Proton Beam Therapy

Medicare Advantage Medical Policy #MA-124
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Applies to all products administered or underwritten by the Health Plan, unless otherwise provided in the applicable contract. Medical technology is constantly evolving, and we reserve the right to review and update Medical Policy periodically.

Note: For all Proton Beam Therapy (PBT) requests outside of approved criteria, case control plan comparison is insufficient justification for PBT. A direct isodose comparison for an intensity-modulated radiotherapy (IMRT) plan specific to the patient request is mandatory for consideration.

When Services Are Eligible for Coverage

Coverage for eligible medical treatments or procedures, drugs, devices or biological products may be provided only if:

- *Benefits are available in the member's contract/certificate, and*
- *Medical necessity criteria and guidelines are met.*

Base of Skull Tumors

Chordoma, Chondrosarcoma
Based on review of available data, the Health Plan may consider proton beam therapy (PBT) for chordoma, or chondrosarcoma to be **eligible for coverage.****

Patient Selection Criterion
Coverage eligibility for PBT for chordoma, or chondrosarcoma may be considered when the following criterion is met:

- As postoperative therapy for individuals who have undergone biopsy or partial resection of a chordoma or low-grade (I or II) chondrosarcoma of the basisphenoid region (e.g., skull-base chordoma or chondrosarcoma), cervical spine, or sacral/lower spine and have residual, localized tumor without evidence of metastasis.

Sinonasal Cancer
Based on review of available data, the Health Plan may consider proton beam therapy (PBT) for locally advanced sinonasal carcinoma to be **eligible for coverage.****

Patient Selection Criterion
Coverage eligibility for PBT for locally advanced sinonasal carcinoma may be considered when the following criterion is met:

- Tumor involves the base of skull and proton therapy is needed to spare the orbit, optic nerve, optic chiasm, or brainstem.

Central Nervous System

Arteriovenous Malformation (AVM)
Based on review of available data, the Health Plan may consider proton beam therapy (PBT) for arteriovenous malformation (AVM) to be **eligible for coverage.****

Patient Selection Criteria
Coverage eligibility for PBT for AVM may be considered when **ANY** of the following criteria are met:

- Intracranial AVM not amenable to surgical excision or other conventional forms of treatment; **OR**
- Adjacent to critical structures such as the optic nerve, brain stem or spinal cord.

Central Nervous System (CNS) Tumors (in adults age 21 and older)
Based on review of available data, the Health Plan may consider proton beam therapy (PBT) for central nervous system (CNS) tumors to be **eligible for coverage.****

Patient Selection Criteria
Coverage eligibility for CNS tumors in adults may be considered when **ALL** of the following criteria are met:

- CNS tumors, such as gliomas **(both must be met):**
    - When adjacent to critical structures such as the optic nerve, brain stem, or spinal cord; **AND**
    - When other standard radiation techniques such as intensity-modulated radiotherapy (IMRT) or standard stereotactic modalities would not reduce the risk of radiation damage to the critical structure.

Hepatobiliary Cancer

Hepatocellular Carcinoma and Intrahepatic Cholangiocarcinoma
Based on review of available data, the Health Plan may consider proton beam therapy (PBT) for hepatocellular cancer or intrahepatic cholangiocarcinoma to be **eligible for coverage.****

Patient Selection Criterion
Coverage eligibility for PBT for hepatocellular cancer or intrahepatic cholangiocarcinoma may be considered when the following criterion is met:

- To treat unresectable, non-metastatic hepatocellular cancer or intrahepatic cholangiocarcinoma with curative intent.

Melanoma

Ocular Melanoma
Based on review of available data, the Health Plan may consider proton beam therapy (PBT) for ocular melanoma to be **eligible for coverage.****

Patient Selection Criterion
Coverage eligibility for PBT for ocular melanoma may be considered when the following criterion is met:

- As primary therapy for melanoma of the uveal tract (including the iris, choroid, or ciliary body) and with no evidence of metastasis or extrascleral extension.

Re-irradiation

Based on review of available data, the Health Plan may consider PBT for re-irradiation to be **eligible for coverage.****

Patient Selection Criterion
Coverage eligibility for PBT for re-irradiation may be considered when the following criterion is met:

- For previously treated fields where the dose tolerance of surrounding normal structures would be exceeded with 3D conformal radiation or IMRT.

When Services Are Considered Not Medically Necessary

The use of PBT is considered to be **not medically necessary**** when patient selection criteria are not met and for all other conditions including, but not limited to the following:

- Breast cancer;
- Esophageal cancer;
- Gastric cancer;
- Gynecologic cancer;
- Head and neck cancer;
- Hepatobiliary cancers not listed above;
- Lung cancer;
- Lymphoma (Hodgkin and non-Hodgkin);
- Pancreatic cancer;
- Prostate cancer.

Policy Guidelines

Evidence is lacking on the definition of age parameters for the use of proton beam therapy in pediatric individuals. Some studies using proton beam therapy in pediatric central nervous system

tumors have mostly included individuals younger than 3 years of age. However, experts cite the benefit of proton beam therapy in pediatric patients of all ages (<21 years of age).

Organs at risk are defined as normal tissues whose radiation sensitivity may significantly influence treatment and/or prescribed radiation dose. These organs at risk may be particularly vulnerable to clinically important complications from radiation toxicity. Table PG1 outlines radiation doses that are generally considered tolerance thresholds for these normal structures in various organ regions. Clinical documentation based on dosimetry plans may be used to demonstrate that radiation by conventional or advanced photon-based radiotherapy, including intensity-modulated radiotherapy (IMRT), volume-modulated arc therapy (VMAT), stereotactic radiosurgery (SRS), or stereotactic body radiation therapy (SBRT), would exceed tolerance doses to structures at risk. For patients with radiation-sensitizing genetic syndromes such as neurofibromatosis type 1 (NF-1) or retinoblastoma, clinical documentation of the condition may be used to demonstrate increased risk from exposure during treatment.

Table P1. Radiation Tolerance Doses for Normal Tissues Table PG1. Radiation Tolerance Doses for Normal Tissues

Site	**TD 5/5 (Gray)[a]**			**TD 50/5 (Gray)[b]**			**Complication End Point**
	Portion of Organ Involved			**Portion of Organ Involved**			
	1/3	2/3	3/3	1/3	2/3	3/3	
Heart	60	45	40	70	55	50	Pericarditis
Lung	45	30	17.5	65	40	24.5	Pneumonitis
Spinal cord	50	50	47	70	70	NP	Myelitis/necrosis
Salivary glands	32	32	32	46	46	46	Xerostemia
Kidney	50	30	23	NP	40	28	Clinical nephritis
Liver	50	35	30	55	45	40	Liver failure
Esophagus	60	58	55	72	70	68	Stricture, perforation
Stomach	60	55	50	70	67	65	Ulceration, perforation
Small intestine	50	NP	40	60	NP	55	Obstruction, perforation
Colon	55	NP	45	65	NP	55	Obstruction, perforation, ulceration, fistula

Site	TD 5/5 (Gray)[a]			TD 50/5 (Gray)[b]			Complication End Point
Rectum	NP	NP	60	NP	NP	80	Severe proctitis, necrosis, stenosis, fistula
Femoral head	NP	NP	52	NP	NP	65	Necrosis

Compiled from 2 sources: (1) Morgan MA (2011). Radiation Oncology. In DeVita, Lawrence, and Rosenberg, Cancer (p.308). Philadelphia: Lippincott Williams and Wilkins; and (2) Kehwar TS, Sharma SC. Use of normal tissue tolerance doses into linear quadratic equation to estimate normal tissue complication probability. Available online at: http://www.rooj.com/Radiation%20Tissue%20Tolerance.htm.
NP: not provided; TD: tolerance dose.
[a] TD 5/5 is the average dose that results in a 5% complication risk within 5 years.
[b] TD 50/5 is the average dose that results in a 50% complication risk within 5 years.

For charged-particle radiotherapy (proton or helium ion) therapy to provide outcomes superior to photon-based radiotherapy, there must be a clinically meaningful decrease in the radiation exposure to normal structures. There is no standard definition for a clinically meaningful decrease in radiation dose. In principle, a clinically meaningful decrease would signify a significant reduction in anticipated complications of radiation exposure. To document a clinically meaningful reduction in dose, dosimetry studies should demonstrate a significant decrease in the maximum dose of radiation delivered per unit of tissue, and/or a significant decrease in the volume of normal tissue exposed to potentially toxic radiation doses. While radiation tolerance dose levels for normal tissues are well-established, the decrease in the volume of tissue exposed that is needed to provide a clinically meaningful benefit has not been standardized. Therefore, precise parameters for a clinically meaningful decrease cannot be provided.

Background/Overview

Proton beam radiation therapy, also known as proton beam therapy (PBT), is a type of external radiation treatment. Using a stereotactic planning and delivery system, positively charged subatomic particles (protons) are targeted to a specific tissue mass. Protons behave differently than x-rays or photons in that they have a low energy deposition rate as they enter the body, followed by a steep increased energy deposition when they reach their target. Although there is essentially no energy deposited beyond the target, there is lateral scatter and some uncertainty about their physical range in tissue. Compared to x-ray treatment, surrounding healthy tissue generally receives less radiation. Despite the proliferation of proton centers in recent years, there is a lack of high-quality evidence demonstrating improved outcomes vs other forms of precision radiation therapy. Proton beam therapy remains an area of active clinical investigation, and recommendations for its use continue to evolve.

Proton beam therapy may be appropriate in circumstances where intensity modulated radiation therapy (IMRT) or stereotactic would potentially damage critical structures, particularly in patients

with a history of prior irradiation. Proton beam therapy is also appropriate for pediatric patients because even low doses of scattered radiation in this population can affect growth and development and increase the risk of secondary malignancies later in life. This technique of radiation delivery is being actively studied in other clinical scenarios, and its role in these situations in many cases remains unclear. In situations where there is a lack of high-quality evidence comparing proton outcomes with photon-based therapies, proton therapy will be considered not medically necessary. In situations where proton therapy is appropriate, PBT should be administered as monotherapy.

Breast Cancer
There are no completed randomized trials of PBT for breast cancer. A recent systematic review discussed nine original investigations of PBT for both whole breast treatment and accelerated partial breast irradiation (APBI). Skin toxicity and esophagitis were comparable to photon therapy. None of the outcomes reported were improved with PBT. There is a randomized trial comparing PBT to photon therapy underway.

Several studies have examined the potential increase in biologic dose delivered with intensity modulated protontherapy (IMPT) compared to the doses calculated with an assumed radiobiologic equivalent (RBE) of 1.1. The variably weighted dose resulted in an increase in the biologic dose to the brachial plexus, ribs, heart, and esophagus ranging from 8%-24%. In another study, although there was significant dose improvement with protons vs photons when an RBE of 1.1 was assumed, no statistically significant difference was seen when a variable RBE was applied. The authors of these studies concluded that a variable RBE model should be considered when evaluating IMPT plans, especially for organs at risk near the end range of each proton beam. These biologic uncertainties underscore the need for further study of PBT and IMPT in this setting. They also argue against drawing conclusions about any potential dosimetric advantages of proton therapy based on historic estimations of the biologic dose.

A randomized trial comparing PBT to photon therapy for breast cancer patients requiring comprehensive nodal irradiation has completed patient enrollment. The Pragmatic Randomized Trial of Proton vs. Photon Therapy for Patients With Non-Metastatic Breast Cancer: A Radiotherapy Comparative Effectiveness (RADCOMP) Consortium Trial (NCT02603341) compares multiple outcomes including quality of life (QOL), cardiovascular problems, and cancer control. Follow-up is ongoing. As with any randomized trial, there is an assumption of equipoise.

The Particle Therapy Cooperative Group recently published a consensus statement on the use of proton beam therapy to treat breast cancer. They highlight several non-randomized trials of fewer than 100 patients which form the basis for the randomized RADCOMP trial. As a method to deliver regional nodal irradiation in high-risk patients, they advocate for proton beam therapy when target or organ at risk constraints cannot be met with a robust photon plan. The authors note that for each 1 Gy increase in mean heart dose, a 0.3%-0.6% reduction in lifetime cardiac adverse events is expected. In addition, RTOG 1304/NSAPB B-51 requires that the mean heart dose (MHD) be limited

to 5 Gy or less. This can be achieved with IMRT techniques in the majority of cases. The quality of the guideline methodology is scored below passing when appraised with AGREE II.

Proton beam therapy is considered not medically necessary for the treatment of breast cancer.

Central Nervous System Lesions
Radiation therapy is commonly used to treat central nervous system (CNS) tumors and other intracranial lesions such as arteriovenous malformations (AVM). Results of proton therapy have been reported for a variety of CNS lesions. In the treatment of gliomas, dose escalation to 68.2 centigray equivalent (CGE) did not improve outcomes in a phase I/II trial of protons in grade 2-3 astrocytoma. In another study, dose escalation to 90 CGE slightly increased median survival, but all patients had marginal failure just beyond the high-dose area and necrosis was seen in one third of patients. A more recent Japanese phase I/II study boosted glioblastomas to 96.6 CGE and reported a handful of long-term survivors, all of whom have developed necrosis. Benign tumors including meningiomas, acoustic neuromas and pituitary adenomas have also been treated with protons.

A randomized phase II trial comparing proton therapy to IMRT for newly diagnosed glioblastoma was recently reported. The primary endpoint was time to cognitive failure. Overall survival (OS), progression-free survival (PFS), and toxicity were also measured. At a median follow-up of 48 months, there were no differences in timeto cognitive failure, OS, or PFS. There was less fatigue reported in the proton group. The investigators concluded that larger randomized trials are needed.

A German phase III study comparing outcomes for treatment of glioblastoma with PBT vs IMRT was recently activated. This study, known as the GRIPS trial (Glioblastoma Radiotherapy via IMRT or Proton Beams, NCT04752280), will evaluate treatment-related toxicity as its primary endpoint. Secondary endpoints include overall survival, progression-free survival, quality of life, and neurocognition.

Results of treatment are similar to those seen with non-proton techniques such as IMRT and stereotactic radiosurgery (SRS). A recent review of PBT to treat CNS lesions by Combs concluded that “no clinical data have shown superiority over advanced photon therapy.”

Use of PBT for CNS lesions is only medically necessary for specific cases where adjacent critical structures cannot be adequately spared with IMRT or SRS.

Chordoma and Chondrosarcoma
Chordomas and chondrosarcomas are rare bone and soft tissue tumors which occur along the spinal axis. The mainstay of treatment is surgery, but in many cases only biopsy or piecemeal resection is possible. Postoperative radiotherapy has been shown to improve outcomes. In the past, tumors occurring in the base of skull area were unable to be treated to high doses with conventional therapy due to the risk of damaging normal tissues. Protons were used to safely treat chordomas in this location with good results. In the most comprehensive review published to date, seven studies of

proton therapy were compared to ten studies of conventional radiotherapy and reported improved local control and survival with protons compared to x-rays. The average five-year local control with protons was 69% vs only 36% with photons. The five-year survival rate was 80% with PBT vs 54% with x-rays. Chordomas and chrondrosarcoma of the spine are similarly difficult to treat given that doses above 70 Gy are given to areas in close proximity to the spinal cord and viscera. A recent prospective phase II trial of protons in this setting showed an impressive 94% five-year local control for primary tumors with acceptable late morbidity.

Results with modern radiotherapy techniques like IMRT and radiosurgery are improved compared to conventional radiotherapy, but given the excellent long-term results seen with protons, they are considered medically necessary for the treatment of base of skull and sacral chordomas and chondrosarcomas.

Head and Neck Cancer
Although there are several trials currently underway, there are currently no published randomized studies comparing proton therapy to IMRT in the treatment of head and neck cancers. In 2010, the AHRQ conducted a systematic review of different radiation modalities used in the treatment of head and neck malignancies including 2D radiation, 3D conformal radiation, IMRT, and PBT. They concluded that there was insufficient evidence comparing PBT to other modalities. This report was updated in 2014 with the same conclusion.

A 2016 single institution report retrospectively compared intensity-modulated proton therapy (IMPT) to IMRT in the treatment of oropharyngeal cancer. There was no difference in progression-free survival between the modalities. IMRT treated patients were more likely to have a gastrostomy tube (G-tube) placed than proton treated patients but this was not statistically significant. Outcomes meeting statistical significance were patient reported xerostomia at three months and weight loss greater than 20% or G-tube presence one year after treatment. The authors concluded that prospective multicenter randomized trials are needed to validate these findings.

This hypothesis-generating report forms the basis for an NCI-sponsored, phase II/III, randomized clinical trial comparing IMRT and PBT in the treatment of oropharynx cancer (NCT01893307). In a recent review, Leeman et al. conclude that “ultimately, such trials will help establish the clinical usefulness of proton beam therapy and will be necessary to provide sufficient evidence regarding toxicity benefits to support wider adoption.”

A recent publication describes the final selection of primary and secondary endpoints to be used for NCT01893307 as this study transitions from phase II to phase III. NRG Oncology, a non-profit research organization formed to conduct clinical research in oncology and to broadly disseminate study results to inform clinical decision-making and health policy, was brought in as a partner and expressed concerns about the proposed endpoints of the study. The initial primary endpoint of physician scored, late onset, grade ≥3 toxicity was scrapped due to a perceived lack of objectivity in physician ratings using the Common Terminology Criteria for Adverse Events (CTCAE) and

insufficient sensitivity to account for other forms of toxicity. The study has now been redesigned as a non-inferiority trial using progression-free survival as the primary endpoint and using an expanded group of toxicity measurements as secondary endpoints.

A systematic review and meta-analysis of charged particle therapy vs x-ray based therapy for treatment of paranasal sinus and nasal cancers was published by Patel et al. There were no head-to-head comparison trials, so their analysis consisted of 41 observational studies. Of these, there were 13 reports for charged particle therapy and 30 cohorts treated with photons. In the meta-analysis of these reports, treatment with charged particle therapy was associated with higher survival at five years. Neurologic toxicity was significantly higher in the charged particle group as well. The studies reviewed included a very heterogeneous group. For photon therapy, treatment techniques included 2D, 3D, IMRT, and brachytherapy. The charged particle cohorts included both protons and carbon ions with most patients being treated with passively scattered protons. A similar proportion of patients in both groups had advanced disease but the photon-treated patients were more likely to have a high-risk histology. The heterogeneity of both the patient populations and treatment techniques as well as the inclusion of inadequate treatment techniques such as 2D and 3D conformal radiotherapy in the photon group make it impossible to draw meaningful conclusions for the entire group. Proton beam therapy may be appropriate to treat certain locally advanced sinonasal cancers involving the base of skull when adjacent critical structures are unable to be adequately spared with IMRT.

A retrospective series of 68 patients treated with PBT for major salivary gland tumors was recently reported. Proton beam treatment showed favorable short-term local control and survival rates. There was no comparisongroup reported.
Proton beam therapy is considered medically necessary to treat locally advanced sinonasal cancers involving the base of skull. Proton beam therapy is not medically necessary for the treatment of other head and neck cancers.

Hepatocellular Cancer
Hepatocellular carcinomas (HCC) are aggressive primary malignancies of the liver. All patients should be evaluated for potentially curative therapies including resection, transplantation and ablative treatment. Ablative therapies include radiofrequency ablation, microwave therapy and alcohol injection. Radiation therapy is considered for patients who are not candidates for resection. There is growing evidence for the use of SBRT. Charged particle therapy such as proton therapy has also been used in the treatment of hepatocellular carcinoma.
There are no randomized trials comparing PBT to other forms of external radiation. A systematic review and meta-analysis comparing charged particle therapy to conventional radiation and SBRT has been reported. Overall survival, progression-free survival, and local control were equivalent for particle therapy and SBRT. Both charged particle therapy and SBRT were superior to conventional radiation.

A single institution retrospective study compared ablative photon vs proton therapy in patients with unresectable hepatocellular carcinoma. The majority of the proton beam patients were treated as part of a phase II single arm clinical trial (NCT 00976898). The primary endpoint was overall survival. Proton therapy was associated with an improved overall survival of 31 months vs 14 months with photons. The proton-treated patients had a significantly lower risk of nonclassic radiation induced liver disease (RILD) (OR 0.26, P = .03) and development of RILD at 3 months was significantly associated with worse overall survival. There was no difference in local failure between the two treatment suggesting that the improved survival is related to the decrease in post- treatment liver decompensation.

Proton therapy has been compared to transarterial chemoembolization (TACE) for HCC in a randomized trial. A total of 69 subjects were reported. The primary endpoint was progression-free survival. There was a trend toward improved progression- free survival (48% vs 31%, p=0.06) favoring protons but no significant difference in overall survival with a median overall survival of 30 months. Total days of hospitalization within 30 days of treatment was 166 days for the 36 TACE patients and 24 days for the proton patients ($p<0.001$).

Another randomized trial compared radiofrequency ablation (RFA) to proton beam therapy for unresectable hepatocellular carcinoma. One hundred forty-four patients were randomly assigned to receive either RFA or PBT. There was significant crossover to the other modality affecting 6 patients assigned to PBT and 19 patients assigned to RFA. For the patients treated per protocol, the two-year local progression-free survival rate was 94.8% in the PBT patients vs 83.9% for RFA ($P < 0.001$). The authors concluded that PBT is non-inferior to RFAin this setting.

Proton beam therapy is considered medically necessary for the treatment of unresectable HCC with curative intent when there is no evidence of metastatic disease.

Other Gastrointestinal Cancers

There have been few reports of PBT to treat esophageal and gastroesophageal junction tumors. Wang et al. published a retrospective report of complications after trimodality therapy looking at IMRT and PBT compared to 3D conformal radiation. A total of 444 patients were reported. Both IMRT and PBT were associated with reduced risk of complications compared to 3D conformal radiation. No direct comparison of IMRT vs PBT was performed.

Lin et al. recently published a small, phase IIB, randomized, study comparing proton beam therapy to IMRT in patients with locally advanced esophageal cancer. A total of 145 patients were enrolled and 107 of these wereevaluable. The IMRT group had 61 patients and the proton group had 46 patients. Median follow-up was 44 months. Three-year progression-free survival was 50.8% for IMRT and 51.2% for protons. Overall survival wasidentical in both arms at 44.5%.

Quality of life (QOL) was assessed at multiple time points during the study and there were no QOL differences between the two treatment arms. The main finding of the study was an improvement in

what the authors term “total toxicity burden” or TTB. The TTB score is a composite of numerous possible treatment related events and/or postoperative complications, with the majority of the TTB benefit attributed to asymptomatic pleural effusion, asymptomatic pericardial effusion and atrial fibrillation. The physicians scoring the TTB were not blinded as to the treatment received, leading to possible bias. This endpoint has not been validated for this use.

In a recent editorial highlighting randomized trials for gastrointestinal cancers, Hallemeier et al. state:

> *Many questions remain unanswered regarding the utility of PBT for esophageal cancer. Importantly, doesreduction in radiation doses to organs at risk lead to improved survival, quality of life, or cost savings?*

There is an ongoing NRG Oncology trial (GI006) which randomizes patients to PBT or IMRT. The primary endpoints of this investigation are overall survival and grade 3+ cardiopulmonary toxicity as measured by theCommon Toxicity Criteria for Adverse Events (CTCAE).

There are no moderate or high-quality studies comparing PBT to 3D conformal radiotherapy or IMRT for gastric or pancreatic cancer.

Proton beam therapy is considered investigational for the treatment of esophageal, gastric or pancreatic cancer.

Lung Cancer

Radiotherapy is used as a primary treatment for early stage non-small cell lung cancer (NSCLC), particularly when surgical resection is not an option. In the treatment of stage I medically inoperable NSCLC, a meta-analysis of studies of PBT and stereotactic body radiotherapy (SBRT) has been reported. Two-year survival rates for stage I NSCLC treated with SBRT were 70% vs 61% for PBT. The five-year survival rates were similar. Both SBRT and proton therapy were significantly better than conventional radiotherapy for stage I disease. Proton beam therapy is considered not medically necessary for small cell lung cancer and stage I NSCLC.

Radiation therapy, usually delivered with concurrent chemotherapy, is the standard of care for the treatment of unresectable stage III NSCLC. In specific cases, IMRT is needed to achieve adequate sparing of organs at risk such as the normal lung. Significant lung and esophageal toxicity are common and these toxicities have hampered attempts at dose escalation.

Proton beam therapy has been used for NSCLC in an attempt to allow dose escalation while minimizing lung and esophageal toxicity. Several institutions have reported on their experience. A systematic review by Widesott examined 17 studies. There were no prospective reports. Nine single institution studies reported on a total of 214 patients, most with stage I or II disease. Several studies focused on dose distributions and technical issues associated with PBT. They concluded that it was impossible to draw definitive conclusions about the superiority of PBT for NSCLC. A subsequent phase II trial by Chang reported encouraging results for unresectable stage III disease. A prospective

randomized trial comparing PBT with photon therapy was completed at MD Anderson Cancer Center, and final results were published in 2018. A total of 255 patients were enrolled and 149 of these were randomized. Proton therapy did not improve local control nor did it improve survival compared to IMRT. The rate of pneumonitis was higher in the proton therapy arm (11%) vs the IMRT arm (7%). This study reinforces the importance of level 1 evidence in the study of proton therapy. NRG/RTOG protocol 1308 is a randomized trial of PBT vs IMRT both with concurrent platinum based chemotherapy in stage II-IIIB non-small cell lung cancer which should provide additional data on how proton therapy compares to standard treatment.

ASTRO has published a clinical practice guideline on the use of radiation therapy for small cell lung cancer which states:

> *However, unlike non-small cell lung cancer (NSCLC), there are limited data on advanced RT techniques in SCLC treatment. Proton therapy could potentially further decrease normal tissue toxicities, but there are limited prospective data on its role in SCLC treatment. Generation of evidence is encouraged through treatment of patients in prospective clinical trials or multi-institutional registries.*
>
> *There are limited data on the role of postoperative RT for SCLC, so the recommendation on indications for RT in this setting is based on NSCLC.*

Proton beam therapy is considered not medically necessary in the treatment of lung cancer.

Lymphoma
Data on PBT for treatment for lymphoma are limited. A recent review examined the use of consolidative PBT after chemotherapy for patients with Hodgkin lymphoma. A total of 138 patients enrolled on tracking protocols or registry studies were reviewed. Forty-two percent of the patients were pediatric and received a median dose of 21 Gy equivalent. Adult patients received a median dose of 30.6 Gy equivalent. With a median follow-up of 32 months, three-year relapse-free survival was 92%. The authors concluded that early survival rates were similar to photon based therapy and the continued follow-up to assess for late effects is needed.

Data on proton therapy for non-Hodgkin lymphoma are limited. A small retrospective cohort has been reported. Eleven patients were treated between 2008 and 2014. Follow-up was 38 months. Two-year local control was 91%. Toxicities were grade 2 or less. The authors concluded that longer-term follow-up and more patients were needed to confirm their findings.

Proton beam therapy is considered not medically necessary for the treatment of Hodgkin lymphoma and non-Hodgkin lymphoma.

Ocular (Uveal) Melanoma
Curative treatment for ocular melanoma with preservation of vision can be achieved with either plaque brachytherapy or with PBT. A systematic review and meta-analysis of charged particle radiation therapy for uveal melanoma demonstrated that charged particle therapy (most commonly PBT) resulted in a lower local recurrence rate than plaque brachytherapy. Proton beam therapy also showed better outcomes in terms of retinopathy and cataract formation. Enucleation and survival were similar with PBT and brachytherapy.

Boker et al. recently compared neoadjuvant proton therapy with adjuvant ruthenium brachytherapy together with transscleral resection for large uveal melanomas. The five-year recurrence rate was 9% for proton-treated patients vs 27.5% in the ruthenium brachytherapy-treated cohort. Metastatic rates were similar as was the risk of enucleation.

Proton therapy is considered medically necessary for the treatment of uveal melanoma.

Prostate Cancer
Historically, PBT was used as a boost technique for prostate cancer due to the ability to deliver a higher dose than could be safely delivered with 2D and 3D techniques. Single institution reports of PBT dose escalation showed favorable disease- free survival and acceptable toxicity in this era. Over the past two decades, there have been significant improvements in technology allowing similar dose escalation to be achieved with IMRT.

The only randomized trial of PBT compared low dose proton boost (19.8 CGE) with high dose proton boost (28.8 CGE) after a dose of 50.4 Gy to the pelvis with x-rays. In that study, the higher dose proton boost improved biochemical recurrence- free survival but also increased the frequency of acute gastrointestinal (GI) and genitourinary (GU) toxicity. There were no significant differences in late toxicity. The study did not evaluate whether proton therapy is more efficacious or less toxic than other forms of conformal radiation.

Although there are no reports from randomized trials comparing proton therapy with IMRT and 3D conformal radiation, there have been retrospective comparative studies. In a large-scale review of outcomes based on Medicare claims data, 684 patients treated with PBT were compared with 9,437 men treated with IMRT. Follow up was 46 to 50 months and the results were propensity score matched to account for baseline characteristics. Rates of urinary incontinence, other urinary morbidity and sexual dysfunction were similar for PBT and IMRT. Compared to IMRT, patients treated with PBT had a higher rate of GI morbidity (17.8 vs 12.2 per 100 person-years). In terms of disease control, IMRT was shown to be better than conformal therapy. Proton therapy did not provide additional benefit over IMRT.

Patient-reported outcomes for 3D conformal radiotherapy, IMRT and PBT have also been reported. Using validated quality of life (QOL) instruments, a 2013 study looked at scores in the immediate post-treatment period and at 12- and 24-month follow- up visits. In the immediate post-treatment

interval, bowel QOL decreased for both 3D and IMRT treated patients but not the PBT group. At 12 and 24 months, all three groups showed decreased bowel/rectal QOL. With regard to urinary toxicity, IMRT treated patients showed decreased GU QOL in the immediate period but this had disappeared by 12 months. At 12 months, the PBT cohort demonstrated decreased urinary QOL while 3D and IMRT patients had returned to baseline. No meaningful urinary QOL changes were seen in any group at 24 months. Although timing of toxicity varied between cohorts, patients reported similar long-term QOL decrements irrespective of modality.

There is significant consensus among radiation oncologists that there is a lack of comparative effectiveness research on PBT for prostate cancer. Multiple evidence-based reviews of this topic have concluded that no clear evidence supports a benefit of proton therapy over IMRT in terms of efficacy or long-term toxicity. These include reports from the Agency for Healthcare Research and Quality (AHRQ), Hayes, the American Urologic Association, the American College of Radiology, and the ASTRO Subcommittee on Emerging Technology. In their 2017 update of the model policy on PBT, ASTRO maintains:

"In the treatment of prostate cancer, the use of PBT is evolving as the comparative efficacy evidence is still being developed. In order for an informed consensus on the role of PBT for prostate cancer to be reached, it is essential to collect further data, especially to understand how the effectiveness of proton therapy compares to other radiation 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."

Li et al. published a systematic review and meta-analysis of efficacy and safety of carbon ion therapy and proton beam therapy in the treatment of prostate cancer. A total of 33 studies were reviewed. Both proton beam therapy and carbon ion therapy had favorable efficacy and safety compared to photon therapy. GRADE assessment of the results indicated that the certainty of evidence was very low. On meta-analysis, treatment with protons or carbon ions did not significantly affect the outcomes. Authors concluded that the quantity and quality of the evidence are insufficient, and that more high-quality controlled studies are needed in the future.

The body of evidence on PBT for prostate cancer largely consists of retrospective studies performed at tertiary centers. The evidence quality is low and there are insufficient data to determine how PBT compares to standard of care photon-based therapies, which are able to achieve excellent outcomes with low toxicity.
Proton beam therapy is considered not medically necessary for the treatment of prostate cancer.

Risk Reduction
There have been multiple publications theorizing a reduced risk of second malignancies with the use of proton therapy. These generally compare dosimetric data from proton plans compared to IMRT plans and use mathematical modeling to predict the cancer risk. These models are largely untested

and there is a dearth of actual data reporting on the risk posed by scattered radiation, especially in adults.

Several studies have looked at the actual risk of second malignancy following radiotherapy and have compared this to patients who have not been irradiated. Zelefsky reported on the 10-year risk of second cancer among men with prostate cancer treated with radical prostatectomy (RP), brachytherapy (BT) and external beam radiotherapy (EBRT). The risk of developing bladder or colorectal cancer was 3% for RP, 2% for BT and 4% for EBRT at 10 years (p=0.29). For all second cancers, there was a slightly higher risk in the irradiated patients but on multivariate analysis this difference was found to be attributable to age and smoking history rather than treatment received. Another report examined the risk of second cancers after radiotherapy in three randomized trials and compared this to patients randomized to no radiotherapy. A total of 2,554 patients were analyzed who had participated in the TME trial for rectal cancer, the PORTEC-1 and PORTEC-2 trials in endometrial cancer. Although all patients in these trials were at somewhat higher risk of second malignancy than the general population, the patients who received radiotherapy had no higher probability of developing second cancers than those treated with surgery alone.

Chung et al. have reported on the incidence of second malignancy in 558 patients treated with proton therapy at the Harvard Cyclotron facility and compared this to matched controls in the Surveillance, Epidemiology, and End Results (SEER) database. The incidence of second cancers in the proton group was approximately 7 per 1000 person-years vs approximately 10 per 1000 person-years in the matched photon group (p=0.085). Limitations include different methods of data collection, lack of radiation field size and dose and the fact that 26% of the proton-treated patients were lost to follow up and second malignancy information was not available for this group. The authors conclude that the results are hypothesis generating and warrant further study.

Uncertainties of Proton Beam Therapy

The longest experience with protons has been using passively scattered beams. This technique is a robust method of proton delivery which is less sensitive to treatment and patient variables. Passive scattered protons produce neutrons and these affect surrounding tissues negatively. Newer proton beam centers use pencil beam scanning technology. This allows for more conformal treatment delivery and has been also termed intensity modulated proton therapy. Long-term follow-up with this technology is lacking. A recent review summarizes the status of IMPT declaring “currently, it is still unclear which patients will exhibit a significantly enhanced therapeutic ratio with IMPT over PSPT or IMRT.” Additionally, there are significant uncertainties about the physics and biology of protons in this setting. These include the complex interaction of scanning beams with moving tissues of different densities, less predictable dose distributions during treatment of radiosensitive HPV-positive tumors and questions about the variable radiobiologic effectiveness of protons in situ. Proton plans generally assume a uniform relative biological effectiveness (RBE) of 1.1 compared to photons. The actual RBE is dependent on the fractionation and depth. At the distal edge of the Bragg peak, RBE has been measured at more than 5 times the assumed value. The existence of this

uncertainty highlights the need for further prospective study of proton therapy, especially as treatment techniques such as pencil beam scanning continue to evolve.

Clinical Trials and Registries
There have been calls to cover the costs of PBT for patients enrolled in registry trials, but these studies lack the basic underpinning of clinical equipoise. Proton beam therapy will not be covered when the PBT is the experimental arm of a clinical trial or when used as part of a clinical registry unless criteria above are otherwise met.

FDA or Other Governmental Regulatory Approval

U.S. Food and Drug Administration (FDA)
Radiotherapy is a procedure and, therefore, not subject to U.S. Food and Drug Administration (FDA) regulations. However, the accelerators and other equipment used to generate and deliver charged-particle radiation (including proton beam) are devices that require FDA oversight. The FDA's Center for Devices and Radiological Health has indicated that the proton beam facilities constructed in the United States prior to enactment of the 1976 Medical Device Amendments were cleared for use in the treatment of human diseases on a "grandfathered" basis, while at least one that was constructed subsequently received a 510(k) marketing clearance. There are 510(k) clearances for devices used for delivery of proton beam therapy and devices considered to be accessory to treatment delivery systems, such as the Proton Therapy Multileaf Collimator (which was cleared in December 2009). Since 2001, several devices classified as medical charged-particle radiation therapy systems have received 510(k) marketing clearance. FDA product code LHN.

Rationale/Source

This medical policy was developed through consideration of peer-reviewed medical literature generally recognized by the relevant medical community, U.S. Food and Drug Administration approval status, nationally accepted standards of medical practice and accepted standards of medical practice in this community, technology evaluation centers, reference to federal regulations, other plan medical policies, and accredited national guidelines.

Supplemental Information

Practice Guidelines and Position Statements
Guidelines or position statements will be considered for inclusion in 'Supplemental Information' if they were issued by, or jointly by, a US professional society, an international society with US representation, or National Institute for Health and Care Excellence (NICE). Priority will be given to guidelines that are informed by a systematic review, include strength of evidence ratings, and include a description of management of conflict of interest.

International Particle Therapy Co-operative Group
A 2016 consensus statement by the International Particle Therapy Co-operative Group (PTCOG) offered the following conclusion about 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...."

In 2021, PTCOG published consensus guidelines on particle therapy for the management of head and neck cancer. The following recommendations were made:

- Nasopharynx: "Consider proton therapy whenever feasible. Most advanced treatment, imaging, and adaptation techniques should be used to minimize risk of neurotoxicity, given anatomic location."
- Reirradiation: "Careful evaluation required for each patient to determine risks/benefits of reirradiation. Enrollment in clinical trial encouraged whenever possible."
- Sinonasal: "Consider proton therapy whenever feasible. Most advanced treatment, imaging, and adaptation techniques should be used to minimize risk of neurotoxicity, given anatomic location."
- Postoperative: "Consider proton therapy whenever feasible. Enrollment in clinical trial encouraged whenever possible."
- Oropharynx: "Consider proton therapy whenever feasible. Enrollment in clinical trial encouraged whenever possible."

American College of Radiology

The 2014 guidelines from the American College of Radiology on external-beam radiotherapy in stage T1 and T2 prostate cancer stated:

- "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."

American Urological Association et al

In 2022, the American Urological Association (AUA) and American Society for Radiation Oncology (ASTRO) published evidence-based guidelines for the management of clinically localized prostate cancer. Part III of the guideline discusses principles of radiation therapy. Regarding the use of proton therapy, the guidelines state the following: "Clinicians may counsel patients with prostate cancer that proton therapy is a treatment option, but it has not been shown to be superior to other radiation modalities in terms of toxicity profile and cancer outcomes. (Conditional Recommendation; Evidence Level: Grade C)" The guidelines additionally note that while dosimetric studies have indicated that proton therapy can deliver lower integral and mean doses to normal tissues, it has not been established whether these dosimetric differences translate to fewer side effects or improvements in quality of life.

National Comprehensive Cancer Network
Uveal Melanoma
National Comprehensive Cancer Network (NCCN) guidelines for uveal melanoma (v.1.2023) support the use of particle beam therapy for definitive radiotherapy of the primary tumor and that its use is appropriate as upfront therapy after diagnosis, after margin-positive enucleation, or for intraocular or orbital recurrence. Treatment recommendations for intraocular tumors include:

- "Using protons, 50-70 cobalt Gray equivalent (CGyE) in 4-5 fractions should be prescribed to encompass the target volume surrounding the tumor.
- Using carbon ions, 60-85 CGyE in 5 fractions should be prescribed to encompass the target volume surrounding the tumor."

Prostate Cancer
NCCN guidelines for prostate cancer (v.3.2024) offer the following conclusion on proton therapy: "The NCCN panel believes no clear evidence supports a benefit or decrement to proton therapy over IMRT [intensity-modulated radiotherapy] 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." The NCCN adds that a prospective randomized trial comparing prostate PBT with x-ray-based IMRT is ongoing and may help to elucidate outcomes, as the evidence to date has not demonstrated a significant difference in benefit, particularly in regard to short and long-term toxicities. The NCCN acknowledges that PBT may deliver less radiation to surrounding tissues (eg, muscle, bone, vessels, fat), but that these tissues do not routinely contribute to the morbidity of prostate radiation. Of greater clinical relevance, is the volume of rectum and bladder that is exposed to radiation. Higher volume, lower dose exposures may minimize risk of long-term treatment morbidity. While in silico dosimetric studies have suggested that the right treatment can make an IMRT plan more favorable compared to a proton therapy plan or vice versa, these studies often do not accurately predict clinically meaningful endpoints.

Non-Small-Cell Lung Cancer
NCCN guidelines for non-small cell lung cancer (NSCLC) (v.4.2024) offer the following recommendations: "[Radiation therapy] has a potential role in all stages of NSCLC as either definitive or palliative therapy... More advanced techniques are appropriate when needed to deliver curative [radiation therapy] safely. These techniques include (but are not limited to) 4D-CT and/or PET/CT stimulation, IMRT/VMAT, motion management, and proton therapy... Image-guided radiation therapy is recommended when using proton with steep dose gradients around the target, when [organs at risk] are in close proximity to high-dose regions, and when using complex motion management techniques." Highly conformal radiation therapies, such as proton therapy, can be used in the setting of prior radiation therapy, potentially with hyperfractionation, to reduce the risk of toxicity. In patients with high-risk N2 disease (eg, extracapsular extension, multi-station involvement, inadequate lymph node dissection/sampling, and/or refusal or intolerance of adjuvant systemic therapy), or those with advanced/metastatic NSCLC or receiving palliative radiotherapy at

higher doses (>30 Gy), technologies to reduce normal tissue irradiation such as IMRT or proton therapy are preferred.

Head and Neck Cancer
NCCN guidelines for head and neck cancers (v.3.2024) indicate that proton therapy may be used per the discretion of the treating physician but is an active area of investigation. Proton therapy may be considered when normal tissue constraints cannot be met by photon-based therapy. Otherwise, IMRT or 3D conformal RT is recommended. The safety and efficacy of PBT when highly conformal dose distributions are important has been established, and is particularly important for patient with primary periocular tumors, tumors invading the orbit, skull base, cavernous sinus, and for patients with intracranial extension or perineural invasion. These treatment approaches are recommended for those being treated with curative intent and/or those with long life expectancies following treatment. However, NCCN adds that without "high-quality prospective comparative data, it is premature to conclude that proton therapy has been established as superior to other established radiation techniques such as IMRT, particularly with regard to tumor control."

American Society for Radiation Oncology
ASTRO (2022) updated its model policy on the medical necessity requirements for the use of proton therapy. ASTRO deemed the following disease sites those for which the evidence frequently supports the use of proton beam therapy:

- Medically inoperable patients with a diagnosis of cancer typically treated with surgery where dose escalation is required due to the inability to receive surgery
- Ocular tumors, including intraocular melanomas
- Tumors that approach or are located at the base of the skull, including but not limited to chordoma and chondrosarcomas
- 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 cancer and intra-hepatic biliary cancers
- Primary malignant or benign bone tumors
- Primary or benign solid tumors in children treated with curative intent and occasional palliative treatment of childhood tumors
- Patients with genetic syndromes making total volume of radiation minimization crucial such as but not limited to NF-1 patients, deleterious ataxia telangiectasia mutated *(*ATM) mutations, Li-Fraumeni, and retinoblastoma patients
- Malignant and benign primary central nervous system tumors (excluding isocitrate dehydrogenase [IDH] wild-type glioblastoma multiforme [GBM])
- Advanced (eg, T4) and/or unresectable head and neck cancers
- Cancers of the nasopharynx, nasal cavity, paranasal sinuses and other accessory sinuses
- Nonmetastatic retroperitoneal sarcomas
- Re-irradiation cases (where cumulative critical structure dose would exceed tolerance dose).
- Primary cancers of the esophagus

- Primary tumors of the mediastinum, including thymic tumors, mediastinal tumors, mediastinal lymphomas and thoracic sarcomas
- Malignant pleural mesothelioma
- Primary and metastatic tumors requiring craniospinal irradiation
- Advanced and unresectable pelvic tumors with significant pelvic and/or peri-aortic nodal disease
- Patient with a single kidney or transplanted pelvic kidney with treatment of an adjacent target volume and in whom maximal avoidance of the organ is critical

U.S. Preventive Services Task Force Recommendations
Not applicable.

Medicare National Coverage
There is no national coverage determination. In the absence of a national coverage determination, coverage decisions are left to the discretion of local Medicare carriers.

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Policy History

Original Effective Date: 10/01/2025
Current Effective Date: 10/01/2025
07/15/2025 Utilization Management Committee review/approval. New policy.
Next Scheduled Review Date: 07/2026

Coding

The five character codes included in the Health Plan Medical Policy Coverage Guidelines are obtained from Current Procedural Terminology (CPT®)‡, copyright 2025 by the American Medical Association (AMA). CPT is developed by the AMA as a listing of descriptive terms and five character identifying codes and modifiers for reporting medical services and procedures performed by physician.

The responsibility for the content of the Health Plan Medical Policy Coverage Guidelines is with the Health Plan and no endorsement by the AMA is intended or should be implied. The AMA disclaims responsibility for any consequences or liability attributable or related to any use, nonuse or interpretation of information contained in the Health Plan Medical Policy Coverage Guidelines. Fee schedules, relative value units, conversion factors and/or related components are not assigned by the AMA, are not part of CPT, and the AMA is not recommending their use. The AMA does not directly or indirectly practice medicine or dispense medical services. The AMA assumes no liability for data contained or not contained herein. Any use of CPT outside of the Health Plan Medical Policy Coverage Guidelines should refer to the most current Current Procedural Terminology which

contains the complete and most current listing of CPT codes and descriptive terms. Applicable FARS/DFARS apply.

Codes used to identify services associated with this policy may include (but may not be limited to) the following:

Code Type	Code
CPT	77520, 77522, 77523, 77525
HCPCS	No codes
ICD-10 Diagnosis	All related diagnoses

**Medically Necessary (or "Medical Necessity") - Health care services, treatment, procedures, equipment, drugs, devices, items or supplies that a Provider, exercising prudent clinical judgment, would provide to a patient for the purpose of preventing, evaluating, diagnosing or treating an illness, injury, disease or its symptoms, and that are:

A. In accordance with nationally accepted standards of medical practice;
B. Clinically appropriate, in terms of type, frequency, extent, level of care, site and duration, and considered effective for the patient's illness, injury or disease; and
C. Not primarily for the personal comfort or convenience of the patient, physician or other health care provider, and not more costly than an alternative service or sequence of services at least as likely to produce equivalent therapeutic or diagnostic results as to the diagnosis or treatment of that patient's illness, injury or disease.

For these purposes, "nationally accepted standards of medical practice" means standards that are based on credible scientific evidence published in peer-reviewed medical literature generally recognized by the relevant medical community, Physician Specialty Society recommendations and the views of Physicians practicing in relevant clinical areas and any other relevant factors.

NOTICE: If the Patient's health insurance contract contains language that differs from the Health Plan's Medical Policy definition noted above, the definition in the health insurance contract will be relied upon for specific coverage determinations.

NOTICE: Medical Policies are scientific based opinions, provided solely for coverage and informational purposes. Medical Policies should not be construed to suggest that the Health Plan recommends, advocates, requires, encourages, or discourages any particular treatment, procedure, or service, or any particular course of treatment, procedure, or service.

NOTICE: Federal and State law, as well as contract language, including definitions and specific contract provisions/exclusions, take precedence over Medical Policy and must be considered first in determining eligibility for coverage.

Medicare Advantage Members
Established coverage criteria for Medicare Advantage members can be found in Medicare coverage guidelines in statutes, regulations, National Coverage Determinations (NCD)s, and Local Coverage Determinations (LCD)s. To determine if a National or Local Coverage Determination addresses coverage for a specific service, refer to the Medicare Coverage Database at the following link: https://www.cms.gov/medicare-coverage-database/search.aspx. You may wish to review the Guide to the MCD Search here: https://www.cms.gov/medicare-coverage-database/help/mcd-benehelp.aspx.

When coverage criteria are not fully established in applicable Medicare statutes, regulations, NCDs or LCDs, internal coverage criteria may be developed. This policy is to serve as the summary of evidence, a list of resources and an explanation of the rationale that supports the adoption of this internal coverage criteria.

InterQual®
Interqual® is utilized as a source of medical evidence to support medical necessity and level of care decisions. InterQual® criteria are intended to be used in connection with the independent professional medical judgment of a qualified health care provider. InterQual® criteria are clinically based on best practice, clinical data, and medical literature. The criteria are updated continually and released annually. InterQual® criteria are a first-level screening tool to assist in determining if the proposed services are clinically indicated and provided in the appropriate level or whether further evaluation is required. The utilization review staff does the first-level screening. If the criteria are met, the case is approved; if the criteria are not met, the case is referred to the medical director.