Health Evidence Review Commission's Health Technology Assessment Subcommittee

June 11, 2015

1:00 PM

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

Section 1.0

Call to Order

AGENDA

HEALTH TECHNOLOGY ASSESSMENT SUBCOMMITTEE (HTAS)
June 11, 2015
1:00pm - 4:00pm

Clackamas Community College
Wilsonville Training Center, Rooms 112
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 February minutes	Som Saha
3	1:10 PM	Staff update	Darren Coffman
4	1:15 PM	Biomarker tests of cancer tissue for prognosis and potential response to treatment • Review written public comment	Robyn Liu Cat Livingston
5	2:30 PM	Indications for proton beam therapy • Review written public comment	Robyn Liu Cat Livingston
6	3:50 PM	Confirmation of the next meeting September 10, 2015	Som Saha
7	3:55 PM	Next Topics	Cat Livingston
8	4:00 PM	Adjournment	Som Saha

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

MINUTES

Health Technology Assessment Subcommittee
Meridian Park Community Health Education Center
19300 SW 65th Avenue, Tualatin, OR
February 23, 2015
1:00-4:00 pm

Members Present: James MacKay, MD, Vice-Chair; Gerald Ahmann, MD, PhD; George Waldmann, MD; Timothy Keenen, MD (arrived 3:15 pm); Mark Bradshaw, MD; Chris Labhart.

Members Absent: None.

Staff Present: Darren Coffman; Wally Shaffer, MD, MPH; Jason Gingerich, Denise Taray (via phone).

Also Attending: Robyn Liu MD, MPH, Valerie King, MD, MPH and Jill Scantlan (CEbP); Patti Brooke (Seattle Cancer Care Alliance Proton Therapy); Devki Saraiya (Myriad).

---

1. CALL TO ORDER

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

---

2. MINUTES REVIEW

No changes were made to the November, 2014 minutes.
Minutes approved 5-0 (Keenen absent).

---

3. ALTERNATIVES TO TRANSURETHRAL RESECTION OF THE PROSTATE (TURP)

A) Review of public comments

Shaffer reviewed the changes to the draft coverage guidance since the last meeting. Robyn Liu reviewed the public comments and the CEbP's recommended responses.

The subcommittee discussed the changes to the draft coverage guidance as highlighted in the meeting materials. With the incorporation of the GOLIATH study, there is a recommendation for coverage for photoselective vaporization of the prostate. The recommendation regarding older laser vaporization techniquest was removed based on expert testimony that these technologies are no longer in use in Oregon. In discussion of the comments regarding prostatic urethral lifts, the subcommittee decided not to add coverage for prostatic urethral lifts based on lack of outcomes beyond 2 years.

DRAFT

DRAFT COVERAGE GUIDANCE

For men with lower urinary tract symptoms (LUTS) due to benign prostate enlargement, coverage of surgical procedures is recommended only if symptoms are severe, and if drug treatment and conservative management options have been unsuccessful or are not appropriate. (*strong recommendation*)

The following are coverage recommendations regarding surgical alternatives to transurethral resection of the prostate (TURP):

Recommended for coverage (*strong recommendation*):

- Bipolar TURP
- Photoselective vaporization of the prostate (PVP)
- Laser enucleation; HoLEP (Holmium Laser Enucleation of Prostate)
- TUIP (Transurethral Incision of the Prostate)

Recommended for coverage (weak recommendation):

- TUNA (Transurethral Needle Ablation of Prostate)
- TUMT (Transurethral Microwave Thermotherapy)
- Bipolar TUVP (Transurethral Electrovaporization of Prostate) (Button procedure)
- Thulium laser vaporization/resection of the prostate

Not recommended for coverage (*weak recommendation*):

- Botulinum toxin
- HIFU (High Intensity Focused Ultrasound)
- TEAP (Transurethral Ethanol Ablation of the Prostate)
- Prostatic urethral lifts

Not recommended for coverage (*strong recommendation*):

- Laser coagulation (for example, VLAP/ILC)
- Prostatic artery embolization

A motion was made to approve the draft coverage guidance as appears in the meeting materials and forward to HERC. **Motion approved 5-0 (Keenen absent).**

---

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

A) Continued review of initial draft coverage guidance

Shaffer reviewed the revisions to the draft coverage guidance, which staff made based on subcommittee request during the previous meeting. After some discussion, MacKay invited verbal public comment.

Devki Saraiya, a genetic counselor from Myriad Genetics, provided public comment. She advocated for coverage of the Prolaris test for prostate cancer based on a recent decision by Medicare. She said there are two clinical utility studies not included in the literature search which show that the test significantly alters treatement decisions and reduces the burden of prostatectomy and radiation. Shaffer requested that she send the articles for consideration during the formal public comment period, so that these studies can be considered when public comments are reviewed.

In the GRADE table, the subcommittee set the resource allocation to low due to the potential for cost savings with reduced medication, and added a rationale to the row for BRAF (used for colorectal cancer).

A motion was made to post the draft coverage guidance for comment. **Motion approved 5-0 (Keenen absent).**

DRAFT 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

B) Review of initial draft coverage guidance

Shaffer reviewed the draft coverage guidance as presented in the meeting materials. After brief discussion, MacKay invited public comment.

Patti Brooke, vice president of marketing from the Seattle Cancer Care Alliance and Proton Therapy Center, testified. She referred to a letter sent by a colleague regarding

the topic. She said that the proton beam center lobby is frequently full, and that there have been 18 patients from Oregon treated in the past year. Her organization would like to be involved in the process.

Shaffer then turned the discussion to several indications for which he was unable to make a recommendation. For adult malignant brain and spinal tumors, ocular hemangiomas and pediatric tumors, the subcommittee downgraded the evidence from low to very low because of the lack of high quality studies. After discussion they decided to start with recommending against coverage for these populations, recognizing that public comments or additional evidence may change this decision. For ocular hemangiomas, the subcommittee elected to make a strong recommendation against coverage, based on the insufficient evidence available to date.

A motion was made to post the draft coverage guidance (as amended) for comment. **Motion approved 6-0.**

DRAFT COVERAGE GUIDANCE

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

Proton beam therapy is not recommended for coverage for adult malignant brain and spinal tumors *(weak recommendation).*

Proton beam therapy is not recommended for coverage for pediatric malignant tumors *(weak recommendation).*

Proton beam therapy is not recommended for coverage for cancer of the bone, head and neck, esophagus, liver, lung, or prostate (*weak recommendation*).

Proton beam therapy is not recommended for coverage for any other cancerous or noncancerous condition (*weak recommendation*).

6. ADJOURNMENT

The meeting was adjourned at 3:20 pm. The next meeting is scheduled for June 11, 2015 from 1:00-4:00 pm, with location to be determined later. The April meeting is cancelled because of Shaffer's upcoming retirement and a lack of clinical staff to fill in prior to his replacement being hired.

Section 2.0

Coverage Guidances-HTAS

HEALTH EVIDENCE REVIEW COMMISSION (HERC)

COVERAGE GUIDANCE: BIOMARKER TESTS OF CANCER TISSUE FOR PROGNOSIS AND POTENTIAL RESPONSE TO TREATMENT

DRAFT for 6/11/15 HTAS meeting materials

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).*

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

Blue Cross Blue Shield (BCBS). (2014). *Gene Expression Analysis for Prostate Cancer Management.* Chicago, IL: BCBS. Retrieved on October 21, 2014, from http://www.bcbs.com/blueresources/tec/vols/28/28_11.pdf

Blue Cross Blue Shield (BCBS). (2013). *Multiple molecular testing of cancers to identify targeted therapies*. Chicago, IL: BCBS. Retrieved on October 21, 2014, from http://www.bcbs.com/blueresources/tec/vols/28/28_01.pdf

Blue Cross Blue Shield (BCBS). (2011). *Special report: companion diagnostics: example of BRAF gene mutation testing to select patients with melanoma for treatment with BRAF kinase inhibitors.* Chicago, IL: BCBS. Retrieved on December 10, 2014, from http://www.bcbs.com/blueresources/tec/vols/26/26_07.pdf

Bunker, K., Kriz, H., Liu, R., Thielke, A., Lorish, K., & King, V. (2011). Oncotype DX Assay for Breast Cancer. Portland, OR: Center for Evidence-based Policy, Oregon Health and Science University.

Canadian Agency for Drugs and Technologies in Health (CADTH). (2014). *Oncotype DX in women and men with ER-positive, HER2-negative early stage breast cancer who are lymph node-positive: a review of clinical effectiveness and guidelines*. Ottawa, CA: CADTH. Retrieved on October 21, 2014, from http://www.cadth.ca/media/pdf/htis/mar-2014/RC0517_OncotypeDX_NodePos%20Final.pdf

Canadian Agency for Drugs and Technologies in Health (CADTH). (2014). *Oncotype DX in women and men with ER-positive, HER2-negative early stage breast cancer who are lymph node-negative: a review of clinical effectiveness and guidelines*. Ottawa, CA: CADTH. Retrieved on October 21, 2014, from http://www.cadth.ca/media/pdf/htis/apr-2014/RC0524%20Oncotype%20DX%20for%20node%20negative%20patients%20Final.pdf

McArthur GA, Chapman PB, Robert C, Larkin J, Haanen JB, Dummer R et al (2014). *Safety and efficacy of vemurafenib in BRAFV600^{E} and BRAFV600^{K} mutation-positive melanoma (BRIM-3): extended follow-up of a phase 3, randomised, open-label study*. The Lancet Oncology, 15(3), 323-332. Retrieved on February 10, 2015, from http://dx.doi.org/10.1016/S1470-2045(14)70012-9. (http://www.sciencedirect.com/science/article/pii/S1470204514700129)

Meleth, S., Reeder-Hayes, K., Ashok, M., Clark, R., Funkhouser, W., Wines, R., et al. (2014). *Technology assessment of molecular pathology testing for the estimation of prognosis for common cancers*. Rockville, MD: Agency for Healthcare Research and Quality. Retrieved

DRAFT

on October 21, 2014, from http://www.cms.gov/Medicare/Coverage/DeterminationProcess/Downloads/id94TA.pdf

Mujoomdar M, Moulton K, & Spry C. (2010). *Epidermal Growth Factor Receptor Mutation Analysis in Advanced Non-Small Cell Lung Cancer: A Review of the Clinical Effectiveness and Guidelines*. Ottawa: CADTH. Retrieved on December 10, 2014, from http://www.cadth.ca/media/pdf/M0017_EGFR_Testing_for_NSCLC_e.pdf

National Institute for Health and Care (NICE). (2014). *Early and locally advanced breast cancer*. London, UK: NICE. Retrieved on November 5, 2014, from http://www.nice.org.uk/guidance/cg80/resources/guidance-early-and-locally-advanced-breast-cancer-pdf

National Institute for Health and Care Excellence (NICE). (2013). *EGFR-TK mutation testing in adults with locally advanced or metastatic non-small-cell lung cancer.* NICE diagnostics guidance 9. London, UK: NICE. Retrieved on December 9, 2014, from http://www.nice.org.uk/guidance/dg9/resources/guidance-egfrtk-mutation-testing-in-adults-with-locally-advanced-or-metastatic-nonsmallcell-lung-cancer-pdf

National Institute for Health and Care (NICE). (2013). *Gene expression profiling and expanded immunohistochemistry tests for guiding adjuvant chemotherapy decisions in early breast cancer management: MammaPrint, Oncotype DX, IHC4 and Mammostrat*. London, UK: NICE. Retrieved on October 21, 2014, from http://www.nice.org.uk/guidance/dg10/resources/guidance-gene-expression-profiling-and-expanded-immunohistochemistry-tests-for-guiding-adjuvant-chemotherapy-decisions-in-early-breast-cancer-management-mammaprint-oncotype-dx-ihc4-and-mammostrat-pdf

Terasawa T, Dahabreh I, Castaldi PJ, Trikalinos TA. (2010). *Systematic reviews on selected pharmacogenetic tests for cancer treatment: CYP2D6 for tamoxifen in breast cancer, KRAS for anti-EGFR antibodies in colorectal cancer, and BCR-ABL1 for tyrosine kinase inhibitors in chronic myeloid leukemia. Technology Assessment Report.* (Prepared by Tufts Evidence-based Practice Center under contract number HHSA 290 2007 100551). Rockville, MD: Agency for Healthcare Research and Quality. Retrieved on December 10, 2014, from http://www.cms.gov/medicare-coverage-database/details/technology-assessments-details.aspx?TAId=76&bc=BAAgAAAAAAAA&

Additional sources

Febbo, P; Ladanyi, R; Aldape, K; De Marzo, A; Hammond, E; Hayes, D, et al. (2011). *NCCN Task Force Report: Evaluating the Clinical Utility of Tumor Markers in Oncology.* Journal of National Comprehensive Cancer Network Vol 9, Suppl 5:S1–S32.

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

DRAFT

EVIDENCE OVERVIEW: BREAST CANCER

Clinical background

Breast cancer is the second most common cancer among women and one of the leading causes of death in the United States. The most recent estimates from the Centers for Disease Control and Prevention report that in 2007, 202,964 women in the United States were diagnosed with breast cancer, and 40,598 women died from breast cancer. However, earlier detection, better risk prediction models, and advancements in preventive therapies are leading to improved outcomes for women diagnosed with breast cancer.

The spread of cancer is described in terms of breast cancer staging. Staging is determined by the size of the tumor and the presence and size of metastases. Stages are defined as 0, I (A or B), II (A or B), III (A, B, or C), or IV. Early stage breast cancer (stage I or stage II) has not spread to distant lymph nodes, but cancer cells may be found in nearby lymph nodes. These lymph nodes include ones in the axilla or near the breast bone.

Treatment for women with early stage breast cancer includes primary therapy (e.g., lumpectomy, mastectomy), but also may include adjuvant hormone therapy and chemotherapy. Studies from the National Surgical Adjuvant Breast and Bowel Project indicate that the probability of distant recurrence is 15% at 10 years in women treated only with tamoxifen. Since more than 15% of women with early stage breast cancer are receiving chemotherapy, this indicates that many women who receive adjuvant chemotherapy would be disease-free without this added therapy. This suggests that there is a population of low-risk patients that derives little additional therapeutic benefit from chemotherapy, and may be at risk of harm from this treatment.

Among women with early stage breast cancer who have undergone any adjuvant therapy, the recurrence rate has been found to be 11% at five years and 20% at 10 years post-treatment. Stratified by the stage of the cancer at diagnosis, the five year residual risk of recurrence is reported to be 7% among those diagnosed with stage I cancer (95% CI: 3 to 15%), 11% among those diagnosed with stage II cancer (95% CI: 9 to 13%), and 13% among those diagnosed with stage III cancer (95% CI: 10 to 17%).

There are a variety of clinical decision-making tools currently in use to estimate breast cancer recurrence risk, including the St. Gallen consensus recommendations, the National Comprehensive Cancer Network guidelines (NCCN), Adjuvant! Online, and the Nottingham Prognostic Index (NPI). These protocols incorporate various factors such as patient demographics (e.g., age, menopausal status, comorbidity) and tumor data (e.g., staging, size, estrogen-receptor (ER) status, number of positive lymph nodes, human epidermal growth factor-2 receptor (HER2) status) to estimate risk and guide choice of treatments.

Although each tool has separately been shown to have predictive ability and is supported by clinical trial data, in comparative studies these tools often disagree about a particular patient's risk, and none of them is considered the gold standard of prediction. Treatment decisions, particularly whether or not to pursue adjuvant chemotherapy, are made partially based on these risk estimates. With advances ine cancer therapy, it is increasingly important to be able to

DRAFT

predict which patients will benefit from particular types of treatment. Multiple genomic tests have been developed for this purpose, of which four will be reviewed here.

Technology description

NICE (2013): Gene Expression Profiling and Immunohistochemistry Tests for Guiding Adjuvant Chemotherapy Decisions in Early Breast Cancer: MammaPrint®, Oncotype DX®, IHC4, Mammostrat®

Some gene expression profiling tests work by identifying and quantifying mRNA transcripts in a specific tissue sample. Because only a fraction of the genes encoded in the genome of a cell are transcribed into mRNA, gene expression profiling provides information about the activity of genes that give rise to these mRNA transcripts. Other gene expression profiling tests work by measuring levels of cDNA, which is synthesized from mRNA. There are a range of different techniques for measuring mRNA levels in breast cancer tumor samples, including real-time reverse transcription polymerase chain reaction (RT-PCR) and DNA microarrays.

Different tests use different protocols for preparing the samples (for example, formalin fixation, paraffin embedding, snap freezing and fresh samples) and different methods for preparing the RNA. Furthermore, there are different algorithms for combining the raw data into a summary profile. All of these factors can affect the reproducibility and reliability of gene expression profiling tests.

- MammaPrint is based on microarray technology and uses an expression profile of 70 genes. MammaPrint is intended as a prognostic test for women of all ages, with LN− and LN+ (up to 3 nodes positive) breast cancer with a tumor size of 5 cm or less. MammaPrint is used to estimate the risk of distant recurrence of early breast cancer. It stratifies patients into 2 distinct groups – low risk (good prognosis) or high risk (poor prognosis) of distant recurrence. MammaPrint has been cleared by the Food and Drug Administration as an In Vitro Diagnostic Multivariate Index Assay. The test uses fresh or formalin-fixed paraffin-embedded samples that are processed centrally at laboratories run by the manufacturer in the USA or The Netherlands.
- Oncotype DX® quantifies the expression of 21 genes in breast cancer tissue by RT-PCR. It predicts the likelihood of recurrence in women of all ages with newly diagnosed stage I or II, ER+, LN− or LN+ (up to 3 nodes positive) breast cancer treated with tamoxifen. The test assigns the breast cancer a continuous recurrence score (RS) and a risk category – low (RS<18), intermediate (18≤RS≤30) or high (RS≥31). The test also reports ER, progesterone receptor (PR) and HER2 status. The test uses formalin-fixed paraffin-embedded samples that are processed centrally at a laboratory run by the manufacturer in the USA.

Immunohistochemistry tests measure protein levels in the tumor sample rather than RNA or cDNA. Some of these tests offer the advantage of using existing immunohistochemical markers (such as ER and HER2), which are routinely tested in UK pathology departments. The term 'expanded' has been used to describe the immunohistochemistry tests evaluated in this assessment that are used in addition to standard immunohistochemistry testing (such as ER and HER2) for early invasive breast cancer. Immunohistochemistry uses staining to identify

DRAFT

protein expression and reports the level of protein expression in tumor tissue. Differences in immunohistochemistry values can be caused by variability in several factors, including fixation of tissue, antigen retrieval (used to enhance staining), reagents, and interpretation.

- IHC4 measures the levels of 4 key proteins (ER, PR, HER2 and Ki-67) in addition to classical clinical and pathological variables (for example, age, nodal status, tumour size and grade) and calculates a risk score for distant recurrence using an algorithm. Quantitative assessments of ER, PR, and Ki-67 are needed for the IHC4 test. An online calculator for IHC4 is in development. The test uses formalin-fixed paraffin-embedded samples that can be processed in local NHS laboratories.
- Mammostrat uses 5 immunohistochemical markers (SLC7A5, HTF9C, P53, NDRG1 and CEACAM5) to stratify patients into risk groups to inform treatment decisions. These markers are independent of one another and do not directly measure either proliferation or hormone receptor status. The test calculates the relative risk of recurrence by using a weighted algorithm that is interpreted in the context of published clinical studies of appropriate patient populations. Patients are classified into 3 risk categories: prognostic index ≤0 defined as the 'low risk' group; prognostic index >0 and ≤0.7 defined as the 'moderate-risk' egroup; prognostic index >0.7 defined as the 'high risk' group. The test uses formalin-fixed paraffin-embedded samples that are processed centrally at a laboratory run by the manufacturer in the USA.

Evidence review

NICE (2014): Early and Locally Advanced Breast Cancer

The NICE Cancer Service Guidance, *Improving outcomes in breast cancer*, recommends that women at intermediate or high risk of recurrence who have not had neoadjuvant chemotherapy should normally be offered multi-agent chemotherapy, which includes anthracyclines. The *Early and locally advanced breast cancer: diagnosis and treatment* guideline recommends that adjuvant therapy should be considered for all patients with early invasive breast cancer after surgery, based on assessment of the prognostic and predictive factors, and the potential benefits and side effects of the treatment. These guidelines do not refer to the use of gene expression profiling and expanded immunohistochemistry tests to aid decision making, but recommend that decisions should be made following discussion of these predictive and prognostic factors with the patient and that Adjuvant! Online should be considered to support estimations of indiviedual prognosis and the absolute benefit of adjuvant treatment. The NPI is also commonly used locally to aid decisions about chemotherapy for patients with early stage breast cancer.

The following outcomes were evaluated for the four included tests:

- Analytical validity (the ability of the test to accurately and reliably measure the expression of mRNA or proteins by breast cancer tumor cells
- Clinical validity (prognostic ability, or the degree to which the test can accurately predict the risk of an outcome, such as the risk of distant metastases in 10 years)

DRAFT

- Clinical utility, defined as the ability of the test to improve clinical outcomes such as overall survival. This includes direct harms arising from the test, reclassification of risk compared with existing tools, its impact on clinical decision-making and the ability of the test to predict benefit from chemotherapy.

MammaPrint®

Systematic reviews indicated that evidence relating to the clinical validity of MammaPrint® was not always conclusive nor supported the prognostic value of the test. Seven additional studies of MammaPrint® were identified by the guidance authors. Of these, four on the clinical validity of MammaPrint® demonstrated that the MammaPrint® score is a strong independent prognostic factor, and may provide additional value to standard clinic-pathological measures. There were no prospective studies of the impact of MammaPrint® on long-term outcomes such as overall survival. Six studies with data on the clinical utility of MammaPrint® were identified, and reported a high level of discordance between MammaPrint® and current classification, although these studies did not demonstrate how this would impact on treatment decisions.

In summary, robust evidence of clinical utility is not available for MammaPrint® so it is not yet clear whether using the test will improve the use of adjuvant chemotherapy in the management of breast cancer in the UK. Most studies of MammaPrint® were retrospective in design, used small sample sizes and had heterogeneous patient populations; some studies included only premenopausal women. The evidence for MammaPrint® is based on the use of the test with fresh samples. It is not clear whether this evidence would apply if the test were used on formalin-fixed paraffin-embedded samples.

Oncotype DX®

Systematic reviews reported evidence that the Oncotype DX® recurrence score was significantly correlated with disease-free survival and overall survival. Furthermore, the recurrence score was shown to be a better predictor of distant recurrence at 10 years than traditional clinico-pathological predictors. The evidence on clinical utility was limited. One study demonstrated a significantly increased benefit from the use of chemotherapy in the Oncotype DX® high-risk group compared with the low-risk group.

The guidance authors identified 12 additional studies of Oncotype DX® supporting the prognostic ability of Oncotype DX®. One large-scale UK study in post-menopausal women with ER+, LN− early bereast cancer found that an increase in risk score was significantly associated with an increased risk of distant recurrence. Furthermore, the evidence base has been extended to include the LN+ population. No prospective studies of the impact of Oncotype DX® on long-term outcomes such as overall survival were identified. Four studies presented further evidence on the impact of Oncotype DX® on clinical decision making. These indicated that the use of Oncotype DX leads to changes in treatment decisions for between 32% and 38% of patients.

Four publications reported evidence that Oncotype DX® predicts benefit from chemotherapy. The first evidence of improvements in quality of life and reduced patient anxiety as a result of using Oncotype DX® have been reported, although the studies had small sample sizes.

In summary, Oncotype DX® is considered to have the most robust evidence base of the tests reviewed in this guidance, with data on the analytical validity, clinical validity, and clinical utility

DRAFT

of the test. The studies varied considerably in their size, design and patient populations. Many of the Oncotype DX studies were small and retrospective.

IHC4

No studies of analytical validity of IHC4 were identified. One study on clinical validity was identified, which reported that the IHC4 score is a highly significant predictor of distant recurrence. No prospective studies of the impact of IHC4 on long-term outcomes such as overall survival, or its ability to change treatment decisions or predict chemotherapy benefit weere identified. In summary, the guidance authors concluded that the evidence base for IHC4 is currently limited to clinical validity (prognostic ability), although this evidence is considered to be relatively robust.

Mammostrat®

The guidance authors did not identify any specific studies on the analytical validity of Mammostrat®, although some limited evidence on analytical validity was reported in studies of clinical validity and clinical utility. Three studies were identified that provided data to support the use of Mammostrat® as an independent prognostic tool for women with ER+, tamoxifen-treated breast ceancer. Although the evidence base for Mammostrat® is at present relatively limited, these studies included a large sample size and appeared to be of reasonable quality. No prospective studies of the impact of Mammostrat on long-term outcomes such as overall survival were identified. Clinical utility data on Mammostrat® from 1 study suggests that the low- and high-risk groups benefit from chemotherapy, but not the intermediate-risk group. There was no published evidence on reclassification of risk groups compared with conventional means of risk classification, and no evidence on the impact of the test on clinical decision-making.

Recommendations

Oncotype DX® is recommended as an option for guiding adjuvant chemotherapy decisions for people with oestrogen receptor positive (ER+), lymph node negative (LN−) and human epidermal growth factor receptor 2 negative (HER2−) early breast cancer if:

- The person is assessed as being at intermediate risk and information on the biological features of the cancer provided by Oncotype DX® is likely to help in predicting the course of the disease and would therefore help when making the decision about prescribing chemotherapy and
- The manufacturer provides Oncotype DX® to NHS organizations according to the confidential arrangement agreed with NICE.
- The analysis leading to this recommendation was based on intermediate risk of distant recurrence being defined as a NPI score above 3.4. It is anticipated that an NPI score can be simply calculated from information that is routinely collected about people with breast cancer. Other decision-making tools or protocols are also currently used in the NHS and these may also be used to identify people at intermediate risk.
- MammaPrint®, IHC4, and Mammostrat® are only recommended for use in research in people with ER+, LN− and HER2− early breast cancer, to collect evidence about

DRAFT

potentially important clinical outcomes and to determine the ability of the tests to predict the benefit of chemotherapy. The tests are not recommended for general use in these people because of uncertainty about their overall clinical benefit and consequently their cost effectiveness.

CADTH (2014): Oncotype DX in Women and Men with ER-Positive, HER2-Negative Early Stage Breast Cancer who are either Lymph Node Negative or Lymph Node Positivee

Lymph Node Negative Disease

The evidence base for the use of Oncotype DX® in women with ER+ HER2- LN- early stage breast cancer to eguide adjuvant chemotherapy treatment decisions includes four recent examples of secondary research (health technology assessments and systematic reviews) and four additional priemary studies. There is no evidence related specifically to men. Results consistently show about 30% of treatment plans are affected, primarily being lower rates of adjuvant chemotherapy for patients determined to be at low recurrence risk. For a smaller proportion determined to be at higher risk, adjuvant chemotherapy is suggested where initial treatment planning did not include it. The most uncertainty relates to the intermediate risk category where evidence is unclear; a large 7-country study (TAILORx) is focusing on the treatment of this group with study completion planned for late 2017.

Lymph Node Positive Disease

A single UK National Institute for Health Research (NIHR) health technology assessment (HTA) by Ward et al. published in October 2013, which reviewed nine gene expression profiling and expanded immunohistochemistry tests used in the adjuvant treatment setting of breast cancer was included in this review. In addition to identifying new evidence, Ward et al. summarized two previous systematic reviews on the topic by Marchionni et al. (all LN- studies) and Smartt. (mix of LN- and LN+ studies). A total of three trials from the HTA were identified that looked at the LN+ population in isolation; the remainder of the evidence applied to the LN- or the undifferentiated (LN-/LN+) population. Smartt included a nested case control study by Goldstein et al. (n=465, LN-/LN+; 1-3 nodes: 43.6%) which examined clinical validity; in the subgroup of LN+ patients, Oncotype DX was found to better predict relapse at 5 years in chemotherapy/hormonal therapy-treated patients than usual clinical features. Two other retrospective cohort studies were identified by Ward et al. Dowsett et al. (n=1231, LN-/LN+; LN+: 25%) also examined clinical validity in the subgroup of LN+ patients and found that the Oncotype DX recurrence score was significantly associated with time to distant recurrence (HR 3.47, 95% CI 1.64 to 7.38; $P < 0.002$). Albain et al. looked at clinical utility in an exclusively LN+ population. RS was found to be prognostic in the tamoxifen alone group (HR 2.64, 95% CI 1.33 to 5.27; $p = 0.006$); there was no benefit of chemotherapy found with a low RS, but improved disease-free survival when RS was high (adjusted HR 0.59, 95% CI 0.35 to 1.01; $P = 0.033$).

In summary, the clinical effectiveness of Oncotype DX®, as defined by its clinical validity and clinical utility in the population of early invasive breast cancer that is ER+, HER2-, and LN+, remains uncertain as only three trials were identified, and they are limited by their retrospective designs.

DRAFT

BCBS (2014). Gene Expression Analysis for Prostate Cancer Management.

Evidence overview: Prostate Cancer

Clinical background

Prostate cancer is the second most common cancer diagnosed among men in the U.S. According to the National Cancer Institute, nearly 240,000 new cases are expected to be ediagnosed in the U.S. in 2013, associated with around 30,000 deaths. Localized prostate cancers meay appear clinically very similar at diagnosis. However, they often exhibit diverse risk of progression that may not be captured by accepted clinical risk categories (e.g., D'Amico criteria) or prognostic tools that are based on clinical findings, including prostate-specific antigen (PSA) titers, Gleason grade, or tumor stage. This creates uncertainty whether or not to treat immediately. A patient may choose definitive treatment comprising radiotherapy, surgery, chemotherapy, or androgen deprivation. Alternatively, the patient may forgo immediate therapy and continue regular monitoring until signs or symptoms of disease progression are evident, at which point curative treatment is instituted. This approach is referred to as "active surveillance." Given the unpredictable behavior of early prostate cancer, additional prognostic tests are under investigation. These include gene expression profiling using RTPCR-based technology. Gene expression profiling refers to analysis of mRNA expression levels of many genes simultaneously in a tumor specimen.

Technology description

Two gene expression profiling tests are now offered, intended to biologically stratify prostate cancers: Prolaris® (Myriad Genetices, Salt Lake City, UT) and Oncotype Dx® Prostate Cancer Assay (Genomic Health, Redwood City, CA). Both use archived tumor specimens as the mRNA source, reverse transcriptase polymerase chain reaction amplification, and a low density RTPCR array platform. Prolaris® is used to quantify expression levels of 31 cell cycle progression (CCP) genes and 15 housekeeper genes to generate a CCP score. Oncotype Dx® Prostate is used to quantify expression levels of 12 cancer-related and 5 reference genes to generate a Genomic Prostate Score (GPS). In the final analysis, the CCP score (median 1.03, interquartile range 0.41–1.74) and GPS (range 0–100) are combined in proprietary algorithms with clinical risk criteria (PSA, Gleason grade, tumor stage) to generate new risk categories (e.g., recelassification) intended to reflect biological indolence or aggressiveness of individual lesions, and thus inform management decisions.

Evidence review

The review sought to answer the primary question: what is the incremental value of gene expression tests for discriminating men with aggressive and indolent disease to guide treatment decisions that improve net health outcomes?

Analytic Validity

No specific information on the analytic validity of Prolaris® or Oncotype Dx® Prostate in the peer-reviewed literature, through an Internet search for grey literature, or on the developers' websites was identified. The FDA website does not contain specific information on either test.

DRAFT

Clinical Validity

Prolaris®

One retrospective validation study on Prolaris® is based on patients (n=349) culled from 6 cancer registries in Great Britain. The study was designed to examine the clinical validity of the test showing association between a CCP gene expression score combined with clinical risk factors (PSA, Gleason score), and risk of prostate cancer death at 10 years post-diagnosis. The test was performed using micro-dissected tissue prepared from archived tumor specimens obtained through needle biopsy. A primary univariate analysis suggests that a 1-unit increase in CCP score was associated with a 2-fold increase in the hazard ratio for death from prostate cancer (hazard ratio=2.02, 95% confidence interval: 1.62 to 2.53, p<10-9). Three other studies of the Prolaris® CCP gene expression test were identified. Two used archived pathological specimens obtained from patients who underwent radical prostatectomy or transurethral resection of the prostate. The role of CCP analysis in those studies was to prognosticate for biochemical recurrence or prostate-specific mortality following treatment or watchful waiting, respectively. A third study reported results of CCP analysis as adjunct to clinical criteria to predict biochemical recurrence in men who underwent external-beam radiotherapy. The patients and management approaches in these studies do not represent the population of interest or address the primary question asked in this review.

Oncotype Dx® Prostate

No full-length peer-reviewed publications on the Oncotype Dx® Prostate test were identified. The developer's website contains information on a validation study to evaluate this test in needle biopsy specimens in a cohort of men in the United States. This study was presented at the 2013 annual meeting of the American Urological Association and had not been published. It evaluated the test in men who could be considered for active surveillance, and who would be representative of patients in contemporary practice. They report that a combination of the GPS from the test and clinical findings (e.g., PSA level, Gleason score) identified patients in specific risk categories and allowed reclassification between groupings as shown in Table 1. However, the number of patients correctly or incorrectly classified between all three categories cannot be ascertained.

Table 1. Reclassification of Prostate Cancer Risk Categories With Oncotype Dx® Prostate

NCCN Risk Level	Number of Patients Using Clinical Assessment (%)	Number of Patients Using GPS Plus Clinical Assessment (%)
Very low	37 (10)	100 (26)
Low	191 (49)	119 (31)
Intermediate	160 (41)	169 (44)

DRAFT

Clinical Utility

No published evidence on the clinical utility of the Prolaris® or Oncotype Dx® Prostate test was identified. In summary, direct evidence is insufficient to establish the analytic validity, clinical validity, or clinical utility of either test.

EVIDENCE OVERVIEW: OTHER CANCERS

AHRQ (2014): Prognosis in Multiple Cancers

Clinical background

Molecular pathology tests that identify pathogenic mutations and cytogenetic translocations help define the molecular subtypes of common cancers. Because several of these acquired mutations/translocations may predict response to specific therapies, screening tests for "targetable" mutations are now commonly available. It is unclear whether these test results can also serve as independent prognostic factors. This review aims to clarify the value of certain molecular pathology tests for improving estimates of prognosis for common cancers (breast, lung, colon, urinary bladder). The main purpose of this review is to determine whether these tests improve estimation of prognosis (for recurrence), affect physician decision making, and/or improve clinical outcomes when compared with traditional assessment of prognosis of recurrence. These genetic tests are used in two different contexts. In one, the tests are used in a specific context of a diagnostic/therapy combination, where the diagnostic test is being used to predict response to a very specific treatment. In the second context, the genetic tests are used to estimate the patient's prognosis, and physicians use this prognostic information to choose from a variety of different treatment options. This report evaluates the second context. Therefore, studies that evaluate specific diagnostic/therapy combinations are excluded from this report.

The following tests are under consideration for this assessment: microsatellite instability (MSI) for colorectal cancer (CRC), MLH1 promoter methylation for CRC, KRAS mutations for CRC, BRAF mutations for CRC, Oncotype DX Colon® mRNA expression for CRC, Oncotype DX Breast® mRNA expression for breast cancer, MammaPrint® mRNA expression for breast cancer, ALK cytogenetics for lung cancer, EGFR mutations for lung cancer, KRAS mutations for lung cancer, and UroVysion cytogenetics for urinary bladder cancer.

Evidence review

No studies directly addressed the overarching question of whether the addition of the specified molecular pathology tests used alone or in combination with traditional prognostic factors changes physician decision making and improves outcomes. In addition, no studies addressed whether modified decisions lead to improved health outcomes.

Analytic Validity

Included studies provide some evidence regarding analytic validity for all of the included tests. Data from included studies was supplemented with proficiency tests results provided by the College of American Pathologists (CAP) for five tests for which this data was available. Data on intra- and interlab reproducibility is available in the primary literature and through national organization proficiency testing programs. The College of American Pathologists sends

DRAFT

proficiency test unknowns to CLIA-approved US clinical laboratories or International clinical laboratories, an excellent mechanism for assessing nationwide interlab reproducibility. The three most recent surveys for each of these analytes showed average accuracy rates of 95% for EGFR, 98% for KRAS, 99% for BRAF, 99% for MSI, and 99% for UroVysion™.

Clinical Validity

Included studies provided some evidence on clinical validity for nine of the included tests, adjusted for known prognostic factors (Table 2). Evidence from multiple studies supports clinical validity, with added value beyond traditional prognostic factors, for MammaPrint®, Oncotype DX Breast®, KRAS mutation testing for lung cancer, BRAF mutation testing for CRC, KRAS mutation testing for CRC, and MSI for CRC for at least one outcome [risk of recurrence (RR), cancer-specific survival (CSS), or overall survival (OS)]. For UroVysion™, limited evidence from 2 small studies (total N=168) rated as low or medium risk of bias supported prognostic value for RR. EGFR lung cancer did not add prognostic value to the traditional factors used to determine prognosis. For CRC, evidence did not adequately support added prognostic value for Oncotype DX Colon®. The metric used to assess the clinical validity of the test for recurrence, CSS, or OS in all of these studies was the hazard ratio (HR), which in this report range from 0.57 to 3.93. If the test is non-informative, it would be expected that the probability of experiencing the end point would be the same for either group, with a HR of 1. If the HR is greater than 1, the probability of the endpoint is higher in the group with the higher hazard. If the HR is lower than 1, the probability of experiencing the endpoint is lower in the group with the lower hazard. For example, an HR of 2 for CSS indicates that one group (e.g., those with high risk results for Oncotype DX Breast®) has twice the rate per unit of time as the comparison group (e.g., those with low-risk test results).

Table 2. Summary of Findings on Clinical Validity

Test: Cancer	Outcome	N studies/ N subjects	Results (95% Confidence Interval)
MammaPrint®: Breast	RR	6/1913	HR: 2.84 (2.11 to 3.89) for poor prognosis vs. good prognosis
	CSS	5/1615	HR: 3.3 (2.22 to 4.9) for poor prognosis vs. good prognosis
	OS	1/144	HR: 1.67 (0.73 to 3.82) for poor prognosis vs. good prognosis
Oncotype DX®: Breast	RR	6/3222	HR: 2.97 (2.19 to 4.02) for high risk vs. low risk
	CSS	2/1234	HR: 2.02 (1.35 to 3.00) for high risk vs. low risk
	OS	1/668	HR: 1.65 (1.24 to 2.19) for high risk vs. low risk
EGFR: Lung	RR	6/1870	HR: 0.87 (0.65 to 1.15); No association
	CSS	0	N/A
	OS	6/ 1820	HR: 0.76 (0.50 to 1.19); No association
KRAS: Lung	RR	4/611	2.84 (1.14 to 7.1) KRAS mutation associated

DRAFT

Test: Cancer	Outcome	N studies/ N subjects	Results (95% Confidence Interval)
			with greater RR
	CSS	0	N/A
	OS	2/253	2.69 (1.91 to 3.8); 3.33 (1.03 to 10.82)
BRAF: CRC	RR	5/4106	HR 1.07 (0.76 to 1.52) for wild-type vs. mutation
	CSS	7/5409	HR 1.50 (1.26 to 1.77) for wild-type vs. mutation
	OS	11/7610	HR 1.45 (1.29 to 1.62) for wild-type vs. mutation
KRAS: CRC	RR	5/4085	HR 1.02 (0.91 to 1.14) for wild-type vs. mutation
	CSS	2/1174	HR 1.30 (1.02 to 1.66) for wild-type vs. mutation
	OS	10/5328	HR 1.22 (0.93 to 1.60) for wild-type vs. mutation
MSI: CRC	RR	10/7130	HR 0.60 (0.50 to 0.72) for MSI-H vs. MSS
	CSS	6/3439	HR 0.65 (0.51 to 0.82) for MSI-H vs. MSS
	OS	12/8839	HR 0.57 (0.43 to 0.77) for MSI-H vs. MSS
Oncotype DX®: CRC	RR	1/690	HR 1.68 (1.18 to 2.38)
	CSS	0	N/A
	OS	0	N/A
UroVysion™: Bladder	eRR	2/168	Association between mutation and RR in 2 small studies
	CSS	0	N/A
	OS	0	N/A

Clinical Utility

The evidence was insufficient to answer the overarching question for most tests. Even in the cases where the tests seemed to add value in determining prognosis (e.g., evidence of clinical validity), no evidence was identified that suggested using the test was related to improved outcomes for patients. For a few tests (EGFR for lung cancer, BRAF for colorectal cancer and KRAS for colorectal cancer), there was low SOE suggesting that using the test would not improve outcomes for patients, since if there is a lack of clinical validity, it is unlikely that the tests will be found to have clinical utility. For impact on treatment decisions, there was moderate SOE that one test, Oncotype DX Breast®, leads to changes in decisions. Although the decision changes were observed in both directions for individual patients, studies consistently showed an overall shift to less-intensive treatment recommendations as a result of using Oncotype DX

Breast®, with fewer recommendations for chemotherapy. In these situations, there is less exposure to potential harms of chemotherapy, however, the studies did not follow patients to actually report on harms or to assess the overall balance of clinical benefits and harms. One study of low or medium risk of bias was found for the impact of MammaPrint® on treatment decisions; the authors concluded that evidence was insufficient to determine the impact of MammaPrint® on treatment decisions, primarily because of unknown consistency and imprecision.

BCBS (2013): Multiple Molecular Testing of Cancers to Identify Targeted Therapies

Clinical Background

Measurement of genetic or other molecular markers in cancer tissue is established in the deiagnosis, staging, and treatment of cancer. Currently, there is interest in the utility of measuring a large number of molecular markers at a single time in order to identify a treatment which targets the biological pathway involving that molecular marker. The available methods, or assays, may include molecular markers that individually might be indicated for a specific cancer, but are not indicated for most cancers. This may result in a different treatment than usually selected for a patient based on the type of cancer and its stage.

The use of multiple molecular testing to select targeted therapy is based on a shift in thinking about cancer behavior and treatment. Rather than thinking about cancer based on site and histology, molecular markers represent biological pathways that may be common across cancers. Choosing treatment based on these biological pathways is hypothesized to be a better method of selecting treatment.

Use of multiple molecular markers to select treatment can generally be categorized in two ways. Performing a large number of tests might increase the probability of a positive test, which indicates possible susceptibility of the cancer to a targeted therapy usually not indicated for that particular cancer. Alternatively, the results of large numbers of tests might be integrated in some manner to construct an interlinked biologic pathway for that particular cancer, thereby providing insight into a potentially more effective targeted therapy for that particular patient.

A variety of techniques are used to profile cancers. Several of the commercially available panels combine different techniques. Some provide highly related or what might be considered redundant information regarding the tumor. Because of rapid changes in technology and the development of novel methods, the actual technique employed may be less relevant than the nature of the information derived from the test. Some types of information such as presence of specific mutations can be obtained from several different techniques. The authors state that it is beyond the scope of their report to detail the many different panels that are commercially available at the time the report was written. This report also does not evaluate the use of multiple molecular testing in the setting where such tests have been selected and combined in a specific computational model to create a single “test” used for prognosis or treatment selection, such as Oncotype DX.

DRAFT

Evidence Review

Three published studies, including a variety of cancers (breast, colon, ovarian, melanoma, thyroid, miscellaneous) report health outcomes for patients whose treatments were selected using multiple molecular marker panels. Two of the studies compare the time to progression on the targeted treatment to the time to progression on the most recently failed treatment. This is not an established measure of efficacy or treatment response. One study compares patients who had targeted treatment to another group of patients who did not have targeted treatment. This study was not randomized and thus may be subject to confounding. In two of the studies, subjects were given targeted treatments in Phase I trials. Outcomes of these patients could be dependent on the experimental treatment rather than the selection strategy. In summary, use of multiple molecular testing to assist in making treatment decisions for cancer patients is rapidly evolving. Strong evidence of clinical effectiveness of this approach is not available, and a number of issues remain to be solved, particularly patient selection.

Supplemental Evidence Searches

Based on expert testimony, the Health Technology Assessment Subcommittee identified three specific tests for additional evidence review: BRAF for melanoma, EGFR for lung cancer, and KRAS for colorectal cancer. BRAF testing in melanoma was not addressed in any other core sources, while EGFR for lung cancer and KRAS for colorectal cancer were both found by AHRQ to lack clinical utility based on low SOE.

Evidence for BRAF testing in melanoma

A Special Report published by BCBS in 2011 investigated the targeted drug design and companion test co-development of vemurafenib (a BRAF inhibitor that targets a mutated form of the BRAF kinase) and the cobas® 4800 BRAF V600 Mutation Test real-time polymerase chain reaction (PCR) test. The primary evidence of clinical validity and utility for the cobas 4800 BRAF V600 Mutation Test is provided by the Phase III clinical trial of vemurafenib, which also supported the FDA approval of the drug.

The Phase I single-arm clinical trial of vemurafenib used a prototype assay to detect BRAFV600E mutations in enrolled patients. After dose determination, the extension phase of the study resulted in 81% of 32 patients responding according to Response Evaluation Criteria in Solid Tumors (RECIST); nearly all were partial responses. The Phase II single-arm clinical trial is currently ongoing; interim results presented at a meeting showed a 53% objective response rate, median progression-free survival of 6.7 months, and median overall survival not reached at the time of analysis. Patients were selected for enrollment based on a finalized version of the cobas 4800 BRAF V600 Mutation Test.

The Phase III comparative trial of vemurafenib versus standard chemotherapy (dacarbazine) also enrolled patients based on the results of the finalized companion test. At a planned interim analysis, the results met the specified criteria for primary endpoints, and patients in the dacarbazine treatment arm were allowed to cross over to vemurafenib. At this time, median survival had not been reached; the hazard ratio for death was 0.37 (95% CI: 0.26–0.55). At 6 months, overall survival was 84% (95% CI: 78 to 89) for vemurafenib-treated patients and 64% (95% CI: 56 to 73) for dacarbazine-treated patients. Progression-free survival was evaluable in

549 patients; the hazard ratio for tumor progression was 0.26 (95% CI: 0.20–0.33). The median progression-free survival was estimated to be 5.3 months for patients treated with vemurafenib and 1.6 months for patients treated with dacarbazine. Tumor response was evaluable in 439 patients; the objective response rate was 48% in patients treated with vemurafenib versus 5% in those treated with dacarbazine. Only 2 patients treated with vemurafenib had a complete response.

Extended follow-up of this trial was published in 2014 by McArthur and colleagues. Median overall survival was significantly longer in the vemurafenib group than in the dacarbazine group (13.6 months [95% CI 12.0–15.2] vs 9.7 months [7.9–12.8]; hazard ratio [HR] 0.70 [95% CI 0.57–0.87]; p=0.0008), as was median progression-free survival (6.9 months [95% CI 6.1–7.0] vs 1.6 months [1.6–2.1]; HR 0.38 [95% CI 0.32–0.46]; p<0.0001). For the 598 (91%) patients with *BRAF* V600^{E} disease, median overall survival in the vemurafenib group was 13.3 months (95% CI 11.9–14.9) compared with 10.0 months (8.0–14.0) in the dacarbazine group (HR 0.75 [95% CI 0.60–0.93]; p=0.0085); median progression-free survival was 6.9 months (95% CI 6.2–7.0) and 1.6 months (1.6–2.1), respectively (HR 0.39 [95% CI 0.33–0.47]; p<0.0001). For the 57 (9%) patients with the more uncommon *BRAF* V600^{K} disease, median overall survival in the vemurafenib group was 14.5 months (95% CI 11.2–not estimable) compared with 7.6 months (6.1–16.6) in the dacarbazine group (HR 0.43 [95% CI 0.21–0.90]; p=0.024); median progression-free survival was 5.9 months (95% CI 4.4–9.0) and 1.7 months (1.4–2.9), respectively (HR 0.30 [95% CI 0.16–0.56]; p<0.0001). The most frequent grade 3–4 events were cutaneous squamous-cell carcinoma (65 [19%] of 337 patients) and keratoacanthomas (34 [10%]), rash (30 [9%]), and abnormal liver function tests (38 [11%]) in the vemurafenib group and neutropenia (26 [9%] of 287 patients) in the dacarbazine group. Eight (2%) patients in the vemurafenib group and seven (2%) in the dacarbazine group had grade 5 events.

The results of the Phase III trial, supported by the results of the earlier trials, support the clinical validity and clinical utility of the cobas 4800 BRAF V600 Mutation Test, the companion diagnostic test for vemurafenib. Using the test to select patients for treatment results in improved outcomes compared to the usual standard of care, dacarbazine. In addition, comparison of these results with the trial results of the recently approved ipilimumab, suggests that treatment with vemurafenib results in improved outcomes compared to ipilimumab. Ipilimumab is notable as the first therapy to show a survival advantage in a Phase III trial for patients with advanced melanoma, and while vemurafenib was in clinical trials, may have become the new treatment standard for late stage disease and thus is an important comparator.

Evidence for EGFR testing in lung cancer

The 2014 AHRQ report referenced above concluded that “EGFR lung cancer did not add prognostic value to the traditional factors used to determine prognosis.” However, other authors have drawn different conclusions. A diagnostics guidance from NICE (2013) concluded that epidermal growth factor receptor tyrosine kinase (EGFR-TK) mutation testing is indicated in adults with previously untreated, locally advanced or metastatic non-small-cell lung cancer (NSCLC). Clinical trials have shown that patients with EGFR-TK mutation-positive tumours gain more benefit from treatment with EGFR-TK inhibitors than from standard chemotherapy treatment. Conversely, patients with EGFR-TK mutation-negative tumours gain more benefit

DRAFT

from standard chemotherapy than from EGFR-TK inhibitors. However, there was no consensus on which laboratory test should be used for clinical decision-making.

A clinical effectiveness review by CADTH (Mujoomdar 2010) concluded that PCR-based tests are likely useful for identifying patients with NSCLC who are likely to respond to treatment with a TKI, and notes that in December 2009, Health Canada approved the TKI gefitinib as a first-line treatment for patients with locally advanced or metastatic NSCLC who also have activating mutations in the EGFR gene.

Evidence for KRAS testing in colorectal cancer

The 2014 AHRQ report concluded that there was low SOE suggesting that using this test would not improve outcomes for patients, since if there is a lack of clinical validity, it is unlikely that the tests will be found to have clinical utility. Other authors have suggested that, although testing may not improve mortality in colorectal cancer, it may save patients from unnecessary treatment by identifying those who are unlikely to benefit from anti-epidermal growth factor receptor monoclonal antibody therapy. A 2010 AHRQ report on selected pharmacogenetic tests for cancer treatment (Terasawa 2010) included 47 eligible studies and concluded that when treated with anti-EGFR antibodies, patients with KRAS mutations were less likely to experience treatment benefit, compared to patients whose tumors were wild-type for KRAS mutations, for all outcomes assessed. These results were confirmed in several RCT-based analyses of progression-free survival that demonstrated a significant treatment-by-KRAS mutation interaction in three out of the four cases where such analyses were reported. The direction of effect was consistent among studies, and formal significance was achieved in the majority of individual studies that reported information on the clinically relevant outcomes of overall and disease-free survival.

A working group convened by Evaluation of Genomic Applications in Practice and Prevention (EGAPP) found that, for patients with metastatic colorectal cancer who are being considered for treatment with cetuximab or panitumumab, there is convincing evidence to recommend clinical use of KRAS mutation analysis to determine which patients are KRAS mutation positive and therefore unlikely to benefit from these agents before initiation of therapy. The level of certainty of the evidence was deemed high, and the magnitude of net health benefit from avoiding potentially ineffective and harmful treatment, along with promoting more immediate access to what could be the next most effective treatment, is at least moderate.

EVIDENCE SUMMARY

For breast cancer, there is moderate quality evidence that Oncotype DX® has adequate analytic validity, clinical validity and clinical utility, at least in intermediate risk women. A similar statement cannot be made for the other gene profiling tests: Mammaprint® has reasonable evidence of clinical validity but insufficient evidence pertaining to clinical utility. The evidence base for IHC4 is limited to clinical validity (no evidence on analytic validity or clinical utility). For Mammostrat®, evidence from three studies suggests adequate clinical validity, however evidence on clinical utility is limited to one study, and is considered insufficient.

This evidence primarily pertains to women with lymph node negative breast cancer. The evidence for lymph node positive cancer is limited to Oncotype DX®, for which only 3 studies

were identified, and clinical utility is uncertain as most women with lymph node positive cancer will receive chemotherapy regardless.

For prostate cancer, there is no analytic validity or clinical utility evidence for either approved test (Prolaris® or OncotypeDX Prostate®). Evidence on the clinical validity is also quite limited for both tests.

For other cancers, AHRQ 2014 found insufficient evidence to suggest that use of any evaluated gene profiling test would result in improved outcomes for patients; but concluded that a low strength of evidence suggests ~~supports that the following tests would not be useful, since they did not demonstrate~~ an absence of clinical validity~~:~~ for EGFR for lung cancer, BRAF for colorectal cancer and KRAS for colorectal cancer. A supplemental MEDLINE search on EGFR for lung cancer and KRAS for colorectal cancer revealed that

~~However,~~ other authors have reached different conclusions ~~on EGFR for lung cancer and KRAS for colorectal cancer~~. Lung cancer patients with wild-type EGFR-TK are more likely to benefit from standard chemotherapy, while patients with mutated EGFR-TK are more likely to respond to targeted gene inhibitors (hence it has demonstrated clinical utility). Colorectal cancer patients with KRAS mutations are unlikely to benefit from anti-EGFR antibodies such as cetuximab or panitumumab – the test has clinical utility in helping to avoid unhelpful treatments. A supplemental search was also conducted for BRAF testing for melanoma, which was not addressed by AHRQ. BRAF testing to select melanoma patients for treatment with a targeted BRAF inhibitor results in improved outcomes compared to the usual standard of care, according to results of a Phase III trial (clinical utility).

There is insufficient evidence of clinical effectiveness pertaining to the use of multiple molecular testing to select targeted therapy in a variety of cancers.

DRAFT

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
Oncotype DX® (lymph node - breast)	Analytic validity: Yes Clinical validity: Yes Clinical utility: Yes ~~Sufficient evidence of clinical validity and utility;~~ Change in treatment decision in ~1/3rd of patients	Moderate#	~~Low~~Moderate, this cost may be offset by the change in treatment decisions	Moderate variability	Recommended for coverage *(strong recommendation)*	There is sufficient moderate quality evidence that there is change in treatment planning, with greater benefit and fewer harms, and resource use is significant but likely justified.
Oncotype DX® (lymph node + breast)	Analytic validity: Yes Clinical validity: Yes Clinical utility: Yes ~~Some evidence of clinical validity and utility~~	Low#	~~Low~~ Moderate	Moderate variability	Do not recommend (*weak recommendation*)	There is some evidence of analytic, clinical validity and clinical utility but it is uncertain how the information will change management,and the test involves

DRAFT

Indication/ Intervention	Balance between desirable and undesirable effects	Quality of evidence*#	Resource allocation	Variability in values and preferences	Coverage recommendation	Rationale
						significant cost. Expert opinion indicates women with lymph positive breast cancer receive chemotherapy regardless of test results. Therefore, additional utility of obtaining this test at this time is unclear, hence a recommendation for noncoverage.
Mammaprint® (breast)	Analytic validity: Insufficient Clinical validity: Yes Clinical utility: Insufficient ~~Unknown~~	Very low#	~~Unknown~~ Moderate	Low variability	Do not recommend (*weak recommendation*)	There is insufficient evidence, unknown benefit/risks and available alternatives.
IHC4 (breast)	Analytic validity: Insufficient Clinical validity: Yes Clinical utility: Insufficient ~~Unknown~~	Very low#	~~Unknown~~ Low	Low variability	Do not recommend (*weak recommendation*)	There is insufficient evidence of harms/benefits and there are available alternatives.
Mammostrat®	Analytic validity:	Very low#	~~Unknown~~	Low variability	Do not recommend (*weak*	There is insufficient evidence of

DRAFT

Indication/ Intervention	Balance between desirable and undesirable effects	Quality of evidence*#	Resource allocation	Variability in values and preferences	Coverage recommendation	Rationale
(breast)	Insufficient Clinical validity: Yes Clinical utility: Insufficient ~~Unknown~~		Moderate		*recommendation*)	harms/benefits and there are available alternatives.
Prolaris®/ Oncotype DX® (prostate)	Analytic validity: Insufficient Clinical validity: Insufficient Clinical utility: Insufficient ~~Unknown~~	Very low*	~~Unknown~~ Moderate	Low variability	Do not recommend (*weak recommendation*)	There is insufficient evidence of harms/benefits and there are available alternatives.
EGFR (Lung)	Analytic validity: Yes Clinical validity: Yes Clinical utility: Yes ~~Some evidence of clinical validity and utility~~	Low*	~~Unknown~~ Moderate, this cost may be offset by change in treatment decisions	Low variability	Recommend *(strong recommendation)*	There is sufficient evidence of clinical validity and utility with less harms. While expensive, the costs may be offset by the change in treatment decisions and patients would likely desire the information.
KRAS (Lung)	Analytic validity: Yes Clinical validity: Yes Clinical utility: Insufficient	Very low*	~~Unknown~~ Low	Low variability	Do not recommend (*weak recommendation*)	There is insufficient evidence of harms/benefits and there are available

DRAFT

Indication/ Intervention	Balance between desirable and undesirable effects	Quality of evidence*#	Resource allocation	Variability in values and preferences	Coverage recommendation	Rationale
	~~Unknown~~					alternatives.
BRAF (CRC)	Analytic validity: Yes Clinical validity: No Clinical utility: Insuficient ~~No clinical validity~~	Low*	~~Unknown~~ Low	Low variability	Do not recommend (*strong recommendation*)	There is sufficient evidence it is ineffective.
KRAS (CRC)	Analytic validity: Yes Clinical validity: Insufficient Clinical utility: Yes ~~Some evidence of clinical validity and utility~~	Low*	~~Unknown~~ Low	Low variability	Recommended for coverage (*strong recommendation*)	There is sufficient evidence that it is more effective and reduces harms clinically, there is low resource allocation and low variability in values and preferences.
MSI (CRC)	Analytic validity: Yes Clinical validity: Yes Clinical utility: Insufficient ~~Unknown~~	Very low*	~~Unknown~~ Low	Low variability	Do not recommend (*weak recommendation*)	Evidence insufficient for clinical utility; available alternatives
Oncotype DX® (CRC)	Analytic validity: Yes Clinical validity: No Clinical utility: Insufficient ~~Unknown~~	Very low*	~~Unknown~~ Moderate	Low variability	Do not recommend (*weak recommendation*)	It is not clinically valid (does not appear to add any prognostic value).
UroVysion™ (Bladder)	Analytic validity: Yes	Very low*	Moderate	Low variability	Do not recommend (*weak*	There is insufficient evidence of

DRAFT

Indication/ Intervention	Balance between desirable and undesirable effects	Quality of evidence*#	Resource allocation	Variability in values and preferences	Coverage recommendation	Rationale
	Clinical validity: Yes Clinical utility: Insufficient ~~Unknown~~				*recommendation*)	harms/benefits and there are available alternatives.
BRAF (melanoma)	Analytic validity: Yes Clinical validity: Yes Clinical utility: Yes ~~Evidence of clinical validity and utility~~	~~Very low~~Low	~~Unknown~~ Low	Low variability	Recommended for coverage (*strong recommendation*)	Sufficient evidence of benefit and of harm reduction, low resource allocation and low variability in values and preferences.

*The Quality of Evidence rating was assigned by the primary evidence source

#The Quality of Evidence rating was assigned by the HERC Subcommittee

Note: GRADE framework elements are described in Appendix A.

DRAFT

POLICY LANDSCAPE

Quality measures

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

Professional society guidelines

The National Comprehensive Cancer Network produced a Task Force report pertaining to the clinical utility of tumor markers in oncology. For this report, they combined the Tumor Marker Utility Grading System (TMUGS) and the levels of evidence standards for using archived tissue to assess the level of evidence that supports a particular test. They are presented in the tables below:

Table 3 Tumor Marker Utility Grading System

Level of evidence	Definition/ Trial Design
I	Prospective, marker primary objective, well-powered or meta-analysis
II	Prospective, marker the secondary objective
III	Retrospective, outcomes, multivariate analysis
IV	Retrospective, outcomes, univariate analysis
V	Retrospective, correlation with other marker, no outcomes

Table 4 Levels of evidence standards for using archived tissue to assess the level of evidence that supports a particular test

Level of Evidence Category	Trial design required to determine clinical validity
A	Prospective, designed to address tumor marker
B	Prospective using archived samples (not designed to address tumor marker, but can accommodate)
C	Prospective observational registry (treatment and follow up not dictated)
D	Retrospective observational

DRAFT

In addition, the NCCN uses categories of evidence and consensus, outlined in Table 5:

Table 5 NCCN Categories of Evidence and Consensus

Category	Definition
1	Based upon high-level evidence, there is uniform NCCN consensus that the intervention is appropriate.
2A	Based upon lower-level evidence, there is uniform NCCN consensus that the intervention is appropriate.
2B	Based upon lower-level evidence, there is NCCN consensus that the intervention is appropriate.
3	Based upon any level of evidence, there is major NCCN disagreement that the intervention is appropriate.

For the cancers considered in this coverage guidance document, the NCCN lists levels and categories of evidence for selected tumor markers. These are outlined in Table 6.

Table 6 Tumor Markers for Selected Cancers With Accepted Clinical Utility

Cancer	Tumor Marker	Level of Evidence	Category of Evidence
Breast	ER/PR	IB	2A
	HER2	IA	2A
	Oncotype DX	Prognostic: IB Predictive: IIA	2A/ 2B
	KRAS mutations	Predictive: IB Prognostic: IIB	2A
Colon	MSI and/or MMR protein loss	Screening: IB Prognostic: IB Predictive: IIB	2A
	CEACAM5	IIC	2A
	BRAF c. 1799T>A	Prognostic: IB Predictive: IIIC	2A
	EGFR mutation	IA	1
Non-Small Cell Lung Cancer	ALK gene fusion	IIB	2A
	PSA (KLK3)	IA	2A
Prostate			

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.

DRAFT

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.
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.

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

DRAFT

APPENDIX B. APPLICABLE CODES

CODES	DESCRIPTION
ICD-9 Diagnosis Codes	
153.0	Malignant neoplasm of hepatic flexure
153.1	Malignant neoplasm of transverse colon
153.2	Malignant neoplasm of descending colon
153.3	Malignant neoplasm of sigmoid colon
153.4	Malignant neoplasm of cecum
153.5	Malignant neoplasm of appendix vermiformis
153.6	Malignant neoplasm of ascending colon
153.7	Malignant neoplasm of splenic flexure
153.8	Malignant neoplasm of other specified sites of large intestine
153.9	Malignant neoplasm of colon unspecified site
154.0	Malignant neoplasm of rectosigmoid junction
154.1	Malignant neoplasm of rectum
154.2	Malignant neoplasm of anal canal
154.3	Malignant neoplasm of anus unspecified site
154.8	Malignant neoplasm of other sites of rectum rectosigmoid junction and anus
162.2	Malignant neoplasm of main bronchus
162.3	Malignant neoplasm of upper lobe bronchus or lung
162.4	Malignant neoplasm of middle lobe bronchus or lung
162.5	Malignant neoplasm of lower lobe bronchus or lung
162.8	Malignant neoplasm of other parts of bronchus or lung
162.9	Malignant neoplasm of bronchus and lung unspecified
174.0	Malignant neoplasm of nipple and areola of female breast
174.1	Malignant neoplasm of central portion of female breast
174.2	Malignant neoplasm of upper-inner quadrant of female breast
174.3	Malignant neoplasm of lower-inner quadrant of female breast
174.4	Malignant neoplasm of upper-outer quadrant of female breast
174.5	Malignant neoplasm of lower-outer quadrant of female breast
174.6	Malignant neoplasm of axillary tail of female breast
174.8	Malignant neoplasm of other specified sites of female breast
174.9	Malignant neoplasm of breast (female) unspecified site
185	Malignant neoplasm of prostate
188.0	Malignant neoplasm of trigone of urinary bladder
188.1	Malignant neoplasm of dome of urinary bladder
188.2	Malignant neoplasm of lateral wall of urinary bladder
188.3	Malignant neoplasm of anterior wall of urinary bladder
188.4	Malignant neoplasm of posterior wall of urinary bladder
188.5	Malignant neoplasm of bladder neck
188.6	Malignant neoplasm of ureteric orifice
188.7	Malignant neoplasm of urachus

DRAFT

188.8	Malignant neoplasm of other specified sites of bladder
188.9	Malignant neoplasm of bladder part unspecified
196.0	Secondary and unspecified malignant neoplasm of lymph nodes of head face and neck
196.1	Secondary and unspecified malignant neoplasm of intrathoracic lymph nodes
196.2	Secondary and unspecified malignant neoplasm of intra-abdominal lymph nodes
196.3	Secondary and unspecified malignant neoplasm of lymph nodes of axilla and upper limb
196.5	Secondary and unspecified malignant neoplasm of lymph nodes of inguinal region and lower limb
196.6	Secondary and unspecified malignant neoplasm of intrapelvic lymph nodes
196.8	Secondary and unspecified malignant neoplasm of lymph nodes of multiple sites
196.9	Secondary and unspecified malignant neoplasm of lymph nodes site unspecified
V07.51	Use of selective estrogen receptor modulators (serms)
V07.52	Use of aromatase inhibitors
V07.59	Use of other agents affecting estrogen receptors and estrogen levels
V10.3	Personal history of malignant neoplasm of breast
V58.11	Encounter for antineoplastic chemotherapy
V84.01	Genetic susceptibility to malignant neoplasm of breast
V86.0	Estrogen receptor positive status [ER+]
V86.1	Estrogen receptor negative status [ER-]
ICD-10 Diagnosis Codes	
C18.3	Malignant neoplasm of hepatic flexure
C18.4	Malignant neoplasm of transverse colon
C18.6	Malignant neoplasm of descending colon
C18.7	Malignant neoplasm of sigmoid colon
C18.0	Malignant neoplasm of cecum
C18.1	Malignant neoplasm of appendix
C18.2	Malignant neoplasm of ascending colon
C18.5	Malignant neoplasm of splenic flexure
C18.8	Malignant neoplasm of overlapping sites of colon
C18.9	Malignant neoplasm of colon, unspecified
C19	Malignant neoplasm of rectosigmoid junction
C20	Malignant neoplasm of rectum
C21.1	Malignant neoplasm of anal canal
C21.0	Malignant neoplasm of anus, unspecified
C21.8	Malignant neoplasm of overlapping sites of rectum, anus and anal canal
C34.00	Malignant neoplasm of unspecified main bronchus
C34.10	Malignant neoplasm of upper lobe, unspecified bronchus or lung
C34.2	Malignant neoplasm of middle lobe, bronchus or lung
C34.30	Malignant neoplasm of lower lobe, unspecified bronchus or lung
C34.80	Malignant neoplasm of overlapping sites of unspecified bronchus and lung
C34.90	Malignant neoplasm of unspecified part of unspecified bronchus or lung
C50.019	Malignant neoplasm of nipple and areola, unspecified female breast
C50.119	Malignant neoplasm of central portion of unspecified female breast

DRAFT

C50.219	Malignant neoplasm of upper-inner quadrant of unspecified female breast
C50.319	Malignant neoplasm of lower-inner quadrant of unspecified female breast
C50.419	Malignant neoplasm of upper-outer quadrant of unspecified female breast
C50.519	Malignant neoplasm of lower-outer quadrant of unspecified female breast
C50.619	Malignant neoplasm of axillary tail of unspecified female breast
C50.819	Malignant neoplasm of overlapping sites of unspecified female breast
C50.919	Malignant neoplasm of unspecified site of unspecified female breast
C61	Malignant neoplasm of prostate
C67.0	Malignant neoplasm of trigone of bladder
C67.1	Malignant neoplasm of dome of bladder
C67.2	Malignant neoplasm of lateral wall of bladder
C67.3	Malignant neoplasm of anterior wall of bladder
C67.4	Malignant neoplasm of posterior wall of bladder
C67.5	Malignant neoplasm of bladder neck
C67.6	Malignant neoplasm of ureteric orifice
C67.7	Malignant neoplasm of urachus
C67.8	Malignant neoplasm of overlapping sites of bladder
C67.9	Malignant neoplasm of bladder, unspecified
C77.0	Secondary and unspecified malignant neoplasm of lymph nodes of head, face and neck
C77.1	Secondary and unspecified malignant neoplasm of intrathoracic lymph nodes
C77.2	Secondary and unspecified malignant neoplasm of intra-abdominal lymph nodes
C77.3	Secondary and unspecified malignant neoplasm of axilla and upper limb lymph nodes
C77.4	Secondary and unspecified malignant neoplasm of inguinal and lower limb lymph nodes
C77.5	Secondary and unspecified malignant neoplasm of intrapelvic lymph nodes
C77.8	Secondary and unspecified malignant neoplasm of lymph nodes of multiple regions
C77.9	Secondary and unspecified malignant neoplasm of lymph node, unspecified
Z79.810	Long term (current) use of selective estrogen receptor modulators (SERMs)
Z79.811	Long term (current) use of aromatase inhibitors
Z79.818	Long term (current) use of other agents affecting estrogen receptors and estrogen levels
Z85.3	Personal history of malignant neoplasm of breast
Z51.11	Encounter for antineoplastic chemotherapy
Z15.01	Genetic susceptibility to malignant neoplasm of breast
Z17.0	Estrogen receptor positive status [ER+]
Z17.1	Estrogen receptor negative status [ER-]
ICD-9 Volume 3 (Procedure Codes)	
32	Excision of lung and bronchus
85.2	Excision or destruction of breast tissue
85.4	Mastectomy
45.7	Open and other partial excision of large intestine
45.8	Total intra-abdominal colectomy
45.9	Intestinal anastomosis
48.4	Pull-through resection of rectum
48.5	Abdominoperineal resection of rectum

DRAFT

48.6	Other resection of rectum
57.4	Transurethral excision or destruction of bladder tissue
57.5	Other excision or destruction of bladder tissue
57.6	Partial cystectomy
57.7	Total cystectomy
60.5	Radical prostatectomy
CPT Codes	
19301	Mastectomy, partial
19302	Mastectomy, with axillary lymphadenectomy
19303	Mastectomy, simple, complete
19304	Mastectomy, subcutaneous
19305	Mastectomy, radical, including pectoral muscles, axillary lymph nodes
19306	Mastectomy, radical, including pectoral muscles, axillary and internal mammary lymph nodes
19307	Mastectomy, modified radical, including axillary lymph nodes, with or without pectoralis minor muscle but excluding pectoralis major muscle
32440	Removal of lung, pneumonectomy
32442	Removal of lung, pneumonectomy; with resection of segment o trachea followed by broncho-tracheal anastomosis
32445	Removal of lung, pneumonectomy; extrapleural
32480	Removal of lung other than pneumonectomy; single lobe
32482	Removal of lung other than pneumonectomy; 2 lobes
32484	Removal of lung other than pneumonectomy; single segment
32486	Removal of lung other than pneumonectomy; with circumferential resection of segment of bronchus followed by broncho-bronchial anastomosis
32488	Removal of lung other than pneumonectomy; with all remaining lung following previous removal of a portion of lung
32491	Removal of lung other than pneumonectomy; with resection-plication of emphysematous lung(s) for lung volume reduction, sternal split or transthoracic approach, includes any pleural procedure, when preformed
32501	Resection and repair of portion of bronchus when performed at a time of lobectomy or segmentectomy
32503	Resection of apical lung tumor including chest wall resection, rib(s) resection(s), neurovascular dissection, when performed; without chest wall reconstruction(s)
32504	Resection of apical lung tumor including chest wall resection, rib(s) resection(s), neurovascular dissection, when performed; with chest wall reconstruction(s)
44139	Mobilization (take-down) of splenic flexure performed in conjunction with partial colectomy (List separately in addition to primary procedure)
44140	Colectomy, partial; with anastomosis
44141	Colectomy, partial; with skin level cecostomy or colostomy
44143	Colectomy, partial; with end colostomy and closure of distal segment (Hartmann type procedure)
44144	Colectomy, partial; with resection, with colostomy or ileostomy and creation of mucofistula
44145	Colectomy, partial; with coloproctostomy (low pelvic anastomosis)
44146	Colectomy, partial; with coloproctostomy (low pelvic anastomosis), with colostomy
44147	Colectomy, partial; abdominal and transanal approach
44150	Colectomy, total, abdominal, without proctectomy; with ileostomy or ileoproctostomy
44151	Colectomy, total, abdominal, without proctectomy; with continent ileostomy

DRAFT

44155	Colectomy, total, abdominal, with proctectomy; with ileostomy
44156	Colectomy, total, abdominal, with proctectomy; with continent ileostomy
44157	Colectomy, total, abdominal, with proctectomy; with ileoanal anastomosis, includes loop ileostomy, and rectal muscosectomy, when performed
44158	Colectomy, total, abdominal, with proctectomy; with ileoanal anastomosis, creation of ileal reservoir (S or J), includes loop ileostomy, and rectal muscosectomy, when perfomed
44160	Colectomy, partial, with removal of terminal ileum with ileocolostomy
51570	Cystectomy, complete; (separate procedure)
51575	Cystectomy, complete; with bilateral pelvic lymphadenectomy, including external iliac, hypogastric, and obturator nodes
51580	Cystectomy, complete, with ureterosigmoidostomy or ureterocutaneous transplantations;
51585	Cystectomy, complete, with ureterosigmoidostomy or ureterocutaneous transplantations; with bilateral pelvic lymphadenectomy, including external iliac, hypogastric, and obturator nodes
51590	Cystectomy, complete, with ureteroileal conduit or sigmoid bladder, including intestine anastomosis;
51595	Cystectomy, complete, with ureteroileal conduit or sigmoid bladder, including intestine anastomosis; with bilateral pelvic lymphadenectomy, including external iliac, hypogastric, and obturator nodes
51596	Cystectomy, complete, with continent diversion, any open technique, using any segment of small and/or large intestine to construct neobladder
51597	Pelvic exenteration, complete, for vesical, prostatic or urethral malignancy, with removal of bladder and ureteral transplantations, with or without hysterectomy and/or abdominoperineal resection of rectum and colon and colostomy, or any combination thereof
55810	Prostatectomy, perineal radical;
55812	Prostatectomy, perineal radical; with lymph node biopsy(s) (limited pelvic lymphadenectomy)
55815	Prostatectomy, perineal radical; with bilateral pelvic lymphadenectomy, including external iliac, hypogastric and obturator nodes
55821	Prostatectomy (including control of postoperative bleeding, vasectomy, meatotomy, urethral calibration and/or dilation, and internal urethrotomy); suprapubic, subtotal, 1 or 2 stages
55831	Prostatectomy (including control of postoperative bleeding, vasectomy, meatotomy, urethral calibration and/or dilation, and internal urethrotomy); retropubic, subtotal
55840	Prostatectomy, retropubic radical, with or without nerve sparing
55842	Prostatectomy, retropubic radical, with or without nerve sparing; with lymph node biopsy(s) (limited pelvic lymphadenectomy)
55842	Prostatectomy, retropubic radical, with or without nerve sparing; with bilateral pelvic lymphadenectomy, including external iliac, hypogastric, and obturator nodes
55860	Exposure of prostate, any approach, for insertion of radioactive substance
55862	Exposure of prostate, any approach, for insertion of radioactive substance; with lymph node biopsy(s) (limited pelvic lymphadenectomy)
55865	Exposure of prostate, any approach, for insertion of radioactive substance; with bilateral pelvic lymphadenectomy, including external iliac, hypogastric, and obturator nodes
81210	BRAF (v-raf murine sarcoma viral oncogene homolog B1) (eg colon cancer) gene analysis, V600E variant
81235	EGFR (epidermal growth factor receptor) (eg non-small lung cancer) gene analysis, common variants (exon 19 LREA deletion, L858R, T790M, G719A, G719S, L861Q)
81504	Oncology (tissue of origin), microarray gene expression profiling of > 2,000 genes, utilizing formalin-fixed paraffin-embedded tissue, algorithm reporting a risk score
83950	Oncoprotein; HER-2/neu

DRAFT

84233	Receptor assay; estrogen
84234	Receptor assay; progesterone
84999	Unlisted chemistry procedure
88239	Tissue culture for neoplastic disorders; bone marrow, blood cells
88240	Cryopreservation, freezing and storage of cells, each cell line
88241	Thawing and expansion of frozen cells, each aliquot
4179F	Tamoxifen or aromatase inhibitor
HCPCS Level II Codes	
S3854	Gene expression profiling panel for the use in the management of breast cancer treatment

Note: Inclusion on this list does not guarantee coverage

DRAFT

HERC Coverage Guidance – Biomarker tests of cancer tissue for prognosis and potential response to treatment
Disposition of Public Comments

Table of Contents

Commenters 1
Public Comments 2
References Provided by Commenters 13

Commenters

Identification	Stakeholder
A	Oncology and Genetics Clinical Nurse Specialist, Providence Cancer Center
B	Senior Director, Health Policy & Reimbursement, Roche Diagnostics Corporation North America
C	President and CEO, ZERO - The End of Prostate Cancer
D	Genetic counselor, Myriad Genetic Laboratories (which performs the Prolaris® test)
E	Urologist, Oregon Urology Institute

DRAFT

Public Comments

Ident.	#	Comment	Disposition
A	1	The National Comprehensive Cancer Network (NCCN), the American Society of Clinical Oncology (ASCO), and the European Society for Clinical Oncology (ESMO) recommend routine microsatellite instability (MSI) testing of either all colorectal (CRC) tumors, or all CRC <70 years, with MSI testing of those >70 if Bethesda guidelines are met. Universal screening for MSI identification is more sensitive than following previously established testing criteria using Bethesda and/or Amsterdam criteria (Balmana, J, et al, 2013).	NCCN guidelines are considered in the CG document. As noted in Table 6, NCCN rates evidence about MSI as category 2A, "based upon lower-level evidence, there is uniform NCCN consensus that the intervention is appropriate." Screening of colon tumor tissue may be done with either MSI or IHC testing, and IHC is considered the more cost-effective option. The AHRQ review found evidence of analytic and clinical validity for MSI testing, but did not identify evidence of improved patient outcomes. Therefore there is not yet evidence of clinical utility. There are also appropriate, perhaps more cost-effective alternatives available, therefore MSI is not recommended for coverage.
A	2	The rationale for routine MSI testing is for its potential to identify individuals with Lynch Syndrome (aka Hereditary non-polyposis colorectal cancer syndrome - HPNCC). Lynch Syndrome is inherited in autosomal dominant fashion and is estimated to be the cause of 2-4% of colorectal cancers.	This background information is correct.
A	3	MSI testing to detect Lynch Syndrome affects the care of colorectal cancer patients. The diagnosis of Lynch Syndrome is useful for determining optimal surgical management in colorectal cancer patients (Balmana, J (2013).	See comment A1. Identifying a syndrome which would affect planning and screening would be an important patient oriented outcome. However, there is an alternative available and there is currently insufficient

DRAFT

Ident.	#	Comment	Disposition
			evidence of clinical utility.
A	4	Patients with Lynch Syndrome are on average, younger at diagnosis, and MSI is associated with improved prognosis. Therefore, the identification of Lynch Syndrome affects the management of colorectal cancer survivors.	AHRQ meta-analysis of 6 studies (total N = 3439) found an overall hazard ratio for cancer-specific survival for patients with MSI-H (microsatellite instability high) tumors compared with MSS (microsatellite stability) tumors of 0.63; 95% CI, (0.51 to 0.79). Risk of bias was rated as medium. MA of 12 studies (total N = 8839) rated as low or medium risk of bias found an overall hazard ratio for overall survival for patients with MSI-H compared with MSS of 0.57; 95% CI (0.43 to 0.77). Despite these numbers, AHRQ found no direct evidence that using the test was related to improved outcomes for patients, even in the cases such as this one where tests had evidence of clinical validity. In other words, there is not yet proof of clinical utility and alternatives are available. Therefore, HTAS has made a weak recommendation against coverage.
A	5	Colorectal cancer patients with Lynch Syndrome are at significantly increased risk for 2nd primary colorectal cancers. Colonoscopy every 1-2 years is recommended by the NCCN for people with Lynch Syndrome.	This NCCN recommendation is correct. See A3.
A	6	Women with Lynch Syndrome are also at substantially increased risk for endometrial and ovarian cancer, which can be prevented with surgery after childbearing is complete.	This is correct. See A3.
A	7	In 2009, the Evaluation of Genomic Applications in Practice and Prevention (EGAPP), a CDC working group, recommended routine MSI testing of all newly diagnosed colorectal cancer. The EGAPP working group concluded that	The EGAPP report from 2009 is considered in the AHRQ review that

DRAFT

Ident.	#	Comment	Disposition
		there was sufficient evidence to support routine MSI testing of patients with newly diagnosed colorectal cancers in order to achieve improved health outcomes for their relatives.	provided the basis of this CG document (reference #1096). Discussion of MSI testing from the AHRQ review has been added to the CG document; AHRQ found insufficient evidence of clinical utility as discussed above.
A	8	In genetics, the standard of care is to consider relatives when choosing tests. This is commonly at odds with the structure of health care reimbursement in the United States. Individuals often have insurance benefits that are dependent on genetic test information from relatives. For individual patients and families at risk for Lynch Syndrome, testing colon tumors for MSI as a first step is usually less expensive and more efficient than initiating testing for germline Lynch Syndrome-causing mutations first, especially in unaffected relatives.	Commenter notes that testing tumors for MSI is more cost-effective than alternatives; no new sources are cited.
A	9	Thank you for your consideration of Oregon Health Plan coverage for routine MSI testing. Please contact me if I can be of assistance.	Thank you for your comments and willingness to assist.
B	10	Dear Health Evidence Review Commission Members: On behalf of The Roche Group ("Roche"), a global leader in research-focused healthcare with combined strengths in pharmaceuticals and diagnostics, I am pleased to submit comments in response to the draft coverage guidance from the Health Evidence Review Commission ("the Commission") entitled "Biomarker Tests of Cancer Tissue for Prognosis and Potential Response to Treatment".	Thank you for your comments.
B	11	In the draft coverage guidance, the Commission recommends (with a strong recommendation) for coverage of BRAF gene testing for melanoma and epidermal growth factor receptor (EGFR) gene mutation testing for non-small-cell lung cancer (NSCLC). Roche applauds the strong recommendation from the Commission regarding BRAF gene mutation testing for melanoma and EGFR gene mutation testing for NSCLC.	Thank you for your comments.
B	12	BRAF Test Citing a Blue Cross Blue Shield Technology Evaluation Center report, the Commission noted that the evidence supports the clinical validity and utility of the cobas® 4800 BRAF V600 Test1 in "[U]sing the test to select patients for treatment results in improved outcomes compared to the usual standard of care."	This is correct.
B	13	The Commission's recommendation is also supported by the National Comprehensive Cancer Network Guidelines (NCCN).2 The Roche cobas® 4800 BRAF V600 test received FDA approval as a test to determine the tumor mutational status and as a companion diagnostic to vemurafenib (Zelboraf™). The drug's "Indications and Usage" section of its labeling specifically notes the use of an FDA approved test: *"ZELBORAF™ is a kinase inhibitor indicated for the treatment of patients with unresectable or metastatic melanoma with BRAFV600E mutation as detected by an FDA-approved test." (3)*	This background information from NCCN is correct.

DRAFT

Ident.	#	Comment	Disposition
B	14	EGFR Test Based on its evaluation, the Commission found that there was sufficient evidence demonstrating that the test was more effective and had similar or less risk than the alternatives. While the reports referenced in the development of this guideline note the differing opinions regarding the usefulness of the test in affecting outcomes, we support the Commission's decision to give the test a strong recommendation.	Thank you for your comments.
B	15	This position is consistent with the NCCN Guidelines on NSCLC which recognize EGFR variants as critical considerations in the selection of targeted therapies for patients with NSCLC. (4)	This is correct.
B	16	The Roche cobas® EGFR Mutation Test also received FDA-approval as a companion diagnostic to erlotinib (Tarceva®) and the drug's "Indications and Usage" section of its labeling specifically notes the use of an FDA approved test: *"First-line treatment of patients with metastatic non-small cell lung cancer (NSCLC) whose tumors have epidermal growth factor receptor (EGFR) exon 19 deletions or exon 21 (L858R) substitution mutations as detected by an FDA-approved test." (5)*	Thank you for your comment. HTAS recommends coverage for EGFR in non small cell lung cancer.
B	17	The Commission's decision to support the use of BRAF and EGFR biomarker tests for the prognosis and potential response to treatment is consistent with that of numerous Medicare Administrative Contractors (MACs) including Palmetto GBA that have decided to provide coverage for these tests under the Medicare program. Palmetto administers Medicare's Molecular Diagnostics Services Program (MolDX), a program that was developed to identify and establish coverage and reimbursement for molecular diagnostic tests. Palmetto, in reviewing the clinical evidence on BRAF and EGFR, developed coverage policies specifically calling out the use of an FDA-approved companion diagnostic in order to receive coverage for the EGFR and BRAF tests.	Thank you for the information.
B	18	We appreciate the opportunity to submit comments on this draft coverage guidance and, again, strongly support the position taken by the Commission.	Thank you for your comments.
C	19	I write today on behalf of ZERO – The End of Prostate Cancer, a national nonprofit organization dedicated to ending prostate cancer. In 2015 alone, more than 228,000 men will be diagnosed with prostate cancer. More than 90 percent of these new cases will be diagnosed at an early stage when the possibility of cure is best.	Thank you for your comments.
C	20	There is a significant problem with over- and under-treatment in prostate cancer which results in some men receiving unnecessary treatments with significant side effects, and some men dying unnecessarily of prostate cancer. Risk stratification in prostate cancer is significantly improved with the addition of genomic testing tools. These tools provide valuable information about how the prostate tumor will behave and the possibility that the cancer will kill helping to shape treatment plans. The National Comprehensive Cancer Network (NCCN) guidelines suggest considering tumor based molecular testing to guide treatment, specifically Oncotype Dx for prostate and Prolaris.	The AHRQ review used as a basis for the coverage guidance found that direct evidence is insufficient to establish the analytic validity, clinical validity, or clinical utility of either test (Prolaris® or Oncotype Dx®).

DRAFT

Ident.	#	Comment	Disposition
C	21	ZERO does not endorse specific products, treatments or brands but we strongly believe that patients should have access to the full array of available tools to make an informed and educated decision about their treatment. We encourage you to approve coverage for the existing molecular tests to improve and save lives of men diagnosed with prostate cancer. As President and CEO of ZERO - The End of Prostate Cancer, I encourage you to consider the thousands of men that can be negatively impacted by not covering these tests.	Thank you for your comments.
D	22	Thank you for the opportunity to comment on HERC's draft biomarker coverage guidance; our comments are particular to Prolaris®, Myriad's prostate cancer prognostic test. We are encouraged by HERC's recognition of the need for additional prognostic tests for prostate cancer. Currently available clinical and pathologic parameters are limited in their ability to distinguish between aggressive and indolent localized prostate tumors. (1-3)	References 1-2 describe PSA as a screening tool for prostate cancer, which is outside the scope of this document. Reference 3 is a validation study of CAPRA, a risk assessment tool for cancer recurrence after radical prostatectomy. This study of 2,096 men in a military database found that "Increasing CAPRA scores were significantly associated with increasing risk of adverse pathologic outcomes."
D	23	Despite a 10-year mortality risk of only 3% (4) and knowledge that many prostate cancers do not cause death when initial management is conservative, nearly 90% of men receive definitive treatment, with the potential for significant treatment-related side effects. (5-8) Under-treatment of men with more aggressive tumors also remains a significant clinical risk. (4)	SEER reports a 98.9% survival rate at 5 years; 10-year survival was not available at the link provided in reference 4. This link also did not opine on the dangers of undertreatment. Reference 5 is a case vignette. Reference 6, Wilt 2012, is an RCT (N=731) of observation vs radical prostatectomy for localized prostate cancer, which found no significant difference in all-cause or cancer-specific mortality through 12 years of follow-up. Reference 7 is a descriptive analysis of trends in cancer treatment,

DRAFT

Ident.	#	Comment	Disposition
			highlighting substantial, unexplained variability in management. The 90% figure provided in the comment is not supported. Reference 8 is a retrospective cohort study (N=32,465) of men who underwent surgery or radiotherapy for prostate cancer, which found that complications of treatment are frequent.
D	24	Clinical validity studies in varied patient cohorts demonstrate Prolaris' consistent ability to better stratify patients based on meaningful oncologic endpoints.[9-14]	References 9, 10, 11, and 12 provide the basis for the analysis done by BCBS, which is the core source for the CG document. The authors conclude that "As a whole, the evidence on clinical validity … is insufficient." Bishoff 2014 (reference 13) was published after the BCBS search date. It is a cohort study (N=582) in which the CCP score (Prolaris® test) was performed on actual or simulated biopsy specimens, and records were analyzed for biochemical recurrence (BCR, defined as postoperative PSA greater than 0.2 ng/ml or secondary treatment [radiation or androgen therapy] for increasing PSA regardless of attaining the 0.2 ng/ml cutoff point) and metastatic disease. No other outcomes were reported (OS, DSS, etc). Because of small sample size and lack of reporting on critical outcomes,

DRAFT

Ident.	#	Comment	Disposition
			HTAS does not consider this evidence sufficient to recommend coverage. Reference 14, Cuzick 2014, is not a peer-reviewed publication.
D	25	Clinical utility studies show that physicians and patients use this new information to alter medical management based on the level of risk predicted by the Prolaris score.[15-17] Prolaris' net effect is to reduce the treatment burden for localized prostate cancer.[15-17]	BCBS did not identify any published data on clinical utility. Shore 2013 (Reference 15) was published after the BCBS search dates; however it would not have been included because it relied on a retrospective questionnaire administered to 15 community urologists. HTAS does not consider this sufficient evidence to guide coverage recommendations. Reference 16 (Crawford 2014) was done similarly, but in a pre-post style survey of clinicians treating 331 patients. It concludes that CCP testing changes treatment decisions in about 65% of cases. Number of clinicians is not stated and it is unknown how patients were selected for CCP testing. Actual treatment decisions were only available for 116 cases and showed 80% concordance with the survey. This study is not of sufficient quality to alter HTAS decision. Reference 17 (Gonzalgo 2014) is not a peer-reviewed publication.
D	26	Independent studies suggest that reducing unnecessary interventions reduces morbidity without increasing mortality.[6,18,19] This shift away from unnecessary treatments yields cost-savings to the healthcare system.	Reference 18 is a guideline panel report from 1995 and is not relevant in the current environment.

DRAFT

Ident.	#	Comment	Disposition
			Reference 19 is a simulation model of a hypothetical cohort demonstrating that active surveillance is a viable option under a wide range of assumptions. This does not inform the HTAS decision on coverage.
D	28	Prolaris received a favorable technical assessment by MolDX[22] and has been incorporated into treatment guidelines[23]. Based on this new information, we request coverage for Prolaris for beneficiaries with biopsy-proven, localized prostate cancer when a clinician requires additional patient-specific information to make treatment recommendations.	It is correct that a LCD has recommended coverage under very specific clinical conditions and only when the ordering physician is certified in the Myriad Prolaris Certification and Training Registry. NCCN states certain men "could consider" biomarker testing in its 2015 guidelines for risk stratification, stating "clinical utility awaits evaluation by prospective, randomized clinical trials, which are unlikely to be done [because the tests are being marketed under the less rigorous FDA regulatory pathway for biomarkers]."
D	29	Evidence: Analytical Validation: Prolaris has well-established analytical validity published and documented in: • Cuzick (2011)[9] (selection process for cell cycle progression genes; development of Prolaris score) Technical specifications (http://www.prolaris.com/information-for-physicians/pathology/technical-specifications/).	See comment D24, this study was considered by the core source and deemed insufficient to establish clinical validity of the test. .
D	30	Clinical Validation: Prolaris was clinically validated in nine cohorts involving >2,900 patients, published in five peer-reviewed publications[9-13] and one poster presentation[14]. The HERC review accurately states that some cohorts include management approaches	See comment D24.

DRAFT

Ident.	#	Comment	Disposition
		not representative of the population of interest; however, each study's goal was to demonstrate the Prolaris score's prognostic significance in treated patients (prostatectomy cohorts) and conservatively managed patients (TURP and biopsy cohorts). The Prolaris score was consistently predictive of meaningful oncologic outcomes (recurrence or disease-specific mortality) with similar hazard ratios around two, and multivariate analyses demonstrated the Prolaris score added significant unique, prognostic information beyond that obtained from standard clinico-pathologic variables.	
D	31	The validation cohorts/outcomes are listed below: • Cuzick (2011)[9] - 353 post-prostatectomy/biochemical recurrence; 337 conservatively managed/10-year mortality • Cuzick (2012)[10] - 349 conservatively managed/10-year mortality • Cooperberg (2013)[11] - 413 post-prostatectomy/biochemical recurrence • Freedland (2013)[12] - 141 post-radiation/biochemical recurrence • Bishoff[13] (2014 - published after the last BCBSA TEC review) – post-prostatectomy (biopsy samples)/biochemical recurrence (283) or metastatic disease (299) Cuzick (2014)[14] - 757 conservatively managed/disease specific mortality	See Comment D24. Cuzick 2011,Cuzick 2012, Cooperberg 2013, and Freedland 2013 are all considered in the core source and found to be insufficient to establish clinical validity of the test. Bishoff 2014 is a multicenter retrospective cohort study (N = 582) in which CCP score is associated with biochemical recurrence and metastatic disease. The study has methodologic limitations including lack of standardization of patient selection and biopsy methods across centers. While this study despite its limitations may support clinical validity, there is no evidence linking the CCP score to critical outcomes such as mortality. Cuzick 2014 is not a peer-reviewed publication.
D	32	Clinical Utility: The Center for Medical Technology Policy (CMTP) recognizes that prospective randomized controlled trials of molecular diagnostics in oncology may not be necessary when evidence exists linking treatment choices to patient outcomes.[20]	The source provided is a PowerPoint presentation from the Center for Medical Technology Policy and in fact states that "Under limited, specified circumstances, longitudinal observational study designs are acceptable options for

DRAFT

Ident.	#	Comment	Disposition
			assessing clinical utility," and that there must be a "compelling rationale" for not doing RCT. This rationale does not exist in prostate cancer; prospective RCTs are feasible and ethical.
D	33	CMTP suggests prospective observational studies to demonstrate clinical utility in specified circumstances, including when "there is genuine uncertainty on the part of the expert medical community regarding the preferred clinical pathway;" as is the case for localized prostate cancer. Prolaris' clinical utility is documented in two decision impact studies[15,16]. A third, larger study is underway; preliminary results were presented in poster form[17] and a manuscript has been submitted for publication. • Shore (2013)[15] - Hypothesis-generating retrospective survey of 15 urologists participating in a clinical validation trial revealed that Prolaris would have led to a change in management for 32% of the 294 cases, with a net-effect of shifting from more aggressive to more conservative treatment. • Crawford (2013)[16] – Prospective study evaluated the impact of Prolaris for 150 physicians in 31 states ordering Prolaris on prostate cancer needle biopsy specimens from 305 patients (low, intermediate and high-risk groups). Surveyed physicians reported that Prolaris influenced their decisions 98% of the time, with a change in recommendations post-Prolaris for 65% of cases. Prostatectomies were reduced by 49.5%; radiation was reduced by 29.6%. Actual treatment selections were confirmed via third-party patient chart audit. Gonzalgo[17] - PROCEDE−1000 is the largest clinically−controlled, prospective registry evaluating Prolaris' impact on prostate cancer treatment by 105 physicians from 20 states, including Oregon. In addition to physician recommendations pre- and post-Prolaris testing, physician/patient consensus treatment decisions and actual treatment administered are evaluated. Interim analysis of 816 patients shows Prolaris resulted in significant reductions in prostatectomies (27%), radiation therapy (44% primary; 56% adjuvant), brachytherapy (46% interstitial, 66% HDR) and hormonal therapy (33% neoadjuvant, 68% concurrent). For every 1-unit increase in mortality risk by Prolaris, there was an associated 3.3% rise in the odds of increase in treatment (vice-versa for decrease in treatment) (estimated OR = 1.033).	Please see above. Shore 2013 was a small retrospective survey. Crawford 2013 had a high loss to follow-up and, in those cases that were audited, an 80% concordance with actual treatment. Gonzalgo is a poster presentation that is not published in a peer-reviewed journal. It is a prospective registry of 816 patients assessing how a physician's recommended treatment was altered by CCP testing. Treatment plans changed in 44.24% of cases, with the majority (31.86%) having less treatment than initially recommended. This is an interim analysis and does not consider critical outcomes such as mortality.
D	34	Positive Technical Assessment and Medicare coverage: MolDX performs technical assessments for Medicare contractors, evaluating clinical utility, analytical validity and clinical validity based on 'ACCE' criteria developed by CDC.[21] Prolaris received a favorable evaluation by MolDx, and an LCD (MolDX: Prolaris™ Prostate Cancer Genomic Assay L35629, effective March 2, 2015) provides coverage for Medicare beneficiaries with biopsy-proven, untreated localized prostate cancer in low and very low-risk groups.[22] Additional	Please see comment D28.

DRAFT

Ident.	#	Comment	Disposition
		registry data and treatment guidelines are being reviewed to consider expanding coverage to intermediate and high-risk cohorts, since clinical validation and clinical utility studies support benefits for all risk levels.	
D	35	Societal Guidelines: National Comprehensive Cancer Network (NCCN) 2015 Prostate Cancer treatment guidelines were updated October 24, 2014 to include Prolaris.[23] Footnote 'b' on page PROS-1 suggests Prolaris be considered in the initial clinical assessment of men with clinically localized disease who are symptomatic or with a life expectancy of >5y, to better stratify risk of adverse outcome (and therefore guide treatment decisions).	NCCN states "could consider," please see Comment D28.
D	36	Cost-Benefit to Healthcare System: A system economic analysis of Prolaris demonstrated a net savings of $2,850 per patient tested over 10 years. (24) Savings result from increased use of active surveillance in low– and intermediate–risk patients, and reduced progression rates in high–risk patients with more aggressive disease who transition to multi–modality therapy. The model estimates over $1 million in savings per year for the Oregon Health Plan with the use of Prolaris for all localized prostate cancer compared with the current approach.	Reference 24 is not a peer-reviewed publication. Thank you for your comments.
E	37	I am a practicing urologist in Springfield with a large population of prostate cancer patients. I strongly urge you to consider coverage through Oregon Medicaid.	Thank you for your comments.
E	38	I have used the test for more than a year and have found it quite beneficial in the decision-making process for treatment of prostate cancer.	Thank you for your comments.
E	39	As you may know, prostate cancer is the most common malignancy in men and the second cause of cancer death.	This information is correct.
E	40	Some cancers are aggressive and need aggressive treatments. Others can be monitored without treatment. Risk stratification is key. The Prolaris test is a useful component of our decision-making process as we decide whom to treat and whom to observe. This has been recognized by the National Comprehensive Cancer Network (NCCN) in their treatment guidelines – arguably the gold standard for cancer treatment.	NCCN guidelines are discussed in the CG document under "Policy Landscape".
E	41	I appreciate your consideration in this matter	Thank you for your comments.

DRAFT

References Provided by Commenters

Commenter	References
A	1. Stoffel, E. M., Mangu, P .B, Bruber, S. B., Hamilton, S. R., Kalady, M. F., Lau, M. W. Y., … Limburg, P. J. (2015). Hereditary colorectal cancer syndromes: American Society of Clinical Oncology clinical practice guideline endorsement of the familial risk – colorectal cancer: European Society for Medical Oncology clinical practice guidelines. *Journal of Clinical Oncology, 33*(2), 209-217. http://jco.ascopubs.org/content/33/2/209.full.pdf+html
A	2. Evaluation of Genomic Applications in Practice and Prevention (EGAPP) Working Group. (2009). Recommendations from the EGAPP Working Group: Genetic testing strategies in newly diagnosed individuals with colorectal cancer aimed at reducing morbidity and mortality from Lynch syndrome in relatives. *Genetics in Medicine, 11*(1), 35-41. http://www.egappreviews.org/docs/EGAPPWG-LynchRec.pdf
A	3. Balmaña, J., Balaguer, F., Cervantes, A., & Arnold, D. (2013). Familial risk – colorectal cancer: ESMO clinical practice guidelines. *Annals of Oncology, 24*(Suppl 6), v73-v80. http://annonc.oxfordjournals.org/content/24/suppl_6/vi73.full.pdf+html
A	4. National Comprehensive Cancer Network. (2015). *Clinical practice guidelines in oncology: Colon cancer (version 2.2015).* http://www.nccn.org/professionals/physician_gls/pdf/genetics_colon.pdf
B	1. National Comprehensive Cancer Network. (2015). *Clinical practice guidelines in oncology: Melanoma (version 3.2015).* http://www.nccn.org/professionals/physician_gls/pdf/melanoma.pdf
B	2. U.S. Food and Drug Administration. (2011). *Prescribing information: Zelboraf™ (vemurafenib) tablet, oral*. http://www.accessdata.fda.gov/drugsatfda_docs/label/2011/202429s000lbl.pdf
B	3. National Comprehensive Cancer Network. (2015). *Clinical practice guidelines in oncology: Non-small cell lung cancer (version 6.2015).* http://www.nccn.org/professionals/physician_gls/pdf/nscl.pdf
B	4. U.S. Food and Drug Administration. (2014). *Prescribing information: Tarceva® (erlotinib) tablets, for oral use*. http://www.accessdata.fda.gov/drugsatfda_docs/label/2014/021743s019lbl.pdf
D	1. Welch, H. G., & Albertsen, P. C. (2009). Prostate cancer diagnosis and treatment after the introduction of prostate-specific antigen screening: 1986–2005. *Journal of the National Cancer Institute, 101*(19), 1325-9. http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2758309/pdf/djp278.pdf
D	2. Carter, H. B., Albertsen, P. C., Barry, M. J., Etzioni, R., Freedland, S. J., Greene, K. L., … Zietman, A. L. (2013). Early detection of prostate cancer: AUA Guideline. *Journal of Urology, 190*(2), 419-26. http://www.ncbi.nlm.nih.gov/pmc/articles/PMC4020420/pdf/nihms-550373.pdf
D	3. Cooperberg, M. R., Freedland, S. J., Pasta, D. J., Elkin, E. P., Presti , J. C., Jr., Amling, C .L., … Carroll, P. R. (2006). Multiinstitutional validation of the UCSF cancer of the prostate risk assessment for prediction of recurrence after radical prostatectomy. *Cancer, 107*(10), 2384-91. http://onlinelibrary.wiley.com/doi/10.1002/cncr.22262/epdf
D	4. National Cancer Institute, Surveillance and Epidemiology End Results (SEER) Program. (2012). *SEER Stat Fact Sheets: Prostate cancer.* http://seer.cancer.gov/statfacts/html/prost.html

DRAFT

Commenter	References
D	5. Walsh, P. C., DeWeese, T. L., & Eisenberger, M. A. (2007). Clinical practice. Localized prostate cancer. *New England Journal of Medicine, 357*(26), 2696-705. DOI: 10.1056/NEJMcp0706784
D	6. Wilt, T. J., Brawer, M. K., Jones, K. M., Barry, M. J., Aronson, W. J., Fox, S., … Wheeler, T. Prostate Cancer Intervention versus Observation Trial (PIVOT) Study Group. (2012). Radical prostatectomy versus observation for localized prostate cancer. *New England Journal of Medicine, 367*(3), 203-13. http://www.nejm.org/doi/pdf/10.1056/NEJMoa1113162
D	7. Cooperberg, M. R., Broering, J. M., & Carroll, P. R. (2010). Time trends and local variation in primary treatment of localized prostate cancer. *Journal of Clinical Oncology, 28*(7), 1117-1123. http://jco.ascopubs.org/content/28/7/1117.full.pdf+html
D	8. Nam, R. K., Cheung, P., Herschorn, S., Saskin, R., Su, J., Klotz, L. H. … Narod, S. A. (2014). Incidence of complications other than urinary incontinence or erectile dysfunction after radical prostatectomy or radiotherapy for prostate cancer: A population-based cohort study. *Lancet Oncology, 15*(2), 223-31. http://www.thelancet.com/pdfs/journals/lanonc/PIIS1470-2045(13)70606-5.pdf
D	9. Cuzick, J., Swanson, G. P., Fisher, G., Brothman, A. R., Berney, D. M., Reid, J. E. … Stone, S. Transatlantic Prostate Group. (2011). Prognostic value of an RNA expression signature derived from cell cycle proliferation genes in patients with prostate cancer: A retrospective study. *Lancet Oncology*, 12(3), 245-55. http://www.thelancet.com/pdfs/journals/lanonc/PIIS1470-2045(10)70295-3.pdf
D	10. Cuzick, J., Berney, D. M., Fisher, G., Mesher, D., Møller, H., Reid, J. E. … Stone, S. Transatlantic Prostate Group. (2012). Prognostic value of a cell cycle progression signature for prostate cancer death in a conservatively managed needle biopsy cohort. *British Journal of Cancer*, *106*(6), 1095-9. http://www.nature.com/bjc/journal/v106/n6/pdf/bjc201239a.pdf
D	11. Cooperberg, M. R., Simko, J. P., Cowan, J. E., Reid, J. E., Djalilvand, A., Bhatnagar, S., … Carroll, P. R. (2013). Validation of a cell-cycle progression gene panel to improve risk stratification in a contemporary prostatectomy cohort. *Journal of Clinical Oncology, 31*(11), 1428-34. http://jco.ascopubs.org/content/31/11/1428.full.pdf+html
D	12. Freedland, S. J., Gerber, L., Reid, J., Welbourn, W., Tikishvili, E., Park, J. … Stone, S. (2013). Prognostic utility of cell cycle progression score in men with prostate cancer after primary external beam radiation therapy. *International Journal of Radiation Oncology, Biology, and Physics, 86*(5), 848-53. DOI: 10.1016/j.ijrobp.2013.04.043.
D	13. Bishoff, J. T., Freedland, S. J., Gerber, L., Tennstedt, P., Reid, J., Welbourn, W. … Schlomm, T. (2014). Prognostic utility of the CCP score generated from biopsy in men treated with prostatectomy. *Journal of Urology, 192*(2), 409-14. DOI: 10.1016/j.juro.2014.02.003
D	14. Cuzick, J., Stone, S., Yang, Z. H., Reid, J., Fischer, G., Berney, D. … Scardino, P. (2014, May). *Validation of a 46-gene cell cycle progression (CCP) RNA signature for predicting prostate cancer death in a conservatively managed watchful waiting needle biopsy cohort*. Presented at the American Urological Association meeting in Orlando, Florida.
D	15. Shore, N., Concepcion, R., Saltzstein, D., Lucia, M. S., van Breda, A., Welbourn, W. … Brawer, M. K. (2014). Clinical utility of a biopsy-based cell cycle gene expression assay in localized prostate cancer. *Current Medical Research and Opinion, 30*(4), 547-53. DOI: 10.1185/03007995.2013.873398.

DRAFT

Commenter	References
D	16. Crawford, E. D., Scholz, M. C., Kar, A. J., Fegan, J. E., Haregewoin, A., Kaldae, R. R., & Brawer, M.K. (2014). Cell cycle progression score and treatment decisions in prostate cancer: Results from an ongoing registry. *Current Medical Research and Opinion*, *30*(6), 1025-31. DOI: 10.1185/03007995.2014.899208.
D	17. Gonzalgo, M. L., Boczko, J., Kella, N., Moran, B., Crawford, E. D., Davis, T. … Shore, N. (2014, December). *Impact of CCP test on personalizing treatment decisions: results from a large prospective registry of newly diagnosed prostate cancer patients*. Poster presented at the Society of Urologic Oncology meeting in Bethesda, Maryland. http://www.prolaris.com/impact-ccp-test-personalizing-treatment-decisions-results-large-prospective-registry-newly-diagnosed-prostate-cancer-patients/
D	18. Middleton, R. G., Thompson, I. M., Austenfeld, M. S., Cooner, W. H., Correa, R. J., Gibbons, R. P. … et al. (1995). Prostate Cancer Clinical Guidelines Panel Summary report on the management of clinically localized prostate cancer. The American Urological Association. *Journal of Urology, 154*(6), 2144-8.
D	19. Hayes, J. H., Ollendorf, D. A., Pearson, S. D., Barry, M. J., Kantoff, P. W., Stewart, S. T., … McMahon, P. M. (2010). Active surveillance compared with initial treatment for men with low-risk prostate cancer: a decision analysis. *Journal of the American Medical Association, 304*(21), 2373-80. http://jama.jamanetwork.com/article.aspx?articleid=186997
D	20. Deverka, P. (2013, May). *Evaluation of clinical validity and clinical utility of actionable molecular diagnostic tests in adult oncology*. Presented at the GPC-USA Inaugural Meeting. http://www.cmtpnet.org/docs/resources/Deverka_Evaluation_of_Clinical_Validity.pdf
D	21. Palmetto GBA. (2015). *MolDx.*: http://www.palmettogba.com/palmetto/MolDX.nsf/DocsCatHome/MolDx
D	22. Centers for Medicare & Medicaid Services. (2015). *Local Coverage Determination (LCD): MolDx: ProlarisTM prostate cancer genomic assay (L35629).* http://www.cms.gov/medicare-coverage-database/details/lcd-details.aspx?LCDId=35629&ContrId=229&ver=7&ContrVer=1&Cntrctr=All&UpdatePeriod=607&bc=AQAAEAAAAAAAAA%3d%3d&
D	23. National Comprehensive Cancer Network. (2015). *Clinical practice guidelines in oncology: Prostate (version 1.2015).* http://www.nccn.org/professionals/physician_gls/pdf/prostate.pdf
D	24. Crawford, D. E., Gustavsen, G., Brawer, M. K., Cole, D., & Lewine, N. (2014, December). *Evaluation of the economic impact of the CCP assay in localized prostate cancer*. Poster presented at the Society of Urologic Oncology meeting in Bethesda, Maryland. http://www.prolaris.com/information-for-physicians/publications/evaluation-economic-impact-ccp-assay-localized-prostate-cancer/

DRAFT

HEALTH EVIDENCE REVIEW COMMISSION (HERC)

COVERAGE GUIDANCE: PROTON BEAM THERAPY

Draft for HTAS meeting materials 6/11/2015

HERC Coverage Guidance

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

Proton beam therapy is/is not recommended for coverage for adult malignant brain and spinal tumors (weak recommendation).

Proton beam therapy is/is not recommended for coverage for pediatric malignant tumors (weak recommendation).

Proton beam therapy is not recommended for coverage for cancer of the bone, head and neck, esophagus, liver, lung, or prostate (*weak recommendation*).

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

Proton beam therapy is not recommended for coverage 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.

DRAFT

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).

DRAFT

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

DRAFT

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

DRAFT

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.

DRAFT

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

DRAFT

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.

DRAFT

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.

DRAFT

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.

DRAFT

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.

DRAFT

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.

DRAFT

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).

DRAFT

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.

DRAFT

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

DRAFT

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

DRAFT

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.

DRAFT

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.

DRAFT

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 net 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 brain/spinal tumors	Incremental ~~Comparable~~ benefit, fewer harms	Very Low**	Moderate, expensive, but lowered net costs due to greater benefit and fewer harms	~~Moderate~~ Low variability (preference for PBT)	Option 1 (prior recommendation): Not recommended for coverage (*weak recommendation*) Option 2 (staff recommendation): recommended for	There is very low quality evidence of incremental benefit compared to alternatives, but also with higher costs. People would like choose what is thought to have fewer harms and

DRAFT

Indication/ Intervention	Balance between desirable and undesirable effects	Quality of evidence*	Resource allocation	Variability in values and preferences	Coverage recommendation	Rationale
					coverage (*weak recommendation*)	greater benefit.
PBT for pediatric tumors	Incremental ~~Comparable~~ benefit, fewer harms	Very Low**	Moderate, expensive, but lowered net costs due to greater benefit and fewer harms	Moderate (significant concerns re radiation therapy, given variety of tumors may have options for alternative therapies)	Option 1 (prior recommendation): Not recommended for coverage (*weak recommendation*) Option 2 (staff recommendation): Recommended for coverage (weak recommendation)	Very low quality evidence suggests ~~comparable~~ incremental benefit, and fewer harms, 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	~~Moderate~~ High	Moderate~~, in part due to limited~~	Do not recommend (*weak recommendation*)	There is sufficient evidence that PBT has comparable

DRAFT

Indication/ Intervention	Balance between desirable and undesirable effects	Quality of evidence*	Resource allocation	Variability in values and preferences	Coverage recommendation	Rationale
				~~availability~~		benefits and harms to alternatives, but is more expensive,
PBT for lung cancer	Comparable benefit, comparable harms	Low	~~Moderate~~ High	Moderate	Do not recommend (*weak recommendation*)	Sufficient evidence of similar effectiveness, similar risk, and more cost.
PBT for prostate cancer	Comparable benefit, comparable harms	Low	~~Moderate~~ 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	~~Moderate~~ High	Moderate to high, due to uncertainty of benefit	Option1 (prior recommendation) Do not recommend (*strong recommendation*) Option 2 (staff recommendation) Do	Insufficient evidence exists, but it is suggesting comparable benefit. Given that there are alternatives available with similar risk and less

DRAFT

Indication/ Intervention	Balance between desirable and undesirable effects	Quality of evidence*	Resource allocation	Variability in values and preferences	Coverage recommendation	Rationale
					not recommend *(weak recommendation)*	expensive, recommendation against coverage.
PBT for bone, breast, esophageal, GI, gynecologic, and head/neck cancer; lymphomas, sarcomas, seminomas, thymomas, AVMs, and other noncancerous conditions	Unknown	Bone, head/neck: Low All others: No evidence	~~Moderate~~ High	Low (most would not choose PBT due to cost, need to travel, uncertain benefit)	Do not recommend (weak recommendation)	Insufficient evidence, unknown risk compared to alternative, and increased cost.

*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

DRAFT

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.

DRAFT

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.

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.

DRAFT

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.
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.

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

DRAFT

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]

DRAFT

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

DRAFT

HERC Coverage Guidance – Proton Beam Therapy
Disposition of Public Comments

Table of Contents

Commenters 1
Public Comments 2
References Provided by Commenters 46
Index of Comments by Cancer Type 56

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

DRAFT

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

DRAFT

ID	#	Comment	Disposition
			inclusion as evidence.
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

DRAFT

ID	#	Comment	Disposition
			showed significantly higher disease-free survival at 5 years (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. *For HTAS discussion*
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 in any way.
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. Heart dose is a surrogate outcome. The

DRAFT

ID	#	Comment	Disposition
			authors state "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	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

DRAFT

ID	#	Comment	Disposition
		it. Every single man I spoke with, no matter how healthy they were or how well their 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.	prostate cancer. "No differences in overall QoL or general health 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.

DRAFT

ID	#	Comment	Disposition
C	21	After reviewing the commission's draft on coverage guidance for proton beam therapy (PBT), I would like to highlight and summarize the pertinent, existing evidence supporting the selective use of protons as part of lymphoma treatment.	Thank you for your comments.
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	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

DRAFT

ID	#	Comment	Disposition
		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 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.	point regarding 20-30 year outcome 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	As noted on Table 1, PBT was

DRAFT

ID	#	Comment	Disposition
		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.	judged to have incremental net health benefit for pediatric cancers.
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 not to 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	Commenter references Bradley JD et al 2015, demonstrating that 74Gy radiotherapy had no

DRAFT

ID	#	Comment	Disposition
		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).	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 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.	Commenter notes ongoing 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

DRAFT

ID	#	Comment	Disposition
			PBRT may improve survival. Comparative studies are not feasible as SBRT cannot be done for these patients. *For HTAS discussion*
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. HTAS may recommend coverage of PBT for centrally located inoperable NSCLC in cases where excessive risk of toxicity makes SBRT contraindicated *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

DRAFT

ID	#	Comment	Disposition
			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 serve as an on-going resource as you are assessing this promising cancer therapy option for Oregonians. Thank you for this opportunity.	Thank you for your comments.
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.

DRAFT

ID	#	Comment	Disposition
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 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

DRAFT

ID	#	Comment	Disposition
			United States, but the magnitude of superiority depends strongly on the patients' anatomical development status."
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 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. *For HTAS discussion*
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. *For HTAS discussion*
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	See comments A10, A11.

DRAFT

ID	#	Comment	Disposition
		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]	
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.
L	67	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:	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; HTAS may recommend coverage in that scenario. *For HTAS discussion*
L	68	Skull Base Tumors	Commenter notes poor local

DRAFT

DRAFT

ID	#	Comment	Disposition
		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 3 5% (1). In contrast, LC for these skull-based chordomas and chondrosarcomas is higher with charged particle therapy, as summarized in the following table:	control rate when dosimetry is limited by nearby organs. Reference 1 is a review article from 1999. Direct comparative studies are not provided.
L	69	TABLE: LC Rates for Sarcomas or Chordomas of the Skull Base treated with α-Particles or Protons Facility / Chordoma / Chondrosarcoma / Sarcoma (other) LBNL (2) / 63% / 78% / 58% HCL-MGH (1,3) / 59% / 99% / LLUMC (3) / 76% / 92% / Orsay (4) / 83% / 90% / Tsukuba (5) / 46% / / PSI (6) / 88% / 100% /	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. 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. Evidence is insufficient regarding net health benefit of PBT versus comparators; therefore the HTAS recommends against coverage.
L	70	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)	This case series of 204 patients was conducted from

ID	#	Comment	Disposition
			1975-1993 and may not represent contemporary practice and technology.
L	71	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.	Thank you for your comments.
L	72	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.	Reference 7 is a 1999 case series of 16 patients. No comparative data are identified.
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

DRAFT

ID	#	Comment	Disposition
			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).	Duplicate of reference A7; please see comment 9.
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.
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-pmticles 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

DRAFT

ID	#	Comment	Disposition
			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."
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	It is noted that comparative

DRAFT

ID	#	Comment	Disposition
		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 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)	studies are unlikely to be conducted in pediatric tumors due to lack of clinical equipoise. *For HTAS discussion*
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	Thank you for your comments.

DRAFT

ID	#	Comment	Disposition
		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.	
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

DRAFT

ID	#	Comment	Disposition
			For HTAS discussion
N	94	Summary of Evidence *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.	Please see comments 59 and 61.
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

DRAFT

ID	#	Comment	Disposition
			subgroup analysis. Reference 7 is an editorial describing long-term follow up 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	References 10-13 are considered in the WAHTA

DRAFT

ID	#	Comment	Disposition
		neurocognitive decline, endocrine dysfunction, and secondary malignancy. (16, 17)	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 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	It is noted that studies of proton beam for GBM are in progress. Studies in progress

DRAFT

ID	#	Comment	Disposition
		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.	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 opportunity to serve as an on-going resource as you are assessing this important cancer therapy option for Oregonians. Thank you for this opportunity.	Thank you for your comments.
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 will recommend coverage for pediatric tumors. *For HTAS discussion*
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	*For HTAS discussion*

DRAFT

ID	#	Comment	Disposition
		benefit from the reduced amount of radiation received in the course of PBT treatment.	
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.
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.	Cuaron (2015) is a case series that assessed dosimetry and early toxicity of PBT in 30 patients with metastatic breast cancer. Holliday (2015) is a case series that assessed local control, relapse-free, and overall survival in 19 patients with chordoma or chondrosarcoma treated with PBT. Mizumoto (2015) is a case series that assessed local

DRAFT

ID	#	Comment	Disposition
		• 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 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 (lMRT), 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, lncalcaterra JR, Kolom C, Tatum LS, Walters RS, Cantor SB, Rosenthal	occurrence and toxicity in 6 pediatric patients with ependymoma treated with PBT. Mailhot Vega (2015) is a cost-effectiveness study of PBT compared with photon therapy for pediatric patients with growth hormone deficiency. 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. Franks (2014) is a case series that assessed toxicity of multifield optimization intensity modulated PBT in 15 patients with head and neck cancer. Kesarwala (2015) is a case series that assessed intensity-modulated PBT dosimetry in 20 patients with locally advanced non-small cell lung cancer. Ladra (2014) is a case series that assessed disease control

DRAFT

ID	#	Comment	Disposition
		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]	and toxicity of 57 pediatric patients with rhabdomyosarcoma treated with PBT. Ling (2014) is a case series that assessed dosimetry of IMRT, 3DCRT and PBT in 10 patients with esophageal cancer. Makita (2015) is a case series that assessed survival, local control, and toxicity in 56 patients with stage I non-small cell lung cancer treated with PBT. 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

DRAFT

ID	#	Comment	Disposition
			groups. Schild (2014) is a narrative review on the use of PBT as part of a multi-modal treatment program for patients with locally advanced lung cancer. Sethi (2014) is a retrospective case series that assessed recurrence rates in 86 patients with retinoblastoma treated with PBT or photon radiotherapy. Thanker (2014) is a case study of two patients with head and neck cancer treated with IMRT and intensity-modulated PBT. 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.
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	The guidelines cited are included in the CG document, with the exception of the NAPT. Staff were unable to identify guidelines via search

DRAFT

ID	#	Comment	Disposition
		coverage for PBT for a number of anatomical sites.	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 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.	This is correct and consistent with the background 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	References 1 and 2 are considered in the WAHTA report.

DRAFT

ID	#	Comment	Disposition
		in local control with the higher dose proton boost with a very low risk of GU or GI complications.	
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.
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%. Comparative data are not available.
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. 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	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

DRAFT

ID	#	Comment	Disposition
		PBT than IMRT. (6)	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 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.	Studies in progress will be 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.

DRAFT

ID	#	Comment	Disposition
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 plans.	See comment A11.
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.

DRAFT

ID	#	Comment	Disposition
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.
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

DRAFT

ID	#	Comment	Disposition
			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.

IMRT (40 fractions)		*PBT (15 fractions)*	
1 New patient visit	99205	1 New patient visit	99205
1 Prescription	77263	1 Planning sim	77014
1 Sim	77290	1 Complex sim	77290
1 Verification sim	77280	1 3D sim	77295
1 IMRT plan	77301	1 Dosimetry calculations	77300
1 IMRT MLC Device	77338	1 Special dosimetry plan	77331
1 Immobilization Device	77334	4 Complex treatment devices	77334
8 Weekly mgmt	77427	4 Apertures/compensators	77334
8 Physics QA	77336	3 Physics QA	77336
40 IMRT treatments	G6015	2 Special physics consults	77370
6 Films	77417	Special treatment procedure	77470
7 Basic dosi calcs	77300	15 IGRT	G6002
40 CTs	77014	15 PBT treatments	77523
1 Follow-up visit	99213	1 Follow-up visit	99213
Total Cost	**$30,678.93**	**Total Cost**	**$21,665.63**

DRAFT

ID	#	Comment	Disposition
S	141	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)	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.
S	142	Dosimetric data as well as phase I clinical data demonstrate that PBT for pancreatic cancer is feasible, tolerable, and 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)	Commenter notes Phase I 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

DRAFT

ID	#	Comment	Disposition
			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 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.	Thank you for your comments.
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	Thank you for your

DRAFT

ID	#	Comment	Disposition
		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' !	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, transportation and entertainment in the area, etc. Always supportive in every way.	Thank you for your comments.
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	Thank you for your comments.

DRAFT

ID	#	Comment	Disposition
		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.	
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 Washington, Alaska, Oregon, Montana, Idaho, and British Columbia.	Thank you for your comments.
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,	Thank you for your

DRAFT

ID	#	Comment	Disposition
		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.	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 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)	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. 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

DRAFT

ID	#	Comment	Disposition
			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 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

DRAFT

ID	#	Comment	Disposition
			Xray craniospinal irradiation in a single patient. Reference 9 is addressed in comment 59. References 10 and 11 are addressed in comment 13. *For HTAS discussion*
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 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	Identical letter to that submitted by commenter P; see responses above

DRAFT

ID	#	Comment	Disposition
		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 • 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.	

DRAFT

ID	#	Comment	Disposition
		• Frank SJ, Cox JD, Gillin M, Mohan R, Garden AS, Rosenthal DI, Gunn GB, Weber RS, Kies MS, Lewin JS, Munsell MF, Palmer MB, Sahoo N, Zhang X, Liu W, Zhu XR. Multifield optimization intensity modulated proton therapy for head and neck tumors: a translation topractice. *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-smallcell 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, lncalcaterra 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 TI, 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] 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 NAPT and endorsed by the Particle Therapy Co-Operative Group	

DRAFT

ID	#	Comment	Disposition
		- North America (PTCOG-NA) all support 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. *NAPT 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.* 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. An example of this more comprehensive analysis is a recent study issued by MD Anderson Cancer Center and presented at the October 2014 meeting ofPTCOG-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. *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	

DRAFT

References Provided by Commenters

Commenter	References
A	1. Darby, S. C., Ewertz, M., & Hall P. (2013). Ischemic heart disease after breast cancer radiotherapy. *New England Journal of Medicine, 368*(26), 2527. http://www.nejm.org/doi/pdf/10.1056/NEJMc1304601
A	2. Thaker, N. G., Guzman, A. B., Feeley, T. W., Jones, T. M., Incalcaterra, J. R., Kolom, C. … Frank, S. J. (2014). Defining the value of proton therapy using time-driven activity-based costing. *Oncology Payers, 1*, 22-28. http://issuu.com/magazineproduction/docs/oncology_payers_issue_1_0814_ezine?e=1127854/8949892
A	3. MacDonald, S. M., Patel, S. A., Hickey, S., Specht, M., Isakoff, S. J., Gadd, M. … Taghian, A.G. (2013). Proton therapy for breast cancer after mastectomy: Early outcomes of a prospective clinical trial. *International Journal of Radiation Oncology, Biology and Physics, 86*(3), 484-90. http://www.redjournal.org/article/S0360-3016(13)00178-8/pdf
A	4. Mailhot Vega, R., Kim, J., Hollander, A., Hattangadi-Gluth, J., Michalski, J., Tarbell, N. J. … MacDonald, S.M. (2015). Cost effectiveness of proton versus photon radiation therapy with respect to the risk of growth hormone deficiency in children. *Cancer, 121*(10), 1694-702. DOI: 10.1002/cncr.29209.
A	5. Mailhot Vega, R. B., Kim, J., Bussière, M., Hattangadi, J., Hollander, A., Michalski, J. … MacDonald, S. M. (2013). Cost effectiveness of proton therapy compared with photon therapy in the management of pediatric medulloblastoma. *Cancer, 119*(24), 4299-307. http://onlinelibrary.wiley.com/doi/10.1002/cncr.28322/epdf
A	6. Mendenhall, N. P., Hoppe, B. S., Nichols, R. C., Mendenhall, W. M., Morris, C. G., Li, Z. … Henderson, R. H. (2014). Five-year outcomes from 3 prospective trials of image-guided proton therapy for prostate cancer. *International Journal of Radiation Oncology, Biology, and Physics, 89*(4), 846-53. http://www.redjournal.org/article/S0360-3016(13)03310-5/pdf
A	7. Patel, S. H., Wang, Z., Wong, W. W., Murad, M. H., Buckey, C. R., Mohammed, K. … Foote, R. L. (2014). Charged particle therapy versus photon therapy for paranasal sinus and nasal cavity malignant diseases: A systematic review and meta-analysis. *Lancet Oncology, 15*(9), 1027-38. DOI: 10.1016/S1470-2045(14)70268-2.
C	1. Galper, S. L., Yu, J. B., Mauch, P. M., Strasser, J. F., Silver, B., Lacasce, A. … Ng, A. K. (2011). Clinically significant cardiac disease in patients with Hodgkin lymphoma treated with mediastinal irradiation. *Blood, 117*(2), 412-8. http://www.bloodjournal.org/content/bloodjournal/117/2/412.full.pdf?sso-checked=true
C	2. Ng, A. K., Li, S., Neuberg, D., Chi, R., Fisher, D. C., Silver, B., & Mauch, P. M. (2008).. A prospective study of pulmonary function in Hodgkin's lymphoma patients. *Annals of Oncology, 19*(10), 1754-8. http://annonc.oxfordjournals.org/content/19/10/1754.full.pdf+html
C	3. Travis, L. B., Hill, D. A., Dores, G. M., Gospodarowicz, M., van Leeuwen, F. E., Holowaty, E. … Gilbert, E. (2003). Breast cancer following radiotherapy and chemotherapy among young women with Hodgkin disease. *Journal of the American Medical Association, 290*(4), 465-75. http://jama.jamanetwork.com/article.aspx?articleid=196992
C	4. Travis, L. B., Gospodarowicz, M., Curtis, R. E., Clarke, E. A., Andersson, M., Glimelius, B. … Gilbert, E. (2002). Lung cancer following chemotherapy and radiotherapy for Hodgkin's disease. *Journal of the National Cancer Institute, 94*(3), 182-92.

DRAFT

Commenter	References
	http://jnci.oxfordjournals.org/content/94/3/182.full.pdf+html
C	5. Morton, L. M., Gilbert, E. S., Stovall, M., van Leeuwen, F. E., Dores, G. M., Lynch, C. F. … Curtis, R. E. (2014). Risk of esophageal cancer following radiotherapy for Hodgkin lymphoma. *Haematologica, 99*(10), e193-196. http://www.ncbi.nlm.nih.gov/pmc/articles/PMC4181268/pdf/099e193.pdf
C	6. Darby, S. C., Ewertz, M., McGale, P., Bennet, A. M., Blom-Goldman, U., Brønnum, D. … Hall, P. (2013). Risk of ischemic heart disease in women after radiotherapy for breast cancer. *New England Journal of Medicine, 368*(11), 987-98. http://www.nejm.org/doi/pdf/10.1056/NEJMoa1209825
C	7. Maraldo, M. V., Brodin, N. P., Aznar, M. C., Vogelius, I. R., Munch af Rosenschöld, P., Petersen, P. M., & Specht, L. (2013). Estimated risk of cardiovascular disease and secondary cancers with modern highly conformal radiotherapy for early-stage mediastinal Hodgkin lymphoma. *Annals of Oncology, 24*(8), 2113-8. http://annonc.oxfordjournals.org/content/24/8/2113.full.pdf+html
C	8. Hoppe, B. S., Flampouri, S., Su, Z., Latif, N., Dang, N. H., Lynch, J. … Mendenhall, M. P. (2012). Effective dose reduction to cardiac structures using protons compared with 3DCRT and IMRT in mediastinal Hodgkin lymphoma. *International Journal of Radiation Oncology, Biology, and Physics, 84*(2), 449-55. DOI: http://dx.doi.org/10.1016/j.ijrobp.2011.12.034
C	9. Chera, B. S., Rodriguez, C., Morris, C. G., Louis, D., Yeung, D., Li, Z., & Mendenhall, N. P. (2009). Dosimetric comparison of three different involved nodal irradiation techniques for stage II Hodgkin's lymphoma patients: conventional radiotherapy, intensity-modulated radiotherapy, and three-dimensional proton radiotherapy. *International Journal of Radiation Oncology, Biology, Physics*, *75*(4), 1173-80. DOI: http://dx.doi.org/10.1016/j.ijrobp.2008.12.048
C	10. Hoppe, B. S., Flampouri, S., Su, Z., Morris, C. G., Latif, N., Dang, N. H. … Mendenhall, N. P. (2012). Consolidative involved-node proton therapy for stage IA-IIIB mediastinal Hodgkin lymphoma: preliminary dosimetric outcomes from a phase II study. *International Journal of Radiation Oncology, Biology, Physics, 83*(1), 260-7. DOI: http://dx.doi.org/10.1016/j.ijrobp.2011.06.1959
C	11. Hoppe, B. S., Flampouri, S., Zaiden, R., Slayton, W., Sandler, E., Ozdemir, S. … Mendenhall, N. P. (2014). Involved-node proton therapy in combined modality therapy for Hodgkin lymphoma: Results of a Phase 2 study. *International Journal of Radiation Oncology, Biology, Physics*, *89*(5), 1053-9. http://www.redjournal.org/article/S0360-3016(14)00500-8/pdf
H	1. Bradley, J. D., Paulus, R., Komaki, R., Masters, G., Blumenschein, G., Schild, S. … Choy, H. (2015). Standard-dose versus high-dose conformal radiotherapy with concurrent and consolidation carboplatin plus paclitaxel with or without cetuximab for patients with stage IIIA or IIIB non-small-cell lung cancer (RTOG 0617): A randomised, two-by-two factorial phase 3 study. *The Lancet Oncology, 16*(2), 187-99. DOI: http://dx.doi.org/10.1016/S1470-2045(14)71207-0
H	2. Chang, J. Y., Komaki, R., Lu, C., Wen, H. Y., Allen, P. K., Tsao, A. … Cox, J. (2011). Phase 2 study of high-dose proton therapy with concurrent chemotherapy for unresectable stage III nonsmall cell lung cancer. *Cancer, 117*(20), 4707-13. http://onlinelibrary.wiley.com/doi/10.1002/cncr.26080/epdf
H	3. Timmerman, R., McGarry, R., Yiannoutsos, C., Papiez, L., Tudor, K., DeLuca, J. … Fletcher, J. (2006). Excessive toxicity when treating central tumors in a phase II study of stereotactic body radiation therapy for medically inoperable early-stage lung cancer. *Journal of Clinical Oncology*, *24*(30), 4833-9.

DRAFT

Commenter	References
	http://jco.ascopubs.org/content/24/30/4833.full.pdf+html
H	4. Bush, D. A., Cheek, G., Zaheer, S., Wallen, J., Mirshahidi, H., Katerelos, A. … Slater, J. D. (2013). High-dose hypofractionated proton beam radiation therapy is safe and effective for central and peripheral early-stage non-small cell lung cancer: Results of a 12-year experience at Loma Linda University Medical Center. *International Journal of Radiation Oncology, Biology, Physics, 86*(5), 964-8. DOI: http://dx.doi.org/10.1016/j.ijrobp.2013.05.002
H	5. McAvoy, S. A., Ciura, K. T., Rineer, J. M., Allen, P. K., Liao, Z., Chang, J. Y., … Gomez, D. R. (2013). Feasibility of proton beam therapy for reirradiation of locoregionally recurrent non-small cell lung cancer. *Radiotherapy & Oncology, 109*(1), 38-44. DOI: http://dx.doi.org/10.1016/j.radonc.2013.08.014
H	6. Mailhot Vega, R. B., Kim, J., Bussiere, M., Hattangadi, J., Hollander, A., Michalski, J. … MacDonald, S. M. (2013). Cost effectiveness of proton therapy compared with photon therapy in the management of pediatric medulloblastoma. *Cancer, 119*(24), 4299-307. http://onlinelibrary.wiley.com/doi/10.1002/cncr.28322/epdf
H	7. Mailhot Vega, R., Kim, J., Hollander, A., Hattangadi-Gluth, J., Michalski, J., Tarbell, N. J. … MacDonald, S. M. (2015). Cost effectiveness of proton versus photon radiation therapy with respect to the risk of growth hormone deficiency in children. *Cancer*, *121*(10), 1694-702. DOI: 10.1002/cncr.29209
L	1. Munzenrider, J. E., & Liebsch, N.J. (1999). Proton therapy for tumors of the skull base. *Strahlentherapie und Onkologie, 175*(Suppl 2), 57-63.
L	2. Castro J. R., Linstadt, D. E., Bahary, J. P., Petti, P. L., Daftari, I., Collier, J. M., … Phillips, T. L. (1994). Experience in charged particle irradiation of tumors of the skull base: 1977-1992. *International Journal of Radiation Oncology, Biology, Physics, 29*(4), 647-655. DOI: http://dx.doi.org/10.1016/0360-3016(94)90550-9
L	3. Fagundes, M. A., Hug, E. B., Liebsch, N. J., Daly, W., Efird, J., & Munzenrider, J. E. (1995). Radiation therapy for chordomas of the base of skull and cervical spine: Patterns of failure and outcome after relapse. *International Journal of Radiation Oncology, Biology, Physics, 33*(3), 579-584. DOI: http://dx.doi.org/10.1016/0360-3016(95)02014-3
L	4. Noel, G., Habrand, J. L., Mammar, H., Pontvert, D., Haie-Méder, C., Hasboun, D. … Mazeron, J. J. (2001). Combination of photon and proton radiation therapy for chordomas and chondrosarcomas of the skull base: The Centre de Protontherapie D'Orsay experience. *International Journal of Radiation Oncology, Biology, Physics, 51*(2), 392-398. DOI: http://dx.doi.org/10.1016/S0360-3016(01)01634-0
L	5. Igaki, H., Tokuuye, K., Okumura, T., Sugahara, S., Kagei, K., Hata, M. … Akine, Y. (2004). Clinical results of proton beam therapy for skull base chordoma. *International Journal of Radiation Oncology, Biology, Physics, 60*(4), 1120-1126. DOI: http://dx.doi.org/10.1016/j.ijrobp.2004.05.064
L	6. Weber, D. C., Rutz, H. P., Pedroni, E. S., Bolsi, A., Timmermann, B., Verwey, J. … Goitein, G. (2005). Results of spot scanning proton radiotherapy for chordoma and chondrosarcoma of the skull base: The Paul Scherre Institut experience. *International Journal of Radiation Oncology, Biology, Physics, 63*(2), 401-409. DOI: http://dx.doi.org/10.1016/j.ijrobp.2005.02.023
L	7. Lin, R., Slater, J. D., Yonemoto, L. T., Grove, R. I., Teichman, S. L., Watt, D. K., & Slater, J. M. Nasopharyngeal carcinoma: Repeat treatment with conformal proton therapy- dose-volume histogram analysis. *Radiology, 213*(2), 489-494. http://pubs.rsna.org/doi/pdf/10.1148/radiology.213.2.r99nv29489

DRAFT

Commenter	References
L	8. Chan, A. W., Liebsch ,N. J., Deschler, D. G., Adams, J. A., Virshall, L. V., McIntyre, J. F. … Busse, P. M. (2004). Proton radiotherapy for T4 nasopharyngeal carcinomas. *Journal of Clinical Oncology, 2004 ASCO Annual Meeting Proceedings,* 22(14S), 5574. http://meeting.ascopubs.org/cgi/content/short/22/14_suppl/5574
L	9. Taheri-Kadkhoda, Z., Bjork-Eriksson, T., Nill, S., Wilkens, J. J., Oelfke, U., Johansson, K. A. … Münter, M. W. (2008). Intensity-modulated radiotherapy of nasopharyngeal carcinoma: A comparative treatment planning study of photons and protons. *Radiation Oncology, 3*, 4. http://www.ro-journal.com/content/pdf/1748-717X-3-4.pdf
L	10. Nishimura, H., Ogino, T., Kawashima, M., Nihei, K., Arahira, S., Onozawa, M. … Nishio, T. (2007). Proton-beam therapy for olfactory neuroblastoma. *International Journal of Radiation Oncology, Biology, Physics, 68*(3), 758-762. DOI: http://dx.doi.org/10.1016/j.ijrobp.2006.12.071
L	11. Chan, A., Pommier, P., Deschler, D. G., Liebsch, N. J., McIntyre, J. F., Adams, J. A. … Thornton, A. F. (2004). Changes in patterns of relapse after combined proton and photon irradiation for locally advanced paranasal sinus cancer. *International Journal of Radiation Oncology, Biology, Physics, 60*(1), S320. DOI: http://dx.doi.org/10.1016/j.ijrobp.2004.07.135
L	12. Patel, S. H., Wang, Z., Wong, W. W., Murad, M. H., Buckley, C. R., Mohammed, K. … Foote, R. L. (2014). Charged particle therapy versus photon therapy for paranasal sinus and nasal cavity malignant diseases: a systematic review and meta-analysis. *The Lancet Oncology,* 15(9), 1027-1038. DOI: http://dx.doi.org/10.1016/S1470-2045(14)70268-2
L	13. Nowakowski, V. A., Castro, J. R., Petti, P. L., Collier, J. M., Daftari, I., Ahn, D. … Phillips, T. L. (1992). Charged particle radiotherapy of paraspinial tumors. *International Journal of Radiation Oncology, Biology, Physics, 22*(2), 295-303. DOI: http://dx.doi.org/10.1016/0360-3016(92)90046-K
L	14. Slater, J. D., Yonemoto, L. T., Mantik, D. W., Bush, D. A., Preston, W., Grove, R. I., … Slater, J. M. (2005). Proton radiation for treatment of cancer of the oropharynx: Early experience at the Lorna Linda University Medical Center using a concomitant boost technique. *International Journal of Radiation Oncology, Biology, Physics, 62*(2), 494-500. DOI: http://dx.doi.org/10.1016/j.ijrobp.2004.09.064
L	15. Frank, S. J., Cox, J. D., Gillin, M., Mohan, R., Garden, A. S., Rosenthal, D. I., … Zhu, X. R. (2014). Multifield optimization intensity modulated proton therapy for head and neck tumors: A translation to practice. *International Journal of Radiation Oncology, Biology, Physics, 89*(4), 846-853. DOI: http://dx.doi.org/10.1016/j.ijrobp.2014.04.019
L	16. Stuschke, M., Kaiser, A., Abu-Jaswd, A., Pöttgen, C., Levegrün, S., & Farr, J. (2013). Re-irradiation of recurrent head and neck carcinomas: Comparison of robust intensity modulated proton theapy plans with helicial tomotherapy. *Radiation Oncology, 8*, 93-100. http://www.ro-journal.com/content/pdf/1748-717X-8-93.pdf
L	17. Van de Water, T. A., Bijl, H. P., Schilstra, C., Pijls-Johannesma, M., & Langendijk, J. A. (2011). The potential benefit of radiotherapy in head and neck cancer with respect to normal tissue sparing: A systematic review of the literature. Oncologist, *16*(3), 366-377. http://theoncologist.alphamedpress.org/content/16/3/366.full.pdf+html
M	1. Kasper, H. B., Raeke, L., Indelicato, D. J., Symecko, H., Hartsell, W., Mahajan, A. … Yeap, B. Y. (2014). The Pediatric Proton Consortium Registry: A Multi-

DRAFT

Commenter	References
	institutional Collaboration in U.S. Proton Centers. *International Journal of Particle Therapy*. http://www.theijpt.org/doi/pdf/10.14338/IJPT.13-00006.1
M	2. Yock, T. I, Bhat, S., Szymonifka, J., Yeap, B. Y., Delahaye, J., Donaldson, S. S. … Kuhlthau, K. A. (2014). Quality of life outcomes in proton and photon treated pediatric brain tumor survivors. *Radiotherapy & Oncology, 113*(1), 89-94. DOI: http://dx.doi.org/10.1016/j.radonc.2014.08.017
M	3. Bishop, A. J., Greenfield, B., Mahajan, A., Paulino, A. C., Okcu, M. F., Allen, P. K. … Grosshans, D. R. (2014). Proton beam therapy versus conformal photon radiation therapy for childhood craniopharyngioma: multi-institutional analysis of outcomes, cyst dynamics, and toxicity. *International Journal of Radiation Oncology, Biology, Physics*, *90*(2), 354-61. DOI: http://dx.doi.org/10.1016/j.ijrobp.2014.05.051
M	4. McGovern, S. L., Okcu, M. F., Munsell, M. F., Kumbalasseriyil, N., Grosshans, D. R., McAleer, M. F., Mahajan, A. (2014). Outcomes and acute toxicities of proton therapy for pediatric atypical teratoid/rhaboid tumor of the central nervous system. *International Journal of Radiation Oncology, Biology, Physics*, *90*(5):1143-52. DOI: http://dx.doi.org/10.1016/j.ijrobp.2014.08.354
M	5. Mailhot Vega, R. B., Kim, J., Bussiere, M., Hattangadi, J., Hollander, A., Michalski, J. … MacDonald, S. M. (2013). Cost effectiveness of proton therapy compared with photon therapy in the management of pediatric medulloblastoma. *Cancer, 119*(24), 4299-307. http://onlinelibrary.wiley.com/doi/10.1002/cncr.28322/epdf
N	1. Jenkin, D., Danjoux, C., & Greenberg, M. (1998). Subsequent quality of life for children irradiated for a brain tumor before age four years. *Medical and Pediatric Oncology, 31*(6), 506-11. DOI: 10.1002/(SICI)1096-911X(199812)31:6<506::AID-MPO7>3.0.CO;2-X
N	2. Merchant, T. E., Hua, C. H., Shukla, H., Ying, X., Nill, S., & Oelfke, U. (2008). Proton versus photon radiotherapy for common pediatric brain tumors: comparison of models of dose characteristics and their relationship to cognitive function. Pediatric Blood & Cancer, 51(1):110-7. DOI: 10.1002/pbc.21530
N	3. Laughton, S. J., Merchant, T. E., Sklar, C. A., Kun, L. E., Fouladi, M., Broniscer, A. … Gajjar, A. (2008). Endocrine outcomes for children with embryonal brain tumors after risk-adapted craniospinal and conformal primary-site irradiation and high-dose chemotherapy with stem-cell rescue on the SJMB-96 trial. *Journal of Clinical Oncology, 26*(7), 1112-8.
N	4. Moeller, B. J., Chintagumpala, M., Philip, J. J., Grosshans, D. R., McAleer, M. F., Woo, S. Y. … Mahajan, A. (2011). Low early ototoxicity rates for pediatric medulloblastoma patients treated with proton radiotherapy. *Radiation Oncology, 6*, 58. http://www.ro-journal.com/content/pdf/1748-717X-6-58.pdf
N	5. Friedman, D. L., Whitton, J., Leisenring, W., Mertens, A. C., Hammond, S., Stovall, M. … Neglia, J. P. (2010). Subsequent Neoplasms in 5-Year Survivors of Childhood Cancer: The Childhood Cancer Survivor Study. *Journal of the National Cancer Institute, 102*(14), 1083-1095. http://jnci.oxfordjournals.org/content/102/14/1083.full.pdf+html
N	6. Cairncross, G., Wang, M., Shaw, E., Jenkins, R., Brachman, D., Buckner, J. … Mehta, M. (2013). Phase III trial of chemoradiotherapy for anaplastic oligodendroglioma: long-term results of RTOG 9402. *Journal of Clinical Oncology, 31*(3), 337-43. http://jco.ascopubs.org/content/31/3/337.full.pdf+html

DRAFT

Commenter	References
N	7. van den Bent, M. J. (2014). Practice changing mature results of RTOG study 9802: another positive PCV trial makes adjuvant chemotherapy part of standard of care in low-grade glioma. Neuro-oncology, 16(12), 1570-4. http://neuro-oncology.oxfordjournals.org/content/16/12/1570.full.pdf+html
N	8. Klein, M., Heimans, J. J., Aaronson, N. K., van der Ploeg, H. M., Muller, M., Postma, T. J. … Taphoorn, M. J. (2002). Effect of radiotherapy and other treatment-related factors on mid-term to long-term cognitive sequelae in low-grade gliomas: A comparative study. Lancet, 360(9343), 1361-8. DOI: http://dx.doi.org/10.1016/S0140-6736(02)11398-5
N	9. Shih, H. A., Sherman, J. C., Nachtigall, L. B., Colvin, M. K., Fullerton, B. C., Daartz, J. … Yeap, B. Y. (2015). Proton therapy for low-grade gliomas: Results from a prospective trial. *Cancer, 121*(10), 1712-9. DOI: 10.1002/cncr.29237
N	10. Weber, D. C., Schneider, R., Goitein, G., Koch, T., Ares, C., Geismar, J. H. … Hug, E. B. (2012). Spot scanning-based proton therapy for intracranial meningioma: long-term results from the Paul Scherrer Institute. *International Journal of Radiation Oncology, Biology, Physics, 83*(3), 865-71. DOI: http://dx.doi.org/10.1016/j.ijrobp.2011.08.027
N	11. Halasz, L. M., Bussiere, M. R., Dennis, E. R., Niemierko, A., Chapman, P. H., Loeffler, J. S., & Shih, H. A. (2011). Proton stereotactic radiosurgery for the treatment of benign meningiomas. *International Journal of Radiation Oncology, Biology, Physics, 81*(5), 1428-35. DOI: http://dx.doi.org/10.1016/j.ijrobp.2010.07.1991
N	12. Boskos, C., Feuvret, L., Noel, G., Habrand, J. L., Pommier, P., Alapetite, C. … Mazeron, J. J. (2009). Combined proton and photon conformal radiotherapy for intracranial atypical and malignant meningioma. *International Journal of Radiation Oncology, Biology, Physics, 75*(2), 399-406. DOI: http://dx.doi.org/10.1016/j.ijrobp.2008.10.053
N	13. Arvold, N. D., Lessell, S., Bussiere ,M,. Beaudette, K., Rizzo, J. F., Loeffler, J. S., & Shih, H. A. (2009). Visual outcome and tumor control after conformal radiotherapy for patients with optic nerve sheath meningioma. *International Journal of Radiation Oncology, Biology, Physics, 75*(4), 1166-72. DOI: http://dx.doi.org/10.1016/j.ijrobp.2008.12.056
N	14. Wattson, D. A., Tanguturi, S. K., Spiegel, D. Y., Niemierko, A., Biller, B. M., Nachtigall, L. B., … Shih, H. A. (2014). Outcomes of proton therapy for patients with functional pituitary adenomas. *International Journal of Radiation Oncology, Biology, Physics, 90*(3), 532-9. DOI: http://dx.doi.org/10.1016/j.ijrobp.2014.06.068
N	15. Niu, N. N., Niemierko, A., Larvie, M., Curtin, H., Loeffler, J. S., McKenna, M. J., & Shih, H. A. (2014). Pretreatment growth rate predicts radiation response in vestibular schwannomas. *International Journal of Radiation Oncology, Biology, Physics, 89*(1), 113-9. DOI: http://dx.doi.org/10.1016/j.ijrobp.2014.01.038
N	16. Arvold, N. D., Niemierko, A., Broussard, G. P., Adams, J., Fullerton, B., Loeffler, J. S., & Shih, H. A. (2012). Projected second tumor risk and dose to neurocognitive structures after proton versus photon radiotherapy for benign meningioma. *International Journal of Radiation Oncology, Biology, Physics, 83*(4), e495-500. DOI: http://dx.doi.org/10.1016/j.ijrobp.2011.10.056
N	17. Winkfield, K. M., Niemierko, A., Bussiere, M. R., Crowley, E. M., Napolitano, B. N., Beaudette, K. P. … Shih, H. A. (2011). Modeling intracranial second tumor risk and estimates of clinical toxicity with various radiation therapy techniques for patients with pituitary adenoma. *Technology in Cancer Research*

DRAFT

Commenter	References
	and Treatment, 10(3), 243-51. DOI: 10.7785/tcrt.2012.500199
N	18. Brown, A. P., Barney, C. L., Grosshans, D. R., McAleer, M. F., de Groot, J. F., Puduvalli, V. K. … Mahajan, A. (2013). Proton beam craniospinal irradiation reduces acute toxicity for adults with medulloblastoma. *International Journal of Radiation Oncology, Biology, Physics, 86*(2), 277-84. http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3954470/pdf/nihms515319.pdf
N	19. Dose-escalated photon IMRT or proton beam radiation versus standard-dose radiation therapy and temozolomide in treating patients with newly diagnosed glioblastoma. (2015). https://clinicaltrials.gov/ct2/show/NCT02179086?term=bn001&rank=1 (Identification No. NCT02179086)
N	20. Bevacizumab with or without radiation therapy in treating patients with recurrent glioblastoma. (2015). https://clinicaltrials.gov/ct2/show/NCT01730950?term=rtog+1205&rank=1 (Identification No. NCT01730950)
N	21. Mailhot Vega, R., Kim, J., Hollander, A., Hattangadi-Gluth, J., Michalski, J., Tarbell, N. J. … MacDonald, S.M. (2015). Cost effectiveness of proton versus photon radiation therapy with respect to the risk of growth hormone deficiency in children. *Cancer, 121*(10), 1694-702. DOI: 10.1002/cncr.29209.
N	22. Mailhot Vega, R. B., Kim, J., Bussière, M., Hattangadi, J., Hollander, A., Michalski, J. … MacDonald, S. M. (2013). Cost effectiveness of proton therapy compared with photon therapy in the management of pediatric medulloblastoma. *Cancer, 119*(24), 4299-307. http://onlinelibrary.wiley.com/doi/10.1002/cncr.28322/epdf
Q	1. Shipley, W. U., Verhey, L. J., Munzenrider, J. E., Suit, H. D., Urie, M. M., McManus, P. L., et al. (1995). Advanced prostate cancer: the results of a randomized comparative trial of high dose irradiation boosting with conformal protons compared with conventional dose irradiation using photons alone. *International Journal of Radiation Oncology, Biology, Physics, 32*(1), 3-12. DOI: http://dx.doi.org/10.1016/0360-3016(95)00063-5
Q	2. Zietman, A. L., Bae, K., Slater, J. D., Shipley, W. U., Efstathiou, J. A., Coen, J. J. … Rossi, C. J. (2010). Randomized trial comparing conventional-dose with high-dose conformal radiation therapy in early-stage adenocarcinoma of the prostate: long-term results from proton radiation oncology group/American College of Radiology 95-09. *Journal of Clinical Oncology, 28*(7), 1106-11. http://jco.ascopubs.org/content/28/7/1106.full.pdf+html
Q	3. Slater, J. D., Rossi, C. J., Jr., Yonemoto, L. T., Bush, D. A., Jabola, B. R, Levy, R. P. … Slater, J. M. (2004). Proton therapy for prostate cancer: the initial Lorna Linda University experience. *International Journal of Radiation Oncology, Biology, Physics, 59*(2), 348-52. DOI: http://dx.doi.org/10.1016/j.ijrobp.2003.10.011
Q	4. Mendenhall, N. P., Hoppem B. S., Nichols, R. C., Mendenhall, W. M., Morris, C. G., Li, Z. … Henderson, R. H. (2014). Five-year outcomes from 3 prospective trials of image-guided proton therapy for prostate cancer. *International Journal of Radiation Oncology, Biology, and Physics, 89*(4), 846-53. http://www.redjournal.org/article/S0360-3016(13)03310-5/pdf
Q	5. al-Abany, M., Helgason, A. R., Cronqvist, A. K., Lind, B., Mavroidis, P., Wersäll, P. … Steineck, G. (2005). Toward a definition of a threshold for harmless doses to the anal-sphincter region and the rectum. *International Journal of Radiation Oncology, Biology, Physics, 61*(4), 1035-44. DOI: http://dx.doi.org/10.1016/j.ijrobp.2004.07.706

DRAFT

Commenter	References
Q	6. Hoppe, B. S., Michalski, J. M., Mendenhall, N. P., Morris, C. G., Henderson, R. H., Nichols, R. C. … Hamstra, D. A. (2014). Comparative effectiveness study of patient-reported outcomes after proton therapy or intensity-modulated radiotherapy for prostate cancer. *Cancer, 120*(7), 1076-82. http://onlinelibrary.wiley.com/doi/10.1002/cncr.28536/epdf
Q	7. Kil, W. J., Nichols, R. C., Jr., Hoppe, B. S., Morris, C. G., Marcus, R. B., Jr., Mendenhall, W. … Henderson, R. H. (2013). Hypofractionated passively scattered proton radiotherapy for low- and intermediate-risk prostate cancer is not associated with post-treatment testosterone suppression. *Acta Oncologica, 52*(3), 492-7. http://informahealthcare.com/doi/pdf/10.3109/0284186X.2013.767983
Q	8. Chung CS, Yock TI, Nelson K, Xu Y, Keating NL, Tarbell NJ. Incidence of second malignancies among patients treated with proton versus photon radiation. *International Journal of Radiation Oncology, Biology, Physics* 2013; 87(1):46-52.
Q	9. https://www.astro.org/News-and-Media/News-Releases/2014/Proton-Beam-Therapy-Model-Policy-issued-by-ASTRO.aspx
R	1. Bush, ,D. A., Do, S., Lum, S., Garberoglio, C., Mirshahidi, H., Patyal, B. … Slater, J. D. (2014). Partial breast radiation therapy with proton beam: 5-year results with cosmetic outcomes. *International Journal of Radiation Oncology, Biology, Physics*, *90*(3), 501-505. DOI: http://dx.doi.org/10.1016/j.ijrobp.2014.05.1308
R	2. Bush, D. A., Slater, J. D., Garberoglio, C., Do, S., Lum, S., & Slater, J. M. (2011). Partial breast irradiation delivered with proton beam: Results of a phase II trial. *Clinical Breast Cancer, 11*(4), 241-245. DOI: http://dx.doi.org/10.1016/j.clbc.2011.03.023
R	3. MacDonald, S. M., Patel, S. A., Hickey, S., Specht, M., Isakoff, S. J., Gadd, M. … Taghian, A.G. (2013). Proton therapy for breast cancer after mastectomy: Early outcomes of a prospective clinical trial. *International Journal of Radiation Oncology, Biology and Physics, 86*(3), 484-90. http://www.redjournal.org/article/S0360-3016(13)00178-8/pdf
R	4. MacDonald, S. M., Jimenez, R., Paetzold, P., Adams, J., Beatty, J., DeLane, T. F. … Lu, H. M. (2013). Proton radiotherapy for chest wall and regional lymphatic radiation; Dose comparisons and treatment delivery. Radiation Oncology, 8, 71-77. http://www.ro-journal.com/content/pdf/1748-717X-8-71.pdf
S	1. Ben-Josef, E., Normolle, D., Ensminger, W. D., Walker, S., Tatro, D., Ten Haken, R. K. … Lawrence, T. S. (2005). Phase ii trial of high-dose conformal radiation therapy with concurrent hepatic artery floxuridine for unresectable intrahepatic malignancies. *Journal of Clinical Oncology, 23*(34), 8739-8747. http://jco.ascopubs.org/content/23/34/8739.full.pdf+html
S	2. Qi, W. X., Fu, S., Zhang, Q., & Guo, X., M. (2015). Charged particle therapy versus photon therapy for patients with hepatocellular carcinoma: A systematic review and meta-analysis. *Radiotherapy and Oncology, 114*(3), 289-95. http://www.thegreenjournal.com/article/S0167-8140(14)00538-6/pdf
S	3. Regine, W. F., Winter, K.A., Abrams, R. A., Safran, H., Hoffman, J. P., Konski, A. … Rich, T. A. (2008). Fluorouracil vs gemcitabine chemotherapy before and after fluorouracil-based chemoradiation following resection of pancreatic adenocarcinoma: A randomized controlled trial. *Journal of the American Medical Association,* 299(9), 1019-1026. http://jama.jamanetwork.com/article.aspx?articleid=181567
S	4. Nichols, R. C., Jr., Huh, S. N., Prado, K. L., Yi, B. Y., Sharma, N. K., Ho, M. W. … Regine, W. F. (2012). Protons offer reduced normal-tissue exposure for patients receiving postoperative radiotherapy for resected pancreatic head cancer. *International Journal of Radiation Oncology, Biology, Physics, 83*(1), 158-

DRAFT

Commenter	References
	163. DOI: http://dx.doi.org/10.1016/j.ijrobp.2011.05.045
S	5. Terashima, K., Demizu, Y., Hashimoto, N., Jin, D., Mina, M., Fujii, O. … Murakami, M. (2012). A phase I/II study of gemcitabine-concurrent proton radiotherapy for locally advanced pancreatic cancer without distant metastasis. *Radiotherapy and Oncology, 103*(1), 25-31. DOI: http://dx.doi.org/10.1016/j.radonc.2011.12.029
S	6. Nichols, R. C., Jr., George, T. J., Zaiden, R. A., Jr., Awad, Z. T., Asbun, H. J., Huh, S. … Hoppe, B. S. (2013). Proton therapy with concomitant capecitabine for pancreatic and ampullary cancers is associated with a low incidence of gastrointestinal toxicity. *Acta Oncologica*, *52*(3), 498-505. http://informahealthcare.com/doi/pdf/10.3109/0284186X.2012.762997
S	7. Lukens, J. N., Mick, R., Demas, K. L., Apisarnthanarax, S., Metz, J. M., McCall, D. … Plastaras, J. P. (2013). Acute toxicity of proton versus photon chemoradiation therapy for pancreatic adenocarcinoma: A cohort study. *International Journal of Radiation Oncology, Biology, Physics, 87*(2), S311. http://www.redjournal.org/article/S0360-3016(13)01487-9/pdf
W	1. Rieber, J. G., Kessel, K. A., Witt, O., Behnisch, W., Kulozik, A. E., Debus, J., & Combs, S. E. (2015). Treatment tolerance of particle therapy in pediatric patients. Acta Oncologica, Jan 23, 1-7. [Epub ahead of print]. DOI:10.3109/0284186X.2014.998273
W	2. Jenkin, D., Danjoux, C., & Greenberg, M. (1998). Subsequent quality of life for children irradiated for a brain tumor before age four years. *Medical and Pediatric Oncology, 31*(6), 506-11. DOI: 10.1002/(SICI)1096-911X(199812)31:6<506::AID-MPO7>3.0.CO;2-X
W	3. Merchant, T. E., Hua, C. H., Shukla, H., Ying, X., Nill, S., & Oelfke, U. (2008). Proton versus photon radiotherapy for common pediatric brain tumors: comparison of models of dose characteristics and their relationship to cognitive function. Pediatric Blood & Cancer, 51(1):110-7. DOI: 10.1002/pbc.21530
W	4. Macdonald, S. M., Sethi, R., Lavally, B., Yeap, B. Y., Marcus, K. J., Caruso, P. … Yock, T. I. (2013). Proton radiotherapy for pediatric central nervous system ependymoma: Clinical outcomes for 70 patients. *Neuro-Oncology, 15*(11), 1552-1559. http://neuro-oncology.oxfordjournals.org/content/early/2013/10/06/neuonc.not121.full.pdf+html
W	5. Greenberger, B. A., Pulsifer, M. B., Ebb, D. H., MacDonald, S. M., Jones, R. M., Butler, W. E. … Yock , T. I. (2014). Clinical outcomes and late endocrine, neurocognitive, and visual profiles of proton radiation for pediatric low-grade gliomas. *International Journal of Radiation Oncology, Biology, Physics 89*(5), 1060-1068. DOI: http://dx.doi.org/10.1016/j.ijrobp.2014.04.053
W	6. Sethi, R. V., Shih, H. A., Yeap, B. Y., Mouw, K. W., Petersen, R., Kim, D. Y. … MacDonald, S. M. (2014). Second nonocular tumors among survivors of retinoblastoma treated with contemporary photon and proton radiotherapy. *Cancer, 120*(1), 126-133. http://onlinelibrary.wiley.com/doi/10.1002/cncr.28387/epdf
W	7. Kumar, R. J*., Zhai, H., Both, S., Tochner, Z., Lustig, R., & Hill-Kayser, C.* (2013). Breast cancer screening for childhood cancer survivors after craniospinal irradiation with protons versus x-rays: a dosimetric analysis and review of the literature. *Journal of Pediatric Hematology/Oncology, 35*(6), 462-467. DOI: 10.1097/MPH.0b013e31829bcdf8

DRAFT

Commenter	References
W	8. Lester-Coli, N. H., Morse, C. B., Zhai, H. A., Both, S., Ginsberg, J. P., Gracia, C. R. … Hill-Kayser, C. E. (2014). Preserving fertility in adolescent girls and young women requiring craniospinal irradiation: a case report and discussion of options to be considered prior to treatment." *Journal of Adolescent and Young Adult Oncology*, 3(2), 96-99. http://www.ncbi.nlm.nih.gov/pmc/articles/PMC4048972/pdf/jayao.2013.0038.pdf
W	9. Zhang, R., Howell, R. M., Taddei, P. J., Giebeler, A., Mahajan, A., & Newhauser, W. D. (2014). A comparative study on the risks of radiogenic second cancers and cardiac mortality in a set of pediatric medulloblastoma patients treated with photon or proton craniospinal irradiation. *Radiotherapy and Oncology, 113*(1), 84-88. DOI: http://dx.doi.org/10.1016/j.radonc.2014.07.003
W	10. Mailhot Vega, R. B., Kim, J., Bussière, M., Hattangadi, J., Hollander, A., Michalski, J. … MacDonald, S. M. (2013). Cost effectiveness of proton therapy compared with photon therapy in the management of pediatric medulloblastoma. *Cancer, 119*(24), 4299-307. http://onlinelibrary.wiley.com/doi/10.1002/cncr.28322/epdf
W	11. Mailhot Vega, R., Kim, J., Hollander, A., Hattangadi-Gluth, J., Michalski, J., Tarbell, N. J. … MacDonald, S.M. (2015). Cost effectiveness of proton versus photon radiation therapy with respect to the risk of growth hormone deficiency in children. *Cancer, 121*(10), 1694-702. DOI: 10.1002/cncr.29209.

DRAFT

Index of Comments by Cancer Type

Brain, spinal, and paraspinal tumors: G34, N93, N99-N102

Breast cancer: A10-A11, J63, R130-R135

Gastrointestinal cancers: S136-S145

Head and neck cancers (including skull base tumors): A8-A9, J62, L68-L82

Liver cancer: S; citizen comments D28, E29, F30, K66, O105, V157, X167

Lung cancer: H37-H48

Lymphomas: C21-C27, T146-T155

Pediatric cancers (e.g., medulloblastoma, retinoblastoma, Ewing's sarcoma): G33, J59-J61, M86-M87, N94-N98, P107-P111, W158-W166, Y168

Prostate cancer: A12, B15-B20, I, Q121-Q129, U156

No comments received: Bone tumors, Esophageal cancer, Gynecologic cancers, Ocular tumor, Soft tissue sarcomas, Seminoma, Thymoma, Noncancerous conditions, Arteriovenous malformations, Hemangiomas, Other benign tumors (e.g., acoustic neuromas, pituitary adenomas)

DRAFT