 year China	RYGB	N = 31	50.8 (5.4)	30.5 (0.9)
			MT	N = 36	51.8 (6.7)	30.3 (2.0)
Parikh, 2014[57,58] Moderate	Adults with BMI 30 to 35 and T2DM who otherwise met NIH bariatric surgery criteria	N = 57 5 years United States	Surgery (RYGB, SG, or AGB)	N = 29	46.8 (8.1)	32.8 (1.7)
			MT	N = 28	53.9 (8.4)	32.4 (1.8)
Schauer, 2012 STAMPEDE[a] Low	Obese adults with poorly controlled T2DM	N = 150 5 years United States	RYGB	N = 50	48.3 (8.4)	37.0 (3.3) BMI < 35: 14 of 50 (28%)
			SG	N = 50	47.9 (8.0)	36.2 (3.9) BMI < 35: 18 of 50 (36%)
			MT	N = 50	49.7 (7.4)	36.8 (3.0) BMI < 35: 19 of 50 (38%)

Notes. [a] Reported results from STAMPEDE are limited to subgroup analyses of participants with BMI < 35.
Abbreviations. AGB: adjustable gastric banding; BMI: body mass index; DSS: diabetes surgery study; MOMS: Microvascular Outcomes after Metabolic Surgery; MT: medical therapy; NIH: National Institutes of Health; RYGB: Roux-en-Y gastric bypass; SG: sleeve gastrectomy; STAMPEDE: Surgical Treatment and Medications Potentially Eradicate Diabetes Efficiently; T2DM: type 2 diabetes mellitus; TRIABETES: Randomized Trial to Compare Surgical and Medical Treatments for Type 2 Diabetes.

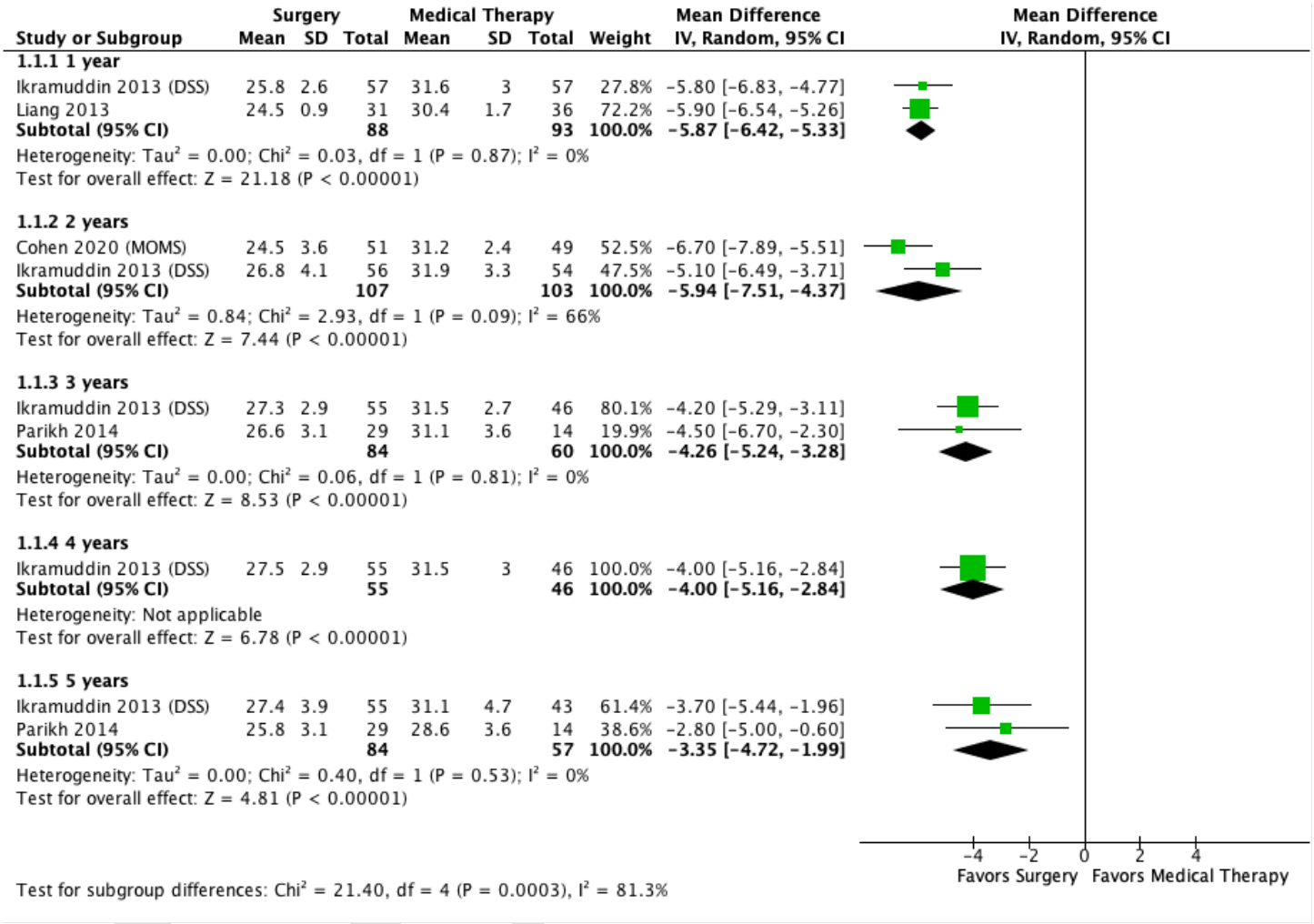
All-cause Mortality

We did not identify any eligible reviews of bariatric procedures that estimated all-cause mortality in adults with BMI 30.0 to 34.9 and T2DM.

Weight Change

Weight change outcomes were reported in all included trials of adults with BMI 30 to 34.9 except for the STAMPEDE study. Weight change was primarily assessed as a factor of mean BMI change (Figure 1) and percentage change in total body weight (Figure 2); additional weight loss outcomes (e.g., mean weight, % excess weight loss) and subgroup data are detailed in Appendix D, Table D6.

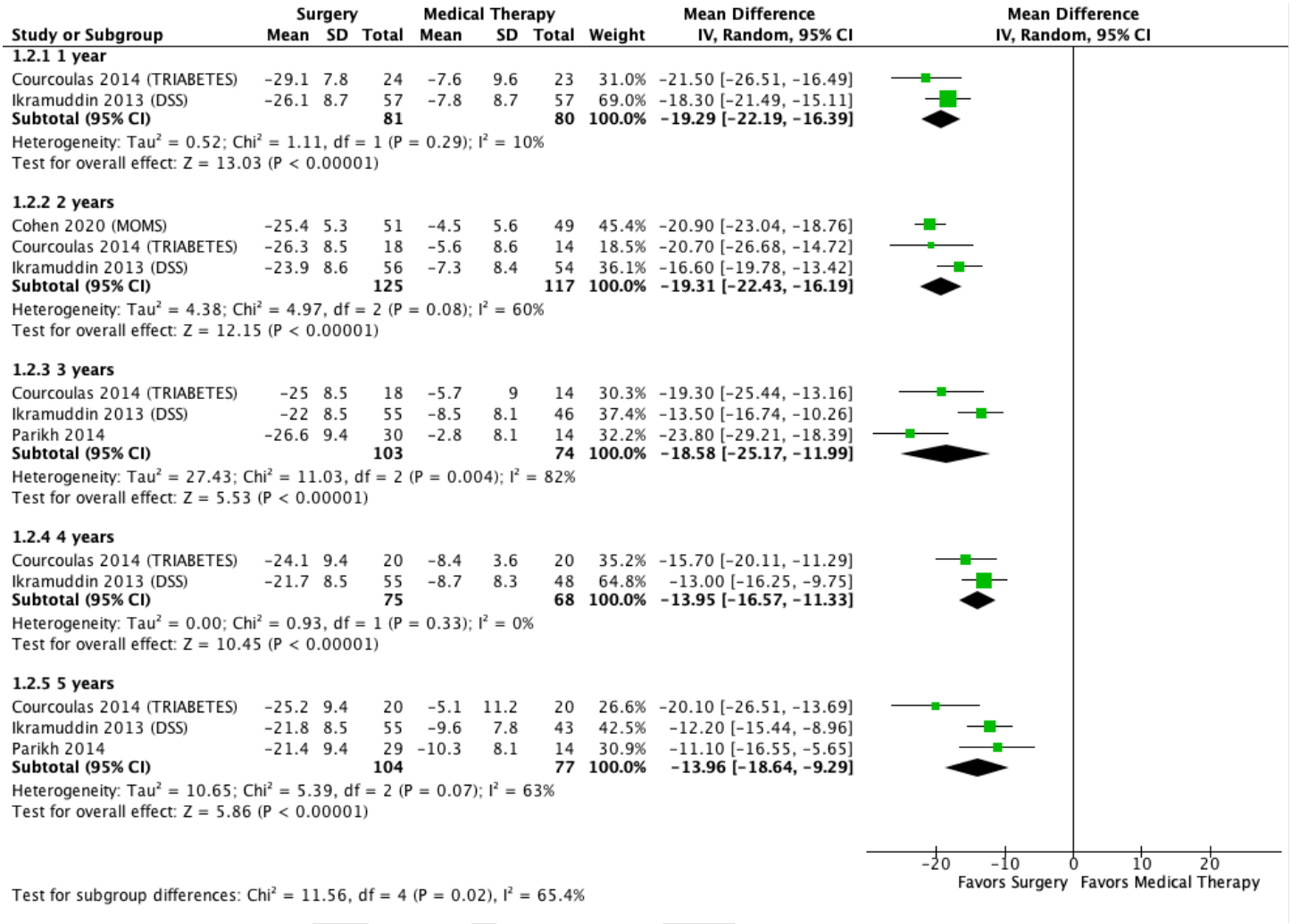
Figure 1. Mean BMI (kg/m^2) at 1 to 5 years Follow-up in Adults with BMI 30 to 34.9



Note. Forest plot generated using Review Manager (RevMan) software, version 5.4

Abbreviations. BMI: body mass index; CI: confidence interval; DSS: diabetes surgery study; IV: inverse variance; MOMS: Microvascular Outcomes after Metabolic Surgery; MT: medical therapy; SD: standard deviation.

Figure 2. Percent Weight Change in Adults with BMI 30 to 34.9



Note. Forest plot generated using Review Manager (RevMan) software, version 5.4

Abbreviations. BMI: body mass index; CI: confidence interval; DSS: diabetes surgery study; IV: inverse variance; MOMS: Microvascular Outcomes after Metabolic Surgery; MT: medical therapy; SD: standard deviation; TRIABETES: Randomized Trial to Compare Surgical and Medical Treatments for Type 2 Diabetes.

Results from our pooled analyses of weight change data showed that adults with T2DM and BMI 30 to 34.9 who underwent bariatric procedures experienced significantly more weight loss compared with those who received medical therapy, as evidenced by statistically significant between-groups differences in mean BMI ranging from -5.9 to -3.4 kg/m^2 ($P < .001$) over 1 to 5 years of follow-up (Figure 1).[53,55-57] The TRIABETES study was excluded from the BMI meta-analysis since mean follow-up values were not reported; however, the bariatric surgery group experienced a mean BMI reduction of -8.6 kg/m^2 from baseline to 5 years compared with -1.2 kg/m^2 in the control group ($P < .001$), which aligns with the pooled 5-year results (Appendix D, Table D6).[54]

Notably, all bariatric surgery groups included in the pooled analyses achieved mean BMIs below the minimum obesity threshold (30 kg/m^2) at all follow-up timepoints (BMI Range, 24.5 to 27.5), whereas the majority of medical therapy groups continued to have mean BMIs > 30 (BMI Range, 28.6 to 31.5).[53,55-57] Moreover, 51% (N = 26) of participants who received bariatric surgery in the Microvascular Outcomes

after Metabolic Surgery (MOMS) study achieved a BMI in the normal range (i.e., 18.5 to 24.9) at the 2-year follow-up compared with none in the medical therapy group ($P < .001$; Appendix D, Table D6).[53]

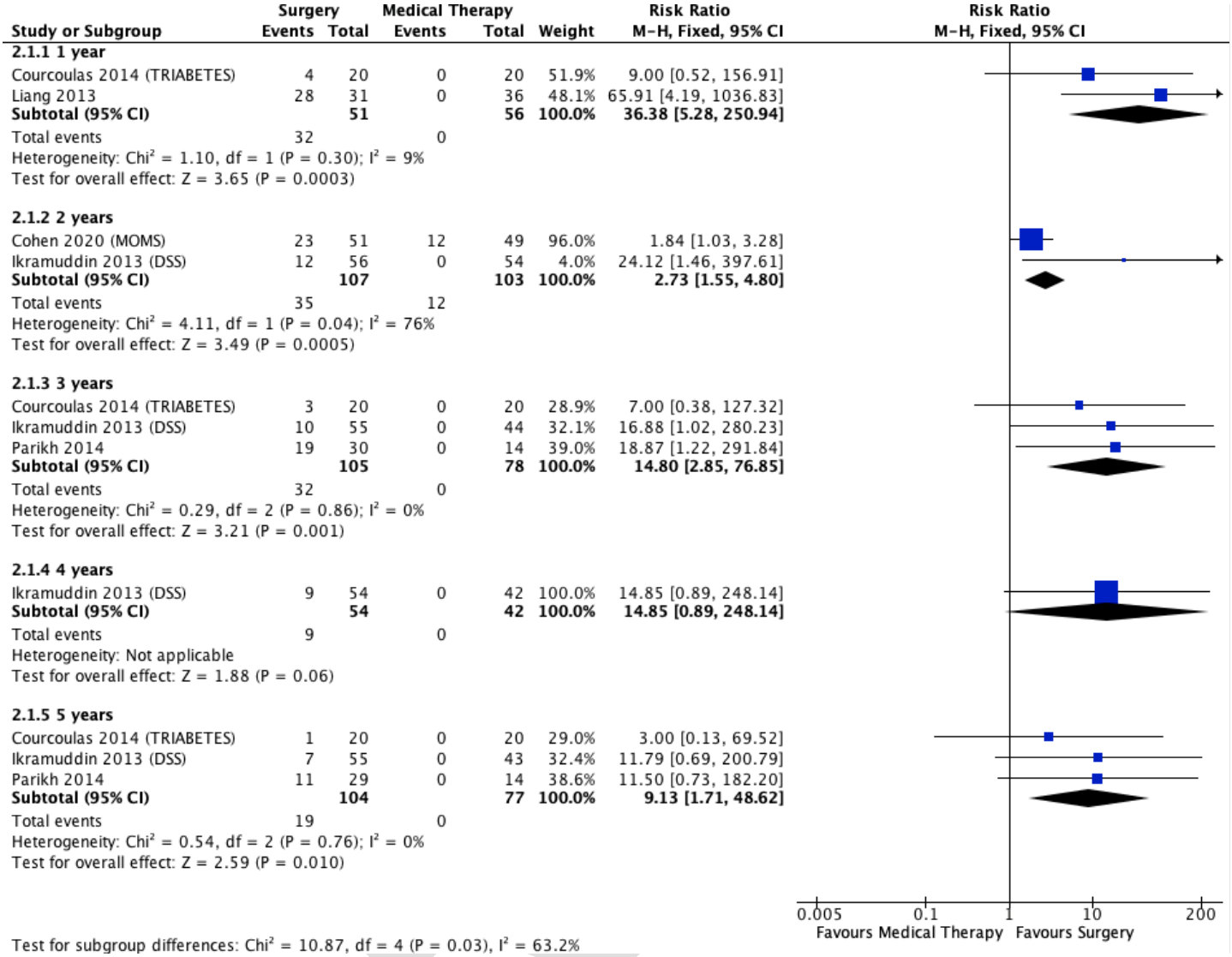
Across the 5 years of available follow-up, our pooled analyses additionally showed that bariatric surgery recipients experienced 14 to 20% greater weight loss compared with medical therapy recipients ($P < .001$), corresponding with mean percent weight loss of around 20 to 30% in bariatric surgery groups versus 5 to 10% in medical therapy groups (Figure 2).[53-57] Additional analyses reported in the MOMS study showed that 95% (N = 49) of participants who received bariatric surgery lost 15% or more of their body weight compared with only 5% (N = 2) in the medical therapy group ($P < .001$; Appendix D, Table D6).[53] Taken together, meta-analyses of mean BMI and percent weight loss data suggest that bariatric surgery results in significant and sustained differential weight loss compared with medical therapy in adults with T2DM and BMI 30 to 34.9.

Change in Chronic Disease Status

Diabetes

All participants in bariatric surgery trials of adults with BMI 30 to 34.9 were required to have a diagnosis of T2DM at baseline to qualify for enrollment. As such, some form of T2DM remission or improvement was reported in all included trials. In these studies, changes in T2DM status were evaluated as dichotomous measures of proportion achieving remission (Figure 3) or as continuous differences in mean HbA1c at follow-up (Figure 4). As with the adult population with BMI >35, definitions used for T2DM remission varied in terms of the nominal HbA1c remission threshold (5.7% vs. 6.5% vs. 6.0%) and whether remission required cessation of diabetic medication use or additional reductions in fasting plasma glucose. To facilitate direct comparison when multiple HbA1c remission thresholds were reported, we analyzed results for those closest to the 6.5% remission threshold endorsed by the American Diabetes Association in 2021.[59] Additional T2DM-related outcomes and subgroup data are detailed in Appendix D, Table D7.

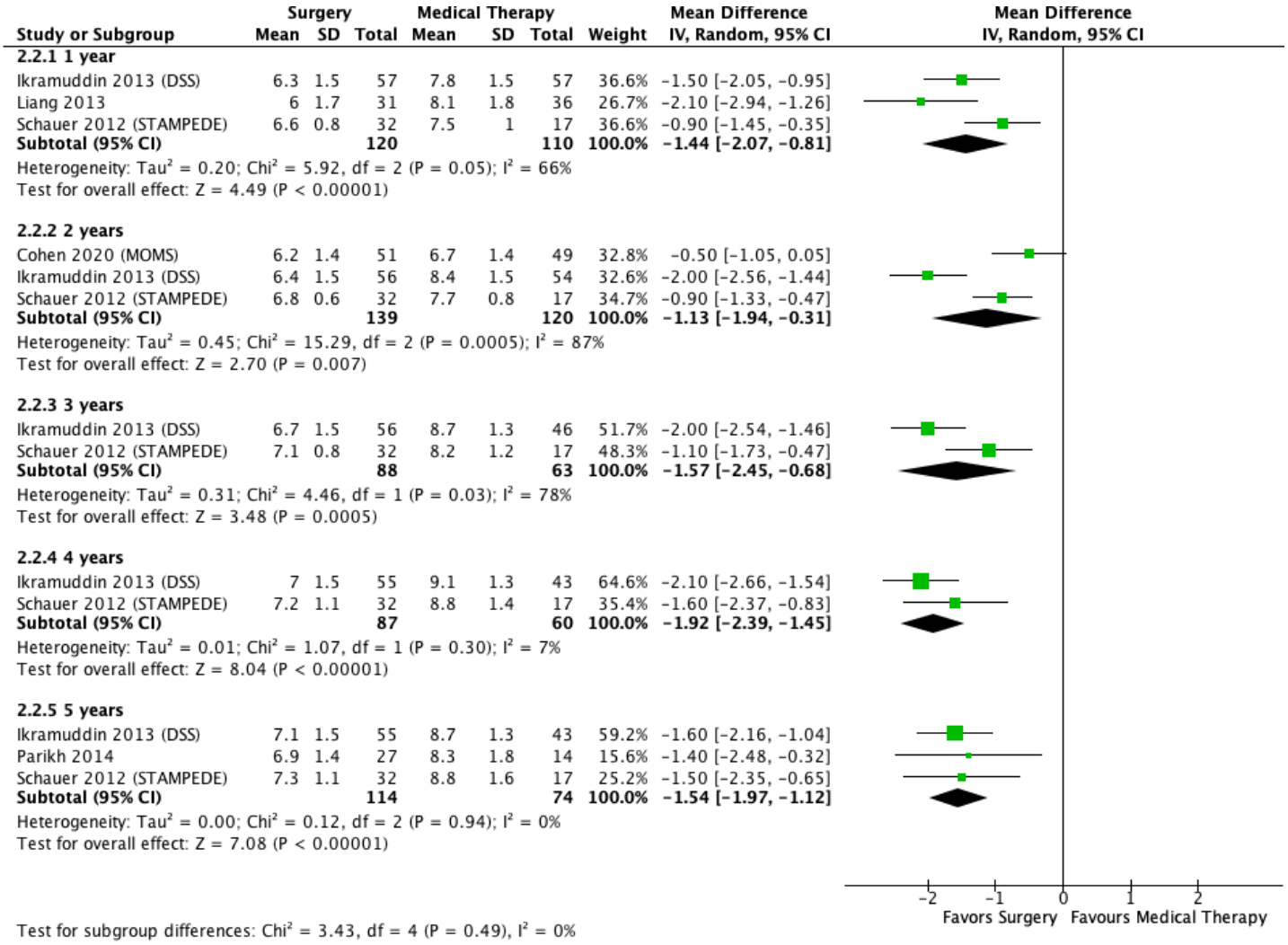
Figure 3. T2DM Remission in Adults with BMI 30 to 34.9



Note. Forest plot generated using Review Manager (RevMan) software, version 5.4

Abbreviations. BMI: body mass index; CI: confidence interval; DSS: diabetes surgery study; MOMS: Microvascular Outcomes after Metabolic Surgery; M-H: Mantel-Haenszel test; TRIABETES: Randomized Trial to Compare Surgical and Medical Treatments for Type 2 Diabetes.

Figure 4. Mean HbA1c (%) in Adults with BMI 30 to 34.9



Note. Forest plot generated using Review Manager (RevMan) software, version 5.4

Abbreviations. BMI: body mass index; CI: confidence interval; DSS: diabetes surgery study; IV: inverse variance; MOMS: Microvascular Outcomes after Metabolic Surgery; TRIABETES: Randomized Trial to Compare Surgical and Medical Treatments for Type 2 Diabetes.

Across 1 to 5 years of available trial follow-up, bariatric surgery was associated with significant differential improvements in T2DM compared with medical therapy in adults with BMI 30 to 34.9.[53-58] Meta-analyses of T2DM remission rates showed that, apart from year 4, bariatric surgery groups were significantly more likely than medical therapy groups (RR range, 2.7 to 36.4) to achieve remission at both short- and long-term follow-up (Figure 3).[53-57] Confidence intervals in the pooled analyses were relatively wide owing to the low rate of observed remission events in the control groups. At maximum study follow-up, the rate of remission in bariatric surgery groups ranged from 16 to 90% versus 0 to 50% in the medical therapy groups (Appendix D, Table D7).[53-57] The wide range of estimates was likely influenced by differences in remission definitions between trials. To that end, analyses of diabetes medication use reported in 4 trials (a component of several remission definitions) indicated that participants who received bariatric surgery were significantly less likely than those who received medical therapy to report continued use of insulin or noninsulin T2DM medications (e.g., metformin) at 2 to 5 years follow-up (Table 13).[53-55,57]

Table 13. T2DM-Related Medication Use in Studies of Adults with BMI 30 to 34.9

AUTHOR, YEAR STUDY NAME	FOLLOW-UP	OUTCOME	MEDICATION USE RATES	*P*VALUE
Cohen, 2020[53] MOMS	2 years	Insulin use	RYGB: 5 of 46 (11%) MT: 25 of 46 (54%)	*P*< .001
		Metformin use	RYGB: 35 of 46 (76%) MT: 45 of 46 (98%)	*P*= .004
Courcoulas, 2014[54] TRIABETES	5 years	Insulin or noninsulin T2DM medication use	RYGB: 7 of 16 (44%) MT: 14 of 14 (100%)	*P*< .001
Ikramuddin, 2013[55] DSS	5 years	Insulin use	RYGB: 9 of 60 (15%) MT: 22 of 60 (37%)	*P*= .02
		Non-insulin T2DM medication use	RYGB: 25 of 60 (42%) MT: 53 of 60 (88%)	*P*< .001
Parikh, 2014[57]	5 years	Insulin use	Surg: 3 of 29 (10%) MT: 7 of 14 (50%)	*P*= .007

Abbreviations. BMI: body mass index; DSS: diabetes surgery study; MOMS: Microvascular Outcomes after Metabolic Surgery; MT: medical therapy; RYGB: Roux-en-Y gastric bypass; Surg: bariatric surgery, any type; T2DM: type 2 diabetes mellitus; TRIABETES: Randomized Trial to Compare Surgical and Medical Treatments for Type 2 Diabetes.

Pooled analyses, presented in Figure 4, also showed that mean HbA1c was significantly lower among participants randomized to bariatric procedures compared with medical therapy across 1 to 5 years of follow-up (MD range, -1.1% to -1.9%; $P < .01$).[53,55-58] Across all years of reported follow-up, mean HbA1c ranged from 6.0 to 7.2% in the intervention groups compared with 6.7 to 9.1% in the control groups; however, no study groups had a mean HbA1c below the American Diabetes Association remission threshold of 6.5% after 2 years.[53,55-58] Almost all surgical participants in the contributing trials received RYGB; however, subgroup analyses by procedure type conducted by Parikh and colleagues did not find any differences in mean HbA1c values at 5 years ($P = .61$) when comparing RYGB, SG, and AGB.[57]

Hypertension

HTN-related outcomes were available for adults with BMI 30 to 34.9 in all included trials except for STAMPEDE. HTN remission, when reported, was generally measured by achievement of certain blood pressure (BP) targets (i.e., systolic BP < 130 mmHg and diastolic BP < 80 mmHg) or the cessation of antihypertensive medications at follow-up (Table 14). However, most trials only compared intermediate HTN indicators, such as mean systolic and diastolic BP, between groups at follow-up (Figures 5 and 6, respectively).

Table 14. Hypertension Remission Outcomes Reported in Trials of Adults with BMI 30 to 34.9

AUTHOR, YEAR STUDY NAME	FOLLOW-UP	REMISSION OUTCOME	RESULTS	*P*VALUE
Cohen, 2020[53] MOMS	2 years	Systolic BP < 130 mmHg	RYGB: 17 of 51 (33%) MT: 19 of 49 (38%)	*P*= .61
		Diastolic BP < 80 mmHg	RYGB: 14 of 51 (28%) MT: 10 of 49 (20%)	*P*= .39
Ikramuddin, 2013[55]	5 years	Systolic BP < 130 mmHg	RYGB: 44 of 60 (73%)	*P*= .06

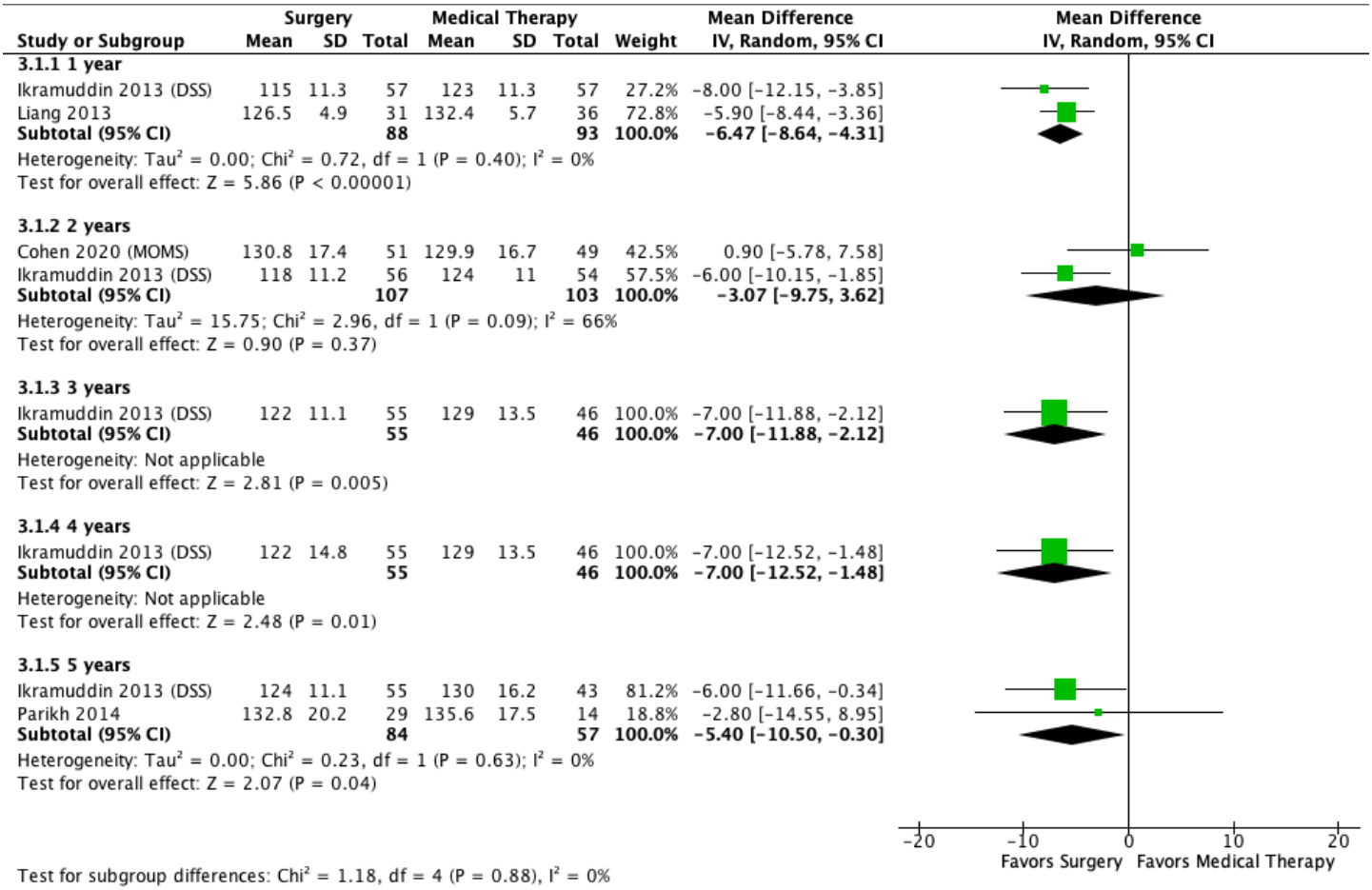
AUTHOR, YEAR STUDY NAME	FOLLOW-UP	REMISSION OUTCOME	RESULTS	*P* VALUE
DSS			MT: 29 of 60 (49%)	
		Antihypertensive medication use	RYGB: 34 to 61 (47%) MT: 51 to 81 (67%)	*P* = .06

Abbreviations. BP: blood pressure; DSS: diabetes surgery study; mmHg: millimeters of mercury; MOMS: Microvascular Outcomes after Metabolic Surgery; MT: medical therapy; RYGB: Roux-en-Y gastric bypass.

As shown in Table 14, comparative HTN remission outcomes were reported in 2 trials.[53,55] Neither trial observed a statistically significant difference in any measure of HTN remission at 2 to 5 years of follow-up.[53,55] In the Diabetes Surgery Study (DSS), which reported yearly follow-up rates up to year 5, there were also no significant differences in the proportion of participants achieving a systolic BP below 130 mmHg at years 1 through 4.[55] In contrast, significantly fewer surgical participants were using antihypertensive medications compared with medical therapy participants at DSS follow-up years 1 through 3, but no between-group differences were observed at years 4 or 5 (Appendix D, Table D7).[55] Additionally, subgroup analyses of antihypertensive medication use at 5 years, conducted by Parikh and colleagues, found no differences in the use of any or more than 1 BP-lowering medications by surgical procedure type (Appendix D, Table D7).[57]

Results regarding the effect of bariatric surgery on mean systolic or diastolic BP were mixed. Meta-analysis of mean values from 4 trials at yearly follow-up timepoints showed that systolic and diastolic BP were generally lower in bariatric surgery groups across 5 years of follow-up, but several timepoints only had data from a single trial and there were no significant between-group differences in either value reported in 2 of the 4 included trials (Figures 5 and 6).[53,55-57] In the DSS trial, the largest included US study, bariatric surgery participants had significantly lower mean systolic BP at all 5 years of follow-up compared with medical therapy participants (MD range, -8.0 to -6.0 mmHg) and significantly lower diastolic BP at years 1 through 4 (MD range, -6.0 to -4.0 mmHg), but not at year 5 (Appendix D, Table D7).[55] Conversely, in the TRIABETES study, which compared mean differences in BP values from baseline, the bariatric surgery group had significantly greater systolic BP reduction than the medical therapy group at year 5 (P = .008), but no significant between-group differences in at years 1 and 3; there were no between-group differences at any follow-up year for diastolic BP (Appendix D, Table D7).[54]

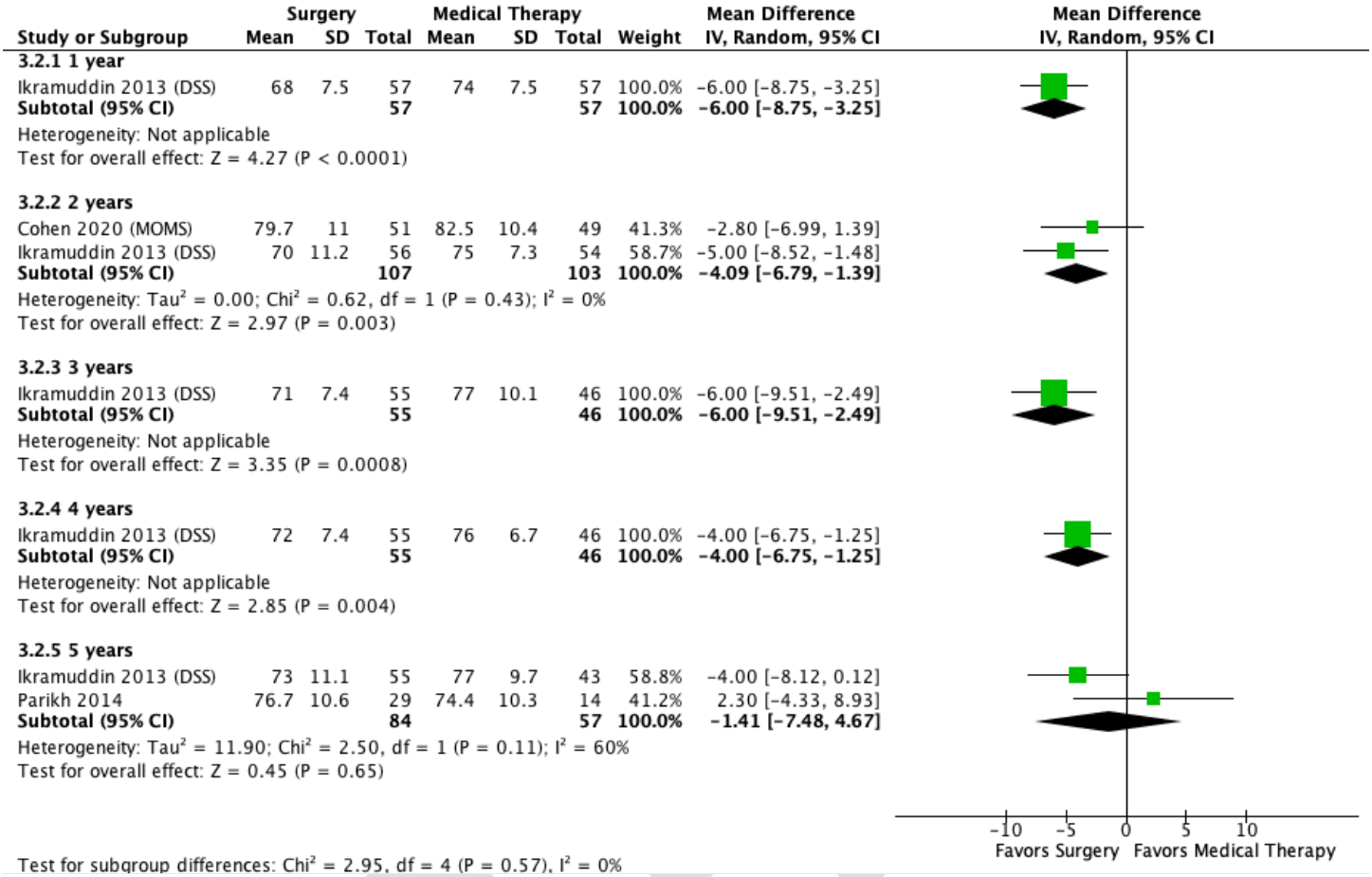
Figure 5. Mean Systolic Blood Pressure (mmHg) in Adults with BMI 30 to 34.9



Note. Forest plot generated using Review Manager (RevMan) software, version 5.4

Abbreviations. BMI: body mass index; CI: confidence interval; DSS: diabetes surgery study; IV: inverse variance; mmHg: millimeters of mercury; MOMS: Microvascular Outcomes after Metabolic Surgery; M-H: Mantel-Haenszel test TRIABETES: Randomized Trial to Compare Surgical and Medical Treatments for Type 2 Diabetes.

Figure 6. Mean Diastolic Blood Pressure (mmHg) in Adults with BMI 30 to 34.9



Note. Forest plot generated using Review Manager (RevMan) software, version 5.4

Abbreviations. BMI: body mass index; CI: confidence interval; DSS: diabetes surgery study; IV: inverse variance; mmHg: millimeters of mercury; MOMS: Microvascular Outcomes after Metabolic Surgery; M-H: Mantel-Haenszel test TRIABETES: Randomized Trial to Compare Surgical and Medical Treatments for Type 2 Diabetes.

It is important to note that mean baseline systolic and diastolic BP values were generally within the range of stage 1 HTN (i.e., systolic BP 130 to 139 mmHg or diastolic BP 80 to 89 mmHg)[49] across trials and, with few exceptions, most study groups achieved mean B*P* values at or below the thresholds for HTN at follow-up, regardless of group assignment (Appendix D, Table D7).[53,55-57]

Coronary Artery Disease

Coronary artery disease-related outcomes were available for adults with BMI 30 to 34.9 in all included trials except for STAMPEDE. Rates of cardiac events were not reported in any trial, but intermediate outcomes such as use of heart disease-related medications and measures associated increased risk for cardiovascular disease (e.g., low-density lipoprotein cholesterol [LDL-C] and triglycerides levels) were available (Tables 15 and 16).

Table 15. Dichotomous Coronary Artery Disease-Related Outcomes Reported in Trials of Adults with BMI 30 to 34.9

AUTHOR, YEAR STUDY NAME	FOLLOW-UP	OUTCOME	RESULTS	*P*VALUE
Cohen, 2020[53] MOMS	2 years	LDL-C < 100 mg/dL	RYGB: 34 of 46 (73%) MT: 24 of 46 (51%)	*P*= .05
		Triglycerides < 150 mg/dL	RYGB: 37 of 46 (80%) MT: 19 of 46 (42%)	*P*< .001
		Beta-blocker use	RYGB: 6 of 46 (13%) MT: 10 of 46 (22%)	*P*= .41
		Calcium channel blocker use	RYGB: 5 of 46 (11%) MT: 10 of 46 (22%)	*P*= .26
		ARB- or ACE-inhibitor use	RYGB: 41 of 46 (89%) MT: 40 of 46 (87%)	*P*= .99
Ikramuddin, 2013[55] DSS	5 years	LDL-C < 100 mg/dL	RYGB: 46 of 60 (77%) MT: 28 of 60 (47%)	*P*= .02

Abbreviations. ACE: angiotensin-converting enzyme; ARB: angiotensin receptor blocker; BMI: body mass index; DSS: diabetes surgery study; LDL-C: low-density lipoprotein cholesterol; mg/dL: milligrams per deciliter; MOMS: Microvascular Outcomes after Metabolic Surgery; MT: medical therapy; RYGB: Roux-en-Y gastric bypass.

Table 16. Continuous Coronary Artery Disease-Relevant Outcomes in Adults with BMI 30 to 34.9

AUTHOR, YEAR STUDY NAME YEAR	BASELINE	MAX FOLLOW-UP	DIFFERENCE (95% CI)	*P*VALUE
LDL-C, mg/dL				
Cohen, 2020[53] MOMS 2 years	RYGB: 102 (36.5) MT: 108.6 (41.1)	RYGB: 85.7 (76.3 to 95.0) MT: 101.6 (92.2 to 110.9)	MD, -15.9 (-29.1 to -2.65)	*P*= .02
Courcoulas, 2014[54] TRIABETES 5 years	RYGB: 117.8 (10.63) MT: 105.5 (7.45)	Mean values NR	RYGB: –9.43 (8.28) MT: –19.3 (8.25)	*P*= .39
Ikramuddin, 2013[55] DSS 5 years	RYGB: 102 (92 to 111) MT: 102 (91 to 113)	RYGB: 83 (75 to 91) MT: 98 (90 to 107)	MD, -15 (-27 to -4)	*P*= .01
Liang, 2013[56] 1 year	RYGB: 3.84 (0.63) MT: 3.72 (0.42)	RYGB: 1.97 (0.45) MT: 3.69 (0.48)	NR -1.72	*P*< .05
Parikh, 2014[57] 5 years	Surg: 106.6 (34.5) MT: 117.6 (60.4)	Surg: 111.0 (41.5) MT: 88.7 (29.6)	Surg: +4.4 (51.4) MT: -28.9 (50.8)	*P*= .054
Triglycerides, mg/dL				
Cohen, 2020[53] MOMS 2 years	RYGB: 195 (145 to 293) MT: 214 (150 to 334)	RYGB: 107.8 (90.6 to 140.3) MT: 180.7 (157.7 to 207.2)	MD, -67 (-102.1 to -31.9)	*P*< .001
Courcoulas, 2014[54] TRIABETES 5 years	RYGB: 169.7 (27.2) MT: 161.2 (24.5)	Mean values NR	RYGB: –78.0 (13.7) MT: –9.3 (14.6)	*P*< .001

AUTHOR, YEAR STUDY NAME YEAR	BASELINE	MAX FOLLOW-UP	DIFFERENCE (95% CI)	*P*VALUE
Ikramuddin, 2013[55] DSS 5 years	RYGB: 258 (154 to 362) MT: 250 (191 to 309)	RYGB: 116 (75 to 157) MT: 183 (137 to 228)	MD, −66 (−127 to −6)	*P*= .03
Liang[56] 1 year	RYGB: 3.39 (1.18) MT: 3.49 (1.32)	RYGB: 1.60 (0.13) MT: 3.50 (1.51)	NR	*P*< .05
Parikh, 2014[57] 5 years	Surg: 173.8 (92.6) MT: 139.5 (60.5)	Surg: 132.4 (58.4) MT: 153.6 (82.6)	Surg: -41.4 (90.3) MT: +14.1 (66.3)	*P*= .04

Abbreviations. CI: confidence interval; DSS: diabetes surgery study; LDL-C: low-density lipoprotein cholesterol; MD: mean difference; mg/dL: milligrams per deciliter; MOMS: Microvascular Outcomes after Metabolic Surgery; MT: medical therapy; NR: not reported; RYGB: Roux-en-Y gastric bypass; Surg: bariatric surgery; TRIABETES: Randomized Trial to Compare Surgical and Medical Treatments for Type 2 Diabetes.

Findings regarding the effect of bariatric surgery on LDL-C were mixed. At final study follow-up, 3 studies observed significantly lower levels at of LDL-C in the bariatric surgery groups compared with medical therapy groups,[53,55,56] whereas 2 studies observed no between-group differences (Table 16).[54,57] In addition, results from 2 studies showed that that surgical participants were significantly more likely to be within the optimal LDL-C range (< 100 mg/dL) at 2- and 5-years follow-up (Table 15).[53,55]

In contrast with the mixed LDL-C findings, all surgical groups had significantly lower mean triglycerides levels over 1 to 5 years of follow-up compared with medical therapy groups (Table 16).[53-57] Moreover, results from the 2-year MOMS study showed that surgical participants were significantly more likely to be within the optimal triglycerides range (i.e., < 150 mg/dL) at follow-up (Table 15).[53]

Medication use was less widely reported. In the MOMS study, no between-group differences were observed the in use of medications to treat or prevent progression of heart disease (e.g., beta blockers) at 2 years (Table 15).[53]

Obstructive Sleep Apnea

We did not identify any eligible studies that assessed improvement or resolution of obstructive sleep apnea in adults with BMI 30.0 to 34.9.

Joint Arthropathy

We did not identify any eligible studies that assessed improvement or resolution of joint arthropathy in adults with BMI 30.0 to 34.9.

Intracranial Hypertension

We did not identify any eligible reviews of bariatric procedures that assessed improvement or resolution of intracranial HTN in adults with BMI 30.0 to 34.9.

Quality of Life

We identified 1 study that reported comparative QoL outcomes for adults with BMI 30 to 34.9 (Table 17). In the MOMS trial, QoL was assessed for all participants at 2 years post randomization and included several domains on the SF-36 scale, which is a validated non-condition-specific QoL survey (range: 0-100, with higher scores representing better health status). Domains for which the study groups differed at

baseline (i.e., pain, social role functioning) were not assessed at the 2-year follow-up. No weight- or diabetes-specific measures of QoL were reported.

Table 17. Quality of Life Outcomes in Adults with BMI 30 to 34.9

AUTHOR, YEAR STUDY NAME SAMPLE SIZE FOLLOW-UP	OUTCOME[a]	SF-36 SCORES[b]	DIFFERENCE (95% CI)	*P* VALUE
Cohen, 2020[53] MOMS N = 100 2 years	General health	RYGB: 78.15 (72.6 to 83.7) MT: 60.3 (54.8 to 65.8)	MD, 17.9 (10.0 to 25.7)	*P*< .001
	Emotional well-being	RYGB: 71.9 (66.2 to 77.8) MT: 63.0 (57.2 to 68.8)	MD, 8.9 (0.7 to 17.2)	*P*= .03
	Physical health	RYGB: 80.4 (68.8 to 92.1) MT: 60.5 (48.9 to 72.1)	MD, 19.9 (3.5 to 36.4)	*P*= .02
	Physical role functioning	RYGB: 84.3 (77.9 to 90.7) MT: 70.2 (63.8 to 76.6)	MD, 14.2 (5.1 to 23.2)	*P*= .002
	Mental health	RYGB: 73.5 (61.5 to 85.6) MT: 62.6 (50.6 to 74.7)	MD not reported	*P*= .21
	Vitality	RYGB: 69.5 (63.6 to 75.4) MT: 55.1 (49.2 to 61.0)	MD, 14.4 (6.1 to 22.7)	*P*= .001

Notes. [a] 24-month scores were only reported for measures where the study groups did not differ at baseline. SF-36 measures not reported due to imbalance at baseline include pain and social role functioning. [b] SF-36 domain scores range from 0 to 100, with higher scores indicating better functioning.

Abbreviations. BMI: body mass index; CI: confidence interval; MD: mean difference; MOMS: Microvascular Outcomes after Metabolic Surgery; MT: medical therapy; RYGB: Roux-en-Y Gastric Bypass; SF-36: Short Form 36 Survey.

Except for mental health, individuals randomized to bariatric surgery reported better health status, as indicated by statistically significantly higher SF-36 scores, for all assessed domains as compared with participants randomized to medical therapy (Table 17).[53] To date, no minimal clinically important difference (MCID) has been established for the SF-36 in populations with obesity or diabetes, but the SF-36 user manual suggests that a difference of 2 to 3 points for any domain is clinically meaningful.[60] Using that threshold, those who received bariatric surgery also experienced clinically significant differential QoL improvement in most assessed domains.[53] The lack of differential mental health related QoL scores between MOMS study groups, despite evidence of significant differential weight loss and T2DM with bariatric surgery, suggests that emotional and social mental health challenges may persist regardless of physical health improvements.[53]

Harms

Harms data varied in both reported outcomes and recorded event types across the included trials of adults with BMI 30 to 34.9. Commonly reported outcomes across studies included surgically related adverse events and serious adverse events (Table 18).

Table 18. Adverse and Serious Adverse Events in Trials of Adults with BMI 30 to 34.9

AUTHOR, YEAR STUDY NAME	FOLLOW-UP	ADVERSE EVENTS	SERIOUS ADVERSE EVENTS
Cohen, 2020[53] MOMS	2 years	RYGB: 6 events in 46 participants MT: 6 events in 46 participants	NR
Courcoulas, 2014[54] TRIABETES	5 years	RYGB: 21 events in 20 participants MT: 14 events in 20 participants	Post-operative (< 30 days) RYGB: 0 events Late-operative (> 30 days) RYGB: 1 event (anastomotic ulcer) Non-operative (> 30 days) RYGB: 0 events MT 0 events
Ikramuddin, 2013[55] DSS	5 years	RYGB: 66 events in 60 participants MT: 38 events in 60 participants	RYGB: 26 events in 60 participants MT: 19 events in 60 participants
Liang, 2013[56]	1 year	NR	No events occurred
Parikh, 2014[57]	5 years	NR	Hospital readmissions or reoperations 11 events in 29 participants

Abbreviations. BMI: body mass index; DSS: diabetes surgery study; MOMS: Microvascular Outcomes after Metabolic Surgery; MT: medical therapy; NR: not reported; RYGB: Roux-en-Y gastric bypass; TRIABETES: Randomized Trial to Compare Surgical and Medical Treatments for Type 2 Diabetes.

Adverse events (i.e., events requiring minimal intervention) were generally more common in bariatric surgery groups compared with medical therapy groups due primarily to early surgical complications (Table 18).[53-57] Common adverse events that occurred outside of the perioperative period (i.e., > 30 days post-surgery) included nausea, dehydration, diarrhea, mild hypoglycemia, and upper gastrointestinal pain.

Few serious adverse events (i.e., events requiring intensive medical intervention) occurred in any study group (Table 18).[53-57] Reported events were generally related to additional surgeries (e.g., gallbladder or appendix removal, or hospitalizations for infection (e.g., sepsis, abscesses). Rates of serious adverse events were higher overall in the DSS trial, which may be due to the wide range of events that were considered for inclusion in event counts (e.g., unplanned pregnancy, bone fractures).[55] Rates of bariatric surgery revisions were not systematically reported in any of the included studies.

Nutritional abnormalities were only reported in the DSS trial (Appendix D, Table D6).[55] There were no between-group differences in instances of vitamin B12 deficiency, vitamin D deficiency, or anemia over the 2-year nutritional analysis.[55] However, rates of iron deficiency were significantly higher in the bariatric surgery group compared with the medical therapy group at 2 years (20% vs. 0%; $P < .01$).[55]

Ongoing Studies

One recent publication described ongoing RCTs for bariatric procedures worldwide including studies representing populations on 6 continents based on a map of registered trials.[52] The authors identified 16 ongoing RCTs evaluating participants with baseline BMIs between 25 and 35 kg/m^2.[52] Studies are open to individuals with and without T2DM. Most of the studies plan to investigate the effectiveness of RYGB and SG and will largely focus on the ability of bariatric surgery to treat chronic conditions related to obesity

(e.g., T2DM, HTN), improve QoL, and increase weight loss.[52] Notably, at least 1 clinical trial in this population intends to evaluate the SADI-S procedure.[52] None of the identified RCTs enrolled participants younger than 18 years of age.[52]

Adolescents

We identified 3 prospective observational studies[24,61,62] and 1 comparative post-hoc analysis[63] of 2 prospective studies of bariatric surgery in adolescents (Table 19). The Teen–Longitudinal Assessment of Bariatric Surgery (Teen-LABS)[61] and Follow-up of Adolescent Bariatric Surgery at 5 Plus years (FABS-5+)[24] were uncontrolled pre-post evaluations of adolescents undergoing bariatric surgery. Adolescent Morbid Obesity Surgery (AMOS)[62] and Teen-LABS/Treatment Options of Type 2 Diabetes in Adolescents and Youth (TODAY)[63] compared adolescents undergoing surgery with those who received behavioral or pharmacologic interventions (i.e., medical therapy). Study sample sizes ranged from 58 to 242 participants with study follow-up durations of 2 to 12.5 years. Most surgical participants received gastric bypass procedures (79%), followed by sleeve gastrectomy (18%) and gastric banding (3%). Although mean age was similar across all study groups (range, 15.3 to 17.1 years), surgical groups had older age ranges than control groups (13 to 21 years vs. 10 to 18 years, respectively). See Appendix D, Table D8 for details regarding study inclusion criteria and additional participant characteristics.

During the literature review we identified one clinical trial that randomized adolescents to bariatric surgery or medical therapy.[64] However, this trial was ultimately excluded because it was published prior to 2012 and all surgical participants received gastric banding.

Table 19. Characteristics of Included Studies of Adolescents

AUTHOR, YEAR STUDY NAME RISK OF BIAS	STUDY POPULATION	TOTAL SAMPLE MAX FOLLOW-UP COUNTRY	STUDY GROUP	N, GROUP	MEAN AGE (YEARS)	MEAN BMI (kg/m^2)
Inge, 2014[61,65-69] Teen-LABS Moderate	Severely obese adolescents undergoing weight loss surgery	N = 242 5 years United States	Surgery (RYGB, SG, or AGB)	N = 242 RYGB: 161 SG: 67 AGB: 14	17.1 (1.6) Range: 13 to 19	50.5 (45.2 to 58.3) Range: 34.0 to 87.7
Inge, 2017[24] FABS-5+ High	Adolescents who received RYGB for clinically severe obesity	N = 58 Mean: 8.0 years Range: 5.4–12.5 years United States	RYGB	N = 58	17.1 (1.7) Range: 13 to 21	58.5 (10.5)
Inge, 2018[63,70] Teen-LABS/TODAY High	Severely obese adolescents with T2DM	N = 93 2 years United States	Surgery (RYGB or SG from Teen-LABS)	N = 30	16.9 (1.3) Range: 13 to 19	54.4 (9.5)
			MT (any TODAY study group)[a]	N = 63	15.3 (1.3) Range: 10 to 17	40.5 (4.9)
Olbers, 2012[62,71] AMOS Moderate	Adolescents (13–18 years) with a BMI range 36–69 kg/m^2	N = 162[b] (adolescent groups only) 5 years Sweden	RYGB	N = 81	16.5 (1.2)	45.5 (6.0)
			MT	N = 81	15.8 (1.2)	42.2 (5.0)

Notes. [a] The TODAY trial compared several forms of medical therapy for adolescent T2DM including lifestyle management alone or in combination with metformin and other weight loss medications. [b] The AMOS study also included an adult RYGB comparison group (N = 80), the results of which are not reported in this coverage guidance. Including the adult group, total AMOS enrollment was 242 individuals.
Abbreviations. AGB: adjustable gastric banding; AMOS: Adolescent Morbid Obesity Surgery; BMI: body mass index; FABS-5+: Follow-up of Adolescent Bariatric Surgery at 5 Plus years; MT: medical therapy; RYGB: Roux-en-Y gastric bypass; SG: sleeve gastrectomy; T2DM: type 2 diabetes mellitus; Teen-LABS: Teen–Longitudinal Assessment of Bariatric Surgery; TODAY: Treatment Options of Type 2 Diabetes in Adolescents and Youth.

All-cause Mortality

We did not identify any eligible studies that estimated all-cause mortality in adolescents.

Weight Change

All 4 included adolescent studies reported weight change outcomes (Table 20; Appendix D, Table D9).[24,61-63] Weight change was described by changes in absolute weight in kilograms and changes in BMI.

Table 20. Weight Change Outcomes from Included Adolescent Studies

STUDY NAME	SAMPLE SIZE STUDY DURATION	BASELINE	FOLLOW-UP	MEAN DIFFERENCE (95% CI)	% CHANGE
Weight, kg					
Teen-LABS[61]	N = 242 3 years	149.0	108.0	-41 (-45 to -37) *P*< .001	-27% (-29 to -25) *P*< .001
AMOS[62]	N = 162 5 years	Surg: 133.0 MT: 124.0	Surg: 96.0 MT: 133.3	Within-group Surg: -36.8 (-40.9 to -32.8) MT: +9.3 (NR) Between group -37.2 (-46.4 to -28.0); *P*< .001	NR
FABS-5+[24]	N = 58 5 to 12 years	170.8	120.9	-50.0 (-56.8 to -43.1)	-29.5% (-33.2 to -25.7)
Teen-LABS/ TODAY[63]	N = 93 2 years	Surg: 155.1 MT: 117.4	Surg: 110.9 MT: 123.2	Surg: -44.2 (-50.6 to -37.8) MT: +5.8 (1.4 to 10.2) *P*< .001	NR
BMI, kg/m^2					
Teen-LABS[61]	N = 242 3 years	53	38	-15 (-16 to -13)	-28% (-30 to -25)
AMOS[62]	N = 162 5 years	Surg: 45.5 MT: 42.2	Surg: 32.3 MT: 44.6	Within-group Surg: -13.1 (-14.5 to -11.8) MT: +3.3 (1.1 to 4.8) Between-group -12.26 (-15.2 to -9.3); *P*< .001	NR
FABS-5+[24]	N = 58 5 to 12 years	58.5	41.5	-17.0 (-19.2 to -14.8)	-29.3% (-33.0 to -25.6)
Teen-LABS/ TODAY[63]	N = 93 2 years	Surg: 51.8 MT: 36.7	Surg: 36.3 MT: 37.9	Surg: -15.1 (-17.3 to -13.0) MT: +1.3 (-0.2 to 2.8) *P*< .001	NR

Abbreviations. AMOS: Adolescent Morbid Obesity Surgery, BMI: body mass index; CI: confidence interval; FABS-5+: Follow-up of Adolescent Bariatric Surgery at 5 Plus years; kg: kilograms; MT: medical therapy; NR: not reported; Surg: bariatric surgery, any type; Teen-LABS: Teen–Longitudinal Assessment of Bariatric Surgery; TODAY: Treatment Options of Type 2 Diabetes in Adolescents and Youth.

Results from these studies showed that adolescents who underwent bariatric procedures experienced statistically significant weight reductions ranging from -36.8 to -50.0 kg and BMI reductions ranging from -13.0 to -17.0 kg/m^2 over 2 to 12 years follow-up.[24,61-63] These findings corresponded to a nearly 30 percent reduction in weight and BMI across studies in surgical study groups (Table 20).[24,61-63] Additionally, in the 3-year Teen-LABS study of adolescents who underwent bariatric surgery (N = 242), 70 percent of participants had BMI reductions of 20 percent or more and only 2 percent of participants exceeded their baseline BMI.[61,66] Despite these observed weight reductions across adolescent studies, it should be noted that a substantial proportion of study participants continued to have obesity following surgical interventions, as indicated by mean postsurgical BMI (range, 32.3 to 41.5).

Subgroup analyses of the Teen-LABS cohort (Appendix D, Table D9) did not find any significant differences in weight change outcomes by age group (i.e., 13–15 years vs. 16–19 years).[61,66] Results stratified by surgical type, however, showed that participants who received AGB did not demonstrate significant percent weight change at the 3-year follow-up (-8.1% [95% CI, -19.9 to 3.6]) compared to participants who underwent RYGB (-28% [95% CI, -30 to -25]) or SG (-26% [95% CI, -30 to -22]).[61,66] Owing to these results, AGB was subsequently excluded from a limited 5-year assessment of BMI in which participants were found to have sustained lower mean BMIs compared with baseline whether they received RYGB (54 vs. 39) or SG (50 vs. 37).[65]

In the Teen-LABS/TODAY and AMOS matched cohort studies, surgical study groups experienced statistically significant (i.e., $P < .001$) mean weight and BMI reductions compared with medical therapy groups.[62,63,71] In the 2-year Teen-LABS/TODAY study, surgical participants experienced significant weight reduction during follow-up whereas medical therapy controls experienced significant weight gain (-44.2 kg [-50.6 to -37.8] vs. +5.8 [1.4 to 10.2]; $P < .001$).[63] These weight changes corresponded with a significant mean BMI reduction in the surgical group compared with no significant change in the control group (-15.1 kg/m^2 [95% CI, -17.3 to -13.0] vs. +1.3 kg/m^2 [95% CI, -0.2 to 2.8]; $P < .001$).[63] In the 5-year AMOS study, surgical participants experienced statistically significant mean weight loss (MD, -37.2 [95% CI, -46.4 to -28.0]; $P < .001$) and mean BMI reduction (MD, -12.26 [95% CI, -15.2 to -9.3]; $P < .001$) compared with the medical therapy group (Table 20).[62,71] Moreover, 70 percent of the surgical group lost 20 percent or more of their total body weight, whereas 69 percent of the medical therapy group gained weight and a greater proportion of surgical participants achieved a BMI less than 30 (37% vs. 3%; Appendix D, Table D9).[62,71] Taken together, these comparative results suggest that bariatric procedures are associated with substantial and sustained weight loss compared with medical therapy interventions in adolescents.

Change in Chronic Disease Status

Table 21 details rates of chronic disease remission or resolution reported in the included adolescent studies.[24,61-63] As with adult populations, definitions for remission or resolution varied between studies, particularly for T2DM.

Table 21. Chronic Disease Resolution in Adolescents

STUDY NAME SAMPLE SIZE	FOLLOW-UP	DIABETES	HYPERTENSION[a]	ELEVATED CVD RISK
Teen-LABS/ TODAY[63] N = 93	2 years	T2DM remission Surg: 85.7% (12 of 14) MT: 0% (0 of 24)	Elevated BP remission Surg: 75% (15 of 20) MT: 0% (0 of 13)	NR
Teen-LABS[61] N = 242	3 years	T2DM remission 95% (19 of 20 participants) Adjusted: 90% (65 to 98) Prediabetes remission 76% (13 of 17) Adjusted: 77% (48 to 92)	Elevated BP remission 74% (56 of 76) Adjusted: 73% (60 to 83)	NR
AMOS[62] N = 162	5 years	T2DM remission Surg: 100% (3 of 3) MT: NR Elevated HbA1c resolution (≥ 39 mmol/mol) Surg: 62.5% (5 of 8) MT: NR Impaired FPG[d] resolution Surg: 100% (13 of 13) MT: NR	Elevated BP remission (SBP ≥140 mmHg or DBP ≥ 90 mmHg) Surg: 100% (12 of 12) MT: NR Elevated SBP (≥ 140 mmHg) remission Surg: 100% (11 of 11) MT: NR Elevated DBP (≥ 90 mmHg) remission Surg: 100% (4 of 4) MT: NR	Elevated LDL-C[b] resolution Surg: 100% (13 of 13) MT: NR Elevated triglycerides[c] resolution Surg: 100% (22 of 22) MT: NR
FABS-5+[24] N = 58	5-12 years	T2DM remission 87.5% (7 of 8)	Elevated BP remission 76% (19 of 25)	NR

Notes. [a] Elevated BP is defined as use of BP-lowering medications or SBP ≥ 95th percentile or DBP ≥ 95th percentile (for age, sex, height) if < 18 years of age; or if ≥ 18 years, SBP > 140 mmHg or DBP > 90 mmHg. Remission of elevated BP required absence of BP-lowering medications, and SBP and DBP in the normal range for age. [b] Elevated LDL-C defined as ≥ 3.37 mmol/L or ≥ 130 mg/dL. [c] Elevated triglycerides defined as ≥ 1.47 mmol/L or ≥ 130 mg/dL. [d] Impaired FPG defined as ≥ 5.6 mmol/L.

Abbreviations. AMOS: Adolescent Morbid Obesity Surgery; BP: blood pressure; CVD: cardiovascular disease; DBP: diastolic blood pressure; FABS-5+: Follow-up of Adolescent Bariatric Surgery at 5 Plus years; FPG: fasting plasma glucose; HbA1c: glycated hemoglobin; LDL-C: low-density lipoprotein cholesterol; MT: medical therapy; NR: not reported; SBP: systolic blood pressure; Surg: bariatric surgery, any type; T2DM: type 2 diabetes mellitus; Teen-LABS: Teen–Longitudinal Assessment of Bariatric Surgery; TODAY: Treatment Options of Type 2 Diabetes in Adolescents and Youth.

Table 22 reports changes in important mean continuous variables reported in the included adolescent studies. Reported measures were intermediate or associated indicators for T2DM (HbA1c and fasting plasma glucose), HTN (systolic and diastolic BP), and risk for heart disease (LDL-C and triglycerides levels).

Table 22. Chronic Condition-Relevant Continuous Outcomes in Adolescents

STUDY NAME	BASELINE	FOLLOW-UP	DIFFERENCE (95% CI)	*P*VALUE
HbA1c, %				
Teen-LABS/ TODAY[63] N = 93	Surg: 6.8% MT: 6.4%	Surg: 5.5% MT: 7.8%	Surg: -1.3 (-2.2 to -0.5) MT: +1.4 (0.9 to 1.9)	*P*< .001
Teen-LABS[61] N = 242	--	--	--	--
AMOS[62] N = 162	Surg: 5% MT: NR	Surg: 5.2% MT: 5.4%	Surg vs. MT -19.7 mg/dL (-29.2 to +19.7)	*P*= .32
FABS-5+[24] N = 58	5.3%	5.2%	NR	NR
FPG, mg/dL				
Teen-LABS/ TODAY[63] N = 93	Surg: 125.1 MT: 119.2	Surg: 89.3 MT: 151.8	Surg: -35.8 (-53.9 to -17.7) MT: +32.6 (21.1 to 44.2)	*P*< .001
Teen-LABS[61] N = 242	--	--	--	--
AMOS[62] N = 162	Surg: 91.8 MT: NR	Surg: 86.4 MT: 93.6	Surg vs. MT -8.1 (-14.4 to -1.8)	*P*= .009
FABS-5+[24] N = 58	96.7	85.5	NR	NR
SBP, mmHg				
Teen-LABS/ TODAY[63] N = 93	Surg: 122.9 MT: 119.3	Surg: 122.0 MT: 120.8	Surg: −0.8 (−6.3 to 4.7) MT: +1.5 (−1.4 to 4.5)	NR
Teen-LABS[61] N = 242	--	--	--	--
AMOS[62] N = 162	Surg: 124.6 MT: NR	Surg: 113.2 MT: 121.4	Surg vs. MT −8.18 (−12.5 to −3.8)	*P*< .001
FABS-5+[24] N = 58	--	--	--	--
DBP, mmHg				
Teen-LABS/ TODAY[63] N = 93	Surg: 75.4 MT: 71.3	Surg: 73.3 MT: 71.4	Surg: −2.1 (−6.2 to 2.0) MT: +0.1 (−2.6 to 2.8)	NR
Teen-LABS[61] N = 242	--	--	--	--
AMOS[62] N = 162	Surg: 76.9 MT: NR	Surg: 69.4 MT: 77.7	Surg vs. MT −8.28 (−12.2 to −4.4)	*P*< .001
FABS-5+[24] N = 58	--	--	--	--
LDL-C, mg/dL				
Teen-LABS/ TODAY[63] N = 93	Surg: 92.0 MT: 89.0	Surg: 85.2 MT: 82.8	Surg: −6.8 (−22.2 to 3.9) MT: −6.2 (−15.4 to 2.9)	NR

STUDY NAME	BASELINE	FOLLOW-UP	DIFFERENCE (95% CI)	*P*VALUE
Teen-LABS[61] N = 242	--	--	--	--
AMOS[62] N = 162	Surg: 100.5 MT: NR	Surg: 85.1 MT: 116.0	Surg vs. MT -34.0 (-46.4 to -23.2)	*P*< .001
FABS-5+[24] N = 58	107.5	94.4	NR	NR
Triglycerides, mg/dL				
Teen-LABS/ TODAY[63] N = 93	Surg: 108.8 MT: 100.7	Surg: 88.1 MT: 116.1	Surg: −20.7 (−24.4 to −17.4) MT: +15.4 (10.4 to 21.8)	NR
Teen-LABS[61] N = 242	--	--	--	--
AMOS[62] N = 162	Surg: 115.0 MT: NR	Surg: 79.7 MT: 123.9	Surg vs. MT -41.6 (-62.0 to 17.7)	*P*< .001
FABS-5+[24] N = 58	128.3	87.6	NR	NR

Abbreviations. AMOS: Adolescent Morbid Obesity Surgery; CI: confidence interval; DBP: diastolic blood pressure; FABS-5+: Follow-up of Adolescent Bariatric Surgery at 5 Plus years; FPG: fasting plasma glucose; HbA1c: glycated hemoglobin; LDL-C: low-density lipoprotein cholesterol; mg/dL: milligrams per deciliter; mmHg: millimeters of mercury; MT: medical therapy; NR: not reported; SBP: systolic blood pressure; Surg: bariatric surgery, any type; Teen-LABS: Teen–Longitudinal Assessment of Bariatric Surgery; TODAY: Treatment Options of Type 2 Diabetes in Adolescents and Youth.

Diabetes

Across all included adolescent studies, substantial proportions of adolescents with T2DM who underwent bariatric procedures (N = 45) experienced remission (86% to 100%).[24,61-63] In comparison, no remission occurred among the medical therapy participants with T2DM (N = 24) in the 2-year Teen-LABS/TODAY analysis, the only study that reported nonsurgical remission rates (Table 21).[63] Additional subgroup analyses of the Teen-LABS bariatric surgery cohort (Appendix D, Table D10) did not find any significant differences in rates of T2DM remission by surgical type (i.e., RYGB, SG) at the 3-year follow-up; however, participants aged 13 to 15 years at enrollment were significantly less likely to achieve T2DM remission compared with participants aged 16 to 19 years (RR, 0.86 [95% CI, 0.74 to 0.99]; *P* = .046).[66]

In the Teen-LABS/TODAY and AMOS matched cohort studies,[62,63,71] surgical study groups experienced statistically significant differential reductions in mean FPG levels compared with medical therapy groups, but the treatment effect on HbA1c concentrations was mixed (Table 22). In the 2-year Teen-LABS/TODAY study, surgical participants experienced statistically significant mean HbA1c and FPG reductions during follow-up, whereas medical therapy controls had a significant increase in both measures (HbA1c: -1.3% vs. +1.4%, *P* < .001; FPG: -35.8 vs. +32.6 mg/dL, *P* < .001) (Table 22).[63] In contrast, although almost 63% of surgical participants with elevated baseline HbA1c values (i.e., ≥ 39 mmol/mol [5.7%]) in the AMOS study were in the normal range at the 5-year follow-up, mean follow-up values were not significantly different from the medical therapy group (33.5 vs. 35.3 mmol/mol; MD, -1.8 mmol/mol [95% CI, -5.4 to 1.8]; *P* = .32).[71] Mean FPG values among surgical participants, however, were statistically lower compared with nonsurgical participants at follow-up (-8.1 mg/dL [95% CI, -14.4 to -

1.8]; *P* = .009) and 100% of participants in the surgical group with impaired FPG (≥ 5.6 mmol/L) at baseline experienced remission at 5 years (Table 22; Appendix D, Table D10).[71]

Hypertension

Across all included adolescent studies, 74 to 100 percent of adolescents with elevated BP (i.e., systolic BP ≥ 120-129 mmHg and diastolic BP < 80 mmHg) or HTN (i.e., BP ≥ 130/80)[72] who underwent bariatric procedures experienced remission over the 2 to 12 years of available study follow-up (Table 21).[24,61-63] Comparatively, no remission occurred among the medical therapy participants with elevated BP (N = 13) in the 2-year Teen-LABS/TODAY analysis, the only study that reported nonsurgical remission rates (Table 21).[63] In addition, no significant differences in remission rates by age or surgical type were observed in subgroup analyses of surgical participants in the Teen-LABS study (Appendix D, Table D10).

Despite the high rates of elevated BP and HTN remission observed among a relatively small cohort of adolescent bariatric surgery recipients, comparative results for mean systolic and diastolic BP values in the Teen-LABS/TODAY and AMOS matched cohort studies were mixed (Table 22). At the 2-year follow-up in the Teen-LABS/TODAY study, there were no clinical (i.e., 20 mmHg for systolic BP, 10 mmHg for diastolic BP) or statistically significant differences from baseline in either study group with respect to mean systolic or diastolic BP values.[63] Compared with medical therapy, bariatric surgery in the AMOS study was associated with significant differential reductions in both systolic BP (-8.18 mmHg [95% CI, -12.5 to -3.8]; *P* < .001) and diastolic BP (-8.28 mmHg [95% CI, -12.2 to -4.4]; *P* < .001) at the 5-year follow-up.[71] However, reported within-group changes from baseline in systolic and diastolic BP in the surgical group (-11.5 and -7.4 mmHg, respectively) did not meet the generally accepted thresholds for clinically significant change; medical therapy within-group changes were not reported.[71]

Coronary Artery Disease

Coronary artery disease in adolescents is rare and, when present, is generally the result of genetic or congenital abnormalities.[73] To that end, we included results of intermediate measures known to be associated with increased risk of heart disease risk, such as elevated LDL-C[74] and triglycerides levels,[75] that were reported within the included adolescent studies.

In the AMOS study, all instances of elevated LDL-C (N = 13) or elevated triglycerides (N = 22) present among bariatric surgery participants at baseline resolved to normal levels at the 5-year follow-up, but no comparator group results were reported (Table 21).[62,71]

Both included comparative studies of adolescents (Teen-LABS/TODAY and AMOS) observed significant differential reductions in mean triglycerides at follow-up among teens who received surgical compared with medical therapy, but results were mixed for LDL-C levels (Table 22).[63,71] In Teen-LABS/TODAY study, participants who received bariatric surgery had a statistically significant reduction in triglycerides at the 2-year follow-up (-20.7 mg/dL [-24.4 to -17.4]) whereas medical therapy participants experienced a significant increase (+15.4 mg/dL [95% CI, 10.4 to 21.8]); however, neither study group experienced a significant change in LDL-C levels.[63] In the AMOS study, surgical participants had statistically significant differential reductions in both triglycerides (MD, -41.6 mg/dL [95% CI, -62.0 to 17.7]; *P* < .001) and LDL-C levels (MD, -34.0 mg/dL [95% CI, -46.4 to -23.2]; *P* < .001) compared with nonsurgical participants.[71]

In addition to observed data, Teen-LABS/TODAY investigators conducted a modeling analysis to estimate between-group 30-year heart disease event risk.[70] The model was based on age-adjusted cardiovascular

disease (CVD) event models from the Framingham Heart Study and included assessment of multiple risk variables (e.g., BMI, BP, T2DM status, lipid profiles, smoking status).[70] Results of the modeling study suggested that the likelihood of 30-year CVD events (e.g., MI, stroke, congestive heart failure) may be substantially lower among adolescents with obesity and T2DM who received bariatric surgery compared with those who received medical therapy only (modeled 30-year risk of any cardiovascular event after 5 years of study follow-up: 6.8% vs 13.6%, respectively).[70]

Obstructive Sleep Apnea

We did not identify any eligible studies that assessed improvement or resolution of OSA in adolescents.

Joint Arthropathy

We identified 1 study (Teen-LABS) that reported on joint-related morbidities among adolescents.[61,68] Prior to surgery, 25 percent of participants reported substantial musculoskeletal pain concerns (i.e., knee, hip, calf, back) during or after a 400-meter walk test.[68] During follow-up assessments, rates of musculoskeletal pain concerns associated with postsurgical walk tests were significantly reduced at both 12 months (8%; RR, 0.62 [95% CI, 0.51 to 0.71]; $P < .01$) and 24 months (12%; RR, 0.47 [95% CI, 0.37 to 0.62]; $P < .01$) after adjusting for age, sex, race or ethnicity, baseline BMI, and surgical center.[68]

Intracranial Hypertension

We did not identify any eligible studies that assessed intracranial HTN.

Quality of Life

Two studies (Teen-LABS and AMOS) reported longitudinal QoL outcomes in their adolescent participants, including weight-related and general QoL measures (Table 23).[61,62]

Table 23. Quality of Life Outcomes in Adolescents

STUDY SAMPLE SIZE FOLLOW-UP	OUTCOME	BASELINE	FOLLOW-UP	DIFFERENCE (95% CI)	*P* VALUE
Teen-LABS[61,66] N = 242 3 years	Weight-related QOL (IWQoL-Kids score)[a]	63 (61 to 65)	83 (81 to 86)	Absolute change: +20.0 (17.4 to 22.7) Percent change: +42.6% (32.6 to 52.5)	*P*< .001 *P*< .001
AMOS[62,71] N = 162 5 years	Weight-related QOL (OP-14 Scale)[b]	Surg: 49.1 MT: NR	Surg: 37.4 MT: 45.1	Surg only -13.0 (-19.6 to -6.4) Surg vs. MT -7.9 (-20.7 to 4.5)	*P*< .001 *P*= .22
	Physical function (SF-36)[c]	Surg: 72.1 MT: NR	Surg: 84.4 MT: 75.9	Surg only 13.5 (8.1 to 19.0) Surg vs. MT 8.8 (0.0 to 17.6)	*P*< .001 *P*= .05
	Physical role function (SF-36)[c]	Surg: 75.9 MT: NR	Surg: 83.9 MT: 71.3	Surg only 11.2 (4.0 to 18.3) Surg vs. MT 13.5 (2.2 to 24.8)	*P*= .002 *P*= .02

STUDY SAMPLE SIZE FOLLOW-UP	OUTCOME	BASELINE	FOLLOW-UP	DIFFERENCE (95% CI)	*P*VALUE
	General health perceptions (SF-36)[c]	Surg: 53.8 MT: NR	Surg: 64.8 MT: 56.2	Surg only 12.4 (6.5 to 18.3) Surg vs. MT 8.7 (-1.1 to 18.5)	*P*< .001 *P*= .08
	Physical component (SF-36)[c]	Surg: 44.1 MT: NR	Surg: 48.3 MT: 45.7	Surg only 5.2 (2.5 to 7.9) Surg vs. MT -2.9 (-6.9 to 1.0)	*P*< .001 *P*= .14
	Other domains (SF-36)[c]	No significant within- or between-group differences at follow-up in the following SF-36 domains: bodily pain, vitality, mental health, social role function, emotional role function, mental component score			

Notes. [a] IWQoL-Kids score range is 0 to 100 with higher scores indicating better weight-related quality of life. [b] OP-14 score range is 0 to 100 with lower scores indicating decreased weight-related problems. [c] SF-36 has a score range of 0 to 100 with higher scores indicating better QOL. Abbreviations. AMOS: Adolescent Morbid Obesity Surgery; CI: confidence interval; IWQoL-Kids: Impact of Weight on Quality of Life-Kids; MT: medical therapy; NR: not reported; OP-14: Obesity-related Problems Scale; QOL: quality of life; SF-36: Short Form-36 Health Survey; Surg: bariatric surgery, any type; Teen-LABS: Teen–Longitudinal Assessment of Bariatric Surgery.

The Teen-LABS and AMOS studies both assessed measures of weight-related QoL (Table 23). At the 3-year follow-up assessment, Teen-LABS study participants–who all received bariatric surgery–reported a statistically significant improvement in the effect of weight on their overall well-being including physical limitations, self-esteem, and interpersonal relationships as measured by the Impact of Weight on Quality of Life-Kids scale (+20-points [95% CI, 17.4 to 22.7]; $P < .001$). These score differences also exceeded the clinically significant threshold of 4.8 points.[66,76] Similarly, surgical participants in the AMOS comparative cohort study reported a significant reduction in weight-related distress during activities such as shopping, swimming, eating at restaurants, and intimate relations at the 5-year assessment, as measured by the Obesity-related Problems Scale (-13.0 points [95% CI, -19.6 to -6.4]; $P < .001$; clinically important threshold not available).[71] However, surgical group scores did not differ significantly from control group scores (37.4 vs. 45.1 points; $P = .22$).[71]

The AMOS study also reported on several measures of general QoL as measured by the SF-36 survey (Table 23). Compared with the nonsurgical group, surgical participants only experienced differential improvements in 2 of the 10 assessed domains (i.e., physical function [+8.8 points; $P = .05$] and physical role limitations [+13.5 points; $P = .02$]).[71] Notably, surgical participants did not experience significant within- or between-group differences in any mental health or emotional functioning domain despite experiencing statistically significant weight loss compared with nonsurgical controls, indicating that mental health QoL issues for adolescents may persist in the long-term even when weight loss occurs.[71] As mental health disorders are common among adolescents regardless of weight status, conclusions regarding mental health outcomes in adolescents undergoing bariatric surgery should consider the multifactorial nature of these conditions.[77]

Harms

Table 24 details adverse events (AE) reported in the included adolescent studies. Event categories include perioperative events (occurring ≤ 30 days postsurgery), long-term AE (e.g., additional surgeries, deaths), and nutritional abnormalities.

Table 24. Harms Outcomes from Included Adolescent Studies

OUTCOME	TEEN-LABS/ TODAY N = 93 2 YEARS	TEEN-LABS N = 242 3 YEARS	AMOS N = 162 5 YEARS	FABS-5+ N = 58 5 TO 12 YEARS
Perioperative events (≤ 30 days)				
Major events (i.e., life-thereatening or additional surgeries)	NR	8% (19 of 242 patients; 20 events)	Surg: 17% (14 of 81 patients; 14 events) -12 sugeries (hernia repair and gall bladder removal) -2 suicide attempts in participants with preexisting depression MT: NR	NR
Minor events	NR	15% (36 of 242 patients; 47 events)	Surg: 5% (8 of 162 partients; 8 events) -4 ED visits for abdominal pain -1 instance of suicidal ideation -3 referrals to psychiatric unit MT: NR	NR
Long-term adverse events (> 30 days)				
Deaths	No deaths	3 deaths	No reported deaths	2 deaths
Additional abdominal surgeries (any)	Surg: 40% (12 of 30) MT: 0	13% (30 of 228 patients; 47 events)	Surg: 25% (20 of 81) MT: NR	12% (7 of 58)
Cholecystecomies		NR, but most of the 47 additional abdominal surgeries were gall bladder removals	Surg: 11% (9 of 81) MT: NR	21% (12 of 58)
Endoscopic procedures	NR	13% (29 of 228 patients; 48 events)	NR	22% (13 of 58)
Anemia-related blood transfusions	Surg: 0 MT: 2% (1 of 63)	NR	Surg: 2% (2 of 81) MT: NR	3% (2 of 58)
Inpatient psychiatric evaluation	NR	NR	Surg: 7% (6 of 81) MT: NR	NR
Nutritional abnormalities				
Low vitamin A	NR	13% (22 of 170)	NR	NR
Low vitamin B12	NR	8% (13 of 160)	Surg: 66% (16 of 73) MT: 6% (2 of 31) *P* = .05	16% (8 of 50)
Low vitamin D	NR	43% (74 of 172)	Surg: 63% (46 of 73) MT: 57% (20 of 35) *P* = .67	78% (39 of 50)

OUTCOME	TEEN-LABS/ TODAY N = 93 2 YEARS	TEEN-LABS N = 242 3 YEARS	AMOS N = 162 5 YEARS	FABS-5+ N = 58 5 TO 12 YEARS
Low iron or ferritin	NR	57% (98 of 171)	Surg: 66% (51 of 77) MT: 29% (12 of 42) *P*< .001	63% (32 of 51)
Anemia	NR	NR	Surg: 32% (25 of 77) MT: 7% (3 of 42) *P*= .001	NR

Abbreviations. AMOS: Adolescent Morbid Obesity Surgery; ED: emergency department; FABS-5+: Follow-up of Adolescent Bariatric Surgery at 5 Plus years; MT: medical therapy; NR: not reported; Surg: bariatric surgery, any type; Teen-LABS: Teen–Longitudinal Assessment of Bariatric Surgery; TODAY: Treatment Options of Type 2 Diabetes in Adolescents and Youth.

Perioperative complications were reported in 2 adolescent studies (Table 24).[61,62] In the Teen-LABS study, most perioperative complications (47 of 67 events) were deemed to be minor (i.e., non-life-threatening or requiring invasive intervention) and almost all events occurred and resolved prior to hospital discharge.[61] In the AMOS study, 14 participants in the surgical study group (17%) had a major perioperative event, of which 12 were related to hernia repair or gall bladder removal and 2 were due to suicide attempts in 2 separate participants.[62] Eight minor events also occurred, 4 of which were related to the need for further psychiatric care or evaluation.[62]

Additional abdominal surgeries were the most common long-term AEs and occurred in 12% to 40% of surgical participants.[24,61-63] The majority of these procedures were cholecystectomies (gall bladder removal surgeries) or hernia repair. Reoperations or revisions to the primary bariatric procedures were not widely reported. Other long-term adverse events included outpatient endoscopic procedures for upper gastrointestinal issues (13% to 22%) and anemia-related blood transfusions (2% to 3%).[24,61-63] Deaths were uncommon, with only 5 reported deaths occurring over 12 years of follow-up among the 525 enrolled study participants.[24,71] No deaths were related to bariatric surgery; however, 2 deaths were attributed to drug overdose.[24] Notably, 7% of surgical participants in the AMOS study were referred for inpatient psychiatric evaluation related to exacerbations of pre-existing depression or anxiety disorders.[71]

Reported rates of nutritional abnormalities in adolescents with bariatric procedures were high (Table 24; Appendix D, Table D9), with up to 66% having low iron or ferritin levels and up to 78% having vitamin D deficiency at 5 or more years post-surgery.[24,66,71] In the AMOS study, almost a third of participants (32%) were found to have clinical anemia. Moreover, comparison of with medical therapy participants showed that rates of low vitamin B12, low iron or ferritin, and clinical anemia were significantly higher among adolescents who received bariatric surgery.[71] These findings highlight the need for adherence to postsurgical monitoring and supplementation therapy in this population.

Ongoing Studies

We identified 2 ongoing clinical trials of bariatric surgery in adolescents.

The Adolescent Morbid Obesity 2 (AMOS2) trial is an RCT comparing bariatric surgery (i.e., RYGB or SG) with intensive non-surgical medical therapy for the treatment of severe obesity (i.e., BMI > 35) in 50 Swedish adolescents aged 13 to 16 years.[78] Participants were recruited from 3 tertiary childhood obesity

treatment clinics across Sweden where they had undergone at least 1 year of unsuccessful comprehensive medical therapy for obesity.[78] The primary study outcome is changes in BMI and secondary outcomes include incidence of cardiovascular illness and cancer, biochemical markers of metabolic health, body composition, bone health, physical fitness, quality of life, and psychological and cognitive functioning.[78] The trial is initially planned for 2 years of follow-up and completed primary data collection in June 2022; additional follow-up is planned for 5, 10, and 15 years from baseline.[78]

The Bariatric Surgery in Children (BASIC) trial is an RCT comparing adjustable gastric banding with intensive nonsurgical medical therapy for the treatment of severe obesity (i.e., BMI > 40) in 60 Dutch adolescents aged 14 to 16 years.[79] Although study investigators acknowledge the evidence supporting greater treatment effectiveness with other forms of bariatric surgery, gastric banding was selected as the primary bariatric intervention due to the reversibility of the procedure, thereby allowing participants to seek more permanent interventions in the future.[79] Eligible study participants had to complete at least 1 year of unsuccessful intensive lifestyle intervention for obesity after which they were referred for treatment at a single university medical center in The Netherlands.[79] Primary study outcomes are percent total weight loss and change in BMI, secondary outcomes include body composition, pubertal development, metabolic and endocrine changes, inflammatory status, cardiovascular abnormalities, non-alcoholic hepatitis, quality of life, and changes in behavior.[79] Follow-up visits are planned for 6 months, 1, 2, and 3 years; primary data collection was completed in December 2022.[79]

Evidence Summary

There is a robust evidence base from systematic reviews of RCTs and large comparative cohort studies supporting the use of bariatric procedures in adults who meet the current NIH criteria (i.e., BMI ≥ 35 kg/m^2 with comorbidities or BMI ≥ 40 kg/m^2 with or without comorbidities), but data are less clear regarding the effectiveness and harms of bariatric procedures for adults with BMI 30.0 to 34.9 kg/m^2, with the least evidence for adolescents with obesity. In the following summaries, low and very-low levels of confidence indicate that if new information from additional studies were published, our understanding of the effectiveness and harms of bariatric procedures for those populations is likely to change.

For Adults with BMI of 35 kg/m^2 or Greater:

- We have high confidence that bariatric procedures are positively associated with clinically significant weight reduction and result in significantly greater weight loss compared with medical therapies for obesity.
- We have moderate confidence that bariatric procedures reduce all-cause mortality compared with medical therapies for obesity.
- We have very low to moderate confidence that, compared with medical therapy, bariatric procedures are associated with the improvement or resolution of certain comorbidities, such as T2DM, HTN, and CAD.
- We have low confidence that bariatric procedures are associated with significantly greater improvement in overall and condition-specific QoL compared with medical therapy.
- We have low confidence that bariatric procedures are not associated with a significant difference in nonsurgical adverse events compared with medical therapy. Overall, bariatric procedures are associated with low rates of perioperative morbidity and mortality but may result in the need for surgical revision or reintervention over time.

- We did not identify any evidence regarding the effectiveness of bariatric procedures for treating obstructive sleep apnea, joint arthropathy, or intracranial HTN.

For Adults with BMI 30.0 to 34.9 kg/m^2:

- Available evidence in this population is limited to adults with T2DM.
- We have moderate confidence that bariatric procedures are associated with clinically significant BMI reduction and results in significantly greater percent weight loss compared with medical therapies for obesity.
- We have low confidence that bariatric procedures are associated with clinically significant HbA1c reduction and results in higher rates of T2DM remission compared with medical therapy interventions.
- We have very low confidence regarding the effect of bariatric procedures on the improvement or resolution of HTN. There was mixed evidence, with some studies indicating BP improvements and HTN resolution, and some evidence for no between-group differences.
- We have very low confidence regarding the effect of bariatric procedures on the improvement of CAD-related outcomes. There was mixed evidence regarding the impact of bariatric surgery on LDL-C and triglycerides levels, and no evidence of effect on the use of medications to treat or prevent heart disease.
- We have very low confidence that bariatric procedures are associated with low rates of AEs, serious AEs, and nutritional abnormalities.
- We did not identify any evidence regarding the effectiveness of bariatric procedures for all-cause mortality, OSA, joint arthropathy, or intracranial HTN.

For Adolescents with Obesity:

- We have low confidence that bariatric procedures are associated with short- and long-term weight reduction and result in greater weight loss compared with medical therapies.
- We have very low confidence that bariatric procedures are associated with substantial reductions in T2DM, elevated BP, and elevated markers of heart disease risk, but there is some mixed evidence based on continuous measures that may indicate that surgery patients do not have significantly different outcomes compared with medical therapy.
- We have very low confidence that bariatric procedures may be associated with a decrease in joint arthropathy as indicated by reduced musculoskeletal pain during physical activity over time.
- We have very low confidence that bariatric procedures are associated with improvements in weight-related QoL, but they may have a limited differential effect from medical therapy in terms of other physical or behavioral QoL outcomes.
- We have very low confidence that mortality after bariatric procedures is rare in adolescents, but rates of vitamin insufficiencies are relatively high.
- We did not identify any evidence regarding the effectiveness of bariatric procedures for all-cause mortality, sleep apnea, or intracranial HTN.

Despite the wide range of studies analyzed in our included reviews, we did not identify eligible clinical evidence for several key interventions and outcomes for this review including intragastric balloons, the SADI-S procedure, and the effect of bariatric procedures on OSA, joint arthropathy in adults, or intracranial HTN. Although we identified several reviews evaluating the efficacy and safety of intragastric

balloons, the primary studies included did not have sufficient length of follow-up for inclusion in our review (i.e., ≥ 12 months). We also identified reviews regarding the efficacy and safety of SADI-S[80] and the effect of bariatric procedures on obstructive sleep apnea[81]; however, in both instances the primary studies were small (i.e., N < 500), uncontrolled case series, or case studies; therefore, none of these studies met our sample size or study design criteria for inclusion.

Limitations in the available evidence include inconsistent or incomplete data reporting. Many outcomes were assessed using multiple measures or outcome definitions (e.g., mean weight loss vs. % excess weight loss), which limited estimations of magnitude of effect for the key outcomes and between population groups. Additionally, outcome data were rarely stratified by control conditions, thereby limiting our ability to understand the effect of bariatric procedures against certain types of medical interventions (e.g., pharmacology vs. lifestyle interventions). Similarly, the included studies largely did not report outcomes stratified by populations that have experienced historical inequities outlined in our scope statement (e.g., race or ethnicity, surgical setting). Finally, statistical methods were inconsistent across included systematic reviews for adults with BMI 35 or greater resulting in lower confidence ratings for some outcomes due to concerns over precision.

POLICY LANDSCAPE

In the following section, we summarize public and private payer policies, clinical guidance from professional societies, and policy statements about bariatric procedures for the treatment of obesity. Table 25 presents a high-level summary of coverage criteria for bariatric procedures across policies and guidance documents, and the text section details differences between policies and published guidance and other details relevant to the treatment of obesity with bariatric procedures.

Table 25. Criteria for Candidate Selection from Clinical Practice Guidelines and Payer Coverage Policies

PATIENT CHARACTERISTICS	ASMBS/ IFSO	AAP	AACE/TOS/ ASMBS/ OMA/ASA	EAES, IFSO-EC, EASO, ESPCOP	Canadian Adult Obesity	NICE	MEDICARE NCD	Aetna, Cigna, Moda, RBCBS	Washington Medicaid (Apple Health)
ADULT POPULATIONS (18 years of age or older)									
≥ 40 BMI with or without comorbidities	✓	NA	✓	✓	✓	✓	X[d]	✓	✓
≥ 35 BMI and one or more severe obesity-related complications remediable by weight loss[a]	X	NA	✓	✓	✓	✓	✓	✓	✓
≥ 35 BMI with or without comorbidities	✓	NA	X	X	X	X	X	X	X
30 to 34.9 BMI plus T2DM or other uncontrolled comorbidities	✓[b]	NA	✓	✓	✓	X	X	X	✓
Requires non-surgical interventions first	X	NA	X	X	X	✓	✓	✓	X
PEDIATRIC POPULATIONS (10 to 19 years of age)									
Class III obesity (140% of the 95th percentile)	✓	✓	NA	NA	NA	X[e]	NA	✓	X[g]
Class II obesity (120% of the 95th percentile) plus a comorbidity[c]	✓	✓	NA	NA	NA	X[e]	NA	✓	X
No current or planned pregnancy within 12 to 18 months of surgery	✓	✓	NA	NA	NA	NA	NA	X	NA
Multidisciplinary care	✓	✓	NA	NA	NA	NA[f]	NA	✓	NA

Table Key. A check indicates that the criterion is endorsed. An X indicates that the criterion is not or not fully endorsed. NA indicates that the associated recommendation or policy does not apply to the specified population.

Notes. [a] For example, T2DM, poorly controlled hypertension, osteoarthritis, or obstructive sleep apnea.[2] [b] Joint ASMBS and IFSO guidelines issued in 2022 recommend bariatric surgery for individuals with BMI 30 to 34.9 in the absence of substantial weight loss or control of any obesity-related comorbidities with nonsurgical therapy.[20] [c] For example, depressed health-related quality of life score, T2DM, or obstructive sleep apnea.[20] [d] Medicare requires the beneficiary have at least 1 comorbidity regardless of BMI.[82] [e] NICE guidelines state that bariatric surgery is generally not recommended in

young people and may only be considered in exceptional circumstances. [f] Bariatric surgery in young people should only be undertaken by a multidisciplinary team. [g] Bariatric surgery is not covered for Washington Medicaid beneficiaries aged < 18 years.

Abbreviations. AACE/TOS/ASMBS/OMA/ASA: American Association of Clinical Endocrinologists/American College of Endocrinology, the Obesity Society, American Society for Metabolic & Bariatric Surgery, Obesity Medicine Association, and American Society of Anesthesiologists; AAP: American Academy of Pediatrics; ASMBS: American Society for Metabolic and Bariatric Surgery; BMI: body mass index; EAES: European Association for Endoscopic Surgery; EASO: European Association for the Study of Obesity; ESPCOP: European Society for the Peri-operative Care of the Obese Patient; IFSO-EC: International Federation for the Surgery of Obesity and Metabolic Disorders; NA: not applicable; NICE: National Institute for Health and Care Excellence; RBCBS: Regence BlueCross BlueShield; T2DM: type 2 diabetes mellitus.

Evidence-based Recommendations

We identified 8 clinical practice guidelines that reviewed substantial published literature regarding studies of bariatric procedures and provided recommendations for patient selection and care; 5 guidelines had good methodological quality,[2,3,83-85] 2 guidelines had fair methodological quality,[20,80] and 1 guideline had poor methodological quality (see Appendix C for guideline methodologic quality assessment criteria).[46] The general criteria for candidate selection are summarized in Table 25, alongside the criteria from payer coverage policies.

The majority of guidelines we identified that made recommendations for adult populations agreed about the following criteria for candidates for bariatric surgery[2,3,83-86]:

- Individuals with BMI 40 or greater, with or without comorbidities
- Individuals with BMI 35 to 40, with at least 1 severe obesity-related comorbidity
- Individuals with BMI between 30 and 35, with poorly controlled T2DM or poorly controlled HTN

Organizations that supported the guideline publications in which those criteria were presented include:

- Obesity Canada
- The Canadian Association of Bariatric Physicians and Surgeons
- American Diabetes Association
- European Association for Endoscopic Surgery
- European Chapter of the International Federation for the Surgery of Obesity
- European Association for the Study of Obesity
- European Society for Perioperative Care of the Obese Patient
- American Association of Clinical Endocrinologists
- American College of Endocrinology
- The Obesity Society
- Obesity Medicine Association
- American Society of Anesthesiologists
- American Academy of Sleep Medicine

In contrast, a joint guideline issued in 2022 by the American Society for Metabolic and Bariatric Surgery (ASMBS) and International Federation for the Surgery of Obesity and Metabolic Disorders (IFSO) recommended bariatric procedures for less highly selected populations of adults[20]:

- Individuals with BMI 35 or greater, with or without comorbidities
- Individuals with BMI between 30 and 34.9 who do not achieve sustained weight loss or control of obesity-related comorbidities using nonsurgical methods

The ASMBS/IFSO guidelines additionally recommend that bariatric interventions be considered for Asian populations with BMI ≥ 25 and for older adults with obesity after careful consideration of the benefits and risks, with no upper age limit.[20]

Clinical practice guidelines for the perioperative nutrition, metabolic, and nonsurgical support of patients undergoing bariatric procedures were published in 2019, and were cosponsored by American Association of Clinical Endocrinologists/American College of Endocrinology, the Obesity Society,

American Society for Metabolic & Bariatric Surgery, Obesity Medicine Association, and American Society of Anesthesiologists (AACE/TOS/ASMBS/OMA/ASA).[2] This publication presented 85 recommendations related to the selection of candidates for bariatric surgery through each step of their clinical care.[2] We assessed this publication as having good methodological quality. This publication additionally recommended that BMI ranges be adjusted for individuals identified as Asian race or ethnicity (i.e., BMI 25 or greater indicates obesity).[2]

Adults with BMI 30.0 to 34.9 kg/m^2

The 2022 joint ASMBS/IFSO guidelines on indications for bariatric surgery recommended consideration of bariatric surgery for individuals with BMI 30.0 to 34.9 who do not achieve substantial or sustained weight loss or improvement of obesity-related comorbidities.[20] These guidelines largely align with the position statement issued by the ASMBS in 2018, with the exception that no upper age restrictions are recommended.[46] We rated this publication as having fair methodological quality by the standards that we use for clinical practice guidelines.

The 2018 ASMBS position statement additionally reviewed the current positions related to BMI 30.0 to 34.9 for top health care organizations, and noted that the following organizations support bariatric surgery for adults with BMI 30.0-34.9 when the individual also has a significant obesity-related comorbidity (e.g., poorly controlled T2DM, poorly controlled HTN):

- International Diabetes Federation and the American Diabetes Association
- National Institute for Health and Care Excellence

Adolescents

The ASMBS pediatric metabolic and bariatric surgery guidelines were published in 2018.[87] We rated this publication as having fair methodological quality primarily due to incomplete reporting of methods and a lack of integration of RoB of the evidence upon which the recommendations were based. For adolescents, ASMBS recommended that individuals with BMI 35.0 to 39.9 plus a severe comorbidity (e.g., cardiovascular disease, T2DM, OSA), or BMI greater than 40 and a less severe morbidity, be considered for bariatric surgery.[87] As described earlier in this coverage guidance, the ASMBS recommended that candidates for bariatric surgery be referred to clinics accredited by the MBSAQIP and receive coordinated care from a multidisciplinary team.[87] The publication also noted implications of bariatric surgery for future pregnancies; overall, there appears to be a benefit for both mother and infant, but there are risks for infant development if vitamin supplementation is inadequate after bariatric surgery.[87]

The American Academy of Pediatrics (AAP) published a policy statement and supporting evidence review detailing the selection and care of adolescent candidates for bariatric procedures in 2019; the criteria closely align with those described by the ASMBS above.[26] In 2023, the AAP issued its first clinical practice guideline for the evaluation and treatment of children and adolescents with obesity.[88] We rated this publication as having fair methodologic quality due to incomplete reporting of methods. The guideline recommended that pediatricians and other pediatric primary care clinicians offer referrals to adolescents aged 13 years and older with severe obesity (BMI ≥ 120% of the 95th percentile for age and sex) for evaluation at comprehensive multidisciplinary pediatric metabolic and bariatric surgery centers.[88] Given the lack of available comparative evidence from high-quality study designs, the guideline authors chose

to issue a recommendation for evaluation, rather than recommend surgery as a standard treatment for severe adolescent obesity outright.[88]

The joint ASMBS/IFSO guidelines also align with the previously established ASMBS and AAP selection criteria.[20] In addition, the guidelines assert that bariatric procedures have not been shown to negatively affect puberty or growth and, therefore, do not recommend a specific Tanner or bone development stage as criteria for surgery.[20] The guidelines also suggest that syndromic obesity, developmental disabilities, and history of trauma should be considered during candidate selection, but should not be used as strict contraindications for bariatric procedures. [20]

Guidelines Addressing Specific Procedures or Approaches

The European Association for Endoscopic Surgery Bariatric Guidelines Group published a consensus document based on a systematic review and network meta-analysis of head-to-head trials of different bariatric surgical procedures in 2022.[85] We assessed this publication as having good methodological quality. In the version of the guideline written for lay audiences, there are also decision aids for selecting appropriate bariatric procedures.[89] Given the evidence review and network meta-analysis, the conclusions of the guideline committee ranked SG and RYGB as preferred interventions, followed by OAGB and SADI-S.[85] However, the committee also stated that individual patient characteristics, values, preferences, other comorbid conditions, and surgeon preference and expertise should inform the selection of bariatric procedure.[85]

The IFSO published a literature review and position statement in 2020 regarding single anastomosis duodenal-ileal bypass with sleeve gastrectomy/one anastomosis duodenal switch (SADI-S/OADS).[80] We rated this publication as having fair methodological quality. The authors concluded that SADI-S/OADS is effective for weight loss and improvement in metabolic health in the medium term, but that long-term safety studies indicated nutritional deficiencies in individuals after this procedure.[80] The publication additionally noted that evidence from RCTs for safety and efficacy was lacking.[80]

The Canadian Adult Obesity Clinical Practice Guideline for bariatric surgery noted that procedure selection should be tailored to the patient's needs and preferences, but that laparoscopic approach should be standard.[3]

Payer Coverage Policies

We identified policies related to covering bariatric surgery from Aetna, Cigna, and Regence BlueCross BlueShield, Moda, the Washington Medicaid program, and a national coverage determination for Medicare. All of these policies consider IGBs to be experimental or investigational, and the interventional procedures guidance published in 2020 by the National Institute for Heal and Care Excellence stated that the evidence was inadequate to support efficacy for swallowable gastric balloon capsules for weight loss.[90]

Medicaid

The Washington State Health Care Authority Health Technology Clinical Committee made a coverage determination about bariatric surgery after an evidence review completed in 2015[91] and the following determination related to bariatric surgery.

For patients age ≥ 18 years of age bariatric surgery is covered for the following conditions[92]:

- BMI ≥ 40
- BMI 35 to < 40 for those patients with at least one obesity-related co-morbidity
- BMI 30 to < 35 with T2DM
- When covered, patients must abide by all other agency surgery program criteria (e.g., using specified centers or practitioners; completing a pre-operative psychological evaluation; participating in pre- and post-operative multidisciplinary care programs)

Bariatric surgery is not covered for patients who are under the age of 18 years, have a BMI under 30, or have a BMI of 30 to 35 without T2DM.[92]

Medicare

We identified 1 national coverage determination for Medicare related to bariatric surgery.[82] We did not identify an additional local coverage determination for contractors with Medicare clients in Oregon.

The national coverage guidance requires[82]:

- The beneficiary has a BMI of 35 or more; at least 1 comorbidity (e.g., T2DM); ruled out disease-causing obesity (e.g., Cushing disease); and have documentation that the beneficiary tried non-surgical medical treatment unsuccessfully
- Covered procedures include open and laparoscopic RYGB, open and laparoscopic BPD/DS or Gastric Reduction Duodenal Switch (BPD/GRDS), or laparoscopic AGB
- The facility be a Medicare-approved Center of Excellence

The national coverage determination additionally specifies that the following are not covered: bariatric surgery for the treatment of obesity alone, open adjustable gastric banding, open SG, open and laparoscopic vertical banded gastroplasty, intestinal bypass surgery, and gastric balloon for treatment of obesity.[82]

Private Payers

Coverage criteria for bariatric procedures was similar across the 4 private payers, and a summary of those criteria is in Table 25. To summarize, these policies indicated coverage of bariatric surgery for individuals with BMI of 40 or greater for primary obesity, and for individuals with BMI of 35 or greater who additionally have a serious obesity-related comorbidity.

Each policy detailed slightly different requirements (e.g., lengths of time, type of documentation) for a pre-surgery, structured intervention overseen by medical professionals for weight loss. In general, the beneficiary is required to have failed to lose a clinically important amount of weight during the course of that intervention prior to being eligible for a bariatric surgery.[93-96]

Policies also varied on whether revisions or reoperations were covered: Moda did not cover any revision, but Aetna, Regence BlueCross BlueShield, and Cigna all covered revisions and reoperations for either development of complications or medical necessity resulting from a failure to lose sufficient weight.[93-96]

In contrast to the Washington Health Technology Assessment coverage determination, the policies for Aetna and Cigna considered bariatric surgery as a treatment for T2DM in patients with a BMI less than 35 to be investigational and experimental.[93,96]

The coverage policy for Cigna stated that an altered threshold for BMI be used for individuals whose providers attest they are of Asian race or ethnicity with a BMI of 37.5 or greater without a comorbidity, or a BMI of 32.5 or greater with a comorbidity.[96]

Common examples of contraindications for bariatric surgery included an ongoing substance use disorder, medically correctable cause of obesity, inability to adhere to post-operation care and lifestyle requirements (determined from psychiatric or medical assessment), or current pregnancy (or pregnancy planned within a year of the operation).

Adolescents

Policies related to bariatric procedures for adolescents, defined as individuals between 10 and 19 years of age by the World Health Organization,[97] had different eligibility criteria than policies for adults. Each policy included a requirement about assessing the skeletal maturity of the individual prior to surgery.[93-96] The Regence BlueCross BlueShield policy required documentation of Tanner 4 or 5 pubertal development,[94] although the ASMBS recommendations for assessing eligibility in pediatric populations states that there is no evidence that bariatric surgery has negative effect on puberty or linear growth.[87]

These policies generally required that adolescents have either[93-96]:

- BMI exceeding 40 with at least 1 serious comorbidity (e.g., OSA, T2DM), or
- BMI exceeding 50 with a less serious comorbidity (e.g., medically refractory HTN, obesity-related psychosocial distress, gastroesophageal reflux disease)

Similar to policies for adults, the adolescents are required to have documentation of having attempted weight loss without significant reduction under the supervision of an intensive multicomponent intervention.

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APPENDIX A. GRADE TABLE ELEMENT DESCRIPTIONS

Table A1. GRADE Table Elements

ELEMENT	DESCRIPTION
Balance of benefits and harms	The larger the difference between the desirable and undesirable effects, the higher the likelihood that a strong recommendation is warranted. An estimate that is not statistically significant or has a confidence interval crossing a predetermined clinical decision threshold will be downgraded.
Quality of evidence	The higher the quality of evidence, the higher the likelihood that a strong recommendation is warranted.
Resource allocation	The higher the costs of an intervention—that is, the greater the resources consumed in the absence of likely cost offsets—the lower the likelihood that a strong recommendation is warranted.
Values and preferences	The more values and preferences vary, or the greater the uncertainty in values and preferences, the higher the likelihood that a weak recommendation is warranted.
Other considerations	Other considerations include issues about the implementation and operationalization of the technology or intervention in health systems and practices within Oregon.

Abbreviation. GRADE: Grading of Recommendations, Assessment, Development, and Evaluations.

Confidence in Estimate Rating Across Studies for the Intervention and Outcome

Assessment of confidence in estimate includes factors such as risk of bias, precision, directness, consistency, and publication bias.

High: The subcommittee is very confident that the true effect lies close to that of the estimate of the effect. Typical sets of studies are randomized controlled trials (RCTs) with few or no limitations, and the estimate of effect is likely stable.

Moderate: The subcommittee is moderately confident in the estimate of effect: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different. Typical sets of studies are RCTs with some limitations or well-performed nonrandomized studies with additional strengths that guard against potential bias and have large estimates of effects.

Low: The subcommittee's confidence in the estimate of effect is limited: The true effect may be substantially different from the estimate of the effect. Typical sets of studies are RCTs with serious limitations or nonrandomized studies without special strengths.

Very low: The subcommittee has very little confidence in the estimate of effect: The true effect is likely to be substantially different from the estimate of effect. Typical sets of studies are nonrandomized studies with serious limitations or inconsistent results across studies.

APPENDIX B. GRADE EVIDENCE PROFILES

Table B1. Certainty Assessment (Confidence in Estimate of Effect) for Adults with BMI ≥ 35 kg/m^2

SUB-OUTCOME	NO. OF STUDIES	RISK OF BIAS	INCONSISTENCY	INDIRECTNESS	IMPRECISION	OTHER FACTORS	LEVEL OF CONFIDENCE
All-cause Mortality							
--	3 reviews with 19 comparative cohort studies	High	Not serious	Not serious	Not serious	None	Moderate ●●●○
Weight Change							
--	5 reviews with 36 RCTs and 5 observational studies	Low	Not serious	Not serious	Not serious	None	High ●●●●
Improvement or Resolution of Chronic Conditions							
Diabetes	5 reviews with 28 RCTs	Low	Not serious	Serious Remission definitions varied across studies	Not serious	Most robust estimates come from a network meta-analysis	Moderate ●●●○
Hypertension	3 reviews with 20 RCTs and 2 comparative cohort studies	Low	Serious	Serious	Not serious	Most robust estimates come from a network meta-analysis	Low ●●○○
Coronary Artery Disease	2 reviews of 7 RCTs and 6 comparative cohort studies	High	Not serious	Serious	Not serious	Some results based on composite outcomes	Low ●●○○
Sleep Apnea	0						No evidence ○○○○
Joint Arthropathy	0						No evidence ○○○○
Intracranial Hypertension	0						No evidence ○○○○
Quality of Life							
--	2 SRs including 8 RCTs and 6 observational studies	High	Not serious	Serious	Not serious	Some analyses based on indirect analysis of a proxy measure	Low ●●○○
Harms							

SUB-OUTCOME	NO. OF STUDIES	RISK OF BIAS	INCONSISTENCY	INDIRECTNESS	IMPRECISION	OTHER FACTORS	LEVEL OF CONFIDENCE
--	6 reviews with 40 RCTs and 67 observational studies	High	Serious	Not serious	Not serious	None	Low ●●○○

Abbreviations. BMI: body mass index; kg/m^2: kilograms per meters squared; No.: number; RCT: randomized controlled trial; SR: systematic review.

Table B2. Certainty Assessment (Confidence in Estimate of Effect) for Adults with BMI 30 to 34.9 kg/m^2

SUB-OUTCOME	NO. OF STUDIES	RISK OF BIAS	INCONSISTENCY	INDIRECTNESS	IMPRECISION	OTHER FACTORS	LEVEL OF CONFIDENCE
All-cause Mortality							
--	0						No evidence ○○○○
Weight Change							
--	5 RCTs N = 391	Moderate Most studies rated as moderate due to imbalances in some baseline demographics and significant attrition in control groups	Not serious Direction and magnitude of effect is the same across studies and across study timepoints	Not serious 2 studies conducted in lower-income non-US countries; several studies included participants above and below the target BMI range, but had qualifying mean BMIs	Not serious Reasonable sample size and confidence intervals in pooled analyses are not overly wide	None	Moderate ●●●○
Improvement or Resolution of Chronic Conditions							
Diabetes	6 RCTs N = 433	Moderate Most studies rated as moderate due to imbalances in some baseline demographics and significant attrition in control groups	Not serious Direction and magnitude of effect is the same across studies and across study timepoints	Serious Multiple definitions for T2DM remission were used across studies	Not serious Good sample size and wide confidence intervals in remission estimates, but those estimates are supported by significantly lower and highly precise HbA1c values	None	Low ●●○○
Hypertension	5 RCTs N = 391	Moderate Most studies rated as moderate due to imbalances in some baseline demographics and significant attrition in control groups	Serious Differences in both mean SBP and mean DBP varied across follow-up timepoints and even within studies	Not serious Also, definitions of HTN did not vary between studies	Serious Several timepoints in the MAs of mean SBP and DBP only had 1 contributing study (low sample sizes), and similarly, several additional outcomes were based on single study estimates	Some selective reporting present (DBP-related results not as widely reported as SBP, even when DBP was collected at baseline)	Very low ●○○○

SUB-OUTCOME	NO. OF STUDIES	RISK OF BIAS	INCONSISTENCY	INDIRECTNESS	IMPRECISION	OTHER FACTORS	LEVEL OF CONFIDENCE
Coronary Artery Disease	5 RCTs N = 391	Moderate Most studies rated as moderate due to imbalances in some baseline demographics and significant attrition in control groups	Serious Mixed results within and between CDV outcomes	Serious All outcomes were intermediate measures of CAD (e.g., LDL-C levels, medication use) vs. direct cardiac events or diagnoses	Serious Confidence intervals and standard deviations were fairly wide due to small sample sizes contributing to lab values	None	Very low ●○○○
Sleep Apnea	0						No evidence ○○○○
Joint Arthropathy	0						No evidence ○○○○
Intracranial Hypertension	0						No evidence ○○○○
Quality of Life							
--	1 RCT N = 100	Moderate 1 moderate ROB study due to imbalances in key baseline chars (surgery group more likely to be white and take lipid lowering medications); adjustment for these imbalances is not widely applied	Not assessable Only 1 study available	Serious Single RCT conducted entirely in Brazil among patients with both T2DM and chronic kidney disease; may make results less generalizable to class I US populations	Serious Confidence intervals and standard deviations were fairly wide (much larger than MID of 2 to 3 points) due to small sample size	None	Very low ●○○○
Harms							
--	5 RCTs N = 391	Moderate Most studies rated as moderate due to imbalances in some baseline demographics and significant attrition in control groups	Serious Much higher rates of SAE in 1 trial, virtually none in other trials	Serious Unclear if the same types of events were considered for AE vs. SAE	Serious Low event rates with no standardized calculations. Only 1 study assessed nutritional deficiencies.	None	Very low ●○○○

Abbreviations. AE; adverse events; BMI: body mass index; CAD: coronary artery disease; DBP: diastolic blood pressure; kg/m^2: kilograms per meters squared; LDL-C: low-density lipoprotein cholesterol; MA: meta-analysis; RCT: randomized controlled trial; RoB: risk of bias; SAE: serious adverse events; SBP: systolic blood pressure; T2DM: type 2 diabetes mellitus.

Table B3. Certainty Assessment (Confidence in Estimate of Effect) for Adolescents

SUB-OUTCOME	NO. OF STUDIES	RISK OF BIAS	INCONSISTENCY	INDIRECTNESS	IMPRECISION	OTHER FACTORS	LEVEL OF CONFIDENCE
All-cause Mortality							
--	0						No evidence ○○○○
Weight Change							
--	4 cohort studies N = 525	High Studies rated as moderate to high due to imbalances in study groups at baseline and lack of adjustment for confounders	Not serious	Serious 2 studies were noncomparative and 1 study used a matched medical therapy comparator group from another trial	Not serious	None	Low ●●○○
Improvement or Resolution of Chronic Conditions							
Diabetes	4 cohort studies N = 525	High Studies rated as moderate to high due to imbalances in study groups at baseline and lack of adjustment for confounders	Serious Conflicting results in terms of HbA1c reduction (improved with surgery at 2 years but no difference vs. MT at 5 years)	Serious 2 studies were noncomparative and 1 study used a matched medical therapy comparator group from another trial	Serious Few observed events in some studies (very few events in reported control groups), and adjusted results were not reported for all studies	None	Very low ●○○○
Hypertension	4 cohort studies N = 525	High Studies rated as moderate to high due to imbalances in study groups at baseline and lack of adjustment for confounders	Serious Comparative results for mean SBP and DBP were mixed across studies	Not serious	Serious Few observed events in some studies (very few events in reported control groups), and adjusted results were not reported for all studies	None	Very low ●○○○
Coronary Artery Disease	2 cohort studies N = 255	Moderate 1 study rated as moderate due to slight differences between groups at baseline	Serious Conflicting results between comparative studies in both mean LDL-C and mean triglycerides	Serious Elevated LDL-C and/or triglycerides are intermediate measures associated with higher risk for coronary artery disease, but are not direct	Serious Few observed events in some studies (very few events in reported control groups), and adjusted results were not reported for all studies	None	Very low ●○○○

SUB-OUTCOME	NO. OF STUDIES	RISK OF BIAS	INCONSISTENCY	INDIRECTNESS	IMPRECISION	OTHER FACTORS	LEVEL OF CONFIDENCE
				evidence of CAD (e.g., cardiac events).			
Sleep Apnea	0						No evidence ○○○○
Joint Arthropathy	1 cohort study N = 206	Moderate 1 moderate RoB study due to lack of a nonsurgical comparator group and low completion of relevant follow-up visits (53%)	Not assessable	Serious Looked at self-reported rates of musculoskeletal pain during walk tests, not diagnosed arthropathies, but seems like an appropriate joint outcome for adolescents	Serious Small sample size: only based on self-reported pain in about 50 (of 206) participants	None	Very low ●○○○
Intracranial Hypertension	0						No evidence ○○○○
Quality of Life							
--	2 cohort studies N = 395	Moderate 2 moderate RoB studies due to lack of medical therapy comparator group and imbalances in some critical baseline characteristics between study groups	Serious Consistent weight-specific benefits within surgical groups (despite the use of differing scales), but no difference when compared with medical therapy controls Mixed results in general QoL domains assessed by SF-36 survey	Not serious	Serious Wide confidence intervals/SDs in some of the SF-36 domains (e.g., mean 50.8 points, SD 23 points on a 100-point scale)	None	Very low ●○○○
Harms							
--	4 cohort studies N = 525	High Studies rated as moderate to high due to imbalances in study groups at baseline and lack of adjustment for confounders					Very low ●○○○

Abbreviations. AE; adverse events; BMI: body mass index; CAD: coronary artery disease; DBP: diastolic blood pressure; kg/m^2: kilograms per meters squared; LDL-C: low-density lipoprotein cholesterol; MA: meta-analysis; MT: medical therapy; QoL: quality of life; RCT: randomized controlled trial; RoB: risk of bias; SAE: serious adverse events; SBP: systolic blood pressure; SD: standard deviation; SF-36: Short Form-36 survey; T2DM: type 2 diabetes mellitus.

APPENDIX C. METHODS

Scope Statement

Populations

Adults and adolescents with obesity (body mass index [BMI] ≥ 30) who are being considered for bariatric procedures

Population scoping notes: Exclude non-obese populations (BMI < 30)

Interventions

Bariatric procedures, for example, adjustable gastric banding, Roux-en-Y gastric bypass (RYGB), biliopancreatic diversion with duodenal switch (BPD/DS), vertical sleeve gastrectomy (VSG), single anastomosis duodenal-ileal bypass with sleeve gastrectomy (SADI-S), and intragastric balloons (IGB)

Intervention exclusions: Bariatric devices that are not approved by the US Food and Drug Administration (FDA) or not available in the United States

Comparators

Nonsurgical treatment (e.g., medical management, pharmacotherapy, intensive multicomponent behavioral interventions, behavioral counseling, structured weight management programs, other devices or procedures, or combinations of these therapies)

Outcomes

Critical: All-cause mortality

Important: Clinically significant improvement or resolution of chronic disease, weight change, quality of life, or harms

Considered but not selected for the Grading of Recommendations, Assessment, Development, and Evaluation (GRADE) table: Specific chronic diseases (e.g., arthritis, sleep apnea) or changes in healthcare utilization

Key Questions

The following Key Questions (KQs) guided our research for the present report:

KQ1. What is the effectiveness of bariatric procedures for the treatment of obesity in adults and adolescents as compared to other treatments?

KQ2. What are the harms of bariatric procedures for the treatment of obesity in adults and adolescents?

KQ3. Is there evidence of differential effectiveness or harms for bariatric procedures by:

a. Age
b. Sex
c. Race/ethnicity
d. BMI category
e. Comparator
f. Whether the patient has received prior bariatric surgery
g. Comorbidities (e.g., medical, behavioral health, other disabilities)

h. Site of procedure (inpatient vs outpatient surgical center, centers of excellence vs not)
i. Time since procedure

Contextual Questions

CQ1. What kinds of accreditation standards and center of excellence designations exist in the United States and what are the requirements of each?
CQ2. What is the appropriate minimum age or developmental stage for bariatric surgery?

Search Strategy

A full search of the core sources was conducted to identify systematic reviews, meta-analyses, randomized controlled trials, cohort studies, and health technology assessments that meet the criteria for the scope described above. Searches of core sources were limited to citations published after 2019, although key publications prior to this date range were sought for the pediatric population.

The following core sources were searched:

- Agency for Healthcare Research and Quality (AHRQ)
- Canadian Agency for Drugs and Technologies in Health (CADTH)
- Cochrane Library (Wiley Online Library)
- Institute for Clinical and Economic Review (ICER)
- National Institute for Health and Care Excellence (NICE)
- Veterans Administration Evidence-based Synthesis Program (ESP)
- Washington State Health Technology Assessment Program

A MEDLINE search was also conducted to identify systematic reviews, meta-analyses, randomized controlled trials (RCTs), cohort studies, and health technology assessments. For systematic reviews and meta-analyses, the search was limited to publications in English published since 2019. For randomized controlled trials and cohort studies, the search was limited to publications in English published since 2012.

Searches for clinical practice guidelines were limited to those published since 2019. A search for relevant clinical practice guidelines was also conducted using MEDLINE and the following sources:

- Canadian Agency for Drugs and Technologies in Health (CADTH)
- Centers for Disease Control and Prevention (CDC)
- Community Preventive Services
- National Institute for Health and Care Excellence (NICE)
- Scottish Intercollegiate Guidelines Network (SIGN)
- United States Preventive Services Task Force (USPSTF)
- Veterans Administration/Department of Defense (VA/DoD) Clinical Practice Guidelines

Inclusion/Exclusion Criteria

Studies were excluded if they were not published in English, did not address the scope statement, or were study designs other than systematic reviews or meta-analyses with RCTs (or comparative cohort studies

for adolescents), or clinical practice guidelines. We required that studies have a minimum of 1 year of follow-up for effectiveness outcomes, or any amount of follow-up for harms.

Risk of Bias and Methodologic Quality of Included Studies

We assessed the risk of bias of the included systematic reviews and methodologic quality of clinical practice guidelines using standard instruments developed and adapted by the Center for Evidence-based Policy (Center) based on a instruments used by the other reputable organizations.[98] One experienced researcher independently rated the risk of bias of included studies. A second experienced researcher reviewed each assessment. Disagreement was managed by discussion.

Systematic Reviews

If a meta-analysis or network meta-analysis was conducted, the risk of bias of the analyses was considered in the overall rating for the systematic review. In brief, low-risk-of-bias systematic reviews include a clearly focused question, a literature search sufficiently rigorous to identify all relevant studies, criteria used to assess study quality and select studies for inclusion (e.g., RCTs), and assessment of similarities between studies to determine whether combining them is appropriate for evidence synthesis. Moderate-risk-of-bias systematic reviews have incomplete information about methods that might mask important limitations or a meaningful conflict of interest. High-risk-of-bias systematic reviews have clear flaws that could introduce significant bias.

Randomized Controlled Trials

Low-risk-of-bias RCTs include a clear description of the population, setting, intervention, and comparison groups; a random and concealed allocation of patients to study groups; low dropout rates; and intention-to-treat analyses. Low-risk-of-bias RCTs also have low potential for bias from conflicts of interest and funding source(s). Moderate-risk-of-bias RCTs have incomplete information about methods that might mask important limitations or a meaningful conflict of interest. High-risk-of-bias RCTs have clear flaws that could introduce significant bias.

Cohort Studies

Low-risk-of-bias cohort studies include a sample that is representative of the source population, have low loss to follow-up, and measure and consider relevant confounding factors. Low-risk-of-bias cohort studies also list their funding source(s) and have a low potential of bias from conflicts of interest. Moderate-risk-of-bias cohort studies might not have measured all relevant confounding factors or adjusted for them in statistical analyses, have loss to follow-up that could bias findings, consist of a sample that is not representative of the source population, or have potential conflicts of interest that are not addressed. High-risk-of-bias cohort studies have a clear, high risk of bias that would affect findings.

Clinical Practice Guidelines

We assessed the methodological quality of the guidelines using an instrument adapted from the Appraisal of Guidelines Research and Evaluation (AGREE) Collaboration.[99-101] Each rater assigned the study a rating of good, fair, or poor based on its adherence to recommended methods and potential for biases. A good-quality guideline fulfills all or most of the criteria outlined in the instrument. A fair-quality guideline fulfills some of the criteria, and its unfulfilled criteria are not likely to alter the recommendations. A poor-quality guideline met few or none of the criteria.

APPENDIX D. ADDITIONAL EVIDENCE TABLES

Table D1. Characteristics of Included Reviews of Adults with BMI ≥ 35

AUTHOR, YEAR	REVIEW POPULATION	LAST SEARCH DATE # OF STUDIES SAMPLE SIZE	ANALYSIS TYPE	INCLUSION/EXCLUSION CRITERIA	BARIATRIC PROCEDURE TYPES	CONTROL GROUP DESCRIPTION	REPORTED OUTCOMES
Ablett, 2019	Adults with BMI ≥ 35	NR 3 RCTs, 6 OS N (RCTS) = 365 N (OS) = 283,040	MA	Inclusion RCTs, non-randomized controlled trials, and observational studies in adults (≥ 18 years), with mean pre-surgery group BMI ≥ 30 kg/m^2 Studies had a minimum follow-up ≥ 1 year Exclusion NR	SG RYGB AGB	Adults with obesity who did not undergo bariatric surgery	Weight change Harms
Arterburn, 2020	Adults with BMI ≥ 35	January 2020 12 RCTs N = 874	--	Inclusion Our search was limited to English-language articles Priority was given to evidence obtained from systematic literature reviews, meta-analyses, and RCTs when possible Exclusion NR	SG RYGB BPD/DS AGB	Medical therapy for obesity	Weight change Harms Chronic condition resolution
Cresci, 2020	Patients with BMI ≥ 35 and T2DM	December 2018 24 RCTs N = 1,351	NMA	Inclusion RCTs comparing different MS techniques versus MT, or comparing two different surgical procedures, with a duration ≥ 24 weeks Exclusion Animal studies were excluded	SG RYGB OAGB BPD/DS AGB	Medical therapy	Weight change QoL Harms Chronic condition resolution
Cui, 2021	Patients with BMI ≥ 35 and T2DM	February 2021 7 RCTs	MA	Inclusion Studies were eligible if they were RCTs (≥ 1 year of follow-up); included individuals with T2D; investigated currently used laparoscopic or open RYGB;	RYGB	Medical therapy for T2DM	Chronic condition resolution

AUTHOR, YEAR	REVIEW POPULATION	LAST SEARCH DATE # OF STUDIES SAMPLE SIZE	ANALYSIS TYPE	INCLUSION/EXCLUSION CRITERIA	BARIATRIC PROCEDURE TYPES	CONTROL GROUP DESCRIPTION	REPORTED OUTCOMES
		N = 447		investigated a comparator medical treatment for T2D; and reported remission of T2D or achievement of ADA's composite triple treatment goal Exclusion The major criteria to exclude studies were use of duplicate data sets, not having raw data available, or being published in a language other than English			
Hussain, 2021	Patients with BMI ≥ 35 and T2DM	March 2020 5 OS N = 49,211	MA	Inclusion Cohort studies with the following elements: (a) obese T2DM patients (BMI ≥ 35 kg/m^2) who underwent bariatric surgery, (b) defined the presence of T2DM based on HbA1c or FSG, (c) defined the outcome assessment criteria (diabetes macrovascular complications), and (d) provided estimates of the association between treatment and outcomes in the form of HR or RR, else the article should have sufficient information to compute HR or RR values Exclusion Reviews, population not of interest, outcome not of interest	RYGB BPD/DS AGB	Usual care (medical nutrition therapy, lifestyle changes, and medications)	All-cause mortality Chronic condition resolution
Khorgami, 2019	Patients with BMI ≥ 35 and T2DM	April 2018 7 RCTs N = 463	MA	Inclusion Studies were included if they (1) were prospective RCTs, (2) included patients diagnosed with T2D, (3) compared remission rates of T2D with medical treatment versus bariatric surgery, and (4) had at least 2 years of follow-up Exclusion NR	SG RYGB BPD/DS AGB	Medical treatment for obesity and T2DM	Chronic condition resolution
Malczak, 2021	Adults with BMI ≥ 35	April 2020	NMA	Inclusion	SG RYGB	Lifestyle interventions	QoL

AUTHOR, YEAR	REVIEW POPULATION	LAST SEARCH DATE # OF STUDIES SAMPLE SIZE	ANALYSIS TYPE	INCLUSION/EXCLUSION CRITERIA	BARIATRIC PROCEDURE TYPES	CONTROL GROUP DESCRIPTION	REPORTED OUTCOMES
		17 RCTs, 30 OS N = 26,629		Studies were eligible for inclusion if they were RCTs or non-randomized studies with a control group, such as cohort studies (prospective or retrospective) The included study had to include at least two arms (one of which is bariatric surgery) and the follow-up period was 1 year, 2 years, 3 years, or 5 years Studies must have reported on health-related QoL using any validated tools <u>Exclusion</u> Letters, editorials, case reports, case-series, and review papers were excluded Published abstracts were not included due to limited information available for analysis and the RoB assessment	OAGB BPD/DS		
Park, 2019	Adults with BMI ≥ 35	February 2018 45 RCTs N = 4,089	MA, NMA	<u>Inclusion</u> (a) Patients: underwent bariatric surgery, (b) intervention: bariatric surgery, (c) comparator: another method of bariatric surgery or standard-of-care without bariatric surgery, and (d) outcome: % EWL from 6 months to 5 years, and T2DM remission rate from 1 to 5 years <u>Exclusion</u> (a) Non-original studies, (b) non-RCTs, (c) non-human studies, (d) unpublished studies, and (e) non-English publications	SG RYGB BPD/DS AGB VBG GP MGB	Standard-of-care without bariatric surgery	Weight change Harms Chronic condition resolution
Pontiroli, 2020	Adults with BMI ≥ 35	October 2019 9 OS N = 607,643	MA	<u>Inclusion</u> Eligible CCS were those comparing bariatric surgery versus no-surgery in persons with morbid obesity, irrespective of publication status or language	SG RYGB BPD/DS	Medical treatment for obesity	All-cause mortality

AUTHOR, YEAR	REVIEW POPULATION	LAST SEARCH DATE # OF STUDIES SAMPLE SIZE	ANALYSIS TYPE	INCLUSION/EXCLUSION CRITERIA	BARIATRIC PROCEDURE TYPES	CONTROL GROUP DESCRIPTION	REPORTED OUTCOMES
				Exclusion Reviews and meta-analyses; studies without measures of dispersion of data were excluded at a second step, as well as studies without comparisons between surgery and control patients			
Robertson, 2020	Adults with BMI ≥ 35	July 2020 58 OS N = 3,650,961	MA	Inclusion English-only studies of at least 1000 patients reporting short-term mortality after bariatric surgery; RCTs with smaller patient numbers were included in the data collection for assessment of pooled mortality rates in this subset of specialized study types but were not included in the main analysis Exclusion Studies that did not report perioperative mortality and studies based on overlapping cohorts of patients were excluded	SG RYGB OAGB BPD/DS AGB	NR - analyses conducted for surgical patients only	Harms
Syn, 2021	Adults with BMI ≥ 35	February 2021 17 OS N = 174,772	MA	Inclusion Low-RoB randomized trials, prospective controlled studies, and matched cohort studies comparing all-cause mortality after metabolic–bariatric surgery versus non-surgical management of obesity published from inception to February 3, 2021 Exclusion Excluded from the meta-analysis were studies that exclusively enrolled patients with specific comorbidities other than T2DM (e.g., end-stage renal failure and type 1 diabetes) or adolescents, non-comparative studies, and case reports	SG RYGB OAGB BPD/DS AGB	Non-surgical management of obesity	All-cause mortality
Wang, 2021	Adults with BMI ≥ 35	May 2021 19 RCTs	MA	Inclusion RCTs (≥ 12-month follow-up); included individuals with a BMI ≥ 28; investigated all currently available	SG RYGB	Nonsurgical treatment for obesity (i.e., diet,	Weight change Harms Chronic

AUTHOR, YEAR	REVIEW POPULATION	LAST SEARCH DATE # OF STUDIES SAMPLE SIZE	ANALYSIS TYPE	INCLUSION/EXCLUSION CRITERIA	BARIATRIC PROCEDURE TYPES	CONTROL GROUP DESCRIPTION	REPORTED OUTCOMES
		N = 663		bariatric surgeries (including LAGB, RYGB, SG, BPD/DS, VBG, DJBL); investigated as comparator nonsurgical treatment for obesity (diet, weight reducing drugs, behavioral therapy); and reported changes in blood pressure or changes in the use of antihypertension medications Exclusion NR	BPD/DS AGB	weight-reducing drugs, behavioral therapy)	condition resolution
Yan, 2019	Adults with BMI ≥ 35 and T2DM	January 2019 4 RCTs, 6 OS N = 50,150	MA	Inclusion (1) RCT or cohort studies; (2) comparison of bariatric surgery including RYGB, AGB, SG, VBG, and BPD/DS to conventional medical therapy; (3) reported at least one of the main outcomes of interest (macrovascular events, mortality, or metabolic outcomes); (4) patient follow-up beyond 5 years; (5) studies enrolling adults with baseline BMI ≥ 35. Exclusion (1) trials without conventional medical therapy as control; (2) severely obese patients without T2DM; (3) follow up less than 5 years; (4) patients with BMI less than 35; (5) did not target our interest outcomes; (6) publication forms other than peer reviewed articles	SG RYGB BPD/DS ESG AGB	Conventional medical therapy for obesity (e.g., intensive lifestyle intervention and pharmacotherapy)	Weight change Chronic condition resolution

Abbreviations. ADA: American Diabetes Association; AGB: adjustable gastric banding; BMI: body mass index; BPD/DS: biliopancreatic diversion with duodenal switch; ESG: Endoscopic sleeve gastroplasty; EWL: excess weight loss; GP: gastric plication; HbA1c: glycated hemoglobin; HR: hazard ratio; kg/m^2: kilograms per meters squared; MA: meta-analyses; MS: multiple sclerosis; MT: medical therapy; NMA: network meta-analysis; NR: not reported; OAGB: one anastomosis gastric bypass; OS: observational studies; QoL: quality of life; RCT: randomized controlled trial; RoB: risk of bias; RR: relative risk; RYGB: Roux-en-Y gastric bypass; SG: sleeve gastrectomy; T2DM: type 2 diabetes mellitus; VBG: vertical banded gastroplasty.

Table D2. Characteristics of Primary Studies in Included Reviews of Adults with BMI ≥ 35

AUTHOR, YEAR	REVIEW POPULATION	PUBLICATION DATE (RANGE)	FOLLOW-UP (RANGE)	SAMPLE SIZE (RANGE)	MEAN AGE (RANGE)	MEAN BMI (RANGE)	% FEMALE (RANGE)	% NON-WHITE (RANGE)	COMORBIDITIES
Ablett, 2019	Adults with BMI ≥ 35	RCTs: 2010 to 2015 OS: 2012 to 2018	RCTs: 2 years max f/u OS: 2.2 to 8.9 years	RCTs: 69 to 150 OS: NR	RCTs: 42.8 to 50.0 years OS: 31.8 to 45.0 years	RCTs: 35.3 to 46.7 OS: 40.8 to 49.0	RCTs: 47.1% to 82.6% OS: 63.7% to 85.3%	RCTs: 7.5% to 32.6% OS: NR	T2DM, HTN, CAD, metabolic syndrome, dyslipidemia
Arterburn, 2020	Adults with BMI ≥ 35	2008 to 2020	1 to 5 years	38 to 150	NR	NR	NR	NR	
Cresci, 2020	Patients with BMI ≥ 35 and T2DM	2008 to 2018	26 to 260 weeks	3 to 120	Min and max 18 to 75 years	29.0 to 48.5	NR	NR	NR
Cui, 2021	Patients with BMI ≥ 35 and T2DM	2012 to 2020	1 to 5 years	32 to 120	RYGB: 43.9 to 52.5 years MT: 43.5 to 54.6 years	RYGB: 32.6 to 44.9 MT: 32.6 to 45.6	RYGB: 45% to 80% MT: 45% to 83%	NR	T2DM
Hussain, 2021	Patients with BMI ≥ 35 and T2DM	2014 to 2018	1.8 to 18.1 years	158 to 15,951	45.8 to 49.5 years	42.0 to 49.9	59% to 78.2%	NR	T2DM
Khorgami, 2019	Patients with BMI ≥ 35 and T2DM	2008 to 2018	2 to 5 years	38 to 120	NR	25 to > 45	NR	NR	T2DM
Malczak, 2021	Adults with BMI ≥ 35	2004 to 2020	NR	NR	NR	33.6 to 55.0	NR	NR	T2DM, HTN, OSA
Park, 2019	Adults with BMI ≥ 35	2005 to 2018	NR	14 to 240	NR	Limited to BMI ≥ 35: 31 studies Includes BMI < 35: 14 studies	NR	NR	NR
Pontiroli, 2020	Adults with BMI ≥ 35	2007 to 2019	4 to 14 years		38 to 46 years	NR	54% to 80%	NR	CAD, T2DM, cancer

AUTHOR, YEAR	REVIEW POPULATION	PUBLICATION DATE (RANGE)	FOLLOW-UP (RANGE)	SAMPLE SIZE (RANGE)	MEAN AGE (RANGE)	MEAN BMI (RANGE)	% FEMALE (RANGE)	% NON-WHITE (RANGE)	COMORBIDITIES
Robertson, 2020	Adults with BMI ≥ 35	2009 to 2020	In-hospital to 90 days post-surgery	1008 to 1,903,273	33.1 to 55.4 years	35.9 to 51.7	NR	NR	NR
Syn, 2021	Adults with BMI ≥ 35	2007 to 2020	2.6 to 24.0 years	535 to 33,540	Surgery: 36 to 62 years Control: 36 to 61 years	Surgery: 37.4 to 48.6 Control: 36.6 to 48.1	Surgery: 26% to 82% Control: 26% to 82%	Surgery: 3.7% to 100% Control: 1.9% to 100%	T2DM, HTN, dyslipidemia, CAD, heart failure, peripheral neuropathy, COPD
Wang, 2021	Adults with BMI ≥ 35	2006 to 2021	Mean, 2.8 years Range, 1 to 10 years	20 to 150	16.5 to 56 years	29.0 to 49.2	31% to 93%	NR	T2DM, metabolic syndrome
Yan, 2019	Adults with BMI ≥ 35 and T2DM	2011 to 2018	5 to 15 years	50 to 20,235	Most studies, ≥ 45 years	≥ 34 to ≤ 45	All studies included both men and women (proportions NR)	NR	T2DM

Abbreviations. BMI: body mass index; CAD: coronary artery disease; COPD: chronic obstructive pulmonary disease; f/u: follow-up; HTN: hypertension; max.: maximum; min.: minimum; MT: medical therapy; NR: not reported; OS: observational studies; OSA: obstructive sleep apnea; RCT: randomized controlled trial; RYGB: Roux-en-Y gastric bypass; T2DM: type 2 diabetes mellitus.

Table D3. Outcomes in Adults with BMI ≥ 35: All-cause Mortality, Weight Change, Quality of Life, and Harms

AUTHOR, YEAR # OF STUDIES SAMPLE SIZE ROB	REVIEW POPULATION	ALL-CAUSE MORTALITY	WEIGHT CHANGE	QUALITY OF LIFE	HARMS
Ablett, 2019 3 RCTs, 6 OS N (RCTS) = 365 N (OS) = 283,040 Moderate	Adults with BMI ≥ 35	NR	MEAN WEIGHT LOSS RCTs only IGn: 159 CGn: 103 MD, -22.2 kg (95% CI, -31.6 to -12.8; *P*< .0001)	NR	FRACTURE RATE RCTs IG: 8 of 226 CG: 5 of 139 RR, 0.82 (95% CI, 0.29 to 2.35; *P* = .72) Observational studies IG: 1,872 of 59,930 CG: 5,408 of 23,110 4 out of the 6 observational studies reported a statistically significant association between bariatric surgery and an increased likelihood of fracture compared to nonsurgical weight loss interventions (HR range, 1.21 to 2.3)
Arterburn, 2020 12 RCTs N = 874 High	Adults with BMI ≥ 35	NR	NR	NR	REOPERATIONS RCT data (5-year results, RYGB vs. SG) SLEEVEPASS trial SG: 8.3% RYGB: 15.1% *P*= .10 SM-BOSS trial SG: 15.8%

AUTHOR, YEAR # OF STUDIES SAMPLE SIZE ROB	REVIEW POPULATION	ALL-CAUSE MORTALITY	WEIGHT CHANGE	QUALITY OF LIFE	HARMS
					RYGB: 22.1% *P*= .33 Cohort study data Overall reoperation rate range, 5% to 22% Rates lower with SG compared with RYGB KP cohort (N = 35,273): HR, 0.78 (95% CI, 0.74 to 0.84) Optum cohort (N =13,027): HR, 0.80 (95% CI, 0.72 to 0.89) National Patient-Centered Clinical Research Network cohort (N = 33,560): HR, 0.72 (95% CI, 0.65 to 0.79) 10- year reoperation rates Among 7 studies of RYGB, rates of reoperation ranged from 8% to 64% (median 29%) In 2 studies of SG, rates of reoperation were 32% and 36%
Cresci, 2020 24 RCTs	Adults with BMI ≥ 35 and T2DM	NR	% WEIGHT LOSS IGn: 355 CGn: 267	SF-36 3 RCTs: superior scores among participants with bariatric	SAE IG: 72 of 386 CG: 44 of 337

AUTHOR, YEAR # OF STUDIES SAMPLE SIZE ROB	REVIEW POPULATION	ALL-CAUSE MORTALITY	WEIGHT CHANGE	QUALITY OF LIFE	HARMS
N = 1,351 Moderate			MD, -16.83 (95% CI, -18.03 to -15.62; *P*< .001)* CHANGE IN MEAN BMI Overall (Surg vs. MT) IGn: 386 CGn: 337 MD, -5.74 (95% CI, -7.05 to -4.43; *P*< .001)* Subgroup: minimum BMI for enrollment BMI < 30 IGn: 156 CGn: 146 MD, -3.80 (95% CI, -5.81 to -1.80; *P*= .003)* BMI 30 to 34.9 IGn: 190 CGn: 171 MD, -5.86 (95% CI, -6.78 to -4.95; *P*< .0001)* BMI ≥ 35 IGn: 40 CGn: 20 MD, -11.30 (95% CI, -14.01 to -8.59; *P*< .0001)* Subgroup: procedure type AGB IGn: 76	procedures (i.e., AGB, BPD/DS, RYGB) vs. controls at 5 years 1 RCT: improvements noted in both groups; no significant between-group difference in scores at 3 years EQ5D 1 RCT: improvements noted in both groups (RYGB vs. medical controls); no significant between-group difference in scores at 1 year IWQoL 1 RCT: superior scores among participants with RYGB vs. controls at 3 years PAID 1 RCT: improvements noted in both groups (RYGB vs. medical controls); no significant between-group difference in scores at 3 years	HR, 1.44 (95% CI, 0.66 to 3.16; *P* = .36) DEATH IG: 0 of 386 CG: 3 of 337 HR, 0.21 (95% CI, 0.03 to 1.32; *P* =.10) REVISIONAL SURGERY IG: 4 of 386 CG: 0 of 337 HR, 3.72 (95% CI, 0.43 to 32.49; *P*= .23) SEVERE HYPOGLYCEMIA IG: 4 of 386 CG: 4 of 337 HR, 0.69 (95% CI, 0.19 to 2.52; *P* = .58)

AUTHOR, YEAR # OF STUDIES SAMPLE SIZE ROB	REVIEW POPULATION	ALL-CAUSE MORTALITY	WEIGHT CHANGE	QUALITY OF LIFE	HARMS
			CGn: 76 MD, -4.22 (95% CI, -7.25 to -1.19; *P*= .006)* RYGB IGn: 215 CGn: 256 MD, -6.22 (95% CI, -7.73 to -4.71; *P*< .001)* BPD IGn: 20 CGn: 20 MD, -11.80 (95% CI, -14.89 to -8.71; *P*< .0001)* SG IGn: 50 CGn: 50 MD, -5.70 (95% CI, -7.06 to -4.34; *P*< .0001)* Subgroup: trial duration > 104 weeks IGn: 285 CGn: 195 MD, -5.62 (95% CI, -7.66 to -3.58; *P*< .0001)* ≤ 104 weeks IGn: 101 CGn: 142		

AUTHOR, YEAR # OF STUDIES SAMPLE SIZE ROB	REVIEW POPULATION	ALL-CAUSE MORTALITY	WEIGHT CHANGE	QUALITY OF LIFE	HARMS
			MD, -5.92 (95% CI, -7.09 to -4.75; *P*= .15)		
Hussain, 2021 5 OS N = 49,211 High	Adults with BMI ≥ 35 and T2DM	RISK OF ALL-CAUSE MORTALITY (Surg. vs. MT) 2 studies (sample sizes by group NR) RR, 0.39 (95% CI, 0.30 to 0.50; *P* < .0001)	NR	NR	
Malczak, 2021 17 RCTs, 30 OS N = 26,629 High	Adults with BMI ≥ 35	NR	NR	OVERALL QOL 3-year follow-up (NMA: 4 RCTs, 6 observational studies) AGB: SMD, 0.78 (95% CI, 0.40 to 1.17) BPD/DS: SMD, 1.16 (95% CI, 0.45 to 1.87) RYGB: SMD, 0.96 (95% CI, 0.65 to 1.29) RYGB (banded): 0.48 (95% CI, -0.50 to 1.46) SG: SMD, 0.9 (95% CI, 0.58 to 1.23) 5 years follow-up (NMA: 4 RCTs, 3 observational studies) BPD/DS: SMD, 1.43 (95% CI, 1.00 to 1.87) OAGB: SMD, 1.01 (95% CI, 0.63 to 1.4) RYGB: SMD, 1.27 (95% CI, 0.94	NR

AUTHOR, YEAR # OF STUDIES SAMPLE SIZE ROB	REVIEW POPULATION	ALL-CAUSE MORTALITY	WEIGHT CHANGE	QUALITY OF LIFE	HARMS
				to 1.61) SG: SMD, 0.92 (95% CI, 0.58 to 1.26) GIQLI Scale (Score range 0 to 144) 3 year follow-up (NMA: 4 RCTs, 6 observational studies) AGB: MD, 17.38 (95% CI, 8.87 to 25.92) BPD/DS: MD, 25.76 (95% CI, 9.88 to 41.58) RYGB: MD, 21.4 (95% CI, 14.37 to 28.51) RYGB (banded): MD, 10.63 (95% CI, -11.08 to 32.28) SG: MD, 20.05 (95% CI, 12.89 to 27.29) 5-year follow-up (NMA: 4 RCTs, 3 observational studies) BPD-DS: MD, 17.49 (95% CI, 12.85 to 24.15) OAGB: MD, 13.01 (8.11 to 17.98) RYGB: MD, 16.36 (95% CI, 12.08 to 20.69) SG: MD, 11.83 (95% CI, 7.53 to 16.18)	
Park, 2019 45 RCTs	Adults with BMI ≥ 35	NR	% EXCESS WEIGHT LOSS (surg vs. control)* 3 years follow-up	NR	MORTALITY RATE AGB: no deaths BPD-DS: no deaths

AUTHOR, YEAR # OF STUDIES SAMPLE SIZE ROB	REVIEW POPULATION	ALL-CAUSE MORTALITY	WEIGHT CHANGE	QUALITY OF LIFE	HARMS
N = 4,089 Low			AGB: MD, 19.0% (95% CI, 0.13 to 37.9) RYGB: MD, 45.0% (95% CI, 21.8 to 68.2) SG: MD, 39.2% (95% CI, 15.2 to 63.3) VBG: MD, 38.1% (95% CI, -27.4 to 103.6) 2 years follow-up AGB: MD, 52.8% (95% CI, 35.3 to 70.4) BPD: MD, 70.1% (95% CI, 50.9 to 90.8) GP: MD, 56.9% (95% CI, 27.0 to 86.8) MGP: MD, 75.0% (95% CI, 42.9 to 107.2) RYGB: MD, 69.8% (95% CI, 52.2 to 87.4) SG: MD, 73.9% (95% CI, 51.3 to 96.5) VBG: MD, 57.0% (95% CI, 31.8 to 82.2) 1 year follow-up AGB: MD, 26.9% (95% CI, 14.6 to 39.1) BPD: MD, 69.5% (95% CI, 42.5 to 96.4) BPD-DS: MD, 70.7% (95% CI, 45.4 to 96.0) GP: MD, 52.7% (95% CI, 27.1 to		GP: 1 death (pulmonary embolism; mortality rate, 1.1%) RYGB: 2 deaths (lymphoma and drug abuse; mortality rate, 0.1% [95% CI, 0.0 to 0.7%]) SG: no deaths VBG: 2 deaths (sepsis and pneumonia; mortality rate 2.0%) SURGICAL ADVERSE EVENTS (proportion) Hernia AGB: NR BPD-DS: 1.8% RYGB: 5.1% (95% CI, 4.0 to 6.5%; *P*< .01) SG: 0.6% Obstruction/stricture AGB: 0.8% BPD-DS: NR RYGB: 4.0% (95% CI, 3.0 to 5.3%; *P*< .01) SG: 1.2% Gastrointestinal bleeding AGB: NR BPD-DS: 3.5% RYGB: 2.0% (95% CI, 1.4 to 3.0%; *P*< .05) SG: 0.8% Leakage/perforation

AUTHOR, YEAR # OF STUDIES SAMPLE SIZE ROB	REVIEW POPULATION	ALL-CAUSE MORTALITY	WEIGHT CHANGE	QUALITY OF LIFE	HARMS
			78.4) MGB: MD, 65.2% (95% CI, 40.2 to 90.2) RYGB: MD, 60.1% (95% CI, 36.7 to 83.5) SG: MD, 60.2% (95% CI, 36.2 to 84.2) VBG: MD, 44.7% (95% CI, 28.3 to 61.0)		AGB: 0.8% BPD-DS: 3.5% RYGB: 0.9% SG: 0.7% Wound infection AGB: 0.3% BPD-DS: 1.8% RYGB: 1.1% SG: 1.1% Ulcer AGB: 0.3% BPD-DS: NR RYGB: 1.5% (95% CI, 1.0 to 2.4%; *P*< .01) SG: 0.2% Dumping syndrome AGB: NR BPD-DS: NR RYGB: 0.7% SG: 0.2% Hemoperitoneum AGB: NR BPD-DS: NR RYGB: 0.1% SG: NR AGB-only Pouch dilatation/slippage: 10.9%

AUTHOR, YEAR # OF STUDIES SAMPLE SIZE ROB	REVIEW POPULATION	ALL-CAUSE MORTALITY	WEIGHT CHANGE	QUALITY OF LIFE	HARMS
					Band erosion: 0.8% Band slippage: 0.8%
Pontiroli, 2020 9 OS N = 607,643 Moderate	Adults with BMI ≥ 35	GLOBAL MORTALITY (8.7 years median follow-up; Surg vs. MT) Overall IG: 2,274 of 72,267 CG: 79,134 of 535,376 OR, 0.29 (95% CI, 0.17 to 0.49; *P* = .001) Subgroup: age Below Median Age IG: 721 of 35,627 CG: 6,695 of 266,160 OR, 0.78 (95% CI, 0.57 to 1.06; *P* = .110) Above Median Age IG: 1,553 of 35,674 CG: 70,165 of 267,097 OR, 0.23 (95% CI, 0.12 to 0.44; *P* = .001)	NR	NR	NR
Robertson, 2020 58 OS N = 3,650,961 Moderate	Adults with BMI ≥ 35	NR	NR	NR	PERIOPERATIVE MORTALITY RATE (%) Overall pooled estimate (any time point up to 90 days) Events: 4,707 of 3,650,961 Rate: 0.08 (95% CI, 0.06 to 0.10) Subgroup: reporting type

AUTHOR, YEAR # OF STUDIES SAMPLE SIZE ROB	REVIEW POPULATION	ALL-CAUSE MORTALITY	WEIGHT CHANGE	QUALITY OF LIFE	HARMS
					30-day mortality: 0.07 (95% CI, 0.05 to 0.08) 90-day mortality: 0.11 (95% CI, 0.06 to 0.17) In-hospital mortality: 0.12 (95% CI, 0.05 to 0.20) Subgroup: procedure type SG: 0.05 (95% CI, 0.02 to 0.07) RYGB: 0.09 (95% CI, 0.06 to 0.13) OAGB: 0.09 (95% CI, 0.03 to 0.19) BPD-DS: 0.41 (95% CI, 0.25 to 0.60) AGB: 0.03 (95% CI, 0 to 0.09) Subgroup: study type Bariatric surgery registry: 0.07 (95% CI, 0.05 to 0.10) Administrative databases: 0.10 (95% CI, 0.06 to 0.14) Large series: 0.08 (95% CI, 0.05 to 0.11)
Syn, 2021 17 OS N = 174,772 Low	Adults with BMI ≥ 35	CUMULATIVE ALL-CAUSE MORTALITY Overall (Surg. vs. MT) IG: 1,813 deaths of 65,785 patients (over 496,771 patient-years) CG: 5,899 of 108,987 (over 659,605 patient-years)	NR	NR	NR

AUTHOR, YEAR # OF STUDIES SAMPLE SIZE ROB	REVIEW POPULATION	ALL-CAUSE MORTALITY	WEIGHT CHANGE	QUALITY OF LIFE	HARMS
		HR, 0.508 (95% CI, 0.481 to 0.537; *P*< .0001) Subgroup: diabetes status Patients with T2DM IG: 456 of 16,190 (over 70,984 PYs) CG: 2939 of 38,853 (over 170,933 PYs) HR, 0.409 (95% CI, 0.370 to 0.453; *P*< .0001) Patients without T2DM IG: 165 of 3256 (over 25,054 PYs) CG: 510 of 5740 (over 44,756 PYs) HR, 0.704 (95% CI, 0.588 to 0.843; *P*< .0001) Subgroup: procedure type RYBG patients vs. matched controls IG: 546 of 23,450 (over 216,413 PYs) CG: 1,070 of 26,554 (over 185,593 PYs) HR, 0.430 (95% CI, 0.387 to 0.478; *P*< .0001) SG patients vs. matched controls IG: 59 of 7,373 (over 38,531 PYs) CG: 209 of 14,097 (over 58,559			

AUTHOR, YEAR # OF STUDIES SAMPLE SIZE ROB	REVIEW POPULATION	ALL-CAUSE MORTALITY	WEIGHT CHANGE	QUALITY OF LIFE	HARMS
		PYs) HR, 0.475 (95% CI, 0.354 to 0.639; *P*< .0001) AGB patients vs. matched controls IG: 96 of 4,815 (over 34,369 PYs) CG: 454 of 12,407 (over 82,038 PYs) HR, 0.500 (95% CI, 0.401 to 0.624; *P*< .0001) RELATIVE HAZARD RATE REDUCTION OF DEATH (with bariatric procedures) Overall: 49.2% (95% CI, 46.3 to 51.9; *P*< .0001) Patients with T2DM: -59.1% Patients without T2DM: -29.6% NUMBER NEEDED TO TREAT (to prevent 1 additional death) 10-year follow-up Overall: 24.4 (95% CI, 23.1 to 26.0) Patients with T2DM: 8.4 (95% CI, 7.8 to 9.1) Patients without T2DM: 29.8 (95% CI, 21.2 to 56.8) 20-year follow-up Overall: 10.8 (95% CI, 10.2 to 11.5)			

AUTHOR, YEAR # OF STUDIES SAMPLE SIZE ROB	REVIEW POPULATION	ALL-CAUSE MORTALITY	WEIGHT CHANGE	QUALITY OF LIFE	HARMS
		Patients with T2DM: 5.3 (95% CI, 4.9 to 5.8) Patients without T2DM: 19.0 (95% CI, 13.4 to 36.3) MEDIAN LIFE EXPECTANCY (gain with bariatric procedures) Overall: +6.1 years (95% CI, 5.2 to 6.9) Patients with T2DM: +9.3 years (95% CI, 7.1 to 11.8) Patients without T2DM: +5.1 years (95% CI, 2.0 to 9.3)			
Wang, 2021 19 RCTs N = 663 Low	Adults with BMI ≥ 35	NR	CHANGE IN BODY WEIGHT (kg) [surg vs. nonsurg control] Overall: WMD, -18.47 (95% CI, -22.99 to -13.93; *P*< .001) Subgroup: procedure type AGB: WMD, -14.83 (95% CI, -22.81 to -6.84; *P*< .05)* SG: WMD, -16.32 (95% CI, -22.30 to -10.34; *P*< .05)* DJBL: WMD, -2.80 (95% CI, -10.93 to 5.33; *P*= NS) RYGB: WMD, -21.36 (95% CI, -26.61 to -16.12; *P*< .05)* BPD: WMD, -33.58 (95% CI, -38.69 to -28.47; *P*< .05)* CHANGE IN BMI Overall: WMD, -4.79 (95% CI, -	NR	ADVERSE EVENTS IG: 603 events (0.28 per person per year) CG: 393 events (0.23 per person per year) DEATHS IG: 2 deaths (1 after CABG surgery; 1 cause not reported) CG: 2 deaths (both fatal MI)

AUTHOR, YEAR # OF STUDIES SAMPLE SIZE ROB	REVIEW POPULATION	ALL-CAUSE MORTALITY	WEIGHT CHANGE	QUALITY OF LIFE	HARMS
			7.92 to -1.66; *P*< .0001) Subgroup: procedure type AGB: WMD, -0.44 (95% CI, -5.02 to 4.13; *P*= NS) SG: WMD, -8.00 (95% CI, -10.06 to -5.94; *P*= NR) DJBL: WMD, -0.90 (95% CI, -3.20 to 1.40; *P*= NR) RYGB: WMD, 8.12 (95% CI, -11.85 to -4.40; *P*< .0001) BPD: WMD, -11.95 (95% CI, -13.55 to -10.35; *P*= .81)		
Yan, 2019 4 RCTs, 6 OS N = 50,150 Moderate	Adults with BMI ≥ 35 and T2DM	NR	MEAN BMI* Overall (5 studies): WMD, -8.49 (95% CI, -9.25 to -2.58) Subgroup: procedure type RYGB (3 studies): WMD, -5.92 (95% CI, -9.25 to -2.58) BPD (2 studies): WMD, -11.90 (95% CI, -29.11 to 5.31)	NR	NR

Abbreviations. AGB: adjustable gastric banding; BMI: body mass index; BPD: biliopancreatic diversion; BPD/DS: biliopancreatic diversion with duodenal switch; CG: control group; CG n: control group sample size; CI: confidence interval; EQ5D: EuroQol-5 Dimensions; GIQLI: Gastrointestinal Quality of Life Index; GP: gastric plication; HR: hazard ratio; IG: intervention group; IG n: intervention group sample size; IWQoL: Impact of Weight on Quality of Life scale; kg: kilogram; MD: mean difference; MGB: mini gastric bypass; MT: medical therapy; NMA: network meta-analysis; Nonsurg: nonsurgical; NR: not reported; OAGB: one anastomosis gastric bypass; OR: odds ratio; OS: observational studies; PAID: Problem Areas in Diabetes scale; PY: per year; QoL: quality of life; RCT: randomized controlled trial; ROB: risk of bias; RR: relative risk or risk ratio; RYGB: Roux-en-Y gastric bypass; SAE: serious adverse events; SF-36: short form 36; SG: sleeve gastrectomy; SLEEVEPASS: Sleeve vs. Bypass Trial; SM-BOSS: Swiss Multicenter Bypass or Sleeve Study; SMD: standardized mean difference; Surg.: bariatric surgery; T2DM: type 2 diabetes mellitus; VBG: vertical banded gastroplasty; WMD: weighted mean difference.

Table D4. Outcomes in Adults with BMI ≥ 35: Improvement or Resolution of Chronic Conditions

AUTHOR, YEAR # OF STUDIES SAMPLE SIZE ROB	REVIEW POPULATION	DIABETES	HYPERTENSION	CONORARY ARTERY DISEASE
Arterburn, 2020 12 RCTs N = 874 High	Adults with BMI ≥ 35	NR	NR	NR
Cresci, 2020 24 RCTs N = 1,351 Moderate	Patients with BMI ≥ 35 and T2DM	T2DM REMISSION IG: 123 of 356 CG: 6 of 307 OR, 19.26 (95% CI, 5.68 to 65.31; *P* = .001)* (Definition: A1c < 6.5% without medication)	HTN RESOLUTION 2 studies: Fewer participants using anti-HTN medications in surgical groups (change range, -28 to -48 percentage points) vs. comparator groups (change range, 0 to +10 percentage points) at end of study SYSTOLIC BP CHANGE IGn: 355 CGn: 267 MD, -2.62 (95% CI, -4.46 to -0.79; *P* = .005) DIASTOLIC BP CHANGE IGn: 355 CGn: 267 MD, 0.91 (95% CI, -1.54 to 3.36; *P* = .46)	NR
Cui, 2021 7 RCTs N = 447 Moderate	Patients with BMI ≥ 35 and T2DM	T2DM REMISSION (RYGB vs. control) Remission at 1 year (4 RCTs) IG: 42 of 149 CG: 1 of 150 RR, 18.01 (95% CI, 4.53 to 71.70; *P* < .0001)	NR	NR

AUTHOR, YEAR # OF STUDIES SAMPLE SIZE ROB	REVIEW POPULATION	DIABETES	HYPERTENSION	CONORARY ARTERY DISEASE
		Remission at 2 years (4 RCTs) IG: 85 of 155 CG: 25 of 152 RR, 12.70 (95% CI, 0.45 to 358.63; *P*= .14) Remission at 3 years (3 RCTs) IG: 47 of 134 CG: 0 of 133 RR, 29.58 (95% CI, 5.92 to 147.82; *P*< .0001) Remission at 5 years (3 RCTs) IG: 33 of 154 CG: 0 of 153 RR, 16.92 (95% CI, 4.15 to 69.00; *P*< .0001)		
Hussain, 2021 5 OS N = 49,211 High	Patients with BMI ≥ 35 and T2DM	NR	NR	MACROVASCULAR COMPLICATIONS IGn: 14,434 CGn: 34,777 RR, 0.50 (95% CI, 0.35 to 0.73; *P*= .0003) Adjusted RR, 0.54 (95% CI, 0.37 to 0.79; *P*= .002)
Khorgami, 2019 7 RCTs N = 463 Moderate	Patients with BMI ≥ 35 and T2DM	T2DM REMISSION Remission at 5 years Overall IG: 62 of 225 CG: 7 of 156 RR, 6.0 (95% CI, 2.7 to 13.0; *P*< .0001)	NR	NR

AUTHOR, YEAR # OF STUDIES SAMPLE SIZE ROB	REVIEW POPULATION	DIABETES	HYPERTENSION	CONORARY ARTERY DISEASE
		Remission at 2 years Overall IG: 138 of 263 CG: 7 of 200 RR, 10.0 (95% CI, 5.5 to 17.9; *P*< .0001) Subgroup: procedure type RYGB IG: 77 of 146 CG: 5 of 144 RR, 15.2 (95% CI, 6.3 to 36.5; *P*< .0001) AGB IG: 40 of 77 CG: 7 of 79 RR, 5.8 (95% CI, 2.8 to 12.1; *P*< .0001)		
Park, 2019 45 RCTs N = 4,089 Low	Patients with BMI ≥ 35	T2DM REMISSION Late Remission (3 to 5 years after surgery) BPD: RR, 31.8 (95% CI, 5.0 to 201.8) BPD-DS: RR, 7.5 (95% CI, 1.9 to 29.5) RYGB: RR, 7.5 (95% CI, 2.0 to 28.5) SG: RR, 6.7 (95% CI, 1.8 to 25.6) Early Remission (1 to 2 years after surgery) AGB: RR, 7.6 (95% CI, 3.4 to 16.8) BPD: RR, 14.3 (95% CI, 5.7 to 36.2) BPD-DS: RR, 11.0 (95% CI, 4.2 to 28.9) GP: RR, 3.6 (95% CI, 1.2 to 11.0) MGB: RR, 12.2 (95% CI, 4.7 to 31.5) RYGB: RR, 11.2 (95% CI, 4.7 to 26.4) SG: RR, 9.1 (95% CI, 3.7 to 22.5)	NR	NR

AUTHOR, YEAR # OF STUDIES SAMPLE SIZE ROB	REVIEW POPULATION	DIABETES	HYPERTENSION	CONORARY ARTERY DISEASE
Wang, 2021 19 RCTs N = 663 Low	Patients with BMI ≥ 35	CHANGE IN USE OF METFORMIN (from baseline)* IG: RR, 0.464 (95% CI, 0.247 to 0.872; *P*= .017) CG: RR, 0.979 (95% CI, 0.808 to 1.186; *P*= .826) CHANGE IN USE OF INSULIN (from baseline)* IG: RR, 0.345 (95% CI, 0.229 to 0.520; *P*< .001) CG: RR, 0.933 (95% CI, 0.748 1.163 to 0.535; *P*< .001) CHANGE IN USE OF OTHER DIABETES MEDICATION (from baseline) IG: RR, 0.549 (95% CI, 0.420 to 0.719; *P*< .001) CG: RR, 0.891 (95% CI, 0.797 to 0.995; *P*< .001)	SYSTOLIC BP (mean change, surg vs. control) Overall: WMD, -3.94 mmHg (95% CI, -6.00 to -1.88; *P*< .001)* Subgroup: age < 45 years: WMD, −2.23 (95% CI, −5.85 to 1.40; *P*= .23) ≥ 45 years: WMD, −4.76 (95% CI, −7.27 to −2.25; *P*< .001)* Subgroup: baseline BMI < 40: WMD, −0.17 (95% CI, −6.25 to 5.91; *P* = .956) > 40: WMD, −4.43 (95% CI, −6.62 to −2.24; *P* < .001) Baseline: baseline HbA1c < 7.0%: WMD, −2.90 (95% CI, −6.59 to 0.78; *P*= .122) > 7.0%: WMD, −4.98 (95% CI, −7.81 to −2.15; *P*= .001)* Subgroup: procedure type AGB: WMD, −2.54 (95% CI, −5.69 to 0.62; *P*= .12) BPD: WMD, −5.60 (95% CI, −16.14 to 4.94; *P* = .30) RYGB: WMD, −5.75 (95% CI, −10.11 to −1.40; *P*= .01)* SG: WMD, −4.30 (95% CI, −15.06 to 6.46; *P*= .43)	NR

AUTHOR, YEAR # OF STUDIES SAMPLE SIZE ROB	REVIEW POPULATION	DIABETES	HYPERTENSION	CONORARY ARTERY DISEASE
			DIASTOLIC BP (mean change, surg vs control) Overall: WMD, -2.69 mmHg (95% CI, -3.99 to -1.39; *P*< .001)* Subgroup: age < 45 years: WMD, −2.43 (95% CI, −5.66 to 0.81; *P*= .14) ≥ 45 years: WMD, −2.73 (95% CI, −4.28 to −1.17; *P*= .001)* Subgroup: baseline BMI < 40: WMD, 0.27 (95% CI, −2.98 to 3.52; *P*= .87) > 40: WMD, −3.26 (95% CI, −4.68 to −1.84; *P* < .001)* Baseline: baseline HbA1c < 7.0%: WMD, −2.15 (95% CI, −4.72 to 0.41; *P*= .10) > 7.0%: WMD, −2.99 (95% CI, −4.74 to −1.25; *P*= .001)* Subgroup: procedure type AGB: WMD, −2.12 (95% CI, −4.63 to 0.39; *P*= .09) BPD: WMD, −1.78 (95% CI, −6.72 to 3.15; *P*= .48) RYGB: WMD, −2.54 (95% CI, −4.69 to −0.38; *P*= .02)* SG: WMD, −3.90 (95% CI, −10.53 to 2.73; *P*= .25)	

AUTHOR, YEAR # OF STUDIES SAMPLE SIZE ROB	REVIEW POPULATION	DIABETES	HYPERTENSION	CONORARY ARTERY DISEASE
			USE OF ANTIHYPERTENSIVES (change in % using from baseline) IG Baseline (mean %): 67.3% (95% CI, 59.2 to 75.3%) Follow-up: 37.3% (95% CI, 29.0 to 45.6%) MD, -0.91 per capita reduction (95% CI, -1.49 to -0.33; *P* = .002) CG Baseline: 70.9% (95% CI, 63.1 to 78.7%) Follow-up: 68.4% (95% CI, 60.3 to 76.5%) MD, -0.05 (95% CI, -0.39 to 0.29; *P* = .776)	
Yan, 2019 4 RCTs, 6 OS N = 50,150 Moderate	Patients with BMI ≥ 35 and T2DM	NR	SYSTOLIC BP (mean change, MBS vs. MT) Subgroup: procedure type RYGB (3 studies): WMD, 0.00 (95% CI, -0.11 to 0.11) BPD (2 studies): WMD, -2.66 (95% CI, -5.46 to 0.14) DIASTOLIC BP (mean change, MBS vs. MT) Subgroup: procedure type RYGB (3 studies): WMD, 0.90 (95% CI, 0.82 to 0.97) BPD (2 studies): WMD, -0.34 (95% CI, -1.94 to 1.27)	MACROVASCULAR COMPLICATIONS Overall IG: 503 of 14,938 CG: 2,525 of 35,125 RR, 0.43 (95% CI, 0.27 to 0.70) Adjusted HR analysis N = 8,569 (4 studies) HR, 0.52 (95% CI, 0.39 to 0.71) Subgroup: Study Design RCTs IG: 68 of 482 CG: 67 of 320 RR, 0.75 (95% CI, 0.44 to 1.26) Prospective cohort studies IG: 270 of 6,497 CG: 568 of 6,420 RR, 0.42 (95% CI, 0.15 to 1.21)

AUTHOR, YEAR # OF STUDIES SAMPLE SIZE ROB	REVIEW POPULATION	DIABETES	HYPERTENSION	CONORARY ARTERY DISEASE
				Retrospective cohort studies IG: 165 of 7,959 CG: 1,890 of 28,385 RR, 0.31 (95% CI, 0.16 to 0.62) CARDIOVASCULAR EVENTS (adjusted HR analysis) N = 8,569 (3 studies) HR, 0.52 (95% CI, 0.39 to 0.71) MYOCARDIAL INFARCTION Overall IG: 148 of 14,517 CG: 754 of 34,785 RR, 0.46 (95% CI, 0.38 to 0.55) Subgroup: Study Design RCTs IG: 38 of 482 CG: 45 of 320 RR, 0.63 (95% CI, 0.43 to 0.93) Prospective cohort studies IG: 24 of 6,154 CG: 70 of 6,160 RR, 0.35 (95% CI, 0.22 to 0.55) Retrospective cohort studies IG: 86 of 7881 CG: 639 of 28,305 RR, 0.45 (95% CI, 0.36 to 0.56)

Abbreviations. AGB: adjustable gastric banding; BMI: body mass index; BP: blood pressure; BPD: biliopancreatic diversion; BPD-DS: biliopancreatic diversion with duodenal switch; CG: control group; CI: confidence interval; GP: gastric plication; HbA1c: glycated hemoglobin; HR: hazard ratio; HTN: hypertension; IG: intervention group; MBS: metabolic and bariatric surgery; MD: mean difference; MGB: mini gastric bypass; mmHg: millimeters of mercury; MT: medical therapy; NR: not reported; OR: odds ratio; OS: observational studies; RCT: randomized controlled trial; ROB: risk of bias; RR: relative risk; RYGB: Roux-en-Y gastric bypass; SG: sleeve gastrectomy; Surg: surgery; T2DM: type 2 diabetes mellitus; WMD: weighted mean difference.

Table D5. Additional Study Characteristics of Included RCTs of Adults with BMI 30 to 34.9

AUTHOR, YEAR STUDY NAME RISK OF BIAS	TOTAL N FOLLOW-UP	POPULATION	INCLUSION CRITERIA	EXCLUSION CRITERIA	CONTROL GROUP DESCRIPTION	% FEMALE	% NON-WHITE
Parikh, 2014 Moderate	N = 57 5 years	Patients with T2DM and BMI 30 to 35 who were otherwise eligible for bariatric surgery by NIH criteria	(1) Overweight for at least 5 years, (2) failure to lose weight with non-surgical means, (3) absence of medical or psychological contraindications, (4) patient understanding of the procedure and its risks, and (5) strong motivation to comply with the post-surgical regimen	(1) Unable to comply with the study protocol (either self-selected or by indicating during screening that s/he could not complete all requested tasks), (2) participation in other obesity- or diabetes-related clinical trials, or (3) diagnosis of cognitive dysfunction or significant psychiatric comorbidity	Intensive MWM Protocol: MWM sessions were held weekly for the first month and then biweekly. In these 30-minute sessions, the clinician offered culturally tailored, patient-specific counseling on diet, physical activity, self-monitoring, and goal setting. The visits included a review of home glucose data and adjustment of diabetes medications. In addition, participants were provided with pedometers to track their progress, with a goal of 150 minutes per week of low-impact physical activity by 6 months.	IG: 79% CG: 79%	IG: 93% CG: 93%
Ikramuddin, 2013 DSS Trial Low	N = 120 5 years	Individuals who had an HbA1c level of ≥ 8.0%, BMI between 30 and 39.9 kg/m^2, C peptide level of >1.0 ng/mL, and T2DM for at least 6 months	Patients were included if they were (1) aged 30 through 67 years, (2) under a physician's care for T2DM for at least 6 months before recruitment, (3) had HbA1c levels of ≥ 8.0% at the time of entry, and (4) had a serum C-peptide level > 1.0 ng/mL 90 minutes after a liquid mixed meal. (5) Participants had a BMI of 30.0 to 39.9 and (6) were willing to accept randomization to either	Conditions that would contraindicate surgery, such as (1) serious cardiovascular disease, (2) previous gastrointestinal surgery, (3) psychological concerns, or (4) history of malignancy	The lifestyle-medical management protocol consisted of 2 components: (1) lifestyle modification designed to produce maximum achievable weight loss including daily weigh-ins, tracking food intake and physical activity, structured diets, and counseling, and (2) medications to control glycemia and cardiovascular disease risk factors while facilitating weight loss. Only FDA–approved medications were used (i.e., orlistat, metformin, sulfonylurea or pioglitazone, insulin, aspirin, ACE or ARB inhibitors, and beta blockers).	IG: 63% CG: 57%	IG: 45% CG: 50%

AUTHOR, YEAR STUDY NAME RISK OF BIAS	TOTAL N FOLLOW-UP	POPULATION	INCLUSION CRITERIA	EXCLUSION CRITERIA	CONTROL GROUP DESCRIPTION	% FEMALE	% NON-WHITE
			treatment group and follow the full treatment protocol.				
Courcoulas, 2014 TRIABETES Moderate	N = 61 5 years	Adults with grades I and II obesity and T2DM	Participants were eligible for enrollment if they were (1) 25 to 55 years of age, (2) had a BMI of 30 to 40, and (3) had confirmed T2DM (i.e., documented FPG level of ≥ 126 mg/dL and/or treatment with antidiabetics) For participants with grade I obesity, treatment with antidiabetics and permission from their treating physician were required to participate	(1) Prior weight loss surgery, (2) impaired mental status, (3) alcohol or other drug addiction, (4) current smoking, (5) pregnancy or planned pregnancy, (6) inability to tolerate general anesthesia owing to poor health, (7) type 1 diabetes, (8) failed nutritional or psychological assessment, (9) unwillingness to be randomized, (10) inability to provide informed consent, or (11) being deemed unlikely to comply with study visits or procedures	Participants randomized to MT underwent a standard 12-month behavioral weight control program delivered using an in-person, individual format based on the intervention developed for the Diabetes Prevention Program. During the initial 6 months of treatment, LWLI participants attended weekly in-person intervention sessions. During months 7 to 12, they attended in-person sessions in the first and third weeks of the month and received brief telephone contacts in the second and fourth weeks. Each session focused on a specific behavioral topic related to weight loss, eating, or exercise behaviors. Participants were provided with supplemental written materials and were asked to self-monitor body weight, eating, and exercise. Lower-level lifestyle weight loss interventions were then delivered for 4 years.	RYGB: 79% MT: 83%	% African American RYGB: 33% MT: 17%
Liang, 2013 Moderate	N = 108 1 year	Obese people with T2DM and hypertension	Individuals with T2DM diagnosed according to WHO criteria Other inclusion criteria were: (1) BMI > 28 kg/m^2	(1) People without diabetes; (2) type 1 diabetes, presence of autoimmune diabetes indicated by antibodies to insulin, islet cells, and	USUAL CARE: Patients were assessed and treated by a multidisciplinary team that included an endocrinologist, a dietitian, a cardiologist, and a nurse. The dose of oral hypoglycemic medications, antihypertensive drugs	RYGB: 29% MT: 33% MT+E: 29%	RYGB: 100% MT: 100% MT+E: 100%

AUTHOR, YEAR STUDY NAME RISK OF BIAS	TOTAL N FOLLOW-UP	POPULATION	INCLUSION CRITERIA	EXCLUSION CRITERIA	CONTROL GROUP DESCRIPTION	% FEMALE	% NON-WHITE
			in accordance with the WHO Asia-Pacific classification for obesity; (2) T2DM with hypertension of 5–10 years with hypertension defined as systolic blood pressure 140 mmHg and/or diastolic blood pressure 90 mmHg as per 1999 WHO/ISH criteria; (3) insulin therapy in combination with oral administration of drugs for 12 months; (4) HbA1c > 7% (5) age: 30–60 years; (6) seronegative for antibodies against insulin, islet cells and GAD; (7) C-peptide level 0.3 mg/L	GAD, and gestational diabetes; (3) patients with heart, liver, or renal function impairment; (4) presence of severe infections or cerebrovascular disease; (5) fasting serum insulin was less than one-third of the normal value; (6) diabetes of more than 10 years duration; (7) age > 60 years or < 30 years	and insulin was optimized on an individual basis with the aim of reaching HbA1c < 7% and blood pressure 140/90 mmHg. The nutrition goal was based on an individual energy intake and reducing fat intake to < 30%, saturated fat to < 10%, and increasing high fiber intake and for physical exercise 30 minutes of moderate-intensity aerobic activity twice a week. USUSAL CARE + EXENATIDE: Exenatide (an antidiabetic medication used to lower blood sugar) was given 1 hour before breakfast or dinner. Patients were injected with 0.5 mg Exenatide subcutaneously twice daily for 1 month, then increased to 1.0 mg twice daily if tolerated.		
Schauer, 2012 STAMPEDE Low	N = 150 5 years	Obese patients with uncontrolled T2DM	(1) Age of 20 to 60 years, (2) a diagnosis of type 2 diabetes (HbA1c level, > 7.0%), (3) and a BMI of 27 to 43	(1) Previous bariatric surgery or other complex abdominal surgery; (2) poorly controlled medical or psychiatric disorders	All patients received intensive medical therapy, as defined by ADA guidelines, including lifestyle counseling, weight management, frequent home glucose monitoring, and the use of newer drug therapies (e.g., incretin analogues) approved by the FDA. All patients were treated with lipid-lowering and antihypertensive medications. Every 3 months for the first 12 months, patients returned for study visits with a	RYGB: 58% SG: 78% MT: 62%	RYGB: 26% SG: 28% MT: 26%

AUTHOR, YEAR STUDY NAME RISK OF BIAS	TOTAL N FOLLOW-UP	POPULATION	INCLUSION CRITERIA	EXCLUSION CRITERIA	CONTROL GROUP DESCRIPTION	% FEMALE	% NON-WHITE
					diabetes specialist at the Cleveland Clinic.		
Cohen, 2020 MOMS Moderate	N = 100 2 years	Patients with early-stage CKD, T2DM, and Class I obesity (BMI 30 to 35)	(1) Age: 18–65 years; (2) BMI: 30–34.9 kg/m^2; (3) < 15 years of history of T2DM; (4) Negative GAD autoantibodies test; (5) Fasting C peptide over 1 ng/mL; (6) Appropriate postprandial C peptide response after a 500 kcal mixed meal challenge	(1) Autoimmune diabetes or type 1 diabetes; (2) Previous abdominal operations that would complicate an RYGB; (3) Pregnancy or women of childbearing age without an effective contraceptive; (4) Alcoholism or illicit drug use; (5) Severe hepatic disease that may complicate RYGB; (6) Inflammatory bowel disease or malabsorptive syndrome; (7) Major cardiovascular event in the past 6 months; (8) Current angina; (9) Severe psychiatric disorders that would complicate follow-up after RYGB; (10) Use of immunosuppressive drugs, chemotherapy and/or radiotherapy; (11) Uncontrolled coagulopathy; (12) Advanced proliferative retinopathy with or without amaurosis; (13) CKD stage 4 or 5 waiting for renal replacement therapy; (14) Stage 3	Best medical treatment: medical treatment algorithms in our protocol were consistent with the updated 2019 ADA and European Association for Study of Diabetes guidelines. Behavioral interventions included counseling with a dietician to reduce food intake and increase physical activity. Pharmacology included T2DM medications, ARBs/ACE inhibitors, statins, and antihypertensives.	RYGB: 45% MT: 45%	RYGB: 10% MT: 31%

AUTHOR, YEAR STUDY NAME RISK OF BIAS	TOTAL N FOLLOW-UP	POPULATION	INCLUSION CRITERIA	EXCLUSION CRITERIA	CONTROL GROUP DESCRIPTION	% FEMALE	% NON-WHITE
				peripheral neuropathy; (15) Pulmonary embolism in the past 2 years			

Abbreviations. ACE: angiotensin-converting enzyme; ADA: American Diabetes Association; ARB: angiotensin receptor blockers; BMI: body mass index; CG: control group; CKD: chronic kidney disease; DSS: diabetes surgery study; FDA: US Food and Drug Administration; FPG: fasting plasma glucose; HbA1c: glycated hemoglobin; kcal: kilocalories; IG: intervention group; kg/m^2: kilograms per meters squared; MOMS: Microvascular Outcomes after Metabolic Surgery; MT: medical therapy; MT+E: medical therapy and exenatide; NIH: National Institutes of Health; RCT: randomized controlled trials; RYGB: Roux-en-Y gastric bypass; SG: sleeve gastrectomy; STAMPEDE: Surgical Treatment and Medications Potentially Eradicate Diabetes Efficiently; T2DM: type 2 diabetes; TRIABETES: Randomized Trial to Compare Surgical and Medical Treatments for Type 2 Diabetes; WHO: World Health Organization.

Table D6. Outcomes in Adults with BMI 30 to 34.9: Weight Change, Quality of Life, Harms

AUTHOR, YEAR STUDY NAME RISK OF BIAS	TOTAL N FOLLOW-UP	WEIGHT CHANGE	QUALITY OF LIFE	HARMS
Parikh, 2014 Moderate	N = 57 5 years	BMI, mean Baseline – IG: 32.8 (1.5), CG: 32.0 (2.2); *P*= .16 3 years – IG: 26.6, CG: 31.1; *P*< .001 5 years – IG: 25.8 (3.1), CG: 28.6 (3.6); *P*= .013 Change – IG: –7.0 (3.2), CG: –3.4 (2.6); *P*< .001 Subgroup: surgery type SG: n = 18, RYGB: n = 8, AGB: n = 3 Baseline – SG: 32.8 (1.7), RYGB: 32.8 (1.2), AGB: 33.0 (.8); *P*= .96 5 years – SG: 27.0 (2.4); RYGB: 24.3 (2.7), AGB: 23.1 (5.4); *P*= .03 Change – SG: –5.9 (1.9), RYGB: –8.6 (3.4), AGB: –9.9 (5.8); *P*= .03 % WEIGHT LOSS 3 years – IG: 26.6%, CG: 2.8%; *P*< .001 5 years – IG: 21.4% (9.4), CG: 10.3% (8.1); *P*= .025 Subgroup: surgery type SG: 18.0 (6.0) RYGB: 26.0 (10.0) AGB: 29.9 (16.9) *P*= .03 % EXCESS WEIGHT LOSS[a] 3 years – IG: 52.9%, CG: 8.7%; *P*< .001	NR	MORTALITIES 6 months – no deaths 3 years – no deaths 5 years – no deaths SAEs (i.e., life-threatening events) 6 months - none 3 years – none 5 years – none HOSPITAL READMISSIONS or REOPERATIONS (IG only) 30-day: 1 of 29 (3%) –> dehydration Longer-term (> 30-day): 4 of 29 (13%) –> abscess requiring drainage, food impaction causing nausea/vomiting, and dehydration/abdominal pain 5 years – 11 of 29 (38%) -> cholecystectomy (n = 4), endoscopy (n = 2), dehydration, B12 deficiency, small bowel obstruction, pancreatitis, and right hemicolectomy for incidentally diagnosed cancer DIABETIC RETINOPATHY 5 years – IG: 0 of 29 (0%), CG: 4 of 14 (29%) PERIPHERAL NEUROPATHY 5 years – IG: 0 of 29 (0%), CG: 6 of 14 (43%)
Ikramuddin, 2013 DSS Trial	N = 120 5 years	BMI, mean Baseline - RYGB: 34.9 (34.1 to 35.7), MT: 34.4 (33.5 to 35.2)	NR	AEs Clinically significant (years 1 to 2) MT: 19

AUTHOR, YEAR STUDY NAME RISK OF BIAS	TOTAL N FOLLOW-UP	WEIGHT CHANGE	QUALITY OF LIFE	HARMS
Low		1 year RYGB: 25.8 (25.09 to 26.6), MT: 31.6 (30.8 to 32.4) MD, −5.8 (−7.0 to −4.7), *P*< .001 2 years RYGB: 26.8 (25.7 to 27.4), MT: 31.9 (31.0 to 32.7) MD, −5.3 (−6.5 to −4.1), *P*< .001 3 years RYGB: 27.3 (26.5 to 28.1), MT: 31.5 (30.7 to 32.4) MD, −4.2 (−5.4 to −3.0), *P*< .001 4 years RYGB: 27.5 (26.5 to 28.3), MT: 31.5 (30.6 to 32.3) MD, −4.0 (−5.2 to −2.8), *P*< .001 5 years RYGB: 27.4 (26.5 to 28.2), MT: 31.1 (30.3 to 32.0) MD, −3.7 (−4.9 to −2.5), *P*< .001 % WEIGHT LOSS, mean (Supplement) 1 year RYGB: 26.1 (23.8 to 28.4), MT: 7.8 (5.5 to 10.1) MD, 18.3 (15.0 to 21.5), *P*< .001 2 years RYGB: 23.9 (21.6 to 26.2), MT: 7.3 (5.0 to 9.9) MD, 16.7 (13.4 to 19.9), *P*< .001 3 years RYGB: 22.0 (19.7 to 24.3), MT: 8.5 (5.1 to 10.9) MD, 13.5 (10.2 to 16.8), *P*< .001 4 years RYGB: 21.7 (19.4 to 24.0), MT: 8.7 (6.2 to 11.1) MD, 13.0 (9.7 to 16.4), *P*< .001 5 years RYGB: 21.8 (19.5 to 24.1), MT: 9.6 (7.2 to 12.0) MD, 12.2 (8.9 to 15.5), *P*< .001		RYGB: 40 - Most of the first-year adverse events in the RYGB group were directly related to surgery - The RYGB group had 7 serious falls with 5 fractures vs. 3 serious falls and 1 fracture in the MT group - 8 infections occurred in the RYGB group vs. 4 in the MT group Serious (years 3 to 5) MT: 19 RYGB: 26 Total (years 1 to 5) MT: 38 events RYGB: 66 events - The most common AEs were 14 episodes of surgical complications in the gastric bypass group, and 15 and 16 gastrointestinal events in the gastric bypass and lifestyle–medical management groups, respectively - Bone fractures had been previously reported in the gastric bypass group but were not seen in years 3 to 5 NUTRITIONAL DEFICIENCIES Iron deficiency Baseline - MT: 2 of 59 (3%), RYGB: 1 of 60 (2%) 1 year - MT: 4 of 59 (7%), RYGB: 8 of 60 (14%) 2 years - MT: 0 of 59 (0%), RYGB: 11 of 60 (20%); *P*< .01 3 years - NR 4 years - NR

AUTHOR, YEAR STUDY NAME RISK OF BIAS	TOTAL N FOLLOW-UP	WEIGHT CHANGE	QUALITY OF LIFE	HARMS
				5 years - NR Anemia (blood Hg < 55 mmol/L) Baseline - MT: 0 of 59 (0%), RYGB: 0 of 60 (0%) 1 year - MT: 1 of 59 (2%), RYGB: 3 of 60 (5%) 2 years - MT: 2 of 59 (4%), RYGB: 0 of 60 (0%) 3 years - NR 4 years - NR 5 years - MT: 0 (0%), RYGB: 3 (6%) Vitamin B12 deficiency Baseline - MT: 0 of 59 (0%), RYGB: 2 of 60 (3%) 1 year - MT: 3 of 59 (6%), RYGB: 1 of 60 (2%) 2 years - MT: MT: 1 of 59 (2%), RYGB: 5 of 60 (9%) 3 years - NR 4 years - NR 5 years - MT: 1 (3%), RYGB: 2 (4%) Vitamin D deficiency (< 6.7 nmol/L) Baseline - MT: 12 of 59 (28%), RYGB: 15 of 60 (34%) 1 year - MT: 6 of 59 (15%), RYGB: 11 of 60 (27%) 2 years - MT: 5 of 59 (15%), RYGB: 7 of 60 (18%) 3 years - NR 4 years - NR 5 years - NR
Courcoulas, 2014 TRIABETES Moderate	N = 61 5 years	MEAN WEIGHT CHANGE (kg) Baseline - RYGB: 99.27 (2.99), MT: 102.0 (3.19) 1 year - RYGB: −28.8 (1.68), MT: −7.52 (1.95); *P* < .001 3 years - RYGB: −24.6 (2.12), MT: −5.03 (2.53); *P*	NR	TOTAL AEs (through 5 years) RYGB: 21 events MT: 14 events DEATHS

AUTHOR, YEAR STUDY NAME RISK OF BIAS	TOTAL N FOLLOW-UP	WEIGHT CHANGE	QUALITY OF LIFE	HARMS
		< .001 5 years - RYGB: −24.9 (2.12), MT: −4.50 (2.51); *P* < .001 % WEIGHT CHANGE Baseline - N/A 1 year - RYGB: −29.1 (1.64), MT: −7.59 (2.00); *P* < .001 3 years - RYGB: −25.0 (2.04), MT: −5.7 (2.42); *P* < .001 5 years - RYGB: −25.2 (2.09), MT: −5.14 (2.46); *P* < .001 MEAN BMI CHANGE (kg/m2) Baseline - RYGB: 35.67 (0.61), MT: 35.75 (0.73) 1 year - RYGB: −10.2 (0.59), MT: −2.38 (0.69); *P* < .001 3 years - RYGB: −8.70 (0.72), MT: −1.75 (0.82); *P* < .001 5 years - RYGB: −8.75 (0.76), MT: −1.20 (0.85); *P* < .001		RYGB: no deaths MT: no deaths SAEs Post-operative SAE (< 30 days) - RYGB: 0 Late-operative SAE (> 30 days) - RYGB: 1 event (anastomotic ulcer) Non-operative SAE (> 30 days) - RYGB: 0; MT 0 NON-SERIOUS AEs Post-operative AE (< 30 days) - RYGB: 3 (2 prolonged hospital stay, 1 nausea requiring IV hydration) Late-operative AE (> 30 days) - RYGB: 1 (reoperation) Non-operative AE (> 30 days) - RYGB: 16; MT: 14
Liang, 2013 Moderate	N = 108 1 year	MEAN BMI Baseline - RYGB: 30.48 (0.94), MT: 30.94 (1.96), MT+E: 30.28 (1.44) 1 year - RYGB: 24.51 (0.91), MT: 30.38 (1.66), MT+E: 26.84 (1.21)* RYGB vs. MT: *P*< .01 RYGB vs. MT+E: *P*< .05	NR	- There were no SAEs observed in any of the three groups - The patients in group B (38%) had a higher incidence of vomiting than group A (8%) and nausea in group C (16%) - 6 patients in group C developed local inflammation around the drainage port and all were successfully treated using conservative regimens
Schauer, 2012 STAMPEDE Low	N = 150 5 years	Figure S4 in 5-yr supplement visualizes changes in BMI stratified by baseline BMI group (above or below 35), but yearly means are not reported	NR	NR

AUTHOR, YEAR STUDY NAME RISK OF BIAS	TOTAL N FOLLOW-UP	WEIGHT CHANGE	QUALITY OF LIFE	HARMS
Cohen, 2020 MOMS Moderate	N = 100 2 years	MEAN BMI Baseline - RYGB: 32.5 (1.9), MT: 32.6 (2.1) 2 years - RYGB: 24.5 (23.5 to 25.0), MT: 31.2 (30.5 to 32.0) MD, −6.9 (−8.0 to −5.8); *P*< .001 BMI IN NORMAL RANGE, % RYGB: 51% MT: 0% *P*< .001 % WEIGHT CHANGE RYGB: −25.4% (−26.9 to −23.8) MT: −4.5% (−6.1 to −3.1) LOST ≥ 15% BODY WEIGHT RYGB: 95% MT: 5%	SF-36 SCORES[b], points General Health RYGB: 78.15 (72.6 to 83.7) MT: 60.3 (54.8 to 65.8) MD, 17.85 (10.0 to 25.7); *P*< .001 Emotional Well-being RYGB: 71.9 (66.2 to 77.8) MT: 63.0 (57.2 to 68.8) MD, 8.9 (0.7 to 17.2); *P*= .03 Physical Health RYGB: 80.4 (68.8 to 92.1) MT: 60.5 (48.9 to 72.1) MD, 19.9 (3.5 to 36.4); *P*= .02 Physical Role Functioning RYGB: 84.3 (77.9 to 90.7) MT: 70.2 (63.8 to 76.6) MD, 14.2 (5.1 to 23.2); *P*= .002 Mental Health RYGB: 73.5 (61.5 to 85.6) MT: 62.6 (50.6 to 74.7) MD not reported; *P*.=.21 Vitality RYGB: 69.5 (63.6 to 75.4) MT: 55.1 (49.2 to 61.0) MD, 14.4 (6.1 to 22.7); *P*= .001	SAEs RYGB: 6 of 46 (13%) MT: 6 of 46 (13%) *P*> .99 - RYGB group: 1 case of sepsis due to osteomyelitis, 1 case of appendicitis, 1 case of gall stones, 1 case of intestinal bleeding, and 2 endoscopic interventions - MT group: 1 case each of kidney stones, chest pain, anaphylactic shock, erysipelas, septic shock due to foot infection, and diabetic foot infection MOST COMMON AEs - GI/abdominal pain - Hypoglycemia - Diarrhea - Vomiting - Musculoskeletal pain OTHER AEs - No deaths, episodes of serious hypoglycemia, malnutrition, or excessive weight loss occurred

Notes. [a] Excess weight loss was calculated based on the Robinson formula for ideal body weight. [b] 24-month scores reported for measures where the study groups did not differ at baseline (measures not reported due to imbalance at baseline: pain, social role function, and mental health).

Abbreviations. AE: adverse event; AGB: adjustable gastric banding; BMI: body mass index; CG: control group; DSS: diabetes surgery study; GI: gastrointestinal; IG: intervention group; kg: kilograms; kg/m^2: kilograms per meters squared; MD: mean difference; MOMS: Microvascular Outcomes after Metabolic Surgery; MT: medical therapy; MT+E: medical therapy and exenatide; NR: not reported;

RYGB: Roux-en-Y gastric bypass; SAE: serious adverse event; SF-36: Short Form-36 survey; SG: sleeve gastrectomy; STAMPEDE: Surgical Treatment and Medications Potentially Eradicate Diabetes Efficiently; TRIABETES: Randomized Trial to Compare Surgical and Medical Treatments for Type 2 Diabetes.

Table D7. Outcomes in Adults with BMI 30 to 34.9: T2DM, Hypertension, Coronary Artery Disease

AUTHOR, YEAR STUDY NAME RISK OF BIAS	TOTAL N FOLLOW-UP	T2DM	HYPERTENSION	CORONARY ARTERY DISEASE
Parikh, 2014 Moderate	N = 57 5 years	T2DM REMISSION[a] 3 years – IG: 19 of 30 (63%), CG: 0 of 14 (0%); *P*< .001 5 years – IG: 11 of 29 (38%), CG: 0 of 14 (0%); *P*= .008 SG: 7 of 18 (39%), RYGB: 4 of 8 (50%), AGB: 0 of 3 (0%) MEAN HbA1c Baseline – IG: 7.50 (1.17), CG: 7.46 (.94); *P* = .91 3 years – IG: 6.91, CG: 8.37; *P*< .001 5 years – IG: 6.93 (1.37), CG: 8.26 (1.80); *P* = .01 Change – IG: –0.57 (1.40), CG: +0.81 (1.47); *P* = .006 Subgroup: surgery type Baseline – SG: 7.39 (1.33), RYGB: 7.66 (.93), AGB: 7.73 (.80); *P*= .83 5 years – SG: 6.91 (1.25), RYGB: 6.67 (1.60), AGB: 7.63 (1.82); *P*= .61 Change – SG: –0.48 (1.48), RYGB: –0.99 (1.28), AGB: –0.10 (1.51); *P*= .62 CHANGE IN USE OF DIABETES MEDICATIONS 3 years – IG: -1.33, CG: +0.13; *P*< .001 % USING INSULIN 5 years – IG: 3 of 29 (10%), CG: 7 of 14 (50%); *P*= .007 –> SG: 2 of 18 (11%), RYGB: 0 of 8 (0%), AGB: 1 of 3 (33%); *P*= .39	% USING ANY HTN MEDS SG: 11 of 18 (61%) RYGB: 4 of 8 (50%) AGB: 2 of 3 (67%) *P*= .59 % USING > 1 HTN MEDS –> SG: 6 of 18 (33%), RYGB: 1 of 8 (13%), AGB: 1 of 3 (33%); *P*= .48 SBP, mean (SD) Baseline – IG: 129.1 (15.5), CG: 128.9 (23.2), *P* = .98 5 years – IG: 132.8 (20.2), CG: 135.6 (17.5), *P*= .66 Change – IG: +3.75 (23.8), CG: +6.7 (25.3), *P* = .71 Subgroup: surgery type Baseline – SG: 133.0 (15.3), RYGB: 124.1 (15.5), AGB: 120.3 (14.7); *P*= .25 5 years – SG: 143.8 (14.8), RYGB: 111.4 (8.8), AGB: 128.0 (26.3); *P*< .001 Change – SG: +10.8 (20.6), RYGB: –12.7 (20.4), AGB: +7.7 (35.5); *P*= .06 DBP, mean (SD) Baseline – IG: 79.2 (12.6), CG: 72.9 (6.2), *P* = .03 5 years – IG: 76.7 (10.6), CG: 74.4 (10.3), *P* = .52 Change – IG: –2.5 (14.9), CG: +1.6 (13.4), *P* = .39	Not abstracted: – Triglycerides – Cholesterol – HDL – LDL

AUTHOR, YEAR STUDY NAME RISK OF BIAS	TOTAL N FOLLOW-UP	T2DM	HYPERTENSION	CORONARY ARTERY DISEASE
		T2DM IMPROVEMENT[b] 3 years – IG: 27 of 30 (90%), CG: 3 of 14 (21%); *P*< .001 T2DM WORSENING[c] 3 years – IG: 1 of 30 (0.03%), CG: 8 of 14 (57%); *P*< .001	Subgroup: surgery type Baseline – SG: 81.4 (13.3), RYGB: 76.8 (9.4), AGB: 73.3 (18.0); *P*= .50 5 years – SG: 79.7 (10.5), RYGB: 73.1 (10.1), AGB: 68.7 (6.0); *P*= .13 Change – SG: –1.7 (14.1), RYGB: –3.6 (17.0), AGB: –4.7 (20.1); *P*= .93	
Ikramuddin, 2013 DSS Trial Low	N = 120 5 years	T2DM REMISSION[d] Full or partial remission Baseline - N/A I year - N/A 2 years - MT: 0% (0 to 7), RYGB: 36% (16 to 61); *P*< .001 3 years - MT: 0% (9 to 8, RYGB:) 35% (16 to 60); *P*< .001 4 years - MT: 5% (1 to 16), RYGB: 32% (14 to 57); *P*< .001 5 years - MT: 5% (1 to 16), RYGB: 16% (6 to 36); *P*= .003 Full remission Baseline - N/A I year - N/A 2 years - MT: 0% (0 to 7), RYGB: 16% (7 to 33); *P*< .001 3 years - MT: 0% (9 to 8), RYGB: 12% (5 to 28); *P*= .002 4 years - MT: 0% (0 to 8) , RYGB: 11% (4 to 25); *P*= .004 5 years - MT: 0% (0 to 8), RYGB: 7% (2 to 19); *P* = .02 USING INSULIN	% USING ANTIHYPERTENSIVES Baseline - MT: 41 of 56 (73%), RYGB: 38 of 57 (67%) 1 year - MT: 71% (58 to 83), RYGB: 37% (24 to 51) OR, 0.02 (0.00 to 0.13); *P*< .001 2 years - MT: 63% (49 to 76), RYGB: 39% (26 to 53) OR, 0.11 (0.02 to 0.55); *P*= .01 3 years - MT: 61% (45 to 76), RYGB: 38% (25 to 52) OR, 0.14 (0.03 to 0.73); *P*= .03 4 years - MT: 62% (46 to 76), RYGB: 44% (31 to 59) OR, 0.19 (0.03 to 1.08); *P*= .10 5 years - MT: 67% (51 to 81), RYGB: 47% (34 to 61) OR, 0.14 (0.02 to 0.84); *P*= .06 SYSTOLIC BLOOD PRESSURE SBP < 130 mmHg Baseline - MT: 25 of 56 (45%), RYGB: 29 of 57 (51%) 1 year - MT: 85% (71 to 93), RYGB: 89% (78 to 95) OR, 1.52 (0.46 to 4.98); *P*= .49	% WITH LDL-C < 100 mg/dL Baseline - MT: 54% (40 to 67), RYGB: 51% (37 to 64) OR, 0.90 (0.43 to 1.88); *P*= .78 1 year - MT: 74% (58 to 86), RYGB: 84% (70 to 92) OR, 1.77 (0.60 to 5.20); *P*= .30 2 years - MT: 77% (61 to 88), RYGB: 81% (67 to 90) OR, 1.28 (0.43 to 3.79); *P*= .65 3 years - MT: 56% (37 to 73), RYGB: 73% (56 to 85) OR, 2.10 (0.72 to 6.09); *P*= .17 4 years - MT: 54% (34 to 72), RYGB: 69% (52 to 83) OR, 1.95 (0.66 to 5.78); *P*= .23 5 years - MT: 47% (29 to 67), RYGB: 77% (61 to 88) OR, 3.66 (1.22 to 11.00); *P*= .02 TRIGLYCERIDES, mg/dL Baseline - MT: 250 (191 to 309), RYGB: 258 (154 to 362) 1 year - MT: 181 (140 to 222), RYGB: 104 (64 to 144) MD, −77 (−134 to −19); *P*= .01

AUTHOR, YEAR STUDY NAME RISK OF BIAS	TOTAL N FOLLOW-UP	T2DM	HYPERTENSION	CORONARY ARTERY DISEASE
		Baseline - MT: 43% (29 to 56), RYGB: 61% (48 to 74) 1 year MT: 43% (30 to 57), RYGB: 18% (9 to 30) OR, 0.10 (0.02 to 0.54); *P*= .004 2 years - MT: 44% (31 to 59), RYGB: 18% (9 to 30) OR, 0.08 (0.01 to 0.46); *P*= .004 3 years - MT: 45% (30 to 61), RYGB: 15% (6 to 27) OR, 0.04 (0.01 to 0.28); *P*= .001 4 years - MT: 36% (22 to 52), RYGB: 13% (5 to 25) OR, 0.06 (0.01 to 0.41); *P*= .01 5 years - MT: 37% (23 to 53), RYGB: 15% (6 to 27) OR, 0.07 (0.01 to 0.44); *P*= .02 USING NONINSULIN T2DM MEDICATION Baseline - MT: 53 of 56 (95%), RYGB: 49 of 57 (86%) 1 year - MT: 98% (90 to 100), RYGB: 35% (23 to 49) OR, 0.00 (0.00 to 0.02); *P*< .001 2 years - MT: 93% (82 to 98), RYGB: 43% (30 to 57) OR, 0.02 (0.00 to 0.12); *P*< .001 3 years - MT: 84% (70 to 93), RYGB: 42% (29 to 56) OR, 0.06 (0.01 to 0.27); *P*< .001 4 years - MT: 90% (77 to 97), RYGB: 41% (28 to 55) OR, 0.02 (0.00 to 0.14); *P*< .001 5 years - 88% (75 to 96), RYGB: 42% (29 to 56)	2 years - MT: 78% (62 to 88), RYGB: 88% (76 to 95) OR, 2.20 (0.70 to 6.95); *P*= .18 3 years - MT: 56% (38 to 73), RYGB: 79% (64 to 89) OR, 2.90 (0.99 to 8.48); *P*= .05 4 years - MT: 65% (45 to 80), RYGB: 79% (63 to 89) OR, 2.04 (0.68 to 6.13); *P*= .20 5 years - MT: 49% (31 to 68), RYGB: 73% (56 to 85) OR, 2.71 (0.95 to 7.78); *P*= .06 SBP < 140 mmHg Baseline - MT: 39 of 56 (70%), RYGB: 46 of 57 (81%) 1 year - MT: 96% (87 to 99), RYGB: 97% (89 to 99) OR, 1.49 (0.24 to 9.07); *P*= .67 2 years - MT: 92% (81 to 97), RYGB: 97% (88 to 99) OR, 2.38 (0.44 to 12.71); *P*= .31 3 years - MT: 82% (65 to 92), RYGB: 97% (88 to 99) OR, 5.90 (1.17 to 29.76); *P*= .03 4 years - MT: 81% (63 to 92), RYGB: 97% (88 to 99) OR, 6.39 (1.25 to 32.61); *P*= .03 5 years - MT: 86% (69 to 94), RYGB: 92% (80 to 97) OR, 1.92 (0.47 to 7.91); *P*= .37 Mean SBP, mmHg Baseline - MT: 132 (129 to 136) 127 (123 to	2 years - MT: 258 (217 to 299), RYGB: 109 (68 to 149) MD, −149 (−207 to −92); *P*< .001 3 years - MT: 237 (192 to 282), RYGB: 110 (70 to 151) MD, −127 (−187 to −66); *P*< .001 4 years - MT: 196 (150 to 242), RYGB: 111 (70 to 152) MD, −85 (−147 to −23); *P*= .01 5 years - MT: 183 (137 to 228), RYGB: 116 (75 to 157) MD, −66 (−127 to −6); *P*= .03

AUTHOR, YEAR STUDY NAME RISK OF BIAS	TOTAL N FOLLOW-UP	T2DM	HYPERTENSION	CORONARY ARTERY DISEASE
		OR, 0.04 (0.01 to 0.19); *P*< .001 HBA1C HbA1C < 7.0% Baseline - MT: 0%, RYGB: 0% 1 year MT: 29% (15 to 47), RYGB: 83% (67 to 92) OR, 12.29 (3.78 to 39.96); *P*< .001 2 years MT: 18% (9 to 35), RYGB: 85% (69 to 93) OR, 24.42 (7.03 to 84.90); *P*< .001 3 years MT: 4% (5 to 30), RYGB: 58% (38 to 76) OR, 8.89 (2.46 to 32.10); *P*= .001 4 years MT: 6% (2 to 18), RYGB: 59% (39 to 76) OR, 21.51 (5.00 to 92.57); *P*< .001 5 years MT: 14% (6 to 31), RYGB: 55% (36 to 73) OR, 7.51 (2.07 to 27.28); *P*= .002 HbA1C < 6.0% Baseline - MT: 0%, RYGB: 0% 1 year - MT: 5% (2 to 16), RYGB: 45% (26 to 65) OR, 13.94 (3.17 to 61.28); *P*= .001 2 years - MT: 3% (1 to 11), RYGB: 35% (18 to 57) OR, 18.25 (3.32 to 100.4); *P*= .001 3 years - MT: 4% (1 to 16), RYGB: 20% (9 to 39) OR, 5.52 (0.97 to 31.49); *P*= .05 4 years - MT: 3% (1 to 13), RYGB: 15% (6 to 32) OR, 6.51 (0.92 to 46.06); *P*= .06 5 years - MT: 3% (0 to 13), RYGB: 11% (4 to 26)	131) 1 year - MT: 123 (120 to127), RYGB: 115 (112 to 119) MD, -8 (-13 to -3); *P*= .002 2 years - MT: 124 (121 to 127), RYGB: 118 (115 to 122) MD, -6 (-10 to -1); *P*= .02 3 years - MT: 129 (125 to 132), RYGB: 122 (119 to 126) MD, -7 (-12 to -2); *P*= .01 4 years - MT: 129 (125 to 132), RYGB: 122 (118 to 125) MD, -7 (-12 to -2); *P*= .01 5 years - MT: 130 (126 to 134), RYGB: 124 (121 to 127) MD, -6 (-11 to -1); *P*= .02 DIASTOLIC BLOOD PRESSURE Mean DBP, mmHg Baseline - MT: 79 (76 to 82), RYGB: 78 (74 to 81) 1 year - MT: 74 (72 to 76), RYGB: 68 (66 to 71) MD, −6 (−9 to −3); *P*< .001 2 years - MT: 75 (73 to 78), RYGB: 70 (67 to 72) MD, −6 (−9 to −2); *P*= .001 3 years - MT: 77 (74 to 79), RYGB: 71 (69 to 73) MD, −5 (−9 to −2); *P*= .002 4 years - MT: 76 (74 to 79), RYGB: 72 (70 to 74) MD, −4 (−8 to −1); *P*= .01 5 years - MT: 77 (74 to 80), RYGB: 73 (70 to 75) MD, −4 (−8 to −1); *P*= .01	

AUTHOR, YEAR STUDY NAME RISK OF BIAS	TOTAL N FOLLOW-UP	T2DM	HYPERTENSION	CORONARY ARTERY DISEASE
		OR, 4.62 (0.64 to 33.13); *P*= .13 Mean HbA1c % Baseline - MT: 9.6 (1.2), RYGB: 9.6 (1.0) 1 year - MT: 7.8 (7.4 to 8.2), RYGB: 6.3 (5.9 to 6.7) MD, -1.5 (-2.0 to -0.9); *P*< .001 2 years - MT: 8.4 (8.0 to 8.8), RYGB: 6.4 (6.0 to 6.8) MD, -1.9 (-2.5 to -1.4); *P*< .001 3 years - MT: 8.7 (8.3 to 9.1), RYGB: 6.7 (6.3 to 7.1) MD, -2.0 (-2.5 to -1.4) ; *P*< .001 4 years - MT: 9.1 (8.7 to 9.6), RYGB: 7.0 (6.6 to 7.4) MD, -2.2 (-2.7 to -1.6); *P*< .001 5 years - MT: 8.7 (8.3 to 9.1), RYGB: 7.1 (6.7 to 7.5) MD, -1.6 (-2.2 to -1.0) ; *P*< .001		
Courcoulas, 2014 TRIABETES Moderate	N = 61 5 years	T2DM REMISSION[e] Partial or complete remission* Baseline - N/A 1 year - RYGB: 12 of 20 (60%), MT: 0 of 20 (0%); *P*< .001 3 years - RYGB: 8 of 20 (40%), MT: 0 of 20 (0%); *P*= .04 5 years - RYGB: 6 of 20 (30%), MT: 0 of 20 (0%); *P*= .02 Complete remission[f] Baseline - N/A 1 year - RYGB: 4 of 20 (20%), MT: 5 of 20 (25%); *P*= .11 3 years - RYGB: 3 of 20 (15%), MT: 0 of 20 (0%)	SBP, mean (mmHg) Baseline - RYGB: 139.7 (2.74), MT: 132.0 (4.00) 1 year - RYGB: −17.3 (3.58), MT: −10.6 (3.91); *P* = .31 3 years - RYGB: −13.0 (4.09), MT: −0.24 (4.58); *P*= .03 5 years - RYGB: −19.5 (4.76), MT: −1.70 (5.03); *P*= .008 DBP, mean (mmHg) Baseline - RYGB: 81.27 (2.14), MT: 76.28 (2.15) 1 year - RYGB: −7.02 (1.82), MT: −4.36 (1.97); *P* = .17 3 years - RYGB: −5.44 (1.82), MT: −2.87 (2.03); *P*= .32	LDL-C Baseline - RYGB: 117.8 (10.63) 105.5 (7.45) 1 year - RYGB: −13.1 (7.41) −11.2 (8.36); *P* = .44 3 years - RYGB: −0.50 (7.96) −7.66 (9.42); *P* = .54 5 years - RYGB: −9.43 (8.28) −19.3 (8.25); *P* = .39 TRIGLYCERIDES Baseline - RYGB: 169.7 (27.16) 161.2 (24.52) 1 year - RYGB: −107 (10.64) −35.2 (11.88); *P* = .19 3 years - RYGB: −95.3 (17.11) −16.9 (20.53); *P* = .002

AUTHOR, YEAR STUDY NAME RISK OF BIAS	TOTAL N FOLLOW-UP	T2DM	HYPERTENSION	CORONARY ARTERY DISEASE
		5 years - RYGB: 1 of 20 (5%), MT: 0 of 20 (0%) DIABETES MEDICATION USE[g] Baseline - RYGB: 20 of 20 (100%), MT: 20 of 20 (100%) 1 year - RYGB: 4 of 18 (22%), MT: 14 of 14 (100%); *P*< .001 3 years - RYGB: 5 of 18 (28%), MT: 13 of 13 (100%); *P*< .001 5 years - RYGB: 7 of 16 (44%), MT: 14 of 14 (100%); *P*< .001 MEAN HbA1c CHANGE Baseline - RYGB: 8.56 (0.46), MT: 7.03 (0.17) 1 year - RYGB: −1.88 (0.35), MT: −0.21 (0.40); *P*< .001 3 years - RYGB: −1.42 (0.34), MT: +0.21 (0.40); *P*< .001 5 years - RYGB: −1.46 (0.39), MT: +0.77 (0.42); *P*< .001	5 years - RYGB: −6.92 (2.42), MT: −0.60 (2.56); *P*= .07	5 years - RYGB: −78.0 (13.74) −9.33 (14.75); *P* < .001
Liang, 2013 Moderate	N = 108 1 year	DIABETES REMISSION AT 1 YEAR RYGB: 28 of 31 (90%) MT: 0 of 36 (0%) MT+E: 0 of 34 (0%) RYGB vs. MT: *P*< .01 RYGB vs. MT+E: *P*< .05 HBA1C Baseline - RYGB: 10.47 (1.17), MT: 10.88 (1.40), MT+E: 10.52 (1.49) 1 year - RYGB: 5.98 (0.30)*, MT: 8.14 (0.27), MT+E: 7.10 (0.26) RYGB vs. MT: *P*< .05 RYGB vs. MT+E: *P*< .05	SBP, mmHg Baseline - RYGB: 160.8 (7.8), MT: 156.6 (11.8), MT+E: 159.9 (8.6) 1 year - RYGB: 126.5 (4.9), MT: 132.4 (5.7)*, MT+E: 130.8 (5.3) Between group comparisons NR	LDL-C, mmol/L Baseline - RYGB: 3.84 (0.63), MT: 3.72 (0.42), MT+E: 3.72 (0.64) 1 year - RYGB: 1.97 (0.45)*, MT: 3.69 (0.48), MT+E: 2.68 (0.33) RYGB vs. MT: *P*< .05 RYGB vs. MT+E: *P*< .05 TRIGLYCERIDES, mmol/L Baseline - RYGB: 3.39 (1.18), MT: 3.49 (1.32), MT+E: 3.56 (1.08) 1 year - RYGB: 1.60 (0.13)*, MT: 3.50 (1.51), MT+E: 2.79 (0.60)

AUTHOR, YEAR STUDY NAME RISK OF BIAS	TOTAL N FOLLOW-UP	T2DM	HYPERTENSION	CORONARY ARTERY DISEASE
				RYGB vs. MT: *P*< .05 RYGB vs. MT+E: *P*< .05
Schauer, 2012 STAMPEDE Low	N = 150 5 years	MEAN HBA1C (participants with BMI < 35) Baseline - Surgery (n = 32): 9.5 (9.1), MT: (n = 17): 8.8 (8.9) 1 year - Surgery: 6.6 (6.7), MT: 7.5 (6.9) 2 years - Surgery: 6.8 (6.8), MT: 7.7 (7.4) 3 years - Surgery: 7.1 (6.7), MT: 8.2 (7.9); *P* = .008 4 years - Surgery: 7.2 (6.8), MT: 8.8 (8.6) 5 years - Surgery: 7.3 (7.1), MT: 8.8 (8.0); *P* < .001	NR	NR
Cohen, 2020 MOMS Moderate	N = 100 2 years	HBA1C Baseline - RYGB: 8.80 (1.86), MT: 8.94 (1.96) 2 years - RYGB: 6.18 (5.80 to 6.56), MT: 6.72 (6.34 to 7.09) Reduction - RYGB: -2.6%, MT: -2.2% MD, −0.54 (−1.07 to −0.004); *P*= .05 HbA1c ≤ 7.0%[h] RYGB: 83.0% (72.4 to 93.60) MT: 70.2% (56.9 to 83.6) MD, 12.7 (−4.3 to 29.7); *P*= .16 HbA1c ≤ 6.5%[i] RYGB: 70.9% (57.8 to 84.0) MT: 50.5% (36.3 to 64.8) MD, 20.4 (1.03 to 39.7); *P*= .05 HbA1c ≤ 6.0%[j] RYGB: 44.5% (29.8 to 59.2) MT: 24.4% (12.3 to 36.7) MD, 20.1 (1.00 to 39.1); *P*= .05	MEAN BP (mmHg) SBP Baseline - RYGB: 141.5 (17.2), MT: 137.3 (15.5) 2 years - RYGB: 130.8 (125.9 to 135.6), MT: 129.9 (125.1 to 134.6) MD, 0.91 (−5.88 to 7.70); *P*= .79 DBP Baseline - RYGB: 88.1 (12.7), MT: 85.7 (8.0) 2 years - RYGB: 79.7 (76.6 to 82.8), MT: 82.5 (79.5 to 85.5) MD, −2.80 (−7.12 to 1.53); *P*= .21 SBP < 130 mm Hg, % RYGB: 32.5 (18.6 to 46.5) MT: 37.8 (23.6 to 51.9) MD, −5.2 (−2.5 to 14.7); *P*= .61 DBP < 80 mm Hg, % RYGB: 28.0 (14.5 to 41.4) MT: 20.1 (8.40 to 31.9) MD, 7.8 (−9.98 to 25.6); *P*= .39	LDL-C Mean LDL-C, mg/dL Baseline - RYGB: 102 (36.5), MT: 108.6 (41.1) 2 years - RYGB: 85.7 (76.3 to 95.0), MT: 101.6 (92.2 to 110.9) MD, −15.9 (−29.1 to −2.65); *P*= .02 LDL-C level <100 mg/dL, % RYGB: 72.6 (59.4 to 85.2) MT: 51.2 (37.1 to 66.5) MD, 20.5 (0.9 to 40); *P*= .05 TRIGLYCERIDES Mean triglycerides, mg/dL Baseline - RYGB: 195 (145 to 293), MT: 214 (150 to 334) 2 years - RYGB: 107.8 (90.6 to 140.3), MT: 180.7 (157.7 to 207.2) MD, −67 (−102.1 to −31.9); *P*< .001 Triglyceride levels < 150 mg/dL, % RYGB: 80.0 (70.2 to 92.6)

AUTHOR, YEAR STUDY NAME RISK OF BIAS	TOTAL N FOLLOW-UP	T2DM	HYPERTENSION	CORONARY ARTERY DISEASE
		DIABETES MEDICATIONS Median number of metabolic medications at 24 months RYGB: 1 (IQR, 1-3) MT: 6 (IQR, 3-9) *P*< .001 Metformin use at 24 months RYGB: 35of 46 (76.1%) MT: 45 of 46 (97.8%) *P*= .004 Insulin use at 24 months RYGB: 5 of 46 (10.9%) MT: 25 of 46 (54.3% *P*< .001		MT: 41.9 (26.9 to 55.1) MD, 40.4 (22.4 to 58); *P*< .001 CVD MEDICATION USE Beta-blocker use at 24 months RYGB: 6 of 46 (13.0%) MT: 10 of 46 (21.7%) *P*= .41 Calcium channel blocker use at 24 months RYGB: 5 of 46 (10.9%) MT: 10 of 46 (21.7%) *P*= .26 ARB or ACE-inhibitor use at 24 months RYGB: 41 of 46 (89.1%) MT: 40 of 46 (87.0%) *P*= .99

Notes. [a] T2DM was defined based on the ADA criteria: (1) fasting glucose ≥ 126 mg/dL, (2) glucose ≥ 200 at 120 minutes after 75 g oral glucose load, or (3) HbA1c ≥ 6.5%. Diabetes remission was defined as no longer meeting the ADA criteria for T2DM, without the use of diabetes medications. [b] T2DM improvement was defined as reduction in medication use. [c] T2DM worsening was defined as an increase in medication use and/or conversion to insulin from an oral agent or an increase in HbA1C on the same medication. [d] Full diabetes remission is defined as an HbA1c level of less than 6.0% at the 4- and 5-year visits and no use of antihyperglycemic medication at either visit. Partial diabetes remission definition replaced the HbA1c level of 6.0% with 6.5% at the same time points. [e] Missing data at follow-up were assumed to be no remission. [f] Partial remission = no use of antidiabetics, HbA1c level of < 6.5%, and fasting plasma glucose level of ≤ 125 mg/dL
Complete remission = no use of antidiabetics, hemoglobin A1c. Remission (partial or complete) for at least 2 consecutive years. [g] Insulin or other medications (e.g., metformin). [h] ADA definition for good glycemic control. [i] ADA definition for partial T2DM remission. [j] ADA definition for full T2DM remission.
Abbreviations. ACE: angiotensin-converting enzyme; ADA: American Diabetes Association; AGB: adjustable gastric banding; ARB: angiotensin receptor blockers; BMI: body mass index; BP: blood pressure; CG: control group; CVD: cardiovascular disease; DBP: diastolic blood pressure; DSS: diabetes surgery study; HbA1c: glycated hemoglobin; HDL: high-density lipoprotein; HTN: hypertension; IG: intervention group; LDL-C: low density lipoprotein cholesterol; MD: mean difference; mg/dL: milligrams per deciliter; mmHg: millimeters of mercury; mmol/L: millimoles per liter; MOMS: Microvascular Outcomes after Metabolic Surgery; MT: medical therapy; MT+E: medical therapy and exenatide; N/A: not applicable; NR: not reported; OR: odds ratio; RYGB: Roux-en-Y gastric bypass; SBP: systolic blood pressure; SG: sleeve gastrectomy; STAMPEDE: Surgical Treatment and Medications Potentially Eradicate Diabetes Efficiently; T2DM: type 2 diabetes; TRIABETES: Randomized Trial to Compare Surgical and Medical Treatments for Type 2 Diabetes.

Table D8. Additional Study Characteristics of Included Adolescent Cohort Studies

AUTHOR, YEAR STUDY NAME RISK OF BIAS	TOTAL N FOLLOW-UP	POPULATION	INCLUSION CRITERIA	EXCLUSION CRITERIA	CONTROL GROUP DESCRIPTION	% FEMALE	% NON-WHITE
Inge, 2018 Teen-LABS/TODAY High	N = 93 2 years	Severely obese adolescents with type 2 diabetes	Teen-LABS participants with type 2 diabetes at the time of surgery TODAY participants (irrespective of treatment group assignment) were frequency matched to the 30 Teen-LABS participants with type 2 diabetes using the following matching characteristics: baseline age (13-18 years), race, sex, ethnicity, and baseline BMI (> 35)	NR	Adolescents (ages 10 to 17 years) with T2DM randomized to (1) metformin alone, (2) metformin combined with rosiglitazone, or (3) a lifestyle-intervention program focusing on weight loss through eating and activity behaviors. The 63 included participants in this analysis were from all 3 medically treated arms.	Teen-LABS: 70% TODAY: 44% *P*= .03	Teen-LABS: 40% TODAY: 29% *P*= .06
Inge, 2014 Teen-LABS Moderate	N = 242 3 years	Severely obese adolescents undergoing weight loss surgery	(1) Subjects ≤ 19 years of age who are approved by clinical team and payor to undergo bariatric surgery by a Teen-LABS-certified surgeon, (2) primary caregivers of adolescent participants (for their weight, height, and demographic variables only) An adolescent was not excluded if their caregiver declined participation	(1) Informed consent not obtained from adolescent or the adolescent's legally authorized representative, (2) unable to communicate with local study staff	NA	75.6%	28.1%
Inge, 2017 FABS-5+ High	N = 58 5 to 12 years	Individuals who underwent RYGB for	Age ≤ 21 years at time of bariatric surgery	(1) Inability to complete self-report forms due to developmental delay, or (2)	NA	64%	14%

AUTHOR, YEAR STUDY NAME RISK OF BIAS	TOTAL N FOLLOW-UP	POPULATION	INCLUSION CRITERIA	EXCLUSION CRITERIA	CONTROL GROUP DESCRIPTION	% FEMALE	% NON-WHITE
		clinically severe obesity at 13 to 21 years of age		death prior to long-term study visit			
Olbers, 2012 AMOS Moderate	N = 161 5 years	Adolescents (13–18 years) with a BMI range 36 to 69 kg/m2	Adolescent surgery group: (1) Age 13–18 years, (2) BMI ≥ 40 or ≥ 35 kg/m^2 with comorbidity (type 2 diabetes, sleep apnea, joint pain, and high blood lipids), (3) pubertal Tanner stage > III and passed peak height growth velocity, (4) participation for ≥ 1 year in a comprehensive weight loss program Adult surgery group: The inclusion age was 35 to 45 years at surgery; all other inclusion and exclusion criteria were similar to adolescents Adolescent MT group: Adolescent controls were selected as conventional treatment comparisons using the same inclusion and exclusion criteria as for the adolescents undergoing surgery; the date of surgery for a surgical patient coincided in time with baseline weight and height registration for a control within ±1 month	All groups: (1) Insufficiently treated psychiatric disorder, (2) ongoing drug abuse, (3) obesity due to syndromes or monogenic disease as clinically assessed (50% had the *MC4* receptor sequenced) or brain injury	Adolescent medical therapy controls were matched from the Swedish Childhood Obesity Treatment Register (BORIS) at the end of the recruitment period of surgical subjects. Controls were selected so that the mean values of the matching variables (BMI, age, and gender) in the control group moved as much as possible in the direction of the mean values in the surgically treated adolescents. The control group was treated with conventional Swedish medical obesity standards. This treatment mainly consists of individualized or family-based counseling and cognitive behavior therapy concerning diet and physical activity. Low-calorie diets and drugs (metformin, orlistat, or sibutramin) were prescribed if found clinically indicated by the treating pediatrician.	RYGB: 65% MT: 57%	NR

Abbreviations. AMOS: Adolescent Morbid Obesity Surgery; BMI: body mass index; FABS-5+: Follow-up of Adolescent Bariatric Surgery at 5 Plus years; kg/m^2: kilograms per meters squared; MT: medical therapy; NA: not applicable; NR: not reported; RYGB: Roux-en-Y gastric bypass; T2DM: type 2 diabetes mellitus; Teen-LABS: Teen–Longitudinal Assessment of Bariatric Surgery; TODAY: Treatment Options of Type 2 Diabetes in Adolescents and Youth.

Table D9. Outcomes in Adolescent Studies: Weight Change, Quality of Life, Harms

AUTHOR, YEAR STUDY NAME RISK OF BIAS	TOTAL N FOLLOW-UP	WEIGHT CHANGE	QUALITY OF LIFE	HARMS
Inge, 2018 Teen-LABS/TODAY High	N = 93 2 years	BMI (kg/m2) Teen-LABS - BL: 51.8, 2yr: 36.3; MD, −15.1 (−17.3 to −13.0) TODAY - BL: 36.7, 2yr: 37.9; MD, +1.3 (−0.2 to 2.8) *P*< .001 WEIGHT (kg) Teen-LABS - BL: 155.1, 2yr: 110.9; MD, −44.2 (−50.6 to −37.8) TODAY - BL: 117.4, 2yr: 123.2; MD, +5.8 (1.4 to 10.2) *P*< .001	NR	HOSPITALIZATIONS Teen-LABS - 7 of 30 (23%) experienced complications that required subsequent operation and/or readmission that were related or possibly related (e.g., cholecystectomy for gallstones) to their prior bariatric surgery - 5 of 30 (17%) required subsequent hospitalization for observation or other interventions (nonabdominal operations) that were unrelated to the prior bariatric operation TODAY - 2 of 63 (3%) participants required hospital admission; the reasons for these admissions included calf swelling and ankle edema in one TODAY participant, and knee pain and anemia in another
Inge, 2014 Teen-LABS Moderate	N = 242 3 years	MEAN WEIGHT (kg) Overall (n = 228) Baseline: 149 (145 to 153) 3 years: 108 (103 to 113) Absolute change: −41 (−45 to −37); *P*< .001 RYGB (n = 161) Baseline: 151 (146 to 156) 3 years: 109 (104 to 115) Absolute change: −42 (−47 to −38); *P*< .001 SG (n = 67) Baseline: 144 (136 to 152) 3 years: 105 (96 to 113) Absolute change: −38 (−44 to −31); *P*< .001	WEIGHT-RELATED QOL (IWQoL-Kids, mean score) Overall (n = 233) Baseline: 63 (61 to 65) 3 years: 83 (81 to 86) Absolute change: +20.0 (17.4 to 22.7); *P* < .001 Percent change: 42.6% (32.6 to 52.5); *P*< .001 RYGB (n = 159) Baseline: 61.9 (58.9 to 64.8) 3 years: 84.0 (81.1 to 86.9) Absolute change: +22.3 (18.9 to 25.8) Percent change: 50.5% (36.6 to 64.4)	POSTOPERATIVE COMPLICATIONS (≤ 30 days) Major (i.e., life-threatening) Complications Overall: 20 events in 19 of 242 patients (7.9%) - RYGB rate: 9.3% (5.3 to 14.9) - SG rate: 4.5% (0.9 to 12.5) - AGB rate: 7.1% (0.2 to 33.9) Minor Complications Overall: 47 events in 36 of 242 patients (14.9%) - RYGB rate: 16.8% (11.4 to 23.5) - SG rate: 11.9% (5.3 to 22.2) - AGB rate: 7.1% (0.2 to 33.9) LT ADVERSE EVENTS (> 30 days to 3 years) Intra-abdominal Operations

AUTHOR, YEAR STUDY NAME RISK OF BIAS	TOTAL N FOLLOW-UP	WEIGHT CHANGE	QUALITY OF LIFE	HARMS
		AGB (n = 11) Baseline: NR 3 years: NR Absolute change: -10.4 (-26.5, 5.7) % WEIGHT CHANGE, 3 years Overall: −27% (−29 to −25); *P*< .001 RYGB: −28% (−30 to −25); *P*< .001 SG: 26% (−30 to −22); *P*< .001 AGB: -8.3% -19.8, 3.2 MEAN BMI (kg/m2) Overall Baseline: 53 (51 to 54) 3 years: 38 (37 to 40) Absolute change: −15 (−16 to −13) Percent change: −28% (−30 to −25) 5-year median: NR RYGB (n = 161) Baseline: 54 (52 to 55) 3 years: 39 (37 to 41) Absolute change: −15 (−17 to −14) Percent change: −28% (−31 to −25) 5-year median (n = 134): 39.0 (32.0 to 48.2); *P* < .001 SG (n = 67) Baseline: 50 (48 to 52) 3 years: 37 (34 to 39) Absolute change: −13 (−15 to −11) Percent change: −26% (−30 to −22) 5-year median (n = 49): 37.0 (32.1 to 40.8); *P*<	SG (n = 62) Baseline: 63.9 (59.9 to 67.9) 3 years: 82.0 (77.0 to 87.0) Absolute change: +16.3 (12.0 to 20.7) Percent change: 27.8% (19.5 to 36.1) AGB (n = 12) Baseline: 72.3 (67.8 to 81.8) 3 years: 77.4 (62.2 to 92.5) Absolute change: +8.2 (-1.2 to 20.7) Percent change: 11.7% (-3.3 to 26.7)	Overall: 47 events in 30 of 228 patients (13%) - Rate: 22.3 (16.8 to 29.7)/300py RYGB: 38 events in 23 of 161 patients (14%) - Rate: 25.0 (18.2 to 34.4)/300py SG: 9 events in 7 of 67 patients (10%) - Rate: 15.4 (8.0 to 29.5)/300py Endoscopic Procedures Overall: 48 events in 29 of 228 patients (13%) - Rate: 22.8 (17.2 to 30.3)/300py RYGB: 41 events in 24 of 161 patients (15%) - Rate: 27.0 (19.9 to 36.6)/300py SG: 7 events in 5 of 67 patients (7%) - Rate: 12.0 (5.7 to 25.1)/300py NUTRITIONAL ABNORMALITIES Low Vitamin B12 (<145 pg/mL) Overall - Baseline: 1 of 222, < 1% (0–1) - 3 years: 13 of 160, 8% (4–12); *P*= .005 - 5 years: NR RYGB - Baseline: 1 of 159, 1% (0–2) - 3 years: 10 of 121, 8% (3–13); *P*= .01 - 5 years: 14 of 122, 12% (6–17); *P*= .06 SG - Baseline: 0 of 63, 0% - 3 years: 3 of 39, 8% (0–16); *P*= NR - 5 years: 3 of 42, 7% (0–15); *P*= NR

AUTHOR, YEAR STUDY NAME RISK OF BIAS	TOTAL N FOLLOW-UP	WEIGHT CHANGE	QUALITY OF LIFE	HARMS
		.001 AGB (n = 11) Baseline: NR 3 years: NR Absolute change: -3.8 (-9.9 to 2.3) Percent change: -8.1% (-19.9 to 3.6) 5-year median: NR Subgroup: Percent BMI change by age group at 5 years 13–15 years: -22.2% (-26.2% to -18.2%) 16–19 years: -24.6% (-27.7% to -22.5%) *P*= .59 CATEGORICAL BMI CHANGE, 3 years Overall Sample ≥ 40% reduction: 38 of 172 (22%) 30-39% reduction: 40 of 172 (23%) 20-29% reduction: 43 of 172 (25%) > 0-19% reduction: 48 of 172 (28%) Exceeded baseline BMI: 4 of 172 (2%)		Low Vitamin D (< 20.1 ng/mL) Overall - Baseline: 83 of 223, 37% (31–44) - 3 years: 74 of 172, 43% (36–50); *P*= .37 - 5 years: NR RYGB - Baseline: 71 of 159, 45% (37–52) - 3 years: 61 of 128, 48% (39–56); *P*= .64 - 5 years: 61 of 119, 51% (42–60); *P*=.82 SG - Baseline: 12 of 64, 19% (9–28) - 3 years: 13 of 44, 30% (16–43); *P*= .36 - 5 years: 14 of 42, 33% (19–48); *P*= .70 Low Ferritin (female: < 10 µg/L, male: < 20 µg/L) Overall - Baseline: 11 of 225, 5% (2–8) - 3 years: 98 of 171, 57% (50–65); *P*< .001 - 5 years: NR RYGB - Baseline: 4 of 160, 2% (<1–5) - 3 years: 83 of 127, 65% (57–74); *P*< .001 - 5 years: 87 of 122, 71% (63–79); *P*< .001 SG - Baseline: 7 of 65, 11% (3–18) - 3 years: 15 of 44, 34% (20–48); *P*= .01 - 5 years: 19 of 42, 45% (30–60); *P*= .002 Low Vitamin A (< 301 µg/L) Overall - Baseline: 13 of 221, 6% (3–9) - 3 years: 22 of 170, 13% (8–18); *P*= .02 - 5 years: NR

AUTHOR, YEAR STUDY NAME RISK OF BIAS	TOTAL N FOLLOW-UP	WEIGHT CHANGE	QUALITY OF LIFE	HARMS
				RYGB - Baseline: 9 of 158, 6% (2–9) - 3 years: 20 of 126, 16% (9–24); *P*= .008 - 5 years: 19 of 121, 16% (9–22); *P*= .09?? SG - Baseline: 4 of 63, 6% (<1–12) - 3 years: 2 of 44, 5% (0–11) ; *P*= .93 - 5 years: 3 of 43, 7% (0–15); *P*= .99 Multiple Nutritional Deficiencies (BL vs. 5 years) ≥ 2 deficiencies RYGB: 12% vs. 59%; *P*< .0001 SG: 6% vs. 27%; *P*= .09 ≥ 3 deficiencies RYGB: 3% vs. 19%; *P*= .0005 SG: 2% vs. 2.3%; *P*= NR
Inge, 2017 FABS-5+ High	N = 58 5 to 12 years	BMI (kg/m2) Baseline: 58.5 (55.8 to 61.3) 1 year Mean: 36.0 (33.8 to 38.1) Absolute change: −22.6 (−24.1 to −21.1) Percent change: −38.6% (−40.5 to −36.7) LT follow-up: Mean: 41.5 (38.4 to 44.7) Absolute change: −17.0 (−19.2 to −14.8) Percent change: −29.3% (−33.0 to −25.6) WEIGHT (kg) Baseline: 170.8 (161.1 to 180.6) 1 year Mean: 105.4 (98.2 to 112.7) Absolute change: −65.6 (−70.4 to −60.9) Percent change: −38.4% (−40.3 to −36.5)	NR	NUTRITIONAL DEFICIENCIES at LT follow-up Vitamin B12 Total: 8 of 50 (16.0%) Female: 5 of 35 (14.3%) Male: 3 of 15 (20.0%) Vitamin D Total: 39 of 50 (78.0%) Female: 27 of 35 (77.1%) Male: 12 of 15 (80.0%) Ferritin Total: 32 of 51 (62.8%) Female: 23 of 35 (65.7%) Male: 9 of 16 (56.3%) ADVERSE EVENTS

AUTHOR, YEAR STUDY NAME RISK OF BIAS	TOTAL N FOLLOW-UP	WEIGHT CHANGE	QUALITY OF LIFE	HARMS
		LT follow-up: Mean: 120.9 (111.0 to 130.9) Absolute change: −50.0 (−56.8 to −43.1) Percent change: −29.5% (−33.2 to −25.7)		Obstetric - 17 (45.9%); Event rate: 85.9 (58.0 to 127.1) Gynecologic - 7 (18.9%); Event rate: 68.7 (44.3 to 106.5) Upper Endoscopy - 13 (22.4%); Event rate: 62.4 (43.3 to 89.7) Cholecystectomy - 12 (20.7%); Event rate: 25.8 (14.7 to 45.4) Excess skin removal - 8 (13.8%); Event rate: 23.7 (13.1 to 42.7) Blood transfusion - 2 (3.4%); Event rate: 6.5 (2.1 to 20.0) Colonoscopy - 2 (3.4%); Event rate: 6.5 (2.1 to 20.0) Parenteral infusion for micronutrient deficiency - 2 (3.4%); Event rate: 6.5 (2.1 to 20.0) Repair GI perforation - 3 (5.2%); Event rate: 6.5 (2.1 to 20.0) Appendectomy - 2 (3.4%); Event rate: 4.3 (1.1 to 17.2) Exploratory laparoscopy/laparotomy - 2 (3.4%); Event rate: 4.3 (1.1 to 17.2)

AUTHOR, YEAR STUDY NAME RISK OF BIAS	TOTAL N FOLLOW-UP	WEIGHT CHANGE	QUALITY OF LIFE	HARMS
				*Event rate = # of events per 1000 person-years (i.e., 100 subjects followed for 10 years).
Olbers, 2012 AMOS Moderate	N = 161 5 years	BMI OUTCOMES Mean BMI (kg/m²) Baseline - RYGB: 45·5 (6·1), MT: 42·2 (5) 5 years - RYGB: 32.3 (6.3), MT: 44.6 (9.5) Within group: RYGB: MD, −13.1 (−14.5 to −11.8); *P*< .001 MT: +3.3 (+1.1 to +4.8); *P*value NR Between group: MD, −12.26 (−15.2 to − 9.3); *P* < .001 BMI < 35 kg/m² at 5 years RYGB: 72% MT: 7% BMI < 30 kg/m² at 5 years RYGB: 37% MT: 3% BODY WEIGHT OUTCOMES Mean body weight (kg) Baseline - RYGB: 133 (22), MT: 124 (21) 5 years - RYGB: 96.0 (22.2), MT: 133.3 (28.9) Within group (RYGB): MD, −36·8 (−40·9 to −32·8); *P*< .001 Between group: MD, −37.21 (−46.4 to − 28.0); *P*< .001 Weight loss at 5 years by % category ≥ 20% total body weight loss RYGB: 70% MT: 2%	WEIGHT-SPECIFIC QOL (OP-14 scale) Baseline - RYGB: 49·1 (26·4) 5 years - RYGB: 37·4 (28·8), MT: 45·1 (34·9) Within group (RYGB): MD, -13·0 (-19·6 to -6·4); *P*< .001* Between group: MD, -7·9 (-20·7 to 4·5); *P*= .22 GENERIC QOL (SF-36 scores) Physical Functioning Baseline - RYGB: 72·1 (22·4) 5 years - RYGB: 84·4 (21·2), MT: 75·9 (23·4) Within group (RYGB): MD, 13·5 (8·1 to 19·0); *P* < .001* Between group: MD, 8·8 (0·0 to 17·6); *P*= .05* Physical Role Functioning Baseline - RYGB: 75·9 (24·6) 5 years - RYGB: 83·9 (25·2), MT: 71·3 (30·9) Within group (RYGB): MD, 11·2 (4·0 to 18·3); *P* = .002* Between group: MD, 13·5 (2·2 to 24·8); *P*= .02* General Health Perceptions Baseline - RYGB: 53·8 (23·4) 5 years - RYGB: 64·8 (22·7), MT: 56·2 (26·6) Within group (RYGB): MD, 12·4 (6·5 to 18·3); *P* < .001* Between group: MD, 8·7 (-1·1 to 18·5); *P*= .08 Physical Component Score Baseline - RYGB: 44·1 (9·5)	NUTRITIONAL DEFICIENCIES Vitamin D Insufficiency (< 50 nmol/L) Baseline - RYGB: 16 of 33 (49%); MT: not reported 5 years - RYGB: 46 of 73 (63%), MT: 20 of 35 (57%); *P*= .67 Vitamin D Deficiency (< 30 nmol/L) Baseline - RYGB: 4 of 33 (12%), MT: not reported 5 years - RYGB: 20 of 73 (27%), MT: 7 of 35 (20%); *P*= .48 Low Vitamin B12 (<145 pmol/L) Baseline - RYGB: 1 of 74 (1%), MT: not reported 5 years - RYGB: 16 of 73 (66%), MT: 2 of 31 (6%); *P*= .05 Low Ferritin (< 45 pmol/L (boys); < 22·5 pmol/L (girls)/Iron (< 9 µmol/L) Levels Baseline - RYGB: 18 of 76 (24%), MT: not reported 5 years - RYGB: 51 of 77 (66%), MT: 12 of 42 (29%); *P*< .001 Anemia (females: Hg < 120 g/dL; males: Hg < 130 g/dL) Baseline - RYGB: 8 of 78 (10%), MT: not reported 5 years - RYGB: 25 of 77 (32%), MT: 3 of 42 (7%); *P*= .001

AUTHOR, YEAR STUDY NAME RISK OF BIAS	TOTAL N FOLLOW-UP	WEIGHT CHANGE	QUALITY OF LIFE	HARMS
		10 to 19% total weight loss RYGB: 18% MT: 8% 0 to 9% total weight loss RYGB: 10% MT: 21% Weight gain RYGB: 2% MT: 69%	5 years - RYGB: 48·3 (10·3), MT: 45·7 (10·0) Within group (RYGB): MD, 5·2 (2·5 to 7·9); *P* < .001 Between group: MD, -2·9 (-6·9 to 1·0); *P* = .14 No Significant Differences (within- or between-group) - Bodily pain - Vitality - Mental health - Social role functioning - Emotional role functioning - Mental component score	ADVERSE EVENTS (RYGB adolescents only) Serious Adverse Events (events involving hospitalization) - Any surgery: 20 of 81 (21 procedures; 25%) - Laparoscopy (bowel obstruction): 11 of 81 (14%) - Cholecystectomy (gall stones): 9 of 81 (11%) - Laparotomy (abdominal pain): 1 of 81 (1%) - Blood transfusion (severe anemia): 2 of 81 (2%) - Overnight observation (abdominal pain): 9 of 81 (11%) - Psychiatric assessment (drug abuse): 6 of 81 (7%) - NO DEATHS OCCURRED Other Adverse Events (not requiring hospitalization) - Anemia: 25 of 77 (32%) - Low vitamin D: 2 of 73 (3%) - Low vitamin B12: 16 of 73 (22%) - Low ferritin or iron: 51 of 77 (66%) - Assessment for eating disorder: 1 of 81 (1%)

Abbreviations. AGB: adjustable gastric banding; AMOS: Adolescent Morbid Obesity Surgery, BL: baseline; BMI: body mass index; FABS-5+: Follow-up of Adolescent Bariatric Surgery at 5 Plus years; kg: kilograms; kg/m^2: kilograms per meters squared; LT: long term; MD: mean difference; MT: medical therapy; nmol/L: nanomoles per liter; OP-14 Scale: Obesity-related Problems 14 Scale; QoL: quality of life; RYGB: Roux-en-Y gastric bypass; SF-36: short form-36 survey; SG: sleeve gastrectomy; Teen-LABS: Teen–Longitudinal Assessment of Bariatric Surgery; TODAY: Treatment Options of Type 2 Diabetes in Adolescents and Youth.

Table D10. Outcomes in Adolescent Studies: T2DM, Hypertension, Coronary Artery Disease, Joint Arthropathy

AUTHOR, YEAR STUDY NAME RISK OF BIAS	TOTAL N FOLLOW-UP	T2DM	HYPERTENSION	CORONARY ARTERY DISEASE	JOINT ARTHROPATHY
Inge, 2018 Teen-LABS/TODAY High	N = 93 2 years	HbA1c (%) Teen-LABS - BL: 6.8, 2yr: 5.5; MD, −1.3 (−2.2 to −0.5) TODAY - BL: 6.4, 2yr: 7.8; MD, +1.4 (0.9 to 1.9) *P*< .001 HbA1c RANGE Normal (< 5.7%) Teen-LABS - BL: 10 of 30 (34%) , 2yr: 15 of 30 (74%) TODAY - BL: 17 of 63 (28%), 2yr: 7 of 63 (13%) Normal to Prediabetes (< 6.5%) Teen-LABS - 2yr: 19 of 30 (94%) TODAY - 2yr: 20 of 63 (38%) *P*= .003 Diabetes (≥ 6.5%) Teen-LABS - NR TODAY - BL: 23 of 63 (35%), 2yr: 34 of 63 (62%) FASTING PLASMA GLUCOSE (mg/dL) Teen-LABS - BL: 125.1, 2yr: 89.3; MD, −35.8 (−53.9 to −17.7) TODAY - BL: 119.2, 2yr: 151.8; MD, +32.6 (21.1 to 44.2) *P*< .001	SYSTOLIC BP (mmHg) Teen-LABS - BL: 122.9, 2yr: 122.0; MD, −0.8 (−6.3 to 4.7) TODAY - BL: 119.3, 2yr: 120.8; MD, +1.5 (−1.4 to 4.5) DIASTOLIC BP (mmHg) Teen-LABS - BL: 75.4, 2yr: 73.3; MD, −2.1 (−6.2 to 2.0) TODAY - BL: 71.3, 2yr: 71.4; MD, +0.1 (−2.6 to 2.8) ELEVATED BP[a] Teen-LABS - BL: 20 of 30; 66.7% (45.3 to 82.9) - 2yr: 5 of 30; 18.6% (6.8 to 41.6) TODAY - BL: 13 of 63; 20.6% (11.6 to 34.1), - 2yr: 23 of 63; 41.9% (27.7 to 57.6)	LDL-C LEVEL (mg/dL) Teen-LABS - BL: 92.0, 2yr: 85.2; MD, −6.8 (−22.2 to 3.9) TODAY - BL: 89.0, 2yr: 82.8; MD, −6.2 (−15.4 to 2.9) TRIGLYCERIDES (mg/dL) Teen-LABS - BL: 108.8, 2yr: 88.1; MD, −20.7 (−24.4 to −17.4) TODAY - BL: 100.7, 2yr: 116.1; MD, +15.4 (10.4 to 21.8)	NR
Inge, 2014 Teen-LABS Moderate	N = 242 3 years	T2DM REMISSION[b], 3 years Observed remission Total: 19 of 20; 95% (85 to 100)	ELEVATED BP REMISSION[d] 3 years Observed remission	NR	REPORTED MUSCULOSKELETAL PAIN DURING OR AFTER

AUTHOR, YEAR STUDY NAME RISK OF BIAS	TOTAL N FOLLOW-UP	T2DM	HYPERTENSION	CORONARY ARTERY DISEASE	JOINT ARTHROPATHY
		RYGB: 17 of 18; 94% (84 to 100) SG: 2 of 2; 100% (100 to 100) Modeled remission rate Total: 90% (65 to 98) RYGB: 94% (66 to 99) SG: 68% (7 to 99) Subgroup analysis: T2DM remission by age group Baseline prev of T2DM 13–15 years: 7 (11%) 16–19 years: 22 (14%) 5-year remission 13–15 years: 6 (83%) 16–19 years: 15 (87%) RR, 0.86 (95% CI, 0.74 to 0.99); *P*= .046 PREDIABETES REMISSION[c], 3 years Observed remission Total: 13 of 17; 76% (56 to 97) RYGB: 11 of 15; 74% (51 to 96) SG: 2 of 2; 100% (100 to 100) Modeled remission rate Total: 77% (48 to 92) RYGB: 94% (66 to 99) SG: not estimable	Total: 56 of 76; 74% (64 to 84) RYGB: 47 of 60; 78% (68 to 89) SG: 9 of 16; 56% (32 to 81) Modeled remission rate Total: 73% (60 to 83) RYGB: 78% (64 to 88) SG: 53% (27 to 78) Subgroup analysis: HTN remission by age group Baseline prev of HTN 13–15 years: 18 of 66 (29%) 16–19 years: 59 of 162 (37%) 5-year remission 13–15 years: 77% (57.1% to 100.0%) 16–19 years: 67% (54.5% to 81.5%) - After adjustment, postoperative HTN remission was similar by age group (*P*= .84)		400 meter WALK TEST (vs. baseline) Baseline: 25% 1 year: 8%; RR: 0.62 (95% CI, 0.51-0.71); *P*< .01 2 years: 12%; RR: 0.47 (95% CI, 0.37-0.62); *P*< .01
Inge, 2017 FABS-5+ High	N = 58 5 to 12 years	DIABETES Baseline: 9 of 56 (16.1%) LT Follow-up: 1 of 55 (1.8%) Remission[e]: 7 of 8 (87.5%) Incidence[f]: 0 of 45 (0%) HBA1C (%)	Baseline: 27 of 57 (47.4%) LT Follow-up: 9 of 55 (16.4%) Remission[e]: 19 of 25 (76.0%) Incidence[f]: 3 of 29 (10.3%)	LDL-C LEVEL (mmol/L) Baseline: 2.78 (2.59 to 2.97) LT Follow-up: 2.44 (2.22 to 2.67) TRIGLYCERIDES (mmol/L) Baseline: 1.45 (1.27 to 1.66) LT Follow-up: 0.99 (0.86 to 1.13)	NR

AUTHOR, YEAR STUDY NAME RISK OF BIAS	TOTAL N FOLLOW-UP	T2DM	HYPERTENSION	CORONARY ARTERY DISEASE	JOINT ARTHROPATHY
		Baseline: 5.3 (5.1 to 5.6) LT Follow-up: 5.2 (4.9 to 5.6) FPG (mmol/L) Baseline: 5.37 (5.11 to 5.65) LT Follow-up: 4.75 (4.17 to 5.34)			
Olbers, 2012 AMOS Moderate	N = 161 5 years	T2DM + RESOLUTION (FPG ≥ 7 mmol/L or HbA1c ≥ 45 mmol/mol) Baseline - RYGB: 3 of 81 (3.7%) 5 years - RYGB: 0 of 79 (0%) , MT: 1 of 44 (2.3%); *P* = .72 Resolution (RYGB only): 3 of 3 (100%); *P* = .25 HBA1C OUTCOMES Mean HbA1c (mmol/mol) Baseline - RYGB: 35·1 (3·9) 5 years - RYGB: 33·5 (3·8), MT: 35·3 (10·6) Within group: MD, −1·56 (−2·5 to −0·6); *P* = .002 Between group: MD, −1·8 (−5·4 to +1·8); *P* = .32 Elevated HbA1c (≥ 39 mmol/mol) Baseline - RYGB: 10 of 80 (12.5%) 5 years - RYGB: 6 of 65 (9.2%), MT: 6 of 37 (16.2%); *P* = .35 Resolution (RYGB only): 5 of 8 (62.5%)*; *P*=.73 FPG OUTCOMES Mean FPG (mmol/L) Baseline - RYGB: 5·1 (0·5)	ELEVATED BP (SBP ≥ 140 mmHg or DBP ≥ 90 mmHg) Baseline - RYGB: 12 of 78 (15.4%) 5 years - RYGB: 2 of 72 (2.8%), MT: 4 of 39 (10.3%); *P* = .18 Resolution (RYGB only): 12 of 12 (100%); *P* = .01 SYSTOLIC BP Mean SBP (mmHg) Baseline - RYGB: 124·6 (12.3) 5 years - RYGB: 113.2 (10·7), MT: 121.4 (11·4) Within group: MD, −11·55 (−14·0 to −9·1); *P* < .001 Between group: MD, −8·18 (−12·5 to −3·8); *P* < .001 Elevated SBP (≥ 140 mmHg) Baseline - RYGB: 11 of 78 (14.1%) 5 years - RYGB: 0 of 72 (0%), MT: 2 of 39 (5.1%); *P* = .12 Resolution (RYGB only): 11 of 11 (100%); *P* = .001 DIASTOLIC BP Mean DBP (mmHg) Baseline - RYGB: 76·9 (9·8)	LDL-C Mean LDL-C (mmol/L) Baseline - RYGB: 2·6 (0·7) 5 years - RYGB: 2·2 (0·7), MT: 3 (0·8) Within group: MD, −0·46 (−0·6 to −0·3); *P* < .001 Between group: MD, −0·88 (−1·2 to −0·6); *P* < .001 Elevated LDL-C (≥ 3·37 mmol/L) Baseline - RYGB: 13 of 81 (16%) 5 years - RYGB: 0 of 76 (0%), MT: 9 of 41 (22%); *P* < .001 Resolution (RYGB only): 13 of 13 (100%); *P* < .001 TRIGLYCERIDES Mean Triglycerides (mmol/L) Baseline - RYGB: 1·3 (0·6) 5 years - RYGB: 0·9 (0·3), MT: 1·4 (0·8) Within group: MD, −0·39 (−0·5 to −0·3); *P* < .001 Between group: MD, −0·47 (−0·7 to −0·2); *P* < .001 Elevated Triglycerides (≥ 1·47 mmol/L) Baseline - RYGB: 25 of 80 (31%) 5 years - RYGB: 0 of 76 (0%), MT: 10 of	

AUTHOR, YEAR STUDY NAME RISK OF BIAS	TOTAL N FOLLOW-UP	T2DM	HYPERTENSION	CORONARY ARTERY DISEASE	JOINT ARTHROPATHY
		5 years - RYGB: 4·8 (0·4), MT: 5·2 (0·7) Within group (RYGB): MD, −0·33 (−0·5 to −0·1); *P*= .001 Between group: MD, −0·45 (−0·8 to −0·1); *P*= .009 Impaired FPG (≥ 5.6 mmol/L) Baseline - RYGB: 16 of 80 (20%) 5 years - RYGB: 0 of 36 (0%), MT: 2 of 18 (11.1%); *P*=.11 Resolution (RYGB only): 13 of 13 (100%)*; *P*= .003	5 years - RYGB: 69·4 (9·9), MT: 77·7 (10·0) Within group: MD, −7·4 (−10·2 to −4·6); *P* < .001 Between group: MD, −8·28 (−12·2 to −4·4); *P*< .001 Elevated DBP (≥ 90 mmHg) Baseline - RYGB: 4 of 78 (5.1%) 5 years - RYGB: 2 of 72 (2.8%), MT: 4 of 39 (10.3%); *P*= .18 Resolution (RYGB only): 4 of 4 (100%); *P* =.69	41 (24%); *P*< .001 Resolution (RYGB only): 22 of 22 (100%)*; *P*< .001	

Notes. [a] Use of BP-lowering medications or SBP ≥ 95th percentile or DBP ≥ 95th percentile (for age, sex, height) if < 18 years of age; or if ≥ 18 years, SBP >140 mmHg or DBP > 90 mmHg. Remission of elevated BP required the absence of BP-lowering medications, and SBP and DBP in the normal range for age. [b] Remission of DM was defined as no use of medication for DM, and HbA1c < 6.5%, or, if HbA1c was not available, FBG < 126 mg/dL. [c] Remission of Pre-DM was defined as HbA1c < 5.7%, or, if HbA1c was not available, FBG < 100 mg/dL. [d] If < 18 years of age, use of BP medications or SBP ≥ 95th percentile or DBP ≥ 95th percentile (for age, sex, height); or if ≥ 18 years, SBP > 140 mmHg or DBP > 90 mmHg. [e] Remission was calculated as the number of participants (with sufficient data to define comorbidity state) who do not have the condition at long-term visit divided by the number of participants who had the condition at baseline. [f] Incidence was calculated as the number of participants (with sufficient data to define comorbidity state) who have the condition at long-term visit divided by the number of participants who did not have the condition at baseline.
Abbreviations. AMOS: Adolescent Morbid Obesity Surgery; BP: blood pressure; CI: confidence interval; DBP: diastolic blood pressure; FABS-5+: Follow-up of Adolescent Bariatric Surgery at 5 Plus years; FPG: fasting plasma glucose; HbA1c: glycated hemoglobin; HTN: hypertension; LDL-C: low density lipoprotein cholesterol; LT: long term; MD, mean difference; mmHg: millimeters of mercury; mmol/L: millimoles per liter; MT: medical therapy; NR: not reported; RR: relative risk; RYGB: Roux-en-Y gastric bypass; SBP: systolic blood pressure; SG: sleeve gastrectomy; T2DM: type 2 diabetes; Teen-LABS: Teen–Longitudinal Assessment of Bariatric Surgery; TODAY: Treatment Options of Type 2 Diabetes in Adolescents and Youth; yr: year.

APPENDIX E. APPLICABLE CODES

CODES	DESCRIPTION	
CPT		**Known as**
43633	Gastrectomy, partial, distal; with Roux-en-Y reconstruction	Roux-en-Y gastric bypass
43644	Laparoscopy, surgical, gastric restrictive procedure; with gastric bypass and Roux-en-Y gastroenterostomy (roux limb 150 cm or less)	Roux-en-Y gastric bypass
43645	Laparoscopy, surgical, gastric restrictive procedure; with gastric bypass and small intestine reconstruction to limit absorption	Roux-en-Y gastric bypass
43659	Unlisted laparoscopy procedure, stomach	Various procedures
43770	Laparoscopy, surgical, gastric restrictive procedure; placement of adjustable gastric restrictive device (e.g., gastric band and subcutaneous port components)	Adjustable gastric banding
43771	Laparoscopy, surgical, gastric restrictive procedure; revision of adjustable gastric restrictive device component only	Adjustable gastric banding revision
43772	Laparoscopy, surgical, gastric restrictive procedure; removal of adjustable gastric restrictive device component only	Adjustable gastric banding removal
43773	Laparoscopy, surgical, gastric restrictive procedure; removal and replacement of adjustable gastric restrictive device component only	Adjustable gastric banding removal and replacement
43774	Laparoscopy, surgical, gastric restrictive procedure; removal of adjustable gastric restrictive device and subcutaneous port components	Adjustable gastric banding removal
43775	Laparoscopy, surgical, gastric restrictive procedure; longitudinal gastrectomy (i.e., sleeve gastrectomy)	Sleeve gastrectomy
43842	Gastric restrictive procedure, without gastric bypass, for morbid obesity; vertical-banded gastroplasty	Vertical banded gastroplasty
43843	Gastric restrictive procedure, without gastric bypass, for morbid obesity; other than vertical-banded gastroplasty	Adjustable 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)	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	Roux-en-Y gastric bypass
43847	Gastric restrictive procedure, with gastric bypass for morbid obesity; with small intestine reconstruction to limit absorption	Roux-en-Y gastric bypass
43848	Revision, open, of gastric restrictive procedure for morbid obesity, other than adjustable gastric restrictive device (separate procedure)	
43860	Revision of gastrojejunal anastomosis (gastrojejunostomy) with reconstruction with or without partial gastrectomy or intestine resection; without vagotomy	
43865	Revision of gastrojejunal anastomosis (gastrojejunostomy) with reconstruction with or without partial gastrectomy or intestine resection; with vagotomy	
43999	Unlisted procedure, stomach	
HCPCS		
S2083	Adjustment of gastric band diameter via subcutaneous port by injection or aspiration of saline	Adjustable gastric banding

CODES	DESCRIPTION	
S2085	Laparoscopy, gastric restrictive procedure, with gastric bypass for morbid obesity, with short limb (less than 100 cm) Roux-en-Y gastroenterostomy	Roux-en-Y gastric bypass
ICD-10-CM		
E66.01	Morbid (severe) obesity due to excess calories	
E66.09	Other obesity due to excess calories	
E66.1	Drug-induced obesity	
E66.2	Morbid (severe) obesity with alveolar hypoventilation	
E66.8	Other obesity	
E66.9	Obesity, unspecified	
Z46.51	Encounter for fitting and adjustment of gastric lap band	
Z68.30	Body mass index [BMI] 30.0-30.9, adult	
Z68.31	Body mass index [BMI] 31.0-31.9, adult	
Z68.32	Body mass index [BMI] 32.0-32.9, adult	
Z68.33	Body mass index [BMI] 33.0-33.9, adult	
Z68.34	Body mass index [BMI] 34.0-34.9, adult	
Z68.35	Body mass index [BMI] 35.0-35.9, adult	
Z68.36	Body mass index [BMI] 36.0-36.9, adult	
Z68.37	Body mass index [BMI] 37.0-37.9, adult	
Z68.38	Body mass index [BMI] 38.0-38.9, adult	
Z68.39	Body mass index [BMI] 39.0-39.9, adult	
Z68.41	Body mass index [BMI] 40.0-44.9, adult	
Z68.42	Body mass index [BMI] 45.0-49.9, adult	
Z68.43	Body mass index [BMI] 50.0-59.9, adult	
Z68.44	Body mass index [BMI] 60.0-69.9, adult	
Z68.45	Body mass index [BMI] 70 or greater, adult	
Z68.53	Body mass index [BMI] pediatric, 85th percentile to less than 95th percentile for age	
Z68.54	Body mass index [BMI] pediatric, greater than or equal to 95th percentile for age	

Note: Inclusion on this list does not guarantee coverage.

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Commenters

Identification	Stakeholder
A	Greg Showell, RN - Program Coordinator, Samaritan Weight Management Institute *[Submitted February 7, 2023]*
B	Derek Rogalsky, MD – Appointed Expert *[Submitted February 11, 2023]*
C	Melody Acosta, MPH, RD – Dietician (Board Certified Specialist in Pediatric Nutrition) [*Submitted February 28, 2023]*
D	Children's Diabetes and Endocrine Center, Randall Children's Hospital *[Submitted March 6, 2023]*: • Maya Hunter, MD – Pediatric Endocrinologist • Radhika Purushothaman, MD - Pediatric Endocrinologist, Director Type 1 Diabetes Program • Karin Selva, MD - Chair, Randall Children's Hospital, Senior Medical Director LMG Pediatric Subspecialties, Diabetes & Endocrine, Nephrology, Neurology, Pulmonary, Rheumatology, Director, Randall Children's Hospital Gender Care Center • David Snyder, MD - Pediatric Endocrinologist • Sevket Yigit, MD - Medical Director, Children's Diabetes Endocrine Center
E	Children's Health Alliance *[Submitted March 7, 2023]:* • Jay Rosenbloom, MD, PhD – Pediatrician, Pediatric Associates of the Northwest; Medical Director • Deborah Rumsey – Executive Director
F	Miriam McDonell, MD, FACOG – Diplomate, American Board of Obesity Medicine; Medical Director- Medicare PacificSource, Health Officer- North Central Public Health District, Physician Supervisor- Northern Oregon Regional Corrections Facilities *[Submitted March 7, 2023]*
G	Walter Lindstrom – Senior Director of Reimbursement and Health Economics, ReShape LifeSciences, Inc. *[Submitted March 8, 2023]*

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Public Comments

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A1	I am writing to encourage the committee to reassess the decision to "not recommend" bariatric coverage for patients with a BMI of 30 to 34.9 with type II diabetes. Listening to the discussion there were some comments that this population could be served by utilizing weight-loss medication. While it is true that some of the newer medications do help patients lose significant amounts of weight, the data suggest that once these medications are stopped, the weight returns. Currently OHA does not cover medications for weight loss. In the event this medication coverage decision was changed, if the patient lost OHA coverage, they would likely lose access to their medications. However, if these same patients had access to bariatric surgery, even if they lose OHA coverage they will still continue to benefit from having the procedure done. Long-term studies have repeatedly shown that bariatric surgery is the only intervention that is proven to have sustainable outcomes. I have been a registered nurse with Samaritan Weight Management Institute for over 10 years and I have seen first-hand just how powerful the tool of weight loss surgery can be. The improvement in quality of life is almost immeasurable. Patients are off of their type II diabetes medications before they even leave the hospital. Seeing the gradual increase in the acceptance of surgery as a primary intervention for type II diabetes and obesity in general has been incredible. Limiting access to the lower BMI cohort especially those with diabetes is short sighted and conflicts with the recommendations recently published by the American Society of Metabolic and Bariatric Surgeons.	*Thank you for your comments.* *We acknowledge that obesity medications are not covered for members of the Oregon Health Plan, or other state-purchased insurance carriers. (as of April 2023)* *The draft coverage guidance recognizes significant benefits of bariatric surgery in this population as evidenced by greater 5-year percent weight loss (MD, -13.95 [95% CI, -18.6 to -9.3) and diabetes remission (RR, 9.1 [95% CI, 1.7 to 48.6]) as well as higher patient-reported quality of life (i.e., higher scores in all but 1 SF-36 domain) compared with medical therapy.* ***For EbGS discussion:*** *Consider modifying the recommendation to include coverage when a diagnosis of Type 2 Diabetes Mellitus is present to prioritize a subset of this BMI population who can potentially benefit most from access to bariatric surgery.*
B1	The guidelines should address revision surgery. The three most common reasons for revision surgery are gastroesophageal reflux disease (GERD), insufficient weight loss and weight regain. De novo or worsening GERD after sleeve gastrectomy is a much discussed and researched topic in bariatric surgery circles. The trouble with GERD after sleeve is that the	*Thank you for your comments.* *Repair of surgical complications are covered, including treatments for GERD which are included on Lines 314, 380 and 513.*

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	fundus of the stomach is no longer available for fundoplication and often the only reasonable surgical alternative is conversion to gastric bypass or recently placement of LINX device. OHP should cover conversion to from sleeve to another form of bariatric surgery or placement of a LINX device for GERD in either the presence of biopsy proven intestinal metaplasia (Barretts), reflux esophagitis, or bravo pH probe with DeMeester score greater than or equal to 14. Without this coverage patients will be left to suffer with GERD, with no recourse except long term high dose PPIs, which often are not as effective in symptom control due to altered stomach anatomy. Insufficient weight loss and weight regain are also vexing problems with highly variable definitions in the medical literature. Both weight regain and insufficient weight loss are most common after sleeve gastrectomy and single anastomosis duodenal ileal bypass with sleeve gastrectomy (SADI-S) has shown real promise as the revision option of choice for patients who either do no lose enough weight after sleeve or gain it back in the long term. I recommend that OHP cover one revision surgery for insufficient weight loss if a patient fails to fall below the initial qualification threshold for bariatric surgery by 18 months after their index procedure. Of course, the patient must be compliant with diet and exercise recommendations following surgery. Furthermore, I recommend that OHP cover one revision surgery for patients who regain weight to a level where they meet the initial criteria again so long as there is documentation of patient compliance with medical, surgical, and dietary recommendations for weight loss and healthy living. Obesity is a disease and we shouldn't automatically jump to blaming patients for its recurrence. Revision surgery for weight loss is widely accepted in professional society guidelines and so long as it is undertaken at a center of excellence, it should be covered.	*LINX devices are not FDA-approved for people who have had bariatric surgery or have a BMI greater than 35:* *LINX is not FDA approved for patients with "prior esophageal or gastric surgery or endoscopic intervention," "esophageal stricture or gross esophageal anatomic abnormalities (Schatzki's ring, obstructive lesions, etc.)" or in patients with "morbid obesity (BMI > 35)."* *Insufficient weight loss and weight regain is not considered a surgical complication. The draft report states that a shared decision-making approach may help patients understand the benefits as well as risks of bariatric surgery.* ***For EbGS discussion***
B2	Next, in a related topic, the guidelines should address the concept of two stage surgery. I saw a young patient in my office the other day with a BMI of 75 who weighed more than 500 pounds. His best option is to start a GLP agonist to get his weight into the 400s, undergo a sleeve gastrectomy and continue his GLP 1 agonist to get his weight into the low 300s and then convert his sleeve to a SADI to bring his weight into the low 200s. Then he	*The practice of performing an index bariatric surgery to later perform a second bariatric surgery, as a two-stage concept, is outside the scope that was approved for this coverage guidance report.*

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	would continue his GLP 1 medication likely for life as maintenance with long term follow up in my bariatric center. Unfortunately, this approach is completely unattainable. First GLP agonists are not covered and second two-stage surgery is not covered. There is evidence from small series that SADI-S and biliopancreatic diversion with duodenal switch (BPD-DS) have higher complication rates when BMI goes above 65. Since both these procedures are basically sleeve gastrectomies with a distal intestinal bypass, they can both be done as two stage procedures where the sleeve gastrectomy is done first, the patient recovers and loses weight for 6-18 months and then undergoes the bypass when the BMI is down to a safer range to keep the weight loss going. I agree with the guideline that patients and surgeons at centers of excellence should be able to choose ASMBS approved operations. Since SADI-S and BPD-DS can be 1 or 2 stage and there are situations where 2 stage is safer, it is my opinion that the guideline should explicitly state that two stage procedures should be approved at the discretion of the surgeon and the timeline should be 6-18 months following the initial sleeve gastrectomy.	*None of the included evidence sources reported on either SADI or BPD-DS as two-stage procedures.* *Currently, conversion from a less intensive (such as gastric band or sleeve gastrectomy) bariatric procedure to a more intensive surgery (e.g. Roux-en-Y) is covered under the Oregon Health Plan (Guideline Note 8). Note that the guideline also specifies that repair of surgical complications (excluding failure to lose sufficient weight) is also covered.* ***For EbGS discussion***
B3	Finally, I would like to address the topic of BMI of 30-34.9 with Type II diabetes. I understand the committee's concern in approving a surgical procedure when the medication horizon is so promising and on average the surgery is as effective as medication in lowering A1c. The question seems to be, if we can achieve a1c reduction with medication, why would we subject patients to surgery? I think the answer is found by reframing the way we are thinking about this health care decision. Ultimately this decision should be a shared decision between doctor and patient. If surgery were just another medication that was effective in lowering A1c and more likely to induce outright long-term remission of diabetes, it would likely win rapid approval. I make this point because given that the treatments are roughly equivalent with a slight edge to surgery in remission, the patient and their physician should get to decide whether surgery with its attendant risks and possible rewards is the path they value or whether medication with its risks and rewards is more in line with their values and goals. One argument against this approach is that surgery is a relatively expensive use of scarce	*See response to A1 regarding the BMI 30.0-34.9 population.*

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	health care dollars. However, a lifetime of GLP 1 agonists at over one thousand dollars a month is actually likely much more expensive to the system in the long run, since patients who stop taking GLP 1 agonists experience weight regain and worsening of A1c. If current trends are any indicator, few patients in this group (BMI 30-34.9) will be referred for surgery, but those who are, may value the chance at remission highly. The effectiveness of surgery as a treatment is not in doubt, and its comparative effectiveness is at least non-inferior. I would argue BMI of 30-34.9 patients with type II diabetes should be offered surgery with the same conditions as BMI of 35. This approach gives patients and their physicians maximum flexibility to choose from effective treatments that match their values.	
C1	QUESTION ONE B) 4. Nutritional (conducted by licensed dietitian) shall include 6 to 12 pre-operative sessions of Medical Nutrition Therapy Patients should make lifestyle changes consistent with their nutritional needs and understand what to expect after surgery. An initial evaluation isn't enough. QUESTION THREE 1. d. Nutritional (conducted by a licensed dietitian) shall include at least 12 pre-operative sessions of Medical Nutrition Therapy, preferably with family in attendance	*Thank you for your comments.* *The current recommendation does not specify the number of appropriate visits per assessment domain; instead, the recommendation includes a requirement that preoperative care must occur in an MBSAQIP-accredited center, to ensure that rigorous assessment protocols and appropriate counseling takes place.* *The MBSAQIP standards do not specify a number of nutritional counseling sessions.*
D1	We are writing this letter in support of Care Oregon Insurance coverage of bariatric surgery for the treatment of obesity in adolescents. Thirty percent of all referrals to Children's Diabetes and Endocrine Center at Randall Children's Hospital at Legacy are for evaluation and management of obesity in children and adolescents. A significant number of these patients have a BMI greater than 35 kg/m2. In February 2023, The American Academy of Pediatrics published Clinical Practice Guidelines covering the treatment of obesity in adolescents. An executive summary from those guidelines recommend referral for adolescents 13 years and older with severe obesity (BMI ≥120% of the 95th	*Thank you for your comments. The draft coverage guidance recommends coverage for this population.* *The three sources you cite are already included in the evidence review section of our draft report.*

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	percentile for age and sex) for evaluation for metabolic and bariatric surgery; preferably to a local or regional comprehensive multidisciplinary pediatric metabolic and bariatric surgery center. Fortunately, in Legacy Health System, such a center exists under the leadership of Dr. Val Halpin and would be able to safely perform these surgeries on qualifying adolescents. It is well known that obesity in children and adolescents if not addressed, has a very high likelihood of persisting in adulthood, bringing with it the usual co-morbidities that adult obesity demonstrates. There is growing evidence on the effects of bariatric surgery in adolescents on their metabolic outcomes. After bariatric surgery, weight loss was reported to be -26 % in adolescents similar to adults (-29 %) (Inge et al, NEJM 2019). Inge et al (J. Pediatrics 2015) also reported reversal of insulin resistance and restoration of beta cell function after bariatric surgery in teens without Type 2 diabetes. The Teen LABS (Longitudinal Assessment of Bariatric Surgery) study coordinated with adult LABS for standardized methodology and definitions showing surgery lower 30-year cardiovascular risks in youth with Type 2 diabetes (Ryder et al, Surg Obes Relat Dis 2021). Obesity is currently considered a chronic disease with significant genetic components, and it is no longer a poor lifestyle issue. Based on the most up-to-date evidence-based data, bariatric surgery induces significant and durable weight loss and reverses many complications of obesity and Type 2 diabetes. We have seen many children and adolescents suffering from obesity and its complications over the years and it is disappointing to see the poor outcomes with conventional lifestyle intervention only, especially in those with significantly elevated BMI values. In conclusion, we deeply support the bariatric surgery intervention in selected cases described in HERC coverage guidance. Your support for this coverage will highly be appreciated, and prevent long term sequelae of obesity in adolescence.	

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Disposition of Public Comments

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E1	The Children's Health Alliance is writing in support of the Oregon Health Plan's coverage of bariatric surgery in adolescents. Obesity is a chronic disease which is highly likely to persist into adulthood if not reversed in the teen years. The long-term consequences to emotional and physical health are well documented in the literature. We do not expect that surgery will be used often for adolescents, but in those rare cases it is important we consider all treatment options. The 170+ pediatrician members of the Children's Health Alliance support the coverage of bariatric procedures for the treatment of obesity in adolescents. Children's Health Alliance pediatricians care for approximately 190,000 children and their families in the Portland metro area and Salem and are committed to improving the health of all Oregon's Children.	*Thank you for your comments. The draft coverage guidance recommends coverage for this population.*
F1	I am writing to request that the subcommittee's recommendation for coverage guidance regarding bariatric procedures for the treatment of obesity in adolescents be readdressed. The rationale noted in the draft proposal is: "We recommend coverage to align with professional society guidelines and expert input. We have added preoperative eligibility requirements based on clinical guideline standards." The American Academy of Pediatrics Clinical Practice Guideline for the Evaluation and Treatment of Children and Adolescents with Obesity was referenced in the discussion of bariatric procedures for adolescents at the EbGS meeting held February 2, 2023. The guideline itself was not reviewed by all staff or members of the subcommittee prior to the meeting. The opportunity to review the studies utilized in the guidelines was lacking, and a more thorough review of the recommendations is warranted. The summary of evidence provided at the subcommittee meeting in support of bariatric procedures for adolescents with obesity was of low confidence or very low confidence, due to the nature of the study designs. The expert opinion provided at the meeting was provided by bariatric surgeons, with some of the information provided strictly anecdotal. I am requesting that the subcommittee review in more detail the recommendations made in The American Academy of Pediatrics Clinical Practice Guideline if it is to be used as a source for decisions, and that the	*Thank you for your comments.* ***For EbGS discussion:*** *The AAP guidelines outline the treatment options for obesity in children and adolescents, including:* • *Motivational interviewing* • *Intensive health behavior and lifestyle treatment (IHBLT) (i.e., ≥ 26 hours of in-person, family-based counseling on nutrition and physical activity of ≥ 3 months duration)* • *Referrals to lower-intensity community-based services (e.g., food provision programs, local parks and recreation programs) when intensive services are unavailable* • *Pharmacotherapy as an adjunct to IHBLT for adolescents 12 years and older* • *Referral and evaluation for bariatric surgery in adolescents 13 years and older with severe obesity (i.e., BMI ≥ 120% of the 95th percentile for age and sex)*

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	subcommittee reassess the recommendation of approval of coverage of bariatric procedures for the treatment of obesity in adolescents.	*Intensive counseling visits for children and adolescents are covered on Line 320. Pharmacotherapy is not a covered treatment modality on the Oregon Health Plan.* *Consider adding a requirement for Question Three as:* *E) A trial of intensive behavior/lifestyle management.*
G1	ReShape Lifesciences™ ("ReShape") appreciates this opportunity to Comment on Bariatric Procedures. We are committed to the delivery of safe, effective, and sustainable therapies which target the global health crisis associated with obesity and metabolic diseases. The current Draft is ReShape's first opportunity to evaluate a glaring omission in coverage that occurred prior to our acquisition of the device in December 2018. ReShape's stewardship of the Lap-Band® is an ongoing commitment to ensuring appropriate patient selection and aftercare with the goal of maximizing patient satisfaction and improved health. This Comment is not seeking to create a battle between accepted operations. Rather, we seek equity and fairness so that the people of Oregon suffering from severe obesity that is amenable to surgical intervention can access-Lap-Band as a minimally invasive, long-term alternative to bariatric stapling procedures ("Stapling procedures" are the RNY, VSG, BPD/DS, OAGB, and SADI-S procedures identified in the Draft Coverage Guidance.). The anti-banding sentiment found in this Draft – with an apparent birth in the fall of 2016 - blatantly advance the incorrect assertion that a "lack of evidence of long-term benefit" prevents the Lap-Band from being a recommended bariatric procedure. We vehemently object to any characterization that there is no evidence of long-term benefit when significant data exists to the contrary. The simplistic notion that Lap-Band is the only procedure that is subject to possible complications is ludicrous and unsupportable. HERC cannot reasonably claim that the Lap-Band lacks evidence of long-term benefit on the one hand yet accept without any analysis or discussion that very new procedures (e.g., SADI-S and OAGB) can somehow demonstrate superior long-term	*Thank you for your comment.* *Adjustable gastric banding (AGB) is of limited relevance to current clinical practice and accounted for <2% of all bariatric procedures performed in 2019, the most recent year for which ASBMS reported statistics (page 21 of the draft report).* *Across all studies disaggregating weight loss by procedure type, AGB conferred the least amount of weight loss as compared to other procedures. Our highest quality evidence sources reported the following observations:* • *Change in BMI (ref# 37)* ○ *AGB: MD, -0.44 (95% CI, -5.02 to 4.13)* ○ *SG: MD, -8.00 (95% CI, -10.06 to -5.94)* ○ *RYGB: MD, -8.12 (95% CI, -11.85 to -4.40)* • *% Excess weight loss at 3 years (ref# 43)* ○ *AGB: MD, 19.0% (95% CI, 0.13 to 37.9)* ○ *SG: MD, 39.2% (95% CI, 15.2 to 63.3)* ○ *RYGB: MD, 45.0% (95% CI, 21.8 to 68.2)* *For type 2 diabetes remission, AGB had the smallest relative effect, whereas gastric bypass procedures had the largest remission effect.* • *Remission at 2 years (ref# 43)*

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	benefits. That simply is not possible given their recency. Where is the rigorous review of those options by this committee? There isn't any. We are specifically requesting that the Lap-Band be added to the list of procedures. Like the stapling procedures, it is an ASMBS-endorsed operation for persons seeking a less invasive alternative. It needs to be among the continuum of covered operations. Failing an outright reversal of this unsupportable coverage position by HERC, at a minimum, we ask for a meaningful opportunity to show how the Commission's role in providing evidence-based information. It appears from the Minutes of the October 6, 2016, HERC meeting that it was this time frame when the committee voted to remove gastric banding procedures from coverage. Obviously, it is impossible to reconstruct discussions, meetings and the events that occurred nearly 7 years ago with any hope of being accurate. However, there are multiple conclusions which are inescapable: - This decision was not reached in a manner which respected a patient's right to choose among multiple clinically appropriate options. - This decision lacked any rigorous evaluation of the data, both pro and con, germane to the Lap-Band. - With due respect to Drs. Halpin and Wolfe as the claimed "experts" involved in the discussion, there was no effort to seek a truly knowledgeable, expert to address this significant elimination of an ASMBS endorsed procedure. In fact, reading the 10/6/2016 Minutes uncovers that similar concerns about the committee's action were raised by Dr. Susan Williams: "[S]he was concerned about changing the coverage guidance document to exclude lap bands because the evidence presented in the document created by HTAS doesn't match that type of recommendation. She feels a responsibility to the evidence. Commissioners who are member of HTAS said generally they feel HERC members are a second set of eyes and are not dismayed if their initial recommendation is amended. The important facts are the coverage guidance should be based on the evidence, studies, testimony, and	○ *AGB: RR, 7.6 (95% CI, 3.4 to 16.8)* ○ *SG: RR, 9.1 (95% CI, 3.7 to 22.5)* ○ *RYGB: RR, 11.2 (95% CI, 4.7 to 26.4)* *Adolescents who received AGB in the Teen-LABS cohort study (the only adolescent study to evaluate AGB) did not demonstrate significant percent weight loss at 3-year follow up (-8.1% [95% CI, -19.9 to 3.6]) and were subsequently dropped from the 5-year analysis due to lack of efficacy (ref# 65 and 66).* *In addition to demonstrating lower weight loss efficacy compared with other common bariatric procedures, about 10% of patients in a systematic review of RCTs adults undergoing bariatric procedures experienced pouch dilatation and slippage which may be severe and necessitate band repositioning or removal (ref# 43).* *Therefore, the inferior weight loss and diabetes outcomes, combined with almost negligible utilization, has led to an exclusion of coverage of this procedure since 2016.*

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	stewardship." The response to her very reasonable objection was to argue until a compromise was agreed upon that it was acceptable to remove placement of gastric bands from the recommendation but not to add a recommendation for noncoverage. Truly this is a distinction without a difference and acts as an unfounded disparagement of ReShape's product that results in the elimination of patient choice. The bias rampant in the process is demonstrated simply by listing many favorable information sources which were not considered in 2016 and establish that HERC's anti-banding position is out-of-step with other authoritative sources HERC claims are guideposts to its decisions. Literature, specialty society support, and payer acceptance are among the areas of information HERC ignored in 2016. Please remember: - Lap-Band surgery remains an ASMBS-endorsed procedure just as much as the stapling procedures HERC recommends for coverage. - Lap-Bands are included with the evidence-based clinical practice guidelines developed by ASMBS and IFSO. - Center of excellence accreditation criteria established under the Metabolic and Bariatric Surgery Accreditation and Quality Improvement Program (MBSAQIP) have always included Lap-Bands. - ASMBS has recently published consensus guidelines addressing the post-operative management of Lap-Band patients, clearly demonstrating its commitment to patient access to the procedure. - Lap-Bands are included in the CMS National Coverage Determination on bariatric surgery no. 100.1. - Lap-Band are covered by the Federal Employee Health Benefit Plan. - The largest U.S. health insurers all include Lap-Band surgery among covered procedures including UHC, Anthem/Elevance, Health Care Service Corporation, Aetna, CIGNA, and Humana. Myriad other reasons exist to support Lap-Band, although a 1000-word	

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	limitation for this Comment makes it impossible to present the evidence at this time. We hope that opportunity will be offered so HERC can assess this on facts and data rather than relying upon misconceptions, evidentiary misstatements and an absence of qualified, fair-minded expertise. Lap-Band remains an important option and we ask that HERC reexamine its position and change its recommendations so Lap-Band is an option in appropriately selected adult patients who meet the FDA labeling requirements. Alternatively, we seek to engage in a meaningful dialogue regarding this important matter.	

Abbreviations. AAP: American Academy of Pediatrics; AGB: adjustable gastric banding; ASMBS: American Society for Metabolic and Bariatric Surgeries; BMI: body mass index; BPD/DS: biliopancreatic diversion with duodenal switch; CI: confidence interval; CMS: Centers for Medicare & Medicaid Services; HERC: Health Evidence Review Commission; IFSO: International Federation for the Surgery of Obesity and Metabolic Disorders; MD: mean difference; MBSAQIP: Metabolic and Bariatric Surgery Accreditation and Quality Improvement Program; OAGB: one anastomosis gastric bypass; RYGB: Roux-en-Y gastric bypass; RR: relative risk; SADI-S: single anastomosis duodenal-ileal bypass with sleeve gastrectomy; SG: sleeve gastrectomy

References Provided by Commenters

ID	References
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D	Inge TH, Prigeon RL, Elder DA, et al. Insulin Sensitivity and β-Cell Function Improve after Gastric Bypass in Severely Obese Adolescents. J Pediatr. 2015;167(5):1042-8.e1.
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