HERC Coverage Guidance – Proton Beam Therapy
Disposition of Public Comments

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Commenters

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

W	Assistant Professor, University of Washington Department of Radiation Oncology
X	Unknown
Y	Executive Director, National Association for Proton Therapy

Public Comments

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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	ASTRO guidelines are considered under the "Policy Landscape"

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		policy framework for coverage.	section of the CG document; a model payer policy is not appropriate for 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

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			therapy with intensity-modulated radiation therapy 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; however, the subcommittee discussed that RCTs may not be feasible or ethical in this setting and that reduced harms in treatment of sinonasal carcinoma with PBT would justify a recommendation for coverage.
A	10	*Breast Cancer*– A recent population-based study of 2168 woman, [Darby et al N Engl J Med. 2013] (3) found that collateral radiation exposure to the heart during breast cancer X-ray treatment increases the subsequent rate of ischemic heart disease.	Darby et al conducted a case-control study of major coronary events in patients who underwent radiotherapy for breast cancer from 1958 to 2001 in Sweden and Denmark. This was prior to modern advances in radiotherapy when radiation doses are generally lower, and does not address comparative safety of PBT.

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A	11	PBRT can significantly reduce this exposure. Macdonald et al reported the results of a prospective trial of protons after mastectomy for patients with excellent clinical outcome and significant reduction in heart dose when compared to X-rays. [Macdonald et al Int J Radiat Oncol Biol Phys. 2013] (4)	MacDonald et al is a noncomparative study of 12 individuals receiving PBT for breast cancer. While a lower heart dose theoretically will decrease future toxicity, study authors concluded "it is too early to determine cardiopulmonary toxicities in our study" as follow-up was conducted at 4 and 8 weeks.
A	12	*Prostate Cancer*– In a recent publication from the University of Florida, 5 year outcomes from 3 prospective trials of PBT for prostate cancer were reported. Five year rates of biochemical and clinical freedom from disease progression were 99%, 99%, and 76% in low, intermediate, and high risk patients, respectively. Reported toxicity rates were low. These results compare very favorably with those published for IMRT. [Mendenhall et al, Int J Radiat Oncol Biol Phys 2014] (5). We highlight our center's participation in the ongoing "PartiQOL" randomized trial comparing IMRT vs protons for prostate cancer.	The Mendenhall study is a noncomparative observational study of 211 patients; its early outcomes (2012) are included in Table 13, Appendix F (single-arm case series) of the WA HTA report.
A	13	*The True Cost of Protons*- In addition to the significant and growing body of clinical evidence, the cost-effectiveness of PBRT has also been explored. We would highlight that although PBRT is more resource-intensive to deliver upfront, it is aligned with the judicious use of health care dollars. Several recent studies, including these from Harvard have shown that when the costs of side-effects are accounted for, PBRT actually significantly *reduces* health care costs when compared to standard radiation therapy. Therefore, protons when used appropriately are *cost-effective* when compared to photon beam radiotherapy due to reduced hospitalization rates, etc. for side effect management. [Mailhot-Vega Cancer 2013 (6); Mailhot-Vega Cancer 2015 (7)].	Mailhot-Vega 2013 is included in the Washington HTA analysis. Mailhot-Vega 2015 is a Markov cohort-simulation model looking specifically at growth-hormone deficiency in pediatric cancers.
A	14	We urge the Commission to support the coverage of proton therapy and welcome the opportunity to serve as an on-going resource as you are assessing this promising cancer therapy option for Oregonians.	Thank you for your comments.
B	15	I am commenting on the proposed policy regarding Proton Therapy.	Thank you for your comments.
B	16	I was diagnosed in February 2012 with prostate cancer after having a biopsy. My PSA reading had been climbing the previous 2 years and when it reached 10.7, I had the biopsy done. The biopsy showed that I had cancer. My urologist, who was a surgeon, suggested having surgery in August of 2012. He also set me up to speak to a radiation oncologist. I had a CT & Pet scan plus explanations on the different forms of radiation treatments that were available, conventional x-	Thank you for your comments. The coverage guidance does reference one fair-quality prospective cohort study of

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		rays and seeds. Also at this time I joined a local prostate support group. I spoke with the men in the support group plus other men I had met that had prostate cancer to find out how they were doing. I spoke with the men who had surgery or either of the two forms of radiation treatments done. Many of them had procedures done years before. None had Proton Therapy or had heard of it. Every single man I spoke with, no matter how healthy they were or how well their 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.	patient-reported quality of life among 185 men treated for 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.

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B	20	The last thing I want to say is, please don't take away or limit the Proton Therapy option for others who may come after me.	Thank you for your comments.
C	21	After reviewing the commission's draft on coverage guidance for proton beam therapy (PBT), I would like to highlight 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	Commenter notes that Hodgkins patients can expect to live decades, making late toxicity an important outcome. However, late toxicity would also be a concern for other cancers that

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		when late effects of treatment may manifest and impact the patient, medical system, and society from a productivity and financial standpoint. By reducing dose to normal organ structures without compromising oncologic outcomes, protons may, in the long term, be associated with less cost secondary to fewer complication rates. Until then, I would urge you to consider the existing, preliminary data suggesting the dosimetric advantages of protons for treatment of 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.	occur in early adulthood with a high likelihood of survival. Recommendation for noncoverage was made due to lack of comparative clinical outcomes data. In cases where clinical outcomes data could be obtained, dosimetric information was felt to be inadequate to demonstrate a superior clinical outcome.
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.	Thank you for your comments.

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		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.	Studies mentioned by commenter are addressed in CG document.
G	33	Decreased integral dose with PBT has considerable advantages in pediatric malignancies. Growth and development are adversely impacted by radiation. PBT causes less injury. The HERC document describes several studies demonstrating the benefits of PBT in pediatric patients. Secondary malignancy reduction takes many years of followup to study. Preliminary data as cited in this document indicates a reduction in secondary malignancy.	As noted on Table 1, PBT was judged to have incremental net health benefit for pediatric cancers.
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

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			is to not cover.
H	38	*Locally Advanced NSCLC*: Definitive chemoradiotherapy is the standard of care for locally advanced non-small cell lung cancer, however this treatment has the potential to carry significant toxicity. At present, LC with standard dose radiotherapy in locally advanced disease is suboptimal, with 50-60% patient experiencing relapse of their disease. One approach to improve LC is increasing the radiation dose delivered to the cancer. However, this potential improvement comes at the expense of greater toxicity. Unfortunately, attempts at dose escalation with standard X-rays in lung cancer have hit a 'toxicity ceiling' whereby the resulting increased toxicity from dose actually may reduce survival, based upon a recent randomized trial with X-rays (1).	Commenter references Bradley JD et al 2015, demonstrating that 74Gy radiotherapy had no additional benefit and possibly increased mortality compared to 60Gy radiotherapy, or a "toxicity ceiling."
H	39	In a phase II trial of dose-escalated PBRT concurrent with chemotherapy for 44 patients with stage III NSCLC, MD 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%,	Commenter notes that SBRT may not be used for centrally located tumors, whereas PBRT

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		and 51%, respectively (P=0.006). (4)	may improve survival by allowing delivery of higher radiation doses. The studies of PBRT in medically inoperable NSCLC were non-comparative and were included in the review by the Washington HTA. Additionally, there is an ongoing RCT (NCT00915005) comparing photon and proton therapy for locoregionally advanced NSCLC (stages II-IIIb, no specific exclusion of patients with medically inoperable tumors).
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.	See comment H41.
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)	There is no comparative evidence currently available that demonstrates the superiority of PBRT to other forms of radiation therapy, surgery, chemotherapy, or palliative care for intrathoracic recurrence of NSCLC.
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	See comment A 13.

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		beam radiotherapy due to reduced hospitalization rates, etc. for side effect management. (6,7)	
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.
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. Discussion of coverage with evidence development and/or reference pricing is not in the

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			purview of this subcommittee.
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 United States, but the magnitude of superiority depends strongly on the patients' anatomical development status.” HTAS has chosen to recommend coverage of PBT for pediatric patients.
J	60	In the case of rhabdomyosarcomas of the head and neck, particularly the orbit, proton radiotherapy allows the	Childs 2012 is included in the

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		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.	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. The subcommittee recommended coverage of PBT for pediatric tumors.
J	62	Head & Neck Cancers -A meta-analysis evaluating the role of photons and charged particle therapy for sinonasal carcinoma demonstrated improved disease-free survival (DFS) and LC with charged particle therapy; subgroup analysis comparing IMRT and PBRT confirmed that 5-year DFS was significantly higher at five years for patients receiving PBRT (72% versus 50%) [Patel et al, Lancet Oncol 2014].	See also comment A9 regarding Patel 2014. PBT for sinonasal carcinoma is recommended for coverage.
J	63	Breast Cancer-A recent population-based study of 2168 woman, [Darby et al N Engl J Med. 2013] found that collateral radiation exposure to the heart during breast cancer X-ray treatment increases the subsequent rate of ischemic heart disease. PBRT can significantly reduce this exposure. Macdonald et al reported the results of a prospective trial of protons after mastectomy for patients with excellent clinical outcome and significant reduction in heart dose when compared to X-rays. [Macdonald et al Int J Radiat Oneal Bioi Phys. 2013]	See comments A10, A11.
J	64	The Cost of Protons for Children-The cost-effectiveness of PBRT in pediatric malignancies has been explored. We would highlight that although PBRT is more resource-intensive to deliver upfront, it is aligned with the judicious use of health care dollars. Lundqvist et al examined the cost of proton beam radiotherapy for childhood medulloblastoma and found that proton therapy was associated with €23,600 in cost savings and 0.68 additional quality-adjusted life-years per	Lundkvist 2005 is discussed extensively in the WAHTA report used for this CG.

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		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]	
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. Following public comment and expert testimony, the subcommittee recommended coverage of PBT for certain head and neck cancers; namely, skull-base tumors, paranasal sinus tumors, and juxtaspinal tumors.
L	68	Skull Base Tumors One of the challenges with skull-based tumors is their proximity to the brainstem and optic structures, which can be dose-limiting organs when treating relatively radio resistant histologies such as chordomas and chondrosarcomas. With conventional photon radiotherapy, dose is limited to 55 Gy and associated with an inferior local control (LC) rate of	Commenter notes poor local control rate when dosimetry is limited by nearby organs. Reference 1 is a review article from 1999. Direct comparative

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<tr><td></td><td></td><td>approximately 30-50% (1). In contrast, LC for these skull-based chordomas and chondrosarcomas is higher with charged particle therapy, as summarized in the following table:</td><td>studies are not provided. HTAS recommends skull base tumors for coverage.</td></tr>
<tr><td>L</td><td>69</td><td>TABLE: LC Rates for Sarcomas or Chordomas of the Skull Base treated with α-Particles or Protons
<table>
<tr><th>Facility</th><th>Chordoma</th><th>Chondrosarcoma</th><th>Sarcoma (other)</th></tr>
<tr><td>LBNL (2)</td><td>63%</td><td>78%</td><td>58%</td></tr>
<tr><td>HCL-MGH (1,3)</td><td>59%</td><td>99%</td><td></td></tr>
<tr><td>LLUMC (3)</td><td>76%</td><td>92%</td><td></td></tr>
<tr><td>Orsay (4)</td><td>83%</td><td>90%</td><td></td></tr>
<tr><td>Tsukuba (5)</td><td>46%</td><td></td><td></td></tr>
<tr><td>PSI (6)</td><td>88%</td><td>100%</td><td></td></tr>
</table></td><td>Reference 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.

The subcommittee heard testimony that comparative data in this setting are not feasible. Treatment decisions are made by dosimetry calculations and these can be impacted by exposure of nearby structures. PBT for skull base tumors is recommended for coverage.</td></tr>
<tr><td>L</td><td>70</td><td>In the Loma Linda University Medical Center (LLUMC) series, all "small and medium size" tumors without brainstem involvement were controlled with only a 7% incidence of late toxicity. (3)</td><td>This case series of 204 patients was conducted from 1975-1993</td></tr>
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			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 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	See also comment A9 regarding

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		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).	Patel 2014. PBT for sinonasal carcinoma is recommended for coverage.
L	78	Juxtaspinal Tumors When tumors are invasive or adherent to critical structures such as the vertebral body, spinal cord, or peripheral nerve roots, complete resection is difficult to achieve. Because the tumor is adjacent to the cord, with conventional radiotherapy techniques, dose to the tumor is limited by the cord's tolerance to radiation, 50-55 Gy. The use of protons or other charged particles allows one to wrap the high dose volume around and avoid the spinal cord; tumors can therefore be treated to 70 CGE with proton radiotherapy.	It is noted that radiation of juxtaspinal tumors is limited by tolerance of adjacent spinal cord.
L	79	Among 51 patients with cervical spine chordomas treated at MGH-HCL, LC was 65% (3). Nowakowski et al described a series of 52 patients with juxtaspinal tumors of varying histologies and locations treated with D-particles at the Lawrence Berkeley Laboratory; 16 of these were located in the cervical spine (13). The overall LC was 58% for 36 patients with previously untreated lesions.	Reference 3 is discussed under comment 69. Reference 13 is a case series of 52 patients treated from 1976-1987. No comparative data are identified.
L	80	Oropharyngeal Tumors Using a combination protons and photons in an accelerated fractionation schema, LLUMC treated 29 patients with locally-advanced, oropharyngeal carcinomas (13). The overall, 5-year actuarial loco regional control rate was 84% (88% primary site, 96% neck nodes); 5-year disease-free survival was 65%.	See comment 79.
L	81	Frank et al presented data at the 55th Annual Meeting of the American Society for Radiation Oncology showing that patients with orophalyngeal tumors treated with protons had a substantially lower requirement for feeding tubes during therapy than a comparable group of patients treated with IMRT (20% vs. 48%) and less nausea, emesis, and mucositis. A subsequent report on 15 head and neck cancer patients treated using multifield optimization of IMPT showed only one case of grade 3 mucositis in the posterior oral cavity; there was no grade 2 or higher mucositis in the anterior oral cavity (15).	Reference 15 is a case series of 15 patients, reporting “the first clinical experience and toxicity of multifield optimization (MFO) intensity modulated proton therapy (IMPT) for patients with head and neck tumors.” No comparative data are identified.
L	82	Retreatment of Treatment Failures Management of patients with recurrent head and neck cancer who have failed an initial, radiation based treatment is challenging. Re-irradiation with photons, with or without chemotherapy, is associated with 34-65% grade 3+ toxicity. For	Reference 16 is a 2013 dose-planning study of 7 patients, comparing helical tomotherapy

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		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).	to IMPT. "IMPT was found not to be uniformly superior to HT… comparative dose planning is recommended if both methods are available." The subcommittee heard testimony that comparative dose planning is standard of care and that PBT will be recommended only when comparative dose planning finds it likely to be superior for a given patient. Coverage of PBT is recommended for malignant brain, spinal, skull base, paranasal, and juxtaspinal tumors [whether they are initial or recurrent]
M	83	Dear Commission Members: The American Society for Radiation Oncology* (ASTRO), appreciates the opportunity to comment on the Oregon Health Evidence Review Commission (HERC) Coverage Guidance for Proton Beam Therapy. We are concerned that the HERC Coverage Guidance is overly restrictive, inconsistent with current literature, and will have a detrimental effect on vulnerable populations who derive the most benefit from access to proton beam therapy.	Thank you for your comments.
M	84	Proton beam therapy (PBT) is neither a new nor an experimental technology for treating cancer with radiation. It utilizes proton radiation particles to deliver highly conformal radiation therapy to a specific tumor target area while giving a much lower dose to the normal tissues in the proton beam's path of entry and exit. PBT's reduced radiation dose to healthy tissues can reduce side effects for patients with demonstrated effectiveness in increasing quality of life. To date, scientific evidence exists confirming that PBT is particularly useful in a number of pediatric cancers, particularly those in the brain, as well as for certain adult cancers, such as ocular melanoma, chordoma, chondrosarcoma, and primary hepatocellular carcinoma. Patients with genetic syndromes and those with tumors near the spinal cord with previous irradiation also benefit from the use of PBT. Additional research on other cancer disease sites, such as breast, prostate and lung, is ongoing with NCI-supported clinical trials currently accruing patients in all three disease sites at the more than 14 proton therapy treatment centers around the country.	This information is correct and consistent with the CG report.

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M	85	In June 2014, ASTRO released a PBT Model Policy that identifies cancer diagnoses that meet ASTRO's evidence-based standards that should be covered by private insurers and Medicare. This Model Policy recommends two coverage groups for PBT: 1) patients with specific diagnoses for which PBT has been proven to be effective; and 2) patients with cancer diagnoses where there is a need for continued clinical evidence development and comparative effectiveness analyses for the appropriate use of PBT. For the patients in group two, coverage with evidence development is recommended for patients if they are enrolled in clinical trials or a multi-institutional registry to collect data and inform consensus on the role of proton therapy.	Please see comment 5.
M	86	The HERC Coverage Guidance is especially concerning because it declines to provide coverage for pediatric malignant tumors. PBT is an important treatment option for certain pediatric tumors, since damage to the surrounding normal tissues in children can produce serious long-term side effects on the growth and development of vital organs and tissues. A growing body of literature shows the late effects, quality of life, and cost effectiveness of proton beam therapy on pediatric patients. Randomized studies are not feasible given the general acceptance of PBT for pediatric 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)	It is noted that comparative studies are unlikely to be conducted in pediatric tumors due to lack of clinical equipoise. The subcommittee recommended coverage of PBT for pediatric tumors.
M	87	Additionally, we are unaware of any coverage policies that deny coverage of PBT for pediatric tumors, and we are concerned that the denial of PBT coverage for pediatric patients will considerably restrict children's access to curative and palliative treatment. ASTRO strongly recommends that HERC extend coverage to include primary or benign solid tumors in children, per the ASTRO PBT Model Policy.	Thank you for your comments.
M	88	PBT has attracted significant attention due to its relative cost, which is usually higher than traditional external beam radiation therapy. However, studies now suggest that proton therapy can be a cost-effective strategy for the management of certain cancers. (2, 3, 4) In one study, proton beam therapy was proven to be associated with higher quality-adjusted life years and lower costs. (5)	The cost studies referenced were considered in the WAHTA report on which our CG is based.
M	89	Furthermore, we are concerned that in developing this coverage guidance, HERC did not consult the opinions of experts in the field nor did they review the full body of evidence surrounding proton beam therapy as an effective form of cancer treatment. We are very surprised that the ASTRO PBT Model Policy, which was carefully developed by leading radiation oncologists and medical physicists and benefitted from balanced input from experts in proton therapy, was not cited as a reference in the HERC Coverage Policy for Proton Beam Therapy.	The coverage guidance process solicits expert input as well as public comment such as this one. Please see comment 5 regarding ASTRO.
M	90	ASTRO is committed to providing evidence-based guidance to payers in the form of recommendations for correct coverage policies for radiation oncology. We encourage HERC to follow the lead of many national private and public insurers by consulting the evidence and following the recommendations in ASTRO's PBT Model Policy when developing coverage policies for PBT. The ASTRO PBT Model Policy is enclosed for your review, in addition to a list of references and	Thank you for your comments.

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		supporting articles.	
M	91	Thank you for your consideration of our comments. Should you have any questions or wish to discuss our concerns further, please contact ASTRO's Director of Health Policy	Thank you for your comments.
N	92	Dear Oregon Health Evidence Review Commission: As a Radiation Oncology faculty member at the University of Washington, I specialize in caring for patients of all ages with central nervous system tumors. A minority of my patients are treated with proton beam therapy. For these patients, proton beam therapy provides the best chance of curing their brain tumors while minimizing significant side effects. Proton beam therapy has no exit radiation dose, which patients would otherwise receive if treated with x-rays. This is especially important in the central nervous system where very low doses of radiation to normal brain can cause neurocognitive decline, hormonal deficits, and secondary malignancies. For spinal cases, low dose radiation to the anterior organs is associated with nausea and lower blood counts in the short term; and heart disease and secondary malignancies in the long term.	Thank you for your comments.
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

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			radiation in the expected treatment field with contraindication to all other forms of therapy, and b) At agency discretion Following public testimony and expert input, the subcommittee recommended coverage of PBT for malignant brain and spinal tumors.
N	94	Summary of Evidence *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	Reference 6 is a phase III trial

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		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)	comparing chemotherapy + radiotherapy vs radiotherapy alone in 291 patients. Median survival was not different between groups for the whole cohort. The 14-year figure applies to patients with codeleted tumors only, which was not a predefined subgroup analysis. Reference 7 is an editorial describing long-term follow up 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.

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			Direct comparative data of PBT vs other treatment is not identified.
N	100	*Adult benign brain tumors (e.g. meningioma, vestibular schwannoma, pituitary adenoma):* Multiple series document the outcomes of proton therapy for the treatment of meningioma (10-13), pituitary adenoma (14), and vestibular schwannoma (15). For patients with benign disease and good long term prognosis, proton beam therapy decreases the risk of neurocognitive decline, endocrine dysfunction, and secondary malignancy. (16, 17)	References 10-13 are considered in the WAHTA evidence review. Reference 14 was published after the WAHTA review. It is a case series of 165 patients with functional pituitary adenoma treated from 1992-2012. Reference 15 is a case series of 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	It is noted that studies of proton

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		radiation therapy. Recent data suggests that increasing the radiation dose for initial treatment or giving a second course of radiation therapy for recurrent gliomas will improve outcomes. However, past efforts to escalate dose or re-irradiate have resulted in considerable toxicity. Thus, we are participating in two national cooperative group NRG Oncology clinical trials, BN001 and RTOG 1205. (19, 20) Both trials use proton therapy with the aim of improving survival for this otherwise devastating disease.	beam for GBM are in progress. Studies in progress will be considered after peer review and publication.
N	103	*Cost effectiveness:* Recent studies that modeled the cost of long term effects of radiation therapy for pediatric patients with brain tumors found that proton therapy is overall cost effective. (21, 22) Indeed, in my practice I find that long term survivors of brain tumors may be cured but have considerable late effects including neurocognitive decline and hormonal deficiency that are costly to the patient in terms of their ability to work and to payers in terms of medical care.	References 21 and 22 are the two papers by Mailhot Vega; please see comment 13.
N	104	I urge the Commission to support coverage of proton therapy for central nervous system tumors and welcome the 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 recommended coverage of PBT for pediatric tumors.
P	108	Evidence on the Effectiveness of PBT for Pediatric Malignant Tumors The proposed coverage guidance gave a weak recommendation for coverage for pediatric malignant tumors, despite the	The HTAS recommended coverage of PBT for pediatric

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		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.	tumors.
P	109	Due to the growing body of evidence in this area, most payors, regulators and providers support the use of PBT for pediatric patients. The consensus is reflected in the American Society for Radiation Oncology (ASTRO) model policy on PBT which supports its use for primary or benign solid tumors treated in children with curative intent (ASTRO, 2014). (1) Examples of published evidence in this area include a recent study of 54 patients with pediatric rhabdomyosarcoma which found that PBT lowers integral dose and improves sparing normal tissue when compared to IMRT [Ladra, MM et al Radiother Oncol 2014]. (2)	Please see comment 5 regarding ASTRO. Ladra 2014 is a prospective cohort study of 54 patients who received proton therapy; IMRT plans were generated for comparison.
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;	Cuaron (2015) is a case series that assessed dosimetry and early toxicity of PBT in 30 patients with metastatic breast cancer. Dosimetry was deemed adequate and toxicity was deemed acceptable. Holliday (2015) is a case series that assessed local control (58%), relapse-free survival (51.9%), and overall survival (93.3%) in 19 patients with

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		DOI:10.1111/ped.12624. • Vega RM, Kim J, Hollander A, Hattangadi-Giuth J, Michalski J, Tarbell NJ, Yock Tl, Bussiere M, MacDonald SM. Cost effectiveness of proton versus photon radiation therapy with respect to the risk of growth hormone deficiency in children. *Cancer.* Published online January 29, 2015. 2014 • Brower *N,* Gans S, Hartsell WF, Goldman S, Fangusaro JR, Patel N, Lulla RR, Smiley NP, Change JH, Gondi V. Proton therapy and helical tomothrapy result in reduced dose deposition to the pancreas in the setting of cranio-spinal irradiation for medulloblastoma: implications for reduced risk of diabetes mellitus in long-term survivors. *Acta Oncol.* 2014 Nov: 1-5. • Frank SJ, Cox JD, Gillin M, Mohan R, Garden AS, Rosenthal DI, Gunn GB, Weber RS, Kies MS, Lewin JS, Munsell MF, Palmer MB, Sahoo N, Zhang X, Liu W, Zhu XR. Multifield optimization intensity modulated proton therapy for head and neck tumors: a translation to practice. *Int J Radiat Oncol Bioi Phys.* 2014 Jul 15;89(4):846-53. • Kesarwala AH, Ko CJ, Ning H, et al. Intensity-modulated proton therapy for elective nodal irradiation and involved-field radiation in the definitive treatment of locally advanced non-small cell lung cancer: a dosimetric study. *Clinical Lung Cancer.* Available online 9 December 2014. • Ladra MM, Szymonifka JD, Mahajan A, et al. Preliminary results of a phase II trial of proton radiotherapy for pediatric rhabdomyosarcoma. *J Clin Oncol.* 2014 Oct 20; epub ahead of print. • Ling TC, Slater JM, et al. Analysis of intensity-modulated radiation therapy (IMRT), proton and 3D conformal radiotherapy (3D-CRT) for reducing perioperative cardiopulmonary complications in esophageal cancer patients. *Cancers.* 2014;6(4):2356-2368. • Makita C, Nakamura T, Takada A, Takayama K. Suzuki M, Amazi Y, Kato T, Tsukiyama I, Hareyama M, Kikuchi Y, Daimon T, Hata M, Inoue T, Fuwa N. High-dose proton beam therapy for stage I non-small cell lung cancer: clinical outcomes and prognostic factors. *Acta Oncol.* 2014Oct 7:1-8 (Epub ahead of print). • Patel SH, Wang Z, Wong WW, Murad MH, Buckey CR, Mohammed K, Alahdab F, Altayar 0, Nabhan M, Schild SE, Foote RL. Charged particle therapy versus photon therapy for paranasal sinus and nasal cavity malignant diseases: a systematic review and meta-analysis. *Lance/ Oncol.*2014 Aug; 15(9): I 028-1038. • Schild SE, Rule WG, Ashman JB, Vora SA, Keole S, Anand A, Liu W, Bues M. Proton beam therapy for locally advanced lung cancer: a review. *World J Clin Oncol.* 2014 Oct 10;5(4):568-75. • Sethi RV, Shih HA, Yeap BY, et al. Second nonocular tumors among survivors of retinoblastoma treated with	chordoma or chondrosarcoma treated with PBT. Patients with primary adjuvant radiation therapy had better 2 year LC than those receiving salvage treatment. Mizumoto (2015) is a case series that assessed local occurrence and toxicity in 6 pediatric patients with ependymoma treated with PBT. Simulation showed that PBT reduces dose to normal brain tissue by half compared to photon therapy. All patients were alive at follow up (13-44 mo) and there was no severe toxicity. Mailhot Vega (2015) is a cost-effectiveness study of PBT compared with photon therapy for pediatric patients with growth hormone deficiency.PBT is cost effective in some scenarios based on hypothalamic sparing. Brower (2014) is a case series that assessed dosimetry of PBT compared with 3DCRT and inverse-planned intensity modulated radiation therapy (IMRT) with helical tomotherapy in five pediatric patients with medulloblastoma. PBT resulted in less radiation to the pancreas

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		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 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]	than other treatments. Franks (2014) is a case series that assessed toxicity of multifield optimization intensity modulated PBT in 15 patients with head and neck cancer. There were no treatment-related deaths, and with a median follow-up time of 28 months (range, 20-35 months), the overall clinical complete response rate was 93.3% Kesarwala (2015) is a case series that assessed intensity-modulated PBT dosimetry in 20 patients with locally advanced non-small cell lung cancer. All evaluated dosimetric parameters improved significantly with proton plans compared with photon IFRT. Ladra (2014) is a case series that assessed disease control and toxicity of 57 pediatric patients with rhabdomyosarcoma treated with PBT. Five-year LC, EFS, and OS rates were similar to those observed in comparable trials that used photon radiation. Acute and late toxicity rates were favorable. Ling (2014) is a case series that assessed dosimetry of IMRT,

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			3DCRT and PBT in 10 patients with esophageal cancer. Authors conclude proton plans are technically feasible while achieving adequate coverage with lower doses delivered to the lungs and cardiac structures. Makita (2015) is a case series that assessed survival, local control, and toxicity in 56 patients with stage I non-small cell lung cancer treated with two PBT protocols. The three-year overall survival, progression-free survival, and local control rates were 81.3%, 73.4%, and 96.0%, respectively. There were no significant differences in outcomes between the two protocols. Late grade 2 and 3 pulmonary toxicities were observed in nine patients and one patient respectively; no grade 4 or 5 toxicities were observed. Patel (2014) is a systematic review and meta-analysis that compares clinical outcomes from PBT and charged particle therapy. Forty-one case series studies were included that reported on overall survival, disease-free survival, and local control. None of the included

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			studies were comparative. The review found higher overall survival and locoregional control for charged particle beam than PBT at longest follow-up (not defined), and no difference in disease-free survival at longest follow-up between groups. Schild (2014) is a narrative review on the use of PBT as part of a multi-modal treatment program for patients with locally advanced lung cancer. "This review was written for the non-radiation oncologist who wishes to understand the use of proton beam therapy (PBT) for locally advanced lung cancer. One randomized study is being performed and another is planned to clarify the differences in outcome for PBT compared to XRT. Newer forms of radiotherapy such as PBT should positively impact lung cancer patients." Sethi (2014) is a retrospective case series that assessed recurrence rates in 86 patients with retinoblastoma treated with PBT or photon radiotherapy. The 10-year cumulative incidence of RT-induced or in-field second

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			malignancies was significantly different between radiation modalities (proton vs photon: 0% vs 14%; P = .015). The 10-year cumulative incidence of all secondary malignancies was also different, although with borderline significance. Thanker (2014) is a time-driven activity-based costing study of two patients with advanced head and neck cancer treated with IMRT and intensity-modulated PBT. It is published in a non-peer-reviewed journal. Authors conclude that the episodic cost of care using IMPT was less costly and of higher value than IMRT. Yock (2014) is a case series that compared parent proxy health-related quality of life scores of 57 pediatric brain tumor patients treated with PBT with those of 63 pediatric brain tumor patients treated with photon beam radiation. The total core HRQoL score for the PRT-C, XRT-C, and normative population differed from one another and was 75.9, 65.4 and 80.9 respectively (p=0.002; p=0.024; p<0.001). HRQoL of pediatric brain tumor survivors

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			treated with PRT compares favorably to those treated with XRT and similar to healthy controls. The HTAS recommended coverage of PBT for pediatric tumors based on reviewing the limited evidence, expert testimony, and the lack of clinical equipoise that means future trials are unlikely to be conducted.
P	113	For further evidence, we highlight the multiple national guidelines that support the use of proton therapy. The National Comprehensive Cancer Network (NCCN) guidelines, the previously cited ASTRO model policy for proton therapy, and the model policy on coverage of proton beam therapy from the National Association of Proton Therapy (NAPT) both approve of the use of proton therapy for certain patients. The basis for these national guidelines is the growing body of evidence supporting the use of proton therapy for positive long-term treatment outcomes and quality of life for oncology patients. The weight of this evidence is reflected in the numerous Medicare contractors and private payors policies that provide coverage for PBT for a number of anatomical sites.	The guidelines cited are included in the CG document, with the exception of the NAPT. Staff were unable to identify guidelines via search of the NAPT website.
P	114	*PTCOG-NA urges you to* postpone finalizing *this coverage guidance and reconsider your methodology of reviewing clinical evidence. We offer the assistance of our clinical leadership to assist you with any review.*	Thank you for your comments.
P	115	Evidence on the Cost Effectiveness of PBT An overarching benefit of PBT versus photon therapy is its precise targeting that spares very sensitive adjacent normal tissue, resulting in reductions in toxicity and other negative occurrences post-treatment. We are very concerned that you failed to consider these benefits. A study published in *Cancer* [Mailhot Vega, RB et al, *Cancer* 2013] found that by avoiding years of costly side effects, PBT can be cost-effective for children with medulloblastoma.	Please see comment 13.
P	116	An example of this more comprehensive analysis is a recent study issued by MD Anderson Cancer Center and presented at the October 2014 meeting of PTCOG-NA (manuscript under development). The study found that the cost of PBT when used for accelerated partial breast irradiation to decrease overall treatment time and toxicity, was estimated at $13,833. Results of the study suggested that the cost of proton therapy is similar to other types of radiation.	Commenter references unpublished data; new published evidence will be considered as the CG enters re-review every 2 years.

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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 in local control with the higher dose proton boost with a very low risk of GU or GI complications.	References 1 and 2 are considered in the WAHTA report.
Q	122	A number of single institutional experiences have also reported excellent long term outcomes with proton therapy. Loma Linda reported a series of 1255 patients with prostate cancer treated with either protons or a combination of x-rays and protons. (3) Survival rates were excellent, and the risk of severe GU or GI complications was extremely low.	Reference 3 is a retrospective cohort study of 1255 patients treated with proton radiation therapy from 1991-1997. Authors concluded that disease-free survival rates were comparable with other forms of local therapy. Authors also concluded that "No difference was seen in toxicity between those treated with combined protons and photons (11 of 731) and those with protons alone (6

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			of 524; p = 0.52).
Q	123	More recently, University of Florida reported their 5-year control rates from 3 prospective PBT trials for prostate cancer: 99%, 99%, and 76% in low, intermediate, and high risk patients, respectively. Among 211 patients, only 1-2% experienced serious late toxicity. These results compare very favorably with published results for IMRT. (4)	Reference 4 is a report of three prospective trials encompassing 211 prostate cancer patients. The data on control rates are correct. Rates of grade 3 GI toxicity were 1.0% and rates of grade 3 urologic toxicity were 5.4%. Within-trial comparative data are not available; commenter is referencing historical IMRT data from other publications.
Q	124	An advantage of PBT is decreased exposure of normal pelvic tissues to low to moderate dose radiation (0-50 Gy). Low-dose radiation to pelvic structures is associated with bowel and bladder urgency, frequency, erectile dysfunction and secondary cancers. (5). These side effects can drastically influence a patient's quality of life (QOL).	Reference 5 is a retrospective questionnaire study of bowel, urinary, and sexual function in 65 patients who received external beam radiation therapy for localized prostate cancer. Within-trial comparative data are not available.
Q	125	No randomized, prospective studies exist comparing IMRT and PBT. Several attempted retrospective comparisons have been conducted using large, national databases including SEER, but these studies suffer from major weaknesses including lack of granular details on side effects such as rectal urgency, poor surrogates for measures of GI toxicity, and comparison based on historical cohorts of small numbers of patients treated with now outdated proton therapy techniques/technology. In one QOL study comparing men treated with IMRT versus PBT, there was less rectal urgency and frequency in men treated with PBT than IMRT. (6)	It is noted that prospective randomized studies exist. Reference 6 is a comparison of QOL data from two different cohort studies, 1243 men receiving PBT and 204 men receiving IMRT. There were **no differences in QOL summary scores** between the IMRT and PT cohorts during early follow-up (up to 2-years). Response to individual questions suggests

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			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. Regarding CED, please see comment J57.
R	130	To Whom It May Concern: This letter is in regards to the Oregon Health Evidence Review Commission coverage guidelines for proton beam therapy. As an assistant professor in the department of radiation oncology at the University of Washington, I sub-specialize in breast cancer and would like to comment on the use of proton beam therapy for breast cancer.	Thank you for your comments.
R	131	Proton beam therapy is currently being used in the treatment of breast cancer in many proton centers across the country. The largest, single-institution experience to date using proton beam therapy for breast cancer comes from Loma Linda, where at last publication in 2014, one hundred women with *early stage breast cancer* had been treated with proton beam therapy following surgery (lumpectomy) as part of breast-conserving therapy. (1) When compared with 3-dimensional conformal photon plans for partial breast irradiation, Bush *et al.* reported a significant reduction in exposure to surrounding normal breast tissue with proton beam therapy that led to improved cosmetic outcomes. (2) There was also nominally lower radiation dose to the lung and heart with proton.	Data from the Loma Linda trial are considered in the WAHTA report. Reference 1 was published after the WAHTA report and reports 5-year follow up data on this phase 2 trial of 100 patients; results are not significantly different from prior

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			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.
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	Thank you for your comments.

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		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.	
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 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	Commenter describes a scenario

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		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.*	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**

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	WAHTA identified no comparative studies of the clinical effectiveness of primary PBT in gastrointestinal cancers. Pancreatic cancer data were

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		compromise full completion of treatment. (3)	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 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*	Thank you for your comments.

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		this important cancer therapy option for Oregonians.	
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 been. The team of radiologists were 'my' team and treated me with respect, humor and a positivity beyond belief. I felt I could share my concerns, emotions and joys with them all. I cried when I had finished my regime of treatments, knowing I wouldn't be seeing them every day again. By the way, my only side affects included some tiredness and hair loss of the area radiated (which has since grown back) and missing 'my team' !	Thank you for your comments.

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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 minimal. The treatment here at the SCCA Proton Center in Seattle has been very professional, and my wife and I both felt very encouraged by the whole process, from intake through the daily treatments and the weekly meetings with nurses and my oncologist.	Thank you for your comments.

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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, 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	Thank you for your comments.

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		pediatric cancers abutting or close to the central nervous system, such as rhabdomyosarcomas of the face and orbit.	
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 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

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			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 Xray craniospinal irradiation in a single patient. Reference 9 is addressed in comment 59. References 10 and 11 are addressed in comment 13. HTAS recommended coverage of pediatric malignant tumors.
W	166	Thank you for this opportunity. Should you have any questions please do not hesitate to contact me	Thank you for your comments.

ID	#	Comment	Disposition
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 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	Identical letter to that submitted by commenter P; see responses above

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		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. • 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	

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		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 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] 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 - 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	

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		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	

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