

Proton Beam Therapy – Re-review

Final evidence report: Peer review, comment and response

April 15, 2019

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Proton Beam Therapy: Re-Review

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April 15, 2019

Responses to clinical and peer reviewers

Aggregate Analytics Inc. is an independent vendor contracted to produce evidence assessment reports for the Washington Health Technology Assessment (HTA) program. For transparency, all comments received during public comment periods are included in this document and attachments. Comments related to program decisions, process or other matters not pertaining to the evidence report, are acknowledged through inclusion only.

Specific responses pertaining to peer reviewer comments are included in **Table 1**. Draft report peer reviewers include:

- Yolanda Tseng, MD, Assistant Professor of Medicine, Department of Oncology, University of Washington Medical Center, Seattle Cancer Care Alliance
- Smith “Jim” Apisarnthanarax, MD, Associate Professor of Radiation Oncology, Associate Residency Program Director, Proton Therapy Fellowship Director, University of Washington School of Medicine

Responses to public comments from medical and professional organizations may be found in **Table 2**. These include:

- Cat Livingston, MD, MPH, Associate Medical Director, Health Evidence Review Commission, Oregon Health Authority
- Scott Warwick, Executive Director, National Association for Proton Therapy (NAPT)
- Annika Andrews, President & CEO, Seattle Cancer Care Alliance (SCCA)
- Ramesh Rengan, MD, PhD, Professor & Interim Chair, UW Dept. of Radiation Oncology; Medical Director SCCA Proton Therapy Center Associate Member, Clinical Research Division, Fred Hutchinson Cancer Research Center
- Jeff Sperring, MD, CEO, Seattle Children’s Hospital
- Daniel E. Smith, Executive Director, Alliance for Proton Therapy Access
- Deepak Khuntia, MD, Senior Vice President and Chief Medical Officer, Varian Medical Systems

We are also grateful to the numerous individuals who provided general public comment (i.e., not addressing evidence, project scope, or draft key questions) on the topic of proton beam therapy. A list of the names of those who contributed can be found after **Table 2** below.

Full texts of peer reviews and public comments may be found in the appendix immediately following the list of individuals who provided general public comment.

Table 1. Responses to Clinical and Peer Reviewers

Comment		Response
Yolanda Tseng, MD, Assistant Professor of Medicine, Department of Oncology, University of Washington Medical Center, Seattle Cancer Care Alliance		
Specific comments		
Executive Summary; page viii	Please add abbreviation for HART, TACE. On subsequent revision, please add line numbers so that it is easier to reference	The requested abbreviations have been added.
ES-1; Paragraph 1	For sentence beginning with “PBT may be most promising for tumors in close proximity to OAR ...”, it may be helpful to clarify what “close proximity” means. Protons do not necessarily have superior sparing of OARs that are immediately adjacent to a tumor (e.g. <1 cm), and the greater benefit of protons may be to spare OARs that are of moderate distance away from the target (e.g. >2 cm).	The wording in this sentence has been changed from “in close proximity to” to “in moderate proximity to (>2 cm)”.
ES-2; line 5, paragraph 2	<p>Would remove “nausea” from the sentence. This depends on the location that is being irradiated, whereas fatigue and skin irritation are nearly universal.</p> <p>For the sentence beginning with “The development of linear accelerators (LINACs) ...”, I would consider the word choice of “accelerated particles”. While a photon is an elementary particle, particle may also be construed as neutrons, protons, carbon ions.</p> <p>For sentence beginning with “Stereotactic radiosurgery and SBRT are similar to IMRT ...” I would clarify that in addition to dose per fraction, another major difference is immobilization (more rigid for SBRT as the planning target volume margins are smaller).</p> <p>For sentence beginning with “Photons are the negatively charged ...” Photons are not negatively charged. They have no mass or charge.</p>	<p>Nausea has been removed from the sentence.</p> <p>The sentence has been modified to reflect the suggested clarification</p> <p>This sentence has been modified to reflect the suggested clarification.</p> <p>This sentence has been changed accordingly.</p>
ES-3; figure 1, paragraph after figure 1	<p>The dose distribution illustrated for the x-ray (photon) beam is inaccurate. The skin dose for photons is generally LOWER than that of the spread out Bragg peak of protons. The original figure from the referenced paper (151) illustrates the correct photon depth-dose distribution relative to protons. I would modify this figure so that it correctly illustrates the physical dose distribution of photons.</p> <p>It is misleading to state that the spread out Bragg peak (SOBP) is comprised from radiation dose from multiple beams, as “beams” usually refer to the different directions that radiation is directed (i.e. an anterior beam and a lateral</p>	<p>This was the figure used in the 2014 ICER report. A modification has replaced in the final report.</p> <p>This sentence has been modified to reflect the suggested clarification.</p>

	beam). The SOBP is created by varying the energy of a proton beam, creating a range of energies. For example, a shallower beam will have lower energy compared to a deeper beam.	
ES-4; Line 7	Would replace “dose level” to “dose per fraction”	These changes have been made.
Line 9-11	Please include reference for the referenced study “one study identified situations ...”	
ES-10; Table	<p>Please include abbreviation for ECON, TSR. For the number of case studies included for a particular disease site (e.g. lymphoma), what was the eligibility/ineligibility criteria for including a case series? I treat heme malignancies and there are >1 case series published among lymphoma patients receiving proton therapy, notably for non-Hodgkin lymphoma. There is also publications on toxicity after proton therapy for lymphoma, in particular pulmonary function tests and cardiac MRIs. I cannot comment on other disease sites as I am not up to date with the pertinent proton literature. However, as there are discrepancies with what case series have been included in the review and other case series that may be pertinent, it may be helpful to provide more detail why certain publications were not included. Was it because they were missed in the initial review of the literature or excluded for eligibility and if so, why?</p>	<p>ECON and TSR have been added to the abbreviation list at the end of the table.</p> <p>We evaluated the citations provided and included those meeting our inclusion criteria.</p> <p>Detail of citations excluded at full text is included in the appendices. Some studies may have been excluded at title/abstract level as they may not have met inclusion criteria. Consistent with the 2014 report, we focused on comparative studies performing a direct comparison of treatments in the same underlying patient population. The report includes over 150 case series across a wide range of tumor types, including studies that may have contained rare tumor types either alone or in combination; descriptive information is provided in the report and detailed in the appendices and provide context regarding the ranges for primary outcomes following PBT. While our report and the previous report likely have not captured all case series for a given cancer or for all rare cancers, the inclusion of additional case series does not provide additional evidence to answer the question of comparative effectiveness particularly with regard to other radiation therapy methods that would be a logical comparator. Some of the included comparative studies included patients with rare</p>

	I would consider separating out primary bone tumors (e.g. chondrosarcomas, chordomas) from head and neck (including base of skull). Primary bone tumors have a different treatment paradigm compared to HN cancers (primarily squamous cell carcinomas, SCC) and are more radioresistant, necessitating higher RT doses, and are not treated with chemotherapy, unlike HN SCC	tumor types in the same study although the impact of PBT was generally described separately by tumor type. We have created separate sections under Head and Neck (including Skull Base) Tumors for chondrosarcomas/chordomas versus sinonasal, oropharynx etc. in order to more clearly delineate primary bone tumors from other head and neck cancers.
ES-14; Bone Tumors, Point 1	Bladder cancer in first sentence should likely be “bone cancer”. I would clarify, does the section on bone tumors include non-base of skull chordomas/chondrosarcomas? Many guidelines (including those listed on page 26), include these as part of brain and spinal tumors. The goal of an executive summary is to give a reader a broad sense of the work, which also means being clear with inclusion/exclusion criteria of included studies. I would consider including in the executive summary the rationale for excluding some case series (e.g. based on the number of patients included). Clearly not all publications in proton therapy were included in the results of this report (see my comment above), and unless you read through the entire report, it is not apparent why	Thank you. We have changed bladder cancer to “bone cancer”. The Executive Summary methods refer the interested reader to the full report which delineates the inclusion/exclusion criteria in an effort to streamline the ES to the extent possible. The focus of the report and key questions is on comparative evidence. Case series do not answer questions of comparative effectiveness and safety. (Please see above)
Introduction	<i>Overview of topic is adequate?</i> <i>Topic of assessment is important to address?</i> <i>Public policy and clinical relevance are well defined?</i> 1. The overview presented in the executive summary was appropriate, including basic review of proton therapy and how this treatment may differ from other radiotherapy modalities. There are some minor inaccuracies regarding technical details of proton therapy, which are highlighted above. 2. The public policy is not well defined. It may be helpful to touch upon what proportion of patients are being treated with proton therapy over time to provide a sense of the magnitude of proton use compared to other RT modalities.	Thank you for your comments. We have addressed the minor inaccuracies addressed previously. The report synthesizes the evidence based on the key questions and PICOTS inclusion/exclusion. No policy is stated, evaluated or recommended in the report.
Introduction; page 14, charts I, II, V, VII	I would consider adding the y-axis to quantify the number of cases by primary dx category. Also, it is not clear to me what the differences are between chart I and II. Do the charts plot the distribution of proton cases but from different agencies	This information is included in the report by the state of Washington. We have made the HCA aware of these concerns.

	(although PEBB/UMP appears present for both)? Why are these separated out as such? This is not clear to me from the text.	
Introduction; page 16, table III	It is not clear to me why there are n=63 patients represented in table 3 but 246 in chart III. Could this be clarified within the text or table legend? Is this because Table 3 does not include patients treated under Medicaid Manage Care?	This information is included in the report by the state of Washington. We have made the HCA aware of these concerns.
Introduction; page 17, chart V	Please comment how chart V differs from chart II and why the data is laid out as such (e.g. combination of PEBB/UMP and Medicare/PEBB versus PEBB/UMP and Medicare/UMP). This section in general would benefit from more text to provide context for the figures.	This information is included in the report by the state of Washington. We have made the HCA aware of these concerns.
Background	<i>Content of literature review/background is sufficient?</i> 1. Overall, the background content is adequate, though there are some technical inaccuracies (please see above for comments). The review provides a summary of prior systematic reviews and HTA of proton therapy. For completeness and for background, I would suggest also including a summary of the WA HTA 2014 in Table 3.	Thank you for your comments. Table 8 provides a high level summary of the findings of the 2014 report and bullet points provide additional context and comparison with the 2019 report.
Background; page 26, table 2	Please provide abbreviations for NICE, AIM, ACR	NICE, AIM, and ACR have been added to the abbreviation list at the end of the table.
Background; page 28, table 3	Please provide abbreviation for SR	The abbreviation for SR is included in the list at the end of the table.
Report Objectives & Key Questions	<i>Aims/objectives clearly address relevant policy and clinical issue?</i> <i>Key questions clearly defined and adequate for achieving aims?</i> The objective and key questions of this report are clearly laid out and are appropriate. The primary comparators chosen were also appropriate, in particular recognition that sometimes the comparator of interest is not another RT modality (e.g. TACE for HCC).	Thank you for your comments
Methods	<i>Method for identifying relevant studies is adequate?</i> <i>Criteria for the inclusion and exclusion of studies is appropriate?</i> <i>Method for Level of Evidence (LoE) rating is appropriate and clearly explained?</i> <i>Data abstraction and analysis/review are adequate?</i> 1. To identify relevant studies, published articles were comprehensively searched through PubMed and other electronic databases. Conference abstracts were excluded, in addition to duplicate publications without different data or follow-up times. Reasons for excluding articles (Appendix C) seemed reasonable and included	Thank you for your comments. Our priority was to identify and synthesize comparative studies. Many of the comparative studies included were on rare tumors. The report includes over 150 case series across a wide range of tumor types, some of which are likely rare. Data are summarized in appendix F. Given that there are over 100 types of tumors, it is

	<p>series in which PBT modality was used for a minority of patients, treatment planning studies, prior publication of the cohort, lack of separate analyses for patients treated with protons versus photons, . My main criticism is below (page 59, exclusion criteria) in regards to rare tumors such as lymphoma. For example, for study #27, a prospective phase II single arm study of 15 lymphoma patients treated with proton therapy, this was excluded as there were <30 patients in the case study. However, Hodgkin lymphoma arguably is a very rare entity. What is the incidence threshold to define if a disease would fall into the “very rare conditions”?</p> <ol style="list-style-type: none"> 2. The LoE rating was clearly explained, which followed criteria that have been used in other systematic reviews and/or groups (GRADE, AHRQ, QHES). 3. The tables laid out showed consistent data abstraction, analysis and review 	<p>likely that case series for some rare tumors were not included. While our report and the previous report likely have not captured all case series for a given cancer or for all rare cancers (although included case series covered a range of tumor types, including studies that may have contained rare tumor types either alone or in combination), the inclusion of additional case series does not provide additional evidence to answer the question of comparative effectiveness particularly with regard to other radiation therapy methods that would be a logical comparator. Some of the included comparative studies included patients with rare tumor types in the same study although the impact of PBT was generally described separately by tumor type.</p>
Methods; page 57, line 14	As part of the inclusion/exclusion criteria, it may be helpful to define what is considered “long term” with respect to clinical outcomes or safety	Thank you for your comments. It is delineated for safety, based on the 2014 report (>3 months for late/long term); in data abstraction and summary tables, time frames are given as reported by authors
Methods; page 59, study design/exclusion	Please define “very rare conditions”; specifically, in which tumors were case series ≥ 10 patients allowed? Certain tumors (e.g. lymphomas) are relatively rare (e.g. HL, 2.5 per 100,000 incidence), which means it is difficult to have a large case series of patients treated with proton therapy. By excluding case series in adult with <30 patients, this may bias the report against rarer tumors.	Thank you for your comments. No strict definition was used. As is seen in table 8 studies for some tumors with lower incidence were included. Please see previous comments regarding case series.
Results	<p><i>Amount of detail presented in the results section appropriate?</i> <i>Key questions are answered?</i> <i>Figures, tables and appendices clear and easy to read?</i> <i>Implications of the major findings clearly stated?</i> <i>Have gaps in the literature been dealt with adequately?</i> <i>Recommendations address limitations of literature?</i></p> <p>The summary of pediatric comparative (text, tables) and case series publications (appendix) on proton therapy is very good with appropriate amount of detail presented and commentary about potential limitations of the available evidence. The figures and tables (both in the appendix and main report) provide an easy-to-read summary and attempt</p>	Thank you for your comments

	<p>to show heterogeneous comparative studies side-by-side. This can be challenging given that outcomes or safety are reported differently (i.e. at different time points, different grades, mixed tumors) across studies. The major findings are fairly stated, in addition to identify current gaps in the literature for pediatric tumors.</p> <p>The summary of the comparative and case series literature for adult tumors is very good, with appropriate detailed presented and limitations of studies or conclusions laid out. In instances where inadequate detail was given in a study (e.g. grade of toxicity, whether toxicity was attributable to just RT), this is highlighted. Potential reasons for why statistical significance was not observed in comparative studies were offered. It is helpful to include the Table number in appendix F if/when this is referenced in the text. This occurred in many, but not all, sections.</p> <p>Please note that I did not confirm the accurateness of the summaries or completeness of literature review across the different disease sites.</p>	
<p>Results; page 112, line 4</p> <p>Table 19</p>	<p>Gy(RBE) refers to proton dose. In the table, 57 Gy was for photons and 50.4-54 Gy(RBE) was for protons/IMRT.</p> <p>It is not clear to me why radiation necrosis that is outside (versus inside) the treatment field is of interest. Radiation necrosis usually occurs within the high dose region (e.g. within the treatment field), so it's not surprising that risk of RT necrosis outside the treatment field is 0%.</p>	<p>Thank you. We have modified this sentence accordingly and have checked the entire report for accuracy regarding the reporting of Gy vs. Gy(RBE).</p> <p>This study did not report whether or not radiation necrosis occurred inside the treatment field; only radiation necrosis outside the treatment field was reported and this outcome was included for completeness.</p>
<p>Results; 2 paragraph under KQ1, last sentence</p>	<p>It may be difficult, if not impossible, to blind patients and treating physicians to RT modality that a patient is randomized to (protons versus photons) as the machines for protons may be in a physically distinct location from that of photons. The use of blinding in RT trials may be more limited compared to drug therapy trials</p>	<p>We understand that blinding of patients may not be possible however, blinding of some outcomes assessments and results analysis is often possible and may protect against some sources of bias. Most studies do not describe blinded analysis. Studies were not downgraded because of lack of blinding.</p>
<p>Results; page 183, first paragraph</p>	<p>I would consider describing more why the quasi-RCT is categorized as "quasi-RCT." Was this a dose escalation (safety) study? For lines 7-8: would rephrase it as 3.0 Gy for 8 daily fractions, 4.0 Gy for 5 fractions, etc. "3.0 Gy in 8 daily fractions" may imply that the total dose was 3 Gy (i.e. 0.375 Gy per fraction).</p>	<p>Thank you for your comments. Additional context has been added and corrections have been made related to radiation dose.</p>

Conclusions	<p><i>Are the conclusions reached valid?</i></p> <p>1. Based on the reported state of the literature, summary of the number and quality of comparative and case series studies, the conclusions reached for each results section (by disease site) are reasonable and fair.</p>	Thank you for your comments
Overall Presentation & Relevancy, General Comments	<p><i>Is the review well-structured and organized?</i> <i>Are the main points clearly presented?</i> <i>Is it relevant to clinical medicine?</i> <i>Is it important for public policy or public health?</i></p> <p>The review overall is organized and systematic, though would benefit by providing more abbreviations upfront. I did not have time to review all the appendix tables, but felt the structure of providing very granular details (e.g. extracted data and then summary tables) provided transparency of how the results were obtained. Results for the key questions were clearly presented, and I appreciated the use of figures to visually describe the outcome and/or toxicity findings in the comparative studies or RCTs. This was quite effective. In light of the multiple new studies in the last few years with proton therapy, this report is timely and relevant to the field. Portions of the report were redundant and perhaps for interest to improve readability, it may be helpful to cut down on the redundant text.</p>	Thank you for your comments. We realize there are redundancies; however different users of the report may prefer different levels of detail. Also, each tumor section is able to “stand alone” should a user be interested in a specific type of cancer.
Quality Rating	<p>Quality of Report</p> <p>Superior Good X Fair Poor</p>	Thank you for your comments
Smith “Jim” Apisarnthanarax, MD, Associate Professor, Director of Clinical Research, Associate Residency Program Director, Proton Therapy Fellowship Director, Department of Radiation Oncology University of Washington, Seattle Cancer Care Alliance		
Specific comments		
Introduction	<p>Overview of topic is very well done.</p> <p>The importance of re-reviewing the clinical data on protons is well described.</p> <p>The impact of protons on public policy and relevance to patient care are well defined.</p>	Thank you for your comments
Background	The content of the literature review and background is adequate and well summarized.	Thank you for your comments
Report Objectives and Key Questions Page 55 Line 3.1.2	Key Questions 1 and 2. Since the main theoretical benefit of protons is reduction of normal tissue toxicity, the comparative impact of protons on acute and late toxicities should be explicitly stated (“health-related quality of life” is related to, but distinct from toxicity metrics)	Thank you for your comments. KQ 1 and 2 refer to efficacy/effectiveness; health related quality of life is listed as a secondary outcome for these questions and are not considered together with safety outcomes,

		which is KQ 3. This is outlined in the PICOTS table.
Methods	Described methods is adequate. Criteria for inclusion/exclusion seem reasonably appropriate. Method for LoE rating is appropriate and clearly explained. Data abstraction and analysis/review appear appropriate.	Thank you for your comments
Results	General comment: because I primarily have clinical expertise in esophageal, GI, liver, and prostate cancers, I will only comment on these disease sections. One general comment for all disease sites is to provide a brief discussion on the clinical context of why protons are being used for each disease site and in what clinical settings.	Thank you for your comments. The general background provides some context for use of PBT.
Results Page 119-130	Esophageal cancer: appropriate studies were included. In the tables and in the charts, it should be distinguished which studies were evaluating protons for definitive treatment or as a part of trimodality treatment (when protons are used for preoperative treatment). This distinction is important as the use and rationale of protons in these settings are different, so the interpretation of the data is different. Protons as preoperative treatment (trimodality) are designed to reduce peri- and post-operative complications and morbidity since radiation is thought to affect surgical complications. In the definitive treatment setting, the benefit and rationale of protons is less clear since surgery is not involved. Protons in the definitive setting may translate to improved outcomes by way of allowing for safe dose escalation and/or less toxicity with standard radiation doses.	Thank you for your comments. We have made the distinctions suggested.
Results Page 150-157	Liver cancer: Kim et al PMID 25381830 - I would consider adding this study to the review. Even though this is single institution study of only 27 patients, this is a prospective phase I study, which in my opinion, has higher scientific quality than a retrospective case series.	This study was found in our search and determined to be excluded due to being a case series of less than 30 patients. The key questions for this report focus on the comparative effectiveness and safety of PBT with other forms of cancer treatment. Case series do not answer questions of comparative effectiveness and safety.
Results Page 180-183	Prostate: Chuong et al PMID 29034790. This is a study looking at the value of whole pelvis protons in 85 patients from the PCG registry database and should be considered to be added to the review. Other than meeting the minimum requirement of number of patients for a case series, this study is unique in the literature in that this is the first study to look at using protons to deliver whole pelvis radiation for prostate cancer patients.	Thank you, this study meets the inclusion criteria and has been added.
Conclusions	Conclusions appear to be valid.	Thank you for your comments

Overall presentation and relevancy	<p>This review overall is well prepared and organized. I found the bar graph figures of comparative studies very useful. One suggestion for these graph figures is to put an asterisk above statistically significant comparisons (rather than having to look for the p values to see which ones are statistically significant) for better ease of reading. The main point of this review to focus on new data from 2014-2018 is clear.</p> <p>The review seems to lump non-randomized prospective trials in with “case series.” In my opinion, these studies should be distinguished between retrospective case series as being in a separate category of evidence.</p>	Thank you for your comments
Quality Rating	Quality of Report Superior Good X Fair Poor	Thank you for your comments

A full text document featuring original comments in the form of tracked changes attached by the peer reviewers is available upon request.

Responses to public comment on draft report

This second section responds to comments received during the public comment period from the following:

- Cat Livingston, MD, MPH, Associate Medical Director, Health Evidence Review Commission, Oregon Health Authority
- Scott Warwick, Executive Director, National Association for Proton Therapy (NAPT)
- Annika Andrews, President & CEO, Seattle Cancer Care Alliance (SCCA)
- Ramesh Rengan, MD, PhD, Professor & Interim Chair, UW Dept. of Radiation Oncology; Medical Director SCCA Proton Therapy Center Associate Member, Clinical Research Division, Fred Hutchinson Cancer Research Center
- Jeff Sperring, MD, CEO, Seattle Children’s Hospital
- Daniel E. Smith, Executive Director, Alliance for Proton Therapy Access
- Deepak Khuntia, MD, Senior Vice President and Chief Medical Officer, Varian Medical Systems

Additionally, numerous individuals provided general public comment (i.e., not addressing evidence, project scope, or draft key questions) on the topic of/their personal experience with proton beam therapy. A complete list of all persons who provided comments can be found below following Table 2.

Complete comments submitted and associated data are attached following the responses below. Attachments included with public comments related to model policies are acknowledged but were too large to append to this document and are available through the Washington State Healthcare Authority.

Table 2. Responses to public comments

Comment		Response
Cat Livingston, MD, MPH, Associate Medical Director, Health Evidence Review Commission, Oregon Health Authority		
Suggestion	How about a single page meta-table that summarizes at a high level the evidence in the executive summary?	Thank you for your comments. Table 8 provides a high level summary.
Scott Warwick, Executive Director, National Association for Proton Therapy (NAPT)		
Background ; Guidelines; section 2.5	The National Comprehensive Cancer Network (NCCN) outlines evidence-based, collectively agreed upon Guidelines that make treatment recommendations to ensure that cancer patients obtain the most optimal outcomes. These Guidelines are broadly acknowledged by the payer community as the standard for determining clinical policy in cancer care. NCCN Guidelines for Head and Neck Cancer (Version 1.2019) recognized the benefit of proton therapy,	Thank you for your comments regarding clinical guidelines. A summary of previously published clinical guidelines can be found in section 2.5.
Results; Head and Neck; section 4.3.7	While the HCA did review a few of the compelling studies on head and neck cancer, a number of the studies were devalued based on a perceived risk of bias or “serious imprecision”. We disagree with that characterization and we also believe that the assessment is missing key articles, including Holliday et al and McDonald et al, which looked at the need for gastronomy tube either during or following treatment.	<p>Thank you for your comments.</p> <p>Accepted methods for risk of bias and strength of evidence appraisal were used (see references for methods). Our methods are consistent with accepted standards for comparative effectiveness reviews. (AHRQ, PCORI, IOM, Cochrane Collaborative).</p> <p>Both of the studies (below) have been screened against inclusion/exclusion criteria and were determined to be includable.</p> <ul style="list-style-type: none"> Holliday EB, Garden AS, Rosenthal DI, et al. Proton therapy reduces treatment-related toxicities for patients with nasopharyngeal cancer: a case-match control study of intensity-modulated proton therapy and intensity-modulated photon therapy. <i>Int J Particle Ther.</i> 2015;2:19–28. McDonald MW, Liu Y, Moore MG, Johnstone PA. Acute toxicity in comprehensive head and neck radiation for nasopharynx and paranasal sinus cancers: cohort comparison of 3D conformal proton therapy and intensity modulated radiation therapy. <i>Radiat Oncol.</i> 2016;11:32.
Results; Head and Neck;	Most of the data on head and neck cancer patients relates to tumors extending to the skull base; however, there are several articles relating to the use of proton	Thank you for your comments. We have screened all of the publications cited in the NAPT Head and Neck Literature Review (as well as the letter submitted by NAPT) against the a priori

	Comment	Response
<p>section 4.3.7</p>	<p>radiotherapy in treating patients with cancers of the oropharynx. Slater et al. reported on 29 patients with stages III and IV oropharyngeal carcinoma who were treated using a combination of photons and PBT.³ They found a 5-year local control rate of 88% at the primary site and 94% in the neck. Frank et al. analyzed patients with oropharyngeal carcinoma treated with PBT at the MD Anderson Cancer Center and compared them to a matched set of control patients treated with photon radiotherapy.⁴ They found a lower rate of dysphagia and less need for a feeding tube in order to get the patients through therapy (20% with PBT as compared to 48% with IMRT). Holliday et al. compared the gastrostomy tube (GT) rates for patients with nasopharyngeal cancer treated with PBT versus IMRT. They found a meaningful reduction in acute toxicity for nasopharyngeal cancer patients treated with PBT as demonstrated by decreased rates of GT placement.</p> <p>Patel et al. published a comprehensive review of proton beam therapy versus photon therapy for paranasal sinus and nasal cavity malignant diseases.⁶ The meta-analysis reviewed 43 different cohorts (covering 1,472 patients) from 41 different non-comparative observational studies published after 1990. In reviewing the studies, they found that patients treated with PBT had better overall survival, disease-free survival, and locoregional control at 5 years. (Emphasis added)</p> <p>Ultimately, PBT has been shown to target tumors, spare surrounding normal organs and tissues from radiation exposure, significantly reduce or eliminate both the acute and chronic toxicities from ionizing radiation, and therefore, improve quality of life of patients. Therefore, many leading cancer centers believe that PBT is an appropriate treatment option for certain head and neck cancer patients. As such, we are respectfully requesting that the HCA and Aggregated Analytics review the compelling evidence supporting PBT for head and neck</p>	<p>inclusion/exclusion criteria. Of the studies mentioned, 10 publications were already included in our report, 32 publications were excluded at the level of Title/Abstract and 7 were excluded after full-text (FT) review. Reasons for exclusion at FT can be found in Main Appendix Table C1. The following 3 studies met inclusion criteria and were thus included in our report:</p> <ul style="list-style-type: none"> • Sharma S, Zhou O, Thompson R, Gabriel P, Chalian A, Rassekh C, Weinstein GS, O'Malley BW, Aggarwal C, Bauml J, Cohen RB, Lukens N, Swisher-McClure S, Ghiam AF, Ahn PH, Lin A. Quality of life of postoperative photon versus proton radiation therapy for oropharynx cancer. International Journal of Particle Therapy. 2018. In-press. • McDonald MW, Liu Y, Moore MG, Johnstone PA. Acute toxicity in comprehensive head and neck radiation for nasopharynx and paranasal sinus cancers: cohort comparison of 3D conformal proton therapy and intensity modulated radiation therapy. Radiat Oncol. 2016;11:32. • Holliday EB, Garden AS, Rosenthal DI, et al. Proton therapy reduces treatment-related toxicities for patients with nasopharyngeal cancer: a case-match control study of intensity-modulated proton therapy and intensity-modulated photon therapy. Int J Particle Ther. 2015;2:19–28.

	Comment	Response
	cancer in our white paper (see Appendix 2), and promptly update its findings on head and neck cancer to incremental benefit.	
Results; Brain, Spinal, Paraspinal Tumors; section 4.2.1 and 4.3.3	<p>In the re-review, the Washington State HCA downgraded its evaluation of proton beam therapy for Central Nervous Systems from incremental to comparable benefit. We strongly disagree with this decision, particularly given (a) the positions taken by the National Comprehensive Care Network Guidelines and the ASTRO Model Policy on treatment of CNS tumors (see below) and (b) the clinical evidence that continues to support the value of PBT.</p> <p>The current evidence base supports the coverage of the following types of CNS tumors with proton beam therapy:</p> <p>A. Tumors where treatment regimen includes craniospinal irradiation including ependymoma, adult medulloblastoma, pineal tumors, germ cell tumors, pineoblastoma, and primitive neuroectodermal tumors</p> <p>B. Grade II and Grade III IDH mutant and 1p19q co-deleted tumors</p> <p>C. Re-irradiation where treatment with proton therapy can significantly limit volume of normal brain parenchyma</p> <p>While the tumors noted above in A are extremely rare tumors in adults, studies have shown substantial improvements in outcomes with proton compared to photon craniospinal radiation in patients with medulloblastoma. With proton craniospinal radiation, patients have significantly less weight loss (16% vs 64%), less grade 2 nausea and vomiting (26% vs 71%), and less esophagitis (5% vs 57%). Even more importantly, since protons significantly reduces mean vertebral doses, there is significantly less reductions in blood counts with protons (white blood cells, P=.04; hemoglobin, P=.009; platelets, P=.05). This benefit of proton therapy is of particular significance, as chemotherapy has been shown to improve survival when given with radiation, so maintaining blood counts after radiotherapy is incredibly important as it</p>	<p>Thank you for your comments.</p> <p>By way of information, the HCA has not made any policy determinations. As the evidence vendor we do not suggest or evaluate policy.</p> <p>As the evidence vendor, we synthesized the evidence and based on the new studies arrived at a different conclusion regarding the evidence. The previous report included 2 small poor quality studies. Comparing the two reports: Different tumors for curative intent (medulloblastoma, intermedullary glioma vs. high grade glioblastoma, high grade glioma) and different PBT protocols and comparators (PBT vs photon, IMRT in 2014, PBT boost vs. photon, PBT vs. photon in 2019) across reports contribute to different conclusions regarding NHB. Studies in the 2019 report were larger, (including one large database study which did not report harms).</p> <p>Citations listed in the reference list were compared against the a priori inclusion/exclusion criteria. Those meeting the criteria were included.</p> <p>The cited Buchner 2016 (radiation plus procarbazine) was excluded at full text as the type of radiation is not described.</p>

	Comment	Response
	<p>allows delivery of full doses of chemotherapy.</p> <p>With respect to IDH mutant tumors and 1p19q co-deleted tumors, patients have an excellent prognosis with survival times often measured in decades. (Buckner et al., 2016) With the excellent prognosis for this patient population, decreasing radiation doses to normal uninvolved brain is essential to preserve cognitive function. Numerous studies have examined the threshold dose for increased risk of cognitive dysfunction and the impact of moderate radiation doses to the brain including to the hippocampus.^{9,10} A phase II trial serially evaluating the cognitive function of patients with low grade gliomas found stable cognitive function years after proton radiotherapy.¹¹ These studies support the use of proton therapy to decrease the cognitive risks of radiotherapy in this good prognosis patient population.</p> <p><i>Given the evidence discussed above, we urge you to revise your findings in the re-review to include coverage for malignant and benign tumors and for re-irradiation where treatment with proton therapy can significantly limit volume of radiation to normal brain tissue.</i></p>	
Results; Economic Studies	<p><i>A recently presented study demonstrated significantly lower costs for PBT when compared to case-matched photon patients.</i> Palmer and Frank of MD Anderson Cancer Center conducted an IRB approved study in collaboration with the University of Texas System, a state-wide self-funded employer, to perform a value-based analysis of PBT in comparison to standard photon radiation therapy (SRT) by analyzing total cost of care, clinical outcomes and toxicities, and patient satisfaction. The three-year study enrolled 57 patients with 22 ultimately treated with PBT and 25 treated with SRT. The disease sites included head & neck, genitourinary, breast, and thoracic cancers. 34 patients were case matched (17 PBT / 17 SRT) with ≥ 6-month follow-up. No grade 4 or 5 toxicities were reported. The results of the study indicated that PBT patients’</p>	<p>The Palmer and Frank study mentioned was a conference abstract and did not meet inclusion criteria</p>

Comment		Response
	Quality of Life returned to baseline faster than SRT and that SRT patients had more ancillary costs (Diagnostic Imaging, Pharmacy, Laboratory Tests, Emergence Department, Internal Medicine). Patients treated with PBT resulted in net employer costs savings with average net billed charges 21% lower than SRT.	
Background ; Model Policies	<p>In our comment letter on the Key Draft Questions, we had noted the importance of reviewing the following in this latest evaluation of proton beam therapy:</p> <ul style="list-style-type: none"> NCCN Guidelines. The National Comprehensive Cancer Network (NCCN)13 published guidelines are often used as the litmus test by payers for determining if they will approve coverage for all types of cancer treatments. Please keep in mind that the NCCN Guidelines most often consist of what is the current standard of care and often do not include emerging technologies until they have been demonstrated as becoming a standard of care. In the past, they have historically been silent on proton therapy but, over the last 24 months, the guidelines have become more encouraging in their comments about the use of proton therapy, embedding proton beam therapy in the guidelines for fourteen different disease sites including head & neck cancer. Model policies from leading medical organizations. The National Association for Proton Therapy has worked together with its members through a consensus and evidence-based approach to draft and update its model policy; the last version of the model policy was just released in February 2019. In 2017, the American Society for Radiation Oncology (ASTRO) released an updated proton beam model policy. These guidelines were promulgated by leaders in the field, many of whom do not have access to protons. 	<p>Thank you for your comments.</p> <p>Your documents for the draft KQ were received and the response to your comments was posted on the HCA website. All publications cited as evidence in these documents were considered for inclusion based on the inclusion/exclusion criteria for the evidence report.</p> <p>Guidelines are summarized in the full report.</p> <p>Evaluation and inclusion of model policies is not within the scope of the evidence report. The HCA has been made aware of them.</p>
Methods	In nearly all indications, the HCA has taken a more restrictive / negative evaluation of the	Thank you for your comments.

	Comment	Response
	evidence compared to the other three clinical resources developed by oncology experts. We believe that this inconsistency in the HCA findings is due in part to the lack of engagement of an oncology expert, and, in particular, radiation oncology expert with PBT experience, in the re-review of proton beam therapy as discussed below.	<p>Peer review was done by 2 radiation oncologists and their comments incorporated in the final report.</p> <p>The evidence report used accepted standards for comparative effectiveness reviews. (AHRQ, PCORI, IOM, Cochrane) and is consistent with methods described in the 2014 report.</p>
Methods	<p>There are two significant issues with the overall process and approach taken by the Washington State Healthcare Authority in its re-review.</p> <p>First, proton beam radiotherapy is a very specific form of radiotherapy that requires specialized clinical training and experience. Clinicians using this modality must have a detailed understanding of the therapy and the type of patients where this treatment approach may or may not be clinically appropriate. A thorough review or assessment of the evidence on this type of technology requires well-informed engagement. We are deeply concerned that Aggregated Analytics did not engage a board-certified radiation oncologist with multiple years of clinical experience at an operating proton therapy center as part of the assessment. We had recommended this approach in our comment letter on the Key Draft Questions and offered to provide a list of physician candidates to serve in this capacity. However, the HCA did not follow our recommendation and, unfortunately, a few of the findings in the report demonstrated a lack of knowledge or expertise in this area.</p> <p>Second, while the HCA is giving physicians an opportunity to speak at the upcoming Healthcare Technology Clinical Committee meeting on May 17, 2019, it appears that Aggregate Analytics will have finalized the report by April 17, 2019. With the quick turnaround following the ending of the comment period, we are concerned as to how much actual feedback from critical stakeholders, including clinical experts in proton beam therapy, will be incorporated into the final report – a report based on</p>	<p>Thank you for your comments.</p> <p>We made numerous attempts to engage such experts locally and in other locations.</p> <p>Peer review was done by 2 radiation oncologists and their comments and corrections based on their clinical perspective were incorporated in the final report.</p> <p>We have evaluated peer review and public comments and made changes accordingly as appropriate to the scope and role defined.</p>

Comment		Response
	which the HTCC is making its coverage determination that directly impacts certain patients fighting cancer.	
Annika Andrews, President & CEO, Seattle Cancer Care Alliance (SCCA) Ramesh Rengan, MD, PhD, Professor & Interim Chair, UW Dept. of Radiation Oncology; Medical Director SCCA Proton Therapy Center Associate Member, Clinical Research Division, Fred Hutchinson Cancer Research Center		
General	<p>When proton therapy was originally reviewed in 2014, there were no consensus model policies available. Since that time, several preeminent cancer organizations have developed consensus model policies through collaboration with their members—engaging in a dispassionate review of the literature to develop their policies for proton therapy coverage. Some of these organizations include The American Society for Radiation Oncology (ASTRO), The National Association of Proton Therapy (NAPT), Alliance of Dedicated Cancer Centers (ADCC), and Particle Therapy Co-Operative Group (PTCOG).</p> <p>These model policies are applied inconsistently in the draft evidence review. For example, ASTRO’s Model Policy is applied to evaluate prostate cancer, but not any other disease sites (Table 2, p 26), despite the fact that it has coverage recommendations on multiple other sites including ocular and hepatocellular cancers. We would call your attention to the fact that these guidelines recommend protons as the treatment of choice, or an acceptable therapeutic recommendation, in a variety of disease indications that the current HTA report is silent on or recommends against the protons.</p> <p>We believe the ASTRO, NAPT, ADCC, and PTCOG model policies are a great resource to provide coverage recommendations across all disease sites. Additionally, model policies such as these would serve as a superior bellwether for coverage decisions</p>	<p>Thank you for your comments.</p> <p>The evidence report does not address, evaluate or apply model policies. The vendor is required to provide information on 2 bellwether health policies.</p> <p>The creation of policy is the purview of the HTCC.</p> <p>Clinical guidelines are summarized in the full report.</p> <p>The evidence report is intended to be an independent assessment of the evidence based on accepted standards for systematic reviews and comparative effectiveness reviews (AHRQ, PCORI, IOM, Cochrane)</p>

Comment		Response
	than either Aetna (transitioned to Evicore) or Anthem, which are cited in the draft report (p. 49). The model policies are produced by experts in radiation oncology whose primary motivation is optimal patient outcomes, not financial returns. Going forward, the HTCC should consider consulting organizations such as these in the development of their evidence review and coverage policies for future technology assessments.	
Methods; Inclusion/Exclusion Criteria; Section 3.1.3	This report sets unreasonably high and inconsistent standards of evidence and interprets the data inconsistently. For instance, it is unreasonable to expect randomized trials for every disease indication. In many areas of medicine, newer technologies and treatments are adapted when there is clear rationale for benefit and strong phase II data, even without a randomized trial being conducted. For example, stereotactic radiosurgery for early stage lung cancer has been the standard of care for over a decade, long before any randomized data existed. There was even a negative randomized trial at one point for survival benefit, and coverage was not impacted because the clinical rationale was well established. Another example would be IMRT coverage for many disease sites, which do not have randomized evidence for superiority with IMRT.	<p>Thank you for your comments.</p> <p>The inclusion criteria were broad with respect to study design; inclusion was not restricted to RCTs. With the exception of 2 RCTs and 1 quasi-RCT, the rest of the included studies were comparative observational. The report included primarily nonrandomized comparative studies, recognizing the difficulties in conducting such trials in children.</p>
Methods	Due to the restrictive nature of the evidence inclusion standards employed by the evidence vendor, there is a significant body of important data missing from this report. This includes multiple studies showing superior outcomes with proton therapy based on nonrandomized comparisons with photon therapy, as well as superior cost-effectiveness (examples of these studies are outlined in our detailed responses per disease site). Inconsistent application of the data has resulted in a draft report that diverges from the original review in confusing ways. Interpretation of the existing data also seems inconsistent. For example, based on the same level of data as in the previous report, the agency determined that the evidence	<p>Thank you for your comments.</p> <p>The majority of comparative studies were retrospective observational studies that met the inclusion criteria. In addition data from over 150 case series were included.</p>

Comment		Response
	(nonrandomized comparisons) for esophageal cancer and liver cancer is sufficient to suggest that protons are beneficial to patients, but similar studies in other sites (such as pediatrics, breast, head & neck, CNS, etc.) do not result in the same determinations.	
Methods	<p>We support the notion of having standards for evidence, but the requirements for proton therapy should not be distinct, and should be on par with all other cancer therapies.</p> <p>The evidence standards for proton therapy, as set out in the draft evidence review, are not equal to the standards used to evaluate other treatments. WA HTA continues to hold PBT to a higher standard of evidence than other types of treatments and does not support this evidence generation as it does other modalities. For example, WA HCA covers IMRT for clinical trials and registries, but not proton therapy.</p>	<p>Thank you for your comments.</p> <p>This re-review follow accepted standards for comparative effectiveness reviews and the methods are consistent with the 2014 review and older AHRQ report.</p>
Methods	<p>Clinical trials on low volume disease sites necessarily require fewer study participants. Despite the fact that the report states that this was considered in the study selection criteria, we noted that several key studies were excluded for low volumes, even in instances of disease sites that are rare (Appendix 1: 32, 29, 33,36, 3,4,6, 12, 16, 27, 54). For example, there are only 250 – 500 children diagnosed with medulloblastoma in the United States each year. However two studies with this population (Appendix 1: 54, 55) were eliminated due to low numbers of participants. It is simply impractical to create studies with a large population when the disease incidence is so low.</p>	<p>Thank you for your comments.</p> <p>All suggested citations were reviewed against the inclusion/exclusion criteria for this report. The key questions for this report focus on the comparative effectiveness and safety of PBT with other forms of cancer treatment. Consistent with the 2014 report, we focused on comparative studies performing a direct comparison of treatments in the same underlying patient population. Case series do not answer questions of comparative effectiveness and safety. With over 100 types of cancer, while our report and the previous report likely have not captured all case series for a given cancer or for all rare cancers (although included case series covered a range of tumor types, including studies that may have contained rare tumor types either alone or in combination), the inclusion of additional case series does not provide additional evidence to answer the question of comparative effectiveness particularly with regard to other radiation therapy methods that would be a logical comparator. Some of the included comparative studies included patients with rare tumor types in the same study although the impact of PBT was generally described separately by tumor type.</p>

	Comment	Response
Methods	<p>We are disappointed by the WA HTA's decision to consistently exclude dosimetric studies as part of their body of evidence used in the evaluation of proton therapy. Radiation Oncologists rely on dosimetric studies as the gold-standard of evidence when evaluating the efficacy of radiation modalities. Dosimetric studies also directly address Key Question 3 regarding the comparative harms of proton therapy versus other alternative treatments. It is well established that excess radiation dose to healthy tissue and organs contributes to secondary malignancies and other complications. Dosimetric studies demonstrate the peerless capability of proton therapy to minimize radiation dose to healthy tissues in some clinical scenarios, while delivering a comparable, if not superior, dose of radiation to the tumor.</p> <p>Further, insurance companies consistently require and rely upon comparative plans when determining medical necessity. In sum, these comparative plans are dosimetric comparisons of a photon plan versus a proton plan, demonstrating which plan provides the superior dose. If medical necessity decisions will be based upon such comparative analyses, we believe that not allowing this evidence to provide context omits an important knowledge base required to provide evaluators with a complete understanding of the efficacy and safety of proton beam therapy.</p>	<p>Thank you for your comments.</p> <p>We understand the concerns regarding the exclusion of dosimetric data. However, as noted in the previous report and this update, the uncertainties that remain regarding proton physics and biology make comparisons of simulated outcomes problematic, and would only be addressed through comparisons of actual clinical outcomes. Our approach is consistent with that of other evidence review organizations and the previous report in this regard. We did include studies of hypofractionation related to prostate cancer for context, but they generally did not provide comparative information on clinical outcomes.</p>
Results	<p>Currently, the draft evidence report would suggest a proton beam therapy coverage policy in Washington State that would be among the most restrictive in the country. For example, proton therapy is well established as an effective treatment and standard of care for ocular melanoma. Not covering proton therapy for ocular melanoma would put WA out of line with almost every state and model policy, as even the most restrictive policies cover this disease site.</p>	<p>Thank you for your comments.</p> <p>The draft report does not suggest policy.</p>
Methods	<p>Aggregate Analytics assembled a team comprised of analysts to create the draft evidence report. We are interested in how</p>	<p>Thank you for your comments.</p>

	Comment	Response
	the evidence report is weighed against the input of the HTCC. Our hope is that the Clinical Committee, which is comprised of medical doctors, will carefully evaluate recommendations in this draft based on their practical clinical experience and understanding of the available clinical literature. We believe that their clinical input is necessary to accurately determine appropriate coverage of proton therapy.	<p>We made numerous attempts to engage such experts locally and in other locations.</p> <p>Peer review was done by 2 radiation oncologists and their comments and corrections based on their clinical perspective were incorporated in the final report.</p> <p>The process is delineated on the HCA website.</p>
Results; Adult Lymphoma; Section 4.3.10	<p>Sources Missing from the study include:</p> <p>Nanda, R., Flampouri, S., Mendenhall, N. P., Indelicato, D. J., Jones, L. M., Seeram, V. K., & Hoppe, B. S. (2017). Pulmonary toxicity following proton therapy for thoracic lymphoma. <i>International Journal of Radiation Oncology• Biology• Physics</i>, 99(2), 494-497.</p> <p>Suzanne Sachsman, Stella Flampouri, Zuofeng Li, James Lynch, Nancy P. Mendenhall & Bradford S. Hoppe (2015) Proton therapy in the management of non-Hodgkin lymphoma, <i>Leukemia & Lymphoma</i>, 56:9, 2608-2612, DOI: 10.3109/10428194.2015.1014364</p> <p>Hoppe, B. S., Flampouri, S., Zaiden, R., Slayton, W., Sandler, E., Ozdemir, S., ... & Mendenhall, N. P. (2014). Involved-node proton therapy in combined modality therapy for Hodgkin lymphoma: results of a phase 2 study. <i>International Journal of Radiation Oncology* Biology* Physics</i>, 89(5), 1053-1059.</p> <p>Bradford S. Hoppe, Henry Tsai, Gary Larson, George E. Laramore, Carlos Vargas, Yolanda D. Tseng, Megan Dunn, Lisa McGee, Oren Cahlon & William Hartsell (2016): Proton therapy patterns-of-care and early outcomes for Hodgkin lymphoma: results from the Proton Collaborative Group Registry, <i>Acta Oncologica</i>, DOI: 10.1080/0284186X.2016.1197422.</p> <p>O'steen, L., Bellardini, J., Cury, J., Jones, L., Seeram, V. K., Mendenhall, N. P., & Hoppe, B. S. (2019). Pulmonary Function after</p>	<p>Thank you for your comments.</p> <p>This study has been included and added to the evidence base.</p> <p>This study was excluded because it did not meet inclusion criteria of having at least 30 patients.</p> <p>This study has been included and added to the evidence base.</p> <p>This study has been included and added to the evidence base.</p> <p>This study was excluded because it has no outcomes of interest, pulmonary function results only (FVC, FEV1, FEV1/FVC ratio, DLCO); also N=15 enrolled, 12 analyzed.</p>

	Comment	Response
	<p>Proton Therapy for Hodgkin Lymphoma Lung function after PT for HL. International Journal of Particle Therapy.</p> <p>Guzhva, L., Mendenhall, N. P., Morris, C. G., Flampouri, S., & Hoppe, B. S. (2017). Evaluating Cardiac Biomarkers after Chemotherapy and Proton Therapy for Mediastinal Hodgkin Lymphoma. International Journal of Particle Therapy, 4(2), 35-38.</p>	<p>This study was excluded because it did not meet inclusion criteria of having at least 30 patients.</p>
<p>Results; Adult Ocular Melanoma; Section 4.3.11</p>	<p>The authors suggest that there have been three comparative studies useful in evaluating proton beam treatment. None of these studies are comparative in nature and none should be used to determine the utility of proton beam for treating uveal melanoma (of which, choroidal melanoma is a subset). One study reports the comparison of two modalities of radiation after a surgery which is not performed in the United States because it is considered unsafe. A second is a comparison of protons with a treatment that is also not considered a gold standard treatment in the United States. A third is a database comparison with many very important flaws and does not compare protons to any other treatment side-by-side.</p> <p>The discussion of pediatric uses of protons should revolve only around retinoblastoma. Children treated for uveal melanoma with proton beam should be lumped into the adult section. The disease process of uveal melanoma is the same whether the patient is 10 years old or 90 years old.</p> <p>Review of Specific Studies Cited in the Report:</p> <p><i>Outcomes of treatment with stereotactic radiosurgery or proton beam therapy for choroidal melanoma. (Sikuade 2015)</i> This is a paper that was suggested as being a valid comparison study. It compares PBT to stereotactic radiosurgery. This is not a relevant comparison as stereotactic radiosurgery is not a standard treatment in the United States. Nevertheless, PBT performs well.</p>	<p>Thank you for your comments.</p> <p>Accepted method for systematic reviews were used to help assure objectivity in finding and selecting studies. Studies identified via structured literature searches of multiple databases and from documents submitted during the public comment period for the KQ (e.g. draft/model policies, etc.) were compared against inclusion criteria set a priori and described in the full the report.</p> <p>We understand your concerns regarding the relevancy of the comparators. Unfortunately we are at the mercy of the literature; the comparative studies included are ones that met our inclusion criteria. We have stated that these comparators may not represent widely used or golden standard treatments for these conditions and thus the results should be interpreted with that in mind. The inclusion of additional case series would not provide additional evidence to answer the question of comparative effectiveness particularly with regard to other radiation therapy methods that would be a logical comparator.</p>

Comment	Response
	<p><i>Neoadjuvant proton beam irradiation vs. adjuvant ruthenium brachytherapy in transscleral resection of uveal melanoma. (Boker 2018)</i> This is presenting a comparison of a treatment that is not performed in the United States and should not be used for any analysis. Trans-scleral resection of melanoma is extremely risky and unnecessary and there is not any physician in the United States who practices this treatment. Furthermore, in this study proton therapy was used in a neo-adjuvant setting, and the plaque in an adjuvant setting. Nevertheless, PBT performs well.</p> <p><i>Patterns of care and outcomes of proton and eye plaque brachytherapy for uveal melanoma. (Lin 2017)</i> This is a paper that attempts to compare PBT to plaque radiotherapy. To do so they use cancer registry information. However, this is an extremely flawed paradigm. Proton beam, during the period of study in this paper, was available in only two centers in the United States: Boston and Sacramento. Patients treated with proton beam during these years were referred to these centers from throughout the country due to the high risk features of the melanoma and the inability to treat with plaque brachytherapy. Tumors treated with protons in the era are larger, thicker, closer to the optic nerve, and are more advanced. The authors even state that patients who had protons traveled further, were more educated, were whiter, and waited longer to obtain treatment. The tumors treated with proton beam in this study are wildly different than those treated with plaques, as stated in the document. Simply controlling for thickness of the tumor is not sufficient to compare these modalities. This absolutely can NOT be used to show the overall survival is worse with proton beam treatment.</p> <p><i>Cost-effectiveness of proton beam therapy for intraocular melanoma. (Moriarty 2015)</i> The cost comparison report that the authors refer to in this study is not relevant. This is a</p>

	Comment	Response
	<p>comparison between enucleation and proton beam treatment. When an eye needs to be enucleated, it will be enucleated primarily. This is a comparison of two treatments whose overlap is extremely narrow. The true comparison of interest is the cost of proton beam vs. other globe salvaging treatments. This comparison does not exist. If it were to exist it would have to consider the following points: plaque radiotherapy reports on average a 90% local tumor control rate while potons reports a 97% control rate. The vast majority of patients undergoing plaque radiotherapy in this country require two surgeries and are admitted to a hospital for an average of 5 days. Patients undergoing proton beam treatment have one surgery and are not admitted to the hospital.</p>	
<p>Results; Adult Ocular Melanoma; Section 4.3.11</p>	<p>The authors quickly write off the many, very large, single center studies that evaluated PBT. They label them as flawed and biased. However, they quickly used the above three studies, which have nearly no role whatsoever in the treatment of uveal melanoma in the United States, as relevant studies. It would be most appropriate to compare the large single center studies evaluated PBT, which are relevant in the United States, with the COMS studies evaluating plaque radiotherapy. These include the following:</p> <p>Gragoudas, E. S. (2006). Proton beam irradiation of uveal melanomas: the first 30 years the weisenfeld lecture. Investigative ophthalmology & visual science, 47(11), 4666-4673.</p> <p>Damato, B., Kacperek, A., Chopra, M., Campbell, I. R., & Errington, R. D. (2005). Proton beam radiotherapy of choroidal melanoma: the Liverpool-Clatterbridge experience. International Journal of Radiation Oncology* Biology* Physics, 62(5), 1405-1411.</p>	<p>Thank you for your comments.</p> <p>The inclusion of additional case series would not provide additional evidence to answer the question of comparative effectiveness particularly with regard to other radiation therapy methods that would be a logical comparator. We understand your concerns regarding the comparators. Unfortunately we are at the mercy of the literature; the comparative studies included are ones that met our inclusion criteria. We have stated that these comparators may not represent widely used or golden standard treatments for these conditions and thus the results should be interpreted with that in mind.</p> <p>This study would not have been captured by our search; its publication date is outside the scope of this report as this is an update to the previously published 2014 report.</p> <p>This study would not have been captured by our search; its publication date is outside the scope of this report as this is an update to the previously published 2014 report.</p>

	Comment	Response
	Desjardins, L., Lumbroso-Le Rouic, L., Levy-Gabriel, C., Cassoux, N., Dendale, R., Mazal, A., & Asselain, B. (2012). Treatment of uveal melanoma by accelerated proton beam. In Current Concepts in Uveal Melanoma (Vol. 49, pp. 41-57). Karger Publishers.	This study would not have been captured by our search; its publication date is outside the scope of this report as this is an update to the previously published 2014 report.
Results; Adult Brain, Spinal, Paraspinal; Section 4.3.3	<p>The deleterious neurocognitive impact of radiation exposure to normal tissue is well-described and well-recognized¹⁵ and there is level 1 evidence of neurocognitive and memory impairment after even low-dose exposure of normal brain tissue to radiation in patients with brain tumors.¹⁶ Proton Beam Radiotherapy for treatment of brain tumors is recognized and supported by scientific evidence. There is no question that excessive radiation dose to the brain is associated with neurocognitive decline. And, there is a growing concern for cognitive deficits secondary to radiation exposure to non-target brain tissue. Proton Therapy has been shown to be associated with lower levels of cognitive decline with brain tumors compared to historic controls. Additionally, recent prospective data suggest that patients receiving proton beam radiotherapy for their CNS tumors experience greater preservation of their cognitive function. As such, the evidentiary support for protons is now greater than that supporting the utilization of IMRT for adult CNS tumors.</p> <p>General Issues with the draft evidence review. The current review does not include an evaluation of current standards. Currently, IMRT is routinely covered for CNS most of the time. There are no trials with the SOE that they are requiring for protons that currently exist for IMRT.</p>	<p>Thank you for your comments.</p> <p>Unfortunately we are at the mercy of the literature; the comparative studies included are ones that met our inclusion criteria.</p>
Results; Adult Head and Neck; Section 4.3.7	<p>Sources Missing from the study include:</p> <p>Romesser PB, Cahlon O, Scher E, et al. Proton beam radiation therapy results in significantly reduced toxicity compared with intensity-modulated radiation therapy for head and neck tumors that require ipsilateral radiation. Radiotherapy and oncology : journal of the European Society</p>	<p>Thank you for your comments.</p> <p>This study is included in our report.</p>

	Comment	Response
	<p>for Therapeutic Radiology and Oncology 2016;118:286-92</p> <p>Sharma, S., Zhou, O., Thompson, R., Gabriel, P., Chalian, A., Rassekh, C., ... & Cohen, R. B. (2018). Quality of Life of Postoperative Photon versus Proton Radiation Therapy for Oropharynx Cancer. International Journal of Particle Therapy, 5(2), 11-17.</p>	<p>This study has been included and added to the evidence base.</p>
<p>Results; Adult Breast; Section 4.3.4</p>	<p>Sources Missing from the study include:</p> <p>Lisa S Kahalley, M Douglas Ris, Anita Mahajan, M Fatih Okcu, Murali Chintagumpala, Arnold C Paulino, William E Whitehead, Charles G Minard, Heather H Stancel, Jessica Orobio, Judy J Xue, Emily A Warren, David R Grosshans; Prospective, Longitudinal Comparison of Neurocognitive Change in Pediatric Brain Tumor Patients Treated with Proton Radiotherapy versus Surgery Only, 2019, Neuro-Oncology, , noz041, https://doi.org/10.1093/neuonc/noz041</p> <p>Mailhot Vega, R. B., Kim, J., Bussière, M., Hattangadi, J., Hollander, A., Michalski, J., ... & MacDonald, S. M. (2013). Cost effectiveness of proton therapy compared with photon therapy in the management of pediatric medulloblastoma. Cancer, 119(24), 4299-4307.</p>	<p>Thank you for your comments.</p> <p>This study has been included and added to the evidence base.</p> <p>This study is included in the report.</p>
<p>Results; Pediatric Other Tumors (Neuroblastoma); Section 4.2.6</p>	<p>Sources Missing from the study include:</p> <p>Hill-Kayser, C. E., Tochner, Z., Li, Y., Kurtz, G., Lustig, R. A., James, P., ... & Mosse, Y. P. (2019). Outcomes after Proton Therapy for Treatment of Pediatric High-Risk Neuroblastoma. International Journal of Radiation Oncology* Biology* Physics.</p>	<p>Thank you for your comments.</p> <p>This study would not have been captured by our search; its publication date is outside the scope of this report as this is an update to the previously published 2014 report.</p>
<p>Results; Prostate; Section 4.3.12</p>	<p>Although the superiority of protons over photons for the treatment of prostate cancer is currently an open scientific question and the subject of multiple ongoing phase III randomized trials, one unquestionable benefit of proton beam radiotherapy when compared to photon beam radiotherapy is a significant reduction in the volume of healthy tissue that is exposed to radiation when compared to IMRT or other X-ray based techniques. This</p>	<p>Thank you for your comments.</p>

Comment		Response
	<p>translates into a significant reduction in the risk of late-radiation side effects, including secondary malignancies. This forms the basis for protons being a “standard of care” for pediatric malignancies in whom radiation is indicated. Although one may reasonably question the magnitude of this benefit in an 80 year old man whose predicted life expectancy is relatively short when compared to the timeframe of late-radiation side effects, 25% of our prostate patients are under the age of 65 and there is little question that the magnitude of this benefit is likely to be substantial. Further, the HTCC is making clinical coverage decisions for patients who are covered by the PEBB and Medicaid and are therefore likely to be younger in age and stand to benefit from the reduction in radiation dose that proton therapy achieves. We also once again advocate for coverage of patients for evidence generation, such as coverage for the randomized trials that the HTA report asks for in evidence review.</p>	
Jeff Sperring, MD, CEO, Seattle Children’s Hospital		
General	<p>Costs and quality of life Proton therapy is a proven and effective tool for many pediatric patients, however, we are selective in our use of protons; treating only those patients that would receive a <i>superior</i> treatment plan from protons over other modalities.</p> <p>Due to the advantages of proton therapy in reducing secondary harmful side effects, there are long-term costs and quality of life implications that must be considered - especially in the context of pediatric patients. Studies consistently show that proton therapy results in reduced cognitive impairments, hearing loss, and neuro-hormonal complications compared to other forms of radiation which results in improved quality of life and both short- and long-term cost savings.</p> <p>Challenges in accruing and randomizing pediatric patients to trials While the committee seeks large comparative trials as evidence of the</p>	<p>Thank you for your comments. Please see the document in the Appendix for the entire correspondence.</p>

Comment	Response
	<p>effectiveness of proton therapy, obtaining such studies is challenging, and at times unethical.</p> <p>To address the issue related to study size first, the occurrence of many of these diseases is rare, and therefore recruiting large volumes is challenging if not impossible. In all of 2018, only 61 pediatric patients were treated using proton therapy in the Pacific Northwest. Of that, a total of 15 were medulloblastoma, five were lymphoma, six were head and neck, and one was ocular. Accruing, and especially randomizing, patients to comparative studies is also beset with challenges and may be unethical. As a healthcare provider, we are seeking to provide the best care to our patients. When there is a known treatment which will result in less harm and improved outcomes, exposing patients to a more harmful option would go against our values and duties to our patients.</p> <p>Additionally, parents are not agnostic to the treatment decisions for their children. We would not ask a parent to treat their child with a modality that may result in their child getting more radiation dose unnecessarily.</p> <p>While there may not be a great deal of comparative trials for each pediatric disease site, the risk of radiation exposure has been studied time and time again. Increased radiation exposure has been directly linked to increased risk of cancer. The properties of proton therapy allow for greatly reduced radiation dose to healthy tissue when compared to traditional photon based modalities. This is why we are able to confidently speak to the reduced harms of proton therapy for pediatric patients. Our pediatric patients can expect to have many decades of life ahead of them, and the reduced risk of secondary malignancy reduces long term costs associated with retreating patients, and improve overall quality of life.</p> <p>We strongly encourage the HTCC to consider the benefits of proton therapy and Seattle Children's unique expertise in pediatric</p>

Comment		Response
	radiation oncology in defining a coverage policy which allows the experts in their field to make the best decision for their patients' health.	
Daniel E. Smith, Executive Director, Alliance for Proton Therapy Access		
General	<p>We are writing to urge you to include the most up-to-date clinical evidence and consensus model policies in your report. Since the time when proton therapy was originally reviewed by the Washington State Health Technology Clinical Committee in 2014, several distinguished cancer organizations – including the American Society for Radiation Oncology (ASTRO), the National Cancer Conference Network (NCCN), the National Association of Proton Therapy (NAPT), and American Society of Clinical Oncology (ASCO) – have developed model policies based on their members' input. We encourage you to ensure their guidance is reflected fully in your report.</p> <p>We also ask that you include a statement of support for providing coverage of PBT for any indications when a patient is enrolled in a clinical trial and/or registry, as this will help generate additional clinical evidence regarding the appropriate use of PBT.</p> <p>Finally, we urge you to consider the experience of patients as you re-evaluate coverage of PBT for various cancer indications. Below are excerpts of stories from two Washington State cancer survivors who benefitted from proton therapy.</p>	<p>Thank you for your comments. Please see the document in the Appendix for the entire correspondence.</p> <p>Evaluation and inclusion of model policies is not within the scope of the evidence report. The HCA has been made aware of them.</p> <p>As the evidence vendor we do not suggest or evaluate policy or make statement of support for coverage. Our purpose is only to objectively evaluate and present the evidence based on the scope; decisions are up to the HTCC. The HCA has been made aware of your position.</p> <p>Thank you. We have added their names to list of other individuals who have provided similar general comments; the list can be found after this table (Table 2).</p>
Deepak Khuntia, MD, Senior Vice President and Chief Medical Officer, Varian Medical Systems		
General	<p>As new evidence has become available since the Health Technology Clinical Committee's Findings and Decision final adoption on July 11, 2014, we appreciate your efforts to reevaluate the conditions under which coverage applies for PBT. This new clinical data supports the benefits of PBT for additional indications not covered in the 2014 Findings and Decision.</p> <p>Varian applauds the committee for recognizing the benefits of PBT and for its determination that PBT should be a covered benefit for the noted indications in the 2014</p>	<p>Thank you for your comments. Please see the document in the Appendix for the entire correspondence.</p> <p>Evaluation and inclusion of model policies is not within the scope of the evidence report. The HCA has been made aware of them.</p>

Comment	Response
	<p>Findings and Decision. Based upon the mounting clinical evidence available since the publication of the Findings and Decision, Varian also recommends coverage for the following, additional indications:</p> <ul style="list-style-type: none"> • Benign or malignant conditions of the base of the skull or axial skeleton including but not limited to chordomas, chondrosarcomas, and osteosarcomas; • Malignant lesions of the head and neck, including but not limited to nasopharyngeal, oropharyngeal, paranasal sinus and nasal cavity cancers as well as benign head and neck tumors with long anticipated survivorship, such as glomus tumors; • Gastrointestinal tumors including pancreatic, rectal, and anal tumors; • Prostate Cancer (non-metastatic); • Breast Cancer; • Thoracic tumors including lung, esophageal cancers, mediastinal lymphomas, thymomas, sarcomas, and mesothelioma; • Hodgkin's Lymphoma; • B-Cell Lymphomas; • Primary or metastatic tumors of the spine where the spinal cord tolerance may be exceeded with conventional treatment or where the spinal cord has previously been irradiated; • Hepatocellular carcinoma and cholangiocarcinoma; • Patients with genetic syndromes making total volume of radiation minimization crucial such as but not limited to NF-1 patients and retinoblastoma patients; and, • Non-metastatic retroperitoneal sarcomas. <p>We strongly encourage coverage of PBT of these additional indications, as well as coverage of all other indications not specified as covered under the 2014 Findings and Decision when the patient is enrolled in a clinical trial and/or registry as there is a need for additional clinical evidence regarding the appropriate use of PBT for various disease sites.</p>

Comment	Response
<p>As you know, PBT has been utilized for many decades. However, there have been recent advancements with proton delivery systems which include spot scanning or intensity modulated proton therapy (IMPT). There are studies underway comparing the effectiveness and substantially improved dose conformity of IMPT to other forms of radiation therapy and traditional scatter proton therapy.</p> <p>Please see the attached documents, the recently released American Society for Radiation Oncology (ASTRO) model policy and the National Association of Proton Therapy's (NAPT) model policy, which address coverage for PBT.</p>	

We are also grateful to the following individuals for providing general public comment (i.e., not addressing evidence, project scope, or draft key questions) on the topic of proton beam therapy:

Barry Belovsky	Bob Hawley	Gilbert Perry
Bill Bennett	Bruce Helm	Keith and Susan Reisman
Charles Bloch	Ron Hoetmer	Don Roberson
Alan Burke	Donald Johnson	Gerald Schommer
Steve Crattsensburg	Curry Kinyon	Michael Skyles
Peter Davidson	Ron Krause	Joe Spiker
Norman Dodge	Greg Lawless	John Stevens
Ed Dodson	Wayne Lehrman	Ross Truesdale
Robert Edwards	Calvin Leibelt	Maria Trujillo
John Ferebauer	Patrick Linnan	Mark Walsh
Daniel Frishman	Cheryl Martin	Craig Weeks
Melba Fujiura	Mike Matzdorff	Mike and Jeanne Welfringer
Robert Grube	Marcia McNannay	Greg Williams
Vern Hasse	Richard Nicolls	Thomas Wright

APPENDIX:

Clinical/Peer Reviews and Public Comments Received

**Peer Reviewer #1: Yolanda Tseng, MD, Assistant Professor of Medicine,
Department of Oncology, University of Washington Medical Center, Seattle
Cancer Care Alliance**

Thank you for your willingness to read and comment on the Comprehensive Evidence-Based Health Technology Assessment Review for the **Proton Beam Therapy Re-review Report**. Your contribution and time are greatly appreciated.

The general time commitment ranges between 2 and 4 hours; we are able to pay a maximum of 6 hours.

The report and appendices are available at: <https://www.hca.wa.gov/about-hca/health-technology-assessment/proton-beam-therapy>

This form can be filled out electronically on your personal computer. Enter your identification information and comments directly into the shaded areas; use the **TAB** key to move from field to field. Please enter the section, page, and line numbers where relevant. The shaded comment field will expand as you type, allowing for unlimited text. You have been provided comment fields in each section. Should you have more comments than this allows for, please continue with a blank page. Additionally, we are very interested in your evaluation of the ease of use of our Peer Review Form. Please use the last field to enter suggestions for improvement.

We will be going through the draft for typographical errors as well as grammatical and minor edits, allowing you to focus on the substance/content of the report.

When the Peer Review form is complete, save it to your hard drive and return as an e-mail attachment to: andrea@aggregate-analytics.com

I will need your review by Friday, March 29, 2019 at the latest.

If you have questions or concerns please contact andrea@aggregate-analytics.com. Thanks!

Reviewer Identification Information

Reviewer Name	Yolanda Tseng
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	State WA
	Zip Code 98195
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<i>Fax</i>	
E-mail	Ydt2@uw.edu

EXECUTIVE SUMMARY Comments

Page viii Line

Please add abbreviation for HART, TACE. On subsequent revision, please add line numbers so that it is easier to reference

Page ES-1 Line
Paragraph
1

For sentence beginning with “PBT may be most promising for tumors in close proximity to OAR ...”, it may be helpful to clarify what “close proximity” means. Protons do not necessarily have superior sparing of OARs that are immediately adjacent to a tumor (e.g. <1 cm), and the greater benefit of protons may be to spare OARs that are of moderate distance away from the target (e.g. >2 cm).

Page ES-2 Line 5

Would remove “nausea” from the sentence. This depends on the location that is being irradiated, whereas fatigue and skin irritation are nearly universal.

Page ES-2 Line
Paragraph
2

For the sentence beginning with “The development of linear accelerators (LINACs) ...”, I would consider the word choice of “accelerated particles”. While a photon is an elementary particle, particle may also be construed as neutrons, protons, carbon ions.

Page ES-2 Paragraph
2

For sentence beginning with “Stereotactic radiosurgery and SBRT are similar to IMRT ...” I would clarify that in addition to dose per fraction, another major difference is immobilization (more rigid for SBRT as the planning target volume margins are smaller)

Page ES-3 Line
Paragraph
2

For sentence beginning with “Photons are the negatively charged ...” Photons are not negatively charged. They have no mass or charge.

Page ES-3 Line Figure
1

The dose distribution illustrated for the x-ray (photon) beam is inaccurate. The skin dose for photons is generally LOWER than that of the spread out Bragg peak of protons. The original figure from the referenced paper (151) illustrates the correct photon depth-dose distribution relative to protons. I would modify this figure so that it correctly illustrates the physical dose distribution of photons.

Page ES-3 Line
Paragraph
after figure
1

It is misleading to state that the spread out Bragg peak (SOBP) is comprised from radiation dose from multiple beams, as “beams” usually refer to the different directions that radiation is directed (i.e. an anterior beam and a lateral beam). The SOBP is created by varying the energy of a proton beam, creating a range of energies. For example, a shallower beam will have lower energy compared to a deeper beam.

Page ES-4 Line 7

Would replace “dose level” to “dose per fraction”

Page ES-4 Line 9-11

Please include reference for the referenced study “one study identified situations ...”

Page ES-10 Line Table

Please include abbreviation for ECON, TSR. For the number of case studies included for a particular disease site (e.g. lymphoma), what was the eligibility/ineligibility criteria for including a case series? I treat heme malignancies and there are >1 case series published among lymphoma patients receiving proton therapy, notably for non-Hodgkin lymphoma. There is also publications on toxicity after proton therapy for lymphoma, in particular pulmonary function tests and cardiac MRIs. I cannot comment on other disease sites as I am not up to date with the pertinent proton literature. However, as there are discrepancies with what case series have been included in the review and other case series that may be pertinent, it may be helpful to provide more detail why certain publications were not included. Was it because they were missed in the initial review of the literature or excluded for eligibility and if so, why?

Page Line

I would consider separating out primary bone tumors (e.g. chondrosarcomas, chordomas) from head and neck (including base of skull). Primary bone tumors have a different treatment paradigm compared to HN

cancers (primarily squamous cell carcinomas, SCC) and are more radioresistant, necessitating higher RT doses, and are not treated with chemotherapy, unlike HN SCC.

Page ES-14 Line Bone
 tumors,
 point 1

Bladder cancer in first sentence should likely be “bone cancer”. I would clarify, does the section on bone tumors include non-base of skull chordomas/chondrosarcomas? Many guidelines (including those listed on page 26), include these as part of brain and spinal tumors.

The goal of an executive summary is to give a reader a broad sense of the work, which also means being clear with inclusion/exclusion criteria of included studies. I would consider including in the executive summary the rationale for excluding some case series (e.g. based on the number of patients included). Clearly not all publications in proton therapy were included in the results of this report (see my comment above), and unless you read through the entire report, it is not apparent why.

INTRODUCTION/APPRAISAL Comments

While reviewing this section please keep the following questions in mind, but please comment on any point:

- Overview of topic is adequate?
- Topic of assessment is important to address?
- Public policy and clinical relevance are well defined?

The overview presented in the executive summary was appropriate, including basic review of proton therapy and how this treatment may differ from other radiotherapy modalities. There are some minor inaccuracies regarding technical details of proton therapy, which are highlighted above.

The public policy is not well defined. It may be helpful to touch upon what proportion of patients are being treated with proton therapy over time to provide a sense of the magnitude of proton use compared to other RT modalities.

Page 14 Line Charts
 I, II, V, VII

I would consider adding the y-axis to quantify the number of cases by primary dx category. Also, it is not clear to me what the differences are between chart I and II. Do the charts plot the distribution of proton cases but from different agencies (although PEBB/UMP appears present for both)? Why are these separated out as such? This is not clear to me from the text.

Page 16 Line Table
 III

It is not clear to me why there are n=63 patients represented in table 3 but 246 in chart III. Could this be clarified within the text or table legend? Is this because Table 3 does not include patients treated under Medicaid Manage Care?

Page 17 Line Chart
V

Please comment how chart V differs from chart II and why the data is laid out as such (e.g. combination of PEBB/UMP and Medicare/PEBB versus PEBB/UMP and Medicare/UMP). This section in general would benefit from more text to provide context for the figures.

BACKGROUND Comments

While reviewing this section please keep the following questions in mind, but please comment on any point:

- Content of literature review/background is sufficient?

Overall, the background content is adequate, though there are some technical inaccuracies (please see above for comments). The review provides a summary of prior systematic reviews and HTA of proton therapy. For completeness and for background, I would suggest also including a summary of the WA HTA 2014 in Table 3.

Page 26 Line Table
2

Please provide abbreviations for NICE, AIM, ACR

Page 28 Line Table
3

Please provide abbreviation for SR

REPORT OBJECTIVES & KEY QUESTIONS Comments

While reviewing this section please keep the following questions in mind, but please comment on any point:

- Aims/objectives clearly address relevant policy and clinical issue?
- Key questions clearly defined and adequate for achieving aims?

The objective and key questions of this report are clearly laid out and are appropriate. The primary comparators chosen were also appropriate, in particular recognition that sometimes the comparator of interest is not another RT modality (e.g. TACE for HCC).

METHODS Comments

While reviewing this section please keep the following questions in mind, but please comment on any point:

- Method for identifying relevant studies is adequate?
- Criteria for the inclusion and exclusion of studies is appropriate?
- Method for Level of Evidence (LoE) rating is appropriate and clearly explained?
- Data abstraction and analysis/review are adequate?

To identify relevant studies, published articles were comprehensively searched through PubMed and other electronic databases. Conferences abstracts were excluded, in addition to duplicate publications without different data or follow-up times. Reasons for excluding articles (Appendix C) seemed reasonable and included series in which PBT modality was used for a minority of patients, treatment planning studies, prior

publication of the cohort, lack of separate analyses for patients treated with protons versus photons, . My main criticism is below (page 59, exclusion criteria) in regards to rare tumors such as lymphoma. For example, for study #27, a prospective phase II single arm study of 15 lymphoma patients treated with proton therapy, this was excluded as there were <30 patients in the case study. However, Hodgkin lymphoma arguably is a very rare entity. What is the incidence threshold to define if a disease would fall into the “very rare conditions”?

The LoE rating was clearly explained, which followed criteria that have been used in other systematic reviews and/or groups (GRADE, AHRQ, QHES). The tables laid out showed consistent data abstraction, analysis and review.

Page 57 *Line 14*

As part of the inclusion/exclusion criteria, it may be helpful to define what is considered “long term” with respect to clinical outcomes or safety.

Page 59 *Line Study design, exclusion*

Please define “very rare conditions”; specifically, in which tumors were case series ≥ 10 patients allowed? Certain tumors (e.g. lymphomas) are relatively rare (e.g. HL, 2.5 per 100,000 incidence), which means it is difficult to have a large case series of patients treated with proton therapy. By excluding case series in adult with <30 patients, this may bias the report against rarer tumors.

Page *Line*

Enter Comments Here

Page *Line*

Enter Comments Here

Page *Line*

Enter Comments Here

RESULTS Comments

While reviewing this section please keep the following questions in mind, but please comment on any point:

- Amount of detail presented in the results section appropriate?
- Key questions are answered?
- Figures, tables and appendices clear and easy to read?
- Implications of the major findings clearly stated?
- Have gaps in the literature been dealt with adequately?
- Recommendations address limitations of literature?

The summary of pediatric comparative (text, tables) and case series publications (appendix) on proton therapy is very good with appropriate amount of detail presented and commentary about potential limitations of the available evidence. The figures and tables (both in the appendix and main report) provide

an easy-to-read summary and attempt to show heterogeneous comparative studies side-by-side. This can be challenging given that outcomes or safety are reported differently (i.e. at different time points, different grades, mixed tumors) across studies. The major findings are fairly stated, in addition to identify current gaps in the literature for pediatric tumors.

The summary of the comparative and case series literature for adult tumors is very good, with appropriate detailed presented and limitations of studies or conclusions laid out. In instances where inadequate detail was given in a study (e.g. grade of toxicity, whether toxicity was attributable to just RT), this is highlighted. Potential reasons for why statistical significance was not observed in comparative studies were offered. It is helpful to include the Table number in appendix F if/when this is referenced in the text. This occurred in many, but not all, sections.

Please note that I did not confirm the accurateness of the summaries or completeness of literature review across the different disease sites.

Page 112 Line 4

Gy(RBE) refers to proton dose. In the table, 57 Gy was for photons and 50.4-54 Gy(RBE) was for protons/IMRT.

Page 112 Line Table
19

It is not clear to me why radiation necrosis that is outside (versus inside) the treatment field is of interest. Radiation necrosis usually occurs within the high dose region (e.g. within the treatment field), so it's not surprising that risk of RT necrosis outside the treatment field is 0%.

Page 158 Line 2nd
paragraph
under KQ1,
last
sentence

It may be difficult, if not impossible, to blind patients and treating physicians to RT modality that a patient is randomized to (protons versus photons) as the machines for protons may be in a physically distinct location from that of photons. The use of blinding in RT trials may be more limited compared to drug therapy trials.

Page 183 Line First
paragraph

I would consider describing more why the quasi-RCT is categorized as “quasi-RCT.” Was this a dose escalation (safety) study? For lines 7-8: would rephrase it as 3.0 Gy for 8 daily fractions, 4.0 Gy for 5 fractions, etc. “3.0 Gy in 8 daily fractions” may imply that the total dose was 3 Gy (i.e. 0.375 Gy per fraction).

CONCLUSIONS Comments

While reviewing this section please keep the following questions in mind, but please comment on any point:

- Are the conclusions reached valid?

Based on the reported state of the literature, summary of the number and quality of comparative and case series studies, the conclusions reached for each results section (by disease site) are reasonable and fair.

OVERALL PRESENTATION and RELEVANCY Comments

While reviewing this section please keep the following questions in mind, but please comment on any point:

- Is the review well structured and organized?
- Are the main points clearly presented?
- Is it relevant to clinical medicine?
- Is it important for public policy or public health?

The review overall is organized and systematic, though would benefit by providing more abbreviations upfront. I did not have time to review all the appendix tables, but felt the structure of providing very granular details (e.g. extracted data and then summary tables) provided transparency of how the results were obtained. Results for the key questions were clearly presented, and I appreciated the use of figures to visually describe the outcome and/or toxicity findings in the comparative studies or RCTs. This was quite effective. In light of the multiple new studies in the last few years with proton therapy, this report is timely and relevant to the field. Portions of the report were redundant and perhaps for interest to improve readability, it may be helpful to cut down on the redundant text.

QUALITY OF REPORT

Quality Of the Report

(Click in the gray box to make your selection)

☐ Superior

☐ Good X

☐ Fair

☐ Poor

We would appreciate any feedback you have on the usability of this form. Please add comments in the field below.

It was helpful to have this form to outline what to focus on. In the future, it would be helpful to have line numbers in the report.

Peer Reviewer #2: Smith “Jim” Apisarnthanarax, MD, Associate Professor of Radiation Oncology, Associate Residency Program Director, Proton Therapy Fellowship Director, University of Washington School of Medicine

Thank you for your willingness to read and comment on the Comprehensive Evidence-Based Health Technology Assessment Review for the **Proton Beam Therapy Re-review Report**. Your contribution and time are greatly appreciated.

The general time commitment ranges between 2 and 4 hours; we are able to pay a maximum of 6 hours.

The report and appendices are available at: <https://www.hca.wa.gov/about-hca/health-technology-assessment/proton-beam-therapy>

This form can be filled out electronically on your personal computer. Enter your identification information and comments directly into the shaded areas; use the **TAB** key to move from field to field. Please enter the section, page, and line numbers where relevant. The shaded comment field will expand as you type, allowing for unlimited text. You have been provided comment fields in each section. Should you have more comments than this allows for, please continue with a blank page. Additionally, we are very interested in your evaluation of the ease of use of our Peer Review Form. Please use the last field to enter suggestions for improvement.

We will be going through the draft for typographical errors as well as grammatical and minor edits, allowing you to focus on the substance/content of the report.

When the Peer Review form is complete, save it to your hard drive and return as an e-mail attachment to: andrea@aggregate-analytics.com

I will need your review by Friday, **March 29, 2019** at the latest.

If you have questions or concerns please contact andrea@aggregate-analytics.com. Thanks!

Reviewer Identification Information

Reviewer Name	Smith Apisarnthanarax
Address	Street 1959 NE Pacific St., Box 356043
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	State WA
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INTRODUCTION Comments

While reviewing this section please keep the following questions in mind, but please comment on any point:

- Overview of topic is adequate?
- Topic of assessment is important to address?
- Public policy and clinical relevance are well defined?

Page	Line
------	------

Overview of topic is very well done.

Page	Line
------	------

The importance of re-reviewing the clinical data on protons is well described.

Page	Line
------	------

The impact of protons on public policy and relevance to patient care are well defined.

BACKGROUND Comments

While reviewing this section please keep the following questions in mind, but please comment on any point:

- Content of literature review/background is sufficient?

Page	Line
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The content of the literature review and background is adequate and well summarized.

REPORT OBJECTIVES & KEY QUESTIONS Comments

While reviewing this section please keep the following questions in mind, but please comment on any point:

- Aims/objectives clearly address relevant policy and clinical issue?
- Key questions clearly defined and adequate for achieving aims?

Page 55	Line 3.1.2
---------	------------

Key Questions 1 and 2. Since the main theoretical benefit of protons is reduction of normal tissue toxicity, the comparative impact of protons on acute and late toxicities should be explicitly stated (“health-related quality of life” is related to, but distinct from toxicity metrics).

METHODS Comments

While reviewing this section please keep the following questions in mind, but please comment on any point:

- Method for identifying relevant studies is adequate?
- Criteria for the inclusion and exclusion of studies is appropriate?
- Method for Level of Evidence (LoE) rating is appropriate and clearly explained?
- Data abstraction and analysis/review are adequate?

Page	Line
------	------

Described methods is adequate. Criteria for inclusion/exclusion seem reasonably appropriate. Method for LoE rating is appropriate and clearly explained. Data abstraction and analysis/review appear appropriate.

RESULTS Comments

While reviewing this section please keep the following questions in mind, but please comment on any point:

- Amount of detail presented in the results section appropriate?
- Key questions are answered?
- Figures, tables and appendices clear and easy to read?
- Implications of the major findings clearly stated?
- Have gaps in the literature been dealt with adequately?
- Recommendations address limitations of literature?

Page	Line
------	------

General comment: because I primarily have clinical expertise in esophageal, GI, liver, and prostate cancers, I will only comment on these disease sections. One general comment for all disease sites is to provide a brief discussion on the clinical context of why protons are being used for each disease site and in what clinical settings.

Page 119-130	Line
--------------	------

Esophageal cancer: appropriate studies were included. In the tables and in the charts, it should be distinguished which studies were evaluating protons for definitive treatment or as a part of trimodality treatment (when protons are used for preoperative treatment). This distinguishment is important as the use and rationale of protons in these settings are different, so the interpretation of the data is different. Protons as preoperative treatment (trimodality) are designed to reduce peri- and post-operative complications and morbidity since radiation is thought to affect surgical complications. In the definitive treatment setting, the benefit and rationale of protons is less clear since surgery is not involved. Protons in the definitive setting may translate to improved outcomes by way of allowing for safe dose escalation and/or less toxicity with standard radiation doses.

Page 150-157	Line
--------------	------

Liver cancer: Kim et al PMID 25381830 - I would consider adding this study to the review. Even though this is single institution study of only 27 patients, this is a prospective phase I study, which in my opinion, has higher scientific quality than a retrospective case series.

Page 180-183	Line
--------------	------

Prostate: Chuong et al PMID 29034790. This is a study looking at the value of whole pelvis protons in 85 patients from the PCG registry database and should be considered to be added to the review. Other than meeting the minimum requirement of number of patients for a case series, this study is unique in the literature in that this is the first study to look at using protons to deliver whole pelvis radiation for prostate cancer patients.

CONCLUSIONS Comments

While reviewing this section please keep the following questions in mind, but please comment on any point:

- Are the conclusions reached valid?

Page	Line
------	------

Conclusions appear to be valid.

OVERALL PRESENTATION and RELEVANCY Comments

While reviewing this section please keep the following questions in mind, but please comment on any point:

- Is the review well structured and organized?
- Are the main points clearly presented?
- Is it relevant to clinical medicine?
- Is it important for public policy or public health?

Page	Line
------	------

This review overall is well prepared and organized. I found the bar graph figures of comparative studies very useful. One suggestion for these graph figures is to put an asterisk above statistically significant comparisons (rather than having to look for the p values to see which ones are statistically significant) for better ease of reading. The main point of this review to focus on new data from 2014-2018 is clear.

The review seems to lump non-randomized prospective trials in with “case series.” In my opinion, these studies should be distinguished between retrospective case series as being in a separate category of evidence.

QUALITY OF REPORT

Quality Of the Report

[\(Click in the gray box to make your selection\)](#)

Superior

Good X

Fair

Poor

We would appreciate any feedback you have on the usability of this form. Please add comments in the field below.

Enter Form Comments Here

From: LIVINGSTON Catherine
Sent: Monday, March 4, 2019 11:36 AM
To: HCA ST Health Tech Assessment Prog
Subject: FW: Proton beam therapy draft report now posted on HCA website

How about a single page meta-table that summarizes at a high level the evidence in the executive summary?

Cat Livingston, MD, MPH
Associate Medical Director
Health Evidence Review Commission
OREGON HEALTH AUTHORITY
Mobile (503) 689-3204
<http://www.oregon.gov/oha/hpa/csi-HERC/>

VIA electronic mail to: shtap@hca.wa.gov

April 1, 2019

Re: Draft Evidence Report for Proton Beam Therapy

Health Technology Assessment Program
Washington State Health Care Authority
626 8th Avenue • P.O. Box 45502
Olympia, WA 98504-5502

To Whom It May Concern:

We thank you for the opportunity to submit comments on the Draft Evidence Report for the 2019 Health Technology Assessment Re-Review of Proton Beam Therapy. At the outset, we believe that proton beam therapy should be covered consistent with the evidence based model policies such as the ones issued by National Association for Proton Therapy (See Appendix 1) or the American Society for Radiation Oncology (ASTRO). In addition, in this letter, we are submitting additional specific comments regarding the findings for selected indications, comparison of the HCA recommendations to other guidelines and policies, and comments on the overall process and approach for the re-review of proton beam therapy.

By way of background, the National Association for Proton Therapy ("NAPT") is a nonprofit organization whose mission is to work collaboratively to: (i) educate and raise awareness of the clinical benefits of proton therapy among patients, providers, payers, policymakers, and other stakeholders, (ii) ensure patient choice and access to affordable proton therapy, and (iii) encourage cooperative research and innovation to advance the appropriate and cost-effective utilization of proton therapy for certain cancers. Its members – both hospital based and freestanding – are world-renowned cancer centers, a number of whom are National Cancer Institute (NCI) designated comprehensive cancer centers and National Comprehensive Care Network (NCCN)[®] members, including the Seattle Cancer Care Alliance Proton Therapy Center.

HEAD AND NECK

The re-review found a comparable benefit for proton beam therapy in the treatment of head & neck cancer; this finding is an improvement given the 2014 finding of insufficient evidence. That being said, given the growth in compelling evidence supporting proton beam therapy for head and neck cancers, the NAPT believes proton beam therapy is the most beneficial radiation modality for the treatment of head and neck malignancies with improvement in quality of life and survival for certain indications.

The National Comprehensive Cancer Network (NCCN) outlines evidence-based, collectively agreed upon Guidelines that make treatment recommendations to ensure that cancer patients obtain the most optimal outcomes. These Guidelines are broadly acknowledged by the payer community as the standard for determining clinical policy in cancer care. NCCN Guidelines for Head and Neck Cancer (Version 1.2019) recognized the benefit of proton therapy, in part, as follows:

*IMRT or other conformal techniques (3-D conformal, helical tomotherapy, volumetric modulated arc therapy [VMAT], and **proton beam therapy [PBT]**) may be used as **appropriate depending on the stage, tumor location, physician training/experience, and available physics support.** (Emphasis added)*

*[A]dvanced radiation therapy technologies such as IMRT, IGRT (image-guided radiation therapy) and **PBT may offer clinically relevant advantages in specific instances to spare important organs at risk (OARs) such as the brain, brain stem, cochlea,***

semicircular canals, optic chiasm and nerves, other cranial nerves, retina, lacrimal glands, cornea, spinal cord, brachial plexus, mucosa, salivary glands, bone (skull base and mandible), pharyngeal constrictors, larynx, and esophagus, and decrease the risk for late, normal tissue damage while still achieving the primary goal of local tumor control. The demonstration of significant dose-sparing of these OARs reflects best clinical practice. (Emphasis added)

[R]andomized studies to test these concepts are unlikely to be done since the above specific clinical scenarios are relatively rare. In light of that, the modalities and techniques that are found best to reduce the doses to the OARs in a clinically meaningful way without compromising target coverage should be considered.

Proton Beam Therapy

Achieving highly conformal dose distributions is especially important for patients whose primary tumors are periocular in location and/or invade the orbit, skull base, and/or cavernous sinus; extend intracranially or exhibit extensive perineural invasion; and who are being treated with curative intent and/or who have long life expectancies following treatment. Nonrandomized single institution clinical reports and systematic comparisons demonstrate safety and efficacy of proton beam therapy in the above mentioned specific clinical scenarios. Proton therapy can be considered when normal tissue constraints cannot be met by photon-based therapy. (Emphasis added)

While the HCA did review a few of the compelling studies on head and neck cancer, a number of the studies were devalued based on a perceived risk of bias or “serious imprecision”. We disagree with that characterization and we also believe that the assessment is missing key articles, including Holliday et al and McDonald et al, which looked at the need for gastronomy tube either during or following treatment.^{1,2}

Most of the data on head and neck cancer patients relates to tumors extending to the skull base; however, there are several articles relating to the use of proton radiotherapy in treating patients with cancers of the oropharynx. Slater et al. reported on 29 patients with stages III and IV oropharyngeal carcinoma who were treated using a combination of photons and PBT.³ They found a 5-year local control rate of 88% at the primary site and 94% in the neck. Frank et al. analyzed patients with oropharyngeal carcinoma treated with PBT at the MD Anderson Cancer Center and compared them to a matched set of control patients treated with photon radiotherapy.⁴ They found a lower rate of dysphagia and less need for a feeding tube in order to get the patients through therapy (20% with PBT as compared to 48% with IMRT). Holliday et al. compared the gastronomy tube (GT) rates for patients with nasopharyngeal cancer treated with PBT versus IMRT. They found a meaningful

¹ Holliday EB, Garden AS, Rosenthal DI, et al. Proton therapy reduces treatment-related toxicities for patients with nasopharyngeal cancer: a case-match control study of intensity-modulated proton therapy and intensity-modulated photon therapy. *Int J Particle Ther.* 2015;2:19–28.

² McDonald MW, Liu Y, Moore MG, Johnstone PA. Acute toxicity in comprehensive head and neck radiation for nasopharynx and paranasal sinus cancers: cohort comparison of 3D conformal proton therapy and intensity modulated radiation therapy. *Radiat Oncol.* 2016;11:32.

³ Slater JD, Yonemoto LT, Mantik DW, et al. Proton radiation for treatment of cancer of the oropharynx: early experience at Loma Linda University Medical Center using a concomitant boost technique. *Int J Radiat Oncol Biol Phys.* 2005;62:494–500.

⁴ Frank SJ, Rosenthal DI, Ang K, et al. Gastrostomy tubes decrease by over 50% with intensity modulated proton therapy (IMPT) during the treatment of oropharyngeal cancer patients: a case-control study. *Int J Radiat Oncol Biol Phys.* 2013;87:S144.

reduction in acute toxicity for nasopharyngeal cancer patients treated with PBT as demonstrated by decreased rates of GT placement.⁵

Patel et al. published a comprehensive review of proton beam therapy versus photon therapy for paranasal sinus and nasal cavity malignant diseases.⁶ The meta-analysis reviewed 43 different cohorts (covering 1,472 patients) from 41 different non-comparative observational studies published after 1990. In reviewing the studies, they found that **patients treated with PBT had better overall survival, disease-free survival, and locoregional control at 5 years.** (Emphasis added)

Ultimately, PBT has been shown to target tumors, spare surrounding normal organs and tissues from radiation exposure, significantly reduce or eliminate both the acute and chronic toxicities from ionizing radiation, and therefore, improve quality of life of patients. Therefore, many leading cancer centers believe that PBT is an appropriate treatment option for certain head and neck cancer patients. As such, we are respectfully requesting that the HCA and Aggregated Analytics review the compelling evidence supporting PBT for head and neck cancer in our white paper (see Appendix 2), and promptly update its findings on head and neck cancer to incremental benefit.

CENTRAL NERVOUS SYSTEM

In the re-review, the Washington State HCA downgraded its evaluation of proton beam therapy for Central Nervous Systems from incremental to comparable benefit. We strongly disagree with this decision, particularly given (a) the positions taken by the National Comprehensive Care Network Guidelines and the ASTRO Model Policy on treatment of CNS tumors (see below) and (b) the clinical evidence that continues to support the value of PBT.

The current evidence base supports the coverage of the following types of CNS tumors with proton beam therapy:

- A. Tumors where treatment regimen includes craniospinal irradiation including ependymoma, adult medulloblastoma, pineal tumors, germ cell tumors, pineoblastoma, and primitive neuroectodermal tumors
- B. Grade II and Grade III IDH mutant and 1p19q co-deleted tumors
- C. Re-irradiation where treatment with proton therapy can significantly limit volume of normal brain parenchyma

While the tumors noted above in A are extremely rare tumors in adults, studies have shown substantial improvements in outcomes with proton compared to photon craniospinal radiation in patients with medulloblastoma.⁷ With proton craniospinal radiation, patients have significantly less weight loss (16% vs 64%), less grade 2 nausea and vomiting (26% vs 71%), and less esophagitis (5% vs 57%). Even more importantly, since protons significantly reduces mean vertebral doses, there is significantly less reductions in blood counts with protons (white blood cells, $P=.04$; hemoglobin, $P=.009$; platelets, $P=.05$). This benefit of proton therapy is of particular significance, as chemotherapy has been shown to improve survival when given with radiation, so maintaining blood counts after radiotherapy is incredibly important as it allows delivery of full doses of chemotherapy.

⁵ Holliday E, Garden AS, Fuller CD, et al. Gastronomy tube rates decrease by over 50% in patients with nasopharyngeal cancer treated with intensity modulated proton therapy: A case-control study. *Int J Radiat Oncol Biol Phys*. 2014;90(1):S528.

⁶ Patel SH, Wang Z, Wong WW, et al. Charged particle therapy versus photon therapy for paranasal sinus and nasal cavity malignant diseases: a systematic review and meta-analysis. *Lancet Oncol*. 2014;15:1027–1038.

⁷ Brown AP, Barney CL, Grosshans DR, et al. Proton beam craniospinal irradiation reduces acute toxicity for adults with medulloblastoma. *Int J Radiat Oncol Biol Phys* 2013;86(2):277-84.

With respect to IDH mutant tumors and 1p19q co-deleted tumors, patients have an excellent prognosis with survival times often measured in decades.⁸ (Buckner et al., 2016) With the excellent prognosis for this patient population, decreasing radiation doses to normal uninvolved brain is essential to preserve cognitive function. Numerous studies have examined the threshold dose for increased risk of cognitive dysfunction and the impact of moderate radiation doses to the brain including to the hippocampus.^{9,10} A phase II trial serially evaluating the cognitive function of patients with low grade gliomas found stable cognitive function years after proton radiotherapy.¹¹ These studies support the use of proton therapy to decrease the cognitive risks of radiotherapy in this good prognosis patient population.

Given the evidence discussed above, we urge you to revise your findings in the re-review to include coverage for malignant and benign tumors and for re-irradiation where treatment with proton therapy can significantly limit volume of radiation to normal brain tissue.

PBT RESULTS IN BETTER OUTCOMES WITH LOWER COSTS FOR STATE EMPLOYEES

A recently presented study demonstrated significantly lower costs for PBT when compared to case-matched photon patients.¹² Palmer and Frank of MD Anderson Cancer Center conducted an IRB approved study in collaboration with the University of Texas System, a state-wide self-funded employer, to perform a value-based analysis of PBT in comparison to standard photon radiation therapy (SRT) by analyzing total cost of care, clinical outcomes and toxicities, and patient satisfaction. The three-year study enrolled 57 patients with 22 ultimately treated with PBT and 25 treated with SRT. The disease sites included head & neck, genitourinary, breast, and thoracic cancers. 34 patients were case matched (17 PBT / 17 SRT) with ≥ 6-month follow-up. No grade 4 or 5 toxicities were reported. The results of the study indicated that PBT patients' Quality of Life returned to baseline faster than SRT and that SRT patients had more ancillary costs (Diagnostic Imaging, Pharmacy, Laboratory Tests, Emergency Department, Internal Medicine). Patients treated with PBT resulted in net employer costs savings with average net billed charges 21% lower than SRT.

COMPARISON TO CLINICAL GUIDELINES AND POLICIES

In our comment letter on the Key Draft Questions, we had noted the importance of reviewing the following in this latest evaluation of proton beam therapy:

- NCCN Guidelines. The National Comprehensive Cancer Network (NCCN)¹³ published guidelines are often used as the litmus test by payers for determining if they will approve coverage for all types of cancer treatments. Please keep in mind that the NCCN Guidelines most often consist of what is the current standard of care and often do not include emerging technologies until they have been demonstrated as becoming a standard of care. In the past, they have historically been silent on proton therapy but, over the last 24 months, the guidelines have become more

⁸ Buckner JC, Shaw EG, Pugh SL, et al. Radiation plus procarbazine, CCNU, and vincristine in low-grade glioma. *N Engl J Med* 2016;374:1344-1355.

⁹ Moore IM, Kramer JH, Wara W, et al. Cognitive function in children with leukemia. Effect of radiation dose and time since irradiation. *Cancer* 1991;68(9):1913-1917.

¹⁰ Gondi V, Paulus R, Bruner DW, et al. Decline in tested and self-reported cognitive functioning after prophylactic cranial irradiation for lung cancer: pooled secondary analysis of Radiation Therapy Oncology Group randomized trials 0212 and 0214. *Int J Radiat Oncol Biol Phys* 2013;86(4):656-664.

¹¹ Shih HA, Sherman JC, Nachtigall LB, et al. Proton therapy for low-grade gliomas: Results from a prospective trial. *Cancer* 2015;121(10):1712-1719.

¹² Palmer MB, Frank SJ, et al. Better Outcomes with Lower Costs: The High Value of Proton Beam Therapy Coverage | A State-Wide Self-Funded Employer Success. National Association for Proton Therapy National Proton Conference 2019. See also Thaker NG, Guzman AB, Feeley TW, et al. Defining the value of proton therapy: Using time-driven activity-based costing. *Oncology Payers*. 2014;1:26-33.

¹³ The NCCN is an alliance of 27 largely academic cancer centers in the U.S. of which most are designated as Comprehensive Cancer Centers by the National Cancer Institute.

encouraging in their comments about the use of proton therapy, embedding proton beam therapy in the guidelines for fourteen different disease sites including head & neck cancer.¹⁴

- Model policies from leading medical organizations. The National Association for Proton Therapy has worked together with its members through a consensus and evidence-based approach to draft and update its model policy; the last version of the model policy was just released in February 2019. In 2017, the American Society for Radiation Oncology (ASTRO) released an updated proton beam model policy. These guidelines were promulgated by leaders in the field, many of whom do not have access to protons.

We conducted a comparison of the findings from the 2014 and 2019 HCA findings versus the ASTRO Model Policy, NAPT Model Policy and NCCN Guidelines.

INDICATION	WA STATE HEALTH CARE AUTHORITY: NET BENEFIT		MEDICARE ^A	ASTRO MODEL POLICY (2017)	NAPT MODEL POLICY (2019)	NCCN GUIDELINES
	2014	2019				
Bone	Not reviewed	Insufficient (Ø)	Group 1	Group 2	Medically necessary	Supports ^B
Breast	Insufficient (Ø)	Insufficient (Ø)	Group 2	Group 2	Medically necessary	
CNS	Incremental (+)	Comparable (=)	Group 1	Group 1	Medically necessary	Supports ^B
Esophageal	Insufficient (Ø)	Incremental (+)	Group 2	Group 2	Medically necessary	Supports ^C
Head & Neck	Insufficient (Ø)	Comparable (=)	Group 1	Group 1*	Medically necessary	Supports ^B
Liver	Comparable (=)	Incremental (+)	Group 1 & 2	Group 1	Medically necessary	Supports ^B
Lung	Comparable (=)	Comparable (=)	Group 2	Group 2	Medically necessary	Supports ^B
Ocular	Superior / Incremental (+)	Inferior (-) (PBT vs. BT)	Group 1	Group 1	Medically necessary	Supports ^B
Prostate	Comparable (=)	Comparable (=)	Group 2	Group 2	Medically necessary**	Supports ^B
Pediatric Brain	Incremental (+)	Incremental (+)	Group 1	Group 1	Medically necessary	
Pediatric Other	Incremental (+)	Insufficient (Ø)	Group 1	Group 1	Medically necessary	

^A Majority of the country is not subject to a local coverage determination as the majority of Medicare contractors have no active LCD on proton beam therapy. In those states where there is no LCD, the physicians must appropriately document that the service is reasonable and necessary. The Group 1 and Group 2 indications listed above are specifically from National Government Services LCD which covers 10 states in the Midwest and Northeast.

Medicare Group 1 = Indications that support the use with PBT

Medicare Group 2 = Indications that support the coverage with providers who have demonstrated experience in data collection and analysis with a history of publication in the peer-reviewed medical literature

ASTRO Group 1 = Indications that support the use with PBT

ASTRO Group 2 = Indications that support the coverage with evidence development

* Group 1 with the exception of non-T4 and resectable head and neck cancers that are group 2

** Non-metastatic

^B Supports use of PBT

^C Supports use of PBT within a clinical trial

In nearly all indications, the HCA has taken a more restrictive / negative evaluation of the evidence compared to the other three clinical resources developed by oncology experts. We believe that this inconsistency in the HCA findings is due in part to the lack of engagement of an oncology expert, and, in particular, radiation oncology expert with PBT experience, in the re-review of proton beam therapy as discussed below.

Overall Process and Approach

¹⁴ Guidelines that embedded proton beam therapy (as of March 25, 2019) include bone cancers, central nervous system cancers, esophageal and esophagogastric junction cancers, head and neck cancers, hepatobiliary cancers, Hodgkin Lymphoma, malignant pleural mesothelioma, uveal melanoma, Non-Hodgkin's Lymphoma (B-Cell and T-Cell), non-small cell lung cancer, prostate cancer, soft tissue sarcoma, and thymomas and thymic carcinomas.

There are two significant issues with the overall process and approach taken by the Washington State Healthcare Authority in its re-review.

First, proton beam radiotherapy is a very specific form of radiotherapy that requires specialized clinical training and experience. Clinicians using this modality must have a detailed understanding of the therapy and the type of patients where this treatment approach may or may not be clinically appropriate. A thorough review or assessment of the evidence on this type of technology requires well-informed engagement. We are deeply concerned that Aggregated Analytics did not engage a board-certified radiation oncologist with multiple years of clinical experience at an operating proton therapy center as part of the assessment. We had recommended this approach in our comment letter on the Key Draft Questions and offered to provide a list of physician candidates to serve in this capacity. However, the HCA did not follow our recommendation and, unfortunately, a few of the findings in the report demonstrated a lack of knowledge or expertise in this area.

Second, while the HCA is giving physicians an opportunity to speak at the upcoming Healthcare Technology Clinical Committee meeting on May 17, 2019, it appears that Aggregate Analytics will have finalized the report by April 17, 2019. With the quick turnaround following the ending of the comment period, we are concerned as to how much actual feedback from critical stakeholders, including clinical experts in proton beam therapy, will be incorporated into the final report – a report based on which the HTCC is making its coverage determination that directly impacts certain patients fighting cancer.

* * * * *

We appreciate your consideration of our feedback on the Draft Evidence Report for the 2019 Health Technology Assessment Re-Review of Proton Beam Therapy. Should you have any questions, please do not hesitate to contact Scott Warwick, NAPT Executive Director, at swarwick@proton-therapy.org.

Respectfully submitted,

A black rectangular redaction box covering the signature of Scott Warwick.

Scott Warwick
Executive Director

April 1, 2019

Washington State Health Care Authority
Health Technology Assessment
Re: Draft Evidence Report of Proton Therapy - Re-review

Dear Health Technology Clinical Committee:

Thank you for allowing us the opportunity to provide feedback on the Draft Evidence Report on Proton Therapy, released on February 28, 2019.

At the SCCA Proton Therapy Center, our goal is to provide each patient with the best possible care. All of our physicians are radiation oncologists in the UW Medicine Department of Radiation Oncology, who treat patients using many modalities of radiation including photon and proton radiation. We make radiation treatment decisions based on available clinical literature, factoring in the patient's overall health status, type and stage of cancer, and patient preferences in their own health management. We also devise comparative proton and photon dosimetry plans for each patient in order to evaluate which modality will most accurately target the cancer, while sparing as much healthy tissue as possible for each patient. These decisions are not made unilaterally, but by a collaborative team comprised of multiple physicians, nurses, radiation therapists, medical physicists, and dosimetrists. A select group of cancer patients will benefit from proton therapy over other treatment modalities, and we work to ensure that we are choosing the modality that will give the patient the best chance of survival and preserves quality of life in the long term. Our physicians choose proton therapy only when it is the superior treatment choice for each patient.

As evidence of the judicious process our physicians employ when selecting appropriate proton therapy patients, our Center has treated only about 50 Washington State employees and 188 Washington Medicaid patients since our opening in 2013. This is far lower than incident rates and enrollment in Washington State plans would suggest. The Public Employees Benefit Board covers about 350,000 lives. Based upon the cancer incidence rate in the state of Washington, the PEBB can expect approximately 1,830 new incidents of cancer annually within their covered lives. Literature suggests that 8- 20% of these cancer patients would benefit from proton therapy. By these estimates, between 140 and 360 PEBB covered lives would benefit from Proton Therapy each year—far fewer than the patients actually treated at our Center. Alternately, Medicaid coverage is especially important for our pediatric patients, as nearly a quarter of them (23%) rely on Washington Medicaid to cover their cancer treatments.

While the low number of patients treated at the center can be partially attributed to our careful selection of proton patients, it cannot explain the entire delta between the incidence potential

and the actual number of patients treated. Restrictive coverage policies and logistical challenges are also likely responsible for reducing the number of PEBB patients that have access to and are treated at our Center.

Proton Therapy is a proven and effective tool that oncologists use to treat cancers of many types around the world. There are 30 proton therapy centers in the United States and over 75 proton therapy centers worldwide. As of June 2015, over 150,000 patients have been treated with proton therapy. As the only full-service proton therapy center within 1,200 miles, we feel fortunate that we are able to provide this important resource to cancer patients in the Pacific Northwest.

After consulting with our physicians and researchers, we feel that this draft report is missing key information that may preclude the HCA from making an informed decision about proton therapy coverage. We have collaborated with our physicians to outline some of the specific issues with various disease sites and have provided some general feedback about this draft that should be incorporated into the final report.

General issues with this report include the inconsistent use of consensus model policies, lack of consideration for long-term healthcare costs, clinical trial coverage, inclusion/exclusion criteria, parity of evidence with other treatments, lack of accounting for rare diseases, lack of studies with dosimetric evidence, setting standards out of sync with the rest of the country, and the interplay between the HTCC and Aggregate Analytics. Specifics about each of these are outlined below.

Utilization of Consensus Model Policies by Preeminent Cancer Organizations

When proton therapy was originally reviewed in 2014, there were no consensus model policies available. Since that time, several preeminent cancer organizations have developed consensus model policies through collaboration with their members—engaging in a dispassionate review of the literature to develop their policies for proton therapy coverage. Some of these organizations include The American Society for Radiation Oncology (ASTRO), The National Association of Proton Therapy (NAPT), Alliance of Dedicated Cancer Centers (ADCC), and Particle Therapy Co-Operative Group (PTCOG).

These model policies are applied inconsistently in the draft evidence review. For example, ASTRO's Model Policy is applied to evaluate prostate cancer, but not any other disease sites (Table 2, p 26), despite the fact that it has coverage recommendations on multiple other sites including ocular and hepatocellular cancers. We would call your attention to the fact that these guidelines recommend protons as the treatment of choice, or an acceptable therapeutic recommendation, in a variety of disease indications that the current HTA report is silent on or recommends against the protons.

We believe the ASTRO, NAPT, ADCC, and PTCOG model policies are a great resource to provide coverage recommendations across all disease sites. Additionally, model policies such as these would serve as a superior bellwether for coverage decisions than either Aetna (transitioned to Evicore) or Anthem, which are cited in the draft report (p. 49). The model policies are produced by experts in radiation oncology whose primary motivation is optimal patient outcomes, not financial returns. Going forward, the HTCC should consider consulting organizations such as

these in the development of their evidence review and coverage policies for future technology assessments.

Long-Term Healthcare Costs Not Considered

The WA State Healthcare Authority should place greater weight on long term health care costs into their coverage decisions. With an average tenure for a public employee of 6.8 years in 2018, compared to just 3.8 years for private-sector employees, it is important to consider the cost of long term effects of cancer treatments. One of the primary benefits of proton therapy is the reduced risk of side effects and secondary cancers, which could result in long term cost savings for the State of Washington.

Clinical Trial Coverage

As part of this re-review we encourage the HTCC to include a statement of commitment to support clinical trials. The draft states that when determining which evidence to include, the greatest weight will be given to high-quality comparative studies. The draft report defines this as a comparative study such as a randomized control trial or comparative cohort study with concurrent controls (section 3.1.3, page 57).

Many private insurance companies cover the cost of proton therapy when a patient enrolls on a clinical trial, however the Washington State Healthcare Authority is not currently supporting evidence generation for proton therapy in this way – a stance that is inconsistent with its own coverage policies for other radiation modalities, including IMRT. Our center has multiple randomized trials open comparing proton therapy versus photon radiation, including for brain tumors, lung cancer, and prostate cancer. This refusal to allow patients to participate in clinical trials is preventing the very data the HCA states that it needs in order to determine whether or not it will cover proton therapy. Demanding specific types of data, while impeding the generation of that data, is a bewildering stance for the HCA to maintain. It is both unfair to the patients the HCA covers and antithetical to its insistence on the presence of that very type of data.

We recommend that the PBT Findings and Decision be updated to explicitly address coverage of patients enrolled in clinical trials. The new language would align with the language included in the HTCC's coverage decision on IMRT and state that Proton Beam Therapy is a covered benefit with conditions for "undergoing treatment in the context of evidence collection/submission of outcome data (e.g., registry, observational study)."

Inclusion/Exclusion Criteria – Section 3.1.3

This report sets unreasonably high and inconsistent standards of evidence and interprets the data inconsistently. For instance, it is unreasonable to expect randomized trials for every disease indication. In many areas of medicine, newer technologies and treatments are adapted when there is clear rationale for benefit and strong phase II data, even without a randomized trial being conducted. For example, stereotactic radiosurgery for early stage lung cancer has been the standard of care for over a decade, long before any randomized data existed. There

was even a negative randomized trial at one point for survival benefit, and coverage was not impacted because the clinical rationale was well established. Another example would be IMRT coverage for many disease sites, which do not have randomized evidence for superiority with IMRT.

Due to the restrictive nature of the evidence inclusion standards employed by the evidence vendor, there is a significant body of important data missing from this report. This includes multiple studies showing superior outcomes with proton therapy based on nonrandomized comparisons with photon therapy, as well as superior cost-effectiveness (examples of these studies are outlined in our detailed responses per disease site). Inconsistent application of the data has resulted in a draft report that diverges from the original review in confusing ways. Interpretation of the existing data also seems inconsistent. For example, based on the same level of data as in the previous report, the agency determined that the evidence (nonrandomized comparisons) for esophageal cancer and liver cancer is sufficient to suggest that protons are beneficial to patients, but similar studies in other sites (such as pediatrics, breast, head & neck, CNS, etc.) do not result in the same determinations.

It is important to note that the majority of therapeutic interventions for cancer are not based on randomized trials. The NCCN is a nonprofit coalition of 28 of the nation's leading cancer centers in the United States, of which 21 are National Cancer Institute Comprehensive Cancer Centers. The NCCN publishes clinical practice guidelines for the treatment of common malignancies. These guidelines are the most comprehensive and widely used oncology standards in clinical practice in the world. Recommendations found in NCCN guidelines are now accepted by the Centers for Medicare and Medicaid Services and most private insurance companies. Recommendations issued in the NCCN guidelines are largely developed from lower levels of evidence, but with uniform expert opinion. In fact, only 6% of treatments recommended by NCCN are based on higher levels of evidence, such as randomized clinical trials.¹

Parity of Evidence with Other Treatments

We support the notion of having standards for evidence, but the requirements for proton therapy should not be distinct, and should be on par with all other cancer therapies.

The evidence standards for proton therapy, as set out in the draft evidence review, are not equal to the standards used to evaluate other treatments. WA HTA continues to hold PBT to a higher standard of evidence than other types of treatments and does not support this evidence generation as it does other modalities. For example, WA HCA covers IMRT for clinical trials and registries, but not proton therapy.

As a result of continued disparity in evidence standards, Oklahoma passed a law in 2016 making this unequal standard of evidence for proton therapy illegal, requiring insurers to hold proton therapy to the same standard as other treatments for cancer (36 OK Stat § 36-6060.9b). Virginia passed a similar law in 2017 stating that insurance carriers that cover cancer therapy shall not hold proton radiation therapy to a higher standard of clinical evidence for decisions regarding

¹ Poonacha, T. K., & Go, R. S. (2010). Level of scientific evidence underlying recommendations arising from the National Comprehensive Cancer Network clinical practice guidelines. *Journal of Clinical Oncology*, 29(2), 186-191.

coverage than is applied in the evaluation of other types of radiation therapy treatment (Code of Virginia § 38.2-3407.14:1).

Lack of Accounting for Rare Diseases

Clinical trials on low volume disease sites necessarily require fewer study participants. Despite the fact that the report states that this was considered in the study selection criteria, we noted that several key studies were excluded for low volumes, even in instances of disease sites that are rare (Appendix 1: 32, 29, 33,36, 3,4,6, 12, 16, 27, 54). For example, there are only 250 – 500 children diagnosed with medulloblastoma in the United States each year. However two studies with this population (Appendix 1: 54, 55) were eliminated due to low numbers of participants. It is simply impractical to create studies with a large population when the disease incidence is so low.

Lack of Studies with Dosimetric Evidence

We are disappointed by the WA HTA's decision to consistently exclude dosimetric studies as part of their body of evidence used in the evaluation of proton therapy. Radiation Oncologists rely on dosimetric studies as the gold-standard of evidence when evaluating the efficacy of radiation modalities. Dosimetric studies also directly address Key Question 3 regarding the comparative harms of proton therapy versus other alternative treatments. It is well established that excess radiation dose to healthy tissue and organs contributes to secondary malignancies and other complications. Dosimetric studies demonstrate the peerless capability of proton therapy to minimize radiation dose to healthy tissues in some clinical scenarios, while delivering a comparable, if not superior, dose of radiation to the tumor.

Further, insurance companies consistently require and rely upon comparative plans when determining medical necessity. In sum, these comparative plans are dosimetric comparisons of a photon plan versus a proton plan, demonstrating which plan provides the superior dose. If medical necessity decisions will be based upon such comparative analyses, we believe that not allowing this evidence to provide context omits an important knowledge base required to provide evaluators with a complete understanding of the efficacy and safety of proton beam therapy.

Coverage for Proton Therapy Would be Out of Sync the rest of the United States

Currently, the draft evidence report would suggest a proton beam therapy coverage policy in Washington State that would be among the most restrictive in the country. For example, proton therapy is well established as an effective treatment and standard of care for ocular melanoma. Not covering proton therapy for ocular melanoma would put WA out of line with almost every state and model policy, as even the most restrictive policies cover this disease site.

In Virginia, where laws have been passed on evidence parity, their policies are far less restrictive and promote further evidence generation through clinical trials/registry enrollment.

Oregon is also looking to legislate the disparate coverage policies for proton therapy. There is a bill currently before the Oregon Senate which proposed to require health benefit plans that cover radiation therapy for cancer to cover proton beam therapy on basis no less favorable than other covered benefits (Oregon SB 740).

Overly restrictive coverage policies can come with severe consequences to patients' health and to the financial well-being of insurers. Recently, Aetna lost a law suit because it failed to cover protons for one of its patients, despite the recommendation of her expert medical team. As a result, Aetna was ordered to pay over \$25 million in settlements and has since updated their medical policies to avoid future settlements.

The table below illustrates the variance in coverage policies and model policies for proton therapy for several bellwether plans in comparison with the WA HTAs coverage policy.

	Ped CNS/Brain	Other Peds	Adult Brain/CNS	Adult MSK	Adult H&N	Adult Lung/Thoracic	Adult Breast	Adult GI/GU	Adult Re-Irradiation	Adult Prostate	Adult Lymphoma	Adult Ocular
Aetna	✓	✓	✗	✓	✗	✗	✗	✓	✓	✗	✗	✓
United Healthcare	✓	✓	✗	✓		✗	✗	✓	✓	✓	✗	✓
Medicare Plans	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Florida Blue	✓	✓	✓	✓	✓	✓	✓	✓		✓	✓	✓
CareFirst BCBS of Maryland, D.C., & Virginia	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
National and State Specific Guidelines for Coverage												
Existing WA HTA Guidelines (2014)	✓	✓	✓	✓	✗	✗	✗	✗	✓	✗	✗	✓
Estimated WA HTA policy based on re-review	✓	✗	✗	✓	✗	✗	✗	✓		✗	✗	✗
ASTRO Group 1	✓	✓	✓	✓	✓	✗	✗	✓	✓	✗	✗	✓
ASTRO Group 2	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Third Party External Reviewers												
AIM	✓	✓	✓	✓	✗	✗	✗	✗	✓	✗	✗	✓
Evicore	✓	✓	✗	✓	✗	✗	✗	✓	✓	✗	✗	✓
✓ Covered ✓ Covered with Conditions ✗ Not Covered												

Evidence Committee

Aggregate Analytics assembled a team comprised of analysts to create the draft evidence report. We are interested in how the evidence report is weighed against the input of the HTCC. Our hope is that the Clinical Committee, which is comprised of medical doctors, will carefully evaluate recommendations in this draft based on their practical clinical experience and understanding of the available clinical literature. We believe that their clinical input is necessary to accurately determine appropriate coverage of proton therapy.

Disease Site Specific Issues

Our radiation oncologists reviewed the draft report by disease site specialty. With limited time, their review of this report is not exhaustive. However, they have pointed to some inconsistencies and omissions in this draft review for the following disease sites: adult lymphoma, adult ocular melanoma, adult breast, adult head and neck, pediatric neuroblastoma, and pediatric brain, spinal, and paraspinal sites. Details for each of these sites are outlined below.

Adult Lymphoma – Section 4.3.10

Comments provided by: Yolanda Tseng, MD, Board certified Radiation Oncologist & Assistant Professor, Department of Radiation Oncology, University of Washington School of Medicine, Seattle Cancer Care Alliance.

The draft evidence review cited only one lymphoma study. It excluded studies that provide important data on toxicity, using proton therapy to manage lymphoma, pulmonary function after proton therapy, and an IRB-approved registry study from four proton therapy centers. Additionally, one study showed patients experienced no increase in cardiac biomarkers 5 years after treatment, even though the lymphoma mass in this study group was mediastinal.

Sources Not Cited. Only one study was cited in the report on Adult Lymphoma – it is the largest to date, but is retrospective.

Sources missing from the study include:

Pulmonary toxicity following proton therapy for thoracic lymphoma.² Significant pulmonary toxicities were rare in this series of 59 patients treated with proton therapy for mediastinal lymphoma, confirming the expectations that proton therapy could be delivered safely without unanticipated acute pulmonary toxicities. There were 0 grade 2 or higher late pulmonary toxicities, although follow-up time is limited for this endpoint, and the acute grade 2 pulmonary toxicity seen in 3 patients was short-lived and possibly unrelated to radiation. The observations are similar to those reported by the Proton Collaborative Group in using proton therapy in the treatment of HL at 4 member proton facilities. The results compare favorably to 3 of the studies published on using IMRT for lymphoma (comprising 40-50 patients) with similarly

² Nanda, R., Flampouri, S., Mendenhall, N. P., Indelicato, D. J., Jones, L. M., Seeram, V. K., & Hoppe, B. S. (2017). Pulmonary toxicity following proton therapy for thoracic lymphoma. *International Journal of Radiation Oncology• Biology• Physics*, 99(2), 494-497.

low rates of grade 3 pneumonitis. Importantly, the present study included more high-risk patients, with two-thirds of patients with bulky mediastinal disease and nearly 20% treated for relapsed or refractory disease.

Proton therapy in the management of non-Hodgkin lymphoma.³ Proton therapy is a feasible and effective treatment for NHL. Early outcomes are favorable. Longer follow-up and additional patients are needed to confirm these findings. Given the variable disease locations, histologies and biologic behaviors of NHL, prospective studies evaluating proton therapy in the treatment of this disease will be complex, and likely require pooled data from multiple institutions to demonstrate adequate local control and lower rates of late toxicities.

Involved-node proton therapy in combined modality therapy for Hodgkin lymphoma: results of a phase 2 study.⁴ The 3-year RFS rate was 93%, and the 3-year EFS rate was 87%. No acute or late grade 3 nonhematologic toxicities were observed. Although decades of follow-up will be needed to realize the likely benefit of PT in reducing the risk of radiation-induced late effects, PT following chemotherapy in patients with HL is well-tolerated, and disease outcomes were similar to those of conventional photon therapy.

Proton therapy patterns-of-care and early outcomes for Hodgkin lymphoma: results from the Proton Collaborative Group Registry.⁵ From September 2010 through March 2015, 50 patients with HL were treated on an institutional review board-approved multi-center registry study (NCT01255748) with PT from four institutions. The two-year relapse-free survival rate was 85%. There were three recurrences, including two in-field recurrences after 21 Gy within the bulky mediastinal disease and one marginal recurrence in the neck, superior to the treatment field. The marginal recurrence would have been out of field with a photon plan as well, as it was superior to the clinical target volume. No grade 3 acute toxicities occurred among the patients. The most common grade 2 side effects were esophagitis (10%), dermatitis (7.5%), fatigue (2.5%), and dyspepsia (2.5%). Consolidation PT is being used for younger patients with HL with predominantly mediastinal involvement. Early results demonstrate an acceptable rate of recurrences. Longer follow-up and a larger patient cohort are needed to confirm these findings.

Pulmonary Function after Proton Therapy for Hodgkin Lymphoma.⁶ 15 patients with mediastinal HL who were enrolled in an institutional HL trial. All patients were treated with combination chemotherapy plus involved-node proton therapy. All patients were to undergo PFTs before starting treatment and at approximately 6 and 12 months after completing proton therapy. No unexpected changes were observed to the lungs as illustrated through follow-up

³ Suzanne Sachsman, Stella Flampouri, Zuofeng Li, James Lynch, Nancy P. Mendenhall & Bradford S. Hoppe (2015) Proton therapy in the management of non-Hodgkin lymphoma, *Leukemia & Lymphoma*, 56:9, 2608-2612, DOI: 10.3109/10428194.2015.1014364

⁴ Hoppe, B. S., Flampouri, S., Zaiden, R., Slayton, W., Sandler, E., Ozdemir, S., ... & Mendenhall, N. P. (2014). Involved-node proton therapy in combined modality therapy for Hodgkin lymphoma: results of a phase 2 study. *International Journal of Radiation Oncology* Biology* Physics*, 89(5), 1053-1059.

⁵ Bradford S. Hoppe, Henry Tsai, Gary Larson, George E. Laramore, Carlos Vargas, Yolanda D. Tseng, Megan Dunn, Lisa McGee, Oren Cahlon & William Hartsell (2016): Proton therapy patterns-of-care and early outcomes for Hodgkin lymphoma: results from the Proton Collaborative Group Registry, *Acta Oncologica*, DOI: 10.1080/0284186X.2016.1197422.

⁶ O'steen, L., Bellardini, J., Cury, J., Jones, L., Seeram, V. K., Mendenhall, N. P., & Hoppe, B. S. (2019). Pulmonary Function after Proton Therapy for Hodgkin Lymphoma Lung function after PT for HL. *International Journal of Particle Therapy*.

PFTs. Long-term follow-up and validation in a larger cohort are needed.

Evaluating Cardiac Biomarkers after Chemotherapy and Proton Therapy for Mediastinal Hodgkin Lymphoma.⁷ In the first 5 years after treatment, no rise in CK-MB or troponin was identified. BNP levels significantly increased following treatment, with larger increases among patients who received higher doses of anthracyclines. Further investigation is warranted.

Adult Ocular Melanoma – Section 4.3.11

Comments provided by: Andrew Stacey, M.D., M.S., Ophthalmologist at the Eye Institute at Harborview, and University of Washington School of Medicine, Assistant Professor of Ophthalmology.

The authors suggest that there have been three comparative studies useful in evaluating proton beam treatment. None of these studies are comparative in nature and none should be used to determine the utility of proton beam for treating uveal melanoma (of which, choroidal melanoma is a subset). One study reports the comparison of two modalities of radiation after a surgery which is not performed in the United States because it is considered unsafe. A second is a comparison of protons with a treatment that is also not considered a gold standard treatment in the United States. A third is a database comparison with many very important flaws and does not compare protons to any other treatment side-by-side.

The discussion of pediatric uses of protons should revolve only around retinoblastoma. Children treated for uveal melanoma with proton beam should be lumped into the adult section. The disease process of uveal melanoma is the same whether the patient is 10 years old or 90 years old.

Review of Specific Studies Cited.

Outcomes of treatment with stereotactic radiosurgery or proton beam therapy for choroidal melanoma.⁸ This is a paper that was suggested as being a valid comparison study. It compares PBT to stereotactic radiosurgery. This is not a relevant comparison as stereotactic radiosurgery is not a standard treatment in the United States. Nevertheless, PBT performs well.

Neoadjuvant proton beam irradiation vs. adjuvant ruthenium brachytherapy in transscleral resection of uveal melanoma.⁹ This is presenting a comparison of a treatment that is not performed in the United States and should not be used for any analysis. Trans-scleral resection of melanoma is extremely risky and unnecessary and there is not any physician in the

⁷ Guzhva, L., Mendenhall, N. P., Morris, C. G., Flampouri, S., & Hoppe, B. S. (2017). Evaluating Cardiac Biomarkers after Chemotherapy and Proton Therapy for Mediastinal Hodgkin Lymphoma. *International Journal of Particle Therapy*, 4(2), 35-38.

⁸ Sikuade MJ, Salvi S, Rundle PA, Errington DG, Kacperek A, Rennie IG. Outcomes of treatment with stereotactic radiosurgery or proton beam therapy for choroidal melanoma. *Eye (London, England)* 2015;29:1194-8.

⁹ Boker A, Pilger D, Cordini D, et al. Neoadjuvant proton beam irradiation vs. adjuvant ruthenium brachytherapy in transscleral resection of uveal melanoma. *Graefe's archive for clinical and experimental ophthalmology = Albrecht von Graefes Archiv fur klinische und experimentelle Ophthalmologie* 2018.

United States who practices this treatment. Furthermore, in this study proton therapy was used in a neo-adjuvant setting, and the plaque in an adjuvant setting. Nevertheless, PBT performs well.

Patterns of care and outcomes of proton and eye plaque brachytherapy for uveal melanoma.¹⁰ This is a paper that attempts to compare PBT to plaque radiotherapy. To do so they use cancer registry information. However, this is an extremely flawed paradigm. Proton beam, during the period of study in this paper, was available in only two centers in the United States: Boston and Sacramento. Patients treated with proton beam during these years were referred to these centers from throughout the country due to the high risk features of the melanoma and the inability to treat with plaque brachytherapy. Tumors treated with protons in the era are larger, thicker, closer to the optic nerve, and are more advanced. The authors even state that patients who had protons traveled further, were more educated, were whiter, and waited longer to obtain treatment. The tumors treated with proton beam in this study are wildly different than those treated with plaques, as stated in the document. Simply controlling for thickness of the tumor is not sufficient to compare these modalities. This absolutely can NOT be used to show the overall survival is worse with proton beam treatment.

Cost-effectiveness of proton beam therapy for intraocular melanoma.¹¹ The cost comparison report that the authors refer to in this study is not relevant. This is a comparison between enucleation and proton beam treatment. When an eye needs to be enucleated, it will be enucleated primarily. This is a comparison of two treatments whose overlap is extremely narrow. The true comparison of interest is the cost of proton beam vs. other globe salvaging treatments. This comparison does not exist. If it were to exist it would have to consider the following points: plaque radiotherapy reports on average a 90% local tumor control rate while protons reports a 97% control rate. The vast majority of patients undergoing plaque radiotherapy in this country require two surgeries and are admitted to a hospital for an average of 5 days. Patients undergoing proton beam treatment have one surgery and are not admitted to the hospital.

Sources Not Cited. The authors quickly write off the many, very large, single center studies that evaluated PBT. They label them as flawed and biased. However, they quickly used the above three studies, which have nearly no role whatsoever in the treatment of uveal melanoma in the United States, as relevant studies. It would be most appropriate to compare the large single center studies evaluated PBT, which are relevant in the United States, with the COMS studies evaluating plaque radiotherapy. These include the following:

Proton beam irradiation of uveal melanomas: the first 30 years the Weisenfeld lecture.¹² The Massachusetts Eye and Ear Infirmary (MEEI) in Boston is a national and international referral center for the diagnosis and treatment of eye neoplasms. The inaugural treatment of proton irradiation for choroidal melanoma was completed at the MEEI in 1975.

¹⁰ Lin AJ, Rao YJ, Acharya S, Schwarz J, Rao PK, Grigsby P. Patterns of care and outcomes of proton and eye plaque brachytherapy for uveal melanoma: Review of the National Cancer Database. Brachytherapy 2017;16:1225-31.

¹¹ Moriarty JP, Borah BJ, Foote RL, Pulido JS, Shah ND. Cost-effectiveness of proton beam therapy for intraocular melanoma. PloS one 2015;10:e0127814.

¹² Gragoudas, E. S. (2006). Proton beam irradiation of uveal melanomas: the first 30 years the weisenfeld lecture. Investigative ophthalmology & visual science, 47(11), 4666-4673.

During the past 30 years, more than 3000 patients with eye melanoma have been treated according to established standardized protocols for evaluation, treatment, and follow-up. The outcomes for these patients, provides convincing evidence of the advantages of proton therapy for patients with uveal melanoma, particularly those with tumors that are large and/or are posteriorly located, for which other types of radiotherapy may be unsuitable or may produce more complications.

Proton beam radiotherapy of choroidal melanoma: the Liverpool-Clatterbridge experience.¹³ A total of 349 patients with choroidal melanoma referred to the Liverpool Ocular Oncology Centre underwent proton beam radiotherapy at Clatterbridge Centre for Oncology (CCO) between January 1993 and December 2003. The 5-year actuarial rates were 3.5% for local tumor recurrence, 9.4% for enucleation, 79.1% for conservation of vision of counting fingers or better, 61.1% for conservation of vision of 20/200 or better, 44.8% for conservation of vision of 20/40 or better, and 10.0% for death from metastasis. Proton beam radiotherapy with a 62 MeV cyclotron achieves high rates of local tumor control and ocular conservation, with visual outcome depending on tumor size and location.

Treatment of uveal melanoma by accelerated proton beam.¹⁴ Proton beam irradiation of uveal melanoma has great advantages compared to brachytherapy because of the homogenous dose delivered to the tumor and the possibility of sparing normal tissue close to the tumor. The metastasis rate at 10 years varies between 25 and 30%. Local control is excellent. The local recurrence rate at 10 years is usually around 5%. Secondary enucleation is performed in 10–15% of patients either due to complications or local recurrence.

Adult Brain, Spinal, Paraspinal – 4.3.3

Comments provided by: Jason Rockhill, M.D., Ph.D., board certified radiation oncologist at UW Medical Center, Harborview and SCCA, and University of Washington School of Medicine, Associate Professor of Radiation Oncology.

The deleterious neurocognitive impact of radiation exposure to normal tissue is well-described and well-recognized¹⁵ and there is level 1 evidence of neurocognitive and memory impairment after even low-dose exposure of normal brain tissue to radiation in patients with brain tumors.¹⁶ Proton Beam Radiotherapy for treatment of brain tumors is recognized and

¹³ Damato, B., Kacperek, A., Chopra, M., Campbell, I. R., & Errington, R. D. (2005). Proton beam radiotherapy of choroidal melanoma: the Liverpool-Clatterbridge experience. *International Journal of Radiation Oncology* Biology* Physics*, 62(5), 1405-1411.

¹⁴ Desjardins, L., Lumbroso-Le Rouic, L., Levy-Gabriel, C., Cassoux, N., Dendale, R., Mazal, A., & Asselain, B. (2012). Treatment of uveal melanoma by accelerated proton beam. In *Current Concepts in Uveal Melanoma* (Vol. 49, pp. 41-57). Karger Publishers.

¹⁵ Saad S, Wang TJ. Neurocognitive Deficits After Radiation Therapy for Brain Malignancies. *American journal of clinical oncology*. 2015;38(6):634-40. doi: 10.1097/COC.000000000000158. PubMed PMID: 25503433.

¹⁶ Sun A, Bae K, Gore EM, Movsas B, Wong SJ, Meyers CA, et al. Phase III trial of prophylactic cranial irradiation compared with observation in patients with locally advanced non-small-cell lung cancer: neurocognitive and quality-of-life analysis. *Journal of clinical oncology: official journal of the American Society of Clinical Oncology*. 2011;29(3):279-86. doi: 10.1200/JCO.2010.29.6053. PubMed PMID: 21135267; PubMed Central PMCID: PMC3056463.

supported by scientific evidence.^{17 18 19 20} There is no question that excessive radiation dose to the brain is associated with neurocognitive decline. And, there is a growing concern for cognitive deficits secondary to radiation exposure to non-target brain tissue.^{21 22} Proton Therapy has been shown to be associated with lower levels of cognitive decline with brain tumors compared to historic controls.¹⁶ Additionally, recent prospective data suggest that patients receiving proton beam radiotherapy for their CNS tumors experience greater preservation of their cognitive function.¹⁹ As such, the evidentiary support for protons is now greater than that supporting the utilization of IMRT for adult CNS tumors.

General Issues with the draft evidence review. The current review does not include an evaluation of current standards. Currently, IMRT is routinely covered for CNS most of the time. There are no trials with the SOE that they are requiring for protons that currently exist for IMRT.

Adult Head & Neck – 4.2.2

Comments provided by: Upendra Parvathaneni, M.D., board certified radiation oncologist at UW Medical Center, SCCA, and University of Washington School of Medicine, Associate Professor of Radiation Oncology.

This draft review excluded two studies with clinical end points that are very important to the quality of life of patients with head and neck cancers. Compared to IMRT, these studies show that patients treated with proton therapy experience better quality of life when measuring side effects such as dysphagia and xerostomia.

¹⁷ Pulsifer MB, Sethi RV, Kuhlthau KA, MacDonald SM, Tarbell NJ, Yock TI. Early Cognitive Outcomes Following Proton Radiation in Pediatric Patients With Brain and Central Nervous System Tumors. *International journal of radiation oncology, biology, physics*. 2015;93(2):400-7. doi: 10.1016/j.ijrobp.2015.06.012. PubMed PMID: 26254679; PubMed Central PMCID: PMC4955513.

¹⁸ Kuhlthau KA, Pulsifer MB, Yeap BY, Rivera Morales D, Delahaye J, Hill KS, et al. Prospective study of health-related quality of life for children with brain tumors treated with proton radiotherapy. *Journal of clinical oncology : official journal of the American Society of Clinical Oncology*. 2012;30(17):2079-86. doi: 10.1200/JCO.2011.37.0577. PubMed PMID: 22565004; PubMed Central PMCID: PMC3397695.

¹⁹ Merchant TE, Hua CH, Shukla H, Ying X, Nill S, Oelfke U. Proton versus photon radiotherapy for common pediatric brain tumors: comparison of models of dose characteristics and their relationship to cognitive function. *Pediatric blood & cancer*. 2008;51(1):110-7. doi: 10.1002/pbc.21530. PubMed PMID: 18306274.

²⁰ Sherman JC, Colvin MK, Mancuso SM, Batchelor TT, Oh KS, Loeffler JS, et al. Neurocognitive effects of proton radiation therapy in adults with low-grade glioma. *Journal of neuro-oncology*. 2016;126(1):157-64. doi: 10.1007/s11060-015-1952-5. PubMed PMID: 26498439.

²¹ Mulhern RK, Merchant TE, Gajjar A, Reddick WE, Kun LE. Late neurocognitive sequelae in survivors of brain tumours in childhood. *The Lancet Oncology*. 2004;5(7):399-408. doi: 10.1016/S1470-2045(04)01507-4. PubMed PMID: 15231246.

²² de Ruiter MA, van Mourik R, Schouten-van Meeteren AY, Grootenhuis MA, Oosterlaan J. Neurocognitive consequences of a paediatric brain tumour and its treatment: a meta-analysis. *Developmental medicine and child neurology*. 2013;55(5):408-17. doi: 10.1111/dmcn.12020. PubMed PMID: 23157447.

Sources Not Cited.

Proton beam radiation therapy results in significantly reduced toxicity compared with intensity-modulated radiation therapy for head and neck tumors that require ipsilateral radiation.²³ The Romesser study showed clinically meaningful end points that favored PBT. These include lower dysphagia, mucositis and nausea. These end points appear to have been left out from this report. The data on page 144 is in favor of proton therapy for several end points. For example, for severe taste loss (dysgeusia), which is very unpleasant for a patient, there is a >10 fold difference. Likewise, for significant nausea which does not need any elaboration, there is a >5 fold difference, and for painful mucositis, there is a >3 fold and so on. This is not accounted for in their basis of their recommendations. Admittedly, this is retrospective data and hence not anywhere nearly as strong as prospective data. However, the differences are not small, and the end points are clinically very meaningful for patients who go through treatment.

Quality of Life of Postoperative Photon versus Proton Radiation Therapy for Oropharynx Cancer.²⁴ This study was omitted that favored PBT over IMRT: Results: Sixty-four patients were treated with adjuvant RT after transoral robotic surgery, 33 (52%) with volumetric arc therapy, and 31 (48%) with PBS. Both groups were similar in terms of age, site, stage, and dose delivered. Patients receiving PBS had significantly less dose to many normal structures than those receiving IMRT. These dosimetric advantages with PBS were reflected in higher scores in head and neck specific, as well as general, QOL measures. Most notable was significantly less xerostomia with PBS, on multiple patient-reported outcomes at multiple timepoints (6 and 12 months). Conclusion: Pencil beam scanning, when compared to IMRT, confers a significant dosimetric advantage to many normal organs at risk, with a corresponding benefit in multiple patient-reported QOL parameters in patients receiving adjuvant RT for oropharyngeal squamous cell cancer.

Adult Breast – 4.3.4

Comments provided by: Li-Ming Christine Fang, M.D., board certified radiation oncologist at UW Medical Center and SCCA, and University of Washington School of Medicine, Assistant Professor of Radiation Oncology, who specializes in treating breast and gynecologic cancers with special expertise in proton beam radiation therapy.

The draft report omitted two important studies with regard to treating breast cancer with proton therapy. One study provided important data on overall survival, and the other on cost-effectiveness.

²³ Romesser PB, Cahlon O, Scher E, et al. Proton beam radiation therapy results in significantly reduced toxicity compared with intensity-modulated radiation therapy for head and neck tumors that require ipsilateral radiation. *Radiotherapy and oncology : journal of the European Society for Therapeutic Radiology and Oncology* 2016;118:286-92

²⁴ Sharma, S., Zhou, O., Thompson, R., Gabriel, P., Chalian, A., Rassekh, C., ... & Cohen, R. B. (2018). Quality of Life of Postoperative Photon versus Proton Radiation Therapy for Oropharynx Cancer. *International Journal of Particle Therapy*, 5(2), 11-17.

Early outcomes of breast cancer patients treated with post-mastectomy uniform scanning proton therapy.²⁵ This study is missing from the draft and is more relevant than the Bush²⁶ study included in the draft since it is locally advanced cases for this attached series. It reports on overall survival, which the assessment asked for.

Establishing cost-effective allocation of proton therapy for breast irradiation.²⁷ The majority of the breast section discussed this single cost-effectiveness study that showed it was cost effective to use protons for patients with pre-existing cardiac risk and in younger women. Yet they do not change their recommendations.

Pediatric Brain, Spinal, Paraspinal – 4.2.6

Comments provided by: Ralph Ermoian, M.D., board certified physician and lead for pediatric and childhood tumors with Radiation Oncology Services at UW Medical Center, Seattle Children's Hospital and SCCA Proton Therapy. He is also a University of Washington School of Medicine, Associate Professor of Radiation Oncology, and an Adjunct Associate Professor of Pediatrics.

General Concerns: Randomized, Clinical Trials for Pediatrics. We understand why randomized trials are the gold standard in evidence and data gathering. However, because proton therapy does such an excellent job sparing healthy tissue, many physicians believe randomizing pediatric patients into photons is unethical. Because proton therapy is effective at killing cancer and sparing more healthy tissue, pediatric radiation oncologists will choose this modality to reduce side effects and the risk of secondary cancers in the long term.

Sources Not Cited. Additionally there are several important studies omitted from this draft report. These studies report on neurocognitive effects of proton therapy on pediatric brain patients, and outcomes for patients with high-risk neuroblastoma treated with proton therapy.

A retrospective evaluation of the benefit of referring pediatric cancer patients to an external proton therapy center.²⁸ This study from Rosenschold, et al in 2016 compared plans on pediatric CNS patients referred for protons and showed clear dosimetric benefits for protons. Although one could critique for selection bias, that would only mean that in at least many cases, protons should be an option if the radiation oncologist thinks there would be a benefit.

²⁵ Luo, L., Cuaron, J., Braunstein, L., Gillespie, E., Kahn, A., McCormick, B., ... & Cahlon, O. (2019). Early outcomes of breast cancer patients treated with post-mastectomy uniform scanning proton therapy. *Radiotherapy and Oncology*, 132, 250-256.

²⁶ Bush DA, Do S, Lum S, et al. Partial breast radiation therapy with proton beam: 5-year results with cosmetic outcomes. *International journal of radiation oncology, biology, physics* 2014;90:501-5.

²⁷ Mailhot Vega RB, Ishaq O, Raldow A, et al. Establishing cost-effective allocation of proton therapy for breast irradiation. *International Journal of Radiation Oncology* Biology* Physics* 2016; 95:11-8.

²⁸ Munck af Rosenschold, P., Engelholm, S. A., Brodin, P. N., Jørgensen, M., Grosshans, D. R., Zhu, R. X., ... & Mahajan, A. (2016). A retrospective evaluation of the benefit of referring pediatric cancer patients to an external proton therapy center. *Pediatric blood & cancer*, 63(2), 262-269.

Prospective, Longitudinal Comparison of Neurocognitive Change in Pediatric Brain Tumor Patients Treated with Proton Radiotherapy versus Surgery Only.²⁹ The HTA draft didn't review literature that provided data on neurocognitive effects for patients treated with protons for CSI tumors. The report authors note that neurocognitive articles are all from MGH except one from Korea. This article from MD Anderson Cancer Center provides impressive data: "Focal PRT was associated with stable neurocognitive functioning into survivorship. Outcomes were similar whether patients received focal PRT or no radiotherapy, even in neurocognitive domains known to be particularly radiosensitive. Proton CSI emerged as a neurocognitive risk factor, consistent with photon outcomes research."

Cost effectiveness of proton therapy compared with photon therapy in the management of pediatric medulloblastoma.³⁰ The reviewers omit this study which shows proton therapy to be cost effective for medulloblastoma.

Pediatric Other Tumors (Neuroblastoma) – 4.2.6

Comments provided by: Ralph Ermoian, M.D., board certified physician and lead for pediatric and childhood tumors with Radiation Oncology Services at UW Medical Center, Seattle Children's Hospital and SCCA Proton Therapy. He is also a University of Washington School of Medicine, Associate Professor of Radiation Oncology, and an Adjunct Associate Professor of Pediatrics.

Source Not Cited. The following study was omitted from the draft evidence report.

Outcomes after Proton Therapy for Treatment of Pediatric High-Risk Neuroblastoma.³¹ For neuroblastoma, this very good case series was just published in the red journal, which showed excellent outcomes for pediatric patients treated with protons for high-risk neuroblastoma: with 82% of patients still alive and 97% of patients free of primary site recurrence, and no patient experienced long-term liver or renal toxicity. In sum, this study showed that proton therapy maximizes normal tissue preservation and is appropriate for this patient population.

Prostate – 4.3.12

Comments provided by: Jing Zeng, M.D., board certified radiation oncologist at UW Medical Center and SCCA. She is also an University of Washington School of Medicine, Associate Professor of Radiation Oncology. She is the head of the GU program at the SCCA proton center and the institution-PI of multiple randomized national trials comparing proton therapy versus

²⁹ Lisa S Kahalley, M Douglas Ris, Anita Mahajan, M Fatih Okcu, Murali Chintagumpala, Arnold C Paulino, William E Whitehead, Charles G Minard, Heather H Stancel, Jessica Orobio, Judy J Xue, Emily A Warren, David R Grosshans; Prospective, Longitudinal Comparison of Neurocognitive Change in Pediatric Brain Tumor Patients Treated with Proton Radiotherapy versus Surgery Only, 2019, *Neuro-Oncology*, , noz041, <https://doi.org/10.1093/neuonc/noz041>

³⁰ Mailhot Vega, R. B., Kim, J., Bussière, M., Hattangadi, J., Hollander, A., Michalski, J., ... & MacDonald, S. M. (2013). Cost effectiveness of proton therapy compared with photon therapy in the management of pediatric medulloblastoma. *Cancer*, 119(24), 4299-4307.

³¹ Hill-Kayser, C. E., Tochner, Z., Li, Y., Kurtz, G., Lustig, R. A., James, P., ... & Mosse, Y. P. (2019). Outcomes after Proton Therapy for Treatment of Pediatric High-Risk Neuroblastoma. *International Journal of Radiation Oncology* Biology* Physics*.

IMRT for prostate cancer, including the PARTIQoL (NCT01617161) and COMPPARE (NCT03561220) trials.

Although the superiority of protons over photons for the treatment of prostate cancer is currently an open scientific question and the subject of multiple ongoing phase III randomized trials, one unquestionable benefit of proton beam radiotherapy when compared to photon beam radiotherapy is a significant reduction in the volume of healthy tissue that is exposed to radiation when compared to IMRT or other X-ray based techniques. This translates into a significant reduction in the risk of late-radiation side effects, including secondary malignancies. This forms the basis for protons being a “standard of care” for pediatric malignancies in whom radiation is indicated. Although one may reasonably question the magnitude of this benefit in an 80 year old man whose predicted life expectancy is relatively short when compared to the timeframe of late-radiation side effects, 25% of our prostate patients are under the age of 65 and there is little question that the magnitude of this benefit is likely to be substantial. Further, the HTCC is making clinical coverage decisions for patients who are covered by the PEBB and Medicaid and are therefore likely to be younger in age and stand to benefit from the reduction in radiation dose that proton therapy achieves. We also once again advocate for coverage of patients for evidence generation, such as coverage for the randomized trials that the HTA report asks for in evidence review.

Summary

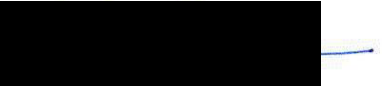
Proton therapy has been in clinical use in the US since the 1970s, and there is now an established record of safety and efficacy in thousands of patients, including advantages in challenging or unique clinical situations. We recognize the importance of continuing to generate high-level evidence in support of proton beam therapy. This is why many of our patients are enrolled on a prospective multicenter clinical registry capturing disease-site specific patient reported quality of life measures before and after treatment, as well as disease control outcomes (Clinicaltrials.gov identifier NCT01255748). This need for continued clinical evidence development (CED) and comparative effectiveness data is recognized by the current ASTRO national model policy for PBT.³² 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.

We encourage the HTCC to take heed of the recommendations and feedback provided in this response and support the continued generation of high quality clinical evidence through a policy which extends coverage to patients enrolled in trials and registries. We further encourage the committee to continue to provide coverage for ocular melanoma, brain/spinal, and all pediatric patients and also expand current coverage policies to include tumors in close proximity to organs at risk such as head and neck cancers, left sided breast cancer and some lymphomas.

³² ASTRO. ASTRO Model policy on proton beam radiotherapy. https://www.astro.org/uploadedFiles/Main_Site/Practice_Management/Reimbursement/ASTRO%20PBT%20Model%20Policy%20FINAL.pdf; American Society for Radiation Oncology, 2014.

The SCCA Proton Therapy Center thanks the HTCC for the opportunity to provide comment on this topic. As the only proton center in the State of Washington and surrounding states, we and our faculty are uniquely qualified to provide feedback to the HTCC on this topic. Please let us know if we may provide further information to the HTCC that would be useful in their evaluation of proton therapy.

Sincerely,

A black rectangular redaction box covering the signature of Annika Andrews.

Annika Andrews
President & CEO
SCCA Proton Therapy Center

A black rectangular redaction box covering the signature of Ramesh Rengan.

Ramesh Rengan, MD, PhD
Professor & Interim Chair,
UW Dept. of Radiation Oncology
Medical Director, SCCA Proton Therapy Center
Associate Member, Clinical Research Division,
Fred Hutchinson Cancer Research Center



Seattle Children's®
HOSPITAL • RESEARCH • FOUNDATION

Jeff Sperring, MD
Chief Executive Officer

April 3, 2019

Health Technology Assessment Program
P.O. Box 42712
Olympia, WA 98504-2712

Re: Comments for the Re-review of Proton Beam Therapy

Dear Sir or Madam,

This letter is in response to the draft evidence report on proton beam therapy released on March 1, 2019.

At Seattle Children's, we deliver superior patient care, advance new discoveries and treatments through pediatric research and serve as the pediatric and adolescent academic medical center for Washington, Alaska, Montana and Idaho – the largest region of any children's hospital in the country. We are honored that in 2018, U.S. News & World Report once again ranked us among the nation's best children's hospitals – for the 26th year in a row.

Regional expertise in pediatric radiation oncology

Seattle Children's is home to Dr. Ralph Ermoian, the only pediatric radiation oncologist in Washington, Wyoming, Alaska, Montana and Idaho. Dr. Ermoian's experience with pediatrics helps him know best whether – and how – to use radiation therapy for each patient. He treats his patients with multiple radiation modalities, including both photon- and proton-based therapies. He also works closely with the physicians at Seattle Children's, UW Medicine, Seattle Cancer Care Alliance, the SCCA Proton Therapy Center, and referring physicians from many states and Canada to develop the most optimal treatment plans for patients' short- and long-term health.

Proton therapy is an important resource for pediatric patients seeking cancer treatment in the Pacific Northwest. A significant portion of the children and teens we treat for cancer get some form of radiation. Of those, more than half benefit from proton therapy due to the reduced radiation dose to the healthy tissues surrounding the tumor.

Costs and quality of life

Proton therapy is a proven and effective tool for many pediatric patients, however, we are selective in our use of protons; treating only those patients that would receive a *superior* treatment plan from protons over other modalities.

jeffrey.sperring@seattlechildrens.org

4800 Sand Point Way NE
M/S RB.2.419 PO Box 5371
Seattle, WA 98145-5005

TEL 206-987-2001

Due to the advantages of proton therapy in reducing secondary harmful side effects, there are long-term costs and quality of life implications that must be considered – especially in the context of pediatric patients. Studies consistently show that proton therapy results in reduced cognitive impairments, hearing loss, and neuro-hormonal complications compared to other forms of radiation which results in improved quality of life and both short- and long-term cost savings.

Challenges in accruing and randomizing pediatric patients to trials

While the committee seeks large comparative trials as evidence of the effectiveness of proton therapy, obtaining such studies is challenging, and at times unethical.

To address the issue related to study size first, the occurrence of many of these diseases is rare, and therefore recruiting large volumes is challenging if not impossible. In all of 2018, only 61 pediatric patients were treated using proton therapy in the Pacific Northwest. Of that, a total of 15 were medulloblastoma, five were lymphoma, six were head and neck, and one was ocular.

Accruing, and especially randomizing, patients to comparative studies is also beset with challenges and may be unethical. As a healthcare provider, we are seeking to provide the best care to our patients. When there is a known treatment which will result in less harm and improved outcomes, exposing patients to a more harmful option would go against our values and duties to our patients. Additionally, parents are not agnostic to the treatment decisions for their children. We would not ask a parent to treat their child with a modality that may result in their child getting more radiation dose unnecessarily.

While there may not be a great deal of comparative trials for each pediatric disease site, the risk of radiation exposure has been studied time and time again. Increased radiation exposure has been directly linked to increased risk of cancer. The properties of proton therapy allow for greatly reduced radiation dose to healthy tissue when compared to traditional photon based modalities. This is why we are able to confidently speak to the reduced harms of proton therapy for pediatric patients. Our pediatric patients can expect to have many decades of life ahead of them, and the reduced risk of secondary malignancy reduces long term costs associated with re-treating patients, and improve overall quality of life. We strongly encourage the HTCC to consider the benefits of proton therapy and Seattle Children's unique expertise in pediatric radiation oncology in defining a coverage policy which allows the experts in their field to make the best decision for their patients' health.

Sincerely,



Jeff Sperring, MD
Chief Executive Officer



Alliance for Proton Therapy Access
4515 Drummond Avenue
Chevy Chase, MD 20815
(202) 999-8923

April 1, 2019

Washington State Health Care Authority
Health Technology Assessment
P.O. Box 42712
Olympia, WA 98504-2712

Dear Health Technology Clinical Committee:

Thank you for providing the opportunity to comment on the Draft Evidence Report on Proton Therapy, released on February 28, 2019.

The Alliance for Proton Therapy Access is a patient-focused advocacy organization, striving to make sure all cancer patients seeking proton therapy receive fair and timely payment decisions from their health insurers. We work directly with patients and caregivers who have benefitted greatly from proton beam therapy (PBT), and with those who have had to endure health risks, anxiety, and financial hardship associated with unfair delays and denials of care after their physicians recommended PBT as their best hope for survival and highest quality of life.

We are writing to urge you to include the most up-to-date clinical evidence and consensus model policies in your report. Since the time when proton therapy was originally reviewed by the Washington State Health Technology Clinical Committee in 2014, several distinguished cancer organizations – including the American Society for Radiation Oncology (ASTRO), the National Cancer Conference Network (NCCN), the National Association of Proton Therapy (NAPT), and American Society of Clinical Oncology (ASCO) – have developed model policies based on their members' input. We encourage you to ensure their guidance is reflected fully in your report.

We also ask that you include a statement of support for providing coverage of PBT for any indications when a patient is enrolled in a clinical trial and/or registry, as this will help generate additional clinical evidence regarding the appropriate use of PBT.

Finally, we urge you to consider the experience of patients as you re-evaluate coverage of PBT for various cancer indications. Below are excerpts of stories from two Washington State cancer survivors who benefitted from proton therapy.

Melba Fujiura wrote about her experience with proton therapy in [Cure Today](#). Her story reinforces the health and costs benefits of a treatment that minimizes side effects and enables patients to live healthy, productive lives. Here is an excerpt:

For 10 years, I've participated in barbecue competitions throughout Washington state. In fact, I'm a registered member of the Pacific Northwest Barbecue Association (PNWBA), which organizes competitions from Canada to California. I started off as a competitor with my husband, but we quickly grew curious about what makes winning barbecue. It didn't take long for us to discover how much fun

it was to judge!

But when I was diagnosed with a recurrence of lung cancer in 2016, I was afraid that I'd have to give it all up. I can still recall the anxiety and fear I experienced when I learned my cancer had returned. During my first battle with lung cancer, my physicians were able to remove the tumor through surgery. A series of tests showed that surgery wasn't an option this time around. My thoracic surgeon recommended a treatment I had never heard of: proton radiation therapy. This precise form of radiation targets the cancerous tumor and spares healthy tissues that surround it. For me, that meant protecting my heart, lungs, esophagus, and spinal cord from excess radiation exposure.

Thankfully, life never skipped a beat during treatment. Minimal side effects meant everyday life and my passion for brisket and the community I had become a part of would not need to take a backseat to cancer treatment... I just feel grateful to my care team for suggesting proton therapy and then helping me live my best life even during treatment.

Marcia McNannay is another Washington State resident. Hers is one of many stories cancer survivors are [sharing on the Alliance website](#) that illustrate the tremendous benefit of proton therapy, and the high costs of not getting physician-recommended treatment. Here is an excerpt:

After my breast cancer came out of remission in April 2017, my doctors recommended getting a second opinion because surgery, chemotherapy, and traditional radiation treatments were found to be ineffective. In search of options, my husband, Rick, made an appointment to see if I would be a good candidate for proton therapy and we met with a team of doctors who highly recommended proton therapy to attack the aggressive cancer in a safe and beneficial way. Though I had never heard or been offered proton therapy before, this gave me such hope and the understanding that I would thrive with this treatment!

My renewed sense of hope was short-lived when my insurance company refused to pay for the treatment. I was shocked that my insurance company continued to deny the only form of treatment I had left. Making phone call after phone call for weeks to fight the denial, I felt the "game" begin. I lived in despair and defeat, getting either conflicting, incorrect answers or no answers at all. I remember my husband coming home from work one night and, through tears I said, "They won, I quit." By that point, I had become emotionally worn down and could not function.

One day in August 2017, I was sitting at home with a mastectomy and no treatment when a life-long friend reached out to me and offered his help. He is an attorney and was just beside himself when we discussed the situation. He was able to reach my insurance company's top lawyer and, within days, the CEO and top executives of the insurance company were apologizing and asking what I wanted. I started proton therapy September 2017.

We appreciate your consideration of our letter as you finalize your evidence report.

Sincerely,

A black rectangular redaction box covering the signature of Daniel E. Smith.

Daniel E. Smith
Executive Director, Alliance for Proton Therapy Access



Varian Medical Systems

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varian.com



April 1, 2019

Sue Birch
Director
Health Technology Assessment Program
P.O. Box 42712
Olympia, WA 98504-2712

Re: Re-review of the Health Technology Assessment Program's Proton Beam Therapy Technology Assessment

Dear Director Birch:

Varian Medical Systems is the world's leading supplier of radiotherapy products for treating cancer. Our products include medical linear accelerators, simulators, proton therapy systems, and a broad range of accessories and interconnected software tools for planning, verifying, and delivering the most advanced radiation, radiosurgical, and brachytherapy treatments. Our electronic medical record facilitates efficient management of treatment for patients undergoing medical or radiation (including proton) therapies. Varian has in-depth knowledge of the significant benefits that radiation therapy, particularly proton beam therapy in certain indications, provides to the health of Americans.

Varian appreciates the opportunity to provide comment on the draft evidence report as part of the re-review of proton beam therapy (PBT). As new evidence has become available since the Health Technology Clinical Committee's Findings and Decision final adoption on July 11, 2014, we appreciate your efforts to reevaluate the conditions under which coverage applies for PBT. This new clinical data supports the benefits of PBT for additional indications not covered in the 2014 Findings and Decision.

As you know, PBT, a radiation therapy that uses protons rather than photons to deposit radiation energy, focuses a beam of radiation to the target tumor tissue. This technology delivers a lower dose of radiation to a patient's healthy tissue than other types of radiation therapy,¹ making PBT particularly important in pediatric and neurological cases.

Varian applauds the committee for recognizing the benefits of PBT and for its determination that PBT should be a covered benefit for the noted indications in the 2014 Findings and Decision. Based upon the mounting clinical evidence available since the publication of the Findings and Decision, Varian also recommends coverage for the following, additional indications:

- Benign or malignant conditions of the base of the skull or axial skeleton including but not limited to chordomas, chondrosarcomas, and osteosarcomas;
- Malignant lesions of the head and neck, including but not limited to nasopharyngeal, oropharyngeal, paranasal sinus and nasal cavity cancers as well as benign head and neck tumors with long anticipated survivorship, such as glomus tumors;
- Gastrointestinal tumors including pancreatic, rectal, and anal tumors;

¹ American Society for Radiation Oncology (ASTRO). Model Policies: Proton Beam Therapy (PBT). ASTRO: June 2017.



- Prostate Cancer (non-metastatic);
- Breast Cancer;
- Thoracic tumors including lung, esophageal cancers, mediastinal lymphomas, thymomas, sarcomas, and mesothelioma;
- Hodgkin's Lymphoma;
- B-Cell Lymphomas;
- Primary or metastatic tumors of the spine where the spinal cord tolerance may be exceeded with conventional treatment or where the spinal cord has previously been irradiated;
- Hepatocellular carcinoma and cholangiocarcinoma;
- Patients with genetic syndromes making total volume of radiation minimization crucial such as but not limited to NF-1 patients and retinoblastoma patients; and,
- Non-metastatic retroperitoneal sarcomas.^{2,3}

In addition, PBT is indicated when:

- The Dose Volume Histogram (DVH) illustrates at least one (1) or more critical structures or organs that must be considered at risk in or adjacent to the treatment volume to be protected by the use of proton beam therapy;
- There is documented clinical rationale that doses generally thought to be above the level otherwise attainable with other radiation methods might improve control rates, and/or;
- Other radiation therapy treatment plans (e.g., photon-based treatment plans) would have a greater probability of causing clinically meaningful acute and late normal tissue toxicity;
- The proposed treatment volume or an immediately adjacent volume has been previously irradiated, and the dose must therefore be tightly conformed to avoid exceeding the tolerance dose of nearby normal organs and tissues and proton therapy would result in less risk; or
- There is documented clinical rationale that the higher levels of precision associated with proton beam therapy compared to other radiation treatments are clinically necessary.⁴

We strongly encourage coverage of PBT of these additional indications, as well as coverage of all other indications not specified as covered under the 2014 Findings and Decision when the patient is enrolled in a clinical trial and/or registry as there is a need for additional clinical evidence regarding the appropriate use of PBT for various disease sites.

As you know, PBT has been utilized for many decades. However, there have been recent advancements with proton delivery systems which include spot scanning or intensity modulated proton therapy (IMPT). There are studies underway comparing the effectiveness and substantially improved dose conformity of IMPT to other forms of radiation therapy and traditional scatter proton therapy.

Please see the attached documents, the recently released American Society for Radiation Oncology (ASTRO) model policy and the National Association of Proton Therapy's (NAPT) model policy, which address coverage for PBT.

We appreciate your consideration on this matter and look forward to working with you in the future on this and other issues.

² ASTRO Model Policies. June 2017

³ National Association of Proton Therapy (NAPT). Model Policy: Coverage of Proton Beam Therapy. NAPT: February 2019.

⁴ NAPT Model Policy. February 2019.

varian

Sincerely,

A black rectangular box redacting the signature of Deepak Khuntia, MD. A small, faint mark is visible to the right of the box.

Deepak Khuntia, MD
Senior Vice President and Chief Medical Officer
Varian Medical Systems

Attachments: American Society for Radiation Oncology (ASTRO). Model Policies: Proton Beam Therapy (PBT).
ASTRO: June 2017.
National Association of Proton Therapy (NAPT). Model Policy: Coverage of Proton Beam Therapy.
NAPT: February 2019.