Randomized Trials of Proton Therapy: Why They Are at Risk, Proposed Solutions, and Implications for Evaluating Advanced Technologies to Diagnose and Treat Cancer

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Background

The National Cancer Institute (NCI) and the Patient-Centered Outcomes Research Institute (PCORI) have made major investments to fund seven randomized clinical trials evaluating the benefits and harms of proton therapy for cancers of the breast, lung, prostate, glioblastoma, esophageal, low-grade glioma, and liver. Each is open for patient enrollment. However, all are enrolling more slowly than expected.

To answer calls to evaluate the comparative effectiveness of this promising advanced medical technology,¹ essential stakeholders should come together to complete these trials. In this commentary, we explain why these trials are important, detail the principal barriers to enrollment, propose actionable solutions, and discuss implications for evaluating advanced medical technologies to diagnose and treat cancer.

Importance of Randomized Trials of Proton Therapy

Proton therapy is a type of radiation therapy for the treatment of cancer. Compared with photon (eg, x-ray) therapies, such as intensity-modulated radiation therapy, proton therapy reduces or eliminates lower radiation dose to normal tissue, possibly either enhancing effectiveness, reducing toxicity, or both. The seven trials evaluate whether proton therapy, compared with photon therapy, improves efficacy or toxicity outcomes, including overall survival and cardiovascular morbidity and mortality (Appendix Table A1, online only).

Proton therapy has greater physical and biologic uncertainties than photon-based treatments, which can, for example, translate to high radiation dose and potential biologic damage to normal tissues immediately adjacent to tumor targets. If the biologic effects of proton therapy differ substantively among various tissues in the body or if uncertainties in physical radiation dose delivery manifest clinically, we might observe expected, or unexpected, toxicity. Some studies have shown the possible benefits of proton therapy in the cancers under study; other studies have reported increased toxicity or reduced effectiveness for some patients.²⁻¹⁰ How the physical and biologic limitations of proton therapy might affect

clinical outcomes underpins the equipoise to test proton therapy in randomized trials.

In addition, the capital and operational costs of proton therapy are greater than for photon-based treatments. The average Medicare reimbursement per course of treatment is approximately \$10,000 to \$20,000 greater for proton therapy than for photon-based intensity-modulated radiation therapy depending on indication¹¹⁻¹⁴; the difference in spending per treatment course is greater in the commercial insurance market.

A Principal Barrier to Enrollment: Insurance Coverage

Based on discussions we conducted with physicians, patient advocates, and insurers involved in the trials, a principal barrier to enrollment is restrictive insurance coverage for proton therapy. We conducted a review of coverage policies for proton therapy among commercial insurers in the health care markets of the proton centers currently accruing patients to at least one of the randomized trials. Nearly all commercial insurers and state Medicaid plans do not cover proton therapy for the indications under study, whereas Medicare typically does cover the treatment through local coverage determinations, which may include clinical study participation requirements (Table 1). Although proton therapy is Food and Drug Administration (FDA) approved, insurance coverage policies generally state that proton therapy is unproven as a clinically more effective or less harmful treatment of the cancers under study.

Radiation therapy centers have argued that insurers should cover proton therapy because it is FDA approved. However, as for medical devices generally, FDA approval is necessary but not sufficient for insurance coverage of proton therapy; after FDA approval, device manufacturers apply to insurers for coverage of their products.¹⁵ Insurers have argued that they should not cover proton therapy because it is more expensive than usual care and not proven to be superior except for a few selected indications (eg, chordomas). There has been some compromise: Some insurers, like Cigna, Independence Blue Cross, and Blue Cross Blue Shield of Florida, cover proton therapy for selected cancers under study or have established coverage with study participation policies. Some

Table 1. Publicly Available, Commercial Insurance Medical Policy Coverage of Proton Therapy for Adult Cancers Under Study by the National Cancer Institute and the Patient-Centered Outcomes Research Institute

Insurer	Breast Cancer	Glioblastoma or Low-Grade Glioma	Lung Cancer	Prostate Cancer	Oropharyngeal Cancer	Esophageal Cancer	Hepatocellular Carcinoma
National							
Aetna	Not covered	Not covered	Not covered	Not covered	Not covered	Not covered	Not covered
Anthem	Not covered	Covered	Not covered	Not covered	Not covered	Not covered	Not covered
Cigna	Covered*	Not covered	Not covered	Covered*	Not covered	Not covered	Covered*
Humana	Not covered	Not covered	Not covered	Not covered	Not covered	Not covered	Not covered
United Healthcare	Not covered	Not covered	Not covered	Not covered	Not covered	Not covered	Not covered
Northeast							
BlueCross BlueShield of Massachusetts	Not covered*	Not covered*	Not covered*	Not covered*	Not covered*	Not covered*	Not covered*
Carefirst BlueCross BlueShield	Not covered	Not covered	Not covered	Not covered	Not covered	Not covered	Not covered
Harvard Pilgrim	Not covered	Not covered	Not covered	Covered*	Not covered	Not covered	Not covered
Horizon/BlueCross BlueShield of New Jersey	Not covered	Not covered	Not covered	Not covered	Not covered	Not covered	Covered
Independence BlueCross	Covered†	Covered	Covered†	Covered†	Covered†	Covered†	Covered†
Tufts	Not covered	Covered	Not covered	Not covered	Not covered	Not covered	Not covered
South							
BlueCross BlueShield Florida	Covered*	Covered	Covered*	Covered*	Not Covered	Not Covered	Covered*
BlueCross BlueShield Tennessee	Not covered	Not covered	Not covered	Not covered	Not covered	Not covered	Not covered
BlueCross BlueShield Texas	Not covered	Not covered	Not covered	Not covered	Not covered	Not covered	Covered*
Midwest							
BlueCross BlueShield Illinois	Not covered	Not covered	Not covered	Not covered	Not covered	Not covered	Covered*
BlueCross BlueShield Minnesota	Not covered	Not covered	Not covered	Covered	Not covered	Not covered	Not covered
Health Partners	Not covered	Covered*	Not covered	Not covered	Not covered	Not covered	Not covered
West							
BlueCross BlueShield Arizona	Not covered	Not covered	Not covered	Not covered	Not covered	Not covered	Not covered
BlueCross BlueShield California	Not covered	Not covered	Not covered	Not covered	Not covered	Not covered	Not covered
BlueCross BlueShield Oklahoma	Not covered	Not covered	Not covered	Not covered	Not covered	Not covered	Covered*
Premiera Blue Cross	Not covered	Covered	Not covered	Not covered	Not covered	Not covered	Not covered
Regence Blue Shield	Not covered	Covered	Not covered	Covered*	Not covered	Not covered	Not covered
Government/military							
Medicaid†	Not covered	Not covered	Not covered	Not covered	Not covered	Not covered	Not covered
Medicare‡	Covered	Covered	Covered	Covered	Covered	Covered	Covered
Tricare	Covered*	Covered*	Covered*	Covered*	Covered*	Covered*	Covered*

*Coverage if medical necessity is determined.

†Coverage with study participation permitted in selected cases. Medicaid coverage may differ by state plan. Generally, to our knowledge, proton therapy is not typically covered by Medicaid for the indications under study.

‡ Medicare does not have a current national coverage policy for proton therapy. Local coverage determinations vary and may require demonstration of medical necessity. Generally, to our knowledge, proton therapy is covered by Medicare for the indications under study.

proton therapy centers, like the University of Pennsylvania, Mayo Clinic, and University of Maryland, engage in reference or discount pricing with or without evidence development,¹⁶ in which the price of proton therapy is set equal to intensity-modulated radiation therapy for insurers and patients. Others, like Northwestern Proton Therapy, Provision CARES Cancer Center, and the Seattle Cancer Alliance, have payment programs for patients in which the proton center, rather than the patient, takes on the financial risk if proton therapy is not covered on appeal. These compromises signal progress, but they are uncommon.

The implications of this impasse are serious. For example, of 893 clinically eligible patients screened in the breast cancer trial through September 2017, 582 (65%) had insurance coverage policies that did not cover proton therapy for breast cancer. Patients cannot enroll in randomized trials designed to answer crucial comparative effectiveness questions about proton therapy if the costs of proton therapy treatment are not reimbursed. In our discussions with clinicians, many have told us that, unless a compromise arrangement is in place, they no longer approach patients with commercial insurance or Medicaid because the likelihood of coverage for patients

assigned to the proton arm is so slim. Restrictive coverage policies for proton therapy have hampered the pace of enrollment in these trials and could threaten the applicability of results.

Other Barriers

Two other important barriers merit discussion. Disincentives to physician engagement common to multi-institutional clinical trials are a barrier and include inadequate reimbursement for trial operational costs, time-consuming consideration by institutional review boards, time pressures in routine care that hinder trial discussions with patients, and under-recognition of individual trial contributions for academic promotion.¹⁷ Patient preference is also a barrier.¹⁷ A survey of 59 clinically eligible patients who were approached for participation in the breast cancer trial asked about their reasons for declining enrollment. Of the 59 patients, 31 (53%) reported “my preference for one or the other treatment”; 20 (34%) reported “my insurance company’s coverage of one or the other treatment”; nine (15%) reported “my doctor’s preference for one or the other treatment”; and the remainder reported other reasons (patients could report more than one reason). Although this was a small sample, the patients’ responses are similar to prior research describing reasons for declining enrollment in NCI studies.^{18,19}

Actionable Solutions

To address these barriers, we propose three solutions. First, commercial insurers, proton therapy centers, hospitals, and patient advocates should come together to establish coverage with a trial participation program for patients who enroll in the NCI- or PCORI-funded randomized radiation therapy treatment trials. Such a proposal has been advocated previously^{16,20-23}; however, prior efforts present sobering lessons.²⁴ For example, in 1990, the NCI engaged with commercial payers to establish coverage with evidence development for the major randomized trial of autologous bone marrow transplantation (ABMT) for breast cancer. The Blue Cross Blue Shield Association was a leader in working with the NCI, placing \$10 million aside to reimburse treatment costs for patients randomly assigned to ABMT in the trial.²⁵ However, lawsuits against insurers to cover ABMT outside of the trial overshadowed these efforts. Despite the NCI’s position that formal scientific evaluation (ought) to precede the routine use of ABMT, policy makers and insurers allowed coverage of ABMT both on and off clinical trials, and accrual was substantially delayed.²⁶ Ultimately, ABMT for breast cancer was found to be both harmful and ineffective in four different randomized trials. Two leading oncologists at the time wrote, “As a society we have to accept that rigorous evaluation of a new treatment is essential. . . . Skipping this step may seem like a compassionate act, but it can have devastating consequences.”^{26(p1091)}

Therefore, we call on insurers, patient advocates, and the medical community to work with the NCI to establish coverage with a trial participation program that provides access to proton therapy through randomized trials designed to assess its benefits and harms. This program could be implemented by leveraging the success of proton access programs that are currently in use at the selected insurers and providers described previously. The NCI applauds these efforts. Given its leadership in coverage with evidence development, the Centers for Medicare and Medicaid

Services could also consider the most appropriate mechanism to support evidence development for proton therapy.

The NCI is charging a task force to determine the most appropriate mechanism to establish such a program. In our view, a public–private partnership to support the program could be in place before the end of 2018. Such a partnership would represent a multistakeholder solution to cover the treatment costs for patients participating in the NCI and PCORI randomized proton trials, distributing the costs across stakeholders with clinical and financial interests in both types of radiation and the outcomes of the trials.

Importantly, radiation therapy manufacturers must also be part of this effort. It has been noted that linear accelerator and proton therapy manufacturers have not underwritten the costs of treatment during evidence development as drug makers might for new drugs because proton therapy units are considered class II devices by the FDA and approved through the 510(k) program.²⁷ The 510(k) program lacks the more stringent evidentiary requirements for efficacy and safety of higher-risk devices or drugs. Nonetheless, the generation of evidence supporting indications for proton therapy is in the interests of manufacturers for many reasons, including providing evidence to expand covered indications. Hitachi Healthcare Americas Corporation, for example, is funding the research costs of a phase III randomized trial of proton therapy versus photon therapy in oropharyngeal cancer that is an extension of a prior NCI-funded phase II trial.²⁸ Thus, manufacturers are natural partners to fund research costs for these trials with the NCI, PCORI, and payers, perhaps focusing on patient out-of-pocket expenses or financial burden during evidence development.²⁰

Second, clinicians and radiation therapy centers should strive to achieve higher enrollment rates. A minimum enrollment benchmark across all sites might be 20% of eligible patients; many sites have enrolled a much higher proportion of patients, but most are still well below this threshold. Academic radiation therapy centers should recognize active clinician investigators by promotion and tenure¹⁷; community sites should offer equivalent recognition, perhaps by publicizing exemplary clinicians with referring physicians and payers.

Third, clinicians and investigators should make every effort to engage with patients to promote enrollment and retention. Research that the NCI and others have conducted has delineated best practices for patient-centered communication to enhance trial participation.²⁹ These strategies have been pioneered by NCI-sponsored investigators and have helped enrollment. For example, the breast cancer trial, funded by PCORI as a patient-centric pragmatic trial with additional technical and funding support from the NCI, expanded eligibility, simplified treatment guidelines, promoted treatment decisions by local treating providers to reflect real-world care, reduced patient research visits, incorporated compensation for research activities completed by patients, wrote patient-friendly informed consent material, opened at more community and academic sites, developed a robust social media presence,³⁰ and conducts peer mentoring for enrolling physicians, physicists, and research staff. In aggregate, these efforts have been associated with increased monthly enrollment (Appendix Table A1). These and similar efforts would be even more fruitful if there were a clear solution to restrictive insurance coverage for proton therapy.

Implications for Evaluating Advanced Technologies to Diagnose and Treat Cancer

The current state of commercial insurance coverage for proton therapy and the barriers to randomized evidence development that have ensued are a prominent example of complex multistakeholder obstacles to evidence development and access to emerging technologies that will likely be encountered with greater frequency going forward. The NCI's Cancer Moonshot initiative, for example, is funding innovations intended to accelerate cancer research.³¹ These include developing new cancer technologies to characterize tumors and test therapies, identifying therapeutic targets to overcome drug resistance, and improving early detection, genetic testing, and our understanding of biomarkers associated with cancer development. As these innovations move into clinical trials, each could face lengthy and costly delays in trial completion without mechanisms for building coalitions among insurers, providers, manufacturers, funders, and patients to provide access with evidence development.

In summary, the seven randomized clinical trials funded by the NCI and PCORI will definitively test the comparative clinical effectiveness of proton therapy. When completed, patients, clinicians, policymakers, and insurers will finally have the evidence to make judgments on the most effective or least harmful treatments for these diagnoses. To get there, multiple stakeholders must come together to complete these trials. If successful, this multistakeholder approach could serve as a model to evaluate the comparative effectiveness of future advanced technologies.

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REFERENCES

1. Institute of Medicine: Initial National Priorities for Comparative Effectiveness Research. Washington, DC, The National Academies Press, 2009. <https://www.nap.edu/read/12648/chapter/1>. Accessed September 5, 2017
2. Liao Z, Lee JJ, Komaki R, et al: Bayesian adaptive randomization trial of passive scattering proton therapy and intensity-modulated photon radiotherapy for locally advanced non-small-cell lung cancer. *J Clin Oncol* doi: 10.1200/JCO.2017.74.0720 [epub ahead of print on January 2, 2018]
3. Ollendorf DA, Colby J: Proton Beam Therapy: ICER Final Evidence Report. https://icer-review.org/wp-content/uploads/2014/07/pbt_final_report_040114.pdf
4. Kralik SF, Ho CY, Finke W, et al: Radiation necrosis in pediatric patients with brain tumors treated with proton radiotherapy. *AJNR Am J Neuroradiol* 36: 1572-1578, 2015
5. Simone CB II, Rengan R: The use of proton therapy in the treatment of lung cancers. *Cancer J* 20:427-432, 2014
6. Hoppe BS, Michalski JM, Mendenhall NP, et al: Comparative effectiveness study of patient-reported outcomes after proton therapy or intensity-modulated radiotherapy for prostate cancer. *Cancer* 120:1076-1082, 2014
7. Holliday EB, Frank SJ: Proton radiation therapy for head and neck cancer: A review of the clinical experience to date. *Int J Radiat Oncol Biol Phys* 89:292-302, 2014
8. MacDonald SM, Patel SA, Hickey S, et al: Proton therapy for breast cancer after mastectomy: Early outcomes of a prospective clinical trial. *Int J Radiat Oncol Biol Phys* 86:484-490, 2013
9. Sheets NC, Goldin GH, Meyer AM, et al: Intensity-modulated radiation therapy, proton therapy, or conformal radiation therapy and morbidity and disease control in localized prostate cancer. *JAMA* 307:1611-1620, 2012
10. De Ruyscher D, Mark Lodge M, Jones B, et al: Charged particles in radiotherapy: A 5-year update of a systematic review. *Radiother Oncol* 103:5-7, 2012
11. Mailhot Vega RB, Ishaq O, Raldow A, et al: Establishing cost-effective allocation of proton therapy for breast irradiation. *Int J Radiat Oncol Biol Phys* 95: 11-18, 2016
12. Muralidhar V, Nguyen PL: Maximizing resources in the local treatment of prostate cancer: A summary of cost-effectiveness studies. *Urol Oncol* 35:76-85, 2017
13. American Medical Association: Summary of 2016 Final Medicare Payment Rules. https://www.varian.com/sites/default/files/resource_attachments/2016_Final_Medicare_Payment_Rules_Rad%23_10405.docx.pdf
14. Yu JB, Soulos P, Herrin J, et al: Proton versus intensity modulated radiotherapy for prostate cancer: Patterns of care and early toxicity. *J Natl Cancer Inst* 105:25-32, 2013
15. Sachs R: Your weekly reminder that FDA approval and insurance coverage are often linked. <http://blogs.harvard.edu/billofhealth/2016/11/30/your-weekly-reminder-that-fda-approval-and-insurance-coverage-are-often-linked/>
16. Bekelman JE, Hahn SM: Reference pricing with evidence development: A way forward for proton therapy. *J Clin Oncol* 32:1540-1542, 2014
17. Institute of Medicine: A National Cancer Clinical Trials System for the 21st Century: Reinvigorating the NCI Cooperative Group Program. Washington, DC, The National Academies Press, 2010
18. Lara PN, Jr., Higdon R, Lim N, et al: Prospective evaluation of cancer clinical trial accrual patterns: Identifying potential barriers to enrollment. *J Clin Oncol* 19: 1728-1733, 2001
19. St Germain D, Denicoff AM, Dimond EP, et al: Use of the National Cancer Institute Community Cancer Centers Program screening and accrual log to address cancer clinical trial accrual. *J Oncol Pract* 10:e73-e80, 2014
20. Steinberg EP, Tunis S, Shapiro D: Insurance coverage for experimental technologies. *Health Aff (Millwood)* 14:143-158, 1995
21. Steinberg ML, Konski A: Proton beam therapy and the convoluted pathway to incorporating emerging technology into routine medical care in the United States. *Cancer J* 15:333-338, 2009
22. Steinberg ML: Protons and the hospital that ate Chicago. *Int J Radiat Oncol Biol Phys* 89:241-242, 2014
23. Shah A, Ricci KI, Efsthathiou JA: Beyond a moonshot: Insurance coverage for proton therapy. *Lancet Oncol* 17:559-561, 2016
24. Tunis SR, Pearson SD: Coverage options for promising technologies: Medicare's 'coverage with evidence development'. *Health Aff (Millwood)* 25: 1218-1230, 2006
25. Suplee C: Blue Cross agrees to fund breast cancer experiment. Women to undergo bone-marrow transplants. *Washington Post* November 13, 1990:A1.
26. Welch HG, Mogilnicki J: Presumed benefit: Lessons from the American experience with marrow transplantation for breast cancer. *BMJ* 324:1088-1092, 2002
27. National Academies of Sciences, Engineering, and Medicine: Appropriate Use of Advanced Technologies for Radiation Therapy and Surgery in Oncology: Workshop Summary. Washington, DC, The National Academies Press, 2016. doi: 10.17226/21859
28. University of Texas MD Anderson Center: MD Anderson and Hitachi to collaborate in research for treatment of oropharyngeal cancer of the head and neck. <https://www.mdanderson.org/newsroom/2017/06/md-anderson-and-hitachi-to-collaborate-in-research-for-treatment-of-oropharyngeal-cancer-of-the-head-and-neck.html>
29. Denicoff AM, McCaskill-Stevens W, Grubbs SS, et al: The National Cancer Institute-American Society of Clinical Oncology Cancer Trial Accrual Symposium: Summary and recommendations. *J Oncol Pract* 9:267-276, 2013
30. The RadComp Study. https://rt16.pmacs.upenn.edu/crcu_html/radcomp/website/index.html
31. National Cancer Institute: Cancer Moonshot. <https://www.cancer.gov/research/key-initiatives/moonshot-cancer-initiative>

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Appendix

Table A1. Current Status of Phase III Randomized Clinical Trials of Proton Therapy Versus Photon Therapy Funded by the National Cancer Institute and the Patient-Centered Outcomes Research Institute

ClinicalTrials.gov Registry Number	Disease Site	Primary End Point	No. of Months Active*	Enrollment of Total Sample Size*	No. of Proton Centers Enrolling*	Average Monthly Accrual, 6 Months*	Average Monthly Accrual, 12 Months*
NCT02603341	Breast cancer	Major cardiovascular events	23	317 of 1,716	20	19.0	17.4
NCT02179086	Glioblastoma	Overall survival	39	96 of 288†	16	3.5	3.2
NCT01993810	Lung cancer	Overall survival	47	101 of 330‡	10	0.7	1
NCT01617161	Prostate cancer	Patient reported bowel outcomes	62	254 of 400	12	4.3	5.1
NCT01512589	Esophageal carcinoma	Progression-free survival and total toxicity burden	69	126 of 180§	1	0.7	1.1
NCT03186898¶	Hepatocellular carcinoma	Overall survival	7	1 of 167	1	0.2	Not applicable
NCT03180502¶	Low-grade glioma	Preservation of neurocognition	6	1 of 120	7	0.2	Not applicable

*As of January 31, 2018.

†Accrual for proton beam therapy randomization.

‡Total accrual goal modified by amendment on December 12, 2017, due to slow accrual.

§Twenty patients unevaluable due to insurance coverage denial for proton therapy.

¶Activated June 22, 2017.

¶Activated August 2, 2017.