Charged-Particle (Proton or Helium Ion) Radiotherapy for Neoplastic Conditions

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Section: Radiology
Place(s) of Service: Outpatient

I. Description

Charged-particle beams consisting of protons or helium ions are a type of particulate radiation therapy (RT). Treatment with charged-particle radiotherapy is proposed for a large number of indications, often for tumors that would benefit from the delivery of a high dose of radiation with limited scatter that is enabled by charged-particle beam radiotherapy.

For individuals who have uveal melanoma(s) who receive charged-particle (proton or helium ion) radiotherapy, the evidence includes RCTs and systematic reviews. Relevant outcomes are overall survival, disease-free survival, change in disease status, and treatment-related morbidity. Systematic reviews, including a 1996 TEC Assessment and a 2013 review of randomized and non-randomized studies, concluded that the technology is at least as effective as alternative therapies for treating uveal melanomas and is better at preserving vision. The evidence is sufficient to determine qualitatively that the technology results in a meaningful improvement in the net health outcome.

For individuals who have skull-based tumor(s) (i.e., cervical chordoma and chondrosarcoma) who receive charged-particle (proton or helium ion) radiotherapy, the evidence includes observational studies and systematic reviews. Relevant outcomes are overall survival, disease-free survival, change in disease status, and treatment-related morbidity. A 1996 TEC Assessment concluded that the technology is at least as effective as alternative therapies for treating skull-based tumors. A 2016 systematic review of observational studies found 5-year survival rates after proton beam therapy ranging from 67% to 94%. The evidence is sufficient to determine qualitatively that the technology results in a meaningful improvement in the net health outcome.

For individuals who have pediatric central nervous system tumor(s) who receive charged-particle (proton or helium ion) radiotherapy, the evidence includes case series, a few nonrandomized comparative studies and systematic reviews. Relevant outcomes are overall survival, disease-free survival, change in disease status, and treatment-related morbidity. There are few comparative studies and studies tended to have small sample sizes. The available observational studies do not
provide sufficient evidence on the efficacy of charged-particle therapy compared with other
treatments e.g., IMRT. The evidence is insufficient to determine the effects of the technology on
health outcomes.

Clinical input obtained in 2013 strongly supported the use of charged-particle radiotherapy for
treating pediatric central nervous system tumors. This modality of treatment of pediatric CNS
tumors has the potential to reduce long-term adverse effects, such as damage to nearby normal
CNS tissue and development of radiation-induced secondary tumors.

For individuals who have pediatric non−central nervous system tumor(s) who receive charged-
particle (proton or helium ion) radiotherapy, the evidence includes dosimetric planning studies in a
small number of patients. Relevant outcomes are overall survival, disease-free survival, change in
disease status, and treatment-related morbidity. There is a lack of randomized and observational
studies evaluating the efficacy and safety of the technology. The evidence is insufficient to
determine the effects of the technology on health outcomes.

For individuals who have localized prostate cancer who receive charged-particle (proton or helium
ion) radiotherapy, the evidence includes 2 RCTs and systematic reviews. Relevant outcomes are
overall survival, disease-free survival, change in disease status, and treatment-related morbidity. A
2010 TEC Assessment addressed the use of PBT for prostate cancer and concluded that it has not
yet been established whether PBT improves outcomes in any setting for clinically localized prostate
cancer. The TEC Assessment included 2 RCTs, only 1 of which included a comparison group of
patients who did not receive proton-beam therapy. No data on the use of PBT for prostate cancer
have been published since 2010 that would alter the conclusions of the TEC Assessment. The
evidence is insufficient to determine the effects of the technology on health outcomes.

For individuals who have non-small-cell lung cancer who receive charged-particle (proton or helium
ion) radiotherapy, the evidence includes case series and systematic reviews. Relevant outcomes are
overall survival, disease-free survival, change in disease status, and treatment-related morbidity. A
2010 TEC Assessment included 8 case series and concluded that the evidence is insufficient to
permit conclusions about proton beam therapy for any stage of non-small cell lung cancer. No
subsequent randomized or non-randomized comparative studies have been published. The
evidence is insufficient to determine the effects of the technology on health outcomes.

For individuals who have head and neck tumors other than skull-based who receive charged-
particle (proton or helium ion) radiotherapy, the evidence includes case series and a systematic
review. Relevant outcomes are overall survival, disease-free survival, change in disease status, and
treatment-related morbidity. The evidence is insufficient to determine the effects of the
technology on health outcomes. The systematic review noted that the studies no charged-particle
therapy were heterogenous in terms of type of particle and delivery techniques, and that there are
no head to head trials comparing charged-particle therapy to other treatments. The evidence is
insufficient to determine the effects of the technology on health outcomes.

II.   Criteria/Guidelines

Charged-particle irradiation with proton or helium ion beams is covered (subject to Limitations and
Administrative Guidelines) in the following clinical situations:
A. Primary therapy for melanoma of the uveal tract (iris, choroid, or ciliary body), with no evidence of metastasis or extrascleral extension, and with tumors up to 24 mm in largest diameter and 14 mm in height;
B. Postoperative therapy (with or without conventional high-energy x-rays) in patients who have undergone biopsy or partial resection of chordoma or low-grade (I or II) chondrosarcoma of the basisphenoid region (skull-base chordoma or chondrosarcoma) or cervical spine. Patients eligible for this treatment have residual localized tumor without evidence of metastasis;
C. Treatment of pediatric central nervous system tumors

III. Limitations
Other applications of charged-particle irradiation with proton ore helium ion beams are not covered because it is not known to be effective in improving health outcomes, including but not limited to:
A. Clinically localized prostate cancer
B. Non-small-cell lung cancer (NSCLC) at any stage or for recurrence
C. Pediatric non-central nervous system tumors
D. Tumors of the head and neck (other than skull based chordoma or chondrosarcoma)

IV. Administrative Guidelines
A. Precertification is required. To precertify, fill out HMSA's Precertification Request and mail or fax the form as indicated. Include the following documentation:
1. History and physical
2. Imaging studies
3. Pathology reports
4. Prior therapies, if applicable.
5. Radiation oncology consultation notes
B. The use of proton beam or helium ion radiation therapy typically consists of a series of CPT codes describing the individual steps required: medical radiation physics, clinical treatment planning, treatment delivery, and clinical treatment management.

<table>
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<th>CPT Codes</th>
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<tr>
<td>77299</td>
<td>Unlisted procedure, therapeutic radiology clinical treatment planning</td>
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<tr>
<td>77399</td>
<td>Unlisted procedure, medical radiation physics, dosimetry and treatment devices, and special services</td>
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<tr>
<td>77499</td>
<td>Unlisted procedure, therapeutic radiology treatment management</td>
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<tr>
<td>77520*</td>
<td>Proton treatment delivery; simple, without compensation</td>
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V. Background
Charged-particle beams consisting of protons or helium ions are a type of particulate radiation therapy. They contrast with conventional electromagnetic (i.e., photon) radiation therapy due to several unique properties including minimal scatter as particulate beams pass through tissue, and deposition of ionizing energy at precise depths (i.e., the Bragg peak). Thus, radiation exposure of surrounding normal tissues is minimized. The theoretical advantages of protons and other charged-particle beams may improve outcomes when the following conditions apply:

- Conventional treatment modalities do not provide adequate local tumor control;
- Evidence shows that local tumor response depends on the dose of radiation delivered; and
- Delivery of adequate radiation doses to the tumor is limited by the proximity of vital radiosensitive tissues or structures.

The use of proton or helium ion radiation therapy has been investigated in two general categories of tumors/abnormalities.

1. Tumors located near vital structures, such as intracranial lesions or lesions along the axial skeleton, such that complete surgical excision or adequate doses of conventional radiation therapy are impossible. These tumors/lesions include uveal melanomas, chordomas, and chondrosarcomas at the base of the skull and along the axial skeleton.

2. Tumors associated with a high rate of local recurrence despite maximal doses of conventional RT. One tumor in this group is locally advanced prostate cancer (i.e., Stages C or D1 [without distant metastases], also classified as T3 or T4).

Advances in photon-based RT such as 3-D conformal RT, intensity-modulated RT (IMRT), and stereotactic body radiotherapy (SBRT) allow improved targeting of conventional therapy. Proton beam therapy can be given with or without stereotactic techniques. Stereotactic approaches are frequently used for uveal tract and skull-based tumors. For stereotactic techniques, 3 to 5 fixed beams of protons or helium ions are used.

VI. Rationale
**Uveal Melanomas and Skull-based Tumors**
The available evidence suggested that charged-particle beam irradiation is at least as effective as, and may be superior to, alternative therapies, including conventional radiation or resection to treat chordomas or chondrosarcoma of the skull base or cervical spine. A TEC Assessment completed in
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1996 reached the same conclusions. A systematic review of charged particle therapy found that local tumor control rate and 5-year overall survival (OS) for skull base chordomas treated with proton therapy were 63% and 81%, respectively, compared to post-surgical treatment with conventional photon therapy with reported local tumor control rates and 5-year OS of 25% and 44%, respectively, and surgery followed by fractionated stereotactic radiotherapy, which resulted in 5-year local tumor control of 50%. A summary of tumor control in published proton therapy studies of chondrosarcoma of the skull base was 95% 5-year local tumor control, similar to the results of conventional therapy.

Charged-particle beam radiation therapy has been most extensively studied in uveal melanomas, where the focus has been to provide adequate local control while still preserving vision. In 2013, Wang et al published a systematic review on charged-particle (proton, helium or carbon ion) radiation therapy for uveal melanoma. The review included 27 controlled and uncontrolled studies that reported health outcomes e.g., mortality, local recurrence. Three of the studies were randomized controlled trials (RCTs). One of the RCTs compared helium ion therapy with an alternative treatment (in this case, brachytherapy). The other 2 RCTs compared different proton beam protocols so cannot be used to draw conclusions about the efficacy of charged-ion particle therapy relative to other treatments. The overall quality of the studies was low; most of the observational studies did not adjust for potential confounding variables. The analysis focused on studies of treatment-naïve patients (all but one of the identified studies). In a pooled analysis of data from 9 studies, there was not a statistically significant difference in mortality with charged-particle therapy compared with brachytherapy (odds ratio [OR], 0.13; 95% confidence interval [CI], 0.01 to 1.63). However, there was a significantly lower rate of local control with charged-particle therapy compared with brachytherapy in a pooled analysis of 14 studies (OR=0.22; 95% CI, 0.21 to 0.23). There were significantly lower rates of radiation retinopathy and cataract formation in patients treated with charged-particle therapy compared with brachytherapy (pooled rates of 0.28 vs. 0.42 and 0.23 vs. 0.68, respectively). According to this review, there is low-quality evidence that charged-particle therapy is at least as effective as alternative therapies as primary treatment of uveal melanoma and is better at preserving vision.

An additional RCT, published in 2015 by Mishra et al, compared charged-particle therapy using helium ions and iodine-125 (I-125) plaque therapy in 184 patients with uveal melanoma. The primary end point was local tumor control. Median follow-up was 14.6 years in charged-particle therapy group and 12.3 years in the I-125 plaque therapy group. The rate of local control at 12 years was significantly higher in the helium ion group (98%; 95% CI, 88% to 100%) than the I-125 plaque therapy group (79%; 95% CI, 68% to 87%; p=0.006). OS at 12 years was 67% (95% CI, 55% to 76%) in the helium ion group and 54% (95% CI, 43% to 63%) in the I-125 plaque therapy group (p=0.02).

**Skull-based Tumors**

A 2016 systematic review by Matloob et al evaluated the literature on proton beam therapy for skull-based chordomas. The review included controlled trials as well as case series with more than 5 patients. Twelve studies met eligibility criteria. The authors did not report study type, but all appear to be case series. Sample sizes ranged from 9 to 367 patients. Six studies reported the 5-year survival rate and these ranged from 67% to 94%.
Pediatric Central Nervous System Tumors
Radiation therapy is an integral component of the treatment of many pediatric central nervous system (CNS) tumors including high-grade gliomas, primitive neuroectodermal tumors (PNETs), medulloblastomas, ependymomas, germ cell tumors, some craniopharyngiomas and subtotally resected low-grade astrocytomas. Children who are cured of their tumor experience long-term sequelae of radiation treatment, which may include developmental, neurocognitive, neuroendocrine, and hearing late effects. Radiation to the cochlea may lead to loss of hearing at doses greater than 35-45 Gy in the absence of chemotherapy and the risk of ototoxicity is increased in children who receive ototoxic platinum-based chemotherapy regimens. Craniospinal irradiation, most commonly used in the treatment of medulloblastoma, has been reported to lead to thyroid dysfunction and damage to the lungs, heart and gastrointestinal tract. In addition, patients who receive radiation at a young age are at an increased risk of developing radiation-induced second tumors compared to their adult counterparts. The development of more conformal radiation techniques has decreased inadvertent radiation to normal tissues; however, while intensity-modulated radiation therapy (IMRT) decreases high doses to nearby normal tissues, it delivers a larger volume of low- and intermediate-dose radiation. Proton beam radiotherapy eliminates the exit dose to normal tissues and may eliminate 50% of radiation to normal tissue.

Merchant and colleagues sought to determine whether proton radiotherapy has clinical advantages over photon radiotherapy in childhood brain tumors. Three-dimensional imaging and treatment-planning data, which included targeted tumor and normal tissues contours, were acquired for 40 patients. Histologic subtypes in the 40 patients were 10 each with optic pathway glioma, craniopharyngioma, infratentorial ependymoma, or medulloblastoma. Dose-volume data were collected for the entire brain, temporal lobes, cochlea, and hypothalamus, and the data were averaged and compared based on treatment modality (protons vs. photons) using dose-cognitive effects models. Clinical outcomes were estimated over 5 years. With protons (compared to photons), relatively small critical normal tissue volumes (e.g. cochlea and hypothalamus) were spared from radiation exposure when not adjacent to the primary tumor volume. Larger normal tissue volumes (e.g. supratentorial brain or temporal lobes) received less of the intermediate and low doses. When these results were applied to longitudinal models of radiation dose-cognitive effects, the differences resulted in clinically significant higher IQ scores for patients with medulloblastoma and craniopharyngioma and academic reading scores in patients with optic pathway glioma. There were extreme differences between proton and photon dose distributions for the patients with ependymoma, which precluded meaningful comparison of the effects of protons versus photons. The authors concluded that the differences in the overall dose distributions, as evidenced by modeling changes in cognitive function, showed that these reductions in the lower-dose volumes or mean dose would result in long-term, improved clinical outcomes for children with medulloblastoma, craniopharyngioma, and glioma of the optic pathway.

In 2016, Leroy et al published a systematic review of the literature on proton therapy (PT) for treatment of pediatric cancers. Their findings on pediatric CNS tumors include the following:

- Craniopharyngioma: Three studies were identified, 2 were retrospective case series and 1 was a retrospective comparative study of PT versus IMRT. They concluded that there is very low-level evidence that survival outcomes are similar with PT and IMRT.
- Ependymoma: One prospective case series and 1 retrospective case series were identified. They concluded that the evidence is insufficient to support or refute the use of PT for this condition.

- Medulloblastoma: One prospective case series and 2 retrospective case series were identified. They concluded that the evidence is insufficient to support or refute the use of PT for this condition.

- CNS germinoma: One retrospective case series was identified. They concluded that the evidence is insufficient to support or refute the use of PT for this condition.

Representative series of PBT in multiple pediatric CNS tumor types are described next.

Loma Linda University Medical Center reported on proton radiation in the treatment of low-grade gliomas in 27 pediatric patients. Six patients experienced local failure; acute side effects were minimal. After a median follow-up of 3 years, all of the children with local control maintained performance status. A dosimetric comparison of protons to photons for 7 optic pathway gliomas treated at Loma Linda showed a decrease in radiation dose to the contralateral optic nerve, temporal lobes, pituitary gland and optic chiasm with the use of protons.

MD Anderson Cancer Center and Methodist Hospital in Houston reported on 52 children with craniopharyngioma treated at 2 centers in Texas; 21 received PBT and 31 received IMRT. Patients received a median dose of 50.4 Gy. At 3 years, OS was 94.1% in the PBT group and 96.8% in the IMRT group (p=0.742). Three-year nodular and cystic failure-free survival rates were also similar between groups. Seventeen patients (33%) were found on imaging to have cyst growth within 3 months of RT, and 14 patients had late cyst growth (>3 months after therapy); rates did not differ significantly between groups. In 14 of the 17 patients with early cyst growth, enlargement was transient.

Massachusetts General Hospital reported on the use of protons in the treatment of germ cell tumors in 22 patients, 13 with germinoma and 9 with non-germinomatous germ cell tumors (NGGCTs). Radiation doses ranged from 30.6 to 57.6 cobalt Gray equivalents. All of the NGGCT patients received chemotherapy prior to radiation therapy. Twenty-one patients were treated with cranial spinal irradiation, whole ventricular radiation therapy, or whole brain radiation followed by an involved field boost; one patient received involved field alone. Median follow-up was 28 months. There were no central nervous system (CNS) recurrences and no deaths. Following radiation therapy, 2 patients developed growth hormone deficiency, and 2 patients developed central hypothyroidism. The authors stated that longer follow-up was necessary to assess the neurocognitive effects of therapy. In the same study, a dosimetric comparison of photons and protons for representative treatments with whole ventricular and involved field boost was done. Proton radiotherapy provided substantial sparing to the whole brain and temporal lobes, and reduced doses to the optic nerves.

Moeller and colleagues reported on 23 children who were enrolled in a prospective observational study and treated with proton beam therapy for medulloblastoma between the years 2006-2009. As hearing loss is common following chemoradiotherapy for children with medulloblastoma, the authors sought to compare whether proton radiotherapy led to a clinical benefit in audiometric outcomes (since, compared to photons, protons reduce radiation dose to the cochlea for these
patients). The children underwent pre- and 1-year post-radiotherapy pure-tone audiometric testing. Ears with moderate-to-severe hearing loss prior to therapy were censored, leaving 35 ears in 19 patients available for analysis. The predicted mean cochlear radiation dose was 30 60Co-Gy Equivalents (range 19-43). Hearing sensitivity significantly declined following radiotherapy across all frequencies analyzed (p<0.05). There was partial sparing of mean post-radiation hearing thresholds at low-to-midrange frequencies; the rate of high-grade (grade 3 or 4) ototoxicity at 1 year was 5%. The authors compared this to a rate of grade 3-4 toxicity following IMRT of 18% in a separate case series. The authors concluded that preservation of hearing in the audible speech range, as observed in their study, may improve both quality of life and cognitive functioning for these patients.

**Pediatric Non-Central Nervous System Tumors**

There is scant data on the use of proton beam therapy in pediatric non-CNS tumors and includes dosimetric planning studies in a small number of pediatric patients with parameningeal rhabdomyosarcoma and late toxicity outcomes in other solid tumors of childhood.

**Localized Prostate Cancer**

A 2010 TEC Assessment addressed the use of proton beam therapy for prostate cancer, and concluded that it has not yet been established whether proton beam therapy improves outcomes in any setting in clinically localized prostate cancer. A total of 9 studies were included in the review; 4 were comparative and 5 were noncomparative. There were 2 RCTs and only 1 of these included a comparison group of patients who did not receive PBT. This study, published in 1995 by Shipley et al, compared treatment with external beam radiotherapy (EBRT) using photons and either a photon or proton beam boost. After a median follow-up of 61 months, the investigators found no statistically significant differences in OS, disease-specific survival or recurrence-free survival. In a subgroup of patients with poorly differentiated tumors, there was superior local control with proton beam versus photon boost; but survival outcomes did not differ. Actuarial incidence of urethral stricture and freedom from rectal bleeding were significantly better in the photon boost group. The TEC Assessment noted that higher doses were delivered to the proton beam boost group and thus better results on survival and tumor control outcomes would be expected. Moreover, the study was published in the mid-1990s and used 2D methods of radiotherapy that are now outmoded. The other RCT, known as Proton Radiation Oncology Group (PROG)/American College of Radiology (ACR), compared 3D conformal EBRT with either a high-dose or conventional-dose proton beam boost. After a median follow-up of 8.9 years, there was not a statistically significant difference between groups in survival. Biochemical failure, an intermediate outcome, was significantly lower in the high-dose proton beam group. The TEC Assessment authors stated that the outcome, biochemical failure, has an unclear relationship to the more clinically important outcome, survival. The rate of acute GI toxicity was worse with the high-dose proton beam boost.

Taking into account data from all 9 studies included in the review, the authors of the TEC Assessment concluded that there was inadequate evidence from comparative studies to permit conclusions about the impact of proton beam therapy on health outcomes. Ideally, RCTs would report long-term health outcomes or intermediate outcomes that consistently predict health outcomes.
No RCTs have been published since the TEC Assessment that compare health outcomes in patients treated with proton beam therapy versus patients treated by other radiation treatment modalities. An RCT compared different protocols for administering hypofractionated proton therapy, but since there was no comparison with an alternative intervention, conclusions cannot be drawn about the efficacy and safety of proton beam therapy. This study was published in 2013 by Kim et al in Korea and included men with androgen-deprivation therapy-naïve stage T1-T3 prostate cancer. The 5 proton beam protocols were as follows: arm 1, 60 CGE (cobalt gray equivalent)/20 fractions for 5 weeks; arm 2, 54 CGE/15 fractions for 5 weeks; arm 3, 47 CGE/10 fractions for 5 weeks; arm 4, 35 CGE/5 fractions for 2.5 weeks; or arm 5, 35 CGE/5 fractions for 5 weeks. Eighty-two patients were randomized, and there was a median follow-up of 42 months. Patients assigned to arm 3 had the lowest rate of acute genitourinary toxicity and those assigned to arm 2 had the lowest rate of late gastrointestinal toxicity.

In 2014, the Agency for Healthcare Research and Quality (AHRQ) published a review of therapies for localized prostate cancer. This report was an update of a 2008 comparative effectiveness review. The authors compared risk and benefits of a number of treatments for localized prostate cancer including radical prostatectomy, EBRT (standard therapy as well as PBT, 3D conformal radiotherapy, IMRT and stereotactic body radiation therapy), interstitial brachytherapy, cryotherapy, watchful waiting, active surveillance, hormonal therapy and high-intensity focused ultrasound. The review concluded that the evidence for most treatment comparisons is inadequate to draw conclusions about comparative risks and benefits. Limited evidence appeared to favor surgery over watchful waiting or EBRT, and radiotherapy plus hormonal therapy over radiotherapy alone. The authors noted that there are advances in technology for many of the treatment options for clinically localized prostate cancer, for example current radiotherapy protocols allow higher doses than those administered in many of the trials included in the report. Moreover, the patient population has changed since most of the studies were conducted. In recent years, most patients with localized prostate cancer are identified via PSA testing and may be younger and healthier than prostate cancer patients identified in the pre-PSA era. Thus, the authors recommend additional studies to validate the comparative effectiveness of emerging therapies such as PBT, robotic-assisted surgery and stereotactic body radiation therapy.

From the published literature, it appears that dose escalation is an accepted concept in treating organ-confined prostate cancer. Proton beam therapy, using 3-D CRT planning or IMRT, is one used to provide dose escalation to a more well-defined target volume. However, dose escalation is more commonly offered with conventional external beam radiation therapy using 3-D CRT or IMRT. The morbidity related to radiation therapy of the prostate is focused on the adjacent bladder and rectal tissues; therefore, dose escalation is only possible if these tissues are spared. Even if IMRT or 3-D CRT permits improved delineation of the target volume, if the dose is not accurately delivered, perhaps due to movement artifact, the complications of dose escalation can be serious, as the bladder and rectal tissues are now exposed to even higher doses. The accuracy of dose delivery applies to both conventional and proton beam therapy.

**Non-Small Cell Lung Cancer**

A 2010 TEC assessment assessed the use of proton beam therapy for NSCLC. The TEC assessment addressed the key question of how health outcomes (overall survival, disease-specific survival, local
control, disease-free survival, and adverse events) with PBT compare with outcomes observed for stereotactic body radiotherapy (SBRT), which is an accepted approach for using radiation therapy to treat NSCLC. Eight PBT case series were identified in the Assessment that included a total of 340 patients. No comparative studies, randomized or nonrandomized, were found. For these studies, stage I comprised 88.5% of all patients, and only 39 patients were in other stages or had recurrent disease. Among 7 studies reporting 2-year overall survival, probabilities ranged between 39% and 98%. At 5 years, the range across 5 studies was 25% to 78%. It is unclear if the heterogeneity of results can be explained by differences in patient and treatment characteristics.

The report concluded that the evidence is insufficient to permit conclusions about the results of PBT for any stage of NSCLC. All PBT studies are case series; there are no studies directly comparing PBT and SBRT. Among study quality concerns, no study mentioned using an independent assessor of patient-reported adverse events; adverse events were generally poorly reported, and details were lacking on several aspects of PBT treatment regimens. The PBT studies were similar in patient age, but there was great variability in percent within stage IA, sex ratio, and percent medically inoperable. There is a high degree of treatment heterogeneity among the PBT studies, particularly with respect to planning volume, total dose, number of fractions, and number of beams. Survival results are highly variable. It is unclear whether the heterogeneity of results can be explained by differences in patient and treatment characteristics. In addition, indirect comparisons between PBT and SBRT, comparing separate sets of single-arm studies on PBT and SBRT may be distorted by confounding. In the absence of randomized controlled trials, the comparative effectiveness of PBT and SBRT is uncertain. The Assessment noted that adverse events reported after PBT generally fell into the following categories: rib fracture, cardiac, esophageal, pulmonary, skin, and soft tissue. Adverse events data in PBT studies are difficult to interpret due to lack of consistent reporting across studies, lack of detail about observation periods and lack of information about rating criteria and grades.

A 2010 indirect meta-analysis reviewed in the Assessment found a nonsignificant difference of 9 percentage points between pooled 2-year overall survival estimates favoring SBRT over PBT for the treatment of NSCLC. The nonsignificant difference of 2.4 percentage points at 5 years also favored SBRT over PBT. Based on separate groups of single-arm studies on SBRT and PBT, it is unclear if this indirect meta-analysis adequately addressed the possible influence of confounding on the comparison of SBRT and PBT.

Pijls-Johannesma et al conducted 2010 systematic literature examining the evidence on the use of particle therapy in lung cancer. Study inclusion criteria included that the series had at least 20 patients and a follow-up period ≥24 months. Eleven studies were included in the review, five investigating protons (n=214) and six C-ions (n=210). The proton studies included one phase 2 study, 2 prospective studies and 2 retrospective studies. The C-ion studies were all prospective and conducted at the same institution in Japan. No phase 3 studies were identified. Most patients had stage 1 disease, however, a wide variety of radiation schedules were used making comparisons of results difficult and local control rates were defined differently across studies. For proton therapy, 2- to 5-year local tumor control rates varied in the range of 57%–87%. The 2- and 5-year overall survival (OS) and 2- and 5-year cause-specific survival (CSS) rates were 31%–74% and 23% and 58%–86% and 46%, respectively. These local control and survival rates are equivalent to or inferior to those achieved with stereotactic radiation therapy. Radiation-induced pneumonitis was
observed in about 10% of patients. For C-ion therapy, the overall local tumor control rate was 77%, but it was 95% when using a hypofractionated radiation schedule. The 5-year OS and CSS rates were 42% and 60%, respectively. Slightly better results were reported when using hypofractionation, 50% and 76%, respectively. The authors concluded that the results with protons and heavier charged particles are promising, but that because of the lack of evidence, there is a need for further investigation in an adequate manner with well-designed trials.

To date, no RCTs or non-RCTs reporting health outcomes in patients treated with PBT versus an alternative treatment have been published.

**Head and Neck tumors, other than skull-based**
A 2014 systematic review evaluated the literature on charged particle therapy versus photon therapy for the treatment of paranasal sinus and nasal cavity malignant disease. The authors identified 41 observational studies that included 13 cohorts treated with charged particle therapy (total n=286 patients) and 30 cohorts treated with photon therapy (total n=1186 patients). There were no head-to-head trials. In a meta-analysis, the pooled event rate of overall survival was significantly higher with charged particle therapy than photon therapy at the longest duration of follow-up (RR: 1.27, 95% CI: 1.01 to 1.59). Findings were similar for the outcome survival at 5 years (RR: 1.51, 95% CI: 1.14 to 1.99). Findings were mixed for the outcomes locoregional control and disease-free survival; photon therapy was significantly better for only 1 of the 2 timeframes (longest follow-up or 5-year follow-up). In terms of adverse effects, there were significantly more neurological toxic effects with charged particle therapy compared with photon therapy (p=0.0002) but other toxic adverse event rates e.g. eye, nasal and hematologic did not differ significantly between groups. The authors noted that the charged particle studies were heterogeneous, e.g. type of charged particles (carbon ion, proton), delivery techniques, etc. It should also be noted that comparisons were indirect and none of the studies included in the review actually compared the two types of treatment in the same patient sample.

Also in 2014, Zenda et al reported on late toxicity in 90 patients after PBT for nasal cavity, paranasal sinuses or skull base malignancies. Eighty seven of the 90 patients had paranasal sinus or nasal cavity cancer. The median observation period was 57.5 months. Grade 3 late toxicities occurred in 17 patients (19%) and Grade 4 occurred in 6 patients (7%). Five patients developed cataracts and 5 had optic nerve disorders. Late toxicities (other than cataracts) developed a median of 39.2 months after PBT.

**Ongoing and Unpublished Clinical Trials**
A search of ClinicTrials.gov in on February 18, 2015 identified the following:

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<td>Comparing Photon Therapy To Proton Therapy To Treat Patients With Lung Cancer</td>
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NCT: national clinical trial.
Summary of Evidence
For individuals who have uveal melanoma(s) who receive charged-particle (proton or helium ion) radiotherapy, the evidence includes RCTs and systematic reviews. Relevant outcomes are overall survival, disease-free survival, change in disease status, and treatment-related morbidity. Systematic reviews, including a 1996 TEC Assessment and a 2013 review of randomized and non-randomized studies, concluded that the technology is at least as effective as alternative therapies for treating uveal melanomas and is better at preserving vision. The evidence is sufficient to determine qualitatively that the technology results in a meaningful improvement in the net health outcome.

For individuals who have skull-based tumor(s) (i.e., cervical chordoma and chondrosarcoma) who receive charged-particle (proton or helium ion) radiotherapy, the evidence includes observational studies and systematic reviews. Relevant outcomes are overall survival, disease-free survival, change in disease status, and treatment-related morbidity. A 1996 TEC Assessment concluded that the technology is at least as effective as alternative therapies for treating skull-based tumors. A 2016 systematic review of observational studies found 5-year survival rates after proton beam therapy ranging from 67% to 94%. The evidence is sufficient to determine qualitatively that the technology results in a meaningful improvement in the net health outcome.

For individuals who have pediatric central nervous system tumor(s) who receive charged-particle (proton or helium ion) radiotherapy, the evidence includes case series, a few nonrandomized comparative studies and systematic reviews. Relevant outcomes are overall survival, disease-free survival, change in disease status, and treatment-related morbidity. There are few comparative studies and studies tended to have small sample sizes. The available observational studies do not provide sufficient evidence on the efficacy of charged-particle therapy compared with other treatments e.g., IMRT. The evidence is insufficient to determine the effects of the technology on health outcomes. Clinical input obtained in 2013 strongly supported the use of charged-particle radiotherapy for treating pediatric central nervous system tumors. This modality of treatment of pediatric CNS tumors has the potential to reduce long-term adverse effects, such as damage to nearby normal CNS tissue and development of radiation-induced secondary tumors.

For individuals who have pediatric non-central nervous system tumor(s) who receive charged-particle (proton or helium ion) radiotherapy, the evidence includes dosimetric planning studies in a small number of patients. Relevant outcomes are overall survival, disease-free survival, change in disease status, and treatment-related morbidity. There is a lack of randomized and observational studies evaluating the efficacy and safety of the technology. The evidence is insufficient to determine the effects of the technology on health outcomes.

For individuals who have localized prostate cancer who receive charged-particle (proton or helium ion) radiotherapy, the evidence includes 2 RCTs and systematic reviews. Relevant outcomes are overall survival, disease-free survival, change in disease status, and treatment-related morbidity. A 2010 TEC Assessment addressed the use of PBT for prostate cancer and concluded that it has not yet been established whether PBT improves outcomes in any setting for clinically localized prostate cancer. The TEC Assessment included 2 RCTs, only 1 of which included a comparison group of patients who did not receive proton-beam therapy. No data on the use of PBT for prostate cancer
have been published since 2010 that would alter the conclusions of the TEC Assessment. The evidence is insufficient to determine the effects of the technology on health outcomes.

For individuals who have non-small-cell lung cancer who receive charged-particle (proton or helium ion) radiotherapy, the evidence includes case series and systematic reviews. Relevant outcomes are overall survival, disease-free survival, change in disease status, and treatment-related morbidity. A 2010 TEC Assessment included 8 case series and concluded that the evidence is insufficient to permit conclusions about proton beam therapy for any stage of non-small cell lung cancer. No subsequent randomized or non-randomized comparative studies have been published. The evidence is insufficient to determine the effects of the technology on health outcomes.

For individuals who have head and neck tumors other than skull-based who receive charged-particle (proton or helium ion) radiotherapy, the evidence includes case series and a systematic review. Relevant outcomes are overall survival, disease-free survival, change in disease status, and treatment-related morbidity. The evidence is insufficient to determine the effects of the technology on health outcomes. The systematic review noted that the studies no charged-particle therapy were heterogenous in terms of type of particle and delivery techniques, and that there are no head to head trials comparing charged-particle therapy to other treatments. The evidence is insufficient to determine the effects of the technology on health outcomes.

Supplemental Information
Clinical Input Received Through Physician Specialty Society and Academic Medical Center
While the various physician specialty societies and academic medical centers may collaborate with and make recommendations during this process through the provision of appropriate reviewers, input received does not represent an endorsement or position statement by the physician specialty societies or academic medical centers, unless otherwise noted.

In response to requests, input was received from 2 physician specialty societies (4 responses) and 4 academic medical centers while this policy was under review for March 2013. There was uniform support for the use of PBT in pediatric CNS tumors. Two reviewers expressed support for the use of PBT in pediatric non-CNS tumors; data for this use are scant. Input on head and neck tumors (nonskull based) was mixed.

Practice Guidelines and Position Statements
Thoracic Subcommittee of the International Particle Therapy Co-operative Group
A 2016 consensus statement had the following conclusion on proton therapy for non-small-cell lung cancer (NSCLC):

“...Promising preliminary clinical outcomes have been reported for patients with early-stage or locally advanced NSCLC who receive proton therapy. However, the expense and technical challenges of proton therapy demand further technique optimization and more clinical studies....”

American College of Radiology (ACR) Appropriateness Criteria
A 2014 guideline on external beam irradiation in Stage T1 and T2 prostate cancer states:

• “There are only limited data comparing proton-beam therapy to other methods of irradiation or to radical prostatectomy for treating stage T1 and T2 prostate cancer. Further studies are needed to clearly define its role for such treatment.
• There are growing data to suggest that hypofractionation at dose per fraction <3.0 Gy per fraction is reasonably safe and efficacious, and although the early results from hypofractionation/ SBRT (stereotactic body radiation therapy) studies at dose per fraction >4.0 Gy seem promising, these approaches should continue to be used with caution until more mature, ongoing phase II and III randomized controlled studies have been completed.

• **National Comprehensive Cancer Network (NCCN)**
  
  **Prostate Cancer**
  
  NCCN guidelines for prostate cancer 3.2016 make the following conclusion on proton therapy: “The NCCN panel believes no clear evidence supports a benefit or decrement to proton therapy over IMRT for either treatment efficacy or long-term toxicity. Conventionally fractionated prostate proton therapy can be considered a reasonable alternative to x-ray-based regimens at clinics with appropriate technology, physics and clinical expertise.

  **Non-Small Cell Lung Cancer**
  
  NCCN guidelines for Non-Small Cell Lung Cancer 4.2016 state that “more advanced technologies are appropriate when needed to deliver curative RT safely. These technologies include . . . proton beam therapy”. Non-randomized comparisons of using advanced technologies versus older techniques demonstrate reduced toxicity and improved survival.

  **Bone Cancer**
  
  NCCN guidelines for Bone Cancer 2.2016 state that “specialized techniques such intensity modulated radiation therapy (IMRT), particle beam RT with protons, carbon ions or other heavy ions, stereotactic radiosurgery or fractionated stereotactic RT should be considered as indicated in order to allow high-dose therapy while maximizing normal tissue sparing.”

• **American Society for Radiation Oncology (ASTRO)**
  
  The Emerging Technology Committee of ASTRO published 2012 evidence-based recommendations declaring a lack of evidence for proton beam therapy (PBT) for malignancies outside of large ocular melanomas and chordomas:

  “Current data do not provide sufficient evidence to recommend PBT outside of clinical trials in lung cancer, head and neck cancer, GI [gastrointestinal] malignancies (with the exception of hepatocellular) and pediatric non-CNS malignancies. In hepatocellular carcinoma and prostate cancer, there is evidence for the efficacy of PBT but no suggestion that it is superior to photon-based approaches. In pediatric CNS malignancies, there is a suggestion from the literature that PBT is superior to photon approaches, but there is currently insufficient data to support a firm recommendation for PBT. In the setting of craniospinal irradiation for pediatric patients, protons appear to offer a dosimetric benefit over photons, but more clinical data are needed. In large ocular melanomas and chordomas, we believe that there is evidence for a benefit of PBT over photon approaches. In all fields, however, further clinical trials are needed and should be encouraged.”

  In September 2013, as part of its national “Choosing Wisely” initiative, ASTRO listed PBT for prostate cancer as one of 5 radiation oncology practices that should not be routinely used because they are not supported by evidence.
In June 2014, ASTRO published a model policy on use of PBT. The document stated that ASTRO supports PBT for the treatment of the following conditions:

- Ocular tumors, including intraocular melanomas
- Tumors that approach or are located at the base of the skull, including but not limited to:
  - Chordoma
  - Chondrosarcoma
- Primary or metastatic tumors of the spine... (selected patients)
- Primary hepatocellular cancer treated in a hypofractionated regimen
- Primary or benign solid tumors in children... (selected patients)
- Patients with genetic syndromes making total volume of radiation minimization crucial such as but not limited to NF-1 patients and retinoblastoma patients.”

The model policy stated the following regarding PBT for treating prostate cancer: “...It is essential to collect further data, especially to understand how the effectiveness of proton therapy compares to other radiation therapy modalities such as IMRT and brachytherapy. There is a need for more well-designed registries and studies with sizable comparator cohorts to help accelerate data collection. Proton beam therapy for primary treatment of prostate cancer should only be performed within the context of a prospective clinical trial or registry.”

**National Association for Proton Therapy**
In March 2015, National Association for Proton Therapy (NAPT) published a model coverage policy. This organization is a nonprofit corporation that “promotes the therapeutic benefits of proton therapy for cancer treatment...” Their model policy was not endorsed by ASTRO or NCCN. Prostate carcinoma was an indication considered medically necessary in this document. The model policy did not include a discussion of the published evidence.

**Medicare National Coverage**
There is no national coverage determination (NCD). In the absence of an NCD, coverage decisions are left to the discretion of local Medicare carriers.

**VI. Important Reminder**
The purpose of this Medical Policy is to provide a guide to coverage. This Medical Policy is not intended to dictate to providers how to practice medicine. Nothing in this Medical Policy is intended to discourage or prohibit providing other medical advice or treatment deemed appropriate by the treating physician.

Benefit determinations are subject to applicable member contract language. To the extent there are any conflicts between these guidelines and the contract language, the contract language will control.

This Medical Policy has been developed through consideration of the medical necessity criteria under Hawaii’s Patients' Bill of Rights and Responsibilities Act (Hawaii Revised Statutes § 432E-1.4), generally accepted standards of medical practice, and review of medical literature and government approval status. HMSA has determined that services not covered under this Medical Policy will not be medically necessary under Hawaii law in most cases. If a treating physician disagrees with HMSA’s determination as to medical necessity in a given case, the physician may request that
HMSA reconsider the application of the medical necessity criteria to the case at issue in light of any supporting documentation.

VII. References
1. Blue Cross and Blue Shield Association Technology Evaluation Center (TEC). Charged particle (proton or helium ion) irradiation for uveal melanoma and for chordoma or chondrosarcoma of the skull base or cervical spine. TEC Assessments 1996; Volume 11, Tab 1.
18. Blue Cross and Blue Shield Association Technology Evaluation Center (TEC). Proton beam therapy for prostate cancer. TEC Assessments 2010; Volume 25, Tab 10
37. American Society for Radiation Oncology (ASTRO). ASTRO releases list of five radiation oncology treatments to question as part of national Choosing Wisely campaign.