Reference Pricing With Evidence Development: A Way Forward for Proton Therapy

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Next month, the Washington State Health Technology Assessment Program (HTAP) will decide whether and under what circumstances the state's public payers will pay for proton therapy, a promising but expensive cancer treatment. HTAP has a unique legislative mandate in the United States to evaluate health technologies and translate evidence of comparative cost-effectiveness into payment policy. HTAP's decisions are closely scrutinized, and they influence the payment policy of other payers in the US health care system. HTAP's examination of proton therapy comes at a decisive moment: major insurers have recently announced policies that restrict coverage for proton therapy to narrow indications.¹ HTAP should not follow suit.

Proton therapy comparative effectiveness research is a particular priority. Compared with photon therapies such as intensity-modulated radiotherapy (IMRT), proton therapy reduces low and intermediate radiation dose to nearby normal tissue, holding promise as more effective or better tolerated radiation treatment. However, proton therapy has greater physical and biologic uncertainties. For example, because we cannot determine where proton therapy terminates in tissue with enough precision, we routinely overshoot tumor targets to ensure adequate radiation coverage. Proton therapy uncertainties could affect clinical outcomes; thus, we must establish whether its novel advantages actually translate into clinical benefits.

Yet, as the HTAP appraisal shows, high-quality comparative effectiveness evidence is woefully lacking.² Moreover, the costs are consequential; median Medicare reimbursement for proton therapy is \$13,000 higher than that for IMRT for prostate cancer and substantially greater in the commercial insurance market. Washington State and other payers face an unenviable choice: pay for an expensive therapy that has not been shown to be better than less expensive alternatives for prevalent malignancies or restrict coverage to rare tumors in which clinical benefit appears compelling. We propose a better way forward: reference pricing with evidence development.

Reference pricing establishes a common level of payment for different therapies with similar outcomes. Under reference pricing, payers pay a set price for whichever therapy is selected from various alternatives. For proton therapy, the reference price should be set at the rate currently paid for IMRT. Patients should have no additional out-of-pocket expenses, and providers should be paid the same irrespective of treatment type.

Reference pricing with evidence development is attractive for proton therapy for three reasons. First, the price premium of proton therapy is not only untenable in the eyes of payers and patients but also an obstacle to evidence development. Not surprisingly, payers' leading

rationale for eliminating coverage of proton therapy for prevalent malignancies like prostate and lung cancer is its price differential despite the evidence gaps. Yet, we can conduct the necessary research only if payers pay for proton therapy and its photon-based alternatives. Reference pricing preserves access to proton therapy and reduces financial barriers to evidence development.

Second, evidence for most malignancies suggests that proton and photon treatments are either therapeutically equivalent or that the benefits of proton therapy are uncertain.² The effectiveness of proton therapy should be evaluated in multicenter trials with adequate sample size to measure patient-centered outcomes. By linking payment for proton therapy to evidence development, we echo prior calls to tie reimbursement for unproven technologies to the broad mandate of comparative effectiveness research.

What types of trials should be conducted? Randomized trials are essential for evaluating the potential benefits of proton therapy when existing evidence suggests modest or uncertain treatment effects, although there is general consensus that observational cohort studies are suitable for discerning effects when existing evidence suggests larger treatment benefits.³ Under this framework, we put forward the following four priorities for evidence generation (which are concordant with an international workshop on the ethics and equipoise of proton therapy research)⁴: (1) phase III randomized trials in prevalent disease sites with existing phase II evidence (eg, prostate, lung, and breast cancer), (2) phase II trials of combined modality regimens (chemotherapy and/or targeted therapies with proton therapy) to increase the therapeutic ratio with a goal to transition to phase III randomized studies (eg, GI cancers), (3) cohort studies in which existing evidence suggests substantially improved radiation dose distributions and/or a large reduction in toxicity with proton therapy (eg, pediatric cancers and benign and malignant CNS and brain tumors), and (4) cohort studies in special situations with limited sample size (eg, re-irradiation). Patients eligible for proton therapy should be treated under one of these four study types as a condition of reimbursement.

Third, reference pricing with evidence development has precedence and is feasible. HTAP previously covered robotic-assisted surgery, another promising but unproven medical technology, under a reference pricing strategy. For proton therapy, Penn Medicine and Independence Blue Cross, a large insurer in southeastern Pennsylvania, partnered in 2010 under a reference pricing contract to conduct proton therapy effectiveness research.⁵ Similarly, Horizon Healthcare Services, New Jersey's largest insurer, allows participation at Penn

Medicine in a randomized clinical trial for prostate cancer (NCT01617161) under reference pricing.

Moreover, our proposal is consistent with and extends prior efforts to fund evidence development for promising expensive therapies. The Centers for Medicare & Medicaid Services and commercial payers have conducted initiatives to link coverage with evidence development in more than a dozen settings by using both randomized and nonrandomized study designs.⁶ These efforts have achieved mixed success and underscore the challenge of balancing access to innovative treatments with establishing clinical benefits and harms, all within constrained medical budgets.⁷

The national experience with autologous bone marrow transplantation for breast cancer is a sobering and instructive example. In 1990, the Blue Cross Blue Shield Association elected to fund bone marrow transplantation for patients enrolled onto randomized trials sponsored by the National Cancer Institute in the context of emotionally charged attention to the possible benefits of transplantation and lawsuits to compel coverage.⁸ Douglas Peters, senior vice president of the Blue Cross Blue Shield Association at the time, said, “By funding some of the clinical care costs associated with the National Cancer Institute trials, we’re able to provide access to this treatment while contributing to the search for a definitive answer to the question of whether or not it works.”⁹

However, under external pressure, payers allowed patients with breast cancer to be treated both on and off clinical trials, thus reducing accrual and delaying evidence generation. Randomized trials ultimately concluded that bone marrow transplantation for breast cancer was not an effective treatment. It is estimated that more than 20,000 patients with breast cancer were treated with bone marrow transplantation at a cost of \$2 billion.⁶ The gaps in clinical evidence and the costs for proton therapy also color today’s impassioned debate in the United States about proton therapy; our proposal aims to simultaneously facilitate widespread access and promote rapid and efficient evidence generation.

Despite its potential benefits, our proposal for proton therapy will face challenges from stakeholders. HTAP and other payers may question their role in paying for evidence development, regardless of pricing approach. Although the US Food and Drug Administration approves medical devices when they are substantially equivalent to prior technologies (eg, proton therapy facilities have been approved under the US Food and Drug Administration’s 510k provision), payers may argue that proton therapy is “investigational” and does not meet criteria for coverage as “medically necessary.”

This old debate, which mirrors the breast cancer experience of the 1990s, has been reignited by unfortunate language in Section 2709 of the Affordable Care Act, which excludes investigational therapy from coverage requirements for clinical trials. We doubt that the Affordable Care Act was written to impede payers’ efforts to participate in or fund evidence generation. We also recognize that other stakeholders, including device manufacturers and providers, are potential candidates to pay for the use of proton therapy during evidence development.¹⁰ In our proposal, for example, we call on proton treatment centers to fund the difference between the reference price paid by insurers and the costs of proton therapy. We welcome national dialogue on who should fund the use of devices for effectiveness research, but it should not deflect from the important role—and economic interest—of payers like Washington State in providing

access to new technologies and ensuring that there is evidence to support widespread use.

Stakeholders may also question what effects reference pricing would have on innovation and diffusion. The capital and personnel costs for proton therapy are, in fact, higher than for photon-based treatments. Our proposal can be situated within other proposals for dynamic pricing in which the price premium for costly technologies depends on effectiveness evidence.¹¹ We advocate for elimination of the price premium for proton therapy now because the access necessary for evidence development is at risk and the evidence gaps are pressing. In the future, the pricing of proton therapy relative to alternatives should be reset on the basis of what the evidence shows and what the costs of treatment are—a price premium for innovation that is more expensive and leads to better outcomes is appropriate. If the evidence shows more pronounced benefits in some patient subgroups but not others, we would advocate for differential pricing by indication. For example, current evidence shows that proton therapy is more effective or less harmful than other radiation treatments for skull-base chordomas and chondrosarcomas and uveal melanomas²; proton therapy for these indications should be reimbursed at a premium to current IMRT rates.

The diffusion of proton therapy is threatened by scarce comparative evidence, not reference pricing. A dozen proton therapy facilities are under development, and manufacturers, responding to market conditions, are designing less expensive technologies. Reference pricing will come as no surprise to investors and hospitals and likely has already been assumed in financial projections for operational or soon-to-be operational proton therapy centers. Although some may argue that reference pricing could threaten the ability of proton therapy centers to recoup their investment, delaying wider access to proton therapy, the current and very real alternative—that is, no reimbursement for proton therapy by major payers for most malignancies¹—is a more imminent challenge. The trade-off is justifiable: reduced reimbursement, at least for a time, to promote evidence generation for a technology that may (or may not) lead to better outcomes for great numbers of patients.

Stakeholders may also question whether our proposal coerces patients to participate in clinical research. As with any clinical research participation, patients would choose to participate in randomized trials and cohort studies of proton therapy as a way to access a promising but unproven medical technology that would not otherwise be available.¹ Bioethicists have voiced public support for the legitimacy and fairness of coverage with evidence development policies, although reasonable debate continues.¹² In addition, mechanisms must remain in place (as they are now) to appeal to payers to cover compelling indications for which studies are pending or unavailable.

In conclusion, Washington State’s HTAP should lead the way forward by deciding on behalf of its public payers to cover proton therapy under a policy of reference pricing with evidence development. Commercial payers should revise their policies similarly. The Centers for Medicare & Medicaid Services should charge a task force with determining the best mechanism to implement the policy in Medicare. To align, design, efficiently execute, and fund research-related costs for high-quality multicenter comparative effectiveness studies, we call for a national proton therapy clinical trials consortium, led by physicians and comprising patients, payers, federal agencies, and device manufacturers. In our view, the consortium, at least a half

dozen study protocols, a public-private partnership to support research costs, and revised payment policies could be in place before the end of 2014.

Although we cannot afford to pay for expensive therapies that provide little benefit to patients, we also cannot afford to stifle evidence development for innovative treatments that may lead to better health outcomes. Reference pricing with evidence development will preserve access to proton therapy and renew efforts to conduct crucial comparative research.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

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