Health Evidence Review Commission's Health Technology Assessment Subcommittee

September 10, 2015

1:00 PM

Clackamas Community College
Wilsonville Training Center, Room 155
29373 SW Town Center Loop E, Wilsonville, Oregon, 97070

Section 1.0

Call to Order

AGENDA

HEALTH TECHNOLOGY ASSESSMENT SUBCOMMITTEE (HTAS)
September 10, 2015
1:00pm - 4:00pm

Clackamas Community College
Wilsonville Training Center, Rooms 155
Wilsonville, Oregon

Public comment will be taken on each topic per HERC policy at the time at which that topic is discussed. Please sign-in to testify.

#	Time	Item	Presenter
1	1:00 PM	Call to Order	Som Saha
2	1:05 PM	Review of June minutes	Som Saha
3	1:10 PM	Staff update	Darren Coffman
4	1:15 PM	**Proton Beam therapy** • Continue review of written public comment on prostate cancer, lung cancer, and adult lymphoma, and recurrent cancer • Finalize coverage guidance to send to VbBS/HERC	Robyn Liu Cat Livingston
5	2:00 PM	**Topic rescan** Scope documents • Continuous blood glucose monitoring • Self-monitoring of blood glucose • Diagnosis of sleep apnea • Breast MRI after diagnosis of breast cancer • PET CT for breast cancer staging and surveillance • Vertebroplasty, kyphoplasty, and sacroplasty Search results • Carotid endarterectomy	Adam Obley Cat Livingston
6	2:45 PM	**Bariatric surgery** • Review draft coverage guidance	Adam Obley Cat Livingston
7	3:50 PM	Confirmation of the next meeting	Som Saha
8	3:55 PM	Next Topics	Cat Livingston
9	4:00 PM	Adjournment	Som Saha

Note: All agenda items are subject to change and times listed are approximate

MINUTES

Health Technology Assessment Subcommittee
Clackamas Community College Wilsonville Training Center
29353 SW Town Center Loop E
Wilsonville, OR 97070
June 11, 2015
1:00-4:00pm

Members Present: Som Saha, MD, MPH (Chair Pro Tempore); Jim MacKay, MD; Chris Labhart; Gerald Ahmann, MD; Mark Bradshaw, MD; Leda Garside, RN.

Members Absent: Tim Keenen, MD.

Staff Present: Darren Coffman; Cat Livingston, MD, MPH; Jason Gingerich.

Also Attending: Adam Obley, MD, Val King, MD, MPH, Robyn Liu, MD, MPH, and Aasta Thielke, OHSU Center for Evidence-based Policy; Troy Rayburn, American Cancer Society; Ronnie Castro, PORCH; Carl Rossi, Scripps; Carol Marquez, OHSU; Ramesh Rengan, Seattle Cancer Care Alliance; Stephen Holm, MD Anderson; Mark Pledger, Novartis.

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1. CALL TO ORDER

Som Saha called the meeting of the Health Technology Assessment Subcommittee (HTAS) to order at 1:00 pm.

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2. MINUTES REVIEW

Minutes from the February 18, 2015 meeting were approved as presented 6-0.

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3. STAFF REPORT

Coffman reported on membership changes. Saha and Garside have joined the HTAS, and membership is now balanced with seven members on each subcommittee. Derrick Sorweide, DO, plans to join the subcommittee in September. King introduced Adam Obley, part of the clinical epidemiology staff at the Center for Evidence-based Policy. He will take over the work Robyn Liu has been doing in recent months. Coffman thanked Liu for her work. Wally Shaffer, who has served as clinical staff to the subcommittee, has retired and Cat Livingston will serve as staff to this subcommittee for the time being.

Coffman reported that the HERC is revising its coverage guidance process to perform additional work up front to prevent the starts and stops that have occurred on more complex topics in the past. We will also be more explicit about important versus critical outcomes as we report evidence, and are working on a revamped GRADE table which includes more specific outcome information when it is available. We will continue to use the GRADE domains including values and preferences, benefits and harms, resource allocation and strength of evidence. The

Coverage Guidance Development Framework (algorithm) has been retired as it has sometimes created confusion and unnecessary complexity. It served its purpose initially but GRADE has proven more useful.

4. BIOMARKER TESTS OF CANCER TISSUE FOR PROGNOSIS AND POTENTIAL RESPONSE TO TREATMENT

Liu reviewed the public comment disposition and staff suggested responses. For MSI for detecting Lynch Syndrome, Saha asked what the alternative test was and for the argument against clinical utility. Liu explained that IHC4 is available and that there are no studies showing MSI to have additional benefit on patient-centered outcomes. Saha asked whether it has better discriminating capacity. Liu said it does not. IHC4 is less costly.

Liu reviewed public comments and responses regarding Prolaris for Prostate Cancer. Saha said that he doesn't believe it's reasonable to hold such a diagnostic test to a standard of decreasing mortality as conducting such a trial would be almost impossible. The utility of the test could also reduced aggressive treatment. He is more interested in whether the test accurately predicts who needs therapy more than whether the test changes decisionmaking or mortality. Ahmann said the test isn't useful because if a man is told he has prostate cancer and is not too old for surgery, he is very likely to opt for surgery unless you can tell him that there is zero chance that the cancer will progress. Saha said a study showing that it would actually prevent surgery may be difficult to conduct. King noted that there were similar issues with Oncotype Dx for breast cancer; the evidence wasn't there a few years ago but now it is. There are competing tests for prostate cancer, and it remains to be seen which will obtain evidence of effectiveness in changing decision-making. She suggested that the subcommittee should revisit this test in two years to see whether the evidence develops. Livingston said that staff will shift the public comment disposition to focus on avoiding unnecessary care rather than mortality.

Saha offered an opportunity for public comment. Carol Marquez, a radiation oncologist at OHSU testified. She disclosed no conflicts of interest. Though she doesn't see prostate cancer patients, she said she has seen an evolution of cancer care in that some patients are now choosing to avoid invasive treatments because of concerns about quality of life and treatment side effects. Ahmann said that most prostate cancer patients are generally over 65, and that much of that generation is very fearful of cancer. Marquez noted that with PSA testing, prostate cancer is sometimes diagnosed earlier in life. Saha asked about cost. Coffman said that staff found data indicating the test costs about $3,400. While acknowledging that the test could prevent some surgeries, Saha said that if the cost of the test were lower, it might not be such an issue as long as there were no potential harms.

Livingston noted that multiple molecular testing is not recommended for coverage, but there is no GRADE row for that. Staff will add one, reflecting the insufficient evidence reported in the body of the text, putting in the validity and utility if possible.

Livingston reviewed the changes to the GRADE table where staff listed the analytic validity, clinical validity or clinical utility. Rationale used to refer to the Coverage Guidance Development Framework (algorithm) which is no longer present. Therefore the rationales have been updated. Livingston reviewed the updated rationales. Saha asked that the definitions of the terms be defined as footnotes to the GRADE table.

The draft coverage guidance was approved for referral to VbBS and HERC with the changes

requested by the subcommittee.

DRAFT HERC COVERAGE GUIDANCE

Oncotype DX is recommended for coverage in early stage breast cancer when used to guide adjuvant chemotherapy treatment decisions for women who are lymph node negative *(strong recommendation)*.

The following genetic tests of cancer tissue are recommended for coverage *(strong recommendation)*:

- BRAF gene mutation testing for melanoma
- Epidermal growth factor receptor (EGFR) gene mutation testing for non-small-cell lung cancer
- KRAS gene mutation testing for colorectal cancer

The following genetic tests of cancer tissue are not recommended for coverage *(weak recommendation)*:

- Mammaprint, ImmunoHistoChemistry 4 (IHC4), and Mammostrat for breast cancer
- Prolaris and Oncotype DX for prostate cancer
- BRAF, microsatellite instability (MSI), and Oncotype DX for colorectal cancer
- KRAS for lung cancer
- Urovysion for bladder cancer
- Oncotype DX for lymph node-positive breast cancer

The use of multiple molecular testing to select targeted cancer therapy is not recommended for coverage *(weak recommendation)*.

5. INDICATIONS FOR PROTON BEAM THERAPY

Liu reviewed the public comment disposition and staff's recommended responses. She reviewed the comments by cancer type, using the groupings from page 56 of the meeting materials.

For brain and paraspinal tumors, Saha asked Liu about the results of the updated literature search. Liu said that the information about cognitive impact and quality of life was new, though the Washington HTA had already recommended coverage based on incremental net benefit, so she's not sure the additional evidence changes the assessment of evidence. For the benefit of the new members, Coffman noted that for this indication and pediatric tumors the subcommittee appeared to be on the fence about its recommendation at the last meeting. The subcommitee previously recommended against coverage but appeared open to changing the recommendation based on public comment. The balance of benefits and harms in the GRADE table has been changed to incremental benefits to match Table 1 of the coverage guidance. Livingston clarified the incremental benefit of the treatment is that there are fewer harms, not some other benefit. There is insufficient comparative evidence about survival or other cancer-related outcomes. Saha requested that staff separate the benefits of treating the cancer from the harms (side effects of treatment). After discussion the subcommittee agreed to make a weak recommendation for coverage related to brain and spinal tumors. Saha then asked about the

cost comparison. The cost is more than IMRT or photon therapy but only approximately twice as expensive (not 10 times more expensive).

For breast cancer, liver cancer and other gastrointestinal cancers the subcommittee made no change based on public comments after minimal discussion.

For head and neck cancers, Saha asked about the rate of local control with typical photon therapy. Liu referred him to comment L68 in which an error was discovered during discussion: the local control rate for skull based tumors with photon therapy is 30-50%, not 3-5% as shown in the disposition document. After brief discussion, the subcommittee decided to recommend coverage for some, but not all, head and neck tumors. After discussion, including testimony and clarification from radiation oncologists Marquez and Rossi, who were in the audience, the subcommittee decided to recommend coverage for brain, skull-based and juxtaspinal and paranasal sinus tumors based on the evidence cited in the public comment disposition. As these are rarer tumors, the subcommittee chose to recommend coverage based on lower-quality evidence which shows better outcomes than is typical with standard therapies.

For nasopharyngeal and oropharyngeal carcinoma, the subcommittee discussed that these tissues are more radiosensitive but also sensitive to chemotherapy. Marquez said that because the tumors are more radiosensitive, there may not be as much benefit of proton therapy over photons. Rengan agreed that they are sensitive to chemotherapy but said that radiation therapy is needed for a cure, and added that for more sensitive tumors the benefit would be the ability to safely increase the dose to the tumor, rather than reduced harms. Rossi said that proton beam centers have only recently developed the ability to target these tumors due to improved technology. After discussion, the subcommittee decided not to recommend coverage for these tumor types, based on insufficient evidence of superiority and the fact that these tumors are common enough that one might expect future evidence development.

In discussion of retreatment, Ahmann asked if people who were retreated were ever cured. A member of the audience said sometimes yes, but often treatment is to improve quality of life or to extend life. The audience member said that these are difficult decisions and depend on the characteristics of each patient. Ahmann noted that treatment of recurrent tumors would significantly differ depending on their location. Saha suggested they are rare enough not to include a restriction for them, so perhaps the subcommittee could remain silent. However in subsequent discussion, Rengan noted that there is a blanket recommendation for all other conditions which could be interpreted as a recommendation of noncoverage for retreatments. Livingston agreed to look into clarifying language around this issue.

Saha asked about liver cancer. Liu reviewed the evidence from the public comments and the cited Chi study. The reported five-year survival benefit was 25 times higher in the proton population, with less dramatic benefits at shorter time horizons. Benefits were, however, similar to stereotactic body radiation therapy (SBRT). Gingerich noted that HERC recently elected not to cover SBRT for liver cancer. Harms of proton therapy were reported as less serious than either SBRT or standard photon radiation, though harms were just general hepatic toxicity, which Saha said are not important as an outcome. Upon further research into this article, King found indications of heterogeneity (high i^2 values) that call these results into question. The subcommittee did not change its recommendation.

Discussion turned to pediatric cancers. Most of the comments on pediatric cancers were for eye, head and neck cancers, which would already be recommended for coverage regardless of age per previous discussion, so the subcommittee did not discuss the comments related to

these cancers. For lymphomas and Ewing sarcomas, Marquez noted that many Ewing Sarcomas occur in the juxtaspinal region. Saha asked about the intent of separating out pediatric and adult tumors. Staff responded that toxicity will develop over decades, so long-term outcomes are more important because children typically have more life expectancy. Rengan said that treatment-related secondary malignancies can appear decades after primary treatment, and that children's tissue is more radiosensitive than adult tissue. Based on these factors, the subcommittee decided to make a weak recommend for coverage for all tumors that occur in children.

Saha invited additional public comments.

Ronnie Castro, of Seattle, offered comment as a patient. He had a skull-based brain tumor, diagnosed in 2013 at age 32. After six months, he was able to raise private funds for proton beam therapy despite an insurance denial and the tumor has not grown again. He wondered what would have happened if he had not been able to raise the money and expressed concern about long-term harms, which may have occurred with photon therapy. He expressed satisfaction at the subcommittee's decision to recommend coverage for these cancers.

Rengan gave a brief presentation focusing on the deleterious effects of radiation exposure to normal tissue. He also said that toxicity of therapy creates costs to the health system. In many cases this creates savings which compensate for the additional cost of proton-based therapies.

Livingston then asked for guidance on completing the next draft for the September meeting. After discussion the subcommittee decided that nasopharyngeal and oropharyngeal carcinoma would remain recommended for noncoverage, and that brain, skull based, juxtaspinal and paranasal sinus tumors would be given a separate row with a weak recommendation for coverage. Rare tumors will not get a separate row on the GRADE table. Malignant pediatric cancers (including lymphoma) will have their own GRADE row with a recommendation for coverage. Staff will research the thinking behind the varied definitions of pediatric, with age limits of 21 and 30 in different sources.

Saha thanked the members of the audience for their testimony and assistance with the coverage guidance and invited them to call in by phone to the next meeting. Prostate cancer, lung cancer and adult lymphoma will be the main areas of interest.

6. NEXT TOPICS

At the next meeting the subcommittee will continue discussion on proton beam therapy and take up a new topic related to bariatric and metabolic surgery.

7. ADJOURNMENT

The meeting was adjourned at 4:10 pm. The next meeting is scheduled for September 10, 2015 from 1:00-4:00 pm in Room 155 of the Clackamas Community College Wilsonville Training Center.

Section 3.0
Indications for Proton Beam therapy

Proton Beam Therapy Discussion Guide

(Note: codes reference public comments; see comment disposition document)

1. **Discuss theory based concerns**
    a. Coverage with evidence development concerns J57 and A129, Q129
    b. Public comment suggests using reference pricing (Same as IMRT) to facilitate evidence development
    c. Public comment suggests coverage based on dosimetric studies alone (for rare, or other cancers) P112, R132
        i. Counterargument would be that comparative studies are possible in many cases, but if not could be considered

2. **Discuss whether to include language about:**
    a. **Recurrence** – prior discussion about need to individualize, sometimes PBT for recurrent cancer may be appropriate. Comment L82 discussed the high level of toxicity but lower toxicity because of PBT. Concern about box language about noncoverage of "all other cancerous and noncancerous conditions" would imply that retreatment is always noncovered.
        i. Decide if language about all other cancerous and noncancerous conditions should be removed
        ii. Clarify intent that recurrent covered cancers are recommended to be covered if appropriate
    b. **Definition of "pediatric**" malignant tumors
        i. See draft additional box language

3. **Review remaining cancer types**
    a. Lung cancer (H37-H48), P112
        i. Locally advanced NSCLC – there are dose ceilings and PBT would allow for higher doses. There is a Phase III trial underway to test whether higher dose allowed with PBT results in better outcomes. (H39). P112 argued for improved dosimetric parameters.
            1. Staff assessment - given ongoing studies and promising theoretical support that is not yet borne out in comparative studies, consider ongoing noncoverage until studies are done
        ii. Medically inoperable non small cell lung cancer – SBRT is relatively contraindicated in some patients with centrally located tumors. Thus comparative studies may not be feasible. There is a dose response

association with survival with PBT in this population, excess toxicity not seen. Suggestion to cover in this population (H40, 41, 42)

1. Staff assessment - in medically inoperable patients PBT offers theoretical benefit and studies are unlikely. Discuss whether coverage is indicated in this scenario

iii. NSCLC requiring re-irradiation – (H43-44) have limited options. unlikely to get comparative data. Case series with promising results.

b. Prostate cancer

i. Public Comment requests coverage based on:
   1. Argument to cover with evidence development based on ASTRO model policy (Q129)
   2. Argument to cover based on prospective noncomparatve studies Q123, A12
   3. Argument to cover based on QOL B16

ii. Staff assessment – evidence source says comparable benefits/harms.

c. Lymphoma – C21-C27

iii. Public comment argument for coverage based on:
   1. Individuals with lymphoma can live decades, so the same benefit of decreasing harms to other nearby organs would accrue as to pediatric cancers
   2. Dosimetric modeling is used for treatment planning, this could be sufficient to guide coverage

iv. Staff assessment - net health benefit v comparator is insufficient (pediatric cancers have incremental benefit)

v. Current draft recommendation made for noncoverage

HEALTH EVIDENCE REVIEW COMMISSION (HERC)

COVERAGE GUIDANCE: PROTON BEAM THERAPY

DRAFT for HTAS meeting materials 9/10/2015

HERC Coverage Guidance

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

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

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

Proton beam therapy is not recommended for coverage for ocular hemangiomas *(**weak/strong** recommendation).*

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

Note: Definitions for strength of recommendation are provided in Appendix A GRADE Element Description

RATIONALE FOR GUIDANCE DEVELOPMENT

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

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

Coverage guidance development follows to translate the evidence review to a policy decision. Coverage guidance may be based on an evidence-based guideline developed by the Evidence-based Guideline Subcommittee or a health technology assessment developed by the Heath Technology Assessment Subcommittee. In addition, coverage guidance may utilize an existing evidence report produced by one of HERC's trusted sources, generally within the last three years.

EVIDENCE SOURCES

Trusted sources

Washington State Health Care Authority Health Technology Assessment Program. (2014). Proton Beam Therapy. Olympia, WA: Health Technology Assessment Program. Retrieved January 22, 2015 from http://www.hca.wa.gov/hta/Pages/proton.aspx.

The summary of evidence in this document is derived directly from this evidence source, and portions are extracted verbatim.

EVIDENCE OVERVIEW

Clinical background

Protons are positively-charged subatomic particles that have been in clinical use as a form of external beam radiotherapy for over 60 years. Compared to the photon X-ray energy used in conventional radiotherapy, proton beams have physical attributes that are potentially appealing. Specifically, protons deposit radiation energy at or around the target, at the end of the range of beam penetration, a phenomenon known as the Bragg peak. The goal of any external beam radiotherapy is to deliver sufficient radiation to the target tumor while mitigating the effects on adjacent normal tissue. This has been a challenge for conventional photon therapy due to the amount of radiation deposited both before and after the target is reached. While the amount of photon radiation at entry into the body is much higher than at exit, photon beams typically "scatter" to normal tissues after leaving the target. This so-called "exit" dose is absent for protons, as tissue beyond the point of peak energy deposition receives little to no radiation.

Initial use of proton beam therapy (PBT) focused on conditions where sparing very sensitive adjacent normal tissues was felt to be of utmost importance, such as cancers or noncancerous malformations of the brain stem, eye, or spinal cord. In addition, proton beam therapy was advocated for many pediatric tumors because even lower-dose irradiation of normal tissue in pediatric patients can result in pronounced acute and long-term toxicity. There are also long-standing concerns regarding radiation's potential to cause secondary malignancy later in life, particularly in those receiving radiation at younger ages. Finally, radiation may produce more nuanced effects in children, such as neurocognitive impairment in pediatric patients treated with radiotherapy for brain cancers.

More recently, however, the use of PBT has been expanded in many settings to treat more common cancers such as those of the prostate, breast, liver, and lung. With the growth in potential patient numbers and reimbursement, the construction of proton centers has grown substantially. There are now 14 operating proton centers in the U.S., including one in Seattle, WA that came online in March 2013. Eleven additional centers are under construction or in the planning stages, and many more are proposed. The construction of cyclotrons at the heart of proton beam facilities is very expensive ($150-$200 million for a multiple gantry facility).

Indications

This appraisal focuses on the use of proton beam therapy (PBT) to treat patients with multiple types of cancer as well as those with selected noncancerous conditions. Within each condition type, two general populations were specified as of interest for this evaluation**:**

- Patients receiving PBT as primary treatment for their condition (i.e., curative intent)
- Patients receiving PBT for recurrent disease or for failure of initial therapy (i.e., salvage)

All forms of PBT were considered for this evaluation, including monotherapy, use of PBT as a "boost" mechanism to conventional radiation therapy, and combination therapy with other modalities such as chemotherapy and surgery. All PBT studies that met entry criteria for this review were included, regardless of manufacturer, treatment protocol, location, or other such concerns.

Conditions included in the evidence review are as follows:

- Cancers
- Bone tumors
- Brain, spinal, and paraspinal tumors
- Breast cancer
- Esophageal cancer
- Gastrointestinal cancers
- Gynecologic cancers
- Head and neck cancers (including skull base tumors)
- Liver cancer
- Lung cancer
- Lymphomas
- Ocular tumors
- Pediatric cancers (e.g., medulloblastoma, retinoblastoma, Ewing's sarcoma)
- Prostate cancer
- Soft tissue sarcomas
- Seminoma
- Thymoma
- Noncancerous Conditions
- Arteriovenous malformations
- Hemangiomas
- Other benign tumors (e.g., acoustic neuromas, pituitary adenomas)

Evidence review

A summary of the net health benefit of PBT vs. alternative treatments and the strength of available evidence on net health benefit, as well as an evaluation of consistency of these findings with clinical guideline statements and public/private coverage policy, can be found in Table 1. The level of comparative evidence was extremely limited for certain conditions and entirely absent for others. We identified a total of six RCTs and 37 nonrandomized comparative

studies across all 19 condition types. Importantly, five of the six RCTs involved different treatment protocols for PBT and had no other comparison groups; while these are included for completeness, primary attention was paid to studies (RCTs and otherwise) that compared PBT to an alternative form of treatment.

Most of the comparative studies identified also had major quality concerns. For example, nearly all non-randomized comparative studies were retrospective in nature, and many involved comparisons of a PBT cohort to a non-contemporaneous group receiving alternative therapy. Major differences in patient demographics and baseline clinical characteristics as well as duration of follow-up were often noted between groups. Of the 6 RCTs identified, 1, 4, and 1 were judged to be of good, fair, and poor quality respectively. Corresponding figures for non-randomized comparative studies were 1, 20, and 16.

As noted on Table 1, PBT was judged to have superior net health benefit for ocular tumors, and incremental net health benefit for adult brain/spinal tumors and pediatric cancers. PBT was comparable to alternative treatment options for patients with liver, lung, and prostate cancer as well as one noncancerous condition (hemangiomas). Importantly, however, the strength of evidence was low for all of these conditions. The evidence base for all other condition types was insufficient to determine net health benefit, including two of the four most prevalent cancers in the U.S.: breast and gastrointestinal (lung and prostate are the other two).

As with information on clinical effectiveness, data on potential harms of PBT come from RCTs, comparative cohort studies, and case series, although comparative harms data are still lacking for many condition types. Across all condition types, a total of 25 studies reported comparative information on treatment-related harms; differences in the types of harms relevant to each condition, as well as variability in harms classification even within conditions, precludes any attempt to summarily present harms data across all 19 condition categories.

Observational data on secondary malignancy with PBT are generally lacking. Two studies were identified with comparative information. One was a fair-quality matched retrospective cohort study comparing 1,116 patients in a linked Medicare-SEER database who received either PBT or photon radiation for a variety of cancers and were followed for a median of 6.4 years. On an unadjusted basis, the incidence rates of any secondary malignancy and malignancies occurring in the prior radiation field were numerically lower for PBT, but not statistically-significantly so. After adjustment for age, sex, primary tumor site, duration of follow-up, and year of diagnosis, PBT was associated with a risk of secondary malignancy approximately one-half that of photon therapy (HR=0.52; 95% CI: 0.32, 0.85; p=0.009). There are challenges with these findings, however. First and foremost, the lower rate of secondary malignancy with PBT appeared to be manifested almost entirely in the first five years after radiotherapy, a time period in which a second cancer event is not typically attributed to prior radiation (Bekelman, 2013). In addition, patients were accrued over a very long time period (1973-2001), only the very end of which included highly conformal photon techniques like IMRT.

The second study was a poor-quality retrospective cohort study comparing PBT to photon radiotherapy in 86 infants who were treated for retinoblastoma and followed for a median of 7 years (PBT) or 13 years (photon radiotherapy). Therapy was received at two different US centers (PBT at MGH and photon radiotherapy at Children's Hospital Boston). Kaplan-Meier

analyses were conducted to control for differential follow-up but no adjustments were made for other differences between groups. Ten-year estimates of the cumulative incidence of secondary malignancy were numerically lower for PBT, but not statistically significantly so (5% vs. 14% for photon, p=0.12). However, when malignancies were restricted to those occurring in-field or thought to be radiation-induced, a significant difference in favor of PBT was observed (0% vs. 14%, p=0.015). In addition, significant differences in favor of PBT in both cumulative incidence and radiotherapy-related malignancy were observed for the subgroup of patients with hereditary disease.

Other harms are presented in detail for each condition type in the sections that follow.

No comparative studies were identified for curative therapy of: breast, esophageal, gastrointestinal, gynecologic, and pediatric cancers; lymphomas, sarcomas, seminomas, and thymomas; arteriovenous malformations.

No comparative studies were identified for salvage treatment of: brain/spinal/paraspinal, breast, esophageal, gastrointestinal, gynecologic, pediatric, and prostate cancers; lymphomas, sarcomas, seminomas, and thymomas; arteriovenous malformations and hemangiomas.

No comparative studies of harms identified for: gastrointestinal and gynecologic cancers; lymphomas, sarcomas, seminomas, and thymomas; arteriovenous malformations.

Cancers

Bone Cancer

Curative

A single poor-quality retrospective comparative cohort study evaluated PBT for primary and recurrent sacral chordomas in 27 patients. Among these patients 21 were treated with surgery and combination PBT /photon therapy (mean radiation dose: 72.8 Gray Equivalents [GyE]), in comparison to six patients who received PBT/photons alone (mean dose: 70.6 GyE). For patients with primary tumors, Kaplan-Meier estimates of local control, disease-free survival and overall survival exceeded 90% among those treated by surgery and radiation (n=14). Only two of the six patients with primary tumors received radiation alone, one of whom had local failure at four years, distant metastases at five years, and died at 5.5 years.

Salvage

In the same study of 27 patients with sacral chordomas who were treated with PBT/photon radiation alone or in combination with surgery, seven radiation/surgery patients and four radiation-only patients had recurrent disease. Among patients in the radiation/surgery group, four patients died of disease 4-10 years after treatment; the remainder was alive with disease at last follow-up. In the radiation-only group, two of four patients died of disease at 4-5 years of follow-up; the other two were alive with disease at last follow-up.

Harms

In the study described above, multiple descriptive harms were reported. Patients receiving radiation alone reported numerically lower rates of abnormal bowel or bladder function as well as difficulty ambulating in comparison to those receiving combination therapy, but rates were not statistically tested. PBT patients also reported higher rates of return to work, although this

was also not tested statistically. Evidence is thus inadequate to compare the potential harms of PBT relative to other radiation modalities in patients with bone cancer.

Brain, Spinal, and Paraspinal Tumors

Curative

Two poor-quality retrospective comparative cohort studies investigated primary PBT for brain, spinal, and paraspinal tumors. One was an evaluation of PBT (mean dose: 54.6 GyE) vs. photon therapy (mean dose: 52.9 Gy) in 40 adults (mean age: 32 years; 65% male) who received surgical and radiation treatment of medulloblastoma at a single US cancer center. PBT patients were followed for a median of 2.2 years, while photon patients were followed for a median of nearly five years. No statistical differences between radiation modalities were seen in Kaplan-Meier assessment of either overall or progression-free survival at two years. A numeric difference was seen in the rate of local or regional failure (5% for PBT vs. 14% for photon), but this was not assessed statistically.

The second study involved 32 patients treated for intramedullary gliomas with either PBT (n=10) or IMRT (n=22). While explicit comparisons were made between groups, the PBT population was primarily pediatric (mean age: 14 years), while the IMRT population was adult (mean age: 44 years). Patients in both groups were followed for a median of 24 months; dose was >50 GyE or Gy in approximately 75% of patients. While the crude mortality rate was lower in the PBT group (20% vs. 32% for IMRT, not tested), in multivariate analyses controlling for age, tumor pathology, and treatment modality, PBT was associated with significantly increased mortality risk (Hazard Ratio [HR]: 40.0, p=0.02). The rate of brain metastasis was numerically higher in the PBT group (10% vs. 5% for IMRT), but this was not statistically tested. Rates of local or regional recurrence did not differ between groups.

Harms

In the first study described above, PBT was associated with statistically-significantly lower rates of weight loss (median % of baseline: -1.2% vs. 5.8% for photon, p=0.004) as well as requirements for medical management of esophagitis (5% vs. 57% respectively, p<0.001). PBT patients also experienced less RTOG grade 2 or greater nausea and vomiting (26% vs. 71%, p=0.004).

In the second study comparing primarily 10 pediatric patients (mean age: 14 years) receiving PBT for spinal cord gliomas to 22 adults receiving IMRT for the same condition (mean age: 44 years) (Kahn, 2011), no cases of long-term toxicity or myelopathy were reported in either group. Minor side-effect rates were reported for the overall cohort only. In summary, limited, low-quality evidence suggests that PBT is associated with reductions in acute radiation-related toxicity relative to photon radiation in patients with brain and spinal tumors.

Table 1: Summary table assessing strength of evidence, direction of benefit, and consistency with relevant guideline statements and coverage policy.

Condition	Incidence (per 100,000)	Net Health Benefit vs. Comparators	Type of Net Health Benefit	Strength of Evidence	Guideline Recommendations	Coverage Policies
Cancer						
Bone	1.3	Insufficient	---	+	M	M
Brain/spinal	9.6	Incremental	B: = H: ↓	+	U	U
Breast	97.7	Insufficient	---	o	NM	NR/NC
Esophageal	7.5	Insufficient	---	o	NM	NR/NC
GI	100.6	Insufficient	---	o	NM	NR/NC
Gynecologic	38.2	Insufficient	---	o	NM	NR/NC
Head/neck	17.2	Insufficient	---	+	NM	M
Liver	12.8	Comparable	B: = H: =	+	NM	M
Lung	95.0	Comparable	B: = H: =	+	M	M
Lymphomas	32.9	Insufficient	---	o	NR/NC	NR/NC
Ocular	1.2	Superior	B: ↑ H: ↓	++	U	U
Pediatric	9.1	Incremental	B: = H: ↓	+	U	U
Prostate	99.4	Comparable	B: = H: =	+	M	M
Sarcomas	4.8	Insufficient	---	o	NM	M
Seminoma	4.0	Insufficient	---	o	NM	NM
Thymoma	0.2	Insufficient	---	o	NM	NM
Noncancerous						
AVMs	1.0	Insufficient	---	o	NM	M
Hemangiomas	2.0	Comparable	B: = H: =	+	NM	NM
Other	2.0	Insufficient	---	o	NM	M

B: Benefits; H: Harms

Strength of Evidence: Low=+; Moderate=++; High=+++; No evidence=o

Legend: U = Universally recommended or covered; M=Mixed recommendations or coverage policies; NM=Not mentioned in guidelines or coverage policies; NR/NC=Not recommended or not covered

Esophageal Cancer

Harms

Two studies were identified that examined comparative harms in patients treated with PBT for esophageal cancer. One was a relatively large, fair-quality, retrospective comparative cohort study of 444 patients (median age: 61 years; 91% male) who were treated with chemotherapy and radiation (PBT, IMRT, or 3D-CRT) followed by surgical resection. Patients were followed for up to 60 days after hospital discharge. After adjustment for patient characteristics and clinical variables, 3D-CRT was associated with a significantly greater risk of postoperative pulmonary complications vs. PBT (Odds Ratio [OR]: 9.13, 95% CI: 1.83, 45.42). No significant differences were observed between PBT and IMRT, however. No differences in the rate of gastrointestinal complications were observed for any treatment comparison.

In addition, a fair-quality comparative study was identified that examined early impact on lung inflammation and irritation in 75 patients receiving PBT, IMRT, or 3D-CRT for esophageal cancer; patients were followed for up to 75 days following radiation. Nearly all outcome and toxicity measures were reported for the entire cohort only. However, the rate of pneumonitis was found to be significantly higher among PBT patients (33% vs. 15% for IMRT/3D-CRT, p=0.04). In summary, evidence is inadequate to compare the potential harms of PBT relative to other radiation modalities in patients with esophageal cancer, particularly in comparison to IMRT.

Head and Neck Cancers

Curative

There were two poor-quality retrospective comparative cohorts of primary PBT in head and neck cancer. One was an evaluation of 33 patients treated with either PBT alone or PBT+photon therapy to a target dose of 76 Gy for a variety of head and neck malignancies in Japan. Treatment groups differed substantially in terms of age, gender, and duration of follow-up (mean: 5.9 vs. 3.1 years). Numeric differences in favor of PBT+photon therapy were seen for local control, recurrence, and mortality, but these were not statistically tested, nor were multivariate adjustments made for differences between groups.

The other study was a very small (n=6) comparison of endoscopic resection followed by either PBT or IMRT as well as endoscopy alone in patients with malignant clival tumors. Limited description of the study suggests that PBT was used only in cases of residual disease, while it is unclear whether IMRT was also used in this manner or as an adjuvant modality. One of the IMRT patients died of causes unrelated to disease; no other deaths were reported.

Salvage

In the first study described above, four patients were identified as having recurrent disease, three of whom received PBT alone. Two of the three PBT-only patients were alive with local tumor control at last follow-up (5 and 17 years respectively); one patient had their cancer recur three months after PBT and died in month 7 of follow-up. The one PBT+photon patient died at 2.5 years of follow-up, but was described as having local tumor control.

Harms

In the first study describe above, rates of tongue ulceration, osteonecrosis, and esophageal stenosis differed somewhat between treatment groups, but were not statistically tested. Overall toxicity rates were estimated to be 22.8% at both three and five years, but were not stratified by treatment modality.

In a separate, fair-quality study comparing rates of vision loss from radiation-induced optic neuropathy in 75 patients treated with PBT or carbon-ion therapy for head and neck or skull base tumors, unadjusted rates of vision loss were similar between modalities (8% and 6% for PBT and carbon-ion respectively, not statistically tested). In multivariate analyses controlling for demographic and clinical characteristics, treatment modality had no effect on rates of vision loss (p=0.42). Another comparison of PBT and carbon-ion therapy in 59 patients with head and neck or skull base tumors was of poor quality (due to no control for differences between patient groups) and focused on the incidence of radiation-induced brain changes. The incidence of CTCAE brain injury of any grade was significantly (p=0.002) lower in the PBT group. MRI-based assessment of brain changes showed a lower rate in the PBT group (17% vs. 64% for carbon-ion), although this was not tested statistically. In summary, evidence is inadequate to compare the potential harms of PBT relative to other radiation modalities in patients with head and neck cancer.

Liver Cancer

Curative

Two fair-quality prospective comparative cohort studies provided evidence of the clinical effectiveness of primary use of PBT in liver cancer. One was an evaluation of 35 patients with unresectable hepatocellular carcinoma (HCC) who were treated with PBT (mean dose: 76.5 GyE) either alone or in combination with chemotherapy and were followed for up to 4 years. While statistical testing was not performed, rates of local tumor control and the proportion of patients experiencing reductions in tumor volume were nearly identical between groups.

The other study was also prospective but compared PBT to another heavy-ion modality not in circulation in the U.S. (carbon ion). In this study, a fair-quality comparison of 350 patients with HCC who received PBT (53-84 GyE) or carbon-ion (53-76 GyE) therapy and were followed for a median of 2.5 years, no statistically-significant differences were observed in 5-year Kaplan-Meier estimates of local control, no biological evidence of disease, or overall survival between treated groups.

Salvage

Two studies were identified with information on recurrent disease. One was a poor-quality comparison of PBT to conventional photon radiation in eight patients with recurrent HCC after hepatectomy. Five patients were treated with PBT (68.8-84.5 GyE), and three with photons (60-70 Gy). Seven of eight patients died of liver failure or lung metastasis a median of 1.5 years after radiation; the one patient alive at the end of follow-up was a photon patient. The rate of local tumor control was 78%, and did not differ between treatment groups.

The other study was a previously-described prospective comparison of PBT to carbon-ion therapy in 350 patients with primary or recurrent HCC. No subgroup analyses were performed, but prior treatment history for HCC was found not to have a statistically-significant impact on local tumor control (p=0.73). Prior treatment was not examined as a risk factor for overall survival, however.

Harms

Two comparative studies were identified with comparative information on radiation-related harms. In a previously-described study of eight patients with recurrent HCC after hepatectomy, there were no instances of bone marrow depression or gastrointestinal complications in either group. Serum aspartate aminotransferase (AST) levels increased in the three photon patients and 4/5 PBT patients, although this was not tested statistically.

In the other study, a previously-described comparison of PBT to carbon-ion therapy in 350 patients with primary or recurrent HCC, rates of toxicities as graded by the Common Terminology Criteria for Adverse Events (CTCAE) framework were comparable between groups, including dermatitis, GI ulcer, pneumonitis, and rib fracture. The rate of grade 3 or higher toxicities was similar between groups (3% vs. 4% for PBT and carbon-ion respectively), although this was not statistically tested.

In summary, limited, low-quality evidence suggests that PBT is associated with comparable rates of toxicity to other radiation modalities in patients with liver cancer.

Lung Cancer

Curative

Three fair-quality comparative cohort studies examined the clinical effectiveness of PBT in lung cancer. Two studies retrospectively compared outcomes with PBT to those with IMRT or older three-dimensional conformal radiotherapy (3D-CRT) at a US cancer center. One study involved 250 patients with non-small-cell lung cancer (NSCLC) who were treated with 66 Gy of photons or 74 GyE of protons and followed for up to one year to assess a key measure of lung function known as diffusing capacity of lung for carbon monoxide (DLCO). While this measure did not differ between PBT and IMRT at 5-8 months after treatment, DLCO declined significantly more in the 3D-CRT group as compared to PBT after adjustment for pretreatment characteristics and other lung function measures (p=0.009).

A second study focused on survival in 202 patients with locally-advanced, unresectable NSCLC who were followed for a median of 1.5 years and treated 74 GyE of PBT or 63 Gy of either IMRT or 3D-CRT. Actuarial estimates of median overall survival were 24.4, 17.6, and 17.7 months for PBT, IMRT, and 3D-CRT respectively, although these differences were not statistically significant (p=0.1061).

A third study was a prospectively-measured cohort but, as with the study of liver cancer mentioned above, compared PBT to carbon ion therapy, evaluating 111 Japanese NSCLC patients over a median of 3.5 years. No statistically-significant differences between groups were observed in three-year actuarial estimates of local control, progression-free survival, or overall survival.

Salvage

In the second study described above, 22% of the study sample was identified as having a prior malignancy of any type. The effects of prior malignancy on overall survival were not reported, however.

Harms

A total of three comparative studies assessed harms in patients with lung cancer. One was a study of severe radiation-induced esophagitis (within six months of treatment) among 652 patients treated for NSCLC with PBT, IMRT, or 3D-CRT at a US cancer center. Rates of grade 3 or higher esophagitis were 6%, 8%, and 28% for PBT, 3D-CRT, and IMRT respectively ($p<.05$ for PBT and 3D-CRT vs. IMRT).

In the previously-described noncontemporaneous case series comparison of patients with locally-advanced, unresectable NSCLC who were treated with PBT, IMRT, or 3D-CRT, hematologic toxicity rates did not differ by radiation modality. Significant differences in favor of PBT were seen in rates of grade 3 or higher esophagitis (5%, 39%, and 18% for PBT, IMRT, and 3D-CRT respectively, $p<0.001$) as well as pneumonitis (2%, 6%, and 30%, $p<0.001$), while rates of grade 3 or higher dermatitis were significantly greater in the PBT group (24% vs. 17% and 7% for IMRT and 3D-CRT, $p<0.001$).

Finally, in a previously-described comparison of PBT to carbon-ion therapy in 111 patients in Japan, rates of pneumonitis, dermatitis, and rib fracture did not differ statistically between radiation modalities across all toxicity grades. In summary, moderate evidence suggests that rates of treatment-related toxicities with PBT are comparable to those seen with other radiation modalities in patients with lung cancer.

Ocular Tumors

Curative

In comparison to other cancer types, the evidence base for ocular tumors was relatively substantial. A total of seven comparative studies were identified of the clinical benefits of primary PBT in such cancers—a single RCT, four retrospective cohort studies, a comparison of a recent case series to the treatment groups from the RCT, and a comparison of noncontemporaneous case series. The RCT compared PBT alone to a combination of PBT and transpupillary thermotherapy (TTT) in 151 patients treated for uveal melanoma and followed for a median of 3 years. Combination therapy was associated with a statistically-significantly ($p=0.02$) reduced likelihood of secondary enucleation; no other outcomes differed significantly between groups. In a separate, poor-quality comparison of these findings to a separate series of patients undergoing PBT with endoresection of the scar, rates of secondary enucleation did not differ between groups, but rates of neovascular glaucoma were significantly lower in the PBT+endoresection group vs. the groups from the RCT (7% vs. 58% and 49% for PBT alone and PBT+TTT respectively, $p<0.0001$). Of note, however, median follow-up was less than two years in the PBT+endoresection series vs. 9 years in the RCT.

Three of the cohort studies were all fair-quality and involved comparisons to surgical enucleation in patients with uveal melanoma at single centers. PBT was associated with statistically-significant improvements in overall survival rates relative to enucleation at 2-5 years in two of these studies. Rates of metastasis-related and all cancer-related death were statistically-significantly lower among PBT patients through two years of follow-up in one study (n=1,051), but were nonsignificant at later timepoints. The 5-year metastasis-free survival rate in a second study (n=67) was 50% higher among PBT patients in a Cox regression model controlling for baseline characteristics (59.0% vs. 39.4% for enucleation, p=0.02). In the third study, Kaplan-Meier curves for all-cause mortality, melanoma-related mortality and metastasis-free survival did not statistically differ for 132 patients treated with PBT and enucleation. Metastasis-free survival also did not differ in Cox regression adjusting for age, sex, and tumor thickness.

Another fair-quality study assessed the impact of PBT + chemotherapy vs. PBT alone in 88 patients with uveal melanoma who were followed for 5-8 years. Five-year overall survival rates did not statistically differ between groups on either an unadjusted or Cox regression-adjusted basis.

Finally, a poor-quality comparison of noncontemporaneous case series evaluated treatment with PBT + laser photocoagulation or PBT alone in 56 patients with choroidal melanoma. At one year, there were no differences in visual acuity between groups.

Salvage

A single comparative study examined PBT in recurrent ocular cancer. In this fair-quality, comparative cohort study, a total of 73 patients with uveal melanoma had recurrence of disease following an initial course of PBT at a US hospital. Patients (mean age: 58 years) were treated with either a second course of PBT (70 GyE) in five fractions or surgical enucleation and followed for 5-7 years. The likelihood of overall survival at five years was significantly (p=0.04) longer in the PBT group (63% vs. 36% for enucleation), as was the probability of being free of metastasis at this timepoint (66% vs. 31% respectively, p=0.028). Findings were similar after Cox proportional hazards regression adjusting for tumor volume and year of retreatment as well as patient age. The likelihood of local tumor recurrence at five years was 31% in the PBT group. No local recurrences were found in the enucleation group, which is not surprising given the nature of the treatment.

Harms

Two comparative studies assessed the harms of PBT for ocular cancers. In the previously-described RCT comparing PBT with thermotherapy to PBT alone in 151 patients with uveal melanoma, no statistically-significant differences were observed between groups in rates of cataracts, maculopathy, papillopathy, glaucoma, or intraocular pressure. The combination therapy group had a significantly lower rate of secondary enucleation (p=0.02), although actual figures were not reported.

In a previously-described comparison of PBT to enucleation in 132 patients treated for unilateral choroidal tumors, rates of eye loss in the PBT arm were assessed and estimated to be 26% at five years of follow-up. In summary, limited, low-quality evidence suggests comparable rates of harm for PBT relative to treatment alternatives in patients with ocular tumors.

Pediatric Cancers

Harms

PBT's theoretical potential to lower radiation-induced toxicity in children serves as the comparative evidence base. Comparative studies are lacking, most likely due to a lack of clinical equipoise.

Other than the study of secondary malignancy described above, no comparative studies of the potential harms of PBT in patients with pediatric cancers were identified.

Prostate Cancer

Curative

The largest evidence base available was for prostate cancer (10 studies). However, only 6 of these studies reported clinical outcomes *and* compared PBT to alternative treatments. These included an RCT, a prospective comparative cohort, and four comparisons of noncontemporaneous case series.

The included RCT was a fair-quality comparison of 202 patients with advanced (stages T3-T4) prostate cancer who were randomized to receive either photon therapy with a proton boost (total dose: 75.2 GyE) or photons alone (67.2 Gy) and were followed for a median of five years. Kaplan-Meier estimates of local tumor control, disease-specific survival, and overall survival were similar at both 5- and 8-year timepoints among the entire intent-to-treat population as well as those completing the trial (n=189). However, in patients with poorly-differentiated tumors (Gleason grades 4 or 5), local control at 8 years was significantly better in patients receiving PBT+photons (85% vs. 40% for photons alone, p=0.0014).

The prospective cohort study was a fair-quality comparison of patient-reported health-related QoL at multiple timepoints among 185 men (mean age: 69 years) with localized prostate cancer who were treated with PBT, PBT+photons, photons alone, surgery, or watchful waiting. Overall QoL, general health status, and treatment-related symptom scales were employed. No differences in overall QoL or general health status were observed at 18 months of follow-up, although men treated with PBT monotherapy reported better physical function in comparison to surgery (p=0.01) or photon radiation (p=0.02), and better emotional functioning in relation to photon radiation (p<0.001). Men receiving PBT+photons also reported significantly fewer urinary symptoms at 18 months in comparison to watchful waiting (p<0.01).

Outcomes were also assessed in three comparisons of noncontemporaneous case series. One was a fair-quality evaluation of high-dose PBT+photons (79.2 GyE) in 141 patients enrolled in a clinical trial who were matched on clinical and demographic criteria to 141 patients treated with brachytherapy. Patients were followed for a median of eight years. Eight-year actuarial estimates of overall survival, freedom from metastasis, and biochemical failure did not statistically differ between groups. The proportion of patients achieving a nadir PSA level of ≤0.5 ng/mL as of their final measurement was significantly higher in the brachytherapy group (92% vs. 74% for PBT, p=0.0003).

Two additional studies were deemed to be of poor quality due to a lack of control for confounding between study populations. One was a comparison of a cohort of 206 brachytherapy patients compared with the same PBT+photon group described above. The difference in the percentage of patients achieving nadir PSA after a median of 5.4 years of follow-up was similar to that reported in the study above (91% vs. 59%), although statistical results were not reported. Five-year estimates of disease-free survival (using biochemical failure definitions) did not statistically differ between groups. The other study involved comparisons of bowel- and urinary-related QoL in three distinct cohorts receiving PBT (n=95; 74-82 GyE), IMRT (n=153; 76-79 Gy), or 3D-CRT (n=123; 66-79 Gy). Statistical changes were assessed within (but not between) each cohort immediately following treatment as well as at 12 and 24 months of follow-up, and were also assessed for whether the change was considered "clinically meaningful" (>0.5 SD of baseline values). Some differences in QoL decrements were seen at earlier timepoints. However, at 24 months, all groups experienced statistically and clinically significant decrements in bowel QoL, and none of the groups had significant declines in urinary QoL.

A fourth, poor-quality comparison of case series involved an evaluation of patient-reported outcomes on the Expanded Prostate Cancer Index Composite (EPIC) questionnaire among a cohort of 1,243 patients receiving PBT for prostate cancer and a group of 204 patients receiving IMRT from a previous multicenter study. Statistically-significant differences between treatment groups were observed for many baseline characteristics, only some of which were adjusted for in multivariate analyses. No differences were observed in summary scores for bowel, urinary, and sexual QoL at two years, although more IMRT patients reported specific bowel frequency (10% vs. 4% for PBT, p=0.05) and urgency (15% vs. 7%, p=0.02) problems at two years.

Harms

Four comparative studies examined the harms associated with PBT and alternative treatments in patients with prostate cancer. The previously-described RCT of PBT+photon therapy vs. photons alone examined rates of rectal bleeding, urethral stricture, hematuria, incontinence, and loss of full potency; no patients in either arm had grade 3 or higher toxicity during radiation therapy. Actuarial estimates of rectal bleeding at eight years were significantly higher in the PBT+photon arm (32% vs. 12% for photons alone, p=0.002), although this was primarily grade 2 or lower toxicity. Rates of urethral stricture, hematuria, incontinence, and loss of potency did not differ between groups.

Three additional studies involved retrospective comparisons using available databases. The most recent was a matched comparison of 314 PBT and 628 IMRT patients treated for early-stage prostate cancer using the linked Chronic Condition Warehouse-Medicare database with a focus on complications occurring within 12 months of treatment. At six months, rates of genitourinary toxicity were significantly lower in the PBT arm (5.9% vs. 9.5%, p=0.03). This difference was not apparent after 12 months of follow-up, however (18.8% vs. 17.5%, p=0.66). Rates of gastrointestinal and other (e.g., infection, nerve damage) complications did not statistically differ at either timepoint.

Another recent study compared matched cohorts of men with prostate cancer in the linked Medicare-SEER database who were treated with PBT or IMRT (684 patients in each arm) and followed for a median of four years. IMRT patients had a statistically-significantly lower rate of gastrointestinal morbidity (12.2 vs. 17.8 per 100 person-years, $p<0.05$). No other statistical differences were noted in genitourinary morbidity, erectile dysfunction, hip fracture, or use of additional cancer therapy.

Finally, there was an analysis of nearly 30,000 men in the Medicare-SEER database who were treated with PBT, IMRT, 3D-CRT, brachytherapy, or conservative management (observation alone) and evaluated for gastrointestinal toxicity. All forms of radiation had higher rates of GI morbidity than conservative management. In pairwise comparisons using Cox proportional hazards regression, PBT was associated with higher rates of GI morbidity than conservative management (HR: 13.7; 95% CI: 9.1, 20.8), 3D-CRT (HR: 2.1; 95% CI: 1.5, 3.1), and IMRT (HR: 3.3; 95% CI: 2.1, 5.2).

In summary, moderate evidence suggests that rates of major harms are comparable between PBT and photon radiation treatments, particularly IMRT.

Noncancerous Conditions

Hemangiomas

Curative

A single poor-quality retrospective study evaluated PBT's clinical effectiveness in 44 patients with diffuse or circumscribed choroidal hemangiomas who were treated with either PBT (20-23 GyE) or photon therapy (16-20 Gy) and followed for an average of 2.5 years. Unadjusted outcomes were reported for the entire cohort only; reduction in tumor thickness, resolution of retinal detachment, and stabilization of visual acuity were observed in >90% of the overall sample. In Kaplan-Meier analysis of outcomes adjusting for differential follow-up between treatment groups, therapeutic modality had no statistically-significant effects on stabilization of visual acuity ($p=0.43$).

Harms

A single, previously-described retrospective comparative cohort study assessed outcomes in patients with circumscribed or diffuse hemangiomas treated with PBT or photon radiation. Small differences in unadjusted rates of optic nerve/disc atrophy, lacrimation (formation of tears) and ocular pressure as well as effects on the retina, lens, and iris were observed between groups, but most side effects were grade 1 or 2. The rate of retinopathy was substantially higher in PBT patients (40% vs. 16% for photons). However, in Cox proportional hazards regression adjusting for between-group differences, no effect of radiation modality on outcomes was observed, including retinopathy ($p=0.12$).

Other Benign Tumors

Curative

Two comparative studies of PBT's clinical effectiveness in other benign tumors were both of poor quality. One was a retrospective cohort of consisting of 20 patients with giant-cell bone tumors who were treated with PBT+photon therapy (mean: 59 GyE) or photons alone (mean: 52

Gy) and followed for median of 9 years. Patients could also have received partial tumor resection. Of note, the PBT population consisted entirely of young adults (mean age: 23 years), while the photon-only population was much older (mean: 46 years); no attempt was made to control for differences between treatment groups. Rates of disease progression, progression-free survival, and distant metastases were numerically similar between groups, although these rates were not statistically tested.

The other study was a small cohort study comparing PBT alone, photon therapy alone, or PBT + photons in 25 patients with optic nerve sheath meningioma. On an overall basis, visual acuity improved in most patients. Rates did not numerically differ between treatment groups, although these were not tested statistically.

Salvage

In the first study described above, five of 20 were identified as having recurrent disease. Two of the five were treated with PBT+photon therapy, one of whom had progression of disease at eight months but no further progression after retreatment at five years of follow-up. The other patient was free of local progression and metastases as of 9 years of follow-up. In the three photon patients, one had local progression at 12 months but no further progression as of year 19 of follow-up, one patient was free of progression and metastases as of five years of follow-up, and one patient had unknown status.

Harms

The previously-described study comparing PBT, PBT+photon, and photon therapy alone in 25 patients treated for optic nerve sheath meningiomas showed numerically lower rates of acute orbital pain and headache for both PBT groups compared to photon therapy, and numerically higher rates of late asymptomatic retinopathy. None of these comparisons were tested statistically, however. Evidence is limited and inadequate to compare the potential harms of PBT relative to other radiation modalities in patients with other benign tumors.

Cost & Cost-Effectiveness

Limited data are available about costs of PBT in most types of cancer. One study of breast cancer patients in the US examined reimbursement for treatment with 3D-conformal partial breast irradiation using protons or photons vs. traditional whole breast irradiation. Payments included those of treatment planning and delivery as well as patient time and transport. Total per-patient costs were substantially higher for PBT vs. photon partial irradiation ($13,200 vs. $5,300) but only modestly increased relative to traditional whole breast irradiation ($10,600), as the latter incurred higher professional service fees and involved a greater amount of patient time. Two additional studies from the same group assessed the cost-effectiveness of PBT vs. photon radiation among women with left-sided breast cancer in Sweden. In the first of these, photon radiation was assumed to increase the risk of ischemic and other cardiovascular disease as well as pneumonitis relative to PBT; clinical effectiveness was assumed to be identical. Reductions in adverse events led to a gain in quality-adjusted life years (QALYs) equivalent to approximately one month (12.35 vs. 12.25 for photon). Costs of PBT were nearly triple those of photon therapy, however ($11,124 vs. $4,950), leading to an incremental cost-effectiveness ratio (ICER) of $65,875 per QALY gained. The other study used essentially the same model but

focused attention only on women at high risk of cardiac disease (43% higher than general population). In this instance, a much lower ICER was observed ($33,913 per QALY gained).

One study evaluated the economic impact of PBT in lung cancers among patients in the Netherlands. A Markov model compared PBT to carbon-ion therapy, stereotactic radiation therapy, and conventional radiation in patients with stage 1 non-small-cell lung cancer (NSCLC) over a 5-year time horizon. Effects of therapy included both overall and disease-related mortality as well as adverse events such as pneumonitis and esophagitis. For inoperable NSCLC, PBT was found to be both more expensive and less effective than either carbon-ion or stereotactic radiation and was therefore not included in subsequent analyses focusing on inoperable disease. While not reported in the paper, PBT's derived cost-effectiveness relative to conventional radiation (based on approximately $5,000 in additional costs and 0.35 additional QALYs) was approximately $18,800 per QALY gained.

Three decision analyses were available that focused on pediatric cancers, all of which focused on a lifetime time horizon in children with medulloblastoma who were treated at 5 years of age. In a US-based model that incorporated costs and patient preference (utility) values of treatment and management of adverse events such as growth hormone deficiency, cardiovascular disease, hypothyroidism, and secondary malignancy, PBT was found to generate lower lifetime costs ($80,000 vs. $112,000 per patient for conventional radiation) and a greater number of QALYs (17.37 vs. 13.91). Reduced risks for PBT were estimated based on data from dosimetric and modeling studies. Sensitivity analyses on the risk of certain adverse events changed the magnitude of PBT's cost-effectiveness, but it remained less costly and more effective in all scenarios.

Pediatric medulloblastoma was assessed in two modeling studies. As with the analysis above, PBT was assumed to reduce both mortality and nonfatal adverse events relative to conventional photon therapy. On a per-patient basis, PBT was assumed to reduce lifetime costs by approximately $24,000 per patient and increase quality-adjusted life expectancy by nearly nine months (12.8 vs. 12.1 QALYs). On a population basis, 25 medulloblastoma patients treated by PBT would have lifetime costs reduced by $600,000 and generate an additional 17.1 QALYs relative to conventional photon radiation.

Finally, four studies were identified that examined costs and cost-effectiveness of PBT for prostate cancer. An analysis of the 2008-2009 Chronic Condition Warehouse examined treatment costs for matched Medicare beneficiaries with prostate cancer who received PBT or IMRT. Median Medicare reimbursements were $32,428 and $18,575 for PBT and IMRT respectively (not statistically tested).

A relatively recent Markov decision analysis estimated the lifetime costs and effectiveness of PBT, IMRT, and stereotactic body radiation therapy (SBRT) for localized prostate cancer. Clinical effectiveness and impact on mortality were assumed to be equivalent across all three groups. SBRT was found to have the lowest treatment costs and shortest time in treatment of the three modalities, and produced slightly more QALYs (8.11 vs. 8.05 and 8.06 for IMRT and PBT respectively) based on an expected rate of sexual dysfunction approximately half that of IMRT or PBT. SBRT was cost-saving or cost-effective vs. PBT in 94% of probabilistic simulations.

An earlier decision analysis estimated the potential cost-effectiveness of a hypothetically-escalated PBT dose (91.8 GyE) vs. 81 Gy delivered with IMRT over a 15-year time horizon. The model focused on mortality and disease progression alone (i.e., toxicities were assumed to be similar between groups), and assumed a 10% reduction in disease progression from PBT's higher dose. This translated into QALY increases of 0.42 and 0.46 years in 70- and 60-year-old men with intermediate-risk disease respectively. Costs of PBT were $25,000-$27,000 higher in these men. ICERs for PBT vs. IMRT were $63,578 and $55,726 per QALY for 70- and 60-year-old men respectively.

Finally, the model also evaluated costs and outcomes for a hypothetical cohort of 300 65 year-old men with prostate cancer. PBT was assumed to result in a 20% reduction in cancer recurrence relative to conventional radiation as well as lower rates of urinary and gastrointestinal toxicities. PBT was estimated to be approximately $8,000 more expensive than conventional radiation over a lifetime but result in a QALY gain of nearly 4 months (0.297). The resulting cost-effectiveness ratio was $26,481 per QALY gained.

EVIDENCE SUMMARY

Proton beam therapy (PBT) has been used for clinical purposes for over 50 years and has been delivered to tens of thousands of patients with a variety of cancers and noncancerous conditions. Despite this, evidence of PBT's comparative clinical effectiveness and comparative value is lacking for nearly all conditions under study in this review. As mentioned previously, it is unlikely that significant comparative study will be forthcoming for childhood cancers despite uncertainty over long-term outcomes, as the potential benefits of PBT over alternative forms of radiation appear to be generally accepted in the clinical and payer communities. In addition, patient recruitment for potential studies may be untenable in very rare conditions (e.g., thymoma, arteriovenous malformations). In other areas, however, including common cancers such as breast and prostate, the poor evidence base and residual uncertainty around the effects of PBT is highly problematic.

The net health benefit of PBT relative to alternative treatments is rated "Superior" (moderate-large net health benefit) in ocular tumors and "Incremental" (small net health benefit) in adult brain/spinal and pediatric cancers. The net health benefit is judged "Comparable" (equivalent net health benefit) in several other cancers, including liver, lung, and prostate cancer, as well as ocular hemangiomas. It should be noted, however, that judgments of comparability were made based on a limited evidence base that provides relatively low certainty that PBT is roughly equivalent to alternative therapies. While further study may reduce uncertainty and clarify differences between treatments, it is currently the case that PBT is far more expensive than its major alternatives, and evidence of its short or long-term relative cost-effectiveness is lacking for many of these conditions. It should also be noted that evidence was examined for 11 cancers and noncancerous conditions not listed above, and it was determined that there was insufficient evidence to obtain even a basic understanding of PBT's comparative clinical effectiveness and comparative value.

GRADE-Informed Framework

The HERC develops recommendations by using the concepts of the Grading of Recommendations Assessment, Development and Evaluation (GRADE) system. GRADE is a transparent and structured process for developing and presenting evidence and for carrying out the steps involved in developing recommendations. There are four elements that determine the strength of a recommendation, as listed in the table below. The HERC reviews the evidence and makes an assessment of each element, which in turn is used to develop the recommendations presented in the coverage guidance box. Balance between desirable and undesirable effects, and quality of evidence, are derived from the evidence presented in this document, while estimated relative costs, values and preferences are assessments of the HERC members.

Indication/ Intervention	Balance between desirable and undesirable effects	Quality of evidence*	Resource allocation	Variability in values and preferences	Coverage recommendation	Rationale
PBT for ocular tumors (excluding hemangiomas)	Superior benefit, fewer harms	Moderate	Moderate; expensive, but lowered projected costs due to greater benefit and fewer harms	Low variability (preference for PBT)	Recommended for coverage (*strong recommendation)*	Moderate quality evidence demonstrates PBT is superior to other therapies with fewer harms, although at a greater cost, and many patients would choose this.
PBT for adult malignant brain/spinal tumors	Comparable benefit but fewer harms.	Very Low**	Moderate; expensive, but lowered projected costs due to fewer harms	Low variability (preference for PBT)	Recommended for coverage (*weak recommendation*)	There is very low quality evidence of incremental benefit compared to alternatives, but also with higher costs. People would likely choose what is thought to have fewer harms and

Indication/ Intervention	Balance between desirable and undesirable effects	Quality of evidence*	Resource allocation	Variability in values and preferences	Coverage recommendation	Rationale
						greater benefit.
PBT for skull base, paranasal sinus, and juxtaspinal tumors	Comparable benefit but fewer harms.	Very Low**	Moderate, expensive, but lowered projected costs due to fewer harms	Low (preference for PBT)	Recommended for coverage *(weak recommendation)*	The subcommittee heard expert testimony that skull-base tumors were one of the first uses of proton beam therapy in the 1960s and that reduction in harms to surrounding structures while delivering adequate dosimetry to tumor tissue is the primary consideration in treatment planning. Based on comparable benefit and fewer harms, allowing for higher costs but patient preference, weak recommendation for coverage.
PBT for malignant pediatric tumors	Comparable benefit but fewer harms.	Very Low**	Moderate, expensive, but lowered projected	Moderate (significant concerns regarding	Recommended for coverage *(weak recommendation)*	Very low quality evidence suggests comparable benefit, and fewer harms,

Indication/ Intervention	Balance between desirable and undesirable effects	Quality of evidence*	Resource allocation	Variability in values and preferences	Coverage recommendation	Rationale
			costs due to fewer harms	radiation therapy, given variety of tumors may have options for alternative therapies)		with a potential health impact over decades. There is a strong theoretical benefit for reducing secondary tumors although there is not good evidence to support this. Cost-effectiveness analyses suggest long term cost savings with PBT for pediatric tumors. There is a lack of clinical equipoise and therefore future studies on this are unlikely.
PBT for liver cancer	Comparable benefit, comparable harms	Low	High	Moderate	Do not recommend (*weak recommendation*)	There is sufficient evidence that PBT has comparable benefits and harms to alternatives, but is more expensive,
PBT for lung cancer	Comparable benefit, comparable harms	Low	High	Moderate	Do not recommend (*weak recommendation*)	Sufficient evidence of similar effectiveness, similar risk, and

Indication/ Intervention	Balance between desirable and undesirable effects	Quality of evidence*	Resource allocation	Variability in values and preferences	Coverage recommendation	Rationale
						more cost.
PBT for prostate cancer	Comparable benefit, comparable harms	Low	High	Moderate	Do not recommend (*weak recommendation*)	There is sufficient evidence of similar effectiveness, similar risk, and more cost. There may be improved local control in poorly differentiated prostate cancer (Glisan 4-5) but no demonstrated impact on survival
PBT for ocular hemangiomas	Comparable benefit, comparable harms	Very Low	High	Moderate to high, due to uncertainty of benefit	OPTION1 (prior recommendation) Do not recommend (*strong recommendation*) OPTION 2 (staff recommendation) Do not recommend *(weak recommendation)*	Insufficient evidence exists, but it is suggesting comparable benefit. Given that there are alternatives available with similar risk and less expensive, recommendation against coverage.
PBT for bone, breast, oropharyngeal, nasopharyngeal, esophageal,	Unknown	Bone: Low All others: No evidence	High	Moderate (many would not choose PBT due to cost, need to	Do not recommend (weak recommendation)	Insufficient evidence, unknown risk compared to alternative, and increased cost.

Indication/ Intervention	Balance between desirable and undesirable effects	Quality of evidence*	Resource allocation	Variability in values and preferences	Coverage recommendation	Rationale
GI, gynecologic, lymphomas, sarcomas, seminomas, thymomas, AVMs, and other noncancerous conditions				travel, uncertain benefit)		

*The Quality of Evidence rating was assigned by the primary evidence source, not the HERC Subcommittee, except as specified.

** The Quality of Evidence rating was assigned by the HERC Subcommittee.

Note: GRADE framework elements are described in Appendix A

POLICY LANDSCAPE

Quality measures

No quality measures were identified when searching the National Quality Measures Clearinghouse.

Professional society guidelines

Guidelines on the use of proton beam therapy are available from the National Comprehensive Cancer Network (NCCN, 2013-2014), American Society for Radiation Oncology (ASTRO, 2013), American College of Radiology (ACR, 2011-2013), American Cancer Society (ACS), and the Alberta Health Services in Canada (2013).

Bone Cancer

NCCN guidelines state that for unresectable high- and low-grade chondrosarcomas of the skull base and axial skeleton, PBT may be indicated to allow for high-dose treatment. Alberta guidelines recommend PBT for sarcomas, including chordoma and chondrosarcoma. According to the ACR, PBT-based treatment plans are considered inappropriate (rated 1-2) in spinal and non-spinal bone metastases.

Brain, Spinal, and Paraspinal Tumors

Alberta guidelines recommend PBT as an option for CNS lesions including craniopharyngioma, germ cell tumors and low-grade gliomas.

Head and Neck Cancers

For ethmoid and maxillary sinus tumors, NCCN considers PBT an investigative therapeutic technique only. Alberta guidelines state that treatment with PBT for adults with acoustic neuromas, and paranasal sinus and nasal cavity tumors is recommended.

Lung Cancer

NCCN considers PBT appropriate for non-small-cell lung cancer. ACR recommends against use of PBT for NSCLC patients with poor performance status or requirements for palliative treatment, while Alberta guidelines do not recommend PBT for NSCLC.

Lymphomas

NCCN states that PBT may be appropriate for patients with Hodgkin and Non-Hodgkin lymphoma as well as soft tissue sarcomas; however, long-term studies are necessary to confirm benefits and harms. Alberta guidelines do recommend PBT for lymphomas only in patients less than 30 years of age.

Ocular Tumors

NCCN guidelines for treatment options in ocular tumors are under development. Alberta guidelines recommend PBT for ocular melanoma.

Pediatric Tumors

Guidelines from Alberta recommend consideration of PBT for pediatric tumors including ependymomas, rhabdomyosarcoma, Ewing's sarcoma, pineal tumors, and patients requiring craniospinal irradiation.

Prostate Cancer

NCCN and Alberta guidelines do not recommend PBT for use in prostate cancer, as superior or equivalent effects have not been demonstrated in comparison to conventional external-beam therapy. In a position statement, ASTRO concluded that the evidence supporting the use of PBT in prostate cancer continues to develop and define its role among current alternate treatment modalities. ASTRO strongly supports the provision of coverage with evidence development to evaluate the comparative effectiveness of PBT relative to other options including IMRT and brachytherapy. The ACR Appropriateness Criteria® consider PBT for treatment planning in T1 and T2 prostate cancer to be appropriate but with lower ratings than for IMRT (6-7 versus 8-9, based on a 1-9 scale).

Non-cancerous conditions

Alberta Health Services guidelines recommend PBT for benign conditions such as AVMs and meningiomas.

APPENDIX A. GRADE ELEMENT DESCRIPTIONS

Element	Description
Balance between desirable and undesirable effects	The larger the difference between the desirable and undesirable effects, the higher the likelihood that a strong recommendation is warranted. The narrower the gradient, the higher the likelihood that a weak recommendation is warranted
Quality of evidence	The higher the quality of evidence, the higher the likelihood that a strong recommendation is warranted
Resource allocation	The higher the costs of an intervention—that is, the greater the resources consumed—the lower the likelihood that a strong recommendation is warranted
Values and preferences	The more values and preferences vary, or the greater the uncertainty in values and preferences, the higher the likelihood that a weak recommendation is warranted

Strong recommendation

In Favor: The subcommittee is confident that the desirable effects of adherence to a recommendation outweigh the undesirable effects, considering the quality of evidence, cost and resource allocation, and values and preferences.
Against: The subcommittee is confident that the undesirable effects of adherence to a recommendation outweigh the desirable effects, considering the quality of evidence, cost and resource allocation, and values and preferences.

Weak recommendation

In Favor: The subcommittee concludes that the desirable effects of adherence to a recommendation probably outweigh the undesirable effects, considering the quality of evidence, cost and resource allocation, and values and preferences, but is not confident.
Against: The subcommittee concludes that the undesirable effects of adherence to a recommendation probably outweigh the desirable effects, considering the quality of evidence, cost and resource allocation, and values and preferences, but is not confident.

Quality or strength of evidence rating across studies for the treatment/outcome[1]

High: The subcommittee is very confident that the true effect lies close to that of the estimate of the effect. Typical sets of studies are RCTs with few or no limitations and the estimate of effect is likely stable.
Moderate: The subcommittee is moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different. Typical sets of studies are RCTs with some limitations or well-performed nonrandomized studies with additional strengths that guard against potential bias and have large estimates of effects.
Low**:** The subcommittee's confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect. Typical sets of studies are RCTs with serious limitations or nonrandomized studies without special strengths.

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

***Very low*:** The subcommittee has very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect. Typical sets of studies are nonrandomized studies with serious limitations or inconsistent results across studies.

APPENDIX B. APPLICABLE CODES

CODES	DESCRIPTION
ICD-9 Diagnosis Codes	
170.0-170.9	Malignant neoplasm of bone and articular cartilage
171.0-171.9	Malignant neoplasm of connective and other soft tissue
189.0	Malignant neoplasm of kidney, except pelvis
190.0	Malignant neoplasm eyeball, except conjunctive, cornea, retina, choroids
190.5	Malignant neoplasm of retina
190.6	Malignant neoplasm of eye, choroid
191.0-191.9	Malignant neoplasm of brain
192.1-192.3	Malignant neoplasm of cerebral meninges, spinal cord, spinal meninges
194.0	Malignant neoplasm of adrenal gland
194.3	Malignant neoplasm of pituitary gland and craniopharyngeal duct
194.4	Malignant neoplasm of pineal gland
198.3	Secondary malignant neoplasm, brain and spinal cord
209.29	Malignant carcinoid tumors of other sites
225.0-225.9	Benign neoplasm of brain and other parts of nervous system
227.3	Benign neoplasm of pituitary gland
234.8	Carcinoma in situ of other specified sites (pituitary)
237.0	Neoplasm of uncertain behavior of pituitary gland
239.7	Neoplasm of unspecified nature, endocrine gland (pituitary)
437.3	Cerebral aneurysm, non-ruptured
437.8-437.9	Other and unspecified cerebrovascular disease
747.81	Anomalies of the cerebrovascular system (AVM)
185	Malignant neoplasm of prostate
198.82	Secondary malignant neoplasm, genital organs
233.4	Carcinoma in situ, prostate
ICD-10 Diagnosis Codes	
C40.00-C41.9	Malignant neoplasm of bone and articular cartilage
C47.0-C47.9	Malignant neoplasm of peripheral nerves and autonomic nerves
C49.0-C49.9	Malignant neoplasm of other connective and soft tissue
C64.1-C64.9	Malignant neoplasm of kidney, except renal pelvis
C69.20-C69.22	Malignant neoplasm of retina
C69.30-C69.32	Malignant neoplasm of choroid
C69.40-C69.42	Malignant neoplasm of ciliary body
C70.0-C70.9	Malignant neoplasm of meninges
C71.0-C71.9	Malignant neoplasm of brain
C72.0-C72.9	Malignant neoplasm of spinal cord, cranial nerves and other parts of central nervous system
C74.00-C74.92	Malignant neoplasm of adrenal gland
C75.1-C75.3	Malignant neoplasm of pituitary gland, craniopharyngeal duct, pineal gland
C7A.8	Other malignant neuroendocrine tumors
C79.31	Secondary malignant neoplasm of brain
C79.40-C79.49	Secondary malignant neoplasm of other and unspecified parts of nervous system
D09.3	Carcinoma in situ of thyroid and other endocrine glands [pituitary]

D32.0-D32.9	Benign neoplasm of meninges
D33.0-D33.9	Benign neoplasm of brain and other parts of central nervous system
D35.2	Benign neoplasm of pituitary gland
D44.3-D44.4	Neoplasm of uncertain behavior of pituitary gland, craniopharyngeal duct
D49.7	Neoplasm of unspecified behavior of endocrine glands and other parts of nervous system [pituitary]
I67.1	Cerebral aneurysm, nonruptured
I67.89-I67.9	Other and unspecified cerebrovascular disease
Q28.2	Arteriovenous malformation of cerebral vessels
C61	Malignant neoplasm of prostate
C79.82	Secondary malignant neoplasm of genital organs
D07.5	Carcinoma in situ of prostate
ICD-10 Procedure Codes	
D0004ZZ	Beam radiation of brain using heavy particles (protons, ions)
D0014ZZ	Beam radiation of brain stem using heavy particles (protons, ions)
D0064ZZ	Beam radiation of spinal cord using heavy particles (protons, ions)
D0074ZZ	Beam radiation of peripheral nerve using heavy particles (protons, ions)
D8004ZZ	Beam radiation of eye using heavy particles (protons, ions)
DP004ZZ-DP0C4ZZ	Beam radiation of bone using heavy particles (protons, ions) [by site; includes codes DP004ZZ, DP024ZZ, DP034ZZ, DP044ZZ, DP054ZZ, DP064ZZ, DP074ZZ, DP084ZZ, DP094ZZ, DP0B4ZZ, DP0C4ZZ]
DT004ZZ	Beam radiation of kidney using heavy particles (protons, ions)
DW014ZZ	Beam radiation of head and neck using heavy particles (protons, ions)
DW024ZZ	Beam radiation of chest using heavy particles (protons, ions)
DW034ZZ	Beam radiation of abdomen using heavy particles (protons, ions)
DW064ZZ	Beam radiation of pelvic region using heavy particles (protons, ions)
CPT Codes	
32701	Thoracic target(s) delineation for stereotactic body radiation therapy (SRS/SBRT), (proton or particle beam), entire course of treatment
77373	Stereotactic body radiation therapy, treatment delivery, per fraction to 1 or more lesions, including image guidance, entire course not to exceed 5 fractions
77421	Stereoscopic X-ray guidance for localized of target volume for the delivery of radiation therapy
77432	Stereotactic radiation treatment management of cranial lesion(s) (complete course of treatment consisting of 1 session)
77435	Stereotactic body radiation therapy, treatment management, per treatment course, 1 or more lesions, including image guidance, entire course not to exceed 5 fractions
77520	Proton treatment delivery; simple, without compensation
77522	Proton treatment delivery; simple, with compensation
77523	Proton treatment delivery; intermediate
77525	Proton treatment delivery; complex
HCPCS Level II Codes	
S8030	Scleral application of tantalum ring(s) for localization of lesions for proton beam therapy

Note: Inclusion on this list does not guarantee coverage

HERC Coverage Guidance – Proton Beam Therapy
Disposition of Public Comments

Table of Contents

Discussion Table

IDs/#s	Summary of Issue	Subcommittee response
C21-27	Commenter notes that **Hodgkins lymphoma** patients can expect to live decades, making late toxicity an important outcome which is unlikely to be in current literature. Reducing dose to normal organ structures through PBT may in the long term be associated with less cost secondary to fewer complication rates. Recommendation for noncoverage was made due to lack of comparative data; however, expert testimony indicates that comparative dosimetric modeling is a standard practice for planning radiation treatment.	
H37-H48	**Locally advanced NSCLC**, **medically inoperable NSCLC**, and **NSCLC requiring re-irradiation** are described by commenter as indications where PBT may be the preferable option. Guidance from professional organizations on PBRT for lung cancer is mixed; NCCN does recommend it but Alberta and ACR guidelines do not. WAHTA found comparable benefits, comparable harms, and increased costs of PBT for lung cancer. For **locally advanced NSCLC**, commenter provided two references. Bradley 2015 demonstrated a "toxicity ceiling" for standard X-ray therapy which prevents the dose escalation that might otherwise improve local control. Chang 2014 is a case series of 44 patients demonstrating that such dose escalation is possible with protons and does in fact improve survival. The CG document describes three comparative studies in	

IDs/#s	Summary of Issue	Subcommittee response
	which PBT and Xray toxicities were found to be similar. For **medically inoperable NSCLC**, Timmermann 2006 (N=70) demonstrated that central tumor location predicted high-grade toxicity from SBRT; thus it is not used for these patients. Bush 2013 demonstrated a positive dose-response relationship between increasing radiation dose with PBT and four-year OS for medically inoperable NSCLC patients; additionally, toxicities were similar between patients with centrally located and peripherally located tumors which is not true of Xrays. Comparative studies between PBT and SBRT cannot be done because SBRT is contraindicated in these patients. For **NSCLC requiring re-irradiation**, commenter notes that options are limited for patients with intrathoracic NSCLC recurrence. McAvoy 2013 (N=31) demonstrated feasibility of PBT for these patients, with 1-year OS 47% and LC 54%. Comparative data demonstrating superiority to conventional radiation were not provided and are unlikely to be obtained.	
J57	**General:** Commenter supports payer coverage with clinical evidence generation for disease sites where dosimetric comparisons suggest superiority of PBT, but clinical evidence is not yet available, citing the value of this approach outlined in a recent article (Bekelman and Hahn, JCO 2014). That editorial urges the Washington State HTAP to pay for proton beam therapy using reference pricing (such as they already do for robotic surgery) to facilitate evidence development. The suggestion is that PBT should be covered at the same rate as IMRT. HTAS also heard testimony that e.g. for rare cancers not likely to undergo a randomized trial, dosimetry studies may be an acceptable way to evaluate appropriateness of PBT.	
Q129	**Prostate Cancer:** Commenter notes that the need for continued clinical evidence development (CED) and comparative effectiveness data for treating prostate cancer is recognized by the current ASTRO national model policy for PBT. Under this policy, enrollment in an IRB approved multi-institutional patient registry that adheres to Medicare requirements for CED is considered an indication for PBT that should be covered by an insurance carrier.	
G33, J59-J61, M86-M87, N94-N98, P107-P111, W158-	Commenters supported coverage for pediatric patients, citing studies showing the effectiveness of PBT in pediatric patients	HTAS has chosen to recommend coverage of PBT for pediatric patients, clarifying this to mean incident cancer at age 21 or younger.

IDs/#s	Summary of Issue	Subcommittee response
W166, Y168		

Commenters

Identification	Stakeholder
A	Seattle Cancer Care Alliance Proton Therapy Center, Medical Director (Washington State)
B	Patient (Washington State)
C	Assistant professor, Department of Radiation Oncology, University of Washington, Seattle Cancer Care Alliance (Washington State)
D	Friend of patient
E	Friend of patient (Washington State)
F	Friend of patient (Washington State)
G	Radiation Oncologist, Corvallis, OR
H	Assistant Professor, Department of Radiation Oncology, University of Washington Medical Center (Washington State)
J	Professor and Chair, Dept. of Radiation Medicine/Professor, Division of Hematology/Oncology, Knight Cancer Institute, Oregon Health & Science University
K	Citizen (no further info provided) (Washington State)
L	Radiation Oncology, University of Washington
M	Health Policy Analyst, American Society for Radiation Oncology (ASTRO)
N	Assistant Professor, Department of Radiation Oncology, Department of Neurological Surgery, UW School of Medicine
O	Friend of patient
P	President, Particle Therapy Cooperative Group – North America
Q	Associate Professor, University of Washington Medical Center, Department of Radiation Oncology
R	Assistant Professor, University of Washington Department of Radiation Oncology
S	Associate Professor, University of Washington Department of Radiation Oncology
T	Retired nurse, Lynden, WA
U	Prostate cancer patient (WA)
V	Unknown
W	Assistant Professor, University of Washington Department of Radiation Oncology
X	Unknown
Y	Executive Director, National Association for Proton Therapy

Public Comments

ID	#	Comment	Disposition
A	1	Thank you for the opportunity to submit scientific information on Proton Beam Radiation Therapy (PBRT). PBRT eliminates the exit radiation dose that patients would otherwise receive if treated with X-rays, thereby protecting normal tissue from damaging radiation exposure. This technique allows the oncologist to (1) increase the dose delivered to tumor in order to improve local control (LC) for radiation resistant tumors and/or (2) reduce acute and long-term morbidity by minimizing normal tissue exposure. These benefits translate into not only an improvement in clinical outcomes, but quality of life and reduction of the short and long-term cost of side effect management due to functional impairment. For these reasons, we feel that it is important that Oregon residents continue to have access to this important weapon for the treatment of cancer. We welcome the opportunity to serve as an on-going resource to this Commission.	Thank you for your comments.
A	2	National Coverage Guidance Supporting the Use of Proton Beam Therapy The National Comprehensive Cancer Network (NCCN) guidelines support the use of protons for a variety of malignancies where clinical outcomes with standard therapy is suboptimal.	NCCN guidelines are summarized in the document under "Policy Landscape."
A	3	Additionally, a number of distinguished national cancer organizations have released model policy guidelines for the judicious and appropriate coverage for PBRT in patients who are most likely to benefit.	Specific guidelines are not named by the commenter. The CG document lists guidelines from the National Comprehensive Cancer Network (NCCN, 2013-2014), American Society for Radiation Oncology (ASTRO, 2013), American College of Radiology (ACR, 2011-2013), American Cancer Society (ACS), and the Alberta Health Services in Canada (2013).
A	4	We also note that the Medicare contractor for Oregon currently provides for PBRT coverage.	Thank you for the information.
A	5	The model policy from the American Society for Radiation Oncology (ASTRO), the pre-eminent and largest radiation oncology organization, released after the Washington HTA report, is one that we call your attention as strong initial policy framework for coverage.	ASTRO guidelines are considered under the "Policy Landscape" section of the CG document; a model payer policy is not appropriate for inclusion as evidence.

ID	#	Comment	Disposition
A	6	2014 Washington State Health Care Authority Health Technology Assessment (HTA) The 2014 Washington HTA on PBRT highlighted the need to gather additional clinical data. We agree with this; in fact, 97% of patients treated at our center are enrolled in either a clinical trial or prospective registry. While long-term efficacy and toxicity data is maturing, we routinely utilize dosimetric comparative data to determine appropriate utilization of PBT. For this reason, we feel that excluding all comparative dosimetric studies was a significant methodological flaw in the Washington HTA report. Dosimetric data is routinely utilized for clinical decision making in radiation oncology. In short, if you can deliver greater dose to the tumor or reduce normal tissue exposure, this is expected to benefit our patients. Finally, we strongly encourage you to support payer coverage with clinical evidence generation for disease sites where dosimetric comparisons suggest superiority of PBT, but clinical evidence is not yet available.	Dosimetric comparative trials of proton beam therapy would only be applicable to this coverage guidance if conventional modalities (such as IMRT) were one of the treatment arms, or if comparison to conventional radiotherapy were not feasible to obtain.
A	7	Summary of Evidence The body of clinical evidence supporting the appropriate use of protons continues to grow. Due to space considerations, we present a small sampling of the evidence. However, we remain available to present a more comprehensive view to this Commission	Thank you for presenting additional sources of evidence.
A	8	*Head & Neck Cancers* – A comparative effectiveness study from MD Anderson suggests that use of intensity modulated PBRT in advanced stage head and neck cancer was less costly and of higher value than IMRT [Frank et al, Oncology Payers 2014] (1).	Frank et al is a costing analysis comparing the experiences of two individual patients. Oncology Payers is not a peer-reviewed journal and is not identified by MEDLINE®, it does not meet the standard for inclusion.
A	9	A meta-analysis evaluating the role of photons and charged particle therapy for sinonasal carcinoma demonstrated improved disease-free survival (DFS) and LC with charged particle therapy; subgroup analysis comparing IMRT and PBRT confirmed that 5-year DFS was significantly higher at five years for patients receiving PBRT (72% versus 50%) [Patel et al, Lancet Oncol 2014] (2).	Patel 2014 was published after the WAHTA, which judged evidence to be insufficient on head & neck cancers. It is a MA of 43 cohorts. A subgroup analysis comparing proton beam therapy with intensity-modulated radiation therapy showed significantly higher disease-free survival at 5 years

ID	#	Comment	Disposition
			(relative risk 1·44, 95% CI 1·01–2·05; p=0·045) and locoregional control at longest follow-up (1·26, 1·05–1·51; p=0·011). Authors encourage prospective study with patient-oriented outcomes to confirm findings. This level of evidence is generally not considered sufficient to guide coverage; however, the subcommittee discussed that RCTs may not be feasible or ethical in this setting and that reduced harms in treatment of sinonasal carcinoma with PBT would justify a recommendation for coverage.
A	10	*Breast Cancer*– A recent population-based study of 2168 woman, [Darby et al N Engl J Med. 2013] (3) found that collateral radiation exposure to the heart during breast cancer X-ray treatment increases the subsequent rate of ischemic heart disease.	Darby et al conducted a case-control study of major coronary events in patients who underwent radiotherapy for breast cancer from 1958 to 2001 in Sweden and Denmark. This was prior to modern advances in radiotherapy when radiation doses are generally lower, and does not address comparative safety of PBT.
A	11	PBRT can significantly reduce this exposure. Macdonald et al reported the results of a prospective trial of protons after mastectomy for patients with excellent clinical outcome and significant reduction in heart dose when compared to X-rays. [Macdonald et al Int J Radiat Oncol Biol Phys. 2013] (4)	MacDonald et al is a noncomparative study of 12 individuals receiving PBT for breast cancer. While a lower

ID	#	Comment	Disposition
			heart dose theoretically will decrease future toxicity, study authors concluded "it is too early to determine cardiopulmonary toxicities in our study" as follow-up was conducted at 4 and 8 weeks.
A	12	*Prostate Cancer*– In a recent publication from the University of Florida, 5 year outcomes from 3 prospective trials of PBT for prostate cancer were reported. Five year rates of biochemical and clinical freedom from disease progression were 99%, 99%, and 76% in low, intermediate, and high risk patients, respectively. Reported toxicity rates were low. These results compare very favorably with those published for IMRT. [Mendenhall et al, Int J Radiat Oncol Biol Phys 2014] (5). We highlight our center's participation in the ongoing "PartiQOL" randomized trial comparing IMRT vs protons for prostate cancer.	The Mendenhall study is a noncomparative observational study of 211 patients; its early outcomes (2012) are included in Table 13, Appendix F (single-arm case series) of the WA HTA report.
A	13	*The True Cost of Protons*- In addition to the significant and growing body of clinical evidence, the cost-effectiveness of PBRT has also been explored. We would highlight that although PBRT is more resource-intensive to deliver upfront, it is aligned with the judicious use of health care dollars. Several recent studies, including these from Harvard have shown that when the costs of side-effects are accounted for, PBRT actually significantly *reduces* health care costs when compared to standard radiation therapy. Therefore, protons when used appropriately are *cost-effective* when compared to photon beam radiotherapy due to reduced hospitalization rates, etc. for side effect management. [Mailhot-Vega Cancer 2013 (6); Mailhot-Vega Cancer 2015 (7)].	Mailhot-Vega 2013 is included in the Washington HTA analysis. Mailhot-Vega 2015 is a Markov cohort-simulation model looking specifically at growth-hormone deficiency in pediatric cancers.
A	14	We urge the Commission to support the coverage of proton therapy and welcome the opportunity to serve as an on-going resource as you are assessing this promising cancer therapy option for Oregonians.	Thank you for your comments.
B	15	I am commenting on the proposed policy regarding Proton Therapy.	Thank you for your comments.
B	16	I was diagnosed in February 2012 with prostate cancer after having a biopsy. My PSA reading had been climbing the previous 2 years and when it reached 10.7, I had the biopsy done. The biopsy showed that I had cancer. My urologist, who was a surgeon, suggested having surgery in August of 2012. He also set me up to speak to a radiation oncologist. I had a CT & Pet scan plus explanations on the different forms of radiation treatments that were available, conventional x-rays and seeds. Also at this time I joined a local prostate support group. I spoke with the men in the support group plus other men I had met that had prostate cancer to find out how they were doing. I spoke with the men who had surgery or either of the two forms of radiation treatments done. Many of them had procedures done years before. None had Proton Therapy or had heard of it. Every single man I spoke with, no matter how healthy they were or how well their	Thank you for your comments. The coverage guidance does reference one fair-quality prospective cohort study of patient-reported quality of life among 185 men treated for prostate cancer. "No differences in overall QoL or general health

ID	#	Comment	Disposition
		procedure went were still having some form of issue. The two main areas of problems were incontinence and sexual function. They had different degrees of problems, from slight to serious, but all of them had something.	status were observed at 18 months of follow-up" (p 13).
B	17	I spoke with a former vice president of my company who was treated for prostate cancer 6 years before at Loma Linda with Proton Therapy. He has had no long-term side effects. When he did his research he talk to over 100 Proton Therapy patients and came to the conclusion that because of the minimal long term side effects it was the best way to go. So I started researching on the Internet and found the same information about the lack of side effects with Proton Therapy. Also, at that time I found out that a Proton Therapy facility was being built in Seattle and would open spring of 2013. I made my decision that this was the best way to go. I went for 9 weeks of treatment; I continued to work the whole time not missing a single day. I went to work in the morning, went for treatments during midday, and then returned to work after treatment. I had no issues during treatment. By the way, I am a bicycle commuter (year round), I ride round trip 14 miles a day for work and I continued to do this even during my treatments. My wife would pick me up and take me to treatments. I am also an avid cross-country skier during the winter months.	Thank you for your comments.
B	18	My urologist had told me that if I had done surgery I would be off work for about 3 months, if I had selected x-rays or seeds I would be off work also for a period of time. Since the end of my treatments I have had 6 follow up PSA tests and my reading keeps going down. It is 0.52 now from the high of 10.7. I have had absolutely no side effects from the Proton treatment since completing treatment in June 2013. I continue to ride my bike to and from work each day. Each August I do a bike ride of 186 miles, which I do with my son each year. No problems. I don't believe I would be doing any of this or enjoying it as much if I had incontinence issues. Try biking or skiing wearing some form of diaper. Can it be done, yes. Would it be enjoyable, probably not. There has been no change in my health from before Proton treatment to now, except the lack of cancer. Is Proton Therapy the right treatment for everyone? I can't answer that, only a doctor or a person with prostate cancer can answer that. But in my case I thank God I found out about it and decided to go that route for treatment.	Thank you for your comments.
B	19	One thing I keep noticing about this whole debate about insurance companies not wanting to pay for Proton Therapy is it seems to come down to cost. Yes, proton Therapy is more expensive than the other more "accepted" forms of cancer treatment, but does anyone actually look at the long term cost from the possible long-term side effects of surgery, x-rays or seeds? I have never seen it mentioned anywhere. Quite frankly it seems no one really cares about the cost of side effects once the patient is out the door. But to me having to spend the rest of my life possibly in diapers or on some other form of medicine for side effects did not thrill me at all. By the way I am 61 years old. I plan on being around for quite a while longer.	Cost and cost-effectiveness analyses, including costs of adverse effects, are considered in the CG document.
B	20	The last thing I want to say is, please don't take away or limit the Proton Therapy option for others who may come after me.	Thank you for your comments.
C	21	After reviewing the commission's draft on coverage guidance for proton beam therapy (PBT), I would like to highlight	Thank you for your comments.

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		and summarize the pertinent, existing evidence supporting the selective use of protons as part of lymphoma treatment.	
C	22	Lymphoma is a heterogeneous disease entity comprised of Hodgkin (HL) and non-Hodgkin lymphoma (NHL). As such, the decision on which radiation technique is best suited for a patient (e.g. PBT vs IMRT/VMAT vs 3D vs other) incorporates multiple variables including patient age, tumor location, and histology.	Thank you for your comments.
C	23	The commission is correct that currently no clinical outcomes data exists comparing photons and protons among HL or NHL patients. In HL patients, in whom the goal is to minimize morbidity and toxicity without compromising already excellent cure rates, the outcomes of interest (e.g. cardiovascular disease [CVD], second malignancy [SM]) generally require at least a decade of follow-up as no intermediate biomarker currently exists as a short-term endpoint.	Thank you for your comments. It is noted that improvements in long-term toxicities will take time to appear in trials.
C	24	Up to 75% of HL patients have disease in the thorax, and the long-term radiation-associated morbidity to this area has been clearly documented including increased rates of cardiac events (1), decreased lung function (2), breast cancer (3), lung cancer (4) and esophageal cancer (5). Furthermore, in these studies, the risk of a SM increased with increasing radiation dose to the lung, breast, or esophagus (i.e. linear no threshold), implying that the lower the radiation dose to these structures, the lower the risk of SM.	Thank you for providing these data on the risk of secondary malignancy in treatment of Hodgkins lymphoma.
C	25	Risk of toxicity appears related to the radiation dose to and volume of normal thoracic structure irradiated (2, 6) and likely will decline in the future as radiation dose and target volumes (i.e. involved-node versus involved field radiation) are currently being reduced. Nonetheless, radiation technique (PBT vs other) may still play an important role as dosimetric comparative studies using modern radiation target volumes and dose demonstrate that, on average, PBT was associated with lower dose to the heart, lungs, and breasts compared with 3D conformal and VMAT photon techniques (7). Based on risk estimates, proton technique was associated with the lowest life-years lost (7). Other dosimetric comparison studies have also shown similar, significant reduction of dose to the heart (8), breast (9, 10), lung (9, 10), and total body (9).	Commenter provides background information on risk of damage to surrounding structures with conventional radiation, and posits that PBT provides lower dose to such structures.
C	26	Thus far, the early results of involved-node radiation with protons demonstrate excellent relapse-free and event-free survival (11), suggesting that target volume coverage and local control is not compromised by using a more conformal technique. Admittedly, the ten to twenty year-local control, event-free survival, overall survival, and late toxicity after treatment with involved-node proton radiation, as compared with 3D conformal photon radiation, will be the gold standard on which to base clinical decisions and cost-effective analyses. Cost can be calculated over various time periods, but arguably for lymphoma patients, this time period should be evaluated over at least 20-30 years, which is when late effects of treatment may manifest and impact the patient, medical system, and society from a productivity and financial standpoint. By reducing dose to normal organ structures without compromising oncologic outcomes, protons may, in the long term, be associated with less cost secondary to fewer complication rates. Until then, I would urge you to consider the existing, preliminary data suggesting the dosimetric advantages of protons for treatment of	Commenter notes that Hodgkins patients can expect to live decades, making late toxicity an important outcome. Recommendation for noncoverage was made due to lack of comparative data. However, commenter's point regarding 20-30 year outcome

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		lymphoma. Rapid adoption of reduced target volumes (e.g. involved-node radiation) among the radiation oncology community has, in part, been driven by the basic understanding that reducing dose to surrounding normal tissues will decrease acute and late morbidity for our patients.	relevance is well-taken. *For HTAS discussion*
C	27	Please do not hesitate to contact me if you have any additional questions, clarifications, or concerns.	Thank you for your comments.
D	28	I support and encourage your covering proton radiation therapy for all forms of cancer or at least liver cancer where it has proven to be efficacious. I encourage you to begin covering it now, not in 3, 5, 10 years. A very close friend of our's sister needs this therapy immediately. She needs your help. She is 'covered' by Regence Blue Shield OR. After all, is that not what insurance is for. Thank you	Commenter addresses Regence; nevertheless, thank you for your comments.
E	29	Please set the example for the country. We have these therapies that give people hope to live longer, yet we make it such a fight. Not fair to family and sick person. I am not sure why drug company does not pay for some of this with regency insurance or any insurance. Please help families stop suffering and let insurance companies and drug companies work together for these treatments. Advocating for our sick health system to get better and for my friend who wants to try this treatment.	Commenter is a resident of Washington State. Thank you for your comments.
F	30	Please cover proton therapy for all forms of cancer, or at very least, liver cancer. Our close friend's sister from Medford is dying of liver cancer, has been approved for proton therapy, but pending insurance coverage decision by Oregon. Thank you for your consideration of this live saving request.	Commenter is a resident of Washington State. Thank you for your comments.
G	31	Between 1984 and 1988 I was a faculty member in the department of Radiation Oncology at Massachusetts General Hospital and Harvard Medical School. My primary clinical responsibility was proton radiation treatment at the Harvard Cyclotron Laboratory which was the first proton facility in the US. Subsequently I spent 18 years in the Department of Radiation Oncology at the University of Washington School of Medicine. Since 2006 I have been in a community practice in Corvallis. Oregon.	Thank you for your comments.
G	32	Through my years in practice I have used virtually all types of radiation treatments available for treating malignancies. Protons have the very significant advantage of delivering the lowest integral dose to a patient; in other words, normal tissues receive less dose with protons than with any other type of radiation including intensity modulated photon radiation treatments. Randomized control studies and nonrandomized comparative studies as discussed in the HERC document show at least equivalent tumor control rates for PBT compared to photons in many tumor types with decreased toxicity in some tumor sites.	Thank you for your comments. Studies mentioned by commenter are addressed in CG document.
G	33	Decreased integral dose with PBT has considerable advantages in pediatric malignancies. Growth and development are adversely impacted by radiation. PBT causes less injury. The HERC document describes several studies demonstrating the benefits of PBT in pediatric patients. Secondary malignancy reduction takes many years of followup to study. Preliminary data as cited in this document indicates a reduction in secondary malignancy.	As noted on Table 1, PBT was judged to have incremental net health benefit for pediatric cancers.

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G	34	Primary brain, skull base and spinal malignancies also benefit from PBT because of decreased integral dose. The physical/spatial characteristics of PBT allow sufficient dose to be delivered to skull base and primary spinal malignancies. All parts of the brain perform important functions. PBT reduces dose to uninvolved areas of the brain in primary brain tumor treatment. This benefit in neurological function can be difficult to demonstrate using standard methods, but with sufficiently sensitive measurements improved function would mostly likely be seen.	As noted on Table 1, PBT was judged to have incremental net health benefit for adult brain/spinal tumors.
G	35	I strongly suggest that HERC reconsider their coverage recommendations to align with the Washington State HTCC recommendations.	Thank you for your comments.
H	36	Thank you for the opportunity to submit scientific information on Proton Beam Radiation Therapy (PBRT). PBRT eliminates the exit radiation dose that patients would otherwise receive if treated with X-rays, thereby protecting normal tissue from damaging radiation exposure. This technique allows the oncologist to (1) increase the dose delivered to tumor in order to improve local control (LC) for radiation resistant tumors and/or (2) reduce acute and long-term morbidity by minimizing normal tissue exposure. These benefits translate into not only an improvement in clinical outcomes, but also quality of life and reduction of the short and long-term cost associated with side effect management. For these reasons, we feel that it is important that Oregon residents continue to have access to this important weapon for cancer treatment.	See comment A1.
H	37	PBRT for non-small cell lung cancer (NSCLC) is currently recommended by the National Comprehensive Cancer Center Guidelines (NCCN V4.2014) and should not be considered experimental, investigational, or unproven.	Guidance from professional organizations on PBRT for lung cancer is mixed. NCCN does recommend; however ACR and Alberta guidelines do not. The SR finds comparable benefits and harms at increased cost; therefore the recommendation is to not cover.
H	38	*Locally Advanced NSCLC*: Definitive chemoradiotherapy is the standard of care for locally advanced non-small cell lung cancer, however this treatment has the potential to carry significant toxicity. At present, LC with standard dose radiotherapy in locally advanced disease is suboptimal, with 50-60% patient experiencing relapse of their disease. One approach to improve LC is increasing the radiation dose delivered to the cancer. However, this potential improvement comes at the expense of greater toxicity. Unfortunately, attempts at dose escalation with standard X-rays in lung cancer have hit a 'toxicity ceiling' whereby the resulting increased toxicity from dose actually may reduce survival, based upon a recent randomized trial with X-rays (1).	Commenter references Bradley JD et al 2015, demonstrating that 74Gy radiotherapy had no additional benefit and possibly increased mortality compared to 60Gy radiotherapy, or a "toxicity ceiling."
H	39	In a phase II trial of dose-escalated PBRT concurrent with chemotherapy for 44 patients with stage III NSCLC, MD	Commenter notes ongoing

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		Anderson demonstrated reduced the side effects, which permitted safe dose escalation to 74 Gy (2). The median overall survival time was 29.4 months, compared with 19 months for patients who were treated with 74Gy with X-rays in RTOG 0617. No patient experienced grade 4 or 5 proton-related adverse events. Based upon these promising results, the RTOG has launched a phase III randomized trial of protons vs photons (RTOG 1308) for locally advanced NSCLC. Our center is participating in this trial.	research on PBRT in locally-advanced NSCLC given evidence of superior tumor control when 74 Gy is delivered via PBT (Chang 2011, case series of 44 patients). A Phase III trial is in progress. Three comparative studies discussed in the CG have found that "rates of treatment-related toxicities with PBT are comparable to those seen with other radiation modalities in patients with lung cancer."
H	40	*Medically Inoperable Early Stage NSCLC:* The current standard therapeutic approach for these patients is stereotactic body radiation therapy (SBRT) or hypofractionated radiotherapy with photons, which provide excellent results. However, patients with centrally located tumors are at a11-fold higher risk of high-grade toxicity or death with SBRT due to radiation exposure to the heart and mediastinal structures. (3) Therefore until a "safe dose" is established, SBRT with photons is relatively contraindicated in patients with centrally located tumors.	Commenter references Timmermann 2006, study of SBRT in 70 patients too frail to undergo surgical resection of NSCLC. Hilar/pericentral location was a strong predictor of high-grade toxicity. No comparison to PBRT is included.
H	41	Bush *et al*. reported the long-term results of a prospective trial of high-dose hypofractionated PBRT for 111 patients with medically inoperable NSCLC. OS improved with increasing dose (51, 60, and 70 Gy) with a 4-year OS of 18%, 32%, and 51%, respectively (P=0.006). (4)	Commenter notes that SBRT may not be used for centrally located tumors, whereas PBRT may improve survival by allowing delivery of higher radiation doses. There is a positive dose-response relationship with OS. Comparative studies are not feasible as SBRT cannot be done for these patients. *For HTAS discussion*

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H	42	Additionally, patients with centrally located tumors did not experience excessive or increased toxicity when compared with peripherally located tumors. (4) This is in contrast to the clinical experience with X-rays. These prospective studies demonstrate that protons are safe and effective for patients with centrally located NSCLC who are medically inoperable. This has ***not*** yet been demonstrated with X-rays.	Commenter notes that PBRT may be superior to SBRT specifically for centrally-located NSCLC tumors. Comparative data on this subpopulation are not available at this time, but given proximity to sensitive tissues, comparative trials may not be feasible. *For HTAS discussion*
H	43	*Patients with NSCLC who require re-irradiation:* Options are limited for patients previously treated with radiation and who subsequently experience intrathoracic NSCLC recurrence. These patients have a poor response to chemotherapy; surgery is extremely high-risk and usually contraindicated.	Commenter notes patients who fail initial radiation have limited options.
H	44	Due to their favorable dose-deposition characteristics, protons are uniquely suited to delivery radiation in this clinical setting. The MD Anderson group reported the results on thirty-one patients (94%) who completed reirradiation with protons. At a median 11 months' follow-up, 1-year rates of overall survival, progression-free survival, locoregional control, and distant metastasis-free survival were 47%, 28%, 54%, and 39%. Rates of severe (grade 3) toxicity were 9% esophageal, 21% pulmonary; 1 patient had grade 4 esophagitis, and 2 had grade 4 pulmonary toxicity. These data demonstrate the feasibility and efficacy of PBRT in this clinical setting. (5)	A study of 31 patients demonstrated feasibility of PBRT for this population. Comparative data demonstrating superiority to conventional radiation are not provided and are unlikely to be obtained. *For HTAS discussion*
H	45	*The Cost of Protons for Lung Cancer*- Patients with lung cancer experience significant toxicity with standard X-ray based therapy.	Commenter references evidence of toxicity above, see H 40.
H	46	Emerging data demonstrate that protons, when used appropriately, can be *cost-effective* when compared to photon beam radiotherapy due to reduced hospitalization rates, etc. for side effect management. (6,7)	See comment A 13.
H	47	We performed a similar analysis of cost using these methods for lung cancer patients and found that for patients treated with IMRT experiencing high grade pulmonary or esophageal toxicities had costs that ***exceeded*** patients treated with protons without this toxicity.	Commenter notes internal analysis demonstrating cost savings with decreased toxicity. Reference to publication not provided.
H	48	We urge the Commission to support the coverage of proton therapy for lung cancer and welcome the opportunity to	Thank you for your comments.

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		serve as an on-going resource as you are assessing this promising cancer therapy option for Oregonians. Thank you for this opportunity.	
J	54	Thank you for the opportunity to submit scientific information on Proton Beam Radiation Therapy (PBRT). I am writing this letter to you in my capacity as Chairman of the Department of Radiation Medicine at Oregon Health Sciences University (OHSU). At the present time, OHSU does not have a proton beam facility and we do not derive any financial benefit from the delivery of proton beam radiation to patients in Oregon. However, we feel that it is important that Oregon residents have access to this important weapon for the treatment of cancer and have sent a number of our patients to proton beam facilities in other states. We send these select patients for proton radiation because we feel strongly that it is in their best clinical interest. While we do not feel that all patients benefit from protons, there are patients, especially pediatric patients in whom protons allow us to reduce risk of normal tissue injury due to radiation exposure in a manner that simply is not achievable with X-rays.	Thank you for your comments.
J	55	National Coverage Guidance Supporting the Use of Proton Beam Therapy I would like to highlight that a number of distinguished national cancer organizations have released model policy guidelines for the judicious and appropriate coverage for PBRT in patients who are most likely to benefit. I would call to your attention that the current draft of the HERC guidelines are out of step with these guidelines.	Guidelines from several organizations are included in the CG document under the "Policy Landscape" section and were considered by the HTAS.
J	56	The model policy from the American Society for Radiation Oncology (ASTRO), the pre-eminent and largest radiation oncology organization, released after the Washington HTA report, is one that we call your attention as a strong initial policy framework for coverage.	See comment A 5.
J	57	I would strongly encourage you to support payer coverage with clinical evidence generation for disease sites where dosimetric comparisons suggest superiority of PBT, but clinical evidence is not yet available. The value of this approach is highlighted in the article by Bekelman and Hahn in the Journal of Clinical Oncology (Bekelman and Hahn, JCO 2014).	Commenter suggests recommendation for coverage with evidence development. *For HTAS discussion*
J	58	Summary of Evidence The body of clinical evidence supporting the appropriate use of protons continues to grow. Due to space considerations, I am presenting a small sampling of the evidence.	Thank you for your comments.
J	59	Pediatric Tumors: In a landmark article, Oeffinger et al [N Engl J Med, 2006] showed that pediatric patients had between 5-10 times the risk of developing severe health complications after radiotherapy compared to their untreated siblings. For medulloblastomas where the radiation treatment involves the brain and spinal cord, data from MD Anderson shows that the ratio of relative risk (RRR) (proton/photon) of cardiac mortality ranged from 0.12 to 0.24. Obviously this is a substantial reduction in risk of injury and mortality in pediatric patients receiving proton beam radiotherapy [Zhang, Rad & One, 2014]	Oeffinger 2006 refers to the Childhood Cancer Survivor Study, a retrospective study of 10,397 survivors and 3034 siblings, which assessed incidence of chronic health

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			conditions among cancer survivors compared to cancer-free siblings. Zhang 2014 is a treatment planning study of 17 pediatric medulloblastoma patients. "Passively scattered proton CSI provides superior predicted outcomes by conferring lower predicted risks of second cancer and cardiac mortality than field-in-field photon CSI for all medulloblastoma patients in a large clinically representative sample in the United States, but the magnitude of superiority depends strongly on the patients' anatomical development status." HTAS has chosen to recommend coverage of PBT for pediatric patients.
J	60	In the case of rhabdomyosarcomas of the head and neck, particularly the orbit, proton radiotherapy allows the treatment of the tumor with much less dose to the brain and growing bones of the skull. Childs et al [Int J Radiat Oneal Bioi Phys, 2012] reported on 17 patients with parameningeal tumors treated at the Massachusetts General Hospital and found local control rates similar to historical treatments with photon radiotherapy but with fewer side effects. Similar considerations apply when treating neuroblastomas and Wilms tumors where standard photon treatments give higher radiation doses to the bowel and kidneys than would be delivered with protons.	Childs 2012 is included in the WAHTA report.
J	61	Brain tumors as a class are the most common pediatric solid tumor. Merchant et al reviewed neurocognitive data for patients treated at St. Jude's, correlated this with radiation doses delivered to various areas of normal brain, calculated the doses that would have been delivered with proton radiotherapy and concluded that the reduced dose afforded by proton radiotherapy resulted in significantly less IQ deterioration than standard radiotherapy [Merchant et al, Pediatr Blood Cancer, 2008].	The referenced study collected radiation dose data for 40 patients, estimated dose that would have been received with PBRT, and applied a model of

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			cognitive impact. The model suggests PBRT may have a lower cognitive impact for pediatric brain tumors. Comparative trials on this outcome are unlikely due to lack of clinical equipoise. The subcommittee recommended coverage of PBT for pediatric tumors.
J	62	Head & Neck Cancers -A meta-analysis evaluating the role of photons and charged particle therapy for sinonasal carcinoma demonstrated improved disease-free survival (DFS) and LC with charged particle therapy; subgroup analysis comparing IMRT and PBRT confirmed that 5-year DFS was significantly higher at five years for patients receiving PBRT (72% versus 50%) [Patel et al, Lancet Oncol 2014].	See also comment A9 regarding Patel 2014. PBT for sinonasal carcinoma is recommended for coverage.
J	63	Breast Cancer-A recent population-based study of 2168 woman, [Darby et al N Engl J Med. 2013] found that collateral radiation exposure to the heart during breast cancer X-ray treatment increases the subsequent rate of ischemic heart disease. PBRT can significantly reduce this exposure. Macdonald et al reported the results of a prospective trial of protons after mastectomy for patients with excellent clinical outcome and significant reduction in heart dose when compared to X-rays. [Macdonald et al Int J Radiat Oneal Bioi Phys. 2013]	See comments A10, A11.
J	64	The Cost of Protons for Children-The cost-effectiveness of PBRT in pediatric malignancies has been explored. We would highlight that although PBRT is more resource-intensive to deliver upfront, it is aligned with the judicious use of health care dollars. Lundqvist et al examined the cost of proton beam radiotherapy for childhood medulloblastoma and found that proton therapy was associated with €23,600 in cost savings and 0.68 additional quality-adjusted life-years per patient. The analyses showed that reductions in IQ loss and GHD contributed to the greatest part of the cost savings and were the most important parameters for cost-effectiveness. [Lundqvist et al, Cancer 2005]	Lundkvist 2005 is discussed extensively in the WAHTA report used for this CG.
J	65	We urge the Commission to support the coverage of proton therapy for a broader range of cancers and specifically highlight pediatric tumors and welcome the opportunity to serve as an on-going resource as you are assessing this promising cancer therapy option for Oregonians. Thank you for taking time to review this letter.	Thank you for your comments.
K	66	Dear Regence, I am writing to encourage you to examine your policy of not covering Proton Therapy where it has been proven effective, such as in the treatment of liver cancer. I think that all insurers should now be offering coverage for this approach to treating disorders in which it has been shown to be efficacious.	Commenter addresses Regence; nevertheless, thank you for your comments.

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<tr><td>L</td><td>67</td><td>We are faculty members of the Department of Radiation Oncology at the University of Washington. The majority of our head and neck patients are not treated with protons; we use it selectively in cases where we feel there is a benefit over standard forms of radiotherapy. While the Seattle Cancer Care Alliance Proton Center is one of the sites where our group practices, we have no equity interest in the center. There is no financial incentive for us to treat patients there as opposed to other sites. We would like to call your attention to the following literature:</td><td>Thank you for your comments.

WAHTA included two very small poor-quality comparative cohort studies for head & neck cancer. References submitted by this commenter are all non-comparative. It may be that individual tumor types are rare enough and proximal tissues sensitive enough that comparative studies are not feasible. Following public comment and expert testimony, the subcommittee recommended coverage of PBT for certain head and neck cancers; namely, skull-base tumors, paranasal sinus tumors, and juxtaspinal tumors.</td></tr>
<tr><td>L</td><td>68</td><td>Skull Base Tumors

One of the challenges with skull-based tumors is their proximity to the brainstem and optic structures, which can be dose-limiting organs when treating relatively radio resistant histologies such as chordomas and chondrosarcomas. With conventional photon radiotherapy, dose is limited to 55 Gy and associated with an inferior local control (LC) rate of approximately 30-50% (1). In contrast, LC for these skull-based chordomas and chondrosarcomas is higher with charged particle therapy, as summarized in the following table:</td><td>Commenter notes poor local control rate when dosimetry is limited by nearby organs. Reference 1 is a review article from 1999. Direct comparative studies are not provided. HTAS recommends skull base tumors for coverage.</td></tr>
<tr><td>L</td><td>69</td><td>TABLE: LC Rates for Sarcomas or Chordomas of the Skull Base treated with α-Particles or Protons
<table>
<tr><th>Facility</th><th>Chordoma</th><th>Chondrosarcoma</th><th>Sarcoma (other)</th></tr>
<tr><td>LBNL (2)</td><td>63%</td><td>78%</td><td>58%</td></tr>
<tr><td>HCL-MGH (1,3)</td><td>59%</td><td>99%</td><td></td></tr>
</table></td><td>Reference 2 is a 1994 case series of 223 patients treated from 1977-1992.

Reference 3 is a 1995 case series of 204 patients treated from 1975-1993.</td></tr>
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<tr><td>LLUMC (3)</td><td>76%</td><td>92%</td><td></td></tr>
<tr><td>Orsay (4)</td><td>83%</td><td>90%</td><td></td></tr>
<tr><td>Tsukuba (5)</td><td>46%</td><td></td><td></td></tr>
<tr><td>PSI (6)</td><td>88%</td><td>100%</td><td></td></tr>
</table>
</td><td>Reference 4 is a 2001 case series of 45 patients treated from 1995-1998.

Reference 5 is a 2004 case series of 13 patients treated from 1989-2000.

Reference 6 is a 2005 case series of 29 patients treated from 1998-2003.

No comparative data are identified.

The subcommittee heard testimony that comparative data in this setting are not feasible. Treatment decisions are made by dosimetry calculations and these can be impacted by exposure of nearby structures. PBT for skull base tumors is recommended for coverage.</td></tr>
<tr><td>L</td><td>70</td><td>In the Loma Linda University Medical Center (LLUMC) series, all "small and medium size" tumors without brainstem involvement were controlled with only a 7% incidence of late toxicity. (3)</td><td>This case series of 204 patients was conducted from 1975-1993 and may not represent contemporary practice and technology.</td></tr>
<tr><td>L</td><td>71</td><td>Nasopharyngeal Carcinomas

Compared with conventional radiotherapy, use of protons for treatment of nasopharyngeal carcinomas is associated with less dose to the optic structures, brain, and inner ears.</td><td>Thank you for your comments.</td></tr>
<tr><td>L</td><td>72</td><td>Lin et al reported on 16 patients with recurrent nasopharyngeal cancer who underwent proton reirradiation to 59.4-70.2 CGE after failing initial photon radiotherapy treatment to 50.0-88.2 Gy (7). Progression-free survival (PFS) was 50% at two years. Among those patients with "optimal" coverage, 2-year PFS was 83%. No patient had significant CNS toxicity.</td><td>Reference 7 is a 1999 case series of 16 patients. No comparative data are identified.</td></tr>
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ID	#	Comment	Disposition
L	73	Chan et al reviewed outcomes for 17 patients with newly-diagnosed T4N0-3 nasopharyngeal tumors treated at either HCL-MGH or the Francis H. Burr Proton Therapy Center with combined proton and photon radiotherapy (8). The median prescribed dose was 73.6 CGE. Ten patients received induction and/or concomitant chemotherapy. LC and overall survival at 3 years were 92% and 74%, respectively.	Reference 8 is a 2004 case series of 17 patients treated from 1990-2002. No comparative data are identified.
L	74	Dosimetric comparative studies have demonstrated improved tumor coverage and conformality with intensity modulated proton therapy (IMPT) as compared to IMRT techniques. Given superior conformality, "avoidance structures" such as the spinal cord, inner ear, and middle ear received a 2-3 times lower median dose than with IMPT (9).	Reference 9 is a treatment planning study comparing potential radiation doses in 8 patients using IMRT or PBT. Study looked at planned/hypothetical radiation doses only.
L	75	Paranasal Sinus Tumors The close proximity of paranasal sinus tumors to brain and optic structures make these tumors amenable for proton radiotherapy. Among 14 patients with esthesioneuroblastomas treated with protons at Chiba, Japan, between 1999 and 2005, 5-year actuarial LC was 84% and overall survival was 93% (10).	Reference 10 is a retrospective cohort study of 14 patients treated from 1999-2005 in Japan. No comparative data are identified.
L	76	Chan et al reported on 91 patients with advanced paranasal sinus tumors who received combined photon and proton radiotherapy at the HCL-MGH to a mean dose of 73.6 CGE (11). The 3-year LC was 83% for squamous cell tumors, 91% for carcinomas having neuroendocrine features, 86% for adenoid cystic carcinomas, and 88% for sarcomas.	Reference 11 is a case series of 91 patients treated from 1988-2002. No comparative data are identified.
L	77	Lastly, outcomes among 1186 patients with paranasal sinus tumors treated with photons were compared with 286 patients treated with charged particle therapy in a meta-analysis. Overall survival and disease-free survival at 5 years were significantly higher among the charged particle therapy group. Among patients treated with proton radiotherapy versus IMRT, 5-year disease free survival and loco regional control at longest follow-up were higher among the proton radiotherapy group (12).	See also comment A9 regarding Patel 2014. PBT for sinonasal carcinoma is recommended for coverage.
L	78	Juxtaspinal Tumors When tumors are invasive or adherent to critical structures such as the vertebral body, spinal cord, or peripheral nerve roots, complete resection is difficult to achieve. Because the tumor is adjacent to the cord, with conventional radiotherapy techniques, dose to the tumor is limited by the cord's tolerance to radiation, 50-55 Gy. The use of protons or other charged particles allows one to wrap the high dose volume around and avoid the spinal cord; tumors can therefore be treated to 70 CGE with proton radiotherapy.	It is noted that radiation of juxtaspinal tumors is limited by tolerance of adjacent spinal cord.

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L	79	Among 51 patients with cervical spine chordomas treated at MGH-HCL, LC was 65% (3). Nowakowski et al described a series of 52 patients with juxtaspinal tumors of varying histologies and locations treated with D-particles at the Lawrence Berkeley Laboratory; 16 of these were located in the cervical spine (13). The overall LC was 58% for 36 patients with previously untreated lesions.	Reference 3 is discussed under comment 69. Reference 13 is a case series of 52 patients treated from 1976-1987. No comparative data are identified.
L	80	Oropharyngeal Tumors Using a combination protons and photons in an accelerated fractionation schema, LLUMC treated 29 patients with locally-advanced, oropharyngeal carcinomas (13). The overall, 5-year actuarial loco regional control rate was 84% (88% primary site, 96% neck nodes); 5-year disease-free survival was 65%.	See comment 79.
L	81	Frank et al presented data at the 55th Annual Meeting of the American Society for Radiation Oncology showing that patients with orophalyngeal tumors treated with protons had a substantially lower requirement for feeding tubes during therapy than a comparable group of patients treated with IMRT (20% vs. 48%) and less nausea, emesis, and mucositis. A subsequent report on 15 head and neck cancer patients treated using multifield optimization of IMPT showed only one case of grade 3 mucositis in the posterior oral cavity; there was no grade 2 or higher mucositis in the anterior oral cavity (15).	Reference 15 is a case series of 15 patients, reporting "the first clinical experience and toxicity of multifield optimization (MFO) intensity modulated proton therapy (IMPT) for patients with head and neck tumors." No comparative data are identified.
L	82	Retreatment of Treatment Failures Management of patients with recurrent head and neck cancer who have failed an initial, radiation based treatment is challenging. Re-irradiation with photons, with or without chemotherapy, is associated with 34-65% grade 3+ toxicity. For non-nasopharyngeal sites, these serious side effects can include osteoradionecrosis, laryngeal and swallowing dysfunction and carotid artery ruptures (16). IMPT is significantly better than IMRT in terms of normal tissue sparing, particularly in the low to intermediate dose regions (17).	Reference 16 is a 2013 dose-planning study of 7 patients, comparing helical tomotherapy to IMPT. "IMPT was found not to be uniformly superior to HT… comparative dose planning is recommended if both methods are available." The subcommittee heard testimony that comparative dose planning is standard of care and that PBT will be recommended only when comparative dose planning finds

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			it likely to be superior for a given patient. Coverage of PBT is recommended for malignant brain, spinal, skull base, paranasal, and juxtaspinal tumors [whether they are initial or recurrent]
M	83	Dear Commission Members: The American Society for Radiation Oncology* (ASTRO), appreciates the opportunity to comment on the Oregon Health Evidence Review Commission (HERC) Coverage Guidance for Proton Beam Therapy. We are concerned that the HERC Coverage Guidance is overly restrictive, inconsistent with current literature, and will have a detrimental effect on vulnerable populations who derive the most benefit from access to proton beam therapy.	Thank you for your comments.
M	84	Proton beam therapy (PBT) is neither a new nor an experimental technology for treating cancer with radiation. It utilizes proton radiation particles to deliver highly conformal radiation therapy to a specific tumor target area while giving a much lower dose to the normal tissues in the proton beam's path of entry and exit. PBT's reduced radiation dose to healthy tissues can reduce side effects for patients with demonstrated effectiveness in increasing quality of life. To date, scientific evidence exists confirming that PBT is particularly useful in a number of pediatric cancers, particularly those in the brain, as well as for certain adult cancers, such as ocular melanoma, chordoma, chondrosarcoma, and primary hepatocellular carcinoma. Patients with genetic syndromes and those with tumors near the spinal cord with previous irradiation also benefit from the use of PBT. Additional research on other cancer disease sites, such as breast, prostate and lung, is ongoing with NCI-supported clinical trials currently accruing patients in all three disease sites at the more than 14 proton therapy treatment centers around the country.	This information is correct and consistent with the CG report.
M	85	In June 2014, ASTRO released a PBT Model Policy that identifies cancer diagnoses that meet ASTRO's evidence-based standards that should be covered by private insurers and Medicare. This Model Policy recommends two coverage groups for PBT: 1) patients with specific diagnoses for which PBT has been proven to be effective; and 2) patients with cancer diagnoses where there is a need for continued clinical evidence development and comparative effectiveness analyses for the appropriate use of PBT. For the patients in group two, coverage with evidence development is recommended for patients if they are enrolled in clinical trials or a multi-institutional registry to collect data and inform consensus on the role of proton therapy.	Please see comment 5.
M	86	The HERC Coverage Guidance is especially concerning because it declines to provide coverage for pediatric malignant tumors. PBT is an important treatment option for certain pediatric tumors, since damage to the surrounding normal tissues in children can produce serious long-term side effects on the growth and development of vital organs and tissues. A growing body of literature shows the late effects, quality of life, and cost effectiveness of proton beam therapy on pediatric patients. Randomized studies are not feasible given the general acceptance of PBT for pediatric	It is noted that comparative studies are unlikely to be conducted in pediatric tumors due to lack of clinical equipoise.

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		patients within the expert community. To account for this, research compares these patients to appropriate historical cohorts. These studies are relatively "small" due to low incidence of these diseases; however, data are being collected prospectively for all children in single and multi-institutional databases. (1)	The subcommittee recommended coverage of PBT for pediatric tumors.
M	87	Additionally, we are unaware of any coverage policies that deny coverage of PBT for pediatric tumors, and we are concerned that the denial of PBT coverage for pediatric patients will considerably restrict children's access to curative and palliative treatment. ASTRO strongly recommends that HERC extend coverage to include primary or benign solid tumors in children, per the ASTRO PBT Model Policy.	Thank you for your comments.
M	88	PBT has attracted significant attention due to its relative cost, which is usually higher than traditional external beam radiation therapy. However, studies now suggest that proton therapy can be a cost-effective strategy for the management of certain cancers. (2, 3, 4) In one study, proton beam therapy was proven to be associated with higher quality-adjusted life years and lower costs. (5)	The cost studies referenced were considered in the WAHTA report on which our CG is based.
M	89	Furthermore, we are concerned that in developing this coverage guidance, HERC did not consult the opinions of experts in the field nor did they review the full body of evidence surrounding proton beam therapy as an effective form of cancer treatment. We are very surprised that the ASTRO PBT Model Policy, which was carefully developed by leading radiation oncologists and medical physicists and benefitted from balanced input from experts in proton therapy, was not cited as a reference in the HERC Coverage Policy for Proton Beam Therapy.	The coverage guidance process solicits expert input as well as public comment such as this one. Please see comment 5 regarding ASTRO.
M	90	ASTRO is committed to providing evidence-based guidance to payers in the form of recommendations for correct coverage policies for radiation oncology. We encourage HERC to follow the lead of many national private and public insurers by consulting the evidence and following the recommendations in ASTRO's PBT Model Policy when developing coverage policies for PBT. The ASTRO PBT Model Policy is enclosed for your review, in addition to a list of references and supporting articles.	Thank you for your comments.
M	91	Thank you for your consideration of our comments. Should you have any questions or wish to discuss our concerns further, please contact ASTRO's Director of Health Policy	Thank you for your comments.
N	92	Dear Oregon Health Evidence Review Commission: As a Radiation Oncology faculty member at the University of Washington, I specialize in caring for patients of all ages with central nervous system tumors. A minority of my patients are treated with proton beam therapy. For these patients, proton beam therapy provides the best chance of curing their brain tumors while minimizing significant side effects. Proton beam therapy has no exit radiation dose, which patients would otherwise receive if treated with x-rays. This is especially important in the central nervous system where very low doses of radiation to normal brain can cause neurocognitive decline, hormonal deficits, and secondary malignancies. For spinal cases, low dose radiation to the anterior organs is associated with nausea and lower blood counts in the short term; and heart disease and secondary malignancies in the long term.	Thank you for your comments.

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N	93	The Washington Health Technology Assessment recently issued a final report where they universally recommended that proton beam therapy for brain/spinal cancers be covered by state insurance. This was based on finding equal benefit and decreased harm for proton beam therapy over conventional therapy. In addition, many other coverage policies agree with this recommendation, and I urge you to do the same.	The WAHTA evidence report formed the basis for this CG document. Following the evidence report and public comment, the Health Technology Clinical Committee voted unanimously to recommend coverage of PBT with conditions, namely: - Ocular tumors - Pediatric cancers (e.g., medulloblastoma, retinoblastoma, Ewing's sarcoma) - Central nervous system tumors (e.g. brain, spinal and paraspinal tumors) - Other non-metastatic cancers with the following conditions: a) Patient has had prior radiation in the expected treatment field with contraindication to all other forms of therapy, and b) At agency discretion Following public testimony and expert input, the subcommittee recommended coverage of PBT for malignant brain and spinal tumors.
N	94	Summary of Evidence	Please see comments 59 and 61.

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		Pediatric central nervous system cancers: Children have developing tissues that are exquisitely sensitive to radiation. Though long term survival is now achieved in the majority of patients, side effects from radiation therapy can have a profound effect on quality of life in survivors.	
N	95	In a study of patients receiving irradiation for a brain tumor before than age of four, only a third of adult survivors were able to have full-time employment. (1) Modeling of the effect of radiation therapy on IQ predicted a significant decrease in neurocognitive decline for older children as well. (2)	Reference 1 is a case series of 222 children treated from 1958-1995. Reference 2 is addressed in comment 61.
N	96	In a St Jude study of children treated for brain tumors, 94% had resulting growth hormone deficiency, 50% had hypothyroidism, and 43% had adrenal insufficiency.3 Proton therapy can decrease the pituitary dose for many cases.2	Please see comment 61.
N	97	Protons allow for sparing of the cochlea, resulting in lower ototoxicity rates. (4)	Reference 4 is considered in the WAHTA evidence review.
N	98	Finally, a recent study of pediatric patients with retinoblastoma showed that the 10 year cumulative incidence of secondary malignancy was 14% in patients treated with photons versus 0% in patients treated with protons. This supports the conclusion that protons will decrease the risk of secondary malignancy, which is 20.5% in 5 year survivors of childhood cancer. (5)	Reference for the comparative study of retinoblastoma treatment is not provided. Reference 5 is a case series of 14,359 survivors of childhood cancers; the 20.5% figure is correct.
N	99	*Adult low grade gliomas:* Recent multicenter randomized trials have shown median survival for patients with grade II gliomas (both astrocytoma and oligodendroglioma) and grade III oligodendroglioma to now be greater than fourteen years with radiation therapy and chemotherapy. (6, 7) However, adult low grade glioma survivors have poor cognitive function when receiving postoperative radiation therapy, which limits their ability to work and decreases their quality of life. (8) A recent prospective phase II trial of proton beam therapy for low grade gliomas showed no evidence of overall decline in cognitive function or quality of life based on neurocognitive assessment and patient questionnaires. (9)	Reference 6 is a phase III trial comparing chemotherapy + radiotherapy vs radiotherapy alone in 291 patients. Median survival was not different between groups for the whole cohort. The 14-year figure applies to patients with codeleted tumors only, which was not a predefined subgroup analysis. Reference 7 is an editorial describing long-term follow up

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			results of the same study. Reference 8 is a cross-sectional study comparing self-reported cognitive function in 195 low-grade glioma survivors with 100 low-grade hematological patients and 195 healthy controls. The authors conclude that "Our findings suggest that the tumour itself has the most deleterious effect on cognitive function and that radiotherapy mainly results in additional long-term cognitive disability when high fraction doses are used." Reference 9 is a prospective single-arm cohort study of 20 patients followed for 5 years after proton therapy. No overall decline in cognitive function was detected. Direct comparative data of PBT vs other treatment is not identified.
N	100	*Adult benign brain tumors (e.g. meningioma, vestibular schwannoma, pituitary adenoma):* Multiple series document the outcomes of proton therapy for the treatment of meningioma (10-13), pituitary adenoma (14), and vestibular schwannoma (15). For patients with benign disease and good long term prognosis, proton beam therapy decreases the risk of neurocognitive decline, endocrine dysfunction, and secondary malignancy. (16, 17)	References 10-13 are considered in the WAHTA evidence review. Reference 14 was published after the WAHTA review. It is a case series of 165 patients with functional pituitary adenoma treated from 1992-2012. Reference 15 is a case series of

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			64 patients treated with stereotactic radiation therapy. It did not discuss proton beam. No comparative data are identified. Reference 16 is a treatment-planning study of 10 patients in which treatment was re-planned with proton radiotherapy and effect differences were estimated based on hypothetical dose. Reference 17 is a similar modeling study in which doses are estimated using 8 different techniques in one standard case.
N	101	*Adult medulloblastoma:* The NCCN guidelines recommend considering proton therapy for craniospinal irradiation for adult medulloblastoma given published data by MD Anderson showing less weight loss and hematologic toxicity for patients undergoing proton therapy compared to photon therapy. (18)	Reference 18 is considered in the WAHTA review.
N	102	*High grade gliomas:* The median survival for glioblastoma multiforme is still roughly one year with chemotherapy and radiation therapy. Recent data suggests that increasing the radiation dose for initial treatment or giving a second course of radiation therapy for recurrent gliomas will improve outcomes. However, past efforts to escalate dose or re-irradiate have resulted in considerable toxicity. Thus, we are participating in two national cooperative group NRG Oncology clinical trials, BN001 and RTOG 1205. (19, 20) Both trials use proton therapy with the aim of improving survival for this otherwise devastating disease.	It is noted that studies of proton beam for GBM are in progress. Studies in progress will be considered after peer review and publication.
N	103	*Cost effectiveness:* Recent studies that modeled the cost of long term effects of radiation therapy for pediatric patients with brain tumors found that proton therapy is overall cost effective. (21, 22) Indeed, in my practice I find that long term survivors of brain tumors may be cured but have considerable late effects including neurocognitive decline and hormonal deficiency that are costly to the patient in terms of their ability to work and to payers in terms of medical care.	References 21 and 22 are the two papers by Mailhot Vega; please see comment 13.
N	104	I urge the Commission to support coverage of proton therapy for central nervous system tumors and welcome the	Thank you for your comments.

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		opportunity to serve as an on-going resource as you are assessing this important cancer therapy option for Oregonians. Thank you for this opportunity.	
O	105	To: Regence It has come to my attention that your insurance does not currently cover proton radiation treatment for all forms of cancer. I am writing to advocate that you at least provide your beneficiaries who have liver cancer, with this coverage. I hope you know that it has proven to be efficacious. Thank you for being responsive to the needs of your beneficiaries.	Commenter addresses Regence; nevertheless, thank you for your comments.
P	106	Dear Oregon Health Evidence Review Commission: On behalf of the Particle Therapy Cooperative Group- Nmih America (PTCOG-NA)1, we respectfully submit comments on Oregon's Health Evidence Review Commission (HERC) Coverage Guidance on Proton Beam Therapy (PBT).	Thank you for your comments.
P	107	While we were pleased to see the strong recommendation for coverage of malignant ocular tumors, we have significant concerns with many of the other recommendations. We were especially surprised and disappointed with the lack of a positive coverage recommendation for pediatric malignant tumors. Because of the strong evidence supporting its use, PBT for pediatric patients is practically universally covered. Additionally, we strongly disagree with your characterization that "PBT is far more expensive than its major alternatives." Recent studies have found that when treating for toxicity and other post-treatment occurrences are considered, PBT has been found to be a cost-effective treatment. We urge you to consider the evidence we provide in this letter in your deliberations.	Available cost-effectiveness data have been considered. The HTAS recommended coverage of PBT for pediatric tumors.
P	108	Evidence on the Effectiveness of PBT for Pediatric Malignant Tumors The proposed coverage guidance gave a weak recommendation for coverage for pediatric malignant tumors, despite the overwhelming consensus on its appropriateness for pediatric patients. We believe eliminating coverage of PBT for pediatric patients is inconsistent with the current state of evidence and would be harmful to a population of patients who would most benefit from the reduced amount of radiation received in the course of PBT treatment.	The HTAS recommended coverage of PBT for pediatric tumors.
P	109	Due to the growing body of evidence in this area, most payors, regulators and providers support the use of PBT for pediatric patients. The consensus is reflected in the American Society for Radiation Oncology (ASTRO) model policy on PBT which supports its use for primary or benign solid tumors treated in children with curative intent (ASTRO, 2014). (1) Examples of published evidence in this area include a recent study of 54 patients with pediatric rhabdomyosarcoma which found that PBT lowers integral dose and improves sparing normal tissue when compared to IMRT [Ladra, MM et al Radiother Oncol 2014]. (2)	Please see comment 5 regarding ASTRO. Ladra 2014 is a prospective cohort study of 54 patients who received proton therapy; IMRT plans were generated for comparison.

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P	110	In another example, a 2012 study of high risk pediatric neuroblastoma found that preliminary outcomes reveal excellent control with proton therapy for this population [Hattagangadi JA, Int J Radiat Oncol Biol Phys, 2012]. (3) While we have cited just two studies, these are consistent with other studies of pediatric patients.	Hattangadi 2012 was considered in the WAHTA document.
P	111	Evidence on the Effectiveness of PBT for Other Sites The proposed guidance concludes, " ... there was insufficient evidence to obtain even a basic understanding of PBT's comparative clinical effectiveness and comparative value." Frankly, we were stunned by this characterization. While we acknowledge (and support) the ongoing development of additional clinical evidence, there is already significant evidence supporting the effectiveness of PBT that this proposed coverage guidance ignores. In addition to the evidence supporting the use of PBT for pediatric tumors, there is significant evidence supporting its use for other tumor sites.	The CG was based on a WAHTA report that came to this conclusion.
P	112	The articles listed below are only from the last 15 months and they reflect the meaningful research being conducted in this area. 2015 • Cuaron JJ, Chon B, Tsai H, Goenka A, DeBlois D, Ho A, Simon P, HugE, Cahlon 0 . Early toxicity in patients treated with postoperative proton therapy for locally advanced breast cancer. *Radiation Oncology.* Published online March 6, 2015. • Holliday EB, Mitra HS, Somerson JS, Rhines LD, Mahajan A, Brown PD, Grosshans DR. Postoperative proton therapy for chordomas and chondrosarcomas of the spine: adjuvant vs. salvage radiation therapy. *Spine.* Published online January 23, 2015. • Mizumoto M, Oshiro Y, Takizawa D, Fukushima T, Fukushima H, Yamamoto T, Muroi A, Okumura T, Koji T, Sakura H. Proton beam therapy for pediatric patients with ependymoma. *Pediatrics International.* 2015; DOI:10.1111/ped.12624. • Vega RM, Kim J, Hollander A, Hattangadi-Giuth J, Michalski J, Tarbell NJ, Yock Tl, Bussiere M, MacDonald SM. Cost effectiveness of proton versus photon radiation therapy with respect to the risk of growth hormone deficiency in children. *Cancer.* Published online January 29, 2015. 2014 • Brower *N,* Gans S, Hartsell WF, Goldman S, Fangusaro JR, Patel N, Lulla RR, Smiley NP, Change JH, Gondi V. Proton therapy and helical tomothrapy result in reduced dose deposition to the pancreas in the setting of cranio-spinal irradiation for medulloblastoma: implications for reduced risk of diabetes mellitus in long-term survivors. *Acta Oncol.* 2014 Nov: 1-5. • Frank SJ, Cox JD, Gillin M, Mohan R, Garden AS, Rosenthal DI, Gunn GB, Weber RS, Kies MS, Lewin JS, Munsell	Cuaron (2015) is a case series that assessed dosimetry and early toxicity of PBT in 30 patients with metastatic breast cancer. Dosimetry was deemed adequate and toxicity was deemed acceptable. Holliday (2015) is a case series that assessed local control (58%), relapse-free survival (51.9%), and overall survival (93.3%) in 19 patients with chordoma or chondrosarcoma treated with PBT. Patients with primary adjuvant radiation therapy had better 2 year LC than those receiving salvage treatment. Mizumoto (2015) is a case series that assessed local occurrence and toxicity in 6 pediatric patients with ependymoma treated with PBT. Simulation showed that PBT reduces dose

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		MF, Palmer MB, Sahoo N, Zhang X, Liu W, Zhu XR. Multifield optimization intensity modulated proton therapy for head and neck tumors: a translation to practice. *Int J Radiat Oncol Bioi Phys.* 2014 Jul 15;89(4):846-53. • Kesarwala AH, Ko CJ, Ning H, et al. Intensity-modulated proton therapy for elective nodal irradiation and involved-field radiation in the definitive treatment of locally advanced non-small cell lung cancer: a dosimetric study. *Clinical Lung Cancer.* Available online 9 December 2014. • Ladra MM, Szymonifka JD, Mahajan A, et al. Preliminary results of a phase II trial of proton radiotherapy for pediatric rhabdomyosarcoma. *J Clin Oncol.* 2014 Oct 20; epub ahead of print. • Ling TC, Slater JM, et al. Analysis of intensity-modulated radiation therapy (IMRT), proton and 3D conformal radiotherapy (3D-CRT) for reducing perioperative cardiopulmonary complications in esophageal cancer patients. *Cancers.* 2014;6(4):2356-2368. • Makita C, Nakamura T, Takada A, Takayama K. Suzuki M, Amazi Y, Kato T, Tsukiyama I, Hareyama M, Kikuchi Y, Daimon T, Hata M, Inoue T, Fuwa N. High-dose proton beam therapy for stage I non-small cell lung cancer: clinical outcomes and prognostic factors. *Acta Oncol.* 2014Oct 7:1-8 (Epub ahead of print). • Patel SH, Wang Z, Wong WW, Murad MH, Buckey CR, Mohammed K, Alahdab F, Altayar 0, Nabhan M, Schild SE, Foote RL. Charged particle therapy versus photon therapy for paranasal sinus and nasal cavity malignant diseases: a systematic review and meta-analysis. *Lance/ Oncol.*2014 Aug; 15(9): I 028-1038. • Schild SE, Rule WG, Ashman JB, Vora SA, Keole S, Anand A, Liu W, Bues M. Proton beam therapy for locally advanced lung cancer: a review. *World J Clin Oncol.* 2014 Oct 10;5(4):568-75. • Sethi RV, Shih HA, Yeap BY, et al. Second nonocular tumors among survivors of retinoblastoma treated with contemporary photon and proton radiotherapy. *Cancer.* 2014;120(1):126-133. • Thaker NG, Guzman AB, Feeley TW, Jones TM, Incalcaterra JR, Kolom C, Tatum LS, Walters RS, Cantor SB, Rosenthal DI, Garden AS, Gunn GB, Fuller CD, Palmer MB, Frank SJ. Defining the value of proton therapy using time-driven activity based costing. On col Payers 1 (1):22-28,2014. • Yock Tl, Bhat S, Szymonifka J, Yeap BY, Delahaye J, Donaldson SS, MacDonald SM, Pulsifer MB, Hill KS, DeLaney TF, Ebb D, Huang M, Tarbell NJ, Fisher PG, Kuhlthau KA. Quality of life outcomes in proton and photon treated pediatric brain tumor survivors. *Radiother Oncol.*2014 Oct 7. [Epub ahead of print]	to normal brain tissue by half compared to photon therapy. All patients were alive at follow up (13-44 mo) and there was no severe toxicity. Mailhot Vega (2015) is a cost-effectiveness study of PBT compared with photon therapy for pediatric patients with growth hormone deficiency.PBT is cost effective in some scenarios based on hypothalamic sparing. Brower (2014) is a case series that assessed dosimetry of PBT compared with 3DCRT and inverse-planned intensity modulated radiation therapy (IMRT) with helical tomotherapy in five pediatric patients with medulloblastoma. PBT resulted in less radiation to the pancreas than other treatments. Franks (2014) is a case series that assessed toxicity of multifield optimization intensity modulated PBT in 15 patients with head and neck cancer. There were no treatment-related deaths, and with a median follow-up time of 28 months (range, 20-35 months), the overall clinical complete

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			response rate was 93.3% Kesarwala (2015) is a case series that assessed intensity-modulated PBT dosimetry in 20 patients with locally advanced non-small cell lung cancer. All evaluated dosimetric parameters improved significantly with proton plans compared with photon IFRT. Ladra (2014) is a case series that assessed disease control and toxicity of 57 pediatric patients with rhabdomyosarcoma treated with PBT. Five-year LC, EFS, and OS rates were similar to those observed in comparable trials that used photon radiation. Acute and late toxicity rates were favorable. Ling (2014) is a case series that assessed dosimetry of IMRT, 3DCRT and PBT in 10 patients with esophageal cancer. Authors conclude proton plans are technically feasible while achieving adequate coverage with lower doses delivered to the lungs and cardiac structures. Makita (2015) is a case series that assessed survival, local control, and toxicity in 56 patients with stage I non-small

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			cell lung cancer treated with two PBT protocols. The three-year overall survival, progression-free survival, and local control rates were 81.3%, 73.4%, and 96.0%, respectively. There were no significant differences in outcomes between the two protocols. Late grade 2 and 3 pulmonary toxicities were observed in nine patients and one patient respectively; no grade 4 or 5 toxicities were observed. Patel (2014) is a systematic review and meta-analysis that compares clinical outcomes from PBT and charged particle therapy. Forty-one case series studies were included that reported on overall survival, disease-free survival, and local control. None of the included studies were comparative. The review found higher overall survival and locoregional control for charged particle beam than PBT at longest follow-up (not defined), and no difference in disease-free survival at longest follow-up between groups. Schild (2014) is a narrative review on the use of PBT as part of a multi-modal treatment

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			program for patients with locally advanced lung cancer. "This review was written for the non-radiation oncologist who wishes to understand the use of proton beam therapy (PBT) for locally advanced lung cancer. One randomized study is being performed and another is planned to clarify the differences in outcome for PBT compared to XRT. Newer forms of radiotherapy such as PBT should positively impact lung cancer patients." Sethi (2014) is a retrospective case series that assessed recurrence rates in 86 patients with retinoblastoma treated with PBT or photon radiotherapy. The 10-year cumulative incidence of RT-induced or in-field second malignancies was significantly different between radiation modalities (proton vs photon: 0% vs 14%; P = .015). The 10-year cumulative incidence of all secondary malignancies was also different, although with borderline significance. Thanker (2014) is a time-driven activity-based costing study of two patients with advanced

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			head and neck cancer treated with IMRT and intensity-modulated PBT. It is published in a non-peer-reviewed journal. Authors conclude that the episodic cost of care using IMPT was less costly and of higher value than IMRT. Yock (2014) is a case series that compared parent proxy health-related quality of life scores of 57 pediatric brain tumor patients treated with PBT with those of 63 pediatric brain tumor patients treated with photon beam radiation. The total core HRQoL score for the PRT-C, XRT-C, and normative population differed from one another and was 75.9, 65.4 and 80.9 respectively ($p=0.002$; $p=0.024$; $p<0.001$). HRQoL of pediatric brain tumor survivors treated with PRT compares favorably to those treated with XRT and similar to healthy controls. The HTAS recommended coverage of PBT for pediatric tumors based on reviewing the limited evidence, expert testimony, and the lack of clinical equipoise that means future trials are unlikely to be

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			conducted.
P	113	For further evidence, we highlight the multiple national guidelines that support the use of proton therapy. The National Comprehensive Cancer Network (NCCN) guidelines, the previously cited ASTRO model policy for proton therapy, and the model policy on coverage of proton beam therapy from the National Association of Proton Therapy (NAPT) both approve of the use of proton therapy for certain patients. The basis for these national guidelines is the growing body of evidence supporting the use of proton therapy for positive long-term treatment outcomes and quality of life for oncology patients. The weight of this evidence is reflected in the numerous Medicare contractors and private payors policies that provide coverage for PBT for a number of anatomical sites.	The guidelines cited are included in the CG document, with the exception of the NAPT. Staff were unable to identify guidelines via search of the NAPT website.
P	114	*PTCOG-NA urges you to* postpone finalizing *this coverage guidance and reconsider your methodology of reviewing clinical evidence. We offer the assistance of our clinical leadership to assist you with any review.*	Thank you for your comments.
P	115	Evidence on the Cost Effectiveness of PBT An overarching benefit of PBT versus photon therapy is its precise targeting that spares very sensitive adjacent normal tissue, resulting in reductions in toxicity and other negative occurrences post-treatment. We are very concerned that you failed to consider these benefits. A study published in *Cancer* [Mailhot Vega, RB et al, *Cancer* 2013] found that by avoiding years of costly side effects, PBT can be cost-effective for children with medulloblastoma.	Please see comment 13.
P	116	An example of this more comprehensive analysis is a recent study issued by MD Anderson Cancer Center and presented at the October 2014 meeting of PTCOG-NA (manuscript under development). The study found that the cost of PBT when used for accelerated partial breast irradiation to decrease overall treatment time and toxicity, was estimated at $13,833. Results of the study suggested that the cost of proton therapy is similar to other types of radiation.	Commenter references unpublished data; new published evidence will be considered as the CG enters re-review every 2 years.
P	117	*PTCOG-NA strongly recommends that you include studies that consider cost of toxicity and other post-treatment conditions that can occur and which certainly impact costs and the quality of life of the patient.*	Thank you for your comments.
P	118	While we appreciate the opportunity to submit comments, we felt very limited in our ability to communicate to you due to the severe limitations on written (1000 word) and oral (3 minutes) comments. We believe the current process may stymie public input. *PTCOG-NA urges you to reconsider these guidelines.* Should you have any questions, please do not hesitate to contact me	Thank you for your comments.
Q	119	Dear Oregon HERC, I write this letter requesting your consideration in the coverage of proton therapy for prostate cancer.	Thank you for your comments.
Q	120	Proton therapy has been in clinical use in the US since the 1970s. There is a long track record establishing safety and efficacy in patients with prostate cancer over decades of experience. Due to the unique physical characteristics of	This is correct and consistent with the background

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		proton beam radiation (PBT), proton therapy is associated with less dose to surrounding normal tissues in the pelvis (e.g. rectum, bladder) than photon/x-ray IMRT. It allows safe delivery of radiation to the prostate while minimizing side effects.	information.
Q	121	Two phase III randomized studies established that protons are a safe and effective means to deliver dose-escalated radiotherapy, the current standard of care in prostate cancer. One study by Massachusetts General Hospital (MGH) randomized patients with prostate cancer to a higher dose proton boost versus lower dose x-ray boost to the prostate following pelvic radiation with xrays. (1) Another study by MGH and Lorna Linda randomized patients with prostate cancer to a higher dose versus lower dose proton boost in combination with x-ray radiation. (2) Both trials showed an improvement in local control with the higher dose proton boost with a very low risk of GU or GI complications.	References 1 and 2 are considered in the WAHTA report.
Q	122	A number of single institutional experiences have also reported excellent long term outcomes with proton therapy. Loma Linda reported a series of 1255 patients with prostate cancer treated with either protons or a combination of x-rays and protons. (3) Survival rates were excellent, and the risk of severe GU or GI complications was extremely low.	Reference 3 is a retrospective cohort study of 1255 patients treated with proton radiation therapy from 1991-1997. Authors concluded that disease-free survival rates were comparable with other forms of local therapy. Authors also concluded that "No difference was seen in toxicity between those treated with combined protons and photons (11 of 731) and those with protons alone (6 of 524; p = 0.52).
Q	123	More recently, University of Florida reported their 5-year control rates from 3 prospective PBT trials for prostate cancer: 99%, 99%, and 76% in low, intermediate, and high risk patients, respectively. Among 211 patients, only 1-2% experienced serious late toxicity. These results compare very favorably with published results for IMRT. (4)	Reference 4 is a report of three prospective trials encompassing 211 prostate cancer patients. The data on control rates are correct. Rates of grade 3 GI toxicity were 1.0% and rates of grade 3 urologic toxicity were 5.4%. Within-trial comparative data are not available; commenter is referencing

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			historical IMRT data from other publications.
Q	124	An advantage of PBT is decreased exposure of normal pelvic tissues to low to moderate dose radiation (0-50 Gy). Low-dose radiation to pelvic structures is associated with bowel and bladder urgency, frequency, erectile dysfunction and secondary cancers. (5). These side effects can drastically influence a patient's quality of life (QOL).	Reference 5 is a retrospective questionnaire study of bowel, urinary, and sexual function in 65 patients who received external beam radiation therapy for localized prostate cancer. Within-trial comparative data are not available.
Q	125	No randomized, prospective studies exist comparing IMRT and PBT. Several attempted retrospective comparisons have been conducted using large, national databases including SEER, but these studies suffer from major weaknesses including lack of granular details on side effects such as rectal urgency, poor surrogates for measures of GI toxicity, and comparison based on historical cohorts of small numbers of patients treated with now outdated proton therapy techniques/technology. In one QOL study comparing men treated with IMRT versus PBT, there was less rectal urgency and frequency in men treated with PBT than IMRT. (6)	It is noted that prospective randomized studies exist. Reference 6 is a comparison of QOL data from two different cohort studies, 1243 men receiving PBT and 204 men receiving IMRT. There were **no differences in QOL summary scores** between the IMRT and PT cohorts during early follow-up (up to 2-years). Response to individual questions suggests possible differences in specific bowel symptoms.
Q	126	Decreases in testosterone, the major male hormone responsible for sex drive and stamina, can adversely affect patient QOL. Minimizing low-dose radiation to the pelvis with PBT has been found to translate into improved ability to maintain normal testosterone levels in patients after treatment compared with x-rays. (7)	Reference 7 is included in the WAHTA report.
Q	127	Lastly, decreasing integral radiation dose to the body is associated with a reduced risk for secondary cancers. This is particularly important for younger men seeking an alternative to surgery. In a matched-cohort study that included 33% of men treated for prostate cancer, PBT led to a 50% reduction in incidence of secondary cancers compared to photon-based radiation. (8)	Reference 8 is included in the WAHTA report.
Q	128	We recognize the importance of generating high level-evidence confirming the benefits of PBT in prostate cancer	Studies in progress will be

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		treatment. We are participating in the ongoing multicenter "PartiQOL" randomized trial comparing IMRT vs protons for prostate cancer. Clinical trials like PartiQOL will help quantify the degree of improvement in patient-reported quality of life with PBT over IMRT. In addition, all of our prostate cancer patients are enrolled on a prospective multicenter clinical registry capturing patient reported QOL measures before and after treatment as well as disease control outcomes.	considered following publication.
Q	129	This need for continued clinical evidence development (CED) and comparative effectiveness data is recognized by the current ASTRO national model policy for PBT. (9) Under this policy, enrollment in an IRB approved multi-institutional patient registry that adheres to Medicare requirements for CED is considered an indication for proton therapy that should be covered by an insurance carrier. These important trials cannot not be completed if PBT is not covered.	Regarding ASTRO, please see comment 5. Recommendation for CED is noted. *For HTAS discussion*
R	130	To Whom It May Concern: This letter is in regards to the Oregon Health Evidence Review Commission coverage guidelines for proton beam therapy. As an assistant professor in the department of radiation oncology at the University of Washington, I sub-specialize in breast cancer and would like to comment on the use of proton beam therapy for breast cancer.	Thank you for your comments.
R	131	Proton beam therapy is currently being used in the treatment of breast cancer in many proton centers across the country. The largest, single-institution experience to date using proton beam therapy for breast cancer comes from Loma Linda, where at last publication in 2014, one hundred women with *early stage breast cancer* had been treated with proton beam therapy following surgery (lumpectomy) as part of breast-conserving therapy. (1) When compared with 3-dimensional conformal photon plans for partial breast irradiation, Bush *et al.* reported a significant reduction in exposure to surrounding normal breast tissue with proton beam therapy that led to improved cosmetic outcomes. (2) There was also nominally lower radiation dose to the lung and heart with proton.	Data from the Loma Linda trial are considered in the WAHTA report. Reference 1 was published after the WAHTA report and reports 5-year follow up data on this phase 2 trial of 100 patients; results are not significantly different from prior publications.
R	132	More recently proton beam therapy has been investigated in *locally advanced breast cancer*. The initial experience from Massachusetts General Hospital was published in 2013 and reported on stage III breast cancer patients that were irradiated with protons after mastectomy to the chest wall and regional lymphatics. (3) A comparative dosimetric analysis between proton and photon plans demonstrated substantial reductions in both lung and heart exposure as defined by well-established metrics for those organs at risk. *In addition, there was improvement in prescription dose coverage to the areas at risk*, i.e. chest wall and regional lymphatics received adequate doses. (4) Acceptable acute toxicity (dermatitis and fatigue) was reported. A separate multi-institutional dosimetric study that compared treated photon/electron plans with created proton plans (in press for publication at the time of this letter) confirmed these findings and found superior chest wall and lymphatic coverage and superior normal tissue avoidance in the proton	See comment A11.

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		plans.	
R	133	Currently, there has been little experience in salvage or palliative treatment with proton beam therapy for breast cancer. However, future investigation of its use in the setting of local breast recurrence after previous breast conservation therapy (lumpectomy followed by radiotherapy) is worthwhile, particularly given that the current standard of care is mastectomy for these women. If repeat breast preservation can be safely achieved by utilizing proton beam therapy (via less repeat exposure to previously irradiated breast tissue), this can have a significant impact on quality of life.	No additional evidence is supplied.
R	134	No recent cost-effectiveness analyses exist for breast cancer treated with proton beam therapy. However, given the preliminary data described above including lower dose to the heart, lungs, without compromise of target volume coverage, there are potential savings associated with decreased long-term toxicity such as cardiac disease, lung disease and poor cosmetic outcomes. The draft coverage guidelines reference a Swedish study from 2005 that can serve as a guideline for future analyses, but an updated study with current costs in the United States and new information regarding radiation dose-effect relationships is necessary. Cost comparisons have been performed between proton beam therapy and alternative radiotherapy methods for accelerated partial breast irradiation, particularly single-entry catheter based systems that utilize high-dose rate brachytherapy as the radiation source. An up-to-date cost comparison can reveal whether there is still a cost advantage with proton beam therapy when using updated (lowered) reimbursement of single-entry catheter techniques.	No additional evidence is supplied.
R	135	In summary, I believe that the use of proton beam therapy for breast cancer is promising and has provided a significant benefit to the women we have treated. Many others will benefit from proton beam therapy when it becomes a standard treatment option.	Thank you for your comments.
S	136	Dear Oregon Health Evidence Review Commission: I am a board certified Radiation Oncologist on the faculty of the University of Washington and specialize in the treatment of gastrointestinal cancers. I am writing to you because I utilize proton beam therapy (PBT) in select patients who may benefit from this technology. Patients with gastrointestinal cancers frequently require multimodality treatments (surgery, chemotherapy, radiation therapy) that are curative. However, these may come at the cost of significant early and late side effects that not only impact patients' quality of life but are also costly to health care systems. Key reasons why radiation therapy for gastrointestinal (GI) cancers is so toxic are the close proximity of critical normal GI organs and their high sensitivity to the damaging effects of radiation therapy.	Thank you for your comments.
S	137	PBT has the unique property of eliminating exit radiation dose that patients would otherwise receive if treated with conventional x-rays. This is especially important in the gastrointestinal system where low to moderate doses of radiation to normal liver, stomach, and bowel cause numerous and potentially debilitating GI side effects, which include but not limited to nausea, vomiting, diarrhea, and liver failure.	This information is correct.

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S	138	I urge the Commission to consider the following additional information and data when reviewing their coverage guidelines for GI cancers: Liver cancers In accordance with the recent ASTRO Model Policy for PBT, primary liver cancers are supported as medically necessary when treated in a hypofractionated regimen based on meeting the medical necessity requirements of PBT and on published clinical data. The liver is one of the most highly radiation sensitive organs in the body; low to moderate doses of radiation have a profound impact on the normal function of this organ, particularly when the liver is cirrhotic (scarred). PBT allows for safe radiation dose escalation to liver tumors, which has been shown in prospective studies to result in improve survival outcomes. (1)	Please see comment 5.
S	139	In addition to the prospective studies of PBT as detailed by the HERC, a recently published systematic review and meta-analysis compared data across 70 observational studies and demonstrated that compared to conventional photon radiotherapy, PBT had significantly superior 5-year overall survival (RR 25.9), progression-free survival (RR 1.86), and locoregional control (RR 4.3). (2) PBT also had significantly less severe acute and late toxicities (6.1% vs. 20% and 2.5% vs. 6.9%, respectively) compared to photon radiotherapy. Notably, hepatic toxicity, which is often highly morbid, life-threatening, and costly, was lower in PBT versus photon treated patients (3.1% vs. 9.9%).	Reference 2 is a systematic review and meta-analysis as described by the commenter. This was published after the WAHTA report. Carbon-ion therapy was included in the same group as PBT under the category of "charged particle therapy." Survival rates were better than conventional radiotherapy but similar to SBRT.
S	140	Furthermore, due to its dosimetric advantages, PBT allows for hypofractionated treatment, particularly for large liver tumors that would not be amenable to conventional fractionation of photon radiotherapy: instead of delivering 40 fractions (8 weeks) of conventionally fractionated photon radiation, PBT can be safely delivered in only 15 fractions (3 weeks) with biologically equivalent doses. As shown in the table below, when using Medicare reimbursement rates (professional and technical fees), *PBT results in cost savings of approximately 30% when compared to IMRT in this setting: $21,665.63 versus $30,678.93, respectively.*	Commenter describes a scenario in which higher doses can be delivered more efficiently with PBT for liver cancer; published citation is not provided and source of this table is not cited.

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<tr><th colspan="2">IMRT (40 fractions)</th><th colspan="2">PBT (15 fractions)</th></tr>
<tr><td>1 New patient visit</td><td>99205</td><td>1 New patient visit</td><td>99205</td></tr>
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<tr><td>1 IMRT plan</td><td>77301</td><td>1 Dosimetry calculations</td><td>77300</td></tr>
<tr><td>1 IMRT MLC Device</td><td>77338</td><td>1 Special dosimetry plan</td><td>77331</td></tr>
<tr><td>1 Immobilization Device</td><td>77334</td><td>4 Complex treatment devices</td><td>77334</td></tr>
<tr><td>8 Weekly mgmt</td><td>77427</td><td>4 Apertures/compensators</td><td>77334</td></tr>
<tr><td>8 Physics QA</td><td>77336</td><td>3 Physics QA</td><td>77336</td></tr>
<tr><td>40 IMRT treatments</td><td>G6015</td><td>2 Special physics consults</td><td>77370</td></tr>
<tr><td>6 Films</td><td>77417</td><td>Special treatment procedure</td><td>77470</td></tr>
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<tr><td>1 Follow-up visit</td><td>99213</td><td>1 Follow-up visit</td><td>99213</td></tr>
<tr><td>Total Cost</td><td>$30,678.93</td><td>Total Cost</td><td>$21,665.63</td></tr>
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<tr><td>S</td><td>141</td><td>Pancreatic cancers

The Commission did not specifically include the review of evidence of PBT in pancreatic cancers. Radiation treatment with concurrent chemotherapy for pancreatic cancer is associated with significant GI toxicity. With conventional radiation, severe acute GI toxicities occur in up to 20% of patients, which can often be treatment-limiting and compromise full completion of treatment. (3)</td><td>WAHTA identified no comparative studies of the clinical effectiveness of primary PBT in gastrointestinal cancers. Pancreatic cancer data were considered under the category of gastrointestinal cancers. Recommendation is not to cover based on insufficient evidence.</td></tr>
<tr><td>S</td><td>142</td><td>Dosimetric data as well as phase I clinical data demonstrate that PBT for pancreatic cancer is feasible, tolerable, and</td><td>Commenter notes Phase I</td></tr>
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		safer than with photon therapy. A dosimetric analysis of proton and photon plans for the adjuvant treatment of pancreatic cancer from the University of Florida showed superior small bowel and stomach sparing with PBT. (4)	clinical data, which was not considered in the CG report. Evidence development for pancreatic cancer is ongoing and will be considered in future updates of the CG.
S	143	A phase I/II study of 50 patients with locally advanced pancreas cancer used 3 dose fractionation schemes of PBT depending on the location of the tumor in relation to other GI structures with concurrent. They found excellent efficacy compared to historical controls of locally advanced pancreas cancer (1-yr local progression free survival 82%, progression free survival 64%, overall survival 77%). (5) The toxicities were low compared to the above mentioned photon based regimens with acute Grade 3 and higher rates as follows: nausea/vomiting 8%, anorexia 8%, weight loss 5%, and fatigue 3%.	Reference 5 is considered in the WAHTA evidence review.
S	144	More recent data from University of Florida and University of Pennsylvania provide additional data that PBT is better tolerated than photons. Nichols et al. from University of Florida demonstrated no grade 3 toxicities or treatment interruptions due to toxicity in 22 patients treated with PBT and concurrent chemotherapy. (6) At the University of Pennsylvania, 13 patients with pancreatic cancer treated with concurrent chemotherapy and proton PBT were compared to a cohort of patients treated during the same time period with photon radiotherapy to similar doses: 24% of the photon patients experienced grade 3 toxicity, whereas only 8% of the PBT cohort had this grade of toxicity. (7)	Reference 6 is considered in the WAHTA evidence review. Reference 7 is a non-randomized comparative study of 13 patients who received proton chemoradiation therapy versus a concurrent cohort of 17 patients who received photon therapy. Rates of toxicity were similar.
S	145	*In summary, there are adequate data from multiple institutions that demonstrate the safety and efficacy of PBT for liver and pancreatic cancers. The reduction in treatment-related toxicities with PBT compared to photon treatment also has the potential to result in cost-savings in these challenging diseases. I urge the Commission to support the coverage of PBT for liver and pancreatic cancers. I welcome the opportunity to serve as an on-going resource as you are assessing this important cancer therapy option for Oregonians.*	Thank you for your comments.
T	146	In 2011, I was diagnosed with Non-Hodgkins's Lymphoma (NHL) of the Central Nervous System with a mass found per MRI and CT Scan in the L) parietal dura of the brain & inoperable). I was told this is a rare mass found in only 3% of the population of those with NHL. After numerous lumbar punctures and samples of spinal fluid, bone marrow biopsies and finally an Craniotomy for an open biopsy, I began mega dose chemotherapy over a nine month period. At completion	Thank you for your comments.

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		and for 12 months I was considered in remission. But after 14 mo MRI check up, they discovered that the mass was returning. At that point, I was given my options of Radiation (radiotherapy with standard Photons) with all it's side affects that would probably include blood brain barrier penetration leaving me with possible irreversible neurological damages, not to mention the probable return of the mass again. There IS limited control with the use of the Photon beams.	
T	147	Or I could endure another long regime of chemo, this time with IT therapy (Intrathecal). Of which there are often high grade toxicities of blood, liver or renal systems). Especially in folks over 60 years of age. Wow, what a choice! (NOT)	Thank you for your comments.
T	148	Then, trying to take all this in for a few days, and pretty much deciding not to do any more treatments, I received a call from my Neuro Oncologist at UW Med Center, stating he had just talked to a specialist at the SCCA Proton Center (new to Seattle about a year before) about my case (my mass was wide but very shallow) and the doctor was interested in using their newest form of therapy called Pencil Beam Scanning (the PBS had only been available for a couple of months at that time). He went on to explain that PBS is higher degree of precision of the Proton Beam with overall minimal exposure and radiation to healthy tissues surrounding the mass. So, I spoke with my family and doctors and decided to take a chance. Then I did my research and discovered that Proton Therapy has been around for 25 years in the U.S. and a few other countries and that it was shown to be effective in treating many types of tumors, including cancers of the brain, CNS, head, neck, prostrate, lung and GI system, as well as cancers that cannot be removed (or completely removed) by surgery or chemo. I was again hopeful.	Thank you for your comments.
T	149	You don't know what it means, or feels like to have someone tell you you're NOT going to have to do the intense treatments that make you feel miserable day after day, to miss family functions or not being able live your life as normally as you'd like.	Thank you for your comments.
T	150	Feb 10, 2014, the first day I entered the Proton Center in Seattle, I felt like I had 'come home' to a new family of folks who are there to help all their patients feel comfortable in their stress-free and friendly environment, as anywhere I had ever been. The team of radiologists were 'my' team and treated me with respect, humor and a positivity beyond belief. I felt I could share my concerns, emotions and joys with them all. I cried when I had finished my regime of treatments, knowing I wouldn't be seeing them every day again. By the way, my only side affects included some tiredness and hair loss of the area radiated (which has since grown back) and missing 'my team' !	Thank you for your comments.
T	151	Well, that was a year ago, and after my MRI last week, I am still mass free and as my docs put it, I have a 'beautiful brain' once again. This would not be the case with the other choices given to me. My daily life during the treatment did not change and I continued to enjoy daily activities. I can also look forward to the fact that the protons therapy reduces a reoccurrence or secondary mass. I can also live without the thought of residual neurological side affects later in my life.	Thank you for your comments.
T	152	The facility itself is a 'step into the future' kinda place. The center meets all needs of their patients, not just the amenities of the building but the non medical support needed especially if you are away from home, including housing,	Thank you for your comments.

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		transportation and entertainment in the area, etc. Always supportive in every way.	
T	153	Being a retired nurse, I can honestly say I have never had a more positive medical experience than that of SCCA Proton Center in Seattle. Believe me, it's different when you're on the receiving end of medical care!	Thank you for your comments.
T	154	I have recommended it to those I know with medical issues that would benefit from Proton Therapy. I'm happy to say that their treatments and positive experiences have been the same as mine. We are blessed to have this 'state of the art' facility in our part of the country. The need is great for more compassionate and successful treatments of all types of cancers. It will definitely be the only way of doing radiation therapy in the near future.	Thank you for your comments.
T	155	I truly feel it would be a disgrace to deny countless lives, the quality (with nil side affects) and compassionate treatment found in Proton Therapy. Please consider SUPPORTING the use of Proton Therapy. It's here to stay. Maybe you would need it someday! Would you want it to be denied to you or a loved one? A true believer in compassionate and quality care!	Thank you for your comments.
U	156	Hello, I chose proton therapy because it has low risk of side effects such as incontinence, impotence and bowel urgency. I also chose proton therapy because I can go to work every day and work a full day's work. I have not missed a single day's work during my treatment. I have been able to perform my work normally with some minimal impact, such as some minor urinary urgency. I would absolutely recommend proton therapy for anyone for whom this is a valid therapy. The impact to my body has been minimal. The treatment here at the SCCA Proton Center in Seattle has been very professional, and my wife and I both felt very encouraged by the whole process, from intake through the daily treatments and the weekly meetings with nurses and my oncologist.	Thank you for your comments.
V	157	Please support proton radiation for liver cancer and other cancer where less tissue damage is critical to success of treatment. Thank you	Thank you for your comments
W	158	Dear Oregon Health Evidence Review Commission: I am a Radiation Oncologist on the faculty of the University of Washington and Seattle Children's Hospital. A majority of my patients are children with cancer, and I treat more children with cancer than any other radiation oncologist in the Northwest. About half of my patients are from the Seattle area, and the other half come from other parts of	Thank you for your comments.

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		Washington, Alaska, Oregon, Montana, Idaho, and British Columbia.	
W	159	The lack of exit dose with proton radiation can be critical for providing the optimal radiation therapy for children with developing bodies. It allows the patient to receive the maximum efficacy of treatment with decreased acute and late effects. On 11 July 2014 the Washington Health Technology Assessment adopted its final decision to recommend universal coverage for pediatric cancers.	This information is correct.
W	160	Nonetheless the best modality of radiation for each patient is individually assessed. I have treated two children from Oregon with proton therapy; however; I have recently supported the decisions by local Oregon radiation oncologists to treat with photon therapy rather than have them travel for proton therapy.	Thank you for your comments.
W	161	I am a member of the Children's Oncology Group (COG), the principle US entity for clinical research about pediatric cancers. It is noteworthy that most clinical trials that call for radiation other than whole brain radiation (including trials for most brain, Ewings, and rhabdomyosarcoma) allow for the clinician to choose the modality of radiation-proton or photon; it is not a study question on any COG clinical trial.	Thank you for your comments.
W	162	It is also noteworthy that even in somewhat resource-constrained, more centrally organized health systems, proton therapy for pediatric patients is increasingly accepted. For example, Britain's National Health Service is constructing two proton facilities that will treat children.	This is correct.
W	163	It is rare for a pediatric patient not to receive insurance coverage for proton therapy, either with public or private insurance. I urge you to continue support for Oregon pediatric patients to receive proton therapy, particularly when there is consensus between the Oregon radiation oncologist and the proton radiation oncologist.	Thank you for your comments.
W	164	Other clinicians will focus on the benefits of treating lymphoma (including pediatric lymphomas) with proton therapy, therefore I will focus on pediatric head and neck and central nervous system tumors. Summary of Evidence for Pediatric head and neck and central nervous system cancers: Although children often survive their pediatric cancers, the long term morbidity of treatment, including radiation, can have dramatic effects on quality of life, which can be mitigated with proton therapy. Although the impact of radiation late effects is most obvious with central nervous system tumors, many of the same considerations apply when treating pediatric cancers abutting or close to the central nervous system, such as rhabdomyosarcomas of the face and orbit.	Thank you for your comments.
W	165	Among the many studies of pediatric patients receiving radiation therapy, some of the most relevant include. • Pediatric patients had improved short term morbidity when comparing a cohort of proton-treated patients with historical controls. (1) • Patients receiving irradiation for a brain tumor before than age of four, only a third of adult survivors were able to	Reference 1 was published after WAHTA and is a case series of 83 patients 21 years and younger treated 2009-2012, who were compared to historical controls.

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		have full -time employment. (2) Modeling of proton therapy versus photon therapy showed decreased effect on neurocognitive development and pituitary ·function with proton therapy. (3) • Young children with ependymoma treated with protons showed patients exhibited remarkably few side effects in terms of hearing loss, neurocognitive effects, and pituitary dysfunction compared to historical controls. (4) • Children treated with protons for low grade gliomas showed almost no neurocognitive, endocrine or visual effects of the treatment in follow up. (5) • Children with retinoblastoma treated with photon radiation had a 14% 10 year cumulative incidence of secondary malignancies versus 0% in patients treated with protons. (6) • Using protons for craniospinal irradiation is likely to mitigate the future risk of breast cancer, ovarian failure, and hemi disease in adult survivors of embryonal brain tumors. (7-9) • Overall, when including future costs of late effects, *proton therapy will be cost-effective compared to photon therapy* for medulloblastoma. (10) • *Proton therapy will be cost-effective* based on growth hormone function preservation when it reduces dose to the hypothalamus (11)	Authors conclude "In comparison to conventional therapy, patients with particle therapy do not suffer from increased acute treatment-related toxicity during the first months." References 2 and 3 are addressed above; please see comments 61 and 95. Reference 4 is considered in the WAHTA evidence review. Reference 5 was published after the WAHTA review and is a case series of 32 pediatric patients treated from 1995 to 2007. Authors conclude, "Proton RT appears to be associated with good clinical outcome, especially when the tumor location allows for increased sparing of the left temporal lobe, hippocampus, and hypothalamic-pituitary axis." Reference 6 was also published after the WAHTA review and is a retrospective comparative cohort study of 55 proton and 31 photon patients. The 10-year cumulative incidence of RT-induced or in-field second malignancies was significantly different between radiation

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			modalities (0% vs 14%). The 10-year cumulative incidence of all second malignancies was also different, although with borderline significance (5% vs 14%). Reference 7 is a treatment modeling study of six female patients that designed photon and proton beam plans to compare radiation dose to the breast. Dose to breast tissues was near zero after proton therapy to the spine. Reference 8 is another modeling study in which proton therapy is compared to oophoropexy followed by Xray craniospinal irradiation in a single patient. Reference 9 is addressed in comment 59. References 10 and 11 are addressed in comment 13. HTAS recommended coverage of pediatric malignant tumors.
W	166	Thank you for this opportunity. Should you have any questions please do not hesitate to contact me	Thank you for your comments.
X	167	Hello, I would like to see Regence cover proton radiation therapy for all forms of cancer, or at least liver cancer where it has proven to be efficacious.	Commenter addresses Regence; nevertheless, thank you for your comments.
Y	168	On behalf of the National Association for Proton Therapy (NAPT), we respectfully submit comments on Oregon's Health	Identical letter to that submitted by commenter P; see responses

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		Evidence Review Commission (HERC) Coverage Guidance on Proton Beam Therapy (PBT). While we were pleased to see the strong recommendation for coverage of malignant ocular tumors, we have significant concerns with many of the other recommendations. We were especially surprised and disappointed with the lack of a positive coverage recommendation for pediatric malignant tumors. Because of the strong evidence supporting its use, PBT for pediatric patients is practically universally covered. Additionally, we strongly disagree with your characterization that "PBT is far more expensive than its major alternatives." Recent studies have found that when treating for toxicity and other post-treatment occurrences are considered, PBT has been found to be a cost-effective treatment. We urge you to consider the evidence we provide in this letter in your deliberations. Evidence on the Effectiveness of PBT for Pediatric Malignant Tumors The proposed coverage guidance gave a weak recommendation for coverage for pediatric malignant tumors, despite the overwhelming consensus on its appropriateness for pediatric patients. We believe eliminating coverage of PBT for pediatric patients is inconsistent with the current state of evidence and would be harmful to a population of patients who would most benefit from the reduced amount of radiation received in the course of PBT treatment. Due to the growing body of evidence in this area, most payors, regulators and providers support the use of PBT for pediatric patients. The consensus is reflected in the American Society for Radiation Oncology (ASTRO) model policy on PBT which supports its use for primary or benign solid tumors treated in children with curative intent (ASTRO, 2014). Examples of published evidence in this area include a recent study of 54 patients with pediatric rhabdomyosarcoma which found that PBT lowers integral dose and improves sparing normal tissue when compared to IMRT [Ladra, MM et al Radiother Oncol 2014]. In another example, a 2012 study of high-risk pediatric neuroblastoma found that preliminary outcomes reveal excellent control with proton therapy for this population [Hattagangadi JA, Int J Radiat Oncol Biol Phys, 2012]. While we have cited just two studies, these are consistent with other studies of pediatric patients. Evidence on the Effectiveness of PBT for Other Sites The proposed guidance concludes, " ... there was insufficient evidence to obtain even a basic understanding of PBT' s comparative clinical effectiveness and comparative value." Frankly, we were stunned by this characterization. While we acknowledge (and support) the ongoing development of additional clinical evidence, there is already significant evidence supporting the effectiveness of PBT that this proposed coverage guidance ignores. In addition to the evidence supporting the use of PBT for pediatric tumors, there is also significant evidence supporting its use for other tumor sites. The articles listed below are only from the last 15 months and they reflect the meaningful research being conducted in this area. 2015	above

ID	#	Comment	Disposition
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		under development). The study found that the cost of PBT when used for accelerated partial breast irradiation to decrease overall treatment time and toxicity, was estimated at $13,833. Results of the study suggested that the cost of proton therapy is similar to other types of radiation. *NAPT strongly recommends that you include studies that consider cost of toxicity and other post-treatment conditions that can occur and which certainly impact costs and the quality of life of the patient.* While we appreciate the opportunity to submit comments, we felt very limited in our ability to communicate to you due to the severe limitations on written (1000 word) and oral (3 minutes) comments. We believe the current process may stymie public input. *NAPT urges you to reconsider these guidelines.* Should you have any questions, please do not hesitate to contact me	

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Index of Comments by Cancer Type

Section 4.0

Coverage Guidance Rescan

2015

Continuous Blood Glucose Monitoring

PICO & Key Questions for Updated Literature Search

Populations

Children, adolescents, and adults with type 1 or type 2 diabetes mellitus (DM) on insulin therapy, including pregnant women

Intervention

Continuous blood glucose monitoring (CBGM), either retrospective or real time

Comparators

Self-monitoring blood glucose (SMBG) and/or routine HbA1c monitoring

Outcomes

Critical: Severe morbidity (e.g. microvascular and macrovascular complications), severe hypoglycemia[1]

Important: Quality-of-life, change in HbA1c, ketoacidosis

Outcomes considered but not selected or GRADE table:
Myocardial infarction, cerebrovascular accident, amputations, neuropathy, retinopathy, nephropathy--we chose to generalize these into "severe morbidity" to simplify consideration; diabetes-related hospitalizations; and emergency department visits.

Key Questions

1. What is the evidence of effectiveness of CGM in improving outcomes in people with diabetes?
2. What are the indications for retrospective and for real time CGM?
3. Is there evidence of differential effectiveness of CGM based on:
    a. Type 1 vs Type 2 DM?
    b. Insulin pump vs multiple daily insulin injections (MDII)?
    c. Frequency and duration of CGM?

[1] "An event requiring assistance of another person to actively administer carbohydrate, glucagons, or other resuscitative actions." (ADA Workgroup on Hypoglycemia, 2005)

Self-Monitoring of Blood Glucose

PICO & Key Questions for Updated Literature Search

Populations

Children, adolescents, and adults with type 2 diabetes mellitus who are not using multiple daily insulin injections (MDII)

Intervention

Self-monitoring of blood glucose (SMBG), with or without structured education and feedback programs.

Comparators

No routine monitoring using SMBG, periodic monitoring of HbA1c

Outcomes

Critical: Severe morbidity (e.g. microvascular and macrovascular complications, severe hypoglycemia[1]

Important: Quality-of-life, change in HbA1c, hyperosmolar hyperglycemic state (HHS)

Outcomes considered but not selected for GRADE table: Hospitalizations, emergency department visits.

Key Questions

1. What is the effectiveness of SMBG in improving outcomes in children, adolescents, and adults with type 2 diabetes mellitus who are not using multiple daily insulin injections (MDII)?
2. What is the evidence of harms associated with SMBG in this population?
3. Is there evidence of differential effectiveness of SMBG based on:
    a. Type of treatment (i.e. diet and exercise, oral antidiabetic agents, basal insulin, non-insulin injectables)
    b. Frequency of testing
    c. Degree of glycemic control at baseline
    d. Association with a structured education and feedback program
4. What are appropriate quantities of testing supplies for this population, and what factors should trigger allowances for additional supplies (e.g. infection, driving, new diagnosis, etc.)

[1] "An event requiring assistance of another person to actively administer carbohydrate, glucagons, or other resuscitative actions." (ADA Workgroup on Hypoglycemia, 2005)

Special considerations

1. We will not search the literature on people with Type I diabetes or Type II diabetes with multiple daily insulin injections, as these are well-established and had a strong recommendation in the last coverage guidance.

Diagnosis of Sleep Apnea in Adults

PICO & Key Questions for Updated Literature Search

Populations

Adults with clinical signs and symptoms of obstructive sleep apnea (OSA)

Intervention

Polysomnography; attended or unattended, sleep lab or at home

Comparators

Usual care

Outcomes

Critical: Major adverse cardiovascular events, fatigue-related accidents

Important: Improvement in HTN, measures of daytime fatigue, quality-of-life

Outcomes considered but not selected for GRADE table: Resolution of metabolic syndrome

Key Questions

KQ1: What is the effectiveness of polysomnography in improving outcomes for patients with suspected OSA?

a. What are the diagnostic cutoffs associated with improved outcomes?

KQ2: What is the differential effectiveness of polysomnography based on the type of device used or the setting in which testing is performed?

KQ3: What are the harms of polysomnography?

Contextual Questions

CQ1: Are there clinically validated tools (i.e. questionnaires and/or physical parameters) to assess the pretest probability of OSA?

a. If validated tools exist, at what levels of pretest probability should polysomnography not be recommended?

Breast MRI after Diagnosis of Breast Cancer

PICO & Key Questions for Updated Literature Search

Population

Adults with recently diagnosed breast cancer

Intervention

Breast MRI

Comparator

Usual care, including other imaging modalities

Outcomes

Critical: All-cause mortality, cancer-specific mortality

Important: Progression-free survival, false-positive test results, quality of life

Outcomes considered but not selected for GRADE table: change in surgical or non-surgical treatment plan

Key Questions

KQ1: What is the comparative effectiveness of breast MRI after the diagnosis of breast cancer for improving patient outcomes?

KQ2: What are the harms of breast MRI after the diagnosis of breast cancer?

Contextual Questions

CQ1: How often do the results of MRI after breast cancer diagnosis lead to changes in the surgical or non-surgical treatment plan?

CQ2: Does the information provided by MRI after breast cancer diagnosis change measurements of decisional conflict?

PET CT for Breast Cancer Staging and Surveillance

PICO & Key Questions for Updated Literature Search

Populations

Adults with early stage breast cancer (DCIS, stage I, or stage II) or who have been treated for breast cancer with curative intent

Interventions

PET CT for initial staging, surveillance, or monitoring response to treatment

Comparators

Usual care (including axillary lymph node dissection [with or without sentinel lymph node biopsy], CT and radionucleide scintigraphy), MRI

Outcomes

Critical: All-cause mortality, cancer-specific mortality

Important: Progression-free survival, false positive tests, quality of life

Outcomes considered but not selected for GRADE table:

Key Questions

KQ1: What is the comparative effectiveness of PET CT in early stage breast cancer or breast cancer treated with curative intent in improving patient important outcomes for staging, monitoring response, or surveillance?

KQ2: What are the harms (including false positive tests, radiation exposure) of PET in early stage breast cancer or breast cancer treated with curative intent?

Contextual Questions

CQ1: How often do the results of PET CT after breast cancer diagnosis lead to changes in the surgical or non-surgical treatment plan?

CQ2: Does the information provided by PET CT after breast cancer diagnosis change measurements of decisional conflict?

Vertebroplasty, Kyphoplasty, and Sacroplasty

PICO & Key Questions for Updated Literature Search

Populations

Adults with acute or chronic vertebral compression or sacral insufficiency fractures

Interventions

Percutaneous vertebral and sacral procedures

Comparators

Open spinal surgical procedures, sham/placebo surgery, medical therapy (including non-pharmacologic interventions like physical therapy or acupuncture)

Outcomes

Critical: All-cause mortality, short- and long-term improvement in function

Important: Short- and long-term improvements in pain or quality of life, recurrent fracture, clinically significant embolization

Outcomes considered but not selected for GRADE table:

Key Questions

KQ1: What is the comparative effectiveness of percutaneous interventions for vertebral compression or sacral insufficiency fractures?

KQ2: What are the harms of percutaneous interventions for vertebral compression or sacral insufficiency fractures?

Carotid Endarterectomy for Carotid Artery Stenosis – 2015 Rescanning Summary

Subcommittee : Health Technology Assessment Subcommittee (December 2013)

Bottom Line: There is new (but limited and contradictory) summary evidence and guidelines about the comparative effectiveness of CEA vs carotid stenting or optimal medical treatment.

Coverage Recommendation (Box Language)

Carotid endarterectomy is recommended for coverage for patients who are symptomatic (recent transient ischemic attack or ischemic stroke) and who have 70-99% carotid stenosis without near-occlusion (*strong recommendation*).

For patients with 50 – 69% carotid stenosis who are symptomatic despite optimal medical management, carotid endarterectomy is recommended for coverage (*weak recommendation*).

Carotid endarterectomy is not recommended for coverage for symptomatic patients with less than 50% carotid stenosis (*strong recommendation*).

Carotid endarterectomy is recommended for coverage for patients with asymptomatic carotid stenosis of at least 60% only for those who do not tolerate (or have contraindications to) best current medical therapy (*weak recommendation*).

Screening for asymptomatic carotid artery stenosis in the general primary care population is not recommended (*strong recommendation*).

Scope Statement

Population description	Adults with carotid stenosis with or without recent symptoms of cerebral ischemia *Population scoping notes:* None
Intervention(s)	Carotid endarterectomy *Intervention exclusions:* None
Comparator(s)	Optimal medical therapy, carotid stenting
Outcome(s) (up to five)	**Critical:** All-cause mortality, cerebrovascular accidents **Important:** Transient ischemic attacks, development/progression

	of vascular dementia, quality of life *Considered but not selected for GRADE table:* Need for reintervention
Key questions	1. What is the comparative effectiveness of carotid endarterectomy for treatment of symptomatic or asymptomatic carotid stenosis? 2. What degree of carotid stenosis predicts clinical utility of carotid endarterectomy? 3. What are the harms of carotid endarterectomy? 4. Under what circumstances should carotid endarterectomy be covered for asymptomatic patients (i.e. when stenosis is found as an incidental finding?)

Original Evidence Sources

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Publication status and date: Edited (no change to conclusions), published in Issue 4, 2008.

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Scanning Results (reviewed for applicability, methodologic quality not assessed)

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Summary

Citation 1 is a large meta-analysis of 44 studies (comprising nearly 600,000 patients) of CEA or carotid stenting. It provides new information on the comparative effectiveness of CEA vs carotid stenting and suggests that the best intervention may vary depending on the age of the patient.

Citation 2 is a systematic review of 50 studies reporting on indications for CEA or carotid stenting in patients with recurrent carotid stenosis after an initial CEA. It does not provide information that would change the coverage guidance.

Citation 3 is a systematic review and multidisciplinary evidence-based guideline from Germany and Austria. The recommendations generally comport with the existing HERC coverage guidance, although they do not require a trial of optimal medical therapy before considering CEA in asymptomatic individuals with >60% stenosis (while also acknowledging that controlled trials of various treatment options for asymptomatic

patients are needed). It also offers guidance on situations in which carotid stenting may be preferable to CEA.

Citation 4 is an AHRQ review of literature on cognitive outcomes after cardiovascular procedures in older adults. It concludes that CEA and endovascular interventions for carotid revascularization result in similar intermediate-term cognitive outcomes.

Citation 5 is a meta-analysis of individual-level patient data on CEA vs carotid stenting for treatment of ipsilateral restenosis after prior CEA. The short-term outcomes of stroke, death, and restenosis were similar between the two interventions.

Citation 6 is a systematic review and meta-analysis of RCTs comparing CEA and medical therapy in patients with symptomatic or asymptomatic carotid stenosis. It concludes that CEA is beneficial for symptomatic patients with >50% stenosis, but offers no benefit in asymptomatic patients. The latter conclusion is potentially at odds with the current HERC coverage guidance.

Citation 7 is a cost-effectiveness study of CEA in the Danish National Health Service. Any conclusions are probably too indirect to influence the HERC coverage guidance.

Citations 8, 9, and 11 comprise updated evidence and USPSTF guidelines regarding screening for carotid stenosis in asymptomatic individuals. They support the current HERC coverage guidance that does not recommend screening in asymptomatic individuals.

Citation 10 is an economic evaluation of carotid stenting with an embolic-prevention device vs CEA for patients at average surgical risk. Because stenting produces only marginally greater QALYs compared with CEA at greater cost, the ICER for stenting is >$200,000. It would provide new contextual information on resource use if the coverage guidance is updated.

Citation 12 is an updated systematic review and meta-analysis of RCTs comparing CEA and carotid stenting. Its overall conclusion is that stenting is inferior to CEA with respect to stroke or death, but because of a lower incidence of myocardial infarction, stenting may be preferable in selected patients.

Citations 13 and 20 summarize evidence on the appropriate use and timing of CEA after thrombolysis for acute ischemic stroke. Generally, these studies support the safety of CEA withing 14 days of an acute ischemic stroke treated with thrombolysis, though the quality of evidence is low.

Citation 14 is a systematic review of studies comparing cognitive function after CEA vs carotid stenting. Due to a high degree of heterogeneity among the included studies, meta-analysis was not performed and definite conclusions could not be drawn.

Citation 15 is a health technology assessment of carotid stenting performed for the Washington HTA. On the basis of these results, the Washington HTA has opted to cover carotid stenting for symptomatic patients with >50% stenosis or asymptomatic patients with >80% stenosis AND who are deemed to be at high operative risk for CEA. This information would potentially change HERC coverage guidance.

Citation 16 is a cost-effectiveness analysis of CEA vs carotid stenting based on a retrospective case series at a single institution. This study design is inadequate to inform HERC coverage guidance.

Citation 17 is a cost-effectiveness study of CEA for asymptomatic individuals in the British National Health Service. Any conclusions are probably too indirect to influence the HERC coverage guidance.

Citation 18 is an economic evaluation of carotid stenting vs CEA for patients at average surgical risk. It concludes that there are trivial differences in the long-term costs between the two interventions. It would provide new contextual information on resource use if the coverage guidance is updated.

Citation 19 is a meta-analysis of 8 trials comparing CEA vs carotid stenting in symptomatic patients. This appears to be a low-quality systematic review and would probably not be included for review in an update of the HERC coverage guidance.

Appendix A. Methods

Search Strategy

A full search of the core sources was conducted to identify systematic reviews, meta-analyses, technology assessments, and clinical practice guidelines using the terms "carotid endarterectomy" and "carotid stenosis." Searches of core sources were limited to citations published after 2011 (the last search date of original evidence sources).

The core sources searched included:

Agency for Healthcare Research and Quality (AHRQ)
Blue Cross/Blue Shield Health Technology Assessment (HTA) program
BMJ Clinical Evidence
Canadian Agency for Drugs and Technologies in Health (CADTH)
Cochrane Library (Wiley Interscience)
Hayes, Inc.
Medicaid Evidence-based Decisions Project (MED)
National Institute for Health and Care Excellence (NICE)
Tufts Cost-effectiveness Analysis Registry
Veterans Administration Evidence-based Synthesis Program (ESP)
Washington State Health Technology Assessment Program

A MEDLINE® (Ovid) search was conducted to identify systematic reviews, meta-analyses, and technology assessments published after the search dates of original evidence sources. The search was limited to publications in English published after 2012 (last search dates of original evidence sources).

Searches for clinical practice guidelines were limited to those published since 2012 (last search date of coverage guidance). A search for relevant clinical practice guidelines was also conducted, using the following sources:

Australian Government National Health and Medical Research Council (NHMRC)
Centers for Disease Control and Prevention (CDC) – Community Preventive Services
Institute for Clinical Systems Improvement (ICSI)
National Guidelines Clearinghouse
New Zealand Guidelines Group
NICE
Scottish Intercollegiate Guidelines Network (SIGN)
United States Preventive Services Task Force (USPSTF)
Veterans Administration/Department of Defense (VA/DOD)

Inclusion/Exclusion Criteria

Studies were excluded if they were not published in English, did not address the scope statement, or were study designs other than systematic reviews, meta-analyses, technology assessment, or clinical practice guidelines.

Section 5.0
Metabolic and bariatric surgery

HEALTH EVIDENCE REVIEW COMMISSION (HERC)

COVERAGE GUIDANCE: BARIATRIC SURGERY

Internal draft 9/02/15

HERC Coverage Guidance

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

- Obese patients (BMI ≥ 35) with diabetes *(strong recommendation)* or with at least two other serious obesity-related comorbidities (i.e., hypertension, coronary heart disease, mechanical arthropathy in major weight bearing joint, sleep apnea) *(weak recommendation)*

- CHOOSE:

  Obese patients (BMI ≥ 40) with at least one other serious obesity related comorbidity *(strong recommendation)*

  OR

  Obese patients (BMI ≥ 40) *(strong recommendation)*

Bariatric surgery is recommended for coverage in these populations only when provided by an experienced surgeon and in a hospital with adequate number of cases. In addition, coverage is recommended only in systems that ensure appropriate follow up, tracking and proof of ongoing effectiveness, and that have acceptable reoperation, morbidity and mortality rates *(weak recommendation).*

Repeat surgery (excluding surgical complications) is not recommended for coverage (*weak recommendation).*

Bariatric surgery is not recommended for coverage in children and adolescents *(weak recommendation).*

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

PLAIN LANGUAGE SUMMARY

[*Staff will insert lay language summary once the coverage guidance has been reviewed by subcommittee*]

RATIONALE FOR GUIDANCE DEVELOPMENT

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

- Represents a significant burden of disease

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

Coverage guidance development follows to translate the evidence review to a policy decision. Coverage guidance may be based on an evidence-based guideline developed by the Evidence-based Guideline Subcommittee or a health technology assessment developed by the Heath Technology Assessment Subcommittee. In addition, coverage guidance may utilize an existing evidence report produced by one of HERC's trusted sources, generally within the last three years.

EVIDENCE OVERVIEW

Clinical background

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

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

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

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

Indications

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

Technology description

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

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

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

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

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

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

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

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

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

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

	Chang (2014)	Colquitt (2014)	Puzziferri (2014)	WA HTA (2015) Range, Median
Mortality <30 days	0.08% in RCTs 0.22% in OSs	NR	NR	NR
Mortality >30 days or not specified	0.31% in RCTs 0.35% in OSs	NR	1% for bypass procedures 0.2% for banding procedures	BPD: 0%-2.9%, 1.4% LAGB: 0%-2.0%, 0.15% RYGB: 0%-4.3%, 1.94% VSG: 0%-3.9%, 0.07%
Complication rate	17% in RCTs 10% in OSs	NR	NR	BPD: 8%-83%, 26.9% LAGB: 0%-53%, 10.1% RYGB: 0%-78%, 9.2% VSG: 0%- 80%, 8.8%
Reoperation rate	7% in RCTs 6% in OSs	2%-13%	NR	BPD: 0%-30%, 3.6% LAGB: 0%-44%, 7.4% RYGB: 0%-22%, 5.8% VSG: 0%-17%, 3.9%
Serious adverse event rate	NR	0-37% in	NR	NR

	Chang (2014)	Colquitt (2014)	Puzziferri (2014)	WA HTA (2015) Range, Median
		surgical groups 0-25% in non-surgical groups		

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

Key Questions

The following key questions (KQ) guided the evidence search and review described below. For additional details about the review scope and methods please see Appendix A.

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

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

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

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

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

Evidence review

General Limitations

The literature on bariatric surgery is voluminous. The search conducted by Center staff yielded more than 20 systematic reviews published in the last two years (see Appendix A for a detailed methods description). These reviews span more than 600 individual studies. It should be noted that there is little

consistency in the inclusion of individual studies across reviews and that many of the systematic reviews did not perform meta-analysis, in part due to high levels of heterogeneity.

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

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

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

Systematic Reviews Addressing Effectiveness in Adults

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

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

Systematic Review (Quality) Total N	No. and Type of Included Studies	Population	Outcomes of Interest
Chang, 2014 **(Good)** **N = 161,756**	37 RCTs 127 observational studies	Pre-surgical BMI (mean): 45 kg/m^2 T2DM: 26% Hypertension: 47%	Mortality (within 30 days of surgery) Complication rate BMI (mean change at 1 and 5 years) T2DM remission Hypertension remission
Colquitt, 2014 **(Good)** **N ~ 600**	7 RCTs	Average pre-surgical BMI (mean): 27 – 55 kg/m^2 5 out of 7 studies required participants have T2DM	BMI T2DM remission Hypertension remission Serious adverse events

Systematic Review (Quality) Total N	No. and Type of Included Studies	Population	Outcomes of Interest
Hayes, 2014 (Good) N = 1,734	18 controlled or comparative studies	Pre-surgical BMI (mean): 25 – 55 kg/m^2 T2DM	BMI T2DM remission
Kwok, 2014 (Good) N = 195,408	14 comparative cohorts	Most studies enrolled participants with BMI > 35 kg/m^2	All-cause mortality Cardiovascular adverse events
Muller-Stich, 2014 (Good) N = 766	7 RCTs 6 Comparative observational studies	Pre-surgical BMI (mean) : < 35 – 37 kg/m^2	BMI T2DM remission Hypertension remission
Puzziferri, 2014 (Good) N = 8,678	10 RCTs 8 cohort studies 11 case series	Pre-surgical BMI (mean) : 44 – 61 kg/m^2	Weight loss T2DM remission Hypertension remission Perioperative mortality
Wang, 2015 (Good) N = 256	4 RCTs	Pre-surgical BMI (mean): 30 – 47 kg/m^2	BMI T2DM remission
WA HTA, 2015 (Good) N = 2,083	14 RCTs 7 comparative cohort studies	Pre-surgical BMI (mean): 30 – 56 kg/m^2	BMI T2DM remission Perioperative mortality and complications

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

Chang (2014)

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

The review and meta-analysis focused on surgical mortality and complications, change in BMI, and resolution of obesity-related comorbid conditions. The overall rate of mortality within 30 days of surgery was 0.08% (95% confidence interval [CI] 0.01% to 0.24%) in the RCTs and 0.22% (95% CI 0.14% to 0.31%) in the observational studies. The overall complication rate was 17% (95% CI 11% to 23%) in the RCTs and 9.8% (95% CI 7.4 to 13.0) in the observational studies.

The overall mean change in BMI at 1 year was -13.53 kg/m^2 in the RCTs and -11.79 kg/m^2 in the observational studies. For those studies reporting outcomes at five years of follow-up, the overall mean change in BMI was -11.40 kg/m^2 in the RCTs and -14.32 kg/m^2 in the observational studies.

In the RCTs, the T2DM remission rates in the surgical groups was 92% (95% CI 84.68 to 97.18) compared with a rate of 17.4% (95% CI 0.98 to 69.27) in the control groups. The observational studies found a T2DM remission rate of 86.5%. In the RCTs, the hypertension remission rate was 75% (95% CI 61.52 to 86.35) in the surgical groups compared with a rate of 49% (95% CI 0 to 99%). These comparisons are both indirect and imprecise because so few of the included studies compared surgical and non-surgical groups directly. Additionally, duration of follow-up for the studies examining comorbid conditions was unclear.

Colquitt (2014)

Colquitt et al. (2014) is a good quality systematic review by the Cochrane Collaboration that includes 22 RCTs, of which 7 studies, comprising approximately 600 patients, compared bariatric surgery to non-surgical controls. Because of differences in the characteristics of participants, interventions, and comparators, meta-analysis was considered inappropriate, and the results were reported narratively.

In terms of BMI, the included studies reported mean changes of -7.4 kg/m^2 to -33.3 kg/m^2 with surgery compared to -0.5 kg/m^2 to -4.7 kg/m^2 in non-surgical controls. The authors conclude that "the direction of the effect was consistently in favour of surgery" based on moderate quality of evidence.

In terms of remission of T2DM, the included studies reported rates of remission ranging from 42% to 90% at 12 to 24 months in surgical groups (73% to 90% if one study with a more stringent definition of A1c < 6 is excluded) compared to remission rates of 0% to 32% in non-surgical controls. The authors conclude that "more people experienced remission following surgery" based on moderate quality of evidence.

Three studies included in the Cochrane review also reported on hypertension outcomes. Two studies reported rates of reduction or discontinuation of antihypertensive medications ranging from 49% to 80% between 12 and 24 months in the surgical groups compared to 0% to 70% in non-surgical controls. One additional study reported that the proportion of patients with systolic blood pressure less than130 mmHg at 12 months was 84% in the surgical group and 79% in non-surgical controls. The authors did not draw any conclusions based on these data.

Hayes (2014)

Hayes (2014) is a good quality systematic review and health technology assessment based on 18 controlled or comparative studies of RYGB in adults with T2DM published between2007 and 2014. Seven of the included studies (5 RCTs and 2 non-randomized controlled trials) compared RYGB with non-

surgical treatments while the remaining 11 compared RYGB with other bariatric surgical procedures. The average follow-up across the included studies was 12 months to 5 years.

In patients undergoing RYGB, BMI was reduced by 20 to 33% compared to baseline and T2DM remission was reported in 38 to 90% of patients. In the non-surgical treatment groups, BMI change ranged from -10% to 1%, and T2DM remission rates ranged from 0 to 33%. Based on this, Hayes concluded that RYGB is superior to intensive lifestyle or medical interventions for the treatment of T2DM. The authors further conclude that RYGB and sleeve gastrectomy are equally effective in the treatment of T2DM. Finally, the authors note that preliminary evidence (from a single study) suggests the RYGB may be equally effective for treatment of T2DM in patients with BMI<35 kg/m^2 and BMI>35 kg/m^2, but that additional studies are needed to establish the safety and effectiveness of RYGB in patients with lower BMIs.

Kwok (2014)

Kwok et al. (2014) is a good quality systematic review and meta-analysis of 14 comparative cohort studies reporting mortality and cardiovascular outcomes amongst 29,208 bariatric surgery patients and 166,200 non-surgical controls. The follow-up period of the included studies ranged from 2 years to 14.7 years. The surgical procedures in the studies included AGB, RYGB, SG, banded gastroplasty, as well as other unspecified bariatric surgical procedures. Most of the included studies reported enrolling patients with BMI >35 kg/m^2. Of the 14 included studies, 10 were deemed to be at low to moderate risk of bias, while four studies were deemed to be at moderate-high risk of bias due to concerns over loss to follow-up and inadequate adjustment for confounding.

In the 14 studies included in the meta-analysis of all-cause mortality, the crude event rate was 1059/29,208 (3.6%) in the surgical group and 18,962/166,200 (11.4%) in the non-surgical control group. The odds ratio (OR) for mortality in the surgical group compared with the non-surgical group was 0.48 (95% CI 0.35 to 0.64). Considering only the 10 studies that reported adjusted estimates, the association was consistent but more conservative with an odds ratio for mortality of 0.60 (95% CI 0.49 to 0.74) favoring the surgical group over the non-surgical controls.

In the four studies included in the meta-analysis of composite cardiovascular adverse events, the crude event rate was 407/17,262 (2.4%) in the surgical group and 1108/27,726 (4.0%) in the non-surgical control group. The odds ratio for composite cardiovascular adverse events in the surgical group compared with the non-surgical group was 0.54 (95% CI 0.41 to 0.70). The pooled estimates for the odds ratio of myocardial infarction and stroke for surgical patient compared to non-surgical controls were 0.46 (95% CI 0.30 to 0.69) and 0.49 (95% CI 0.32 to 0.75) respectively.

Overall, the authors conclude that long-term follow-up data from comparative cohort studies suggest that bariatric surgery is associated with lower rates of mortality (3.6% vs 11.4% for non-surgical controls, number needed to treat [NNT] = 13) and composite adverse cardiovascular events (2.4% vs 4.0% for non-surgical controls, NNT = 62).

Muller-Stich (2014)

Muller-Stich et al. (2014) is a good quality systematic review and meta-analysis of studies comparing surgical and medical treatment of T2DM in non-severely obese patients. The systematic review included seven RCTs and six comparative observational studies comprising 818 diabetic patients. All of the studies

included patients with BMI <35 kg/m^2 and eight of the studies were performed exclusively in patients with BMI <35 kg/m^2; among the remaining seven studies the highest average BMI was 37.1 kg/m^2. The surgical procedures performed in the included studies were AGB, BPD, RYGB, and SG. The follow-up periods ranged from 12 to 36 months.

In the meta-analysis of studies reporting remission of T2DM, 129 of 280 patients achieved remission in the surgical group compared with 6 of 252 patients in the medical treatment group. The combined odds ratio for T2DM resolution after surgery compared with medical treatment was 14.11 (95% CI 6.67 to 29.86).

In the meta-analysis of studies reporting change in BMI, the absolute mean difference in BMI was -5.5 kg/m^2 (95% CI -6.7 to -4.3) favoring the surgical group.

In the meta-analysis of studies reporting presence of arterial hypertension at the end of the study, the 76 of 274 patients in the surgical group and 101/189 patients in the medical treatment group had arterial hypertension. The combined odds ratio for arterial hypertension after surgery compared with medical treatment was 0.25 (95% CI 0.12 to 0.50).

The authors performed a network meta-analysis to compare the treatment effects of the different surgical procedures. Although point estimates of the odds ratio for T2DM remission compared to medical treatment ranged from 12.23 for AGB to 55.05 for RYGB, the 95% confidence intervals overlapped for all four included procedures, and all were superior to medical treatment.

Overall, the authors conclude that among non-severely obese patients with T2DM bariatric surgery results in greater short-term improvements in diabetes remission, weight loss, and arterial hypertension when compared with medical treatment.

Puzziferri (2014)

Puzziferri et al. (2014) is a good quality systematic review and meta-analysis of 29 studies with long-term follow-up and low rates of attrition. Specifically, only studies of gastric bypass, gastric band, or sleeve gastrectomy performed in patients with a BMI of >35 and that reported outcomes with a minimum of two years of follow-up and at least 80% of the original study participants were included in the review. Only 29 studies (of nearly 8,000 citations reviewed) met the inclusion criteria. Among the included studies were 10 RCTs, one matched cohort, six prospective cohorts, one retrospective cohort, and 11 case series.

Weight loss outcomes in this review were reported as percentage of mean excess weight loss (EWL). The sample size weighted mean EWL was 65.7% after gastric bypass, 64.5% after sleeve gastrectomy, and 45% after gastric banding.

Six of the included studies reported on remission of T2DM (defined as glycated hemoglobin <6.5% without medications). Sample size weighted T2DM remission rates were 66.7% after gastric bypass and 28.6% after gastric banding.

Three of the included studies reported on remission of hypertension (defined as blood pressure <140/90 without medications). The reported hypertension remission rate was 38.2% after gastric bypass and 17.4% after gastric banding.

Wang (2015)

Wang et al. (2015) is a good quality, though narrowly focused, systematic review and meta-analysis of randomized controlled trials comparing laparoscopic RYGB with sleeve gastrectomy in overweight or obese adults with T2DM. Three RCTs judged to be at low risk of bias and one RCT with an unclear risk of bias were included. The average baseline BMI in the studies ranged from 30 to 46 kg/m^2. Laparoscopic RYGB and sleeve gastrectomy resulted in similar improvements in HbA1c, fasting plasma glucose, need for any diabetic medication, and BMI. Improvements in HDL and LDL cholesterol were statistically significantly greater in the RYGB group. The absolute or relative improvements in these outcomes compared to baseline were not included. Overall, the authors conclude that RYGB and sleeve gastrectomy offer equivalent results in terms of weight loss and T2DM remission, but that RYGB affords greater improvements in lipid parameters and may thus significantly decrease cardiovascular risk.

Washington Health Technology Assessment Report (2015)

The WA HTA report (2015) is a good quality systematic review and health technology assessment summarizing results from 179 comparative studies (35 RCTs, 59 prospective cohorts, 85 retrospective cohorts). Notably, one large cohort study with long-term follow-up, the Swedish Obese Subjects study, was not included as a primary source for the Washington HTA report because most of the patients in that study received a surgical procedure (gastroplasty) that is no longer widely performed. Only 15% of the included studies were judged to be of high quality, with an additional 41% deemed fair quality. When performing meta-analysis, the authors included only good or fair quality RCTs.

Overall or cause-specific mortality was not directly addressed in the WA HTA report because none of the included comparative studies reported those outcomes. However, the WA HTA report does note that evidence from at least one recent comparative cohort study found significantly lower all-cause mortality at 1 to 14 years of follow-up in surgical subjects (hazard ratio [HR] 0.45, 95% CI 0.36 to 0.56) (Arterburn, 2015).

The comparison of bariatric surgery to non-surgical management included 21 good- or fair-quality studies (14 RCTs, 7 comparative cohorts). These studies reported on RYGB (13 studies), AGB (6 studies), VSG (4 studies) and BPD/DS (3 studies). The non-surgical comparators included diet and lifestyle interventions and/or medical interventions (some variably defined as “intensive”). Meta-analytic results were available for weight loss and resolution of T2DM. The pooled mean difference in BMI was 7.4 (95% CI 6.2 to 8.6) favoring surgery, based on 10 studies. Resolution of T2DM had a log odds ratio of 3.62 (95% CI 2.49 to 4.73) favoring surgery, based on nine studies. Meta-analysis of studies reporting resolution of HTN was not done, but the report noted that “[o]ther individual comorbidities commonly evaluated in these comparative studies included hypertension and hyperlipidemia. In studies evaluating resolution of these conditions and/or discontinuation of relevant medications as a binary variable, bariatric surgery was associated with two- to three-fold reductions in the prevalence of these comorbidities [hypertension and hyperlipidemia] at the end of follow-up, while nonsurgical management resulted in no appreciable change from baseline…” (WA HTA, 2015, p. 34).

The WA HTA report is the only systematic review staff identified that summarizes key clinical outcomes stratified by procedure and mean pre-operative BMI. Those tables are included in Appendix F. Nine

good- or fair-quality RCTs and prospective cohorts comparing bariatric surgery and non-surgical management enrolled patients with BMI<35. Seven of those studies included presence of T2DM or metabolic syndrome as an entry criterion, while two did not report comorbid condition-based entry criteria. The authors conclude that for those with a mean pre-operative BMI of 30 to 35.9 "patterns of weight loss across procedures were similar to those in studies of patients at higher BMI" (WA HTA, 2015, p. ES-41). Furthermore, among studies of patients at lower BMI levels that reported on remission of T2DM at 12 to 24 months the results favored surgery (remission rates of 26% to 73%) over non-surgical treatment (remission rates of 0% to 16%).

Systematic Reviews Addressing Effectiveness in Children and Adolescents

Three fair or good quality systematic reviews address the effectiveness of bariatric surgery in children and adolescents (Aikenhead, Knai, & Lobstein, 2011; Black, White, Viner, & Simmons, 2013; Treadwell, Sun, & Schoelles, 2011). These studies are summarized in Table 4 and discussed below by systematic review.

Table 4. Summary of Systematic Reviews – Effectiveness of Bariatric Surgery for Children and Adolescents

Systematic Review (Quality) Total N	No. and Type of Included Studies	Population	Outcomes of Interest
Aikenhead, 2011 **(Fair)** **N = 831**	1 RCT 8 cohort studies 14 observational studies 12 case series	≤ 19 years old	BMI
Black, 2013 **(Fair)** **N = 637**	1 RCT 22 observational studies	Pre-surgical BMI (mean): 46 – 52 Age: 5 – 23 years	BMI
Treadwell, 2008 **(Treadwell)** **N = 644**	18 RCTs	Pre-surgical BMI (mean): 46 – 52 Age: 9 – 21 years	BMI

Abbreviations: BMI – body mass index; RCT – randomized controlled trial

Aikenhead (2011)

Aikenhead et al. (2011) is a fair quality narrative systematic review of 37 studies of effectiveness of bariatric surgery spanning 831 patients age 19 years old or younger. The authors note several general limitations of the pediatric bariatric surgery literature including predominately observational study designs, small sample sizes (the largest of the included trials had 68 patients), and sparse information on low frequency outcomes.

Thirteen of the included studies (all but one observational) assessed gastric banding. Twelve of these studies reported mean BMI reductions of 8.5 kg/m^2 to 43 kg/m^2, while one study (a case report of gastric banding and truncal vagotomy in an adolescent with a rare mutation in a gene implicated in regulation of appetite and energy balance) found an increase in BMI of 2.2 kg/m^2. Rates of resolution of comorbid conditions ranged from 11 to 100%.

Eight of the included studies (all observational) assessed RYGB. The studies reported mean reductions in BMI of 9 kg/m^2 to 25 kg/m^2. The authors note that four of the studies reported on comorbid conditions and three of those four studies found 100% rates of resolution for dyslipidemia, degenerative joint disease, asthma, and gastroesophageal reflux disease.

Fourteen of the included studies (all observational) reported on other bariatric procedures (sleeve gastrectomy, BPD/DS, vertical banded gastroplasty). These studies reported mean BMI reductions of 9 kg/m^2 to 24 kg/m^2. The authors note that changes in comorbid conditions were reported in 12 of the 14 studies, but additional details are not included.

The authors' overall conclusion is that "[i]n the context of a general lack of effective tools for primary prevention or behavioural treatment of obesity, surgical treatment may be advocated as a preferred and cost-effective solution for certain children and adolescents" (Aikenhead, 2011, p. 18)

Black (2013)

Black et al. (2013) is a fair quality systematic review and meta-analysis of bariatric surgery for obese children and adolescents. Twenty-three studies (22 observational and 1 RCT) comprising 637 patients undergoing RYGB, AGB, or SG were included. The mean pre-surgical BMI was 52.4 kg/m^2 in the RYGB studies, 49.6 kg/m^2 in the SG studies, and 46.1 kg/m^2 in the AGB studies. The ages of patients in the included studies ranged from 5 to 23 years old.

Overall, the average weighted BMI difference from baseline to one year postoperatively was -13.5 kg/m^2 (95% CI -15.1 to -11.9). The greatest BMI reductions were observed in patients undergoing RYGB (average weighted difference of -17.2 kg/m^2) and the smallest BMI reductions were observed in the AGB group (average weighted difference of -10.5 kg/m^2).

The authors note that they were unable to provide summary estimates of the effects on comorbidity resolution because the data were of poor quality and adequate definitions of resolution were not provided. The rates of reported resolution of T2DM from baseline to follow-up ranged from 0 to 100% in the eight studies that reported this outcome. However, excluding one study with only a single T2DM patient who did not experience resolution, the rate of resolution for T2DM would range from 50 to 100%. The rates of reported resolution of hypertension from baseline to follow-up ranged from 50 to 100% in the 10 studies that reported this outcome.

Treadwell (2008)

Treadwell et al (2008) is a good quality systematic review and meta-analysis of bariatric surgery for pediatric obesity. This review included 18 studies of children ages 9 to 21 years (mean age 16.7 years) with mean BMI ranging from 45.8 kg/m^2 to 51.8 kg/m^2. In 14 of the 18 studies, patients must have failed a trial of non-surgical weight loss before undergoing bariatric surgery. Only one of the included studies

reported a non-surgical control group and significant differences in baseline characteristics between the groups were noted including baseline BMI and comorbidities. Thus, the authors note that, in effect, the included studies were all case series.

Meta-analysis of change in BMI in six studies of AGB found a 95% CI of -13.7 kg/m^2 to -10.6 kg/m^2 at mean length of follow-up of one to three years. Two of the studies of AGB reported T2DM remission rates of 80 to 100% and three of the studies reported hypertension remission rates of 50 to 100%.

Meta-analysis of change in BMI in six studies of RYGB found a 95% CI of -17.8 kg/m^2 to -22.3 kg/m^2 at mean length of follow-up of one to six years. Only one of the studies of RYGB reported remission of T2DM. Three studies of RYGB reported rates of hypertension remission of 50 to 100%.

Because of the small number of studies and patients undergoing other procedures, summary information on weight changes or comorbidity resolution was not presented.

Overall, the authors conclude that there is weak to moderate evidence that AGB achieves weight loss at one year or longer and weak evidence of resolution of T2DM and hypertension. For RYGB, the authors conclude that there is weak to moderate evidence of weight loss at one year or longer, weak evidence of resolution of hypertension, and insufficient evidence of resolution of T2DM. There was insufficient evidence for any outcomes from other bariatric procedures.

Systematic Reviews Addressing Patient Selection

One poor quality and two good quality systematic reviews address patient selection criteria (Ochner, Dambkowski, Teomans, Teizeira, & Xavier Pi-Sunyer, 2012; Thomas & Agrqwal, 2012; WA HTA, 2015).

Ochner (2012)

Ochner et al. (2012) is a good quality narrative systematic review of 29 studies examining the effects of preoperative weight loss requirements on postoperative outcomes. The authors note that heterogeneity in the included studies precluded formal quantitative synthesis. Overall, the included studies were mostly observations and were mixed on the effects of preoperative weight loss requirements on postoperative weight loss outcomes. As the authors note, “studies of the relation between pre- and post-operative changes in body weight range from a positive relationship (preoperative weight loss associated with greater postoperative weight loss) to a negative relationship (preoperative weight loss associated with less postoperative weight loss) and many in between (no relationship)” (Ochner et al., 2012, p. 1381). The only included RCT deemed “viable” by the authors randomized 100 patients undergoing RYGB to a group with a requirement of 10% preoperative weight loss or a group with no preoperative weigh loss requirement. At six months after surgery, patients in the preoperative weight loss group had lost 54% of excess body weight compared to 51% excess body weight loss in the in the group without a preoperative weight loss requirement, but because only 37% of the original sample was analyzed at six months there was insufficient power to detect an effect.

The review also examined studies reporting on the effects of preoperative weight loss requirements on other outcomes including resolution of comorbid conditions. One study of 90 RYGB patients found that preoperative weight loss of >5% of excess body weight was associated with shorter operative times (36 minutes on average) but no difference in complications or resolution of comorbid conditions. Another

study demonstrated that patients with preoperative weight loss of >5% of excess body weight were less likely to have a postoperative length of stay of >4 days. The RCT referenced above found no difference in the complication rate or resolution of comorbid conditions at six months. A fourth study found no correlation between preoperative weight changes and remission of diabetes or hypertension.

The authors' overall conclusion is that "[g]iven the inconsistency and questionable validity of the extant research…on the question of the effect of preoperative weight loss on peri and postoperative outcomes, it is the opinion of these authors that insufficient evidence is currently available to justify a pre-bariatric surgery weight loss mandate" (Ochner et al., 2012, p. 1386).

Thomas (2012)

Thomas & Agarwal (2012) is a poor quality systematic review of a preoperative risk stratification tool known as the obesity surgery mortality risk score (OS-MRS). The OS-MRS assigns one point each for age greatr than45 years, male gender, BMI > 50 kg/m^2, hypertension, and known risk factors for pulmonary embolism. Scores of 0 to 1 are considered class A or lowest risk, scores of 2 to 3 reflect class B or intermediate risk, and scores of 4 to 5 are class C or high risk. This review included six studies reporting on 9,382 patients evaluating the validity of OS-MRS to predict postoperative mortality risk. Overall, there were 83 death in the 9,382 patients (0.88%). There were 13 deaths among the 4,912 class A patients (0.26%), 55 deaths among the 4,124 class B patients (1.33%), and 14 deaths among the 346 class C patients (4.34%). The mortality difference between classes were statistically significant at $p<0.05$. The authors conclude that use of the OS-MRS can stratify mortality risk in patients undergoing bariatric surgery (particularly RYGB which was the predominately studied procedure in the included studies).

WA HTA (2015)

The WA HTA report included a single retrospective comparative cohort study that stratified outcomes by patient adherence to preoperative program recommendations. In the laparoscopic AGB group, patients who did not attend >75% of their pre-procedure appointments had attenuated weight loss at 12 months of follow-up (23% EWL vs 32% EWL in patients with fewer missed appointment, p=0.01). There were no differences in RYGB performance related to pre-procedure appointment adherence.

A single study included in the WA HTA report concluded that patients with congestive heart failure and cardiac arrhythmias had a significantly increased risk of post-surgical complications compared with the overall cohort (40% vs 13.4% for open RYGB, 21.1% vs 8.6% for laparoscopic RYGB, and 17.4% vs 3.1% for laparoscopic AGB, all p-values <0.001). The same study reported that patients with peripheral vascular disease undergoing RYGB had significantly increased complication rates compared to those without peripheral vascular disease (32.0% vs 8.4%, $p<0.001$).

The WA HTA report also notes that it did not find studies that stratified outcomes by smoking status or psychosocial health that met inclusion criteria.

Systematic Reviews Addressing Systems of Care

One good quality systematic review addresses the effect of systems of care on bariatric surgery outcomes (Zevin, Aggarwal, & Grantcharov, 2012).

Zevin (2012)

Zevin et al. (2012) is a good quality systematic review of volume-outcome associations in bariatric surgery. The article reviews 24 observational studies comprising almost 460,000 patients. Meta-analysis was not performed due to a high level of heterogeneity that resulted, in part, from differences in duration of follow-up and risk-adjustment.

Thirteen studies addressed the relationship between annual surgeon case volume and patient outcomes. Across the five cohort studies that were included, there was consistent evidence of improved outcomes with increasing surgeon volume. The results of lower quality studies (primarily retrospective cohorts) were mixed, but six of the eight studies supported an association between surgeon volume and outcomes.

Seventeen studies addressed the association between hospital volume and outcomes. While the two case-control studies that were included did not support an association between facility volume and outcomes, the preponderance of retrospective case series (14/15 studies) that were included found an association between facility volume and outcomes.

The authors conclude that there is strong evidence to support the association between surgeon volume and patient outcomes, and that weaker evidence supports the association between hospital volume and outcomes. Overall, they conclude that the literature "supports the BSCOE accreditation and the bariatric surgery fellowship training programs" (Zevin et al., 2012, p. 70).

WA HTA (2015)

The WA HTA report notes that pre-procedure support groups have shown little benefit, but that there is some evidence that patients in postoperative support groups experience improvements in psychological comorbidities and achieve greater weight loss. The WA HTA report cites one RCT of 144 Hispanic-American RYGB patients randomized to "comprehensive nutrition and lifestyle support or brief, printed healthy lifestyle guidelines…" At one year after surgery, patients in the comprehensive support group had greater reductions in BMI (6.48 kg/m^2 vs 3.63 kg/m^2, $p<0.001$).

Systematic Reviews Addressing Cost-effectiveness

WA HTA (2015)

The WA HTA report (2015) performed a cost-effectiveness analysis based on a model constructed by the authors. This analysis assumed a public payer perspective. The base-case analysis compared RYGB with standard care over a 10 year time horizon; other base-case assumptions included a procedural cost of $24,277, 20% worsening in BMI after 12 months, mean BMI at baseline of 40 kg/m^2, and a discounting rate of 3%. In the base-case analysis, the incremental cost-effectiveness of RYGB compared to standard care was $37,423 per quality-adjusted life year (QALY) gained. In the deterministic sensitivity analyses, the incremental cost-effectiveness estimates ranged from $5,444 per QALY to $84,971 per QALY. The estimates were most sensitive to changes in the time horizon, the cost of the bariatric surgical procedure, maintenance of weight loss after surgery, and baseline BMI. The WA HTA cost-effectiveness estimates, stratified by procedure and baseline BMI, are included in Appendix G).

There is very sparse evidence on the cost-effectiveness of bariatric surgery in children and adolescents. The only included systematic review which addresses this question is Aikenhead et al. (2011). The conclusions of this review are limited by the small number of studies, use of economic models that are not directly applicable to the U.S., and inferences from cost-effectiveness studies of bariatric surgery in adults.

EVIDENCE SUMMARY

Despite the existence of a large number of studies and systematic reviews, there remain substantial limitations to the evidence regarding bariatric surgery. Differences in patient characteristics, choice of surgical procedure, and individual components and intensity of non-surgical management arms make it difficult to summarize effects across studies. Variable measures of weight loss and wide variation in definitions of remission or resolution of comorbid conditions pose additional problems. Many of the studies included in the reviews were non-comparative, and the comparative observational studies suffer from risk of bias related to patient selection and residual confounding. The data from RCTs is limited by questions regarding proper allocation concealment and the universal absence of blinding. Perhaps the greatest concern is the limited long term follow-up of patients from RCTs and incomplete outcomes data due to high rates of attrition in most studies.

Overall, the following conclusions can be drawn based on review of the summary literature:

1. Bariatric surgery is associated with lower rates of all-cause mortality and major adverse cardiovascular events in adults, despite a short term increased risk of perioperative mortality and complications (based on low certainty evidence from cohort studies with long term follow-up, with study populations consisting predominantly of patients with BMI ≥35).
2. Bariatric surgery is associated with significant reductions in BMI in adults, despite a short term increased risk of perioperative mortality and complications (based on moderate certainty evidence from a mix of observational and randomized trials). The effects on weight loss appear to be greatest in patients with baseline BMI ≥40 based on the BMI stratification provided in the WA HTA report.
3. Bariatric surgery is associated with remission or resolution of T2DM and hypertension in adults with BMI ≥ 35, despite a short term increased risk of perioperative mortality and complications (based on moderate certainty evidence from a mix of observational and randomized trials).
    - The effects on remission of T2DM appear to be greatest in patients with baseline BMI ≥40 based on the BMI stratification provided in the WA HTA report.
    - Preliminary evidence suggests that adults with BMI < 35 may also achieve significant reductions in BMI and improvement in comorbid T2DM and hypertension, though the long term effects are not yet clear.
4. Bariatric surgery is associated with significant reductions in BMI in children and adolescents, despite a short term increased risk of perioperative mortality and complications (based on

low certainty evidence primarily from small, non-comparative observational trials of bariatric surgery for pediatric obesity).

5. Bariatric surgery is associated with remission or resolution of T2DM and hypertension in children or adolescents, despite a short term increased risk of perioperative mortality and complications (based on very low certainty evidence from a small number of trials).
6. There is no evidence-based minimum age recommendation for pediatric bariatric surgery. Patients as young as five years old were included in the studies reported in the summary literature.
7. There is low certainty conflicting evidence on the effects of preoperative weight loss requirements.
8. The obesity surgery mortality risk score (OR-MRS) is a validated preoperative assessment of perioperative mortality risk (particularly for RYGB procedures) and may be useful in selecting patients for surgery or counseling them on surgical risks.
9. Harms of bariatric surgery include a perioperative mortality rate that probably ranges from 0.10 to 2%, and an overall complication rate that is probably on the order of 8 to 25%. The estimated reoperation rate is likely between 2 and 13%. There is limited evidence from a single study that comorbid congestive heart failure, cardiac arrhythmias, and peripheral vascular disease are associated with higher rates of complications after bariatric surgery.
10. There is low certainty evidence that surgeon experience is associated with improved outcomes and very low certainty evidence that hospital bariatric surgical volume is associated with improved outcomes.

OTHER DECISION FACTORS

Resource allocation

Bariatric surgery for adults is costly, but improved outcomes compared with non-surgical management may offset these costs. The WA HTA report cites total costs of bariatric surgical procedures as ranging from $17,483 for gastric banding to $36,160 for biliopancreatic diversion. By comparison, standard non-surgical care has a reported total cost of $3,746. Accounting for reductions in BMI, resolution of comorbid conditions, and complications of surgery and projecting costs and effectiveness over a 10-year horizon, bariatric surgical procedures are uniformly cost-effective at a willingness-to-pay threshold of $100,000 per QALY gained. This was true across BMI thresholds and surgical procedures. Excerpts from the economic analysis in the WA HTA report are provided in Appendix G.

Bariatric surgery for children is also costly, but improved outcomes may offset these costs, and the beneficial effects could accrue over the longer time horizon afforded by earlier intervention in children and adolescents. However, there is very limited evidence of cost-effectiveness of pediatric bariatric surgery. The pediatric cost-effectiveness information included in the review by Aikenhead et al. in 2011 used assumptions from Australia that are likely too indirect to influence deliberations on resource allocation.

Values and preferences

Adults

Based on staff assessment, most people would prefer to avoid surgery and its attendant risks if similar results could be attained through safer and less invasive interventions. However, patients who may have failed to achieve adequate weight loss with less invasive interventions may decide that the superior outcomes of bariatric surgery (including long term improvements in all-cause mortality) outweigh the upfront risks of surgery. Overall, there would be a moderate variability given these considerations.

Children and adolescents

Similar to adults, most children and their parents would prefer to avoid surgery and its attendant risks if similar results could be attained through safer and less invasive interventions. However, patients who may have failed to achieve adequate weight loss with less invasive interventions may decide that bariatric surgery offers the best chance at weight reduction. The significant social pressures of obesity at a young age may also push children and their parents to have strong interest in an effective treatment. Children though would likely have a great fear of surgery and the associated procedures and loss of social/academic participation. However, additional uncertainties related to malnutrition in this age group and its effects on growth, development, and reproductive capacity may make surgery less appealing in children and adolescents. Long term remission rates of morbid obesity and recurrence of the comorbidities are unknown; most studies report outcomes at one year, although a few studies report outcomes at up to three years. Given these considerations, there would be high variability in children's and parents preferences.

GRADE-INFORMED FRAMEWORK

Coverage question: Should bariatric surgery be recommended for coverage in adults?					
Outcomes		**Estimate of Effect for Outcome** **Confidence in Estimate of Effect**	**Resource allocation**	**Values and Preferences**	**Other considerations**
Critical outcomes	All-cause mortality	Long term relative risk: 0.68 Long term absolute risk reduction: 0.08 Number needed to treat = 13 ●●○○ to (low certainty based on consistent but indirect observational studies)	Bariatric surgery costs tens of thousands of dollars per surgery, but has been shown to be cost effective across BMI thresholds and surgery types.	Moderate variability. Patients would balance surgery and its risks with risks of living with morbid obesity. Many patients who have failed conservative attempts at weight loss may elect surgery.	The greatest benefit may be with BMI ≥ 40 but otherwise specific subpopulations which would benefit the most from bariatric surgery are not well characterized. The pre-operative requirements for achieving optimal outcomes are unclear. Given the rate of complications and need for reoperation reported in the summary literature, benefit plans may wish to consider alternative payment methodologies like bundled payments or a pay-for-outcomes approach. Surgeon case volume, and to a lesser extent hospital case volume, appear to affect outcomes for patients undergoing bariatric surgery and requirements regarding surgeon or facility volume may be reasonable.
	Major adverse cardiovascular events	Long term relative risk: 0.40 Long term absolute risk reduction: 0.016 Number needed to treat = 62 ●●○○ (low certainty based on consistent but indirect observational studies)			
Important outcomes	Type 2 DM remission / resolution	Odds ratio: 3.6 to 52.4 (favoring surgery) Number needed to treat: 1 to 5 ●●●○ (moderate certainty based on a mix of RCTs and observational studies with consistent but imprecise effects)			

Coverage question: Should bariatric surgery be recommended for coverage in adults?					
Outcomes		**Estimate of Effect for Outcome** **Confidence in Estimate of Effect**	**Resource allocation**	**Values and Preferences**	**Other considerations**
	Hypertension remission/ resolution	Odds ratio: 2.99 to 3.12 (favoring surgery) Number needed to treat: 4 ●●●○ (moderate certainty based on a mix of RCTs and observational studies with consistent but imprecise effects)			
	Change in BMI	Mean difference at 1 year: -5.5 to -33.35 kg/m^2 (favoring surgery) Pooled mean difference: -7.4 kg/m^2 (favoring surgery) ●●●○ (moderate certainty based on a mix of RCTs and observational studies with consistent but imprecise effects)			
Rationale: Bariatric surgery appears to lower all-cause mortality and major adverse cardiovascular events in obese adults (low certainty), and significantly reduces BMI, and results in resolution of type 2 diabetes and hypertension. Though bariatric surgery is costly and carries significant perioperative risks, the health benefits and savings associated with improved outcomes are likely to mean that bariatric surgery is cost-effective at commonly accepted thresholds of willingness-to-pay.					
Recommendation: Coverage of bariatric surgery (including Roux-en-Y gastric bypass, gastric banding, and sleeve gastrectomy) is recommended *(weak recommendation)* for: • Obese patients (BMI ≥ 35) with diabetes or with at least two other serious obesity-related comorbidities (i.e. hypertension, coronary heart disease, mechanical arthropathy in major weight bearing joint, sleep apnea) • Obese patients (BMI ≥ 40) with at least one other serious obesity related comorbidity					

Coverage question: Should bariatric surgery be recommended for coverage in adults?				
Outcomes	**Estimate of Effect for Outcome** **Confidence in Estimate of Effect**	**Resource allocation**	**Values and Preferences**	**Other considerations**
OR Obese patients (BMI ≥ 40) Bariatric surgery is recommended for coverage in these populations only when provided by an experienced surgeon and in a hospital with adequate number of cases. In addition, coverage is recommended only in systems that ensure appropriate follow up, tracking and proof of ongoing effectiveness, and that have acceptable reoperation rates, morbidity and mortality rates *(weak recommendation).* Repeat surgery (excluding surgical complications) is not recommended for coverage *(weak recommendation).*				

Coverage question: Should bariatric surgery be recommended for coverage in children and adolescents?					
Outcomes		**Estimate of Effect for Outcome** **Confidence in Estimate of Effect**	**Resource allocation**	**Values and Preferences**	**Other considerations**
Critical outcomes	All-cause mortality	Insufficient evidence in this population Insufficient evidence	High cost (tens of thousands of dollars) but may be cost effective especially given the long time horizon if weight loss is maintained However, it is unknown what the long term nutritional, growth, remission rate, and other complications that may occur decades after surgery which could significantly alter estimates of cost-effectiveness.	High variability. If conservative treatments have failed, children, adolescents and their parents would be highly motivated to find an effective alternative intervention. Children would likely have a significant fear of surgery, but the profound social and emotional impact of obesity may override their concerns. Parents are likely to be more concerned about the long term health impacts of obesity than children, and may be concerned about the uncertainty about the long term benefits.	Parental involvement in weight management plans is likely necessary to assist the effectiveness of obesity treatments (based on expert opinion). Pediatric bariatric surgery is likely to be available at only a few highly specialized centers. The American Academy of Pediatrics has 10 criteria that pediatric bariatric surgery programs should meet.
	Major adverse cardiovascular events	Insufficient evidence in this population Insufficient evidence			
Important outcomes	Type 2 DM remission / resolution	Rates of remission of T2DM ranged from 50 to 100% ●○○○ (very low certainty based on mostly small observational trials with imprecise effects)			
	Hypertension remission/ resolution	Rates of remission of hypertension ranged from 50 to 100% ●○○○ (very low certainty based on mostly small observational trials with imprecise effects)			
	Change in BMI	Mean weighted difference in BMI at 1 year (from baseline): -10.5 to -17.2 kg/m^2			

Coverage question: Should bariatric surgery be recommended for coverage in children and adolescents?					
Outcomes		**Estimate of Effect for Outcome** **Confidence in Estimate of Effect**	**Resource allocation**	**Values and Preferences**	**Other considerations**
		●●○○ (low certainty based on mostly small observational trials)			
Rationale: Bariatric surgery likely results in significant reductions in BMI (low certainty) and is associated with remission of type 2 diabetes and hypertension (very low certainty). However, coverage is not recommended because of insufficient evidence about overall long-term benefits and harms of bariatric surgery in this population as well as the high variability in values and preferences.					
Recommendation: Bariatric surgery is not recommended for coverage in children and adolescents *(weak recommendation).*					

Note: GRADE framework elements are described in Appendix B

POLICY LANDSCAPE SOURCES

Quality measures

One bariatric surgery-specific quality measure was identified when searching the National Quality Measures Clearinghouse:

- Prevention and management of obesity for adults: percentage of patients with a BMI greater than or equal to 40 who have been provided with a referral to a bariatric specialist (Institute for Clinical Systems Improvement)

Payer coverage policies

Medicare (National Coverage Determination [NCD] 100.1), Washington Medicaid, Aetna, Cigna, Regence Blue Cross Blue Shield, and Moda all provide coverage of bariatric surgery. Each coverage policy outlines specific coverage criteria that must be met prior to bariatric surgery being approved. These criteria are described below and provided in more detail in Appendix D.

Age

All six payers provide coverage of bariatric surgery for adults (defined as at least 18 years), and Aetna and Cigna additionally provides coverage for adolescents (defined as an individual with completed skeletal growth). Washington limits the procedure type to LAGB only for individuals aged 18 to 20 years.

Body Mass Index

For adults, Aetna, Cigna and Moda require individuals have a BMI of greater than or equal to 40 kg/m^2, or greater than or equal to 35 kg/m^2 with specific comorbidities. Washington and NCD 100.1 cover individuals with a BMI of greater than or equal to 35 kg/m^2 with comorbidities, and Regence BCBS requires that an individual have a BMI of greater than or equal to 40 kg/m^2 or a BMI of greater than, or equal to 35 kg/m^2 with type 2 diabetes or at least two other specified comorbidities. Washington is the only identified payer that explicitly requires individuals not be pregnant at the time of the surgery.

For adolescents, Aetna covers individuals with a BMI of greater than 40 kg/m^2 who have serious comorbidities, or individuals with a BMI of greater than 50 kg/m^2 with less serious comorbidities. Cigna uses the same BMI criteria as the adult population.

Comorbidities

Diabetes is the only comorbidity specified by all five payers. Payers specify various combinations of other comorbid conditions including coronary heart disease, dyslipidemia, hypertension, lower extremity lymphatic or venous obstruction, mechanical arthopathy in major weight bearing joint, rare comorbid conditions (e.g., pseudo tumor cerebri), and obstructive sleep apnea. Aetna specifies several less severe comorbidities for adolescents with a BMI of over 50 including gastroesphageal reflux disease, intertriginous soft-tissue infection, nonalcoholic steatohepatitis, obesity-related psychosocial distress, significant impairments in daily living, and stress urinary incontinence.

Pre-Surgical Requirements

Five payers require individuals to undergo a comprehensive psychosocial evaluation and participate in a formal weight loss program prior to being approved for bariatric surgery (Aetna, Cigna, Moda, Regence BCBS, Washington). Three payers require a separate medical evaluation (Washington, Cigna, Moda), surgical evaluation (Washington, Cigna), and nutritional evaluation (Cigna, Moda) prior to surgery. The NCD 100.1 requires that individuals have been previously unsuccessful with medical treatment for obesity.

Payers require an individual attend a formal weight loss program within six months (Washington) to two years of surgery (Aetna, Regence BCBS, Moda). The weight loss program must be greater than or equal to three (Cigna) to six months in duration (Washington, Aetna, Regence BCBS, Moda). Both Washington and Moda require that individuals lose 5% of their initial body weight as part of the weight loss program prior to surgery. Aetna's policy states that there can be no net weight gain during weight loss program attendance. Payer coverage policies include a variety of additional required program components including counseling by a registered dietitian, patient journal of participation, regular face-to-face provider visits, behavior modification, supervised exercise regimen, and hypocaloric diet changes.

Provider Requirements

Washington Medicaid and Moda state that bariatric surgery is only covered if provided by an approved facility, defined by Moda as a Center of Excellence and by Washington with specific criteria. Bariatric surgery facilities approved by Washington Medicaid must have performed a minimum of 100 bariatric surgical procedures, be under the direction of an experienced board-certified surgeon, been in operation for at least five years, have a 2% or less mortality rate, have a 15% or less morbidity rate, have at least five years of patient follow-up data, have an average of at least 50% patient weight loss at five years, and have a reoperation / revision rate of 5% or less.

The Centers for Medicaid and Medicare have approved six facilities in Oregon to perform bariatric surgery: Bay Area Hospital, Legacy Good Samaritan Hospital and Medical Center, Oregon Health & Science University, Sacred Heart Medical Center, Salem Hospital, St. Charles Medical Center – Bend.

Repeat Surgery Coverage

Aetna, Cigna and Regence BCBS address repeat bariatric surgery and outline specific circumstances under which it is covered. All three payers provide coverage to correct complication from the initial surgery, and conversion from gastric banding to sleeve gastrectomy, RYGB or BPD/DS. Aetna and Cigna specify that conversion surgery is covered for individuals who have not lost more than 50% of their body weight two years following the primary bariatric surgery. Cigna will cover the adjustment of the silicone gastric band and repeat surgery for a failed dilation of a gastric pouch. Aetna will additionally cover removal of a gastric band, replacement of adjustable band, and repeat surgery for a failed dilation of a gastric pouch.

Non-Covered Procedures

Aetna, Cigna, and Regence BCBS outline specific conditions and procedures that are not in the coverage of bariatric surgery. Across all three payers, gastroplasty ("stomach stapling"), laparoscopic gastric

plication, mini gastric bypass, transoral endoscopic surgery (e.g., OverStich suturing device, StomaphX™, TOGA®), are not covered. In addition, Aetna and Cigna do not cover gastrointestinal liners (e.g., EndoBarrier™), intragastric balloon, loop gastric bypass, silastic ring vertical gastric bypass (e.g., Fobi pouch), or vagus nerve blocking. Aetna and Regence BCBS do not cover band over bypass surgeries, band or sleeve gastrectomy surgeries, sclerotherapy for the treatment of dilated gastrojejunostomy following bariatric surgery, or for gastroesophageal reflux disease in non-obese individuals. Cigna and Regence BCBS do not cover intestinal bypass (jejunoileal bypass) or restorative obesity surgery (e.g., ROSE). Regence BCBS specifically does not cover vertical banded gastroplasty; Aetna covers this procedure for members who are at increased risk of adverse consequences from Roux-en-Y gastric bypass due to certain gastrointestinal conditions (see Appendix D).

The NCD 100.1 does not provide coverage for open adjustable gastric banding, open sleeve gastrectomy, open and laparoscopic vertical banded gastroplasty, intestinal bypass surgery, and gastric balloon for treatment of obesity.

Professional society guidelines

Adults

The Institute for Clinical Systems Improvement (ICSI) (Fitch et al, 2013a) (good quality), Veterans Administration (VA) (Management of Overweight and Obesity Working Group, 2014) (good quality), the American Association of Clinical Endocrinologists, Obesity Society, American Society for Metabolic & Bariatric Surgery (Mechanic et al., 2013)(poor quality primarily), the Australian National Health and Medical Research Council (NHMRC) (NHMRC, 2013)(good quality), and the National Institute for Health and Care Excellence (NICE) (NICE, 2014) (good quality) provide recommendations on the use of bariatric surgery in adults. The guideline from the American Heart Association / American College of Cardiology / The Obesity Society (Jensen et al, 2014) (good quality) provides a summary of the evidence related to the long-term effectiveness of bariatric surgeries and the long-term effects of these procedures on varying BMI levels with and without comorbidities. The guideline does not provide clinical practice recommendations.

All identified guidelines consistently recommend bariatric surgery for individuals with a BMI of greater than 40 kg/m^2, or greater than 35 kg/m^2 with significant comorbidities. There is some variance between guidelines in what comorbidities are considered significant. For example, only two of the five guidelines list gastroesophageal reflux disease as a significant comorbidity. Four guidelines (AACD/OS/ASMBS, ICSI, NHMRC, NICE) recommend bariatric surgery be considered for individuals with a BMI of greater than 30 kg/m^2 who have severe comorbidities such as diabetes, and NICE recommends bariatric surgery for individuals of Asian descent with recent-onset diabetes who may have a lower BMI than other populations. The VA determined that there was insufficient evidence to recommend the use of bariatric surgery for individuals with a BMI less than 35 kg/m^2.

The AACD/OS/ASMBS and NICE guidelines recommend individuals have pre-surgical comprehensive medical and psychological evaluations. The use of multidisciplinary teams consisting of surgical, medical, nutrition, and psychological expertise is recommended by NICE and NHMRC.

Children

The ICSI (Fitch et al., 2013b) (good quality), the Australian NHMRC (NHMRC, 2013), and NICE (NICE, 2014) provide recommendations on indications for bariatric surgery in the pediatric population. Both the ICSI and NHMRC guidelines recommend bariatric surgery as an option for adolescents with a BMI greater than 40, or greater than 35 with severe comorbidities. The NHMRC specifies that only laparoscopic gastric banding performed by a specialist bariatric/pediatric surgical team is recommended for adolescents. The guideline from ICSI is the most comprehensive and recommends detailed pre-surgical evaluations, failed attempts at weight loss through formal weight loss programs, and the use of multidisciplinary team at regional bariatric centers of excellence. ICSI further recommends that children have attained Tanner stage 4 or 5 or have bone age of ≥13 years in girls or ≥15 years in boys before considering bariatric surgery. Pediatric bariatric surgery is not recommended by NICE except in the case of exceptional circumstances.

Assessment of congruence between guidelines and evidence

In general, the clinical practice guideline recommendations for adults are supported by the available evidence. Patients with BMI ≥40 kg/m^2 or with BMI 35 to 39.9 with obesity-related comorbid conditions have been well studied in the literature, and the clinical practice guidelines reflect this stronger evidence base. The divergence in the recommendations for patients with BMI 30 to 34.9 probably reflects the smaller number of studies that specifically address this population and the shorter follow-up periods reported in these studies. Recommendations regarding pre-surgical evaluations may reflect expert practice tips, but are not directly supported by the summary literature. Similarly, recommendations regarding preoperative weight loss are based on expert opinion and are not directly supported by the summary literature.

The wider variation in the recommendations for bariatric surgery in children reflects greater uncertainty about both the effectiveness and the adverse effects of surgery. When surgery is recommended for children, there is general agreement based on expert opinion that this should be performed at regional centers of excellence.

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Coverage guidance is prepared by the Health Evidence Review Commission (HERC), HERC staff, and subcommittee members. The evidence summary is prepared by the Center for Evidence-based Policy at Oregon Health & Science University (the Center). This document is intended to guide public and private purchasers in Oregon in making informed decisions about health care services.

The Center is not engaged in rendering any clinical, legal, business or other professional advice. The statements in this document do not represent official policy positions of the Center. Researchers involved in preparing this document have no affiliations or financial involvement that conflict with material presented in this document.

APPENDIX A. METHODS

Scope Statement

Populations

Obese individuals who are being considered for bariatric or metabolic surgery

Population scoping notes: *Include <18. Exclude overweight (BMI<30)*

Interventions

Bariatric or metabolic surgery (Adjustable gastric banding, Roux-en-y gastric bypass, biliopancreatic diversion, duodenal switch, vertical sleeve gastrectomy)

Intervention exclusions: *Gastric balloon (not FDA approved)*

Comparators

Nonsurgical treatment (medical management, pharmacotherapy, intensive multicomponent behavioral interventions, behavioral counseling, structured weight management programs (e.g. Weight Watchers)

Outcomes

Critical: All-cause mortality, Major Cardiac Events (MACE)

Important**:** Resolution of hypertension, weight loss, resolution of type 2 diabetes

Considered but not selected for the GRADE table: Hyperlipidemia, arthritis, sleep apnea, CPAP use, medication use

Key Questions

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

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

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

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

Search Strategy

A full search of the core sources was conducted to identify systematic reviews, meta-analyses, technology assessments, and clinical practice guidelines using the terms "bariatric." Searches of core sources were limited to citations published after 2004 with one exception (see inclusion criteria).

The core sources searched included:

Agency for Healthcare Research and Quality (AHRQ)
Blue Cross/Blue Shield Health Technology Assessment (HTA) program
BMJ Clinical Evidence
Canadian Agency for Drugs and Technologies in Health (CADTH)
Cochrane Library (Wiley Interscience)
Hayes, Inc.
Institute for Clinical and Economic Review (ICER)
Medicaid Evidence-based Decisions Project (MED)
National Institute for Health and Care Excellence (NICE)
Tufts Cost-effectiveness Analysis Registry
Veterans Administration Evidence-based Synthesis Program (ESP)
Washington State Health Technology Assessment Program (WA HTA)

A recent technology assessment from the WA HTA program was identified as the most comprehensive review identified (WA HTA, 2015). A MEDLINE® (Ovid) search was then conducted to identify systematic reviews, meta-analyses, and technology assessments published after the search dates of the WA HTA report. The search was limited to publications in English published after 2014 (the end search date for the WA HTA systematic review).

Searches for clinical practice guidelines were limited to those published since 2010. A search for relevant clinical practice guidelines was also conducted, using the following sources:

Australian Government National Health and Medical Research Council (NHMRC)
Centers for Disease Control and Prevention (CDC) – Community Preventive Services
Choosing Wisely
Institute for Clinical Systems Improvement (ICSI)
National Guidelines Clearinghouse
New Zealand Guidelines Group
NICE
Scottish Intercollegiate Guidelines Network (SIGN)
United States Preventive Services Task Force (USPSTF)
Veterans Administration/Department of Defense (VA/DOD)

Inclusion/Exclusion Criteria

Due to the volume of available literature related to the effectiveness of bariatric surgery in adults (Key Question #1), reviews were limited to those published after 2013. Center staff dual quality assessed the identified reviews and only included those that were rated as good quality.

Studies were excluded if they were not published in English, did not address the scope statement, or were study designs other than systematic reviews, meta-analyses, technology assessments, or clinical practice guidelines.

APPENDIX B. GRADE INFORMED FRAMEWORK - ELEMENT DESCRIPTIONS

Element	Description
Balance between desirable and undesirable effects	The larger the difference between the desirable and undesirable effects, the higher the likelihood that a strong recommendation is warranted. The narrower the gradient, the higher the likelihood that a weak recommendation is warranted
Quality of evidence	The higher the quality of evidence, the higher the likelihood that a strong recommendation is warranted
Resource allocation	The higher the costs of an intervention—that is, the greater the resources consumed—the lower the likelihood that a strong recommendation is warranted
Values and preferences	The more values and preferences vary, or the greater the uncertainty in values and preferences, the higher the likelihood that a weak recommendation is warranted
Other considerations	Other considerations include issue about the implementation and operationalization of the technology or intervention in health systems and practices within Oregon.

Strong recommendation

In Favor: The subcommittee is confident that the desirable effects of adherence to a recommendation outweigh the undesirable effects, considering the quality of evidence, cost and resource allocation, and values and preferences.

Against: The subcommittee is confident that the undesirable effects of adherence to a recommendation outweigh the desirable effects, considering the quality of evidence, cost and resource allocation, and values and preferences.

Weak recommendation

In Favor: The subcommittee concludes that the desirable effects of adherence to a recommendation probably outweigh the undesirable effects, considering the quality of evidence, cost and resource allocation, and values and preferences, but is not confident.

Against: The subcommittee concludes that the undesirable effects of adherence to a recommendation probably outweigh the desirable effects, considering the quality of evidence, cost and resource allocation, and values and preferences, but is not confident.

Quality or strength of evidence rating across studies for the treatment/outcome[1]

High: The subcommittee is very confident that the true effect lies close to that of the estimate of the effect. Typical sets of studies are RCTs with few or no limitations and the estimate of effect is likely stable.

Moderate: The subcommittee is moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different. Typical sets of studies are RCTs with some limitations or well-performed nonrandomized studies with additional strengths that guard against potential bias and have large estimates of effects.

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

***Low*:** The subcommittee's confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect. Typical sets of studies are RCTs with serious limitations or nonrandomized studies without special strengths.

***Very low*:** The subcommittee has very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect. Typical sets of studies are nonrandomized studies with serious limitations or inconsistent results across studies.

APPENDIX C. GRADE EVIDENCE PROFILE

Quality Assessment (Confidence in Estimate of Effect) – Adults							
No. of Studies	**Study Design(s)**	**Risk of Bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other Factors**	**Quality**
All-cause Mortality[1]							
14	Cohort	Moderate	Consistent	Direct	No serious imprecision	Large effect size	Low confidence in estimate of effect ●●○○
Major Adverse Cardiovascular Events[1]							
4	Cohort	Moderate	Consistent	Direct	No serious imprecision	Large effect size	Low confidence in estimate of effect ●●○○
Type 2 DM Remission/Resolution[2]							
60	15 RCTs; 45 observational studies	Moderate to High	Consistent	Direct	Imprecise	None	Moderate confidence in estimate of effect ●●●○
Hypertension Remission / Resolution[2]							
52	13 RCTs; 39 observational studies	Moderate	Consistent	Direct	Imprecise	None	Moderate confidence in estimate of effect ●●●○
Change in BMI[2]							
101	28 RCTs; 73 observational studies	Moderate to High	Consistent	Direct	Imprecise	None	Moderate confidence in estimate of effect ●●●○

[1] Studies from Tables 1 and 2(Kwok, 2014). Strength of evidence assessment based on Table 2 in Kwok (2014).

[2]Studies and strength of evidence assessment based on Figure 2 of Colquitt (2014), Supplemental Table 1 of Muller-Stich (2015), and the description of study quality from the WA HTA review (2015, p.27-28). Chang (2014) does not provide individual study risk of bias assessments.

Quality Assessment (Confidence in Estimate of Effect) – Children and Adolescents							
No. of Studies	**Study Design(s)**	**Risk of Bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other Factors**	**Quality**
All-cause Mortality							
0	NA	NA	NA	NA	NA	NA	Insufficient evidence
Major Adverse Cardiovascular Events							
0	NA	NA	NA	NA	NA	NA	Insufficient evidence
Type 2 DM Remission/Resolution[1]							
13	13 observational studies	High	Consistent	Direct	Imprecise	None	Very low confidence in estimate of effect ●○○○
Hypertension Remission / Resolution[1]							
15	15 observational studies	High	Consistent	Direct	Imprecise	None	Very low confidence in estimate of effect ●○○○
Change in BMI[1]							
28	1 RCT; 27 observational studies	High	Consistent	Direct	Imprecise	None	Low confidence in estimate of effect ●●○○

[1] Studies from Black (2013) and Treadwell (2008).

APPENDIX D. BARIATRIC SURGERY COVERAGE

Table 1. Bariatric Surgery Coverage – Adults

Coverage criteria	Payer				
	Washington Medicaid	Aetna[1]	Cigna[2]	Regence BCBS[3]	Moda
Patient Characteristics					
Age	18 – 20 yrs (LAGB obly) 21 – 59 yrs (all procedures)	≥ 18 yrs	≥ 18 yrs	≥ 18 yrs	≥ 18 yrs
BMI	≥ 35 with comorbidities (*see below*)	> 40 > 35 with comorbidities (*see below*)	≥ 40 ≥ 35 with comorbidities (*see below*)	≥ 40 ≥ 35 with DM2 or at least two other comorbidities (*see below*)	≥ 40 ≥ 35 with comorbidities (*see below*)
Not pregnant	√	---	---	---	---
Comorbidities					
Coronary heart disease	---	√	√	√	√
Diabetes	√	√	√	√	√
Dyslipidemia	---	---	√	√	---
Hypertension	---	√	√ (poorly controlled or pulmonary)	√	√
Lower extremity lymphatic or venous obstruction	---	---	√	---	---
Mechanical arthopathy in major weight bearing joint	√	---	√	---	√
Rare comorbid conditions (e.g., pseudo tumor cerebri)	√[4]	---	---	---	---
Sleep apnea	---	√	√	√	√
Absence of other medical conditions (e.g., multiple sclerosis)	√	---	---	---	√

Key: √ – required; --- – not in policy description

Abbreviations: BCBS – Blue Cross Blue Shield; BMI – body mass index; LAGB – laparoscopic adjustable gastric banding; yrs – years

Notes:

1. Specific to open or laparoscopic Roux-en-Y gastric bypass (RYGB), laparoscopic adjustable silicone gastric banding (LASGB), open or laparoscopic sleeve gastrectomy, open or laparoscopic biliopancreatic diversion (BPD), and duodenal switch (DS).

2. Specific to open or laparoscopic Roux-en-Y gastric bypass, open or laparoscopic adjustable silicone gastric banding (LAP-BAND®, REALIZE™), open or laparoscopic biliopancreatic diversity with duodenal switch (BPD/DS) for individuals with a BMI >50, open or laparoscopic sleeve gastrectomy, open or laparoscopic vertical banded gastroplasty
3. Roux-en-Y with an alimentary limb of 150 cm or less, sleeve gastrectomy as a stand-alone procedure, or adjustable gastric banding
4. Must be medical evidence that bariatric surgery is medically necessary and that the benefits of bariatric surgery outweigh the risk of surgical mortality

Table 2. Bariatric Surgery Coverage – Children

Coverage criteria	Payer	
	Aetna[1]	Cigna[2]
Patient Characteristics		
Age	Adolescents who have completed bone growth (~13 yrs in girls, ~15 yrs in boys)	Reached full expected skeletal growth
BMI	> 40 with serious comorbidities > 50 with less serious comorbidities	≥ 40 ≥ 35 with comorbidities
Comorbidities		
Coronary artery disease	---	√
Diabetes	√ (>40 BMI)	√
Dislipidemias	√ (> 50 BMI)	√
Gastroesophageal reflux disease	√ (> 50 BMI)	---
Hypertension	√ (> 50 BMI)	√ (poorly controlled or pulmonary)
Intertriginous soft-tissue infection	√ (> 50 BMI)	---
Mechanical arthropathy in a major weight bearing joint	√ (> 50 BMI)	√
Nonalcoholic steatohepatitis	√ (> 50 BMI)	---
Obesity-related psychosocial distress	√ (> 50 BMI)	---
Rare comorbid conditions (e.g., pseudo tumor cerebri)	√ (>40 BMI)	---
Significant impairments in daily living	√ (> 50 BMI)	---
Sleep apnea	√ (>40 BMI)	√
Stress urinary incontinence	√ (> 50 BMI)	---
Venous stasis disease	√ (> 50 BMI)	√

Key: √ – required; --- – not in policy description Abbreviations; BMI – body mass index; yrs - years

Notes:

1. Specific to open or laparoscopic Roun-en-Y gastric bypass (RYGB), laparoscopic adjustable silicone gastric banding (LASGB), open or laparoscopic sleeve gastrectomy, open or laparoscopic biliopancreatic diversion (BPD), and duodenal switch (DS).
2. Specific to open or laparoscopic Roux-en-Y gastric bypass, open or laparoscopic adjustable silicone gastric banding (LAP-BAND®, REALIZE™), open or laparoscopic biliopancreatic diversity with duodenal switch (BPD/DS) for individuals with a BMI >50, open or laparoscopic sleeve gastrectomy, open or laparoscopic vertical banded gastroplasty

Table 3. Pre-Surgical Requirements

Coverage criteria	Payer				
	Washington Medicaid	Aetna[1]	Cigna[4]	Regence BCBS	Moda
Patient Evaluation					
Comprehensive psychosocial evaluation	√[2]	√[3]	√	√	√
Internal medicine evaluation	√	---	√	---	√
Surgical evaluation	√	---	√	---	---
Nutrition evaluation	---	---	√	---	√
Weight Loss Program					
Required	√	√ (physician-supervised *or* multi-disciplinary surgical prep regimen)	√ (physican- or registered dietician-supervised)	√ (physician-supervised)	√
Timing	Within 180 days of surgery	Within 2 years of surgery (physician-supervised) Within 6 months of surgery (surgical prep regimen)	Within 1 year of surgery	Within 2 years of surgery	Within 2 years of surgery
Duration	≥ 6 months	Cumulative total ≥ 6 months, one program ≥ 3 months (physician-supervised) ≥ 3 months (surgical prep regimen)	≥ 3 months	≥ 6 months	≥ 6 months
Required weight loss	5% of initial body weight	No net weight gain during program	---	----	5% of initial body weight over 6 months
Program Components	Supervised by licensed provider; monthly provider visits; 2x/month counseling by a registered dietitian; patient	Physician-supervised: medical record documentation with program compliance record; supervised nutrition and exercise program must have face-to-face component	---	Three visits for medical supervision (no more than 4 months apart); provided by MD, DO, NP, PA, or RD under supervision of MD, DO, NP or	Hypocaloric diet changes, nutritional education, physical activity, behavior change strategies;

Coverage criteria	Payer				
	Washington Medicaid	Aetna[1]	Cigna[4]	Regence BCBS	Moda
	journal of participation	Surgical Prep Regimen: Behavior modification program; dietician or nutritionist consultation; medical record documentation; supervised exercise regimen; substantial face-to-face component; reduced-calorie diet supervised by a dietitian or nutritionist		PA; assessment and counseling on weight, diet, exercise and behavior modification; clinical documentation of willingness to comply with pre- and post-operative treatment plan	three or more primary care visits; completion of a 8-week health education, weight management program

Key: √ – required; --- – not in policy description

Abbreviations: DO – doctor of osteopathy; MD – medical doctor; NP – nurse practitioner; PA – physician assistant; RD – registered dietician

Notes:

1. Specific to open or laparoscopic Roun-en-Y gastric bypass (RYGB), laparoscopic adjustable silicone gastric banding (LASGB), open or laparoscopic sleeve gastrectomy, open or laparoscopic biliopancreatic diversion (BPD), and duodenal switch (DS).
2. Provider must be a psychiatrist, licensed psychiatric ARNP, or licensed independent social worker with a minimum of two years postmasters' experience in a mental health setting.
3. For members who have a history of severe psychiatric disturbance (schizophrenia, borderline personality disorder, suicidal ideation, severe depression) or who are currently under the care of a psychologist/psychiatrist or who are on psychotropic medications
4. Specific to open or laparoscopic Roux-en-Y gastric bypass, open or laparoscopic adjustable silicone gastric banding (LAP-BAND®, REALIZE™), open or laparoscopic biliopancreatic diversity with duodenal switch (BPD/DS) for individuals with a BMI >50, open or laparoscopic sleeve gastrectomy, open or laparoscopic vertical banded gastroplasty

Table 4. Facility Requirements

Approved Facility Requirements	Payers Washington Medicaid
Minimum number of bariatric surgical procedures performed	100
Direction	Experience board-certified surgeon
Time in operation	≥ 5 years
Mortality rate	≤ 2%
Morbidity rate	≤ 15%
Patient follow-up	≥ 5 years
Average patient weight loss at 5 years	≥ 50%
Reoperation / revision rate	≤ 5%

Table 5. Repeat Surgery Coverage

Circumstances	Payers		
	Aetna	Cigna	Regence BCBS
Adjustment of silicone gastric band	---	√	---
Removal of gastric band	√	---	---
Correct complications	√	√	√
Conversion to sleeve gastrectomy, RYGB or BPD/DS	√[1, 2]	√[2]	√
Failed dilation of gastric pouch after primary surgery	√[1] (if primary surgery was successful in inducing weight loss)	√	---
Replacement of adjustable band	√ (for complications)	---	---
Conversion from adjustable band to sleeve gastrectomy, RYGB or BPD/DS	√[1] (for complications that cannot be corrected with band manipulation, adjustments or replacement)	---	---

Key: √ – covered; --- – not in policy description

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

Notes:

1. If patient has been compliant with a prescribed nutrition and exercise program following the procedure.
2. For members who have not lost > 50% of body weight 2 years following primary surgery.

Table 6. Non-Covered Conditions and Procedures

	Payers		
	Aetna	**Cigna**	**Regence BCBS**
Conditions			
Idiopathic intracranial hypertension	X	---	---
Infertility	X	---	---
DM2 w/BMI <35	X	X[1]	
Gastroesophageal reflux in non-obese persons	X	---	X
Gastroparesis	X	---	---
Procedures			
Band over bypass	X	---	X
Band over sleeve	X	---	X
Roux-en-Y gastric bypass combined with simultaneous BPD without DS	---	X	---
Gastrointestinal liners (EndoBarrier™)	X	X	---
Gastroplasty ("stomach stapling")	X	X	X
Intragastric balloon	X	X	
Laparoscopic gastric plication	X	X	X
Loop gastric bypass	X	X	
Mini gastric bypass	X	X	X
Sclerotherapy for the treatment of dilated gastrojejunostomy following bariatric surgery	X	---	X
Silastic ring vertical gastric bypass (Fobi pouch)	X	X	---
Transoral endocopic surgery (OverStitch suturing device or StomaphyX™ device)	X	X (including TOGA®)	X
Vagus nerve blocking	X	X	---
Gastric electrical stimulation or gastric pacing	---	X	---
Intestinal bypass (jejunoileal bypass)	---	X	X
restorative obesity surgery, endoluminal (ROSE)	---	X	X
Vagus nerve stimulation	---	X	---
Distal gastric bypass (long limb gastric bypass, >150 cm)	---	---	X
Biliopancreatic bypass (Scopinaro procedure)	---	---	X
Biliopancreatic bypass with duodenal switch	---	---	X
Two-stage produres	---	---	X
Vertical banded gastroplasty	---	---	X

EndoCinch™	---	---	X

Key: √ – covered; X – not covered; --- – not in policy description

Notes:

1. Not covered when performed solely for treatment of diabetes mellitus
2. Specific requirements for vertical banded gastroplasty (members who are at increased risk of adverse consequences from Roux-en-Y Gastric bypass due to the presence of:
    - Demonstrated complications from extensive adhesions involving the intestines from prior major abdominal surgery, multiple minor surgeries, or major trauma
    - Hepatic cirrhosis with elevated liver function tests
    - Inflammatory bowel disease (Crohn's disease or ulcerative colitis)
    - Poorly controlled systemic disease
    - Radiation enteritis.

APPENDIX E. APPLICABLE CODES

CODES	DESCRIPTION
ICD-10	
E11.0 – E11.9	Diabetes, type 2
E66.01-E66.9	Overweight, Obesity and Morbid Obesity
G47.30 – G47.39	Sleep apnea
I10	Essential hypertension
ICD-9-CM Volume I Codes	
250.00, 250.02; 250.10, 250.12, 250.20, 250.22, 250.30, 250.32, 250.40, 250.42, 250.50, 250.52, 250.60, 250.62, 250.70, 250.72, 250.80, 250.82, 250.90, 250.92	Diabetes, Type II
278.00 – 278.03	Overweight, Obesity, and Morbid Obesity
327.20 – 327.29; 780.57	Sleep apnea
401.0 – 401.9	Hypertension
ICD-9-CM Volume III Codes	
43.82	Laparoscopic vertical (sleeve) gastrectomy
43.89	Open and other partial gastrectomy
44.31	High gastric bypass
44.38	Laparoscopic gastroenterostomy
44.5	Revision of gastric anastomosis
44.68	Laparoscopic gastroplasty
44.69	Other repair of stomach
44.95	Laparoscopic gastric restrictive procedure
44.96	Laparoscopic revision of gastric restrictive procedure
44.97	Laparoscopic removal of gastric restrictive device(s)
44.98	Laparoscopic) adjustment of size of adjustable gastric restrictive device
45.51	Isolation of segment of small intestine
45.91	Small-to-small intestinal anastomosis

CPT Codes	
43644	Laparoscopy, surgical, gastric restrictive procedure; with gastric bypass and Roux-en-Y gastroenterostomy (roux limb 150 cm or less)
43645	Laparoscopy, surgical, gastric restrictive procedure; with gastric bypass and small intestine reconstruction to limit absorption
43770	Laparoscopy, surgical, gastric restrictive procedure; placement of adjustable gastric restrictive device (eg, gastric band and subcutaneous port components)
43771	Laparoscopy, surgical, gastric restrictive procedure; revision of adjustable gastric restrictive device component only
43772	Laparoscopy, surgical, gastric restrictive procedure; removal of adjustable gastric restrictive device component only
43773	Laparoscopy, surgical, gastric restrictive procedure; removal and replacement of adjustable gastric restrictive device component only
43774	Laparoscopy, surgical, gastric restrictive procedure; removal of adjustable gastric restrictive device and subcutaneous port components
43775	Laparoscopy, surgical, gastric restrictive procedure; longitudinal gastrectomy (ie, sleeve gastrectomy)
43842	Gastric restrictive procedure, without gastric bypass, for morbid obesity; vertical-banded gastroplasty
43843	Gastric restrictive procedure, without gastric bypass, for morbid obesity; other than vertical-banded gastroplasty
43845	Gastric restrictive procedure with partial gastrectomy, pylorus-preserving duodenoileostomy and ileoileostomy (50 to 100 cm common channel) to limit absorption (biliopancreatic diversion with duodenal switch)
43846	Gastric restrictive procedure, with gastric bypass for morbid obesity; with short limb (150 cm or less) Roux-en-Y gastroenterostomy
43847	Gastric restrictive procedure, with gastric bypass for morbid obesity; with small intestine reconstruction to limit absorption
43848	Revision, open, of gastric restrictive procedure for morbid obesity, other than adjustable gastric restrictive device (separate procedure)
43886	Gastric restrictive procedure, open; revision of subcutaneous port component only
43887	Gastric restrictive procedure, open; removal of subcutaneous port component only
43888	Gastric restrictive procedure, open; removal and replacement of subcutaneous port component only
HCPCS Level II Codes	
S2083	Adjustment of gastric band diameter via subcutaneous port by injection or aspiration of saline

Note: Inclusion on this list does not guarantee coverage

APPENDIX F. OUTCOMES BY BASELINE MEAN BMI FROM THE WA HTA REPORT (P. 64-65)

		Baseline Mean BMI Category							
		30-34.99		35-39.99		40-49.99		>50	
		Median	Range	Median	Range	Median	Range	Median	Range
% Decrease BMI	RYGB	25.4	(19.6-34.3)	26.0	(24.1-33.1)	32.2	(7.5-52.3)	34	(10.1-46.7)
	VSG	21.3	(21.3-21.3)	22.0	(19.1-22.5)	28.4	(15.0-37.1)	30.1	(11.0-39.4)
	LAGB	16.8	(11.8-21.7)	16.8	(13.0-17.5)	20.4	(6.0-46.8)	17.7	(1.0-31.8)
	BPD/DS	31.8	(17.3-46.3)			32.6	(15.9-50.8)	43.4	(39.2-47.7)
	Follow-up (months)	12.0	(3.0-45.2)	15.3	(12.0-60.0)	12.0	(0.5-120.0)	22.6	(1.2-84.0)
	No. Studies	7		6		79		22	
	Good/Fair/Poor	2/3/2		3/1/2		9/34/36		4/10/8	
% EWL	RYGB	70.0		77.0	(61.0-92.9)	67.0	(27.1-88.0)	61.8	(43.8-72.3)
	VSG			58.5	(51.0-66.0)	59.2	(30.7-83.0)	47.5	(25.4-75.0)
	LAGB	87.2		50.1	(34.0-62.5)	43.5	(18.2-78.8)	45.9	(31.0-73.0)
	BPD/DS					52.7	(34.9-70.4)	73.4	63.0-84.0)
	Follow-up (months)	18.0	(12.0-24.0)	30.0	(18.7-60.0)	24.0	(0.47-120)	24.0	(12.0-84.0)
	No. Studies	2		4		57		15	
	Good/Fair/Poor	1/0/1		1/1/2		6/27/24		1/8/6	
% Improvement Hypertension	RYGB			90.0		71.0	(22.0-100.0)	62.6	(60.7-69.2)
	VSG					64.3	(23.5-100.0)		
	LAGB			40.0		57.5	(18.0-100.0)	54.3	(33.3-66.7)
	BPD/DS	67.0				81.4	(68.6-87.0)	68.3	(66.7-69.9)
	Follow-up (months)	36.0		60.0		21.0	(3.5-84.0)	24.0	(12.0-50.4)
	No. Studies	1		1		29		5	
	Good/Fair/Poor	0/1/0		0/0/1		4/12/13		1/3/1	

Baseline Mean BMI Category									
		30-34.99		35-39.99		40-49.99		>50	
		Median	Range	Median	Range	Median	Range	Median	Range
% Improvement T2DM	RYGB	51.1	(33.0-92.3)	73.4	(66.7-80.0)	79.0	(33.0-100.0)	77.1	(40.0-100.0)
	VSG	50.0	(50.0-50.0)			77.3	(36.0-100.0)	88.9	(88.9-88.9)
	LAGB	33.0	(21.1-100.0)	50.0	(25.0-73.0)	50.0	(17.0-100.0)	52.3	(36.4-66.7)
	BPD/DS	84.8	(83.0-84.8)			87.1	(81.5-92.7)	91.4	(82.7-100.0)
	Follow-up (months)	12.0	(3.0-45.2)	24.0	(12.0-60.0)	16.0	(1.0-62.7)	24.0	(1.5-50.4)
	No. Studies	6		3		35		7	
	Good/Fair/Poor	0/3/3		2/0/1		3/14/18		1/4/2	
% Improvement Sleep Apnea	RYGB	89.0				70.5	(10.0-100.0)	56.7	(49.3-88.0)
	VSG					62.0	(6.0-99.0)		
	LAGB					29.0	(3.0-55.0)	46.2	(39.3-66.7)
	BPD/DS	90.0						79.5	(78.9-80.0)
	Follow-up (months)	45.15				21.6	(12.0-36.0)	20.1	(12.0-20.1)
	No. Studies	1		0		11		4	
	Good/Fair/Poor	0/0/1				2/5/4		1/3/0	
% Improvement Dyslipidemia	RYGB			100.0		64.5	(6.0-100.0)	52.9	(27.3-58.8)
	VSG					67.5	(35.0-67.5)		
	LAGB			38.0		36.5	(0.0-36.5)	34.4	(23.3-45.5)
	BPD/DS					90.0	(90.0-90.0)		
	Follow-up (months)			60.0		24.0	(12.0-62.7)	16.2	(12.0-50.4)
	No. Studies	0		1		18		3	
	Good/Fair/Poor	0		0/0/1		2/9/7		1/1/1	

APPENDIX G. COST-EFFECTIVENESS ESTIMATES FROM THE WA HTA REPORT (P. 80)

BMI Level/ Procedure	Cost ($)	Effectiveness (QALYs)	Cost-effectiveness ($/QALY gained)	
			Vs. SC	Vs. RYGB
BMI≥30				
Standard care	$34,923	7.5680	NA	NA
RYGB	$54,110	8.0807	$37,423	NA
VSG	$48,702	8.0417	$29,087	Less expensive & less effective
LAGB	$47,668	7.9252	$35,680	Less expensive & less effective
BPD/DS	$65,741	8.2307	$46,508	$77,574
BMI 30-34.9				
Standard care	$27,943	7.9418	NA	NA
RYGB	$49,735	8.3529	$53,021	NA
VSG	$44,298	8.3211	$43,122	Less expensive & less effective
LAGB	$42,738	8.2273	$51,826	Less expensive & less effective
BPD/DS	$61,410	8.4730	$63,011	$97,194
BMI 35-39.9				
Standard care	$32,538	7.6567	NA	NA
RYGB	$52,886	8.1351	$42,534	NA
VSG	$47,468	8.0986	$33,789	Less expensive & less effective
LAGB	$46,217	7.9898	$41,073	Less expensive & less effective
BPD/DS	$64,533	8.2751	$51,743	$83,224
BMI≥40				
Standard care	$40,329	7.2846	NA	NA
RYGB	$58,257	7.8630	$30,995	NA
VSG	$53,047	7.8194	$23,784	Less expensive & less effective
LAGB	$52,255	7.6882	$29,552	Less expensive & less effective
BPD/DS	$69,329	8.0322	$38,790	$65,431

BPD = biliopancreatic diversion; ICER = incremental cost-effectiveness ratio; LAGB = laparoscopic adjustable gastric banding; RYGB = Roux-en-Y gastric bypass; VSG = vertical sleeve gastrectomy.

NOTE: Because of rounding, performing calculations may not produce the exact results shown.