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March 30, 2018

Re: eviCore Radiation Clinical Guidelines effective April 1, 2018

[INSERT PAYOR]

Dr. [INSERT PLAN MEDICAL DIRECTOR]:

We are writing in response to the eviCore recently released Radiation Clinical Guidelines on Proton Beam Therapy (PBT) ("Clinical Guidelines") that are to become effective as of April 1, 2018. As the leaders in the field of proton beam treatment delivery, we are very concerned with the Clinical Guidelines as currently written. The Clinical Guidelines are very limited in scope with respect to disease sites for which eviCore has determined proton beam therapy is medically necessary. ***It is our opinion that the conclusions drawn in the Clinical Guidelines are based on older evidence, misinterpretation of evidence, and omission of recent evidence.*** In addition, the findings in the document are often in conflict with the National Comprehensive Care Network (NCCN) Guidelines and/or the American Society for Radiation Oncology (ASTRO) Proton Beam Therapy Model Policy. ***As the health plan who is ultimately responsible for the members you are covering (or administering coverage for), we are requesting that you promptly review this information, update your policy, and take other appropriate corrective actions to ensure that this vital therapy is available as an option where clinically appropriate for patients facing cancer.***

We have set forth below our observations and recommendations on the Key Clinical Points and disease site recommendations in the Clinical Guidelines. In support of our recommendations, we have also included a list of citations by disease site in Appendix A.

KEY CLINICAL POINTS

In the Clinical Guidelines, eviCore cites Brada et al. (2009) and Olsen et al.(2007) to support its positions that the "rationale for PBT is often associated with a low level of evidence" and that "there is insufficient data clearly demonstrating its benefit over conventional forms of radiation therapy". We strongly disagree with this broad generalization for a number of reasons. First, the Clinical Guidelines do not cite a specific "evidentiary standard" upon which to base its "low level" characterization. Second, there have been and continue to be many clinical trials that address the use of proton beam therapy for individual disease sites and coverage policies by payers on proton beam therapy and other radiation oncology modalities are ultimately determined by disease site, not at a higher level. Third, Poonacha et al. found that less than 20% of NCCN Guidelines are based upon high-levels of evidence. (Poonacha et al., 2011) Fourth, there is a major failing in the quality of evidence cited and in the age of the evidence as demonstrated by the following key points:

- The two articles cited (Brada et al. and Olsen et al.) in the Clinical Guidelines to support their broader position on proton beam therapy are nine and eleven years old respectively;
- The Clinical Guidelines only have a limited number of references (88) compared to the ASTRO Proton Beam Therapy Model Policy (196), and the National Association for Proton Therapy (NAPT) Model Policy (802);

- The vast majority of the evidence cited in the Clinical Guidelines is from 2014 or earlier; and
- Only two NCCN guidelines are cited in the Clinical Guidelines, omitting at least 8 NCCN guidelines that reference utilization of proton beam therapy.

While we agree that continued evidence development is important, protons have a similar evidentiary basis to other interventions in routine oncologic practice that eviCore recommends and the evidence used to make the broad clinical recommendations in the Clinical Guidelines is not current or of high quality.

The guideline cites the Gunther et al.:

> *A recent retrospective analysis (Gunther et al., 2015) compared outcomes in pediatric patients who underwent proton therapy and intensity-modulated radiation therapy (IMRT) for ependymoma and found increased rates of post-radiation magnetic resonance imaging (MRI) changes, and neurologic deficits from brainstem necrosis in those who underwent proton therapy vs. IMRT.*

While the paper highlighted higher incidence in asymptomatic imaging changes with proton therapy relative to IMRT, the rates of symptomatic imaging changes were not different in the IMRT versus the proton therapy cohort (3 of 35 vs. 4 of 37). (Gunther et al., 2015) In addition, Gentile et al. specifically addressed serious toxicity, brainstem injury, in pediatric patients with posterior fossa tumors and show no increased rate of brainstem injury with protons compared to photons. (Gentile et al., 2018) Rates from both types of radiation are quite low actually, <2% incidence.

The guideline also cites the ASTRO evidence-based review of PBT (presumably from 2012) in support of its position of low-level of evidence on proton beam therapy. This evaluation was published nearly six years ago and the body of clinical evidence on the benefits of proton beam therapy for selected indications has grown dramatically during that time with over 430 articles published. More importantly, ASTRO has published at least two iterations of its model policy since that assessment was completed including the most recent version published in June 2017 which includes "malignant and benign primary CNS tumors" and "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" as disease sites that support the use of proton beam therapy. (ASTRO, 2017)

CENTRAL NERVOUS SYSTEM

The Clinical Guidelines does not specifically list treatment of CNS tumors in its indications for which proton beam therapy is considered medically necessary and as such, it falls under the category of "experimental, investigational, and/or unproven". We strongly disagree with this decision, particularly given (a) the position taken by the National Comprehensive Care Network Guidelines and the ASTRO Model Policy on treatment of CNS tumors and (b) the inaccuracies and omission of critical evidence in its review.

In its discussion on secondary malignancies after cranial irradiation with SRS, the guideline discusses the 2007 study by Rowe et al. on 5,000 patients but cites the wrong study (Kollmeier et al.). More importantly, while the guideline outlines limitations of other studies such as Chung et al., it does not discuss the corresponding limitations of the Rowe et al. study:

- Limited follow-up of patients on this epidemiologic study (median follow-up of the 4,877 patients was 5.2 years; 2,438 patients had less than 5.2 years of follow-up and only 364 patients had longer than 15 years follow-up)
- Study was only able to capture malignant secondary tumors and could not account for secondary tumors labeled as benign

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

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

While the tumors noted above in A are extremely rare tumors in adults, studies have shown substantial improvements in outcomes with proton compared to photon craniospinal radiation in patients with medulloblastoma. (Brown et al., 2013) With proton craniospinal radiation, patients have significantly less weight loss (16% vs 64%), less grade 2 nausea and vomiting (26% vs 71%), and less esophagitis (5% vs 57%). Even more importantly, since protons significantly reduces mean vertebral doses, there is significantly less reductions in blood counts with protons (white blood cells, P=.04; hemoglobin, P=.009; platelets, P=.05). This benefit of proton therapy is of particular significance, as chemotherapy has been shown to improve survival when given with radiation, so maintaining blood counts after radiotherapy is incredibly important as it allows delivery of full doses of chemotherapy.

With respect to IDH mutant tumors and 1p19q co-deleted tumors, patients have an excellent prognosis with survival times often measured in decades. (Buckner et al., 2016) With the excellent prognosis for this patient population, decreasing radiation doses to normal uninvolved brain is essential to preserve cognitive function. Numerous studies have examined the threshold dose for increased risk of cognitive dysfunction and the impact of moderate radiation doses to the brain including to the hippocampus. (Moore et al, 2013; Gondi et al., 2013) A phase II trial serially evaluating the cognitive function of patients with low grade gliomas found stable cognitive function years after proton radiotherapy. (Shih et al., 2015) These studies support the use of proton therapy to decrease the cognitive risks of radiotherapy in this good prognosis patient population.

Given the evidence discussed above as well as the positions taken by the NCCN Guideline as well as the ASTRO Model Policy from 2017, we urge you to revise your clinical guidelines to include coverage for malignant and benign tumors and for re-irradiation where treatment with proton therapy can significantly limit volume of normal brain parenchyma.

ESOPHAGUS

According to the Clinical Guidelines as currently written, proton beam therapy for the treatment of esophageal cancer is not specifically addressed and as such, it falls under the category of "experimental, investigational, and/or unproven". We disagree with this position, particularly given the evidence on dosimetric and clinical benefit of proton therapy.

Lin et al. studied the whether the type of radiation therapy modality – 3D conformal RT (3DCRT), IMRT, or proton beam therapy – used for neoadjuvant chemoradiation was associated with different postoperative outcomes. (Lin et al., 2017) The study found that the type of RT modality was statistically significantly associated with the average length of stay (13.2 days for 3DCRT, 11.6 days for IMRT, and 9.3 days for PBT) as well as for the incidence of cardiac, pulmonary, and wound complications. It also found that the 90-day post-operative mortality rates were lowest for PBT compared to IMRT and 3DCRT (0.9% versus 4.3% and 4.2%). Proton beam therapy displayed the greatest benefit in a number of clinical endpoints. These findings are consistent with Wang et al. who found an increase in post-operative pulmonary and gastrointestinal complications in patients treated with 3D conformal RT versus IMRT and proton beam. (Wang et al., 2013)

Analyzing IMRT versus proton beam therapy, Xi et al. examined the clinical outcomes of patients with esophageal cancer who were treated with chemoradiotherapy. (Xi et al., 2017) The study retrospectively analyzed 132 patients who had received proton beam therapy versus 211 patients receiving IMRT. Patients receiving proton beam therapy had significantly better progression-free survival (P=0.001), distant metastasis-

free survival (*P*=0.031) and overall survival (*P*=0.11). When further analyzing by clinical stage, the five-year OS and PFS rates were still significantly higher for proton beam therapy patients with stage III disease.

Davuluri et al. examined the extent to which lymphopenia had an impact on patient survival. (Davuluri et al., 2017) The study found that grade 4 (G4) nadir was associated with poor outcomes including statistically significant difference (*P*=0.027) in overall survival rate compared to G0-2 nadir (median OS of 2.8 versus 5.0 years respectively). Fang et al. assessed the lymphocyte-sparing effect of proton beam therapy versus IMRT in patients treated with definitive chemoradiation for esophageal cancer. A higher percent of IMRT patients had G4 lymphopenia compared to proton beam therapy (60.5% versus 39.5%) (P=0.001); the study also found that patients with Grade 4 lymphopenia had a higher – on average – planning treatment volume.

Given the evidence on the clinical benefits of proton beam therapy, we urge you to revise your Clinical Guidelines to include coverage for esophageal cancer.

HEAD AND NECK

The Clinical Guidelines stated that there is insufficient data to consider proton beam therapy for head and neck cancers medically necessary and as such, cases would be considered on a case-by-case basis. We strongly disagree with this position given the evidence and given the position taken in the latest versions of the NCCN Clinical Guidelines and ASTRO Proton Beam Therapy Model Policy.

In its discussion of head and neck cancers, the Clinical Guidelines cite the ASTRO Emerging Technology Committee report as supporting its position that there is insufficient evidence to support proton beam therapy. As discussed above, this ASTRO evaluation was published nearly six years ago and the body of clinical evidence on the benefits of proton beam therapy for selected indications has grown dramatically during that time. More importantly, ASTRO has published at least two iterations of its proton beam therapy model policy since that assessment was completed including the most recent version published in June 2017 which includes advanced (e.g., T4) and/or unresectable head and neck cancers in Group 1 and non-T4 and resectable head and neck cancers in Group 2. (ASTRO, 2017)

The NCCN is continuously reviewing its evidence, regularly updating the clinical guidelines by disease site. In the latest version of the NCCN Guidelines on Head & Neck Cancer, the guideline states the following on proton beam therapy:

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

The NCCN guidelines cite 21 different clinical articles in support of the position on proton beam therapy. It also notes that proton beam therapy is the predominant particle therapy under continued clinical investigation in the United States.

In its discussion of the promise of proton beam therapy for head and neck cancers, the Clinical Guidelines cite review by Holliday and Frank published in 2014. An updated version of the review of proton beam therapy for head and neck cancers was published in 2018. (Blanchard et al., 2018)

> *Proton therapy represents the latest technical improvement of radiation therapy, and has demonstrated clinical efficacy and the potential for toxicity reduction compared with photon therapy. Per National Comprehensive Cancer Network guidelines, proton therapy is a standard of care for base of skull tumors and is an option for periorbital tumors. The use of proton therapy is*

> *expanding for other head and neck tumor sites as well. Novel forms of proton therapy such as IMPT, and technical improvements in dose modeling, patient setup, image guidance and radiobiology, will help further enhance the benefits of proton therapy. Prospective studies are underway to quantify the benefits of proton therapy and to better predict patient response and toxicity within the framework of personalized medicine.*

The Clinical Guidelines note that there is insufficient data to make the determination of medical necessity more broadly for head and neck cancers. The challenge is that randomized clinical trials are not possible on any tumor type for head and neck cancers other than oropharyngeal tumors (which are currently underway).

While we appreciate that eviCore has determined that proton beam therapy for chordomas and chondrosarcomas of the skull base is medically necessary, we urge you to broaden your indications to peri-orbital, skull base, nasopharynx, oropharynx, para-nasal sinus tumors, re-irradiation, and salivary gland tumors. The evidence discussed above and the support of proton beam therapy by the NCCN Guidelines clearly demonstrates that protons are safe and effective for head and neck cancers.

HEPATOCELLULAR

The Clinical Guidelines state that proton beam therapy is medically necessary in select cases of localized unresectable hepatocellular carcinoma (HCC), specifically for patients who are "not optimally treated with radiofrequency ablation or SBRT". We disagree with the limited scenarios during which proton beam therapy is considered medically necessary as the evidence supports broader coverage.

Charged particle therapy, including proton beam therapy, has been assessed in both retrospective and prospective trials in primary hepatic malignancies. The properties of proton beam therapy - rapid energy deposition at the end of range followed by sharp dose fall-off – enable delivery of increasing doses of radiotherapy to a given target while still minimizing dose received by surrounding areas, making it particularly intriguing treatment modality for both HCC and intrahepatic cholangiocarcinoma (ICC). A retrospective comparison of proton and photon treatment plans found that proton therapy was associated with increased sparing of normal tissues. (Wang et al., 2008)

Hong et al. conducted a Phase II, multi-institutional study to evaluate the efficacy and safety of high-dose, hypofractionated proton beam therapy for HCC and ICC. In the study, the dose schema was tailored to ensure that the mean liver dose was less than or equal to 24 GyE. The outcome of the study was an 2-year overall survival rate of 63.2% and 45.8% for HCC and ICC respectively, and 2-year local control rates of 94.8% and 93.1% respectively for HCC and ICC. (Hong et al., 2016) Treatment was well-tolerated with the dosing approach deployed with only 3 patients (3.6%) having a decline in Child-Pugh score from CP A to CP B, and only four patients (4.8%) having a grade ≥ 3 toxicity.

Given the evidence on the clinical benefits of proton beam therapy, we urge you to revise your Clinical Guidelines to include coverage for ICC and allow for broader set of criteria for coverage for HCC.

LUNG

According to the April 2018 Clinical Guidelines as currently written, proton beam therapy for the treatment of lung cancer is not specifically addressed and as such, it falls under the category of "experimental, investigational, and/or unproven". We disagree with this position, particularly given the evidence to support the use of proton beam therapy for the treatment of non-small cell lung cancer (NSCLC).

In the Clinical Guidelines, it cited Grutters et al. and found that "[t]he report concluded that the evidence is insufficient to permit conclusions about the results of PBT for any stage of NSCLC." It is important to note that (a) the statement is taken from a paragraph that only discusses Stage I lung cancer and it is not based on the data within that paragraph but rather from an indirect meta-analysis. If eviCore seeks to address the use of proton

beam therapy for Stage I cancer, there is agreement that there is very little prospective data. The specific reasons to use proton beam therapy in this setting are often patient-specific, such as a posteriorly located Stage I lung cancer near the spinal cord, near a critical structure adjacent to previously irradiated lung cancer, or another critical location where one needs to avoid a threshold dose to a critical structure (e.g., a patient with severe lung disease at risk of pneumonitis). Such cases should be addressed on a case-by-case status. As such, we recommend that the appropriate standard would be for protons to be considered where standard SBRT is contra-indicated or felt to be high risk (for example central location) based upon the prospective single arm data suggesting a greater safety profile for protons in this setting. (Bush et al., 2013)

The Clinical Guidelines also state that "[i]n the absence of randomized controlled trials, the comparative effectiveness of PBT and SBRT is uncertain." As with the citation above, this statement is specifically referring to Stage I lung cancer. We agree that decisions on use of proton beam therapy for Stage I lung cancer should be reviewed on a case-by-case basis. However, it is important to note that requiring a randomized trial to compare proton beam to photon-based SBRT in this setting is not realistic. In addition, similar attempts to compare SBRT to surgery and SBRT to standard photon RT in the randomized setting have failed and SBRT is an approved indication as per eviCore policy for Stage I lung cancer (see page 118 of the Clinical Guidelines). While it is medically appropriate for SBRT to be approved for this indication, but it is inconsistent to hold proton beam radiotherapy to a higher standard than SBRT. Specific cases where proton beam may be helpful in the management of Stage I lung cancer include tumor near the spinal cord, near a previously irradiated lung cancer, and/or adjacent to a critical structure (spinal cord, bronchus, esophagus, etc).

In discussing locally advanced NSCLC, the Clinical Guidelines state the following:

> "At this time, there are only three published clinical trials (phase I and II) on PBT for locally advanced NSCLC. This is insufficient to consider PBT standard therapy for lung cancer (Chang et al., 2011; Hoppe et al., 2012; Jiang et al., 2012). A phase III trial comparing proton beam radiation therapy vs. photon beam radiotherapy is currently accruing patients (RTOG 1308). Therefore, at this time, PBT is considered EIU in the treatment of lung cancer."

We strongly disagree with this position based on the current level of evidence. Chang et al. published long-term results of a prospective phase II study in 2017 in which the median overall survival was 26.5 months and the 5-year overall survival was 29%, which is amongst the highest reported rates to date in this patient population. (Chang et al., 2017) Additionally, the primary analysis of the RTOG 0617 randomized trial of 60Gy v 74Gy identified heart dose as a significant predictor of mortality. (Bradley et al., 2015) Other studies have confirmed this finding. (Dess et al., 2017; Wang et al., 2017) Multiple studies have demonstrated that protons significantly reduce cardiac dose when compared with photon based approaches in locally advanced NSCLC. (Zhang et al., 2010; Chang et al., 2017) As such, there are at least 3 ongoing current clinical trials that address proton beam therapy for unresectable stage III NSCLC. RTOG 1308 is a phase III randomized trial comparing proton beam to photon beam radiation therapy with concurrent chemotherapy. There are two other ongoing phase II trials that use a hypofractionated regimen (i.e. 60 Gy in 15 fractions) with and without concurrent chemotherapy, respectively, based on encouraging Phase I results. ***With these results and on-going studies, proton therapy should NOT be considered experimental (EIU) in this setting and the clinical guidelines (coverage policy) should cover patients who are enrolled on these prospective clinical trials.***

Finally, the Clinical Guidelines are silent on patients with recurrent lung cancer within a previously irradiated volume. Proton beam should be considered medically necessary in this setting. There are multiple emerging sources of data showing that protons achieve fairly high rates of local control in this patient population. Such patients have not been typically considered for re-irradiation because the photon-based technology was not adequate and toxicity was high. Proton beam therapy can achieve local control at low rates of toxicity and should be available to patients with local-regional only disease. Achieving local control in such patients is very important for both potential cure and quality of life. ***Given that there is NO alternate modality to provide local control in this setting as both surgery and photon-based radiation are usually contraindicated, protons should be covered for these patients.***

LYMPHOMA

According to the Clinical Guidelines as currently written, proton beam therapy for the treatment of lymphoma is not specifically addressed and as such, it falls under the category of "experimental, investigational, and/or unproven". We disagree with this position, particularly given eviCore's recommendation to cover Stage IIA Seminoma due to a higher risk of secondary malignancy.

The expected cure rates for patients with mediastinal Hodgkin lymphoma treated with chemotherapy and radiotherapy is 80%. Consequently, there are a large number of long-term (i.e., 20+ years) survivors of mediastinal lymphoma, who have subsequently developed significant late toxicities from their earlier treatment. A study by Oeffinger et al., published in 2006, demonstrated that mediastinal lymphoma survivors are at the highest risk of developing grade 3 or higher late effects at approximately 40% twenty-five years following treatment. In a 2011 follow-up study, Castellino et al. demonstrated a 25% rate of development of a secondary cancer and a 10% rate of serious cardiac problem twenty-five years following treatment, attributed for the most part to the radiation to their mediastinum.

A number of other studies have investigated risk factors among mediastinal lymphoma survivors that might predict for increased risk of cardiac problems and secondary cancers. The studies have all demonstrated a direct correlation with radiation dose to the affected organ and subsequent problem (i.e., cardiac problem = heart, breast cancer = breast, lung cancer = lung, etc.). Increased risks of these serious problems have been shown to occur with even low doses of radiation, including doses as low as 4Gy to the breast being associated with increased risk of breast cancer, 5 Gy to the lung being associated with increased risk of lung cancer, and 5 Gy to the heart being associated with increased cardiac death. (Travis et al., 2003; Travis et al., 2002; Tukenova et al., 2010)

Although radiation oncologists do not seek to purposely irradiate normal organs and tissue outside of the targeted treatment volume, unintentional irradiation of the breasts, heart, lung, esophagus, etc. occurs due to the properties of conventional photon (X-ray) radiation. Although more conformal radiation techniques using photons exist (such as IMRT, rapid arc, tomotherapy), these techniques actually just redistribute the radiation to other areas of the body that would not have been otherwise irradiated. Thus, many have suggested caution with IMRT and volumetric modulated arc therapy (VMAT) in Hodgkin's Lymphoma, since it may actually increase the risk of a secondary cancer compared with conventional 3DCRT. (De Sanctis V et al., 2012) On the other hand, proton therapy has been shown to consistently decrease the volume of normal tissue irradiated. Specifically, in the mediastinum, proton therapy can substantially reduce the radiation dose to the heart, lung, breasts, and esophagus compared with either IMRT or 3DCRT. In a prospective study, evaluating 20 patients with lymphoma involving the mediastinum, all 20 patients received lower doses to the major organs with proton therapy compared with other techniques. (Hoppe et al., 2012) A recent study from Copenhagen reported that proton therapy was the superior modern technique to treat mediastinal lymphoma involving the mediastinum with the fewest life years lost as assessed by expected radiation toxicity compared with either 3DCRT or VMAT. (Maraldo et al., 2013) Other studies have also confirmed these findings (Knausl B et al., 2013).

There is clinical data available demonstrating fewer secondary cancers among patients treated with proton therapy. Chung et al. recently reported on patients treated at Massachusetts General Hospital (MGH) with proton therapy had significantly less risk (half the number) of secondary cancers compared with patients in the SEER registry.

Based on its regular review of available data, the NCCN guideline committee for Hodgkin Lymphoma endorsed the use of proton therapy for Hodgkin Lymphoma to reduce the radiation dose to the major organs at risk, specifically stating the following:

> "Treatment with photons, electrons, or ***protons*** may all be appropriate, depending on clinical circumstances. Advanced radiation therapy technologies such as IMRT, breath hold or respiratory gating, image-guided therapy, or ***proton therapy*** may offer significant and clinically relevant

> advantages in specific instances to spare important OARs such as the heart (including coronary arteries, valves and left ventricle), lungs, kidneys, spinal cord, esophagus, carotid artery, bone marrow, breasts, stomach, muscle/soft tissue, and salivary glands and decrease the risk for late, normal tissue damage while still achieving the primary goal of local tumor control. Achieving highly conformal dose distributions is especially important for patients who are being treated with curative intent or who have long life expectancies following therapy … Randomized studies to test these concepts are unlikely to be done since these techniques are designed to decrease late effects, which take 10+ years to develop. In light of that, the modalities and techniques that are found to best reduce the doses to the OARs in a clinically meaningful way without compromising target coverage should be considered." (Version 01.2018) (Emphasis added)

In summary, many studies have demonstrated that increasing radiation dose to normal organs increases the risk of cardiac problems and secondary cancers in lymphoma survivors. Multiple studies have shown that proton therapy can substantially reduce the radiation dose to the normal organs compared with other forms of photon radiation. Therefore, proton therapy will translate to less significant problems for mediastinal lymphoma survivors. This position is endorsed by the NCCN guideline committee and most recently summarized by the PTCOG lymphoma subcommittee evidence-based review on proton therapy for lymphoma. (Tseng et al., 2017) ***Therefore, we urge you to revise your clinical guidelines to include coverage for Hodgkin and Non-Hodgkin Lymphoma involving the mediastinum or in non-mediastinal sites where proton beam therapy has the potential to reduce the risk of late effects of radiation therapy (secondary cancer, cardiovascular disease, or other chronic health conditions)***.

PANCREAS

According to the Clinical Guidelines as currently written, proton beam therapy for the treatment of pancreatic cancer is not specifically addressed and as such, it falls under the category of "experimental, investigational, and/or unproven". We disagree with this position given the evidence to support the use of proton beam therapy in selected cases.

Proton therapy has the benefit of delivering high dose to the target tumor with minimal to no exit dose in the beam path. In the case of pancreatic cancer treatment, this benefit translates to a potentially lesser dose to the adjacent duodenum, stomach, liver and small bowel, and thereby reducing both radiation-related acute and late toxicities. A dosimetric study, comparing IMRT and proton plans in patients with unresectable pancreatic cancer, showed that proton plans achieved significantly lower doses to the stomach, duodenum and small bowel in the intermediate to low dose regions compared to IMRT. (Thompson et al., 2014) Furthermore, proton plans had significantly lesser mean liver (50% reduction) and kidney (18% reduction) doses than IMRT plans.

A Phase I/ II prospective study by Hong et al. utilizing hypofractionated proton therapy (25Gy/ 5 fractions) in the neoadjuvant setting demonstrated good outcomes with minimal late toxicity. (Hong et al., 2014) Overall, in a cohort of 48 patients, they achieved a median progression free and overall survival of 10.4 and 17.3 months, respectively, with a 2-year overall survival of 42%. Out of the 48 patients, 11 patients did not have surgery. In the 37 patients who had surgery achieved a median progression-free and overall survival of 14.5 months and 27 months. Only 2 patients developed Grade 3 or higher late toxicity – one with colitis and another with chest wall pain. In another prospective study, Sachsman et al. investigated the use of proton therapy in a group of patients with unresectable pancreatic cancer who had previously received conventionally fractionated radiotherapy (59.4Gy/ 33 fractions). (Sachsman et al., 2014) This cohort of patients achieved a 2-year overall survival and freedom from local progression of 31% and 69%, indicating that proton therapy is effective in providing local control. No patients in this cohort developed Grade 3 or higher late toxicity.

For patients who had local recurrence with minimal distant disease burden, radiotherapy may be a feasible option to achieve local control. In patients who had previous radiotherapy, re-irradiation can cause significant and potentially fatal late effects, depending on the cumulative doses to the surrounding radiosensitive normal

structures. Therefore the goal during treatment planning is to maximize the dose to the tumor whilst delivering minimal to no dose to the adjacent normal tissue, which have previously been irradiated, to limit the risk of radiation-related toxicity. Although there is no literature to support the use of proton therapy in the recurrent setting, the physical property of proton with almost no exit dose after the intended target is considered to be beneficial and ideal in a patient who has had prior irradiation to the region. As a prospective study in this subgroup of patients can be a challenge to perform due to the scarcity of such patients, patient and radiation modality selection for re-irradiation are usually based on treating physicians' experience and clinical acumen. ***Based on the evidence and clinical benefits of proton beam therapy, we urge you to revise your clinical guidelines to include coverage for pancreatic cancer patients in the neoadjuvant/definitive and recurrent settings***.

PEDIATRICS

As with many other indications, the use of proton beam therapy in pediatric cases is not specifically addressed in the April 2018 clinical guidelines and as such, it falls under the category of "experimental, investigational, and/or unproven". We believe that this position is based on inaccurate interpretation of a single study and a failure to review other evidence to support coverage for certain pediatric cases including for ependymoma.

As discussed above, the Clinical Guidelines make an inaccurate interpretation of the Gunther et al. study in the Key Clinical Points section. The conclusion drawn from the study is based on imaging-based changes rather than actual clinical toxicity. In addition, the findings from this article are inconsistent with other evidence including a recently published article by Gentile et al. which found that incidence of brainstem injury in pediatric patients with posterior fossa tumors was consistent with previous reports in the photon setting. (Gentile et al., 2018) Other studies, as highlighted in the table below, suggest that proton beam therapy is associated with up to a 50% reduction in symptomatic brainstem necrosis in comparison to photon therapy.

Modality	Symptomatic Brainstem Toxicity	
	Rate	Percent
Photon		
Merchant (Lancet 2009)	3/153	2.0%
SATO (Cancer 2017)	3/38	7.9%
Nanda (Int J Radiat Oncol Biol Phys 2017)	5/16	31.3%
Subtotal	***11/207***	***5.3%***
Proton		
Macdonald (Neuro Oncol 2013)	0/70	0.0%
SATO (Cancer 2017)	3/41	7.3%
Ares (J Neurooncol 2016)	1/50	2.0%
Subtotal	***4/161***	***2.5%***

It is also important to understand that in the largest single institution series of children treated with ependymoma, the patients received proton beam therapy. Findings from this series included disease control *comparable to photon therapy* and no unexpected toxicity due to the therapy. (Indelicato et al., 2017)

We urge you to revise your clinical guidelines to include coverage for solid tumors for children up to the age of 18.

PROSTATE

The April 2018 clinical guidelines state that proton beam therapy is considered not medically necessary for the treatment of newly diagnosed prostate cancer and is considered experimental, investigational, and/or unproven

for the treatment of prostate cancer after prostatectomy. In our review of these guidelines, the document appears to contain a number of omissions of important data in the assessment of the role of proton therapy for prostate cancer. These omissions have the potential to lead to the erroneous conclusion that proton therapy is not associated with improved outcomes compared to x-ray based therapies and, as such, is not a medically necessary intervention.

We believe that currently available data demonstrate proton therapy to be a superior treatment modality based specifically, but not exclusively, on higher PSA control rates compared to x-ray based therapy without an increase in normal tissue toxicity. Proton-based radiation therapy in this setting is likely to be associated with a lower risk of secondary radiation-induced malignancy which could be particularly relevant for younger patients.

The most glaring weakness in the discussion on proton beam therapy and prostate cancer involves the age of the evidence which argues that proton therapy is not a superior modality to x-ray based therapies. Specifically, the cited publications by Brada (2007 and 2009), Olsen (2007), DeRuysscher (2012) and Efstathiou (2009) were all published based on data from first generation proton therapy facilities without taking into account the technological advances achieved in the contemporary facilities which first came online around 2006. For all intents and purposes, in our opinion, these studies should be disregarded for the evaluation of proton therapy in this setting.

The studies cited in Table 1 (see page 31) are misleading for number of reasons:

i. The publication by Zeitman (2010) reports on patients for whom protons were used only as a boost rather than as definitive treatment. Specifically, all patients received 50.4 Gy using 3DCRT to the prostate and seminal vesicles and then were randomized to receive proton boost doses of either 19.8Gy(RBE) or 28.8Gy(RBE). The reported gastrointestinal toxicity is more likely to be related to the x-ray therapy than the proton therapy. Additionally, while the 91% 5 year and 83% 10 year PSA control rates are low when compared to contemporary series, they are actually significantly higher than what was to have been expected with x-ray therapy in the era when that study accrued patients. (Kuban et al., 2008)

ii. The publication by Spratt (2013) presents the best results for patients with localized prostate cancer treated with intensity modulated radiation therapy. Of note, the high-dose arm in this study received a very high dose of 86.4 gray. While the low risk patients' 7 year PSA control rate was between 97.7 and 100%, the intermediate risk patients had a PSA control rate of 85.6%. This outcome is inferior to the study from University of Florida demonstrating a 94% PSA control rate at 5 years for intermediate risk patients treated with 78Gy(RBE) in 39 fractions. (Bryant et al., 2016) It is similarly inferior to the 93% PSA control rate at 5 years for intermediate risk patients treated with moderately hypofractionated protons to a dose of 72.5Gy(RBE) in 29 fractions. (Henderson et al., 2017) Based on this data for a large group of closely followed patients, it is reasonable to conclude that proton therapy, in fact, represents a superior modality for the treatment of intermediate risk patients. With regard to low risk patients, while all series demonstrate high PSA control rates using the Phoenix criteria for patients followed for 5 or 7 years, it is reasonable to believe that, with further follow-up, the more effective modality for intermediate risk patients (protons) will also be associated with a superior outcome for patients who are currently categorized as having low risk disease.

iii. It is not possible to fairly compare brachytherapy outcomes with external beam radiation therapy outcomes given the fact that brachytherapy toxicities are qualitatively different than those associated with external beam radiation. Specifically, the problems of urinary urgency and urge incontinence–commonly associated with brachytherapy but rarely seen with external beam therapy–are poorly evaluated by most toxicity scoring systems.

Perhaps the most problematic publication cited is the one by Sheets (2012). This study, using Medicare claims data, compared early toxicity for 421 patients treated with proton therapy and 842 matched case controls treated with IMRT. Patients were treated between 2000 and 2009. In that particular era, IMRT was a relatively new technology and it was rare to see practicing radiation oncologists willing to deliver a dose above 75.6 gray.

Virtually all of the proton patients however were treated on dose escalation protocols at the Loma Linda Center with doses in the range of 80 gray. As such, it is not surprising that a higher gastrointestinal toxicity rate would be identified in the latter group of patients. While this study is statistically valid, the conclusions are at best misleading and at worst disingenuous.

Currently in North America, it is only a small minority of radiation oncologists who are able to offer proton therapy for their patients. As such, it is not surprising that ASTRO would choose to overlook data demonstrating higher PSA control rates with protons compared to patients treated with x-rays. As such, we believe that it would be wrong to blindly accept the ASTRO "choosing wisely" campaign as a definitive evaluation of the relevance of proton therapy in the treatment of prostate cancer. It is worth noting however that the 2017 version of ASTRO Model Policy on proton beam therapy specifically *supports the use of proton therapy for prostate cancer patients* treated on prospective trials or multi-center registries.

Finally, the risk for secondary cancers after radiation for prostate cancer is also likely to be lower for proton therapy than IMRT. Yoon et al. measured secondary neutron doses in a humanoid phantom produced by scattering–mode proton-based RT and compared this with the secondary photon doses from IMRT for a prostate cancer patient. (Yoon et al., 2010) With protons, the average secondary dose 20 cm from the isocenter was 0.39 mSv/Gy with protons versus 3.11 mSv/Gy observed during IMRT – a 10 fold reduction in scatter dose. Based on this, the authors estimated that proton therapy would be associated with a fivefold reduction in the risk of radiation induced malignancy compared to treatment with IMRT. Studies looking at testosterone levels after both x-ray therapy and proton therapy offer biochemical validation of these measurements (Nichols et al., 2011; Kil et al., 2013; Nichols et al, 2017).

Given the more recent evidence on the clinical benefits of proton beam therapy that demonstrates higher PSA control rates compared to x-ray based therapy without an increase in normal tissue toxicity along with a lower risk of secondary cancers after radiation, we urge you to revise your Clinical Guidelines to include coverage for prostate cancer.

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Given the concerns about the evidence on which the Clinical Guidelines conclusions are based, we are requesting that you consider this feedback, update your coverage policy, and take other appropriate corrective actions to ensure that this vital therapy is available as an option where clinically appropriate for patients facing cancer. ***As you review and revise your policy, we encourage you to strongly consider the indications, conditions, and supporting evidence included in the most current NCCN Guidelines, the ASTRO Proton Beam Therapy Model Policy and the ADCC / NAPT / PTCOG-NA Proton Beam Therapy Model Policy***[1].

[1] Model policy from Alliance of Dedicated Cancer Centers (ADCC), Particle Therapy Cooperative Group - North America, and the National Association for Proton Therapy (NAPT)

We appreciate your consideration of our feedback on the eviCore April 2018 Radiation Clinical Guidelines on Proton Beam Therapy. Should you have any questions, please do not hesitate to contact Scott Warwick, NAPT Executive Director, at SWarwick@proton-therapy.org. In addition, we welcome the opportunity to connect you with one or more members of the proton community's clinical leadership team to discuss the available evidence, the current standard of practice and the like.

Respectfully submitted,

National Association of Proton Therapy	March 30, 2018
	Date

Supporting Physicians:

Physician Signature	UF Health Proton Therapy Institute	3/27/2018
	Organization Name	Date
Physician Signature	UT MD Anderson Cancer Center	Mar. 26, 2018
	Organization Name	Date

J. Herman, Professor and Division Head Ad Interim, Radiation Oncology

Physician Signature	UT MD Anderson Cancer Center	Mar. 26, 2018
	Organization Name	Date

A. Koong, Professor and Chair of Radiation Oncology

Physician Signature	UT MD Anderson Cancer Center	Mar. 26, 2018
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S.J. Frank, Professor, Deputy Division Head, Radiation Oncology, Medical Director, Proton Therapy Center

Physician Signature	UT MD Anderson Cancer Center	Mar. 26, 2018
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S. Lin, Associate Professor, Radiation Oncology

Physician Signature	The Roberts Proton Therapy Center	Apr. 2, 2018
	Organization Name	Date

Physician Signature	Organization Name	Date
	Mayo Clinic	3/26/18
	Mayo Clinic	3/26/2018
	Mayo Clinic	3/26/2018
	Mayo Clinic	3/26/2018
	Mayo Clinic	3/26/2018
	MAYO CLINIC	3/26/2018
	Mayo Clinic	3/26/2018
	Mayo Clinic	9/26/2018
	Mayo clinic	3/26/2018
	MAYO CLINIC	3/26/2018
	Mayo Clinic	3/26/2018
	UF Health Proton therapy Institute	3/29/18
Ben Wilkenson	Provision Proton therapy Center	3/24/2018
	University of Pennsylvania	4/1/18

Physician Signature	Organization Name	Date
	HUPTI	3/30/18
	HUPTI	3/30/18
	Texas Center for Proton Therapy	03/25/2018
	Procure Proton Therapy Center	03/25/2018
	Provision Nashville	3/25/18
	University of Florida	3/25/18
	Mayo Clinic	3/25/18
	MDA PTC	26 March 2018
	Washington University	3/26/18

APPENDIX A. CITATIONS BY DISEASE SITE

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