Exhibit 3 – Economic Analysis

MARCH 13, 2020

Acquisition of Equipment Utilizing Technology That Has Not Previously Been Utilized in the State and a Computed Tomography ("CT") Simulator Certificate of Need Completeness Letter: Response to Question 22
Docket Number: 19-32339-CON

PREPARED FOR SUBMISSION TO THE CONNECTICUT
OFFICE OF HEALTH STRATEGY

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Table of Contents

Table of Figures

Table of Tables

I. OVERVIEW AND SUMMARY OF FINDINGS

Connecticut Proton Therapy Center, LLC, Yale New Haven Health Services Corporation ("YNHHS") and Hartford HealthCare Corporation ("HHC") plan to establish and operate a proton therapy center ("PBTC") in Wallingford, CT for the benefit of Connecticut cancer patients. The endeavor will be owned and operated by Connecticut Proton Therapy Center, LLC ("CPTC") under a newly formed joint venture of YNHHS and HHC.

This new service offering requires the acquisition of an IBA Proteus®ONE Compact Imagine-Guided IMPT, a technology new to the State of Connecticut, as well as the acquisition of a CT Simulator for treatment planning purposes. This purchase and operation of this new technology required CPTC to file for approval under the Connecticut Certificate of Need ("CON") statutes.

The Connecticut Office of Health Strategy ("OHS") which administers the CON process, has asked for additional information as part of its review. The CPTC has asked FTI's Center for Healthcare Economics & Policy to provide an independent analysis and review of issues raised in Question 22 of the OHS's letter dated January 15, 2020. Specifically,

> *Prepare and submit a comprehensive report, authored by a national subject matter expert or group of subject matter experts, not involved with the current project that includes:*
>
> *a. an economic analysis comparing the cost of proton therapy versus conventional radiation therapy for the types of cancers proposed for treatment at the Center; and*
>
> b. *a qualitative analysis that examines the effectiveness of proton therapy versus conventional radiation therapy for the types of cancers proposed for treatment at the Center*.

To address this request, the CPTC has asked FTI to focus on particular issues that will inform the OHS's requests. Specifically, this paper reports on the results of the independent review and analysis of the following issues:

- State of competition and financial viability and sustainability of PBTC nationwide as a basis for determining the likely success of the proposed Connecticut PBTC ("CT PBTC");
- Comparative analysis of the proposed CT PBTC with other centers operating in the United States;
- Economic analysis comparing the cost of proton therapy versus conventional radiation therapy for the types of cancer proposed at the CT PBTC, including the relative costs and benefits for patients, payers, the public welfare, and employer stakeholders; and
- Qualitative analysis reviewing the academic and professional literature on the effectiveness of proton therapy versus conventional radiation therapy and the implications of these findings for the types of cancers proposed for treatment at the CT PBTC.

A. Relevant background information on the CT PBTC informing our analyses

Below is a brief summary of the proposed CT PBTC:

- HHC and YNHHS will initially own and control 50% of the joint venture company. With approval of the requested CON, the health systems intend to partner with a third-party, who will serve as both the developer/operator of the Center, and the future majority (non-controlling) equity owner. The Health Systems will maintain governing control over CPTC and have certain reserved powers with respect to the operation of both the entity and the Center.
- Proton International is the expected third-party partner. It is an established and experienced international developer of one and two-room PBTCs. It currently operates the South Florida Proton Therapy Institute in Delray Beach, FL and currently is developing the PBTC at the University of Alabama Birmingham, which is expected to open in March 2020.
- Both HHC and YNHHS offer highly respected cancer programs serving the residents of Connecticut and beyond. Both health systems regard the CT PBTC as an extension and clinical enhancement of their current cancer services programs. Both health systems have substantial experience in operating comprehensive cancer programs across multiple locations.
    - YNHHS operates five short-term acute care hospitals in CT. As part its Yale-New Haven Hospital, it also operates the Smilow Cancer Hospital and Yale-New Haven Children's Hospital. The Smilow Cancer Hospital provides comprehensive, multi-disciplinary cancer program services for more than a dozen types of cancers. It is a National Cancer Institute-designated cancer center. It also provides interdisciplinary cancer research in basic science, translational research and prevention and control, and clinical trial opportunities not available at most hospitals. The Smilow Cancer Hospital also offers cancer services at 15 Smilow Cancer Hospital Care Centers in Connecticut and Rhode Island.
    - The Hartford HealthCare Cancer Institute encompasses comprehensive cancer centers at seven hospitals and five satellite locations across Connecticut. It has an alliance with the Memorial Sloan Kettering Cancer Center. The Cancer Institute is accredited by the American College of Surgeons' Commission on Cancer as an Integrated Network Cancer Program, one of a select few institutes recognized nationwide as a system rather than an individual cancer center.
- The proposed CT PBTC will be located in Wallingford, CT, a central location between the primary cancer facilities at HHC and YNHHS. Included at the PBTC will be services necessary to plan and provide proton therapy radiation to patients, specifically a CT simulator and a one-room proton therapy delivery system, exam rooms, changing rooms, physics and dosimetry work areas, administrative areas and appropriate waiting rooms, support space and building infrastructure requirements.
- Proton beam therapy ("PBT") will be made available to patients across the State as well as potential patients located in nearby states. It is the only PBTC planned for the State of

Connecticut and will provide a closer alternative treatment center for patients who now must travel to other states to receive treatment.

- Assuming CON approval is granted, the PBTC will take 18-24 months to complete, opening approximately by October 2022.
- For planning purposes, the parties have estimated patient volume at the CT PBCT by assuming that a percentage of patients with certain types of cancer which historically have been treated at the parties' cancer facilities with radiation therapy would be treated with proton beam. The estimate assumes a gradual ramp-up over a two-year period reaching near capacity by the third year. The estimate also projects 62% government and 38% non-government payer mix by the third year.

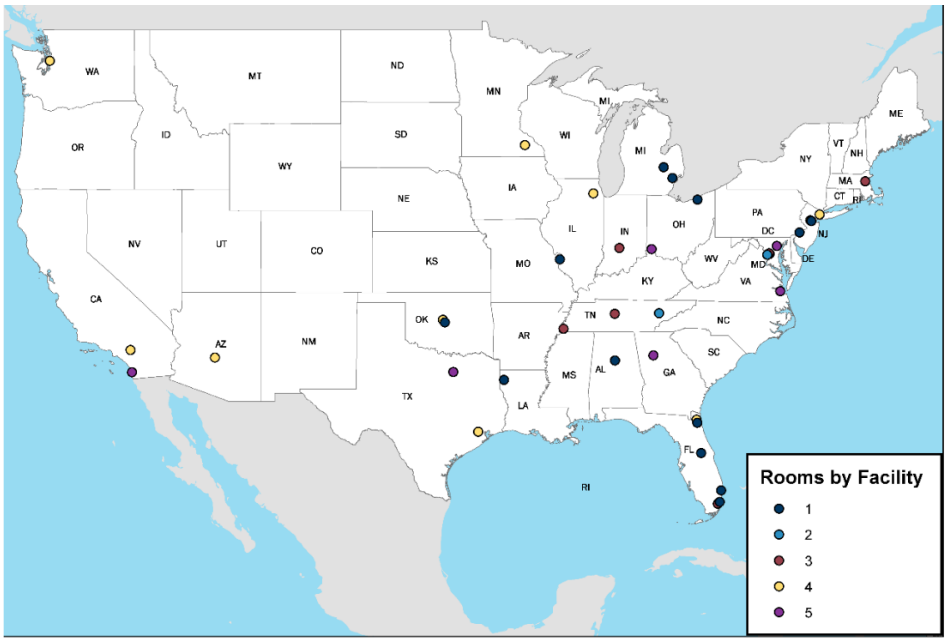
II. STATE OF COMPETITION AND FINANCIAL VIABILITY/SUSTAINABILITY OF PBTCS NATIONWIDE

A. PBTCs in U.S.

Currently, there are 35 PBTCs operating in the United States.[1] Between 2004 and 2019, 32 PBTCs were built.[2] One facility, the Dallas Proton Treatment Center, was partially built but went bankrupt and never opened. The Indiana University Health Proton Therapy Center in Bloomington, IN opened in 2004 but closed in 2014. The 35 opened PBTCs have operated with varying degrees of success. Four more centers currently are under construction—three are planned to open in 2020 and another one in 2021. Figure 1 presents a map showing the location of these PBTCs throughout the United States, differentiated by number of treatment rooms available. The map includes PBTCs expected to open in 2020 and 2021.

[1] This does not include UC Davis which only performs ocular PBT.
[2] The University of Alabama at Birmingham Proton Therapy Center opened the week of March 8, 2020.

Figure 1: Map of PBTCs Expected to Open in 2020 and 2021



The discussion below delves into the attributes of these PBTCs, examining their similarities and differences and how these attributes factor into their economic viability within the context of demand, supply and competitive dynamics.

B. Economic viability of PBTCs operating in the United States

The success of a PBTC depends largely on the demand for its services, the supply of services available and efficiencies in meeting demand, and the competitive alternatives available in terms of competing PBT suppliers and alternative treatment substitutes.

1. Demand considerations

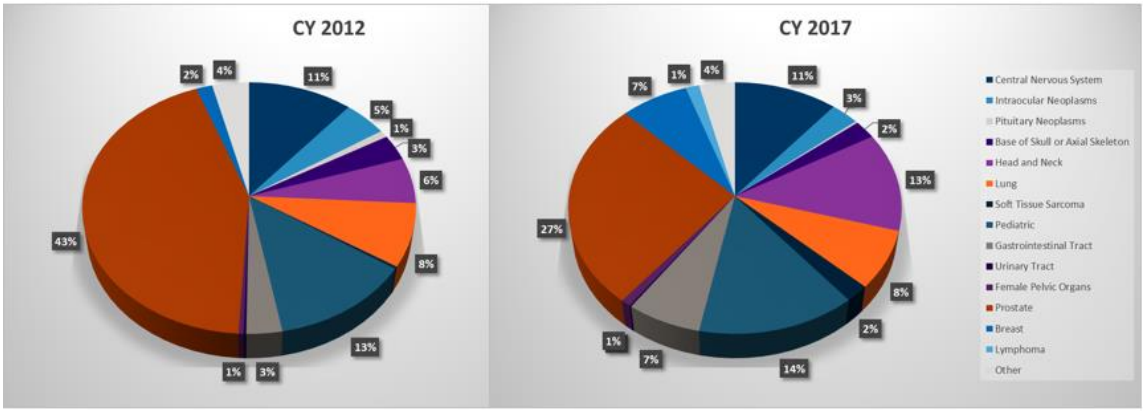
Four significant demand factors affect the likely economic viability of a PBTC: (1) the incidence of cancers treatable with PBT, (2) the center's likely patient draw or referrals area, (3) the availability of demand substitutes, and (4) payers' willingness to pay for treatment. Included in these factors are economic considerations of time (e.g., treatment time, travel time, recovery), quality of life, out-of-pocket costs, and other factors.

PBT is a form of cancer radiotherapy. Because of protons' different properties, it is better able to target energy at the tumor, thus minimizing damage to surrounding healthy tissue. The array of cancers effectively treated by proton beam has expanded over time which has been a critical factor in supporting the expansion and viability of new centers, as shown in Figure 2.[3]. In the late 1990s, the James M. Slater MD Proton Treatment & Research Center at Loma Linda University Cancer Center and the Massachusetts General Hospital ("MGH") Francis H. Burr Proton Therapy Center worked with payers

[3] National Association of Proton Therapy, Annual Survey, CY2017.

to remove the "experimental" and "investigational" designations for proton beam treatment and more studies were published showing the clinical benefits of the treatment for pediatric, eye, base of skull and spinal tumors.[4] By 2012, clinical studies at the 10 U.S. PBTCs were being conducted on cancers of the lung, head and neck, gastrointestinal tract, prostate, breast, brain, gynecologic sites, lymphoma, and recurrent tumors.

Figure 2: Percentage of Proton Beam Treatments, by Cancer Type, 2012 and 2017



Similar to the period 1990-2012, prostate cancer accounted for a significant volume of proton beam treatments in the 2012-2017 period.[5] Other cancers with significant and increasing volume included pediatric cancers (CNS, lymphoma, other), central nervous system (brain and other), head and neck, and gastrointestinal tract (pancreas, esophagus, hepatobiliary, colon, rectal, other) and breast cancers. The predominance of PBT in treating prostate cancers during this period was negatively affected by studies emerging in 2012 which showed that PBT provided no relative clinical value over other forms of treatment. Many insurers stopped paying for the treatment and PBTCs that focused on delivering prostate cancer treatments suffered in terms of volumes and financial conditions.

The incidence and prevalence of cancers in the United States depends on several factors, including genetics, demographics, environmental and lifestyle factors.[6] The risks of cancer can be reduced by making healthy lifestyle choices, such as healthy weight, avoiding tobacco, limiting alcohol consumption, and protecting the body from high intensity sun exposure. Vaccines also may reduce the risks of some cancers, such as cervical and liver cancers. Screening tests may lower the severity of cancers by detecting certain types of cancers early, such as breast, cervical, lung, prostate, and colorectal cancer. Both the incidence and prevalence of cancers vary by location. Connecticut has a higher than average incidence and prevalence of cancers compared with other states.

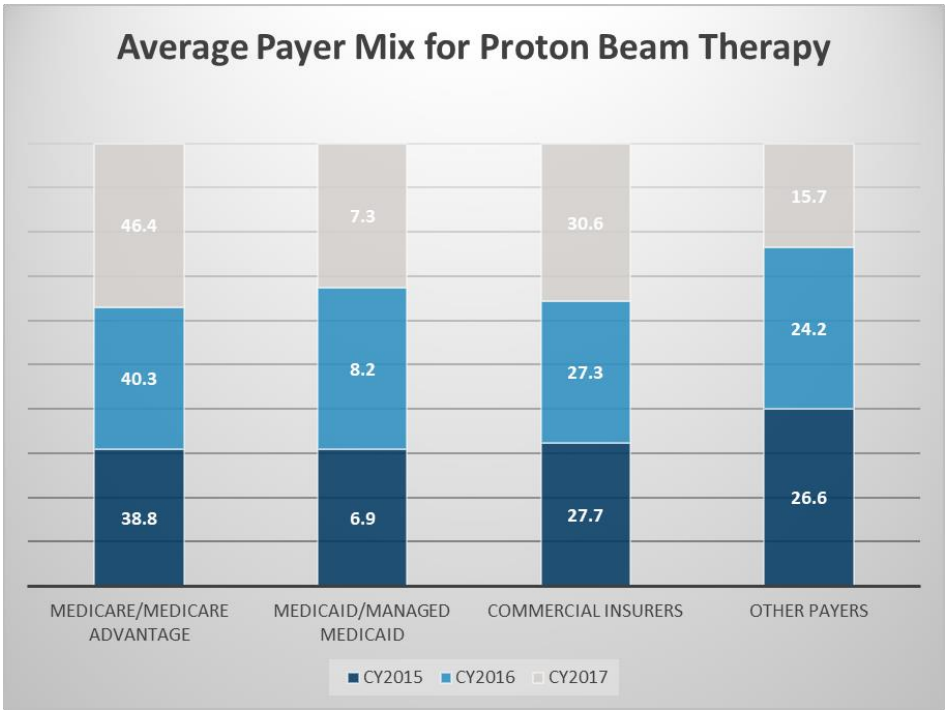
[4] "Historical perspective and evolution of charged particle beam therapy," Huan Giap and Bosco Giap, Transl Cancer Res 2012:1(3):127-136.
[5] The National Association for Proton Therapy. Most recent data available.
[6] Incidence captures the number of individuals newly diagnosed with cancer. Prevalence captures the number or percent of individuals at a point in time who have had a diagnosis of cancer.

The draw area for a PBTC varies depending on many factors, the most important being physician referral patterns. PBTCs that are aligned with or established with support from academic medical schools or healthcare systems with established cancer programs generally have a stronger network of oncologists or radiation oncologists to refer patients to the center. Affiliation with the National Comprehensive Cancer Network ("NCCN") or a National Cancer Institute ("NCI" Designated Cancer Center increases the referral potential of a center since these institutions would have a strong network of oncologists and radio-oncologists from which to refer patients to a PBTC. The failure of Indiana University Proton Center is due, in part, to many factors, including its distance from Indiana University Medical School. Generally, the draw area for PBTCs is about 85 miles although some center draw areas can be more related to state boundaries based on payer network construction. Nearby competing PBTCs also may reduce the potential draw area for a center.

Depending on the type of cancer, alternative treatment modalities may include external beam radiation therapy, including 3-D conformal radiation, image-guided radiation therapy (IGRT), intensity-modulation radiation therapy (IMRT), intraoperative radiation therapy (IORT), internal radiation therapy, i.e., brachytherapy, and other forms of treatment, such as chemotherapy. These alternatives may be strong or weak substitutes depending on the type of cancer, price, quality of life considerations, and in some cases, these alternatives may also be complements to proton beam treatment. Various organizations offer guidance on PBT based on clinical trials. The National Comprehensive Care Network ("NCCN") Guidelines are include as Attachment 1 for consideration.

Another important factor in determining the potential demand for PBT is the willingness of payers to pay for the treatment, particularly in considering the relative efficacy and cost of treatment compared with other alternative treatments. During the period 2015 through 2017, Medicare and Medicare Advantage reimbursements increased for PBT, along with a slight uptick in overall commercial payor reimbursements, and significant decline in other payors, e.g., self-pay. Figure 3 below presents the relative percentages based on information from the National Association for Proton Therapy for CY2016 through CY2017.

Figure 3: Average Payer Mix for Proton Beam Therapy



Since this period, insurers have been pressured to change their reimbursement policies towards proton beam treatment coverage due to multiple lawsuits, state interventions, and increases in clinical trial data showing the benefits of proton beam treatment compared with alternatives. The American Society for Radiation Oncology ("ASTRO") issues policy guidance on reimbursement coverage. ASTRO groups coverage recommendations for PBT into two groups based on medical necessity requirements and clinical data: (1) diseases that frequently support the use of PBT and (2) those diseases suitable for Coverage with Evidence Development (i.e., patients enrolled in either an IRB-approved clinical trial or in a multi-institutional patient registry adhering to Medicare requirements for CED). The ASTRO Policy for Proton Beam Treatment is included in Attachment 2. In addition, most national healthcare insurance carriers also issue policy guidance on proton beam treatment. A summary of these guidelines and policies can be found in Section IV.C.

2. Supply considerations

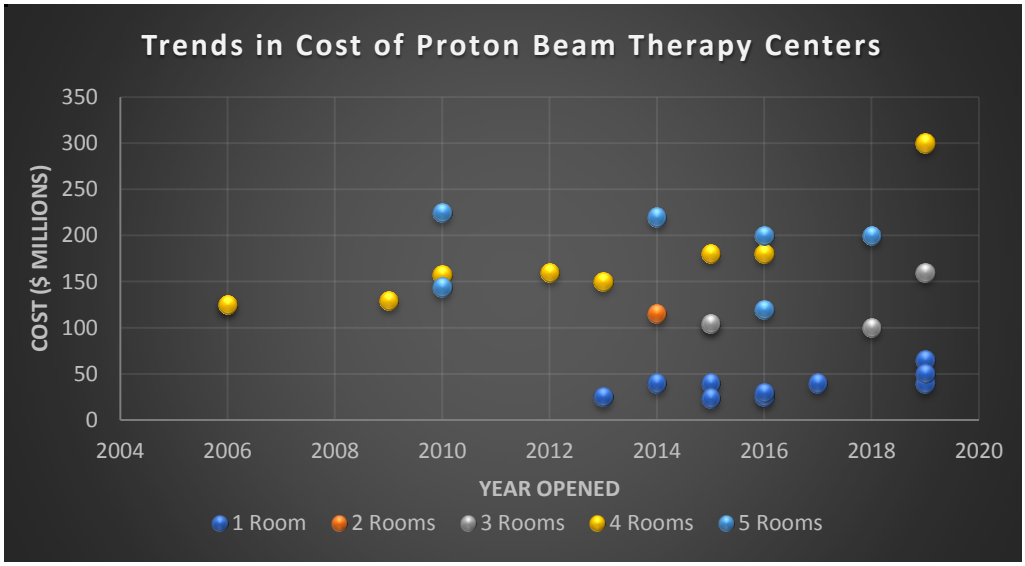
Supply considerations enter into the calculus of economic viability. Supply factors include: (1) characteristics of PBTCs, including technology, size, capacity, and capital structure, (2) supply substitutes, including alternative PBTCs and other treatment modalities, and (3) efficiencies, including throughput.

A review of the economics literature on PBTCs suggests some early learnings linking certain center characteristics with financial performance. With respect to technology, early PBT adopters tended to re-purpose existing cyclotron technology for patient treatment. Patients were treated with Broad Beam Technique, also called double scattering. This had some effect on the types of cancers treated and the

efficiency of the treatments. Technological advances quickly evolved to improve treatment delivery and to reduce costs of treatment. This included pencil beam scanning ("PBS") which enabled Intensity Modulated Proton Therapy ("IMPT"). The advantage of this development is that it allows much higher levels of conformity with the targeted tumor while lowering the dose to surrounding tissue when compared with the Broad Beam Technique. In addition, PBS also includes countermeasures to reduce the effect of organ movement during treatment.[7]

Another key technological advancement was single-room PBS systems. Figure 4 shows the growth in single-room PBSs over time.[8] This technology significantly lowered the costs of constructing and operating PBTCs. An additional development has been combining PBS treatment with volumetric imaging modalities that enables providers to more accurately position patients for treatment and to make anatomical treatment modifications as treatments progress.

Figure 4: Trends in Cost of Proton Beam Therapy Centers



Note: Loma Linda, UCSF CNL Ocular, MGH, IU, and Miami PBT Centers not included due to missing year or cost information

These technological advances are important in the economic viability of PBTC. Combining volumetric imaging at the patient site of delivery allows greater precision and therefore, increases the competitive advantage of PBT over other radiation modalities. Single-room PBS has significantly lowered the start-up and operational costs of offering PBT, thus enabling the entry of new PBTCs with more cost-effective capital structures and appropriate sizing for patient demand. Single-room PBS systems now dominate new PBTCs with multi-room centers becoming the exception. Whereas multi-room centers often saddled owners with significant debt, single-room PBS with lower costs and advanced technologies facilitate adoption by more providers. The greater number of PBTCs has also enabled more clinical trials,

[7] See, for example, "Proton Therapy in Oncology, A General Overview of Current Practice, Opportunities and Challenges," IBA 2015.
[8] The University of Florida Health Proton Institute and the Massachusetts General Hospital just recently added new single-room PBTs to their existing facilities

which has led to more evidenced-based analysis of the benefits of PBT compared with other cancer treatment modalities. These analyses and clinical trial results have further improved and expanded reimbursement policies for the use of PBT in treating cancers, which contributes to the financial viability of new PBTCs.

PBT is only one of several approved treatments for cancer. As noted above, competing technologies include other forms of external radiation such as 3-D conformal radiation, IGRT, IMRT, IORT; internal radiation therapy, i.e., brachytherapy; and other forms of treatment, such as chemotherapy. Clinical trials have shown the comparative clinical advantage of PBT for some types of cancers. These include ocular tumors; tumors that are located at the base of the skull, such as chondrosarcomas and chordoma; tumors of the spine; hepatocellular cancer; certain pediatric cancers; primary CNS tumors; head and neck cancers; and tumors located near vital organs.[9] For prostate cancer, clinical trials started to emerge in 2009 which showed that the more expensive PBT did not have greater clinical efficacy and fewer side effects than other forms of radiation treatment (see Section IV and Appendix 3 for more detailed review of the literature). Alternative therapies developed which redirected volume from PBT, including robotic-assisted prostatectomy and stereotactic body radiation treatment. Many PBTCs built before 2009 relied on the increasing number of prostate cancers to feed volume to their centers.

Another key economic viability consideration is the efficiency of the technology and center operations. As with most high capital cost medical technologies, capacity utilization and throughput are vital elements of economic viability, particularly for PBTCs carrying high debt structure. PBS and single-room therapy centers relieve some of the economic pressures of PBTCs by lowering capital costs and required volume of patients to make a center viable. PBS combined with volumetric imaging is more efficient. Length of treatment times with PBS with combined volumetric imaging for non-complex cancers have declined by half. This frees up capacity to increase the number of treatments per day. In addition, advances in radiation treatment, including PBS, for lung, prostate and breast cancers that enable an increase in the daily dose also allows for a decrease in the number of fractions in a course of treatment (referred to as hypofractionation). This also results in a more efficient utilization of equipment and staff. Other key operating factors affecting efficiencies include the make-up of complex versus non-complex cancer cases, the need for anesthesia, and the mix of pediatric versus adult cases.

3. Competitive dynamics

Demand and supply factors intersect to determine the competitive dynamics that govern the volume of patients available to the proposed CT PBT, the likelihood of referrals and patients choosing the Center, and its resulting economic viability. We provide analysis of these issues specific to the proposed Center in Section III and IV below.

C. Operations and financial characteristics of U.S. PBTCs

[9] Section V of this report provides greater insight on findings on competing technologies in terms of clinical and economic efficacy with respect to specific types of cancers treated with PBT.

The 35 operating PBTCs differ across many attributes. Appendix 1 presents a list of these centers with particular relevant attributes that are publicly available. These include:

- Owner/operator
- Year opened
- CON applicable for PBT
- Academic medical center or hospital affiliation
- NCI-Designated Cancer Center affiliation
- NCCN affiliation
- Treatment rooms
- Number of gantries
- Number of fixed beam direction units
- Total cost
- Patient volume information
- Financial status

1. Growth of U.S. PBTCs

Figure 5 shows the annual growth in U.S. PBTCs from inception in 1990 through projected 2021. Growth in measured in terms of the number of centers and treatment rooms, the latter being a key determinant of capacity. In addition, the number of single-room PBSs is shown starting with the first installation in 2013.

Figure 5: Growth in Proton Beam Center, 1990-2021

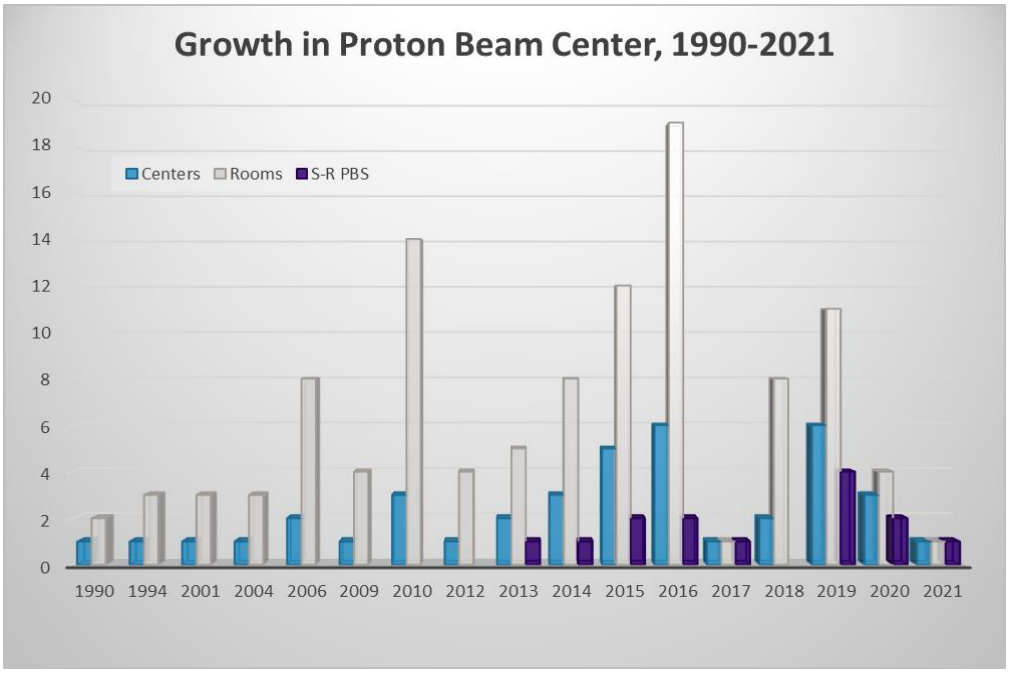
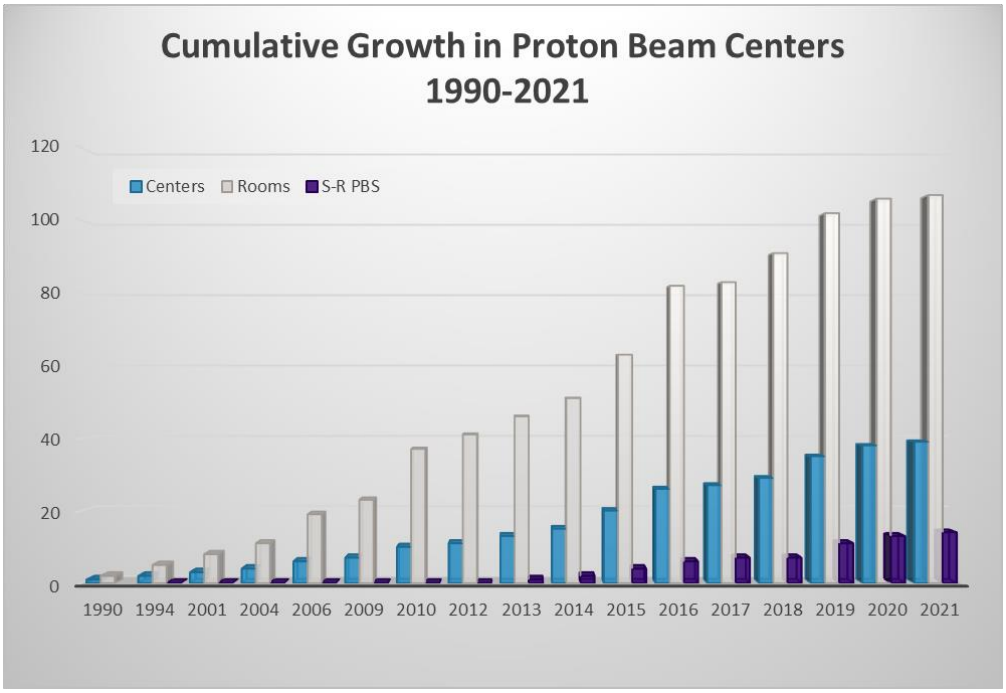


Figure 6 shows the cumulated growth over time.

Figure 6: Cumulative Growth in Proton Beam Centers, 1990-2021



The evolution of PBTCs in the U.S. falls somewhat neatly into four periods—1990-2001, 2004-2012, 2013-17, and 2018 to present.

a) 1990-2001

Three PBTCs were opened during this period.

The origins of these initial PBTCs is informative of the future success of newer centers.

- Loma Linda University Cancer Center opened and has continually operated since 1990. The center was largely funded by federal grants. Throughout its initial two decades of operations, it focused on treating high volume of patients with prostate cancer and has treated more patients than any other PBT facility in the world.
- The next center, UCSF-CNL Ocular Melanoma Proton Center in Davis, CA opened in 1994 treating only one particular type of cancer, ocular melanoma. The Proton Eye Treatment Facility was established at the Crocker Nuclear Laboratory at UC Davis making use of shared technology with the UC Davis lab. It often is not included in the count of PBT centers in the United States because of its specialized low radiation PBT which is not applicable to other types of cancers.
- The MGH Francis H. Burr Proton Therapy Center opened in 2001. Prior to 2001, MGH's PBT operations were primarily funded with Federal grants and MGH was able to seed its commercial cancer treatment technology using technology located at Harvard's Cyclotron Laboratory. In 2001, the new Francis H. Burr Proton Therapy Center opened at MGH's main campus with one operating treatment room. Two additional treatment rooms were opened in 2002 and 2003. In

2004, a second treatment station within an existing treatment room opened, followed in 2006 with another treatment station opening within another existing treatment room. In total, the Francis Burr center offers two double scattered gantries and one fixed horizontal beam room, and a second experimental horizontal beam room. MGH plans to open separate PBS gantry within its Massachusetts General Hospital's Department of Radiation Oncology. Approximately 47% of the 1,487 adult patients treated at Francis Burr were for ocular cancers from 2001-September 2006. During the same period, 51% of the 257 children treated at Burr were for CNS.[10]

Each of these three centers has been economically and clinically viable from their openings. Using existing technology largely funded through federal grants contributed to a solid capital structure. In addition, operating initially with limited competition enabled these centers to draw patients from a large geographic area, even nationally. Loma Linda faced no PBT competition regionally until Scripts (now California Proton Cancer Therapy Center) opened in 2014. Even then, the Scripts facility was financially challenged from its beginning, unable to attract sufficient patients to meet its financially burdensome capital structure. Similarly, MGH's Francis Burr center served the northeast U.S. until the ProCure Proton Treatment Center opened in Somerset, NJ in 2012. MGH benefits from a substantial patient catchment area in New England and in particular, the Boston MSA, and a leading first-mover advantage in delivering PBT. Its decision to expand its operations to include a new PBS at its main hospital suggests that MGH may be attempting to modernize its operations to better compete with new centers opening, such as the New York Proton Center, and perhaps even the other possible new entrants, such as the proposed CT PBT.

b) 2004-2012

The period from 2004 through 2012 marks the advent of true commercial focus on PBT. During this period, significant new capacity was added in the United States--eight new PBTCs offering a total of 43 new treatment rooms. All of these centers offered 3 to 5 treatment rooms and the costs of these facilities ranged from $125 million to $225 million (based on best publicly available information). Most of these centers were funded at least partially by investor groups. Some information is available on expected patient flow or total number of patients treated at a point in time. Of the eight centers that opened, five are known to be operating at risk, changed ownership, or refinanced their debt obligations. The Indiana University Health Proton Therapy Center closed in 2014 after operating unprofitably for ten years.

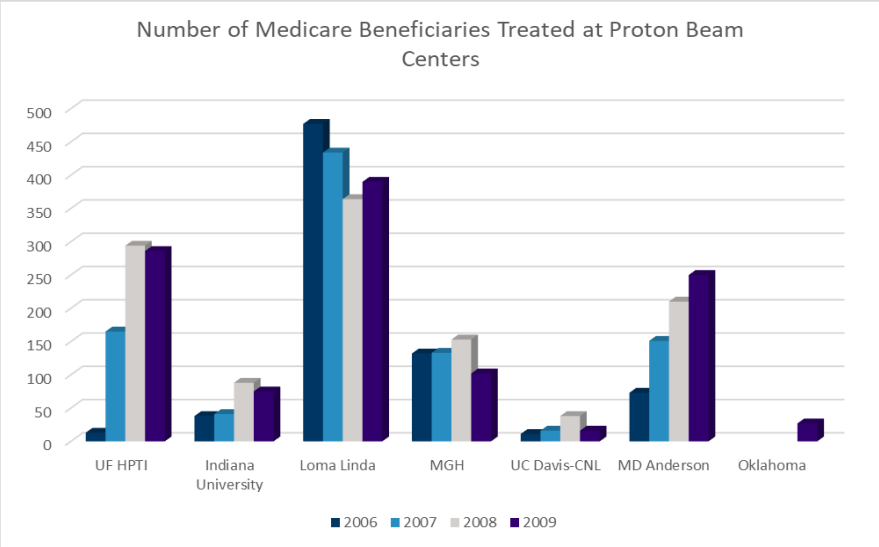
Indiana University Health Proton Therapy Center, which opened in 2004, also benefited initially from federal grants and existing cyclotron that was part of the University's physics lab. As it attempted to repurpose the existing cyclotron for clinical cancer treatment as federal funding diminished, it was unable to attract sufficient patient volume necessary to maintain its financial viability and was shuttered in 2014. Old technology equipment did little to attract referrals or patients and was highly inefficient. The Indiana PBTC also suffered from its location in Bloomington, IN which was more than 80 miles from

[10] Francis H. Burr Proton Therapy Center Presentation, 2006.

the Indiana University School of Medicine and had a commensurate lack of support from the medical school.

Little information is publicly available on the numbers of patients treated at PBTCs. To provide some reference, Figure 7 charts the number of Medicare beneficiaries treated at seven PBTCs between 2006 and 2009. Loma Linda had the greatest numbers of patients treated, although the number of Medicare patients declined during the period. The chart shows few patients treated at UC Davis-CNL, but this is not surprising given its narrower clinical focus. Both new facilities, MD Anderson and UF HPTI, showed increasing number of Medicare patients treated, whereas Indiana University continued to be challenged in attracting patients.

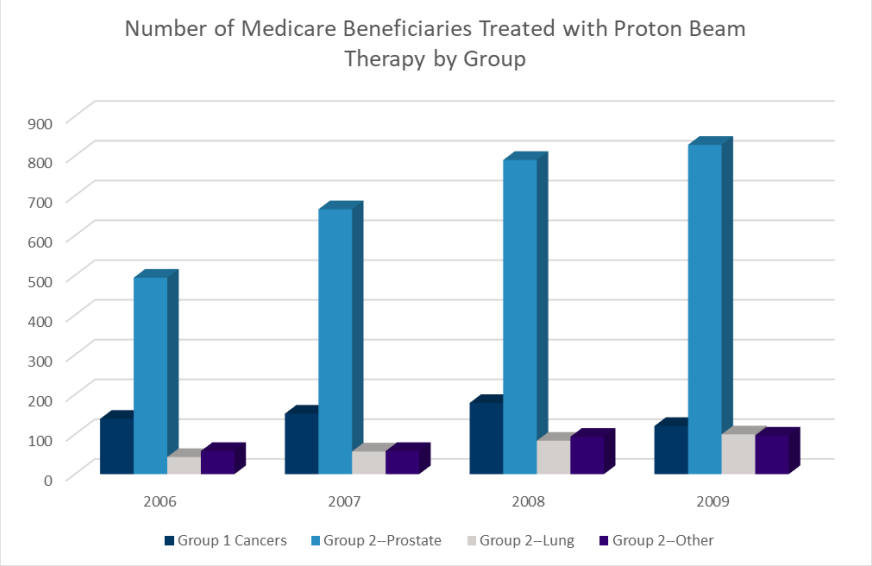
Figure 7: Number of Medicare Beneficiaries Treated at Proton Beam Centers



Source: AHRQ, Proton beam radiotherapy in the U.S. Medicare population: growth in use between 2006 and 2009

Most centers sited during this period expected to take advantage of the uptick in prostate cancer diagnoses and higher rates of proton beam treatment reimbursements, both government-funded and commercial insurance. Examining publicly available data on proton beam treatments for Medicare patients, the largest share of proton beam treatments in 2006 through 2009 were for prostate cancer. Investors and healthcare providers saw this as a steady, increasing flow of patient volume to support a center's highly debt-laden capital structure. Group 1 cancers, i.e., those recognized with established comparative clinical benefits when treated with proton beam, made up a small overall share of patients treated during these years, as shown in Figure 8.

Figure 8: Number of Medicare Beneficiaries Treated with Proton Beam Therapy by Group



Source: AHRQ, Proton beam radiotherapy in the U.S. Medicare population: growth in use between 2006 and 2009

In 2012, however, clinical trials began questioning the differential value or quality-adjusted price of PBT to treat prostate cancer. In particular, the California Technology Assessment Forum determined that no established support for a comparative advantage of PBT over other alternative treatment modalities. Similar findings were also published by the American Cancer Society. In addition, clinical research also was reporting findings of possible overtreatment of localized prostate cancer with Gleason scores of 6 or less.[11] This resulted in a marked change in treatment protocols for prostate cancers that adversely impacted PBTCs. These prostate cancer findings led to changes in reimbursement policies by government and commercial insurers either unwilling to pay for proton beam to treat prostate cancers at all or unwilling to reimburse at rates greater than competing treatment modalities.

The cohort of new PBTCs opening during this period shared common high capital cost structures and large capacity that required significant patient volumes to be economically viable. Many of these centers initially were able to draw patients, particularly prostate cancer patients, but were unable over the longer term to gain sufficient patient volume to support heavy debt.

c) 2013-2017

PBTCs opening during this period are a mix of large capacity, high capital cost facilities and new facilities taking advantage of new single-room pencil beam scanning technologies. Of the 18 centers that opened, four experienced some form of financial challenges over time—Seattle, San Diego, Knoxville, and Baltimore. All of these financially troubled PBTCs had high capital costs. Three of the four were not

[11] Gleason scores are a grading system used to evaluate the prognosis of prostate cancer based on prostate biopsy samples. Gleason scores range from 6-10. The higher the Gleason score, the more likely the cancer will grow and spread quickly. A score of 6 or less is considered indicative of a slow growing cancer.

aligned with any major academic medical center with a comprehensive cancer program. Five other centers opening during this period also had high capital costs, but these centers were all associated with a major academic medical center with large draw areas and an NCI-designated comprehensive cancer program.

Some limited public information is available on cancers treated with proton beam. Table 1 showing national data from The National Association of Proton Therapy ("NAPT") show that prostate cancer continued to be the driver for patient volumes during this period. The data also show some cancers treated with proton beam grew significantly and achieved significant volumes, including CNS, head and neck, lung, gastrointestinal tract, and breast cancers. The increase in clinical trials showing the comparative clinical efficacy of proton beam treatment for these particular cancers may have influenced these positive trends.

Table 1: Conditions Treated with Proton Beam, 2012-2017

Conditions Treated with Proton Beam: 2012-2017						
Conditions Treated	**CY2012**	**CY2013**	**CY2014**	**CY2015**	**CY2016**	**CY2017**
Central Nervous System	598	639	714	1,014	1,169	1,201
Intraocular Neoplasms	250	250	276	296	390	328
Pituitary Neoplams	50	64	71	44	35	28
Base of Skull or Axial Skeleton	179	239	270	232	249	259
Head and Neck	316	387	576	808	973	1,389
Lung	437	490	595	596	612	818
Soft Tissue Sarcoma	16	22	16	209	242	234
Pediatric	685	749	940	1,090	1,110	1,536
Gastrointestinal Tract	170	308	427	520	664	721
Urinary Tract	13	13	24	35	37	21
Female Pelvic Organs	24	29	42	38	59	96
Prostate	2,336	2,094	2,355	2,311	2,606	2,909
Breast	93	183	319	425	666	787
Lymphoma					164	158
Other	210	367	459	273	200	415
Total	5,377	5,834	7,084	7,891	9,176	10,900
Number of PBTCs	11	13	16	20	24	27
*Number of patients treated were estimated based on publicly available information (1 in 2015, 2 in 2016 and 1 in 2017)						

Source: NAPT

Another important metric of economic viability is the mix of complex and non-complex treatments which directly affects throughput and capacity utilization. Throughput is much greater for simple cases than for complex cases. The NAPT chart below shows that *simple, with compensation* and *intermediate* levels of complexity dominated the mix of treatments. The percentage of complex cases increased as a percent of total cases, from 11.2% in CY2012 to 16.7% in CY2017 while the percentage of simple cases decreased as a percent of total from 43.3% in CY2012 to 17.1% in CY2017, as shown in Table 2.

Table 2: Levels of Proton Beam Treatment Complexity, 2012-2017

Levels of Proton Beam Treatment Complexity: 2012-2017							
CPT	**Codes/Descriptions**	**CY2012**	**CY2013**	**CY2014**	**CY2015**	**CY2016**	**CY2017**
77520	Simple, w/o compensation	1,078	1,045	1,416	1,346	4,083	1,497
77522	Simple, w/compensation	58,260	48,876	40,620	45,086	42,968	48,187
77523	Intermediate	62,321	69,552	95,551	108,232	168,350	187,899
77525	Complex	15,369	20,662	28,741	26,890	34,439	48,414
77373	SBRT						4,353
Total		137,028	140,135	166,328	181,554	249,840	290,350
Total Respondents		9	11	14	16	21	26
Ratio of Treatments/Patient		28.8	29.3	27.4	27.4	27.5	26.9
Source: NAPT							

Payer mix also is an important factor in the viability of a PBTC (see Figure 3). Commercial insurers typically are willing to reimburse centers at a higher rate than government-funded payers, i.e., Medicare and Medicaid. Average payor mix accounted for by Medicare, Medicare-Advantage, Medicaid and Managed Medicaid shifted from 45.7% in CY2015 of total payor mix to 53.7% in CY2017.

This shift likely reflects commercial insurers' unwillingness during this period to cover PBT for cancers in which clinical trials had not established improved clinical efficacy over other alternative treatment modalities, given the higher reimbursement cost of proton beam treatment.

d) 2018 to present

Seven PBTCs opened between 2018 and 2019. Three of these, Georgetown MedStar, South Florida, and Stephensen in Oklahoma City, are single-room PBS centers. The remaining four, Emory, Provision CARES in Tennessee, Johns Hopkins in DC, and the New York Proton Center—exceeded $100 million in total cost, which is consistent with constructing 3-5 treatment rooms. Emory with five treatment rooms opened in 2018 after a lengthy delay caused by financing issues and an eventual change of ownership to complete the project. Of particular interest will be the likely competition between two centers located in Washington, DC. Georgetown MedStar opened in 2019 with one single-room PBS, expecting to treat 200 patients per year. It has reportedly achieved this projected volume. Johns Hopkins National Proton Center opened at Sibley Hospital in 2019 and has been advertising heavily in the DC metro area since opening. It is operating three single-room PBS treatment rooms and has the capacity to serve 1,500 patients per year. In addition, INOVA Schar Cancer Institute in Fairfax, VA is constructing a new PBTC that will house two treatment rooms. Together, six treatment rooms will be available within the DC-VA-MD MSA serving a population of 6.2 million (2017). This compares with the newly opened New York Proton Center which is supported by a consortium of leading hospitals in New York City--Memorial Sloan Kettering Cancer Center, Montefiore Health System, and Mount Sinai Health System—which expects to treat 1,400 patients annually.

2. Comparative assessment of financially challenged and successful PBTC

The proposed CT PBTC shares a number of potentially relevant attributes with other U.S. PBT centers that may be informative in understanding why some PBTC have or are financially challenged compared with PBTC that appear to be financially sound. The authors examined six attributes for which information was readily available on each PBTC as predictors of financial health. Our working hypotheses are:

- Affiliation with an academic medical center—affiliation increases the likelihood of financial soundness due to clinical focus, potential for clinical trials, access to patients with cancers treatable with proton beam, and referral base;
- Certificate of need requirement, either for siting new facility or purchasing significant capital equipment—requirement tends to constrain or limit capacity and creates additional hurdles to overcome for establishing financial soundness;
- Affiliation with an NCI-Designated Cancer Center—affiliation increases the likelihood of financial soundness due to clinical focus, potential for clinical trials, access to patients with cancers treatable with proton beam, and referral base;
- Affiliation with an NCCN—affiliation increases the likelihood of financial soundness due to clinical focus, potential for clinical trials, access to patients with cancers treatable with proton beam, and referral base;
- Single-room operation—attribute decreases volume of patient referrals required, reduces potential excess capacity, and lowers overall costs of treatment and capital costs, thereby contributing to financial soundness;
- PBS—attribute increases the precision and reduces potential long-term side effects from treatment, which increases likely volumes; and
- Capital cost less than $100 million—lower capital costs reduces need for large volume of patient referrals, reduces likelihood of significant debt exposure, thereby contributing to financial soundness.

Using publicly available information, the authors designated 11 PBTCs that are or have been financially challenged, as shown in Figure 9.[12] These include those that are currently operating, one that failed to open (Dallas), and another that closed (Indiana):

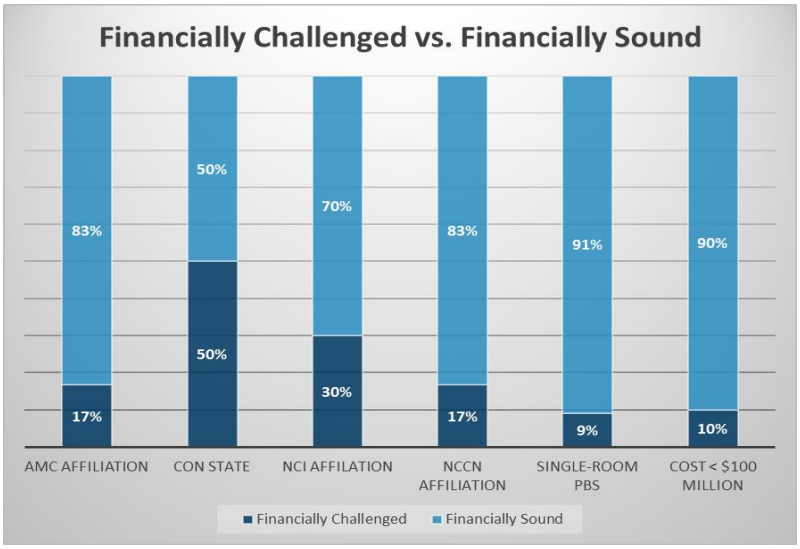
[12] Our designation of PBTCs as financially challenged is based on historical financial and other public data for purposes of informing this report. Initiatives not publicly available may alter these conditions in the near or long term.

Figure 9: Financially-Challenged U.S. Proton Beam Therapy Centers

California Protons Cancer Therapy Center	ProCure Proton Treatment Center – New Jersey
Emory Proton Therapy Center	Oklahoma Proton Center
Northwestern Medicine Proton Center	Provision CARES Proton Therapy Center – Knoxville
Indiana University Health Proton Therapy Center	Hampton University Proton Therapy Institute
Maryland Proton Treatment Center	Seattle Cancer Care Alliance Proton Therapy Center
Dallas Proton Treatment Center	

Figure 10 shows the results of an analysis of the above attributes cross-referenced with whether the PBTC is financially challenged.

Figure 10: Financially Challenged vs. Financially Sound



These results suggest that the CT PBTC shares the same attributes with other PBTCs that may contribute to financial soundness.

We recognize that other attributes, such as patient volume and payor mix, along with non-measurable attributes such as community support, leadership, and commitment, also contribute to viability and financial soundness. We lack sufficient visibility into these attributes at PBTCs to test their association with financial soundness.

The single-room PBS center with lower capital costs and required patient volume may foretell of a not insignificant increase in the construction of these centers. PBTCs aligned with NCI-Designated Comprehensive Cancer Centers, NCCN, or academic medical centers offer greater clinical focus, potential for clinical trials, access to patients with cancers treatable with proton beam, and a broader referral base than unaligned or associated centers. Based on review of the PBTCs, these factors appear to be associated with more financially sound PBT operations.

Currently, there are about 50 NCI-Designated Cancer Centers that are not affiliated with a PBTC. Similarly, there are 17 NCCN centers that have no affiliation with a PBTC. Should the single-room PBTCs continue to be financially sound over time, it is reasonable to expect that other NCI-Designated Cancer Centers or NCCN centers will follow HHC/YNHHS's efforts to set up proton beam treatment centers, thus increasing the competition for patients and clinical trials to establish the comparative efficacy of PBT.

III. COMPARATIVE ANALYSIS OF PROPOSED CT PBTC WITH OTHER CENTERS OPERATING IN THE U.S.

A. Changing dynamics of patients treated and willingness of commercial insurers to reimburse for treatment

Reimbursement for PBT has long been a conundrum. Three factors contribute to this dilemma:

- Lack of consistency in indications covered—Both commercial and government-funded reimbursements for PBT generally follow indication procedures established in 2009. Indications fall into two groups. Group 1 sets forth a list of indications for which PBT is determined to be medically necessary (or reasonable). This group has almost always consisted of at least ocular, brain, and CNS. Group 2 sets forth a longer list of indications for which it has been determined that PBT *may be* medically necessary (or reasonable) if certain requirements are met and documented. These requirements often vary by insurer, but typically have included evidence that PBT is clinically superior to alternative treatments and/or that the patient is being treated as part of a clinical trial. The dilemma has been that the number of clinical trials, particularly randomized clinical trials or RCTs, have been lagging due to the limited number of PBTCs.
- Establishing Medicare coverage rates—More formal reimbursement procedures emerged after the American Medical Association (AMA) set up procedure codes for PBT in the late 1990s. Prior to 2009, Medicare covered PBT generally but only set up individual treatment codes in 2009 and even then, reimbursement coverage fell to local coverage decisions (i.e., local Medicare administrative contractors).[13] Commercial reimbursements generally have followed Medicare, but at a premium, and often by restricting reimbursements to fewer medically-necessary cancers and greater numbers of coverage denials. Moreover, Medicare rates have been variable, increasing steadily from 2000 to 2007, then taking a sharp decrease from 2007 to 2009, followed by a return to 2007 levels in 2010 and 2011.
- Rates of coverage denials—Studies have shown fairly significant initial coverage denial rates followed by eventual approval for many medically reasonable indications.[14] In addition, one study found a significant disparity between Medicare and private insurance coverage for initial

[13] Ning MS, Gomez DR, Shah AK, et al. The insurance approval process for proton radiation therapy: A significant barrier to patient care. Int J Radiat Oncol Biol Phys 2019;104:724-733; Gupta A, Khan AJ, Goyal S, et al. Insurance approval for proton beam therapy and its impact on delays in treatment. Int J Radiat Oncol Biol Phys 2019;104:714-723; 6. Ojerholm E, Hill-Kayser CE. Insurance coverage decisions for pediatric proton therapy. Pediatric Blood Cancer 2018;65.
[14] Id.

requests. Prior authorizations can take up to four months. Patients may lose valuable treatment delays, and a significant number may simply choose to accept alternative treatments rather than continue with the delay authorization process.

Another source of reimbursement uncertainty is healthcare reform at both the state and national level. Efforts by both state and federal governments to moderate the increase in total healthcare expenditures in targeted at high cost providers and services. PBTCs with better capital structure, particularly lower or more favorable debt financing, more efficient technologies and operations, and more appropriately-sized capacity, will likely be better positioned to withstand changes in the payor mix and overall lower reimbursements for PBT.

B. Characteristics most similar to financially successful PBTCs

The key attribute of the proposed CT PBTC is that it is a single-room facility. As described above, single-room PBTCs have a smaller capacity, and therefore require fewer overall patients and treatments to operate at or near full capacity. Excess capacity is highly inefficient and contributes to poor financial performance. Table 3 identifies U.S. single-room current and proposed PBTCs.

Attributes discussed above as contributing to a PBTC's financial soundness are presented in Table 3**Error! Reference source not found.**. This chart compares attributes at the proposed CT PBTC with other single-room PBTCs. All of the single-room PBTCs for which public information is available also share the under $100 million cost structure.

Table 3: Single-Room PBTC Attributes

PBTC	State	Year Opened	CON Applicable for PBT	AMC	NCI-Designated Cancer Center affiliation	NCCN affiliation	Pencil Beam Scanning	Total Cost	Info on Patient volumes
Connecticut Proton Therapy Center, LLC	*Connecticut*	2022	√	√	√	√	√	$ 70,000,000	*Expected just under 500 patients per year at full ramp-up.*
Willis-Knighton Cancer Center	Louisiana	2014					√	$ 40,000,000	Treated about 200 patients [as of 2016]
Ackerman Cancer Center Proton Therapy Center	Florida	2015						$ 40,000,000	1000 patient treated [as of 2018]
The Laurie Proton Therapy Center at RWJ Barnabas Health	New Jersey	2015	√	√	√			$ 23,600,000	Not found
The Marjorie & Leonard Williams Center for Proton Therapy at Orlando Health	Florida	2016		√				$ 25,000,000	Expects 125 Patients/year; capacity of 225 patients
University Hospitals Proton Therapy Center	Ohio	2016		√	√	√		$ 30,000,000	Expected to treat 20-25 patients per day; 400 total treatments (June 2019); Below forecast
Beaumont Proton Therapy Center	Michigan	2017	√				√	$ 40,000,000	Expected 300 to 500 patients a year. Since July 2017, has treated 350 patients [as of 2019]; Below forecast
MedStar Georgetown University Hospital Proton Therapy Center	DC	2019	√	√	√		√	$ 40,000,000	Expected 200 patients a year; at capacity so far
South Florida Proton Therapy Institute	Florida	2019					√	$ 50,000,000	NA
Stephensen Cancer Center	Oklahoma	2019		√	√		√		
University of Alabama, Birmingham	Alabama	2020	√	√	√	√	√		
University of Miami Sylvester Comprehensive Cancer Center	Florida	2020		√	√		√		
Penn Medicine	Pennsylvania	2021		√	√	√	√		
S. Lee Kling Center for Proton Therapy Center at the Siteman Cancer Center	Missouri	2013	√	√	√	√	√ (2020)	$ 25,000,000	Treated 100 patients (2014)

Only two other PBTCs share all of the positive attributes identified as increasing the likelihood of financial soundness—University of Alabama Birmingham and the S. Lee Kling Center for Proton Therapy Center at the Siteman Cancer Center in St. Louis, MO. The Birmingham PBTC is scheduled to open in 2020 and is also a Proton International facility. Although the St. Louis PBTC opened in 2013, it currently does not have a PBS but will offer the technology this year. In terms of volume, CT PBTC's expected volumes are most similar to the Beaumont Michigan PBTC at 300-500 patients per year. No publicly-available information was available on actual volumes that have materialized at the Beaumont PBTC.

Most of the listed single-room PBTCs are affiliated with an AMC and most also have an affiliation with an NCI-designated comprehensive cancer center. Only a few have an NCCN affiliation. Few were required to undergo a CON approval process. None of the PBTCs in Table 3 are identified as financially challenged either currently or in the past.

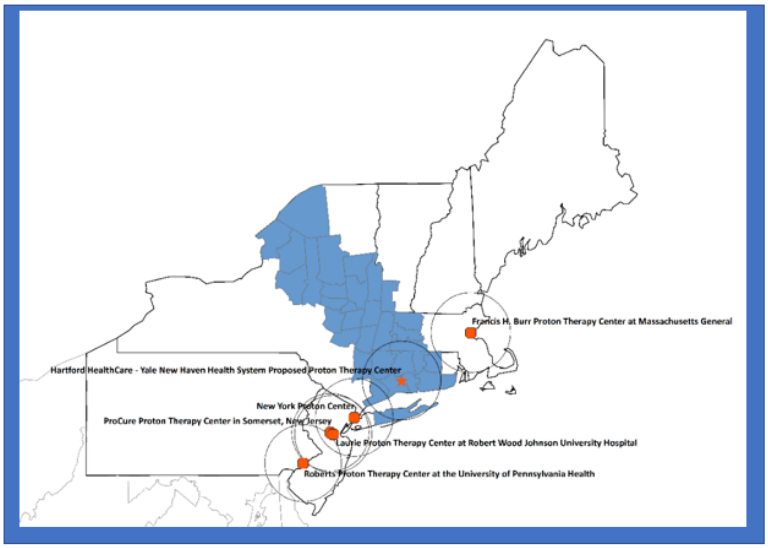
It is reasonable to infer a strong clinical focus from the affiliation of the PBTC with an AMC, NCI-designated comprehensive cancer center and NCCN. These affiliations increase the likelihood of patient referrals, and particularly, a sufficiently strong base of complex cancer patients most likely to benefit from PBT. In addition, the CT PBTC will benefit from having the technologically advanced PBT, including PBS, stereotactic radiosurgery, and IMPT, and associated treatment planning technologies. These attributes, along with lower capital costs than many earlier PBTCs, are consistent with other PBTCs that have not confronted significant financial challenges.

C. Competitive dynamics

1. Competitive analysis of PBTCs in New England / northeast, including specific attributes described above

Four PBTCs currently operate in the Northeast and upper Mid-Atlantic geographic areas. These would be the closest geographically-positioned competitors of the proposed CT PBTC. Figure 11 displays the location of these PBTCs and an 80-mile radius around the centers.

Figure 11: Map of CT PBTC Competitors and an 80-mile Radius



a) The MGH Francis H. Burr Proton Therapy Center

The MGH Francis H Burr Proton Therapy Center opened in 2002 and has treated more than 10,000 patients. It is also an international referral center for pediatric radiation oncology and has treated over 1,600 children.

The facility is located at Massachusetts General Hospital. Before 2002, patients were treated with protons at the Harvard Cyclotron Laboratory across the river at Harvard University. The facility is equipped with an IBA 230 MeV cyclotron which delivers the treatment beam to two 360° rotational gantries and a third treatment room housing a dedicated fixed horizontal beam ocular treatment line with a 70 MeV beam and a single scatter stereotactic assisted radiosurgery (STAR). It also has an experimental room with a horizontal beam. The two treatment rooms with gantries primarily treat pediatrics, brain, and head and neck cancers. Pencil beam scanning was added in the Fall of 2008.

A Radiance 330 single-room pencil beam scanning and integrated imaging and control system was installed at Massachusetts General's Department of Radiation in 2015. This was the first time that such technology had been installed within an existing, operating radiation oncology department. Modifications were subsequently made at the clinical site and the FDA approved the device in October 2019.

The main campus provides comprehensive therapeutic radiation services including brachytherapy (HDR and LDR), intraoperative electron therapy, TBI, SBRT, SRS, and kilovoltage treatments. In 2012, the department relocated most of the photon services into a new building on the main campus, located immediately adjacent to the FH Burr Proton Therapy Center.

The Center is affiliated with an NCI-Designated Comprehensive Cancer Center through MGH's membership in the Dana-Farber/Harvard Cancer Center. It also has an NCCH affiliation.

b) Laurie Proton Therapy Center at Robert Wood Johnson University Hospital (partner with Rutgers Cancer Institute of New Jersey)

The Laurie Proton Therapy Center opened at the Robert Wood Johnson Hospital in 2015 in a renovated MRI center. Other partners include the Rutgers Cancer Institute of New Jersey, which provides academic radiation oncologists to the Center, and the Rutgers Robert Wood Johnson Medical School. Bristol-Myers Squibb Children's Hospital provides on-site dedicated pediatric radiologists and anesthesiologists, pediatric neurosurgeons, urologists and medical oncologists. It cost $23.6 million and is a single-room pencil beam treatment center. The PBTC's affiliation with Rutgers Cancer Institute provides access to an NCI-designated comprehensive cancer center. Information also indicates that it receives patients from other NCI-designated comprehensive cancer centers, such as the Yale Cancer Center.

Publicly-available information indicates that the PBTC has operated at 98% capacity since opening. It currently treats 15-20 patients per day. Treatment mix is as follows: (1) intracranial region, 16.8%; (2) lungs, 14.4%; (3) craniospinal region, 4%; (4) prostate, 6.4%; (5) head and neck, 12%; (6) other 46.4%.[15]

[15] "Unprecedented Clinical Go-Live: Robert Wood Johnson University Hospital," www.mevion.com.

c) ProCure Proton Therapy Center in Somerset New Jersey

The ProCure Proton Therapy Center opened in 2012 and is the only center in New Jersey to offer pencil beam scanning. The Center has treated more than 5,000 patients since 2012, including many from the New York metro area. It had or may still have clinical affiliation agreements with Memorial Sloan Kettering, NYU, Northwell Health, Montefiore, and Mount Sinai. Presumably, those hospitals that are now part of the New York Proton Center consortium (all but Northwell) likely have or will end these affiliations now that the New York Proton Center has opened. It is not directly affiliated with an NCI-designated cancer center or part of the NCCN.

The PBTC operates four treatment rooms, including two inclined-beam rooms, a fixed beam room and a leading edge 360° gantry room. To assist in treatment planning and accuracy, the PBTC also has real-time imaging and robotic patient-positioning systems. Publicly-available information indicates that the Center cost $160 million.

d) New York Proton Center

The New York Proton Center opened in July 2019 in East Harlem as a for-profit partnership, owned and operated by a hospital consortium composed of Memorial Sloan Kettering Cancer Center, Montefiore Health System, Mount Sinai Health System. ProHEALTH, which is a multi-specialty health care network, provides back end business support for the center. The estimated cost of the PBTC has been announced at $300-$330 million. It will offer not only patient treatments but also will engage in clinical trials. The PBTC consists of the latest technological advances, including a second-generation pencil beam scanning and volumetric imaging to assist physicians in more precisely identifying and targeting cancers. Construction did not start until July 2015 although it had been in the planning stage for five years prior to construction start. Publicly-available information indicates that 40% of the costs is associated with the treatment equipment itself. The PBTC has a staff of 23 proton therapy trained radiation oncologists.

Expected patient volume at full capacity is 1,400 patient per year drawn primarily from the New York metro area, including an estimated 200 pediatric patients. Prior to opening, patients in New York metro area were referred to the ProCure center in Somerset NJ (4 treatment rooms) and the Laurie Proton Therapy Center at the Robert Woods Johnson University Hospital (1 treatment room) in New Brunswick, NJ. Pediatric patients were often referred to PBTs in Boston or Philadelphia.[16]

The New York Health Facility Planning originally filed with the New York State Hospital Review and Planning Council in March 2010. At that time, there were eight operating PBTCs in the United States and the ProCure PBT center in southern New Jersey was in development. It would operate a single gantry, two inclined beam rooms and a fixed beam room. [17]

At the time of application, New York Proton estimated that of the 99,124 new cancer cases in New York between 2003 and 2006, more than 13,000 of these cancer cases involved tumors sites that could

[16] WSJ, "New York's First Proton Therapy Center to Open in July", May 16, 2019.
[17] Memorandum to Members of the State Hospital Review and Planning Council from Thomas Jung, Acting Director, Division of Health Facility Planning, March 11, 2010 re Proton Beam Therapy.

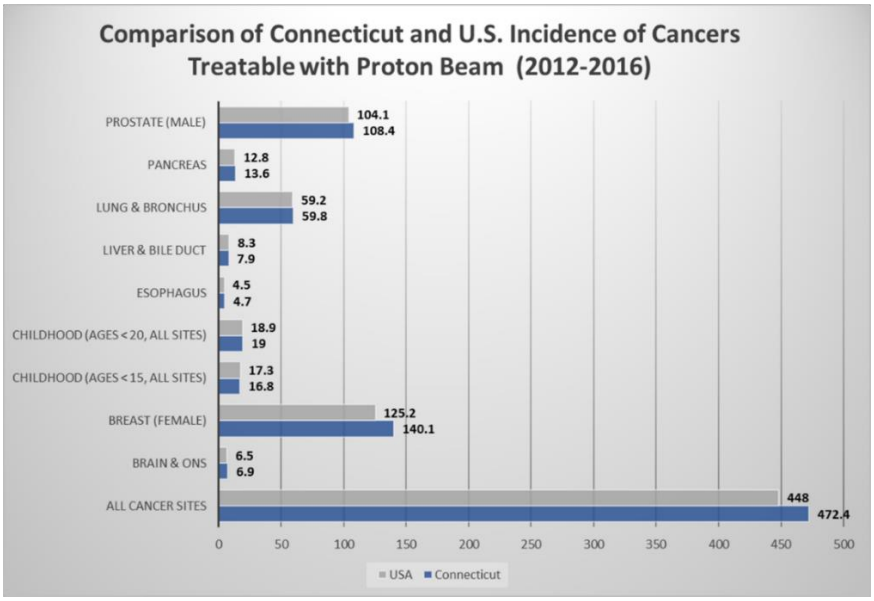
comparatively benefit from proton beam treatment.[18] New York Health Facility Planning was promoting the idea of a consortium for establishing the PBTC. Advantages cited were: "(1) the ability to pool clinical, financial, and administrative resources in developing an expensive and complex facility; (2) the opportunity to collaborate in developing treatment protocols and clinical studies; and (3) the opportunity to concentrate patients in a single facility, in order to improve clinical experience through high patient volume, rather than dispersing patients to duplicative facilities." The Planning authority cited governance and administrative issues as possible disadvantages.

2. Assumptions used to estimate CT PBTC patient volumes

Several factors enter into assessing whether the projected PBT patient volumes provided in the CT PBTC CON application are aggressive or conservative. This section evaluates those factors and the assumptions used in the projected patient volumes for reasonableness and support. As discussed above, early assumptions of patient volumes at PBTC contributed to significant financial challenges when projected volumes failed to materialize. Several PBTCs were forced to restructure or re-finance debt obligations and several developers filed for bankruptcy. Factors affecting patient volumes generally include (1) the incidence of cancers treatable with PBT, (2) the center's likely patient draw or referrals area, (3) the availability of demand substitutes, and (4) payers' willingness to pay for treatment. These are discussed in more detail in Section II above.

Connecticut's relative incidence of cancers that are considered treatable with proton beam are shown in Figure 12. Connecticut's cancer incidence is higher than the overall U.S. incidences for all PBT treatable cancers except childhood cancer for ages below 15. This suggests that potential demand for PBT may be somewhat higher in Connecticut relative to the U.S. based on disease incidence.

Figure 12: Comparison of CT and U.S. Incidence of Cancers Treatable with Proton Beam, 2012-2016



[18] *Id*.

a) HHC/YNHHS methodology for estimating patient volumes

Targeted PBTC draw areas have included regional, state, and metropolitan areas. Early on, PBTCs assumed large regional if not national draw areas for patient volumes. The New York Proton Center projects its volume will primarily draw from the NYC metro area. Data from Medicare indicate that Connecticut residents have obtained PBT from neighboring New Jersey.[19] We are aware that hospitals in the New York metro area, including the partners in the New York Proton Center, have referred patients to the New Jersey PBTCs, particularly the Somerset PBTC in the past. We would expect that with the opening of the New York Proton Center, both the Francis H. Burr PBTC in Boston and the two New Jersey PTBCs will see a decline in patients from the New York metro area as those patients will now be referred into the New York PBTC. Similarly, patients from Connecticut that may have been referred to Boston or New Jersey will likely find it more convenient to receive PBT at the CTPBTC. Moreover, because HHC and YNHHS provide a large portion of cancer clinical and support services in Connecticut, receiving treatment at a facility within the YNHHS and HHC systems is in furtherance of more integrated clinical protocols of care, which in our experience, leads to better patient satisfaction, better outcomes, and lower total cost of care. This issue is addressed in more detail in Section IV.

In projecting patient volumes for the CT PBTC, HHC/YNHHS assumes a patient draw area commensurate with the state of Connecticut. As there are no other PBTCs in Connecticut, this assumption seems reasonable. Moreover, the closest PBTCs to any Connecticut resident is the New York Proton Center (70 miles from YNHHS and 110 miles from HHC), Francis H Burr center in Boston (140 miles from YNHHS and 100 miles from HHC), and the ProCure center in Somerset, NJ (130 miles from YNHHS and 150 miles from HHC).[20] Each of these PBTCs is further for residents in Connecticut, and in many cases significantly further, than the planned Wallingford site.

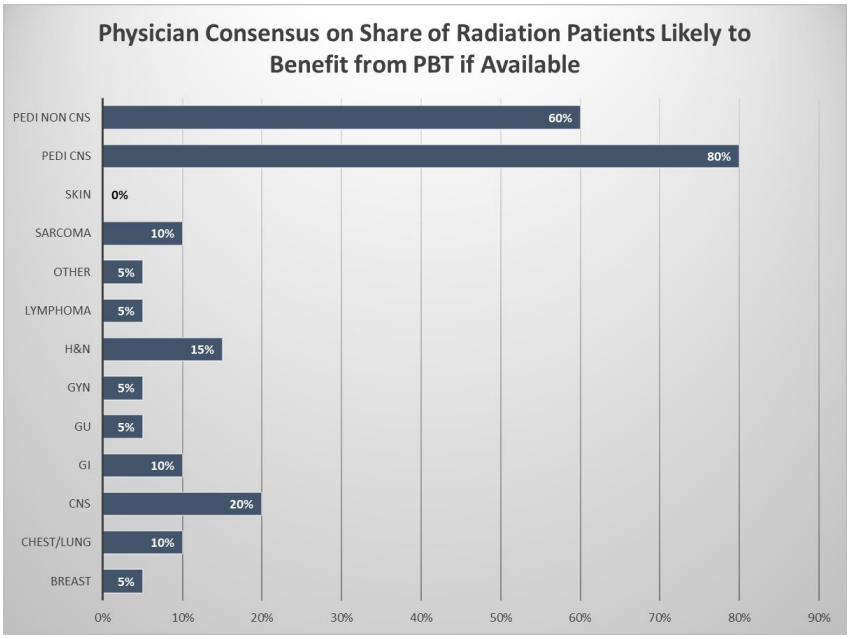
HHC/YNHHS estimated projected patient volumes based on 2012-2016 data from the Connecticut Tumor Registry ("CTTR"). To estimate cancer incidences for 2018, the starting point for this analysis, the methodology begins by averaging 2012-2016 cancer incidence for cancers most likely to be treated with PBT. From this, HHC/YNHHS estimates a tumor cancer base of 23,749 on an average annual basis. HHC/YNHHS assumes based on their own experience that approximately 60% of these patients are treated with radiation therapy. Using MOSAIC which tracks radiation oncology patients, YNHHS and HHC identify actual 2018 patients diagnosed and treated with radiation therapy at HHC or YNHHS facilities for each of these cancers.[21] This results in 3,241 radiation oncology patients at YNHHS and 2,637 patients at HHC in 2018.

To estimate potential volume at the proposed CT PBTC, HHC and YNHHS worked with in-house radiation oncologists and other experts to reach a consensus on the percentage of cancer patients that would likely be referred for PBT, by type of cancer, as shown in Figure 13. This consensus on referrals is applied

[19] It is possible that Connecticut residents have also sought PBT from the Francis H. Burr PBTC. However, Medicare data for the Burr PBTC is not available.
[20] Miles are approximate and rounded.
[21] YNHHS excludes patients treated with gamma knife as these patients would not be referred to proton beam. HHC also excludes some sarcoma cancer patients treated with radiation to reflect lower expected referrals to PBT for this type of cancer at HHC.

to YNHHS, HHC and the State tumor registry (after applying the 60% adjustment for radiation treatment).

Figure 13: Physician Consensus on Share of Radiation Patients Likely to Benefit from PBT, if Available



This results in a total statewide PBT eligible patient base of 992, of which 281 originate from YNHHS and 253 from HHC. The remaining 458 PBT eligible patients are assumed to originate from all other providers. Radiation treatments referred by YNHHS or HHC to community-based radiation oncologist are captured in Other. From this, HHC/YNHHS assumes that 10% of referred patients to the new CT PBTC will originate from Other providers in the first year of operation. This increases to 15% in the second year and thereafter, 20% of CT PBTC patients originate from Other providers. Of the remaining volume, YNHHS refers about 53% and HHC refers 47% each year.

The methodology assumes that patient volumes ramp-up over a two-year period before reaching expected capacity. Table 4 shows the modeled patient volumes for Year 1 (FY2022) through Year 4 (FY2025).

Table 4: Modeled Proton Volumes, Year 1 to Year 4

	Modeled Proton Volumes	Shifted Volumes from Conventional RT		
	Total	YNHHS	HHC	Other
Year 1	208	98	89	21
Year 2	397	178	160	60
Year 3	479	202	182	96
Year 4	487	205	185	97
Total	1,571	682	615	274

These projected CT PBTC patient volumes can be compared with the 2018 estimated base of 992 PBT eligible patients. Applying the consensus referral rates for specific types of cancers, HHC/YNHHS's

methodology results in conservative CT PBTC volumes for Year 1 (2022) through Year 4 (2025) relative to 2018 estimates of the eligible patients, i.e., approximately 21% in Year 1, 40% in Year 2, 48% in Year 3, and 48% in Year 4.

3. Impact on other competing CT radiation oncology programs

The projected volumes for the CT PBTC are based on a shift in treatment from standard radiation oncology treatments to PBT. These treatments include 3-D conformal radiation, IGRT, IMRT, IORT, and internal radiation therapy, i.e., brachytherapy. Other providers in Connecticut currently offer these services to patients, including HHC and YNHHS. Table 5 shows acute care general hospitals and Children's hospitals that offer radiation oncology treatment. These programs are expected to lose some patient volumes to the proposed CT PBTC.

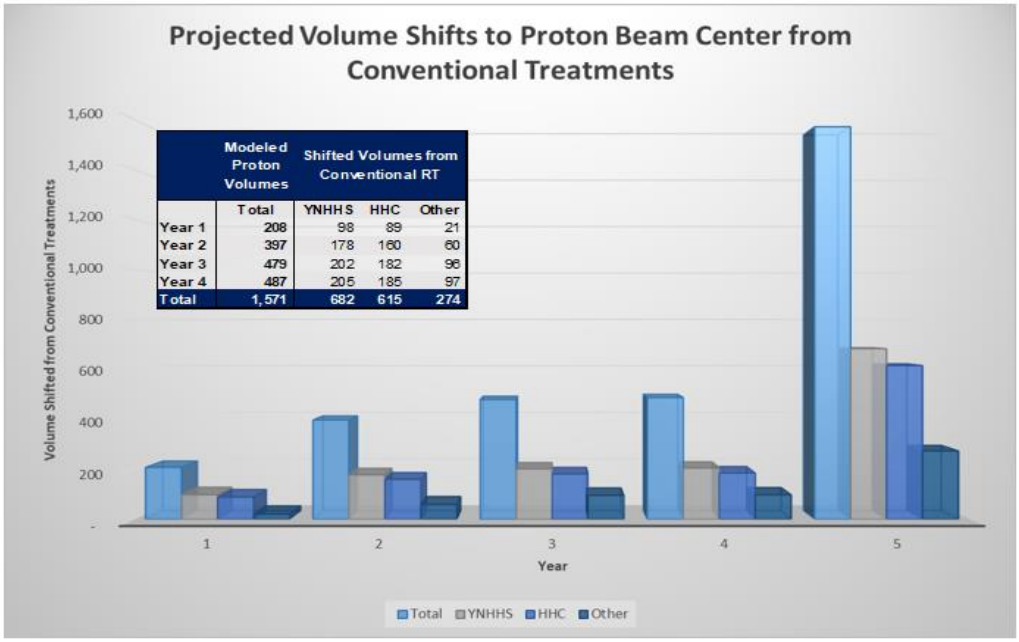
Table 5: Connecticut Acute Care General and Children's General Hospitals Oncology Treatment-Related Service Lines

SERVICE LINES	Backus	Bridgeport	CCMC	Danbury	Dempsey	Greenwich	Griffin	Hartford	HOCC	Hungerford	Johnson	L&M	Manchester	Middlesex	MidState	New Milford[a]	Norwalk	Rockville	Sharon	St. Francis	St. Mary's	St. Vincent's	Stamford	Waterbury	Windham	Yale NH
Radiation Oncology - Inpatient	x	x	x	x	x	x	x	x	x	x		x	*n*	x	x	x	x	*n*		x	x	x	x			x
Radiation Oncology - Outpatient	x	x	x	x	x	x	x	x	x	x	m	x	*n*	x	x	x	x	*n*		x	*j*	x	x	*j*		x

[a]New Milford Hospital is a satellite campus of Danbury Hospital under same license. The service lines at this satellite location continue to be listed in the New Milford column.
[i]PET-CT scanning, outpatient chemotherapy services, outpatient medical oncology services and outpatient radiation oncology services for St. Mary's Hospital and Waterbury Hospital by The Harold Leever Regional Cancer Center.
[m]Outpatient radiation oncology services are provide for patients of Johnson Memorial Hospital by its affiliate, the Northeast Regional Radiation Oncology Network (NRRON).
[n]Outpatient Cancer Center services are provided for patients of Manchester and Rockville by its affiliate, the NRRON.
Source: Connecticut Office of Health Strategy

Figure 14 shows the trended projected volume shifts to the proposed CT PBTC from conventional radiation treatments at YNHHS, HHC, and other radiation treatment facilities. The majority of the impact occurs internally at YNHHS and HHC.

Figure 14: Proton Volume Shifts to Proton Beam Center from Conventional Treatments



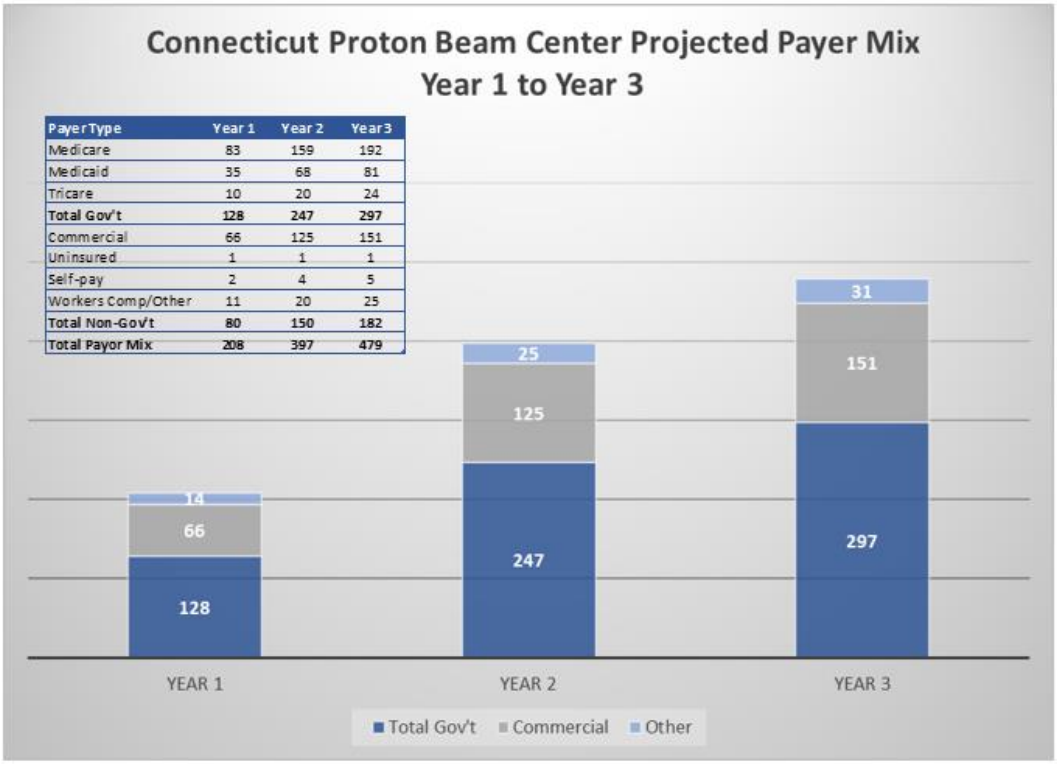
Section IV below discusses the relative costs and benefits of radiation treatments compared with PBT.

4. Assumptions relating to reimbursement and payer mix

a) CT PBT payer mix assumptions

As presented in the CON application, Proton International estimated likely payer mix at the proposed CT PBTC using payer mix volume data from their respective cancer services programs and general knowledge of the marketplace. The projected payer mix is based on Proton International's experience and knowledge of PBTC reimbursements, as shown in Figure 15.

Figure 15: Connecticut Proton Beam Center Project Payer Mix, Year 1 to Year 3



b) References to established ASTRO Model Policies and insurer guidelines and policies for PBT reimbursement

As part of our independent analysis, we reviewed the most current ASTRO Model Policy dated June 2017 and 2020 PBT reimbursement policies of the major healthcare insurers in Connecticut. These insurer reimbursement policies are summarized in Table 6.

Table 6: Top Commercial Insurers in Connecticut

Cancer Type	Top Commercial Insurers in Connecticut									
	Anthem BCBS		UHC/Oxford		Aetna (eviCore)		Emblem Health (ConnecticutCare)		Cigna (eviCore)	
	Policy	Appeal	Policy	Appeal	Policy	Appeal	Policy	Appeal*	Policy	Appeal
Bone & Soft Tissue				✓						
Brain & CNS	✓		✓		✓		√++		✓	
Breast		✓		✓						
Cervix & Uterine				✓						
Chest/Lung				✓						
Genitourinary				✓						
GI (Digestive)		✓***	✓**	✓	✓**	✓***	✓**		✓**	✓***
Head & Neck	✓		✓		✓				✓	
Lymphoma				✓						
Other	✓*		✓*		✓*		✓*		✓*	
Skin				✓						
Pediatric	✓		✓		✓				✓	
Prostate				✓			√+			

✓*	Ocula Melanomas	√+	Chondrosarcomas, chordomas, malignancies requiring CSI
✓**	Unresectable hepatocelluluar carcinomas	√++	Stage IIA seminoma
✓***	Pancreatic	*	Not available

As is apparent from this chart, it is reasonable to assume that cancers falling into ASTRO Group 1 likely would be reimbursed at some negotiated rate by commercial insurers, although some only after denials and appeals. Those cancers falling outside of Group 1 are more uncertain and may require a diligent reimbursement process to ensure PBT eligible patients are approved and receive timely treatment.

In estimating patient volumes at CT PBTC, HHC/YNHHS have conservatively factored these issues into their estimates by assuming only a portion of the estimated radiation oncology patients would benefit from PBT (thus designated as PBT eligible) and further, less than half of those PBT eligible patients would actually be referred to the CT PBTC. The consensus percentages applied to radiation oncology patients follows fairly closely with Group 1 and non-Group 1 cancers, although the tumor categories are much broader in scope. Based on our review of these reimbursement policies, we find this approach to be reasonable.

c) Relevant litigation/legislative outcomes

Another factor that likely will increase the propensity of commercial insurers to approve cancer patients for PBT are lawsuits by insured members against insurers that deny PBT coverage. Aetna and UnitedHealthcare have been sued and lost in member lawsuits. Successful lawsuits have focused on incidences where the patient's oncologists have recommended PBT due to potential risk factors, such as toxicity or location of the tumor. Aetna, for example, was found liable in 2018 in Oklahoma for $15.5 million in actual damages and $10 million in punitive damages when it denied coverage to a member with stage 4 nasopharyngeal cancer. The deceased member's physician recommended PBT because the

tumor was near the brainstem. Aetna denied coverage citing PBT was experimental and investigational.[22]

Such lawsuits have spawned legislation at the state level to ensure that patients receive insurance coverage where appropriate. The Proton Therapy Access Act granting Tennessee state employees access to PBT took effect on January 1, 2020. Access to PBT allows any person covered by a state employee health plan who is diagnosed with cancer to receive hypofractionated proton therapy if the physician and patient believe it would be beneficial to their treatment plan. The Virginia legislature passed a bill in 2017 making it illegal to hold PBT to a different standard than other treatment modalities. The Mississippi legislature has a similar bill currently before it.

The Illinois legislature also is considering legislation that would guarantee coverage for "medically necessary hypofractionated proton therapy protocol to deliver a biological effective dose by paying the same aggregate amount as would be paid for the delivery of the same biological effective dose with a standard radiation therapy protocol delivered with intensity modulated radiation therapy for the same indication if specified conditions are satisfied." The bill would further require that the insurer "may not impose an annual deductible, coinsurance, or other cost-sharing limitation that is greater than that required for radiation therapy and other similar benefits within the insurance policy or contract." [23]

Activity around proposed and enacted legislation involving proton beam reimbursements centers on ensuring access to proton beam therapy when physicians and patients believe the treatment to be medically necessary or in the best clinical interest of the patient or barring holding PBT to a different approval standard than other alternative treatments. In addition, some legislation has proposed that insurers must pay at least the rates commensurate with alternative radiation treatment modalities to ensure non-discriminatory access by patients. The latter is a risk to PBTCs in that it fails to recognize the higher costs currently associated with delivering PBT although it could prompt greater patient volumes by making payers indifferent between PBT and alternative radiation treatments. It is uncertain what form access to PBT will take in the future, but there is at least some appetite on the part of some states to legislate access to PBT rather than allow litigation to set the standard.

d) Reasonableness of the assumed payer reimbursement rates

The financial projections for the proposed CT PBTC assume estimated reimbursement rates by type of payer. Table 7 presents the current Medicare payment rates that were used in the financial projections.

[22] "Jurors' Decision Against Aetna Highlights Proton Beam Therapy in Cancer Care," November 15, 2018 at https://www.ajmc.com/focus-of-the-week/jurors-decision-against-aetna-highlights-proton-beam-therapy-in-cancer-care.
[23] Illinois HB5230.

Table 7: Current Medicare Payment Rates for PBT Procedures

Procedure Code	Description	Par Amount
77520	Proton, simple without compensation	$818.20
77522	Proton simple	$840.24
77523	Proton, intermediate	$996.93
77525	Proton, complex	$1,061.46

These rates do not include associated procedures necessary to conduct PBT, such as treatment planning, quality assurance, and imaging. Proton International estimates that on average, the Medicare reimbursement rate is around $1,180 per fraction, recognizing that Procedure Code 77523 is the most commonly coded. Basing all other reimbursement rates as an "upcharge" on Medicare rates, the financials assume the rates by payer mix as shown in Table 8.

Table 8: CT PBTC Assumed PBT Reimbursement Rates by Payer

Payer	% of Medicare
Medicare	98%
Medicaid	65%
CHAMPUS & TriCare	120%
Commercial	230%
Uninsured	25%
Self-pay	149%
Workers Comp	100%
Other	200%

We understand that these upcharges are based on the experience and marketplace knowledge of Proton International. We evaluated the reasonableness of these estimates by reference to MarketScan® data, which indicates that commercial reimbursements appear to be 310-340% of Medicare. As a result, the commercial estimates used in the financial analysis appear reasonable to us. For Medicare, the estimated reimbursements also appear consistent with Medicare data we have reviewed.

e) Reasonableness of the HHC/YNHHS approach to estimating payer mix

As discussed earlier, a degree of uncertainty continues to exist around both government-funded and commercial reimbursements for PBT. Several factors weigh in favor of relatively greater volumes of patients being approved for PBT in the future relative to today's approvals. More clinical trials are underway, particularly RCTs, that have tended to show the longer-term clinical benefits of PBT relative to other radiation therapies. In addition, smaller, more efficient PBTCs with both greater clinical and economic efficacy will likely bring down the cost of PBT relative to alternative treatment modalities. Using historical reimbursement payer mixes to project PBT payer mix seems reasonable in that it implicitly captures cancer incidence by age which affects payer mix. Moreover, as discussed elsewhere in this report, Medicare approval rates for PBT are greater than commercial approval rates. All of these

factors weigh in favor of the reasonableness and conservativeness of the payer mix projection methodology used by HHC/YNHHS.

D. Review of financial modeling—potential sensitivity analyses around key underlying assumptions to show robustness of estimates

The three key assumptions driving revenues in the HHC/YNHHS financial model are patient volumes, payer mix, and reimbursement rates. Our review of the methodologies and assumptions used by HHC and YNHHS appear to be reasonable and conservative based on the data available.

IV. ECONOMIC ANALYSIS COMPARING THE COST OF PROTON THERAPY VERSUS CONVENTIONAL RADIATION THERAPY FOR THE TYPES OF CANCERS PROPOSED FOR TREATMENT AT THE CENTER

In assessing the costs and benefits of PBT versus conventional radiation treatment, we examine the relative costs of such treatments in terms of patients' out-of-pocket costs and insurer reimbursements to providers. We also examine the relative cost to employers in terms of absenteeism and presenteeism. Lastly, we examine the costs and benefits to the state of developing the CT PBTC.

For estimating the relative costs of PBT versus other treatment modalities, we rely on three data sources:

- The IBM® Watson MarketScan® Commercial Claims and Encounters outpatient data consist of commercial claims from 2015-2018 and includes approximately 25 million covered lives.[24] The dataset captures person-specific healthcare utilization and expenditures across a spectrum of care including inpatient, outpatient, and prescription drug utilization. The dataset contains actual payment information at both the individual (i.e. the copay and/or deductible) and the insurer level for the relevant patient sample. These data can be used to provide an understanding of existing demand for services by detailing the frequency of specific diagnoses in a given MSA sample or other sample.[25] The claims data allow us to report the frequency of procedures and the payment paid to perform specific procedures in a geographic area. Patients have unique enrollment IDs which permit tracking over time to the extent the person remains enrolled with the captured insurer. The data represents a sample and should not be construed to capture all patients undergoing PBT and radiation therapy treatment in any given geographic areas covered.
- The CMS Medicare claims database contains a 100% sample of Medicare Inpatient Discharges and hospital-based outpatient visits. The dataset includes attending physicians' NPI (physician identifier), procedure (HCPCS Codes), diagnoses (up to 21, including principal diagnosis), payment information from both provider and beneficiary (i.e. Part B deductible and coinsurance), and patient information (including county and a unique identifier). As with the IBM® Watson MarketScan® data, the data provides the diagnoses a patient received and

[24] Copyright © 2020 International Business Machines Corporation. All Rights Reserved. Certain data used in this study were supplied by International Business Machines Corporation. The analysis is solely that of the authors, and not IBM.
[25] Locational information refers to the patient location, not the provider location.

procedures she underwent, and when and where they occurred. In addition to tracking patients over time, the data allows us to track the physicians providing care to patients. The data spans 2015 to 2017.

- CMS Medicare Provider Utilization and Payment Data: Physician and Other Supplier (Physician Payments). This dataset spans three years (2015-2017) and contains data on payments, utilization, place of service, and procedure provided to Medicare beneficiaries by over 980,000 healthcare providers. The data are sourced from the CMS's National Claims History Standard Analytic Files, which includes 100% of Medicare Part B final action claims for enrolled fee-for-service beneficiaries. The data only includes fee-for-service beneficiaries and censors providers with fewer than ten patients seen.

A. Cost / benefit analysis for patient stakeholders

1. Relative treatment costs, including cost borne directly by patients, e.g., travel time, out-of-pocket costs, indirect costs (absenteeism, presenteeism)

a) Travel Time

Because PBTCs require large capital investments to build and operate, these centers typically require a much larger patient draw area than traditional radiation cancer treatments. Consequently, a large number of patients will travel fairly large distances to reach one.

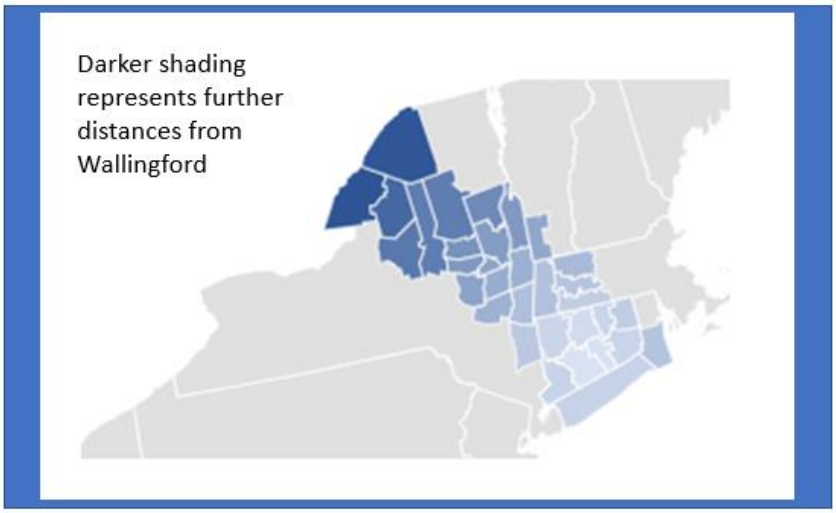
The average distance the patient travels for PBT is 86 miles.[26] For MGH's facility in Boston, MA, the number is very close to the average, 85.3 miles. Perhaps not surprisingly, The Mayo Clinic has among the highest travel distances for its patients, second only to Loma Linda in Los Angeles.

Of the 62,676 PBT visits in the Medicare data for Connecticut providers, for approximately 4,201 visits, the proposed facility would be closer than another facility visited. This includes patients who travel beyond their closest facility. Of those, 86% (3,600) were visits to Francis H Burr center at MGH. Unfortunately, the Medicare hospital-based outpatient data does not include the New York Proton Center since it just opened, and those patients are not yet included in these statistics.

Figure 16 shows the counties that would be closer to the proposed PBT center than to any other PBT center (darker color gradients represent further distances from the proposed PBT). For the 39 counties where the proposed PBT center is closer, the average distance saved is 31 miles.

[26] These estimates are based on hospital-based Medicare claims for PBT. Neither non-hospital based Medicare claims, nor the commercial claims database include geographic information for both the payer and the provider. These values, therefore, do not represent all patients or all PBT facilities.

Figure 16: Counties Close to New PBT Center



B. Utilization and Payment by Cancer Type

Table 9 below shows the volume, number of visits, and payments broken out by cancer type for commercial payments across the United States. The sample volumes are not especially high, and the visits reinforce the fact that, while most PBT patients have five sessions a week, the number of weeks treatment lasts for PBT varies by type of cancer. Also, because the volumes are low and patients' cancers are not uniform, there is natural variability in the estimated volumes from year to year.

There is large variability in the out-of-pocket costs, ranging from zero (usually in years and for cancers with few enrollees) to $2,722 in 2015 for prostate cancer. The average, however, ranges from about $700 in 2018 to nearly $1,000 in 2015. Average insurer payments in 2018 tend to be lower than 2015 in total insurer payment for most cancer types, the exceptions being ocular and other, as shown in Table 9.

Table 9: Commercial PBT Utilization and Payments by Cancer Type, 2015-2018

		2015				2016				2017				2018			
Group	Cancer	Unique Enrollees	Average Visits	Average OOP	Average Insurer Payment	Unique Enrollees	Average Visits	Average OOP	Average Insurer Payment	Unique Enrollees	Average Visits	Average OOP	Average Insurer Payment	Unique Enrollees	Average Visits	Average OOP	Average Insurer Payment
1	Liver	12	15	$ -	$ 70,700	12	15	$ -	$ 52,149	8	20	$ -	$ 57,860	7	16	$ -	$ 35,272
1	Ocular	89	7	$ 95	$ 18,307	80	6	$ 223	$ 16,555	130	7	$ 62	$ 20,160	72	7	$ 666	$ 25,383
1	Pediatric	408	24	$ 208	$ 89,992	436	22	$ 888	$ 81,861	503	19	$ 618	$ 69,447	848	21	$ 943	$ 71,344
1	Reirradiation	24	18	$ 993	$ 77,688	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
1	Spine	30	22	$ -	$ 84,389	12	29	$ 1,466	$ 150,330	61	24	$ -	$ 68,852	36	21	$ 613	$ 54,305
2	Bone	142	28	$ 650	$ 97,079	196	23	$ 676	$ 73,391	183	24	$ 557	$ 62,685	251	26	$ 889	$ 96,703
2	Lung	65	19	$ 22	$ 67,180	55	21	$ 945	$ 88,039	84	23	$ 259	$ 66,973	36	13	$ 540	$ 36,234
2	Prostate	508	32	$ 2,722	$ 85,111	478	30	$ 1,285	$ 72,123	313	27	$ 617	$ 60,557	287	25	$ 1,168	$ 57,851
	Other	993	22	$ 815	$ 74,397	1,313	23	$ 1,061	$ 81,387	1,586	22	$ 574	$ 77,095	1,774	20	$ 510	$ 75,503

Source: Marketscan Data
Notes: Group 1 cancers identified from ASTROPBTModelPolicy.pdf

Table 10 presents similar information derived from the hospital-based Medicare data. Here, too, all other types of cancers represent the majority of PBT treatments. Also, the Medicare payments are generally lower than commercial, but the out-of-pocket costs for beneficiaries are higher.

Table 10: Medicare PBT Utilization and Payments by Cancer Type, 2015-2017

Group	Cancer	2015 Unique Enrollees	2015 Average Visits	2015 Average OOP	2015 Average Insurer Payment	2016 Unique Enrollees	2016 Average Visits	2016 Average OOP	2016 Average Insurer Payment	2017 Unique Enrollees	2017 Average Visits	2017 Average OOP	2017 Average Insurer Payment
1	Liver	7	12	$ 2,745	$ 10,759	19	15	$ 3,748	$ 14,691	25	14	$ 3,047	$ 11,945
1	Ocular*												
1	Spine*												
2	Bone	9	21	$ 4,884	$ 19,144	9	25	$ 6,060	$ 23,755	8	18	$ 3,370	$ 13,211
2	Lung	76	24	$ 5,572	$ 21,807	76	25	$ 6,123	$ 24,000	81	23	$ 4,983	$ 19,534
2	Prostate	70	29	$ 6,621	$ 25,952	109	27	$ 6,667	$ 26,089	107	26	$ 5,544	$ 21,731
	Other	788	26	$ 6,148	$ 24,036	1,066	25	$ 6,300	$ 24,642	1,451	25	$ 5,296	$ 20,686

Source: Medicare Data

Notes: Group 1 cancers identified from ASTROPBTModelPolicy.pdf

*Denotes that these Cancers had fewer than five unique beneficiaries and have been censored from output

a) OOP and Provider Treatment Costs

Nationally, average commercial costs for PBT are higher compared to the other radiation modalities, both for the patient and insurers. The relative treatment costs of PBT is more than 2x the costs of the second most expensive radiation therapy, IMRT. In 2018, insurers and patients paid $73,003 and $714 respectively for PBT, whereas they paid $34,248 and $390 for IMRT. Despite higher costs, based on the available data, providers covered 99% of approved PBT treatment costs and patients only paid the remaining 1% out of pocket.

Patient out-of-pocket costs in 2018 for other alternative radiation modalities, brachytherapy, 3-D conformal radiation, IGRT and other ranged between $68 to $199 as shown in Table 11. Insurers paid between $3,413 to $11,991 for these treatments. Unlike other treatment modalities, PBT insurer reimbursements decreased between 2015 and 2018.

Table 11: Commercial Treatment Costs, 2015-2018

Radiation Therapy Average Annual Payments	2015 Patient Out-of-Pocket Costs	2015 Insurer Costs	2016 Patient Out-of-Pocket Costs	2016 Insurer Costs	2017 Patient Out-of-Pocket Costs	2017 Insurer Costs	2018 Patient Out-of-Pocket Costs	2018 Insurer Costs
Brachytherapy	$ 72	$ 1,499	$ 89	$ 5,363	$ 98	$ 5,521	$ 103	$ 5,330
3-D Conformal Radiation	$ 58	$ 1,827	$ 78	$ 2,272	$ 73	$ 2,318	$ 75	$ 2,219
Intensity-modulation Radiation Therapy (IMRT)	$ 333	$ 28,754	$ 326	$30,322	$ 345	$31,622	$ 390	$34,248
Image-guided Radiation Therapy (IGRT)	$ 52	$ 2,828	$ 61	$ 3,283	$ 66	$ 3,200	$ 68	$ 3,413
Proton Beam Therapy (PBT)	$ 1,067	$ 79,384	$ 1,027	$78,592	$ 547	$70,875	$ 714	$73,003
Other	$ 192	$ 9,988	$ 180	$10,508	$ 187	$11,083	$ 199	$11,991

Source: MarketScan® CCAE Outpatient, 2015-2018

Medicare payments for hospital-based PBT treatment nationally are much lower compared to commercial payments, $20,968 and $70,875 in 2017 respectively (see Table 12). In contrast to commercial reimbursements, patient out-of-pocket costs are higher. In 2017, Medicare patients paid $5,365 whereas commercial patients paid $547. Based on available data, Medicare in practice covered 80% of PBT costs and patients paid 20% out-of-pocket.

Table 12: Medicare Treatment Costs, 2015-2017

Medicare Payments	2015		2016		2017	
Radiation Therapy	Out-of-Pocket Costs	Insurer Payments	Out-of-Pocket Costs	Insurer Payments	Out-of-Pocket Costs	Insurer Payments
Brachytherapy	$ 111	$ 405	$ 608	$ 2,371	$ 658	$ 2,554
3-D Conformal Radiation	$ 120	$ 313	$ 97	$ 225	$ 158	$ 339
Intensity-modulation Radiation Therapy (IMRT)	$ 2,707	$ 10,359	$ 2,724	$ 10,389	$ 2,639	$ 10,020
Image-guided Radiation Therapy (IGRT)	$ 670	$ 1,879	$ 610	$ 1,474	$ 598	$ 1,390
Proton Beam Therapy (PBT)	$ 6,204	$ 24,263	$ 6,435	$ 25,174	$ 5,365	$ 20,968
Other	$ 901	$ 3,759	$ 895	$ 3,529	$ 932	$ 3,665

Source: Medicare, 2015-2017

These data indicate that on average nationally, commercial PBT insurers paid PBT providers about 340% of Medicare in 2017, 310% in 2016 and 330% in 2015. These percentages are higher than the CT PBTC's assumed commercial reimbursement as a percent of Medicare (230%). Some of the difference may be due to the composition of insurers or patient mix.

1. Relative quality of care, including relative number of treatments, radiation exposure, recovery, long term effects)

a) Relative quality of care

The comparative benefits of PBT relative to other types of cancer treatment are well-known and generally derive from the fact that protons are more targeted than are photons and can deliver energy to a more localized region, as has been discussed previously. Targeting the energy this way ensures that it is directed at and adversely affects only the tumor and reduces damage done to nearby organs. In this section, advantages of PBT relative to other treatment types are described for several aspects of the patient experience. "PBT may improve patient survival by improving the local tumor treatment rate while reducing injury to normal organs, which may result in fewer radiation-induced adverse effects."[27]

While traditional radiation therapy using photons is targeted to a tumor, the dose of radiation administered during treatment is dispersed over a relatively wider area. Proton beam therapy, on the other hand, has been widely recognized as a modality of treatment that can reduce radiation-induced adverse side effects for tumors that are located near vital organs.[28] This is due to the physical properties of PBT that allow the radiation to penetrate to a specific depth, reducing unnecessary radiation and injury to nearby tissues and organs. Sparing nearby tissue and organs can have a significant impact on a patient's health status and overall well-being.

Radiation-induced side effects can be profound, and research has shown that PBT can reduce the occurrence of these side effects. McDonald et al. (2016) evaluated a subset of patients with head and neck cancers receiving either PBT or IMRT. [29] They found that patients receiving PBT were less likely to

[27] https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5772792/

[28] Tian et al. 2018. "The evolution of proton beam therapy: Current and future status (Review)" Molecular and Clinical Oncology.

[29] McDonald et al. 2016. "Acute toxicity in comprehensive head and neck radiation for nasopharynx and paranasal sinus cancers: cohort comparison of 3D conformal proton therapy and intensity modulated radiation therapy" Radiation Oncology.

need a gastrostomy tube. The use of opioid pain medication was also studied, and the researchers found that those patients receiving PBT required lower levels of opioid pain medication as compared to those receiving IMRT.

For head and neck tumors, studies show that the comparatively small dose of radiation that reaches the mandible, salivary glands, and maxilla reduces the risk of xerostomia, dental extractions, dental caries, and osteoradionecrosis.[30] In lung cancer, PBT reduces the effect on the esophagus, lungs and bone marrow.[31]

Increasing evidence indicates that proton-beam therapy reduces risk of toxicity compared to traditional radiation therapies in esophageal and gastroesophageal cancers. PBT can deliver a large irradiation dose to the tumor and spare surrounding normal tissues.[32] Several studies showed that patients receiving PBT experienced the least number of adverse effects compared to other radiations treatments.[33]

For breast cancer, the primary benefit of PBT is to reduce exposure to organs-at-risk, especially the lungs and heart.[34] one study showed that PBT had beneficial effects by reducing the potential damage to heart and lung tissue,[35] another demonstrated a statistically significant reduction in radiation dose delivered to the lung and heart.[36]

Because children's organs and tissues are still developing, the adverse effects of traditional radiation can be significantly larger in pediatric cancers. In children, radiation can also have negative effects on

[30] Van de Water TA, Lomax AJ, Bijl HP, De Jong ME, Schilstra C, Hug EB, Langendijk JA. Potential benefits of scanned intensity-modulated proton therapy versus advanced photon therapy with regard to sparing of the salivary glands in oropharyngeal cancer. Int J Radiat Oncol Biol Phys. 2011;79:1216–1224. Slater JD, Yonemoto LT, Mantik DW, Bush DA, Preston W, Grove RI, Miller DW, Slater JM. Proton radiation for treatment of cancer of the oropharynx: Early experience at Loma Linda university medical center using a concomitant boost technique. Int J Radiat Oncol Biol Phys. 2005;62:494–500. Fitzek MM, Thornton AF, Varvares M, Ancukiewicz M, Mcintyre J, Adams J, Rosenthal S, Joseph M, Amrein P. Neuroendocrine tumors of the sinonasal tract. Results of a prospective study incorporating chemotherapy, surgery, and combined proton-photon radiotherapy. Cancer. 2002;94:2623–2634. Truong MT, Kamat UR, Liebsch NJ, Curry WT, Lin DT, Barker FG, II, Loeffler JS, Chan AW. Proton radiation therapy for primary sphenoid sinus malignancies: Treatment outcome and prognostic factors. Head Neck. 2009;31:1297–1308.

[31] Berman AT, James SS, Rengan R. Proton beam therapy for non-small cell lung cancer: Current clinical evidence and future directions. Cancers (Basel) 2015;7:1178–1190.

[32] http://ar.iiarjournals.org/content/35/3/1757.long

[33] Sugahara, Shinji, et al. "Clinical results of proton beam therapy for cancer of the esophagus." *International Journal of Radiation Oncology* Biology* Physics* 61, no. 1 (2005): 76-84. Mizumoto, Masashi, et al. "Clinical results of proton-beam therapy for locoregionally advanced esophageal cancer." *Strahlentherapie und Onkologie* 186, no. 9 (2010): 482-488. Makishima, Hirokazu, et al. "Comparison of adverse effects of proton and X-ray chemoradiotherapy for esophageal cancer using an adaptive dose–volume histogram analysis." *Journal of radiation research* 56, no. 3 (2015): 568-576.

[34] Weber, D.C., Ares, C., Lomax, A.J. *et al.* Radiation therapy planning with photons and protons for early and advanced breast cancer: an overview. *Radiat Oncol* **1,** 22 (2006). https://doi.org/10.1186/1748-717X-1-22

[35] Johansson J, Isacsson U, Lindman H, Montelius A, Glimelius B. Node-positive left-sided breast cancer patients after breast-conserving surgery: Potential outcomes of radiotherapy modalities and techniques. Radiother Oncol. 2002;65:89–98.

[36] Kozak KR, Katz A, Adams J, Crowley EM, Nyamwanda JA, Feng JK, Doppke KP, Delaney TF, Taghian AG. Dosimetric comparison of proton and photon three-dimensional, conformal, external beam accelerated partial breast irradiation techniques. Int J Radiat Oncol Biol Phys. 2006;65:1572–1578.

growth, intellectual development, and endocrine organs. It can also lead to more frequent development of secondary cancers. There have been numerous studies on how PBT positively compares to traditional radiation.[37] Consequently, PBT is often indicated for pediatric cancers more broadly than in adults.

In addition, PBT also has advantages for several other cancers because of its lower dosage on the surrounding tissues. If used for rectal and anal cancers, damage to the bladder and bowel would be limited. Similarly, for pancreatic, gastric and hepatobiliary cancers, it would reduce damage to the liver, small bowel, lungs, heart, spinal cord, and kidneys. One other benefit of PBT is that it may allow increased chemotherapy dosages in gastrointestinal and thoracic cancers because of the reduced damage from radiation.[38]

b) Relative number of treatments

The number of treatment sessions for PBT depends on the type and stage of cancer, but typically a patient has five sessions a week for several weeks;[39] eight weeks is common for prostate cancer while four-eight weeks is common for other types.[40]

For Prostate Cancer, both PBT and traditional therapy typically require daily treatments five days a week for up to eight weeks.[41] For Head and Neck cancer, both treatments are typically 5 days a week, but for only 5-7 weeks.[42] See Table 9 and Table 10 for further detail on the relative number of treatments by cancer type.

c) Radiation exposure

As discussed previously, PBT's main benefit is to reduce the amount of radiation exposure to healthy tissue and organs. One study showed that PBT reduced the mean rectal and bladder dose in Prostate

[37] Sethi RV, Shih HA, Yeap BY, Mouw KW, Petersen R, Kim DY, Munzenrider JE, Grabowski E, Rodriguez-Galindo C, Yock TI, et al. Second nonocular tumors among survivors of retinoblastoma treated with contemporary photon and proton radiotherapy. Cancer. 2014;120:126–133. Taddei PJ, Mirkovic D, Fontenot JD, Giebeler A, Zheng Y, Kornguth D, Mohan R, Newhauser WD. Stray radiation dose and second cancer risk for a pediatric patient receiving craniospinal irradiation with proton beams. Phys Med Biol. 2009;54:2259–2275. Merchant TE, Kiehna EN, Li C, Shukla H, Sengupta S, Xiong X, Gajjar A, Mulhern RK. Modeling radiation dosimetry to predict cognitive outcomes in pediatric patients with CNS embryonal tumors including medulloblastoma. Int J Radiat Oncol Biol Phys. 2006;65:210–221. Miralbell R, Lomax A, Cella L, Schneider U. Potential reduction of the incidence of radiation-induced second cancers by using proton beams in the treatment of pediatric tumors. Int J Radiat Oncol Biol Phys. 2002;54:824–829. Athar BS, Paganetti H. Comparison of second cancer risk due to out-of-field doses from 6-MV IMRT and proton therapy based on 6 pediatric patient treatment plans. Radiother Oncol. 2011;98:87–92. (62–66).

[38] Sejpal S, Komaki R, Tsao A, Chang JY, Liao Z, Wei X, Allen PK, Lu C, Gillin M, Cox JD. Early findings on toxicity of proton beam therapy with concurrent chemotherapy for non-small cell lung cancer. Cancer. 2011;117:3004–3013..

[39] https://www.mayoclinic.org/tests-procedures/proton-therapy/about/pac-20384758

[40] https://www.floridaproton.org/what-is-proton-therapy/faq#q13

[41] https://www.floridaproton.org/what-is-proton-therapy/faq#q14 and https://www.webmd.com/prostate-cancer/guide/prostate-cancer-radiation-therapy#1

[42] https://www.sccaprotontherapy.com/resources/2018_Head_and_Neck_Trifold_for_web.pdf and https://www.radiologyinfo.org/en/info.cfm?pg=hdneck

Cancer treatment by 59% and 35% respectively.[43] Another study found that PBT decreased mean doses to at-risk organs even when the photon-based treatments were at low and medium dose levels.[44] PBT is associated with a smaller dose of secondary radiation for lung cancer versus IMRT as well.[45]

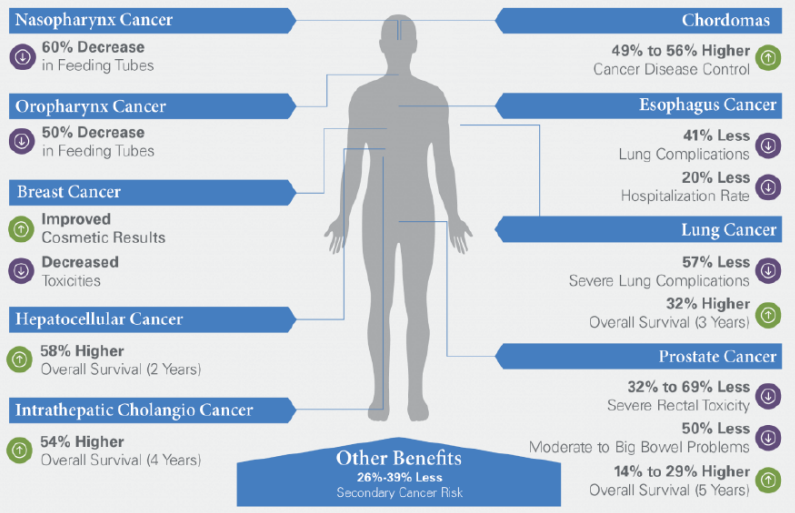
d) Recovery

Another effect of the reduced radiation is that recovery could be faster for PBT with fewer complications. A multi-institutional analysis of treatment for esophageal cancer bore this out. The average length of stay was 9.3 days for PBT versus 11.6 and 13.2 days, respectively, for 3DCRT and IMRT. Additionally, the mortality rate for PBT was substantially lower than the other two modalities: 0.9% for PBT after 90 days versus 4.2% and 4.3% for #DCRT and IMRT.[46]

e) Long term effects

Figure 17 summarizes many of the benefits by cancer type from using PBT instead of IMRT.

Figure 17: Benefits from Using PBT instead of IMRT by Cancer Type



Source: MD Anderson Proton Pals Support Group Presentation[47]

[43] Vargas C, Fryer A, Mahajan C, Indelicato D, Horne D, Chellini A, McKenzie C, Lawlor P, Henderson R, Li Z, Lin L, Olivier K, Keole S. Dose-volume comparison of proton therapy and intensity-modulated radiotherapy for prostate cancer. Int J Radiat Oncol Biol Phys. 2008 Mar 1; 70(3):744-51.

[44] Mock U, Bogner J, Georg D, et al. Comparative treatment planning on localized prostate carcinoma conformal photon-versus proton-based radiotherapy. Strahlenther Onkol. 2005;181:448–455.

[45] Seonkyu Kim, Byung JunMin, Myonggeun Yoon, Jinsung Kim, Dong Ho Shin, Se Byeong Lee, Sung Yong Park, Sungkoo Cho, Dae Hyun Kim. "Secondary radiation doses of intensity-modulated radiotherapy and proton beam therapy in patients with lung and liver cancer." *Radiotherapy and Oncology*. Volume 98, Issue 3, March 2011, Pages 335-339

[46] Lin SH, Merrell KW, Shen J, et al. Multi-institutional analysis of radiation modality use and postoperative outcomes of neoadjuvant chemoradiation for esophageal cancer. Radiother Oncol 2017;123:376-81.

[47] http://www.protonpals.org/wp-content/uploads/2019/12/Proton-Therapy-Present-and-Future.pdf

Importantly, PBT has been shown to reduce the chances of secondary cancers. One study showed that PBT reduced the risk of secondary cancers for prostate cancer by between 26 and 39%.[48] Between 1974 and 2001, 1450 prostate cancer patients treated with PBT went on to develop a second malignancy in 6.4% of patients versus 12.8% of photon patients.[49] Another study, for esophageal cancer, found that PBT survival rates were significantly better than other treatment types, but only for people with stage III cancers.[50]

C. Cost / benefit for payer stakeholders

PBT is widely known to be more expensive per treatment than is IMRT and other radiation treatments.[51] Payment rates vary widely depending on the payer and also the cancer being treated (see Table 11 and Table 12). The number of treatment sessions for PBT depends on the type and stage of cancer, but typically a patient has five sessions a week for several weeks;[52] eight weeks is common for prostate cancer while four-eight weeks is common for other types.[53]

Because of the wide variation between patients, it is difficult to estimate a true cost comparison to alternative treatments. Verma, et. al. (2016)[54] did a survey of cost comparisons and report some of these, however. For prostate cancer, one dataset indicated that PBT cost $43,000 on average compared to $30,000 for IMRT and another study reported that the median Medicare reimbursement for PBT was $32,000 for PBT vs $19,000 for IMRT. In both cases PBT is the more expensive treatment, less than 50% more expensive than IMRT.

Other cancer types showed slightly different numbers. For pediatric cancers, PBT cost $12,000 versus $5,000 for Radiotherapy. For head and neck cancers costs were $48,000 for PBT versus $14,000 for RT and for skull base cancers, $37,000 versus $17,000 (see Table 9 and Table 10 above). Each shows the significantly higher initial costs of treatment for PBT. But these numbers are strictly the payments for treatment itself and do not include any follow-on costs from over exposure to radiation or quality of life impacts.

1. Payer Coverage

Though there is controversy on the clinical use of PBT, there is medical consensus that proton beam therapy is the more efficacious treatment compared to other modalities for certain cancers. Of the major commercial insurers, all but Blue Cross and Blue Shield cover all pediatric cancers, and typically all commercial insurers also cover cancers that have already been treated extensively with traditional

[48] Fontenot JD, Lee AK, Newhauser WD. Risk of secondary malignant neoplasms from proton therapy and intensity-modulated x-ray therapy for early-stage prostate cancer. Int J Radiat Oncol Biol Phys. 2009;74:616–622.
[49] Chung CS, Keating N, Yock T, Tarbell N. Comparative analysis of second malignancy risk in patients treated with proton therapy versus conventional photon therapy. Int J Radiat Oncol Biol Phys. 2008;72(suppl):S8.
[50] https://www.ncbi.nlm.nih.gov/pubmed/29280461
[51] Hu, M., Jiang, L., Cui, X., Zhang, J., & Yu, J. (2018). Proton beam therapy for cancer in the era of precision medicine. Journal of hematology & oncology, 11(1), 136.
[52] https://www.mayoclinic.org/tests-procedures/proton-therapy/about/pac-20384758
[53] https://www.floridaproton.org/what-is-proton-therapy/faq#q13
[54] Verma, Vivek, Mishra, Mark, and Mehta, Minesh. "A Systematic Review of the Cost and Cost-Effectiveness Studies of Proton Radiotherapy." *Cancer*. 2016 May 15, 122(1), 1483-501.

radiation. Finally, reimbursing for skull base cancers and uveal melanoma is common. Medicare does reimburse for PBT and does not do so selectively depending on type of cancer.

Most commercial insurers await large-scale randomized phase 3 trials showing clinical superior results for PBT before designating PBT as a covered treatment modality. These clinical trials are underway, and results are being published. Additionally, there have been technological advances in PBT that offer improved outcomes over traditional radiation treatment and earlier PBT technologies. The expanded use of pencil beam scanning (PBS) and image-guided proton therapy (IMPT) offer improved outcomes for certain cancers that were previously not identified as benefiting from PBT relative to other treatments. These include patients with radioresistant neoplasm such as chordomas, chondrosarcomas, and ocular melanomas, all of which require high radiation doses for local control that simply are not achievable with photons owing to exit dose limitations.[55] Definitive coverage for PBT and movement away from the "denial then approval" process across cancer types may change in favor of greater reimbursement as these clinical trials are published and as these more advanced and clinical effectively PBT technologies become more widespread. Section III.C.2 provides greater detail on commercial insurance coverage for major insurers serving Connecticut.

Table 13 shows the Medicare payment rates for different radiation services and compares the 2020 rate to 2019. For PBT, the 2020 rate increased by 16%.[56]

Table 13: Medicare Payment Rates for Different Radiation Services, 2019-2020

Radiation Oncology - Ambulatory Payment Classification Final 2020 Payment Rates				
APC	Descriptor	2019 Rate	2020 Final Rate	% Change
5611	Level 1 Therapeutic Radiation Treatment Preparati	$ 124	$ 127	2%
5612	Level 2 Therapeutic Radiation Treatment Preparation	$ 322	$ 335	4%
5613	Level 3 Therapeutic Radiation Treatment Preparati	$ 1,192	$ 1,245	4%
5621	Level 1 Radiation Therapy	$ 117	$ 123	5%
5622	Level 2 Radiation Therapy	$ 224	$ 236	5%
5623	Level 3 Radiation Therapy	$ 520	$ 539	4%
5624	Level 4 Radiation Therapy - HDR Brachytherapy	$ 705	$ 740	5%
5625	Level 5 Radiation Therapy - Proton Therapy	$ 1,079	$ 1,247	16%
5626	Level 6 Radiation Therapy - SBRT	$ 1,691	$ 1,768	5%

a) Bundled Payments

As some payers consider and experiment with bundled payments in an effort to push risk to providers, the consequences for PBT might be harsh. Many oncology providers have criticized a proposed Medicare

[55] Chuong, M. D., Mehta, M. P., Langen, K., & Regine, W. F. (2014). Is proton beam therapy better than standard radiation therapy? The available evidence points to benefits of proton beam therapy. Clinical advances in hematology & oncology: H&O, 12(12), 861.
[56] https://www.astro.org/ASTRO/media/ASTRO/Daily%20Practice/PDFs/2020HOPPSFRSummary.pdf

bundling rule for radiation therapy because it would disproportionately affect proton beam therapy.[57] If bundles are created based on traditional radiation therapy, since that treatment modality costs less on average, the bundled payments wouldn't be large enough to cover PBT treatments. What this bundling ignores is that those costs are sometimes needed to reduce certain adverse effects or because PBT is the better treatment in specific situations. A bundled payment would elide those mitigating factors that recommend PBT and will inappropriately lead to lower quality treatment.

For commercial payers, there is little development of bundled payments for cancer. There was notably a pilot at The University of Texas MD Anderson Cancer Center with UnitedHealthcare, but it focused on head and neck cancers and excluded proton beam therapies from the payment.[58]

Future uncertainty exists in both government-funded and commercial PBT reimbursements due to two additional factors: (1) increasing use of value-based reimbursement, particularly bundled payments (see Section IV.B for details), and (2) healthcare reform at the national and/or state level. CMS has proposed a radiation oncology bundled services model to test an episodic payment structure. It would focus on 17 cancer types and include the most common radiation therapy modalities, including PBT. The test would include a cohort of U.S. hospitals and freestanding cancer centers. This proposal has elicited significant pushback, particularly from PBTCs. Because PBT is a more expensive treatment, its potential use may be adversely affected for all but established indications where long term clinical benefits of PBT outweigh other treatments, such as for ocular tumors, pediatric cancers, and brain and spinal tumors. Again, the lack of sufficient completed clinical trials on the clinical and comparative economic efficacy of PBT for other cancers works against PBT at this stage of consideration in such bundled payment initiatives. CMS is considering excluding patients that are in federally-funded, multi-organizational RCTs from the five-year model testing program.[59] The risks to PBTCs at this stage is whether the PBTC is included in the random cohort for the five-year model testing program. Given the pace at which new PBTCs and the PBT technology itself has progressed in recent years, there is great uncertainty about how this would impact PBTCs after the test programs have run, and results considered and implemented in practice.

b) Relative total cost of care in short and long term versus other treatment protocols

Verma, et. al. (2016)[60] performed a thorough analysis of the literature that compares PBT to IMRT over several cancer types. Comparing PBT to IMRT is a difficult proposition because the treatments vary across multiple dimensions: cost of treatment, number of treatments, side effects, necessity of follow-ups, etc. Several of these dimensions cannot be adequately estimated given data limitations (the consequences of side effects may last for many years and may never be recorded in health data at all). Consequently, researchers developed modeling techniques to use expected effects and assign dollar values to them, in order to compare the total costs of PBT to IMRT. Total costs include both the cost of

[57] https://www.modernhealthcare.com/payment/medicares-bundled-radiation-therapy-payments-could-impact-quality

[58] https://ascopubs.org/doi/full/10.1200/JOP.2017.027029

[59] Notice of Proposed Rulemaking, CMS, July 10, 2019, 42 CFR Part 512, [CMS-5527-P], RIN 0938-AT89 Medicare Program; Specialty Care Models to Improve Quality of Care and Reduce Expenditures, Proposed Rule. See also Alliance for Proton Therapy Access Letter to CMS dated September 16, 2019.

[60] Verma, Vivek, Mishra, Mark, and Mehta, Minesh. "A Systematic Review of the Cost and Cost-Effectiveness Studies of Proton Radiotherapy." *Cancer*. 2016 May 15; 122(10) 1483-501.

the initial treatment and the estimated follow-on costs, and were estimated using a synthetic population, based on actual data to generate expected costs depending on treatment, while accounting for the follow-on costs.

Their findings were mixed and depended on the type of cancer, and not surprisingly, are well-aligned with commercial payer guidelines. For prostate cancer, for men older than 60, the total cost of PBT was estimated to be above $60,000[61] compared to IMRT where the total cost was between $33,000 and $40,000.

For breast cancer, PBT's costs were estimated to be $13,600 compared to $6,100[62] for whole breast irradiation. For lung cancer, PBT was the costliest treatment option, at $43,000 compared to $30,000 for IMRT. There has been considerable research on lung cancers, and the majority shows that PBT is not cost effective.

There have been few studies comparing the total costs of treatment for head and neck tumors. One study found higher costs for PBT but balanced out by an increase in quality of life.

Studies of PBT treatment for pediatric cancers mostly show that PBT is superior. When accounting for total costs of care and other factors studies show that PBT's cost savings range from $20,000 to $33,000. One study found that PBT reduces IQ loss and hearing loss.

For uveal melanoma, the costs of PBT, enucleation, and plaque brachytherapy were all very similar, ranging from $23,000 to $29,000. PBT is also showing improved outcomes in recent trials, suggesting it may be the superior alternative.

D. Cost/ benefit analysis for State stakeholder

1. PBTC's economic impact prior to operating

As a component of the Certificate of Need application, and in response to requests, this section of this Report aims to provide an estimate of the direct, indirect, and induced economic impacts generated from the construction of a PBT center on the state of Connecticut and New Haven County, CT.[63]

a) Overview of Economic Impact Model

The study uses standard input-output (I/O) modeling through the use of IMPLAN ("IMpact analysis for PLANning") economic modeling software to quantify the various levels of economic impacts caused by the construction of the proton beam therapy center.[64] I/O modeling provides a means to account for the

[61] PBT can also be used to deliver Stereostactic body radiation therapy (SBRT), which costs substantially less than PBT.
[62] These figures are from a Swedish report and reflect generally lower pricing but shouldn't be compared to US prices.
[63] Wallingford, CT is a town in New Haven County, CT.
[64] Developed by Nobel Prize winner Wassily Leontief in the mid-1900s, I/O modeling takes into account that changes in demand for the output of one industry will have impacts throughout an economy, causing changes in demand for other linked industries. See R. Bess, and Z. Ambargis, "Input-Output Models for Impact Analysis: Suggestions for Practitioners Using RIMS II Multipliers," *U.S. Bureau of Economic Analysis* (March 2011), https://www.bea.gov/system/files/papers/WP2012-3.pdf (accessed February 2020).

different sizes of industries and their specific multipliers allowing for meaningful estimations of the indirect and induced impacts.[65]

More specifically, this study uses Multi-Regional Input-Output Analysis (MRIO) to quantify the economic impact of the construction activities of in one area (New Haven County, CT), as well as the economic impact dispersed into other surrounding areas (the rest of the state of Connecticut) and how these effects create additional local economic impact. The MRIO model utilizes interregional commodity trade and commuting flows to quantify the demand changes across many regions stemming from a change in production and in another region. In an MRIO analysis, the direct effect in one region can trigger indirect and induced effects in linked regions. This approach captures substantial amount of what would have been a leakage in a traditional I/O model, allows for economic interdependence of regions, and thereby provides a more accurate picture than the traditional I/O model.[66]

The IMPLAN program from MIG ("Minnesota IMPLAN Group") is a software package for regional I/O modeling and economic forecasting that was developed in a 1979 collaboration between the USDA Forest Service and the University of Minnesota. It uses publicly provided data to generate complete estimates of the values of the direct, indirect, and induced impacts for key economic indicators, including employment, labor income, value added, output, and tax revenues.[67] The software has been used in a number of applications, including evaluating the economic impact of general acute care hospitals and construction of healthcare facilities on state and local economies.[68]

IMPLAN generates three effects: direct, indirect, and induced impacts. Direct effects are the set of expenditures applied to the model for the analysis. These are direct expenditures made by producers/consumers as a result of the construction activity. Indirect effects are the impacts of local industries buying goods and services from other local industries. Induced effects represent household spending of labor income, after removing taxes, savings, and commuters.

[65] The I/O modeling technique permits economists a structured way to identify and track the flow of expenditures in a defined locality or geographic area between households, businesses and governments and to estimate the overall impact of specific activities. Underlying I/O models have location- and industry-specific matrices based on estimates of the strength and magnitude of the relationship between each pair of industries in the economy. The model tracks dollars exchanged between agents in the local economy; thereby estimating the value of economic activity generated by a particular industry within a predefined geographic area. Although I/O modeling has limitations, it has been implemented by academic economists, public policy experts, governments and businesses in a number of different industries to estimate economic impacts.

[66] "MRIO: Introduction to Multi-Regional Input-Output Analysis," *IMPLAN,* https://implanhelp.zendesk.com/hc/en-us/articles/115009713448-MRIO-Introduction-to-Multi-Regional-Input-Output-Analysis (accessed February 2020).

[67] These data come from the U.S. Bureau of Labor Statistics, the U.S. Bureau of Economic Analysis, the U.S. Census Bureau, and the U.S. Department of Agriculture (USDA Census). The data are compiled at the zip-code level and can be combined at the county level to specify unique and substantive geographic units of analysis. See "IMPLAN Data Sources," *IMPLAN*, https://implanhelp.zendesk.com/hc/en-us/articles/115009674448-IMPLAN-Data-Sources (accessed February 2020).

[68] The use of IMPLAN modeling is a common technique to estimate the economic impacts of healthcare providers within a defined geography. State hospital associations have used IMPLAN modeling to estimate the impact of the acute care hospital industry on economic indicators.

b) Inputs

The total proposed capital expenditure for the construction of the proton therapy center is estimated at $72 million (Table 14). The study assumes the proposed expenditures will be spent in 2020.[69]

Table 14: Total Proposal Capital Expenditure

Category	Cost
Equipment (specify the type)	
IBA Proteus One	$26,360,721
CT Simulator	$675,000
Land (purchase price)	$1,996,500
Building/Construction	$31,839,040
Furniture, Fixtures and Equipment	$1,327,500
Other (specify):	
Overall Project Contingency	$3,196,239
Legal, Permit & Other Fees	$2,605,000
Development Cost	$4,000,000
Total Capital Expenditure	**$72,000,000**

The inputs used for the IMPLAN model are in Table 15. Construction impact is assessed by evaluating the total construction budget which includes building/construction, project contingencies, and development costs.

Land sales, equipment costs, and legal fees have limited direct impact on the economy. Land sales are considered asset transfers and has no value in IMPLAN.[70] Furniture, fixtures, and equipment (FF&E) are defined as large, moveable investments that businesses make. These consist of movable furniture, fixtures, and other equipment that is not directly attached to the building. Most likely, FF&E investments are not produced in the regions of study. These items are typically brought in from outside of the region and are considered leakage costs. Legal, permit, and other government fees do not contribute directly to impacts in the model. Not all government fees and taxes may return to the region. Thus, these land sales, equipment costs, and legal fees are omitted from the model. The results presented in Table 15 show a conservative economic impact estimate of constructing the PBT center.

[69] The model uses 2018 data to generate results. Inputs and outputs are presented in 2020 USD.

[70] See "Construction: Building the Analysis," *IMPLAN,* https://implanhelp.zendesk.com/hc/en-us/articles/360038792834-Construction-Building-the-Right-Model (accessed February 2020).

Table 15: Economic Impact Model Inputs – Construction Costs

Category	Cost
Building/Construction	$31,839,040
Overall Project Contingency	$3,196,239
Development Cost	$4,000,000
Total	**$39,035,279**

c) Economic Impact on Connecticut

The MRIO analysis shows the economic impact for construction expenditures spent in New Haven County, CT and shows additional indirect and induced impacts in the rest of Connecticut.[71] Table 16 summarizes the results of the economic impact of construction of the PBT center across Connecticut. The model estimated a total of 438 jobs, over $31.2 million in labor income, and over $69.4 million in total economic output.

Table 16: Economic Impact of Construction of PBT Center across Connecticut

Impact	Employment	Labor Income	Value Added	Output
Direct	268	$20,738,982	$21,902,427	$39,035,279
Indirect	58	$4,503,695	$7,327,879	$12,928,643
Induced	112	$5,993,394	$10,772,535	$17,507,506
Total	438	$31,236,071	$40,002,842	$69,471,428

In New Haven County alone, construction activity is estimated to generate $9.4 million in indirect impacts and $16.8 million in induced impacts. Additional indirect impact of $3.5 million and approximately $723,000 in induced impact will be generated in other counties across Connecticut.

Construction activity is estimated to generate $5.9 million in federal taxes and $2.9 million in state and local taxes across Connecticut (Table 17). New Haven County will contribute $5.6 million in federal taxes and $2.7 million in state/local taxes. The remaining $304,800 in federal taxes and $185,900 in state/local taxes will come from the remaining counties in Connecticut.

Table 17: Tax Impact of Construction of PBT Center across Connecticut

Impact	Federal Tax	State/Local Govt Tax	Total
Direct	$3,741,586	$917,420	$4,659,006
Indirect	$926,438	$732,356	$1,658,794
Induced	$1,268,697	$1,283,555	$2,552,251
Total	$5,936,720	$2,933,331	$8,870,051

[71] Replication of the model may produce slightly different results due to rounding. The overall impact does not change significantly.

Figure 18 presents the top 5 employment industries due to construction of the PBT center on Connecticut. It is estimated that the construction industry will add over 250 jobs. The other top employment industries are other real estate, hospitals, full-service restaurants and other durable goods merchant wholesalers.

Figure 18: Top 5 Employment Industries

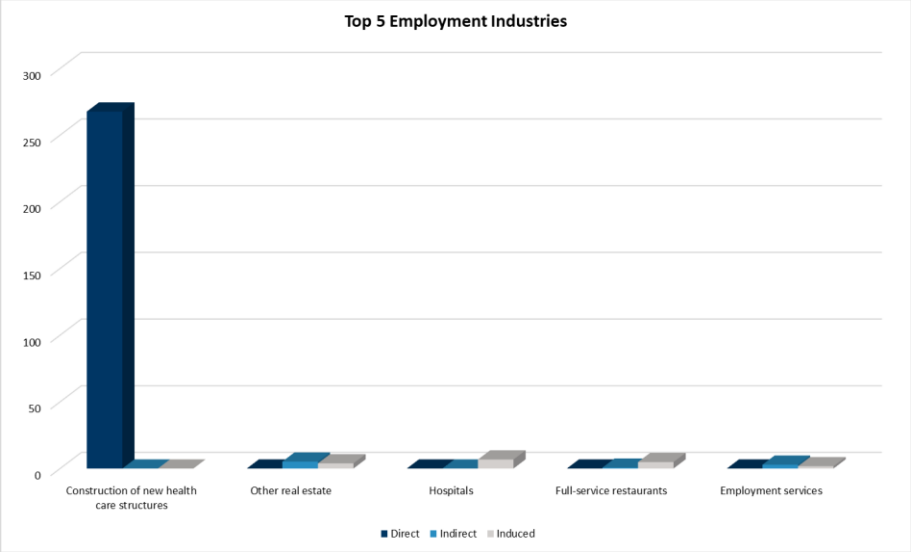


Figure 19 presents the top 5 output industries due to construction of the PBT center on Connecticut. Approximately $40 million of direct output will be generated from the construction industry. Owner-occupied dwellings, other real estate, and hospitals represent over $4 million of induced output.

Figure 19: Top 5 Output Industries

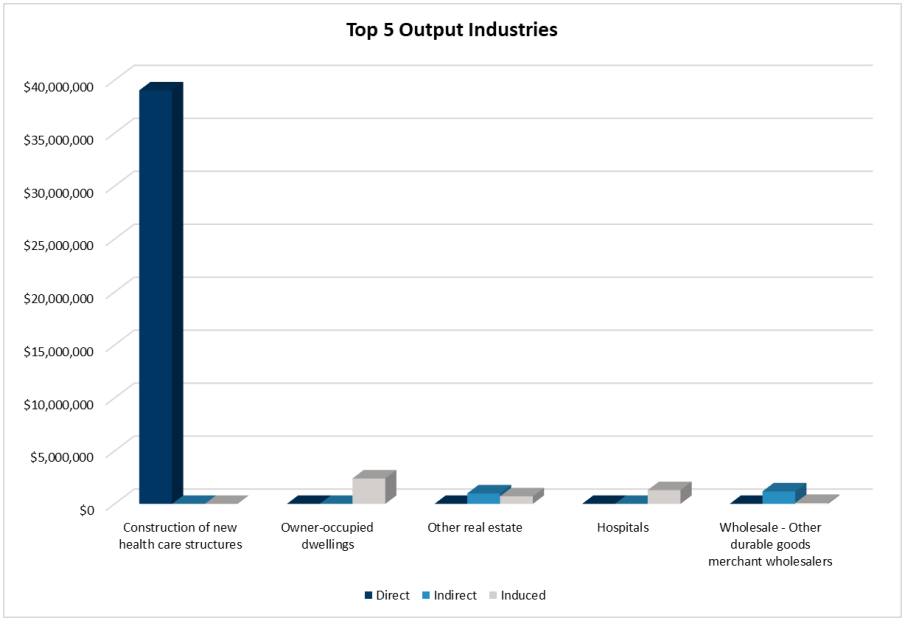
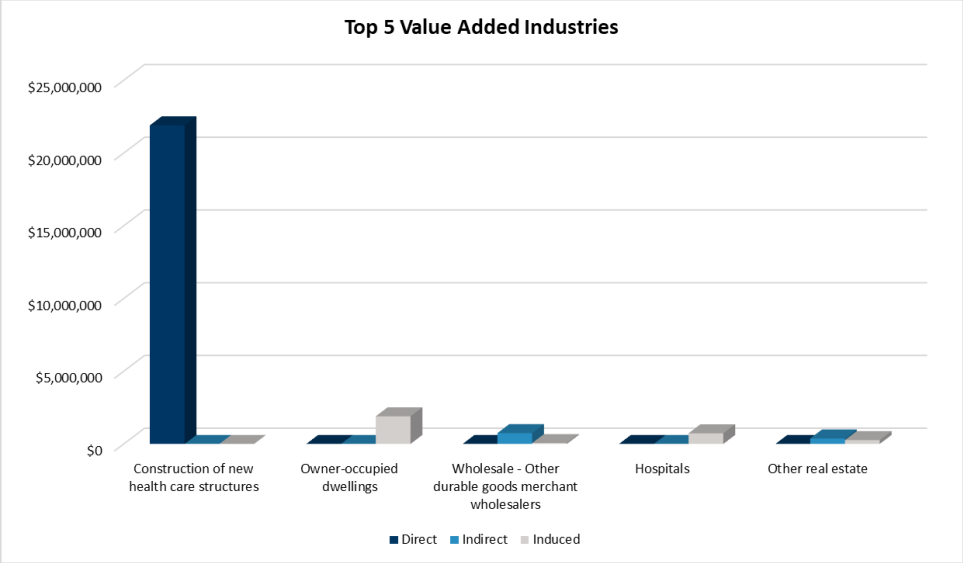


Figure 20 presents the top 5 value added industries due to construction of the PBT center on Connecticut. Owner-occupied dwellings, other real estate, and hospitals represent almost $3 million of induced output.

Figure 20: Top 5 Value Added Industries



E. Cost/benefit to employer stakeholders

1. Absenteeism and Presentism—estimate productivity costs

The presence and severity of radiation-related side effects not only effect a patient's overall health status, but conceivably impact the degree to which an individual can carry on with activities of daily living and employment. For example, patients requiring lower level of opioid pain medication may be more likely to continue working, impacting productivity. The financial impacts related to absenteeism can be significant, as indicated in Table 18 below. Conservatively estimating that PBT reduces absenteeism by 1 day among the sample working age Connecticut adults eligible for PBT, proton treatment would be associated with approximately $100,000 in productivity costs savings annually. If the differential in absenteeism is 10 days, productivity costs savings approach $1 million

Table 18: Estimated Absenteeism Impact from PBT

Estimated Absenteeism Impact from PBT							
	Population	Absenteeism - # of Days			Absenteeism Costs - # of Days		
Adult Cases (excluding Medicare population)		1	5	10	1	5	10
25% of Eligible Cases - Employed Population	157	157	785	1,571	$ 36,717.82	$183,589.12	$ 367,178.24
50% of Eligible Cases - Employed Population	314	314	1,571	3,141	$ 73,435.65	$367,178.24	$ 734,356.48
75% of Eligible Cases - Employed Population	471	471	2,356	4,712	$ 110,153.47	$550,767.36	$ 1,101,534.73

Notes: PB eligible cases are based on the State Tumor Registry Data. Approximately 5% of cases were assumed to be pediatric cases based on the share of pediatric cases recorded in HHC and YNHHS data. 33% of cases were assumed to be Medicare beneficiaries. Both pediatric and Medicare cases were excluded from the productivity costs estimates. Absenteeism costs are estimated using the average hourly wage rate in Connecticut ($29.22) per BLS data. See https://www.bls.gov/oes/2018/may/oes_ct.htm#00-0000. To limit the sample to the working age population, case counts are scaled to reflect non-Medicare coverage by applying a factor of .67 consistent with HHC/YNHHS assumptions.

While these estimates are based on days of missed work, presenteeism (employees showing up for work but exhibiting reduced productivity while physically present) which is harder to quantify, could be also represent significance productivity costs. Finally, these estimates do not account for caregivers or family members.

V. QUALITATIVE ANALYSIS EXAMINING THE EFFECTIVENESS OF PROTON THERAPY VERSUS CONVENTIONAL RADIATION THERAPY FOR THE TYPES OF CANCERS PROPOSED FOR TREATMENT AT THE CENTER

This report makes references to clinical trial data and other clinical studies of the clinical benefits and risks of PBT relative to traditional radiation therapy. We also reference studies that have examined the comparative costs of these alternative treatments. Appendices 2 and 3 provide summaries of the most recent literature examining PBT in terms of clinical efficacy (Appendix 2) and comparative cost efficacy (Appendix 3). This literature, as well as studies conducted earlier, provide insight into the reasonableness of the assumptions underpinning the proposed CT PBTC.

A. Implications for volume of treatments

The most recent literature has focused on the clinical efficacy of certain cancers that are treated with PBT. These include: (1) breast, (2) brain and CNS, (3) gastrointestinal, (4) head & neck, (5) lung, (6) lymphoma, (7) prostate, (8) thymus, and (9) esophageal. These studies are summarized in Appendix 2. Other studies have examined the clinical efficacy of liver, ocular, sarcomas, and skull-based cancers as well as cancers affecting pediatric patients.

As discussed above, ASTRO and most insurers recognize that PBT is medically necessary for Group 1 cancers. These include:

- Ocular tumors, including intraocular melanomas
- Tumors that approach or are located at the base of skull, including but not limited to:
    - Chordoma
    - 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
- Primary or benign solid tumors in children treated with curative intent and occasional palliative treatment of childhood tumors when at least one of the four criteria noted above apply
- Patients with genetic syndromes making total volume of radiation minimization crucial such as but not limited to NF-1 patients and retinoblastoma patients
- Malignant and benign primary CNS tumors
- Advanced (e.g., T4) and/or unresectable head and neck cancers
- Cancers of the paranasal sinuses and other accessory sinuses
- Non-metastatic retroperitoneal sarcomas
- Re-irradiation cases (where cumulative critical structure dose would exceed tolerance dose)

All other cancers are deemed by ASTRO to be appropriate for Coverage with Evidence Development, including:

- Non-T4 and resectable head and neck cancers
- Thoracic malignancies, including non-metastatic primary lung and esophageal cancers, and mediastinal lymphomas
- Abdominal malignancies, including non-metastatic primary pancreatic, biliary and adrenal cancers
- Pelvic malignancies, including non-metastatic rectal, anal, bladder and cervical cancers
- Non-metastatic prostate cancer
- Breast cancer

This list may be compared with the list of cancers on which CT PBTC has based its projected patient volumes. Table 19 presents a descriptive listing of Group 1 and Group 2 cancers. Included in the matrix is whether the cancers are covered by most commercial insurers. It also includes the HHC/YNHHS proton treatment consensus on percentage of patients with such cancers that would be effectively treated with PBT rather than traditional radiation therapy, along with the estimated percent of patient volume that would be treated at CT PBTC. Cancers are identified based on whether there are studies supporting PBT from a clinical and comparative (relative to traditional radiation treatment) efficacy.

Table 19: Approximate CT PBTC Coverage by ASTRO Group 1 and 2

Approximate CT PBTC Coverage by ASTRO Group 1 and 2					
ASTRO Group 1	**Covered by Most Commercial Insurers**	**HHC/YNHHS Treatment Consensus**	**HHC/YNHHS Projected Cancer Mix**	**Studies supporting clinical efficacy**	**Studies supporting comparative efficacy**
Ocular	√		0%	√	√
Chest/Lung	√	10%	16%	√	√
Certain Brain & CNS		20%	28%	√	√
H&N	√	15%	10%	√	√
Lymphoma		5%	5%	√	
Certain Sarcoma		10%	9%	√	
Certain Gastrointestinal	√	10%	6%	√	
Pedi CNS	√			√	√
Pedi Non CNS	√			√	√
Group 1 Total			74%		
ASTRO Group 2					
Breast		5%	14%	Mixed	Mixed
Genitourinary (e.g.,prostate)		5%	8%	Mixed	Mixed
Skin		0%	0%		√
Gynecological		5%	3%		
Other		5%	1%		
Group 2 Total			26%		

Both the clinical and comparative studies support the reasonableness of the HHC/YNHHS treatment consensus and projected cancer treatment mix. The studies summarized in Appendices 2 and 3 show

that for breast and prostate cancers, there are studies supporting both the clinical and comparative efficacy of PBT. Most clinical studies show that for certain breast cancers, left-side near heart, PBT is clinically beneficial. For prostate cancers, the results have been mixed, but more recent studies shown in Appendices 2 and 3 tend to show that newer technologies, such as PBS and IMPT, reduce toxicity and produce better outcomes. Assuming that the 5% consensus treatment rate for prostate and breast cancers reflect those cancers

APPENDIX 1: U.S. PROTON BEAM THERAPY CENTERS

Appendix Table 1: U.S. Proton Beam Therapy Centers

PBT Center	State	City	Owners/Operators	Year Opened	CON Applicable for PBT	Academic Medical Center or Hospital Alignment	NCI-Designated Cancer Center Affiliation	NCCN Affiliation	Rooms	Gantries	Pencil Beam Scanning	Beam Direction	Total Cost	Patient Volumes	Financial Situation
James M. Slater, MD Proton Treatment & Research Center at Loma Linda University Cancer Center	California	Loma Linda	Developed from grant funding and the Federal National Accelerator Fermi Lab	1990	No	AMC	No	No	4	3	No	1 horizontal fixed beam	NA	As of 2018, have treated 18,000 patients, significant clinical focus	Funded by $19.6M in Federal grants. Operating since 1992, highest volume continuously operating center in the industry. Added two gantries in 2004.
UC Davis-CNL	California	Davis	UC Davis	1994	No	AMC	Yes	No	NA	NA	No	1 horizontal fixed beam		Treats ocular melanoma only	Operating
MGH Francis H. Burr Proton Therapy Center	Massachusetts	Boston	Massachusetts General Hospital	2001	CapEX CON	AMC	Yes, MGH is member of Dana-Farber/Harvard Cancer Center	Yes	3	2 with spread beam and pencil beam scanning; plans to add another gantry in 2020	Yes	1 horizontal fixed beam	NA	Significant clinical focus, expected 500 patients annually; reached patient goal by fourth year	Operating
Indiana University Health Proton Therapy Center	Indiana	Bloomington	Indiana University Research and Technology Corp and IU Health	2004	No	No	Yes, although not co-located with IU cancer center	No	3		No		NA	Closed in 2014 due to lack of patient volume, lack of proximity to medical school, old technology and unsupportable financial structure.	Closed in 2014. Old technology with poor capital structure, operated 3 gantries. Used existing research cyclotron and built treatment rooms
University of Florida Health Proton Therapy Institute	Florida	Jacksonville	University of Florida	2006	No	AMC	No	No	4	3 with spread beam and pencil beam scanning plus new single room with pencil beam scanning	Yes	1 horizontal fixed beam	$ 125,000,000	7200 total patients; capacity 150-200 patients a day	Operating, expanded with new Proteus@One single-room in 2019
MD Anderson Cancer Center Proton Therapy Center	Texas	Houston	Private investors, operated by UT's MD Anderson Cancer Center	2006	No	AMC	Yes	Yes	4	3 with spread beam and pencil beam scanning	Yes	1 horizontal fixed beam	$ 125,000,000	NA	Operating, Houston's MD Anderson investing $159M into treatment room expansion for 2023
Oklahoma Proton Center at Integris Cancer Institute	Oklahoma	Oklahoma City	Integris Health	2009	No	No	Yes	No	4	1	No	3 horizontal fixed beam	$ 130,000,000	3000 patients treated as of 2019; capacity to treat 1,500 per year	Bankruptcy auction occurred, shut down in early 2019 and opened back up with new ownership
Northwestern Medicine Proton Center	Illinois	Warrenville	Northwestern	2010	Facilities/CapEx CON	AMC, but not co-located	Yes	Yes	4	1 with spread beam and pencil beam scanning	No	3 fixed beams	$ 157,600,000	Treats about 500 patients a year	Operating; ownership change, now affiliated with Northwestern Medicine
Hampton University Proton Therapy Institute	Virginia	Hampton	Hampton University	2010	Facilities/CapEx CON	No	No	No	5	4	No	1 fixed beam	$ 225,000,000	Expected to treat 2000 patients per year	Operating: At Risk

PBT Center	State	City	Owners/Operators	Year Opened	CON Applicable for PBT	Academic Medical Center or Hospital Alignment	NCI-Designated Cancer Center Affiliation	NCCN Affiliation	Rooms	Gantries	Pencil Beam Scanning	Beam Direction	Total Cost	Patient Volumes	Financial Situation
Roberts Proton Therapy Center at the University of Pennsylvania Health	Pennsylvania	Philadelphia	University of Pennsylvania Health	2010	No	AMC	Yes	Yes	5	4 with spread beam and pencil beam scanning	Yes	1 horizontal fixed beam	$ 144,000,000	Expected 3000 patients; treated 6000 Patients (2019); Below forecast	Operating
ProCure Proton Treatment Center – New Jersey	New Jersey	Somerset	ProCure	2012	Facilities/CapEx CON	No	No	No	4	4 with spread beam and pencil beam scanning	Yes	Yes	$ 160,000,000	Treated 3000 patients [written in 2018]	Operating, refinanced
Seattle Cancer Care Alliance Proton Therapy Center	Washington	Seattle	Seattle Cancer Care Alliance	2013	CapEx CON	Hospital consortium	Yes	Yes	4	1 gantry	Yes	1 horizontal fixed beam; two inclined beam	$ 150,000,000	Treated 2179 patients (Nov 2018); capacity to treat about 1400 patients a year	Pre-packaged bankruptcy; previously, SCCA Proton Therapy Center. A center associated with SCCA, a hospital consortium, in Washington State lost $19 million in the 2015 fiscal year before restructuring its debt
S. Lee Kling Center for Proton Therapy Center at the Siteman Cancer Center	Missouri	St. Louis	Washington University School of Medicine and Barnes-Jewish Hospital	2013	CapEx CON	AMC	Yes	Yes	2, as of 2020	2, as of 2020	Yes, as of 2020		$ 25,000,000	treated 100 patients (2014)	Operating
California Protons Cancer Therapy Center	California	San Diego	Loughlin Management Partners	2014	No	No	No	No	5	3 with pencil beam scanning	Yes	2 horizontal fixed beam	$ 220,000,000	Expected 2400 patients a year; treated less than 1400 after 2014,	Originally an Advanced Particle Treatment center; Scripps filed bankruptcy. California Proton arranged a $16 million bridge loan (restructured). California Protons has been operating it since December 2017
Provision CARES Proton Therapy Center – Knoxville	Tennessee	Knoxville	Provision CARES	2014	No	No	No	No	2	3 with pencil beam scanning	Yes		$ 132,000,000	Treated over 2500 patients since opening	Operating, In Knoxville, Tenn., the Provision CARES Proton Therapy Center lost $1.7 million last year on revenue of $23 million, $5 million short its target
Willis-Knighton Cancer Center	Louisiana	Shreveport	Willis-Knighton	2014	No	Hospital system	No	No	1	1 with pencil beam scanning	Yes		$ 40,000,000	Treated about 200 patients [written in 2016]	Operating
The Mayo Clinic Proton Beam Therapy Center – Minnesota	Minnesota	Rochester	The Mayo Clinic	2015	No	Hospital	Yes	Yes	4	4 with ' pencil beam scanning	Yes		$ 180,000,000	Mayo clinic expects both AZ and MN to treat a combined total of 2400 patients by 2020	Operating; partially funded through $100M gift, no investors.
St. Jude Red Frog Events Proton Therapy Center	Tennessee	Memphis	St. Jude Red Frog Events	2015	No	AMC	Yes	Yes	3	2 with pencil beam scanning	Yes	1 horizontal fixed beam	$ 105,000,000	Expected 100 patients in first year.	Operating
Ackerman Cancer Center Proton Therapy Center	Florida	Jacksonville	Physician-owned; Dr. Scot Ackerman	2015	No	No	No	No	1	1	No		$ 40,000,000	1000 patient treated [written in 2018]	Operating: Full

PBT Center	State	City	Owners/Operators	Year Opened	CON Applicable for PBT	Academic Medical Center or Hospital Alignment	NCI-Designated Cancer Center Affiliation	NCCN Affiliation	Rooms	Gantries	Pencil Beam Scanning	Beam Direction	Total Cost	Patient Volumes	Financial Situation
Texas Center for Proton Therapy	Texas	Irving	Texas Oncology, Baylor Scott & White Health, and McKesson Specialty Health	2015	No	AMC/provider consortium	Yes	No	3	2 with pencil beam scanning	Yes	1 horizontal fixed beam	$ 105,000,000	NA	Operating
The Laurie Proton Therapy Center at RWJ Barnabas Health	New Jersey	New Brunswick	Blanche and Irving Laurie Foundation gift; Barnabas Health and RWJ University Hospital; partnership with Rutgers Cancer institute of New Jersey and RWJ Medical School	2015	Facilities/CapEx CON	AMC/hospital consortium	Yes	No	1	1	No		$ 23,600,000	NA	Operating
The Marjorie & Leonard Williams Center for Proton Therapy at Orlando Health	Florida	Orlando	Orlando Health	2016	No	AMC but not co-located	No	No	1	1	No		$ 25,000,000	Expects 125 Patients/year; capacity of 225 patients	Operating
Maryland Proton Treatment Center	Maryland	Baltimore	Maryland Proton Treatment Holdings, LLC	2016	Facilities/CapEx CON	AMC	Yes	No	5	4 with pencil beam scanning	Yes	1 horizontal fixed beam	$ 200,000,000	MPTC has treated 2000 patients [written in 2019]	Operating; financially struggling due to patient volume
The Mayo Clinic Proton Beam Therapy Center – Arizona	Arizona	Phoenix	The Mayo Clinic	2016	No	Hospital system	Yes, although not co-located with Mayo Clinic	Yes, although not co-located with Mayo Clinic	4	4 with pencil beam scanning	Yes		$ 180,000,000	Mayo clinic expects both AZ and MN to treat a combined total of 2400 patients by 2020	Operating
Miami Cancer Institute Proton Therapy Center at Baptist Health South Florida	Florida	Miami	Baptist Health	2016	No	Hospital system	No	No	3	3 with pencil beam scanning	Yes			Treated 500 Patients (67 children) [written in Dec 2019]	Operating
Cincinnati Children's Pediatric Proton Therapy Center	Ohio	Liberty Township	Cincinnati Children's Hospital	2016	No	Hospital	No	No	5	3 with pencil beam scanning	Yes		$ 120,000,000	Expected 300 adult patients a year;	Operating
University Hospitals Proton Therapy Center	Ohio	Cleveland	University Hospitals	2016	No	AMC	Yes	Yes	1	1	No		$ 30,000,000	Expected to treat 20-25 patients per day; 400 total treatments(June 2019); Below forecast	Operating
Beaumont Proton Therapy Center	Michigan	Royal Oak	Beaumont Health; Proton International	2017	Facilities/CapEx CON	Hospital system	No	No	1	1 with pencil beam scanning	Yes		$ 40,000,000	Expected 300 to 500 patients a year. Since July 2017, has treated 350 patients [written in 2019]; Below forecast	Operating
Emory Proton Therapy Center	Georgia	Atlanta	Provident Resources Group (partial)	2018	Facilities/CapEx CON	AMC	Yes	No	5	3 with pencil beam scanning	Yes	2 horizontal fixed beam with pencil beam scanning	$ 200,000,000	Expected 400 patients in first year;	Operating; delayed due to financing , APT running out of money

PBT Center	State	City	Owners/Operators	Year Opened	CON Applicable for PBT	Academic Medical Center or Hospital Alignment	NCI-Designated Cancer Center Affiliation	NCCN Affiliation	Rooms	Gantries	Pencil Beam Scanning	Beam Direction	Total Cost	Patient Volumes	Financial Situation
Provision CARES Proton Therapy Center – Nashville	Tennessee	Franklin	Provision CARES	2018	No	No	No	No	3	2 with pencil beam scanning	Yes		$ 100,000,000	Capacity of up to 1500 patients a year	Operating
McLaren Proton Therapy Center	Michigan	Flint	McLaren; Karamanos Cancer Network	2019	Facilities/CapEx CON	Hospital system	No	No	1	3 with pencil beam scanning	Yes		$ 65,000,000	Expected 100 patients in first year. McLaren has treated 38 patients [written fall 2019], with projected second-year total of more than 150; Below forecast	McLaren assumed management of the center after Texas-based ProTom International Inc. filed for bankruptcy.
MedStar Georgetown University Hospital Proton Therapy Center	DC	Washington, DC	Medstar	2019	Facilities/CapEx CON	AMC	Yes	No	1	1 with pencil beam scanning	Yes		$ 40,000,000	Expected 200 patients a year; at capacity so far	MedStar Georgetown's proton beam center has been at capacity since it opened, and the D.C.-area health system is putting another facility in one of its sister hospital
South Florida Proton Therapy Institute	Florida	Delray Beach	Proton International LLC	2019	No	No	No	No	1	1 with pencil beam scanning	Yes		$ 50,000,000	Operating above forecasted volume	Operating
Stephensen Cancer Center	Oklahoma	Oklahoma City	Oklahoma University	2019	No	AMC	Yes	No	1	1 with pencil beam scanning	Yes				State Legislature, OU Medicine, the Oklahoma Tobacco Settlement Endowment Trust (TSET) and the state's philanthropic community
The Johns Hopkins National Proton Center	DC	Washington, DC	Johns Hopkins University	2019	Facilities/CapEx CON	AMC, but not co-located	Yes, although not co-located with JH Sidney Kimmel Center	Yes, although not co-located with JH Sidney Kimmel Center	3	3 with pencil beam scanning	Yes	1 horizontal fixed beam	$ 160,000,000	NA	Operating
The New York Proton Center	New York	New York City	Memorial Sloan Kettering Cancer Center, Montefiore Health System, Mount Sinai Health System	2019	Facilities/CapEx CON	Hospital consortium	Yes	Yes	4	3 with pencil beam scanning	Yes		$ 300,000,000	1400 (Expected)	Operating
University of Alabama, Birmingham	Alabama	Birmingham	University of Alabama Medicine and Proton International	2020	CapEX CON	AMC	Yes	Yes	1	1	Yes				
University of Miami Sylvester Comprehensive Cancer Center	Florida	Miami	University of Miami Health System	2020	No	AMC	Yes		1	1	Yes				
INOVA Schar Cancer Institute	Virginia	Fairfax	INOVA	2020	Facilities/CapEx CON	Hospital system			2	2	Yes		$ 60,000,000		
Penn Medicine	Pennsylvania	Philadelphia	Penn Medicine	2021	No	AMC	Yes	Yes	1	1	Yes				
Dallas Proton Treatment Center	Texas	Dallas	Investor group	NA	No	No			5				$ 225,000,000		Partially Built; Bankrupt

A. Implications for financial viability

We are not in a position to independently assess the financial analysis conducted by HHC/YNHHS and Proton International and provided in the CON application, except with respect to the reasonableness of demand and supply assumptions factored into the analysis. Our review of the current state of PBT and PBTCs in the U.S., combined with our review of the clinical and comparative efficacy of PBT , lead us to conclude that the demand and supply assumptions used by HHC/YNHHS are reasonable and support CON approval of proposed Connecticut Proton Therapy Center.

APPENDIX 2: LITERATURE REVIEW – CLINICAL EFFICACY

Appendix Table 2: Literature Review – Clinical Efficacy

Source	Year Published	Title	Author	Type of Cancer	Conclusion
International Journal of Radiation Oncology, Vol 105, Issue 1, Supplement, September 1, 2019	2019	"Proton Beam Accelerated Partial Breast Irradiation: Prospective Multi-Institutional PCG Registry Analysis"	Anderson et al.	Breast	In this study, proton accelerated partial breast irradiation (APBI) was administered to 43 patients. Proton APBI was successful and no patient experienced local recurrence, metastasis or death; 7% of patients experienced grade 2 (G2) toxicity; over 18% of patients experienced no radiation related toxicities as of last follow-up.
Mayo Clinic	2017	"Multi-institutional Results of Breast Proton Radiation Therapy: An Analysis of the PCG Registry"	Brunnhoelzl et al.	Breast	A prospective registry of 335 breast cancer patients was analyzed. Median follow-up was 1.1 year. Re-RT was delivered to 15.5%, chest wall RT to 40.3%, whole breast to 32.3%, and partial breast RT to 11.9%. AEs ≥G3 or ≥G2 were different between retreatment and de novo (13.3% vs. 7.1% G3; 82.7% vs 67.5% G2). Proton bream therapy was associated with low chronic G3 (one incidence) toxicity adverse events including in re-treatment cases. Volume treated was a predictor of G2 or G3 AEs. For ≥G3, the dose threshold was 61.3 Gy; and, for ≥G2 it was 45.5 Gy.
International Journal of Radiation Oncology, Vol 105, Issue 1, Supplement, September 1, 2019	2019	"A Clinical Outcomes after Proton Partial Breast Radiotherapy for Early Stage- Hormone Receptor Positive Breast Cancer: 3-Year Outcomes of a Phase II Trial"	Choi et al.	Breast	In this study, authors explore efficacy, toxicity and cosmetic outcomes of proton PBI. Proton therapy is a safe and effective method of PBI delivery, with exceptional disease control, minimal toxicity, and acceptable patient-and physician-reported cosmesis and quality of life outcomes with longer-term follow-up. At 3 years, proton PBI provides 100% cancer control for early stage, ER-positive breast cancer. Acute toxicities are minimal, and patient-reported QOL remains acceptable with continued follow-up.
Particle Therapy Cooperative Group - North America	2017	"Excellent Acute Toxicity Outcomes with Proton Therapy for Partial Breast Irradiation in Early Stage Breast Cancer: Initial Results of a Multi-institutional Phase II Trial"	Choi et al.	Breast	In this study, 40 patients initiated protocol treatment. The primary objectives of the study were to assess freedom from ipsilateral breast recurrence and evaluate toxicity. 100% of patients saw freedom from ipsilateral breast cancer recurrence as well as distant disease control. There were 6 events of G2 toxicity (AEs: RD, lymphedema, hot flashes, and fatigue); 1 event of G3. QOL results indicated a score of 4 for change in nipple appearance (n=2), breast shape (n=2), and scar tissue formation (n=2). Need continued follow-up to assess late toxicity and long term disease control.
Breast Cancer Management, Vol. 7, Issue 1	2018	"Proton therapy for breast cancer: progress & pitfalls"	Corbin & Mutter	Breast	Because of unique physical properties, PBT reduces nontarget normal tissue exposure and may improve target coverage of difficult to treat areas such as the internal mammary nodes which lie adjacent to the heart and lungs. The improved target coverage and normal tissue avoidance of PBT over conventional photon therapies are well established. Pencil-beam scanning PBT enables skin sparing similar to photon therapy, something that was not possible with previous scattered proton delivery technology. Reports from clinical trials suggest that the acute toxicity profile of PBT is favorable photons. Long-term follow-up is needed to establish tumor control and delayed toxicity outcomes. PBT has promise to improve long-term treatment outcomes. PBT, however, can be more costly than conventional photon therapy and has unique technical challenges.
American Radiology Society, Vol. 29, Issue 4	2015	"Breast cancer treatment with uniform scanning proton therapy on an incline beam line"	McGee et al.	Breast	Examines the feasibility of adjuvant breast cancer treatment with USPT on an incline beam line. Acute toxicity results appear acceptable. All patients experienced acute radiation dermatitis: grade 1 (n = 8), grade 2 (n = 26), and grade 3 (n = 3). Five patients required a break in treatment, and two patients did not complete their full course of prescribed PT due to skin toxicity. Also, 16 patients experienced grade 1 esophagitis, and 13 patients experienced grade 1 chest wall pain. Two patients experienced skin infection following treatment, requiring antibiotic treatment, which occurred the second week following treatment completion.
International Journal of Radiation Oncology, Vol 105, Issue 1, Supplement, September 1, 2019	2019	"Post-Mastectomy Radiotherapy using Proton Beam Therapy: Prospective Multi-Institutional PCG Registry Analysis"	Niska et al.	Breast	In this prospective cohort study, the researchers evaluated the adverse events and disease outcomes of 125 patients who were administered PBT post-mastectomy radiotherapy (PMRT). Maximum AE was G3 in 13% of patients (acute G3 pain 8% and acute G3 dermatitis 8%). No patient had late AE greater than G2.
American Association of Medical Dosimetrist	2013	"Simulation, planning, and delivery of breast/chest wall treatment using uniform scanning proton beam therapy"	Schmidt et al.	Breast	This presentation gives an overview of the delivery of USPT for breast cancer patients. The selection criteria for the patients in this particular presentation is that they must have had "Stage III disease either post-mastectomy or lumpectomy and require treatment to ipsilateral supraclavicular, axillary, and internal mammary lymph nodes. Or, must have had RT to the same side previously." The conclusion was that they will continue to offer PT to these subgroups of patients, since PT spares organs. USPT was not compared to RT.
The Breast Journal, Volume 25, Issue 6	2019	"Proton beam therapy reirradiation for breast cancer: Multi-institutional prospective PCG registry analysis"	Thorpe et al.	Breast	In this prospective cohort study, 50 patients received PBT (pencil beam 24%; uniform scanning 52%) reirradiation (reRT) for breast cancer. Acute AEs occurred within 180 days from start of reRT while late AEs began or persisted beyond 180 days. Fisher's exact and Mann-Whitney rank-sum tests were utilized. Kaplan-Meier methods were used to estimate overall survival (OS) and local recurrence-free survival (LFRS). Patient pool consisted of different surgeries: 44% patients who had mastectomies and 26% who had no surgery. There were no G4 and above toxicities. Acute G3 toxicity was experienced by 10% of the sample (AEs: pain, RD, lymphedema, and anorexia. Late G3 toxicity in 8% of patients (AEs: pain, RD, and wound infection). The calculated 1-year OS was 97% and LRFS was 93%. A longer follow-up is needed.
Acta Oncologica, Vol. 57, Issue 7	2018	"First Report of Proton Beam Therapy for Breast Angiosarcoma from the Perspective PCG Registry"	Thorpe et al.	Breast	In this study, 4 patients presenting with a second angiosarcoma were treated with PBT instead of RT. The follow-up outcomes were that the cancer patients survived after PBT treatment (2-24 month follow-up). All patients experienced acute G2 RD; however, no late toxicity or toxicity greater than grade 2.

Source	Year Published	Title	Author	Type of Cancer	Conclusion
ASTRO	2017	"Acute and Late Toxicity of Uniform Scanning Proton Therapy for Breast Cancer Patients"	Zheng et al.	Breast	The objective of this study was "to analyze the acute and late toxicity patterns of failure of uniform scanning PT (USPT) for breast cancer patients." 100 patients were included in the study and USPT was well-tolerated and an effective treatment for breast cancer. No patients had experienced grade 4 or above toxicity. The most common AE's was dermatitis (31% G1, 52% G2, 6% G3). Post-treatment AE's included hot flashes, arthralgia, lymphedema, breast pain, and brachial plexopathy.
International Journal of Particle Therapy	2017	"Toxicity of Uniform Scanning Proton Therapy for Breast Cancer"	Zheng et al.	Breast	Uniform scanning proton beam theory is well-tolerated for breast cancer treatment. No grade 4 or above was observed. Most common post-treatment toxicities were hot flashes, arthralgia, lymphedema nipple deformity, breast pain and brachial plexopathy, with incidence of 3% or lower.
Particle Therapy Cooperative Group - North America	2015	"Initial results of a multi-institutional proton accelerated partial breast irradiation trial"	Chang et al.	Breast	The objective of this study was to determine "freedom from ipsilateral breast recurrence occurrences receiving partial breast proton radiation therapy at 3 years." 26 patients enrolled in the study had no cancer recurrences and low acute and late toxicity. Acute toxicity: 46% G1 RD, 15% G2 RD, 0.03% G3 RD. Late toxicity: 11.5% G1 cosmesis, 0.07% G2 cosmesis, and no G3+.
International Journal of Radiation Oncology, Vol. 93, Issue 3, Supplement, November 1, 2015	2015	"Acute toxicity outcomes in breast cancer patients treated with adjuvant proton therapy"	Iftekaruddin et al.	Breast	Adjuvant radiotherapy for breast cancer is associated with high risks of long-term complications. PT is utilized in this retrospective study to assess the acute toxicity outcomes of breast cancer patients. The 41 patients received PT as well as neoadjuvant and adjuvant chemotherapy. "PT for BCa patients requiring regional nodal irradiation (RNI) appears well tolerated with acceptable acute toxicity." Acute G2 RD was found in 70.7% patients; 12.2% with G3 toxicity. AEs include esophagitis, chest wall pain.
International Journey of Radiation Oncology, Biology, Physics vol. 105, Issue 1, Supplement, Page E107	2019	" Clinical Outcomes in Patients with Recurrent Glioblastoma Treated with Proton Beam Therapy Reirradiation: Analysis of the Multi-Institutional Proton Collaborative Group Registry"	Saeed et al.	CNS	Identified 45 recurrent 23 females and 22 males from 7 proton centers who underwent PBT-reirradiation between 2012 and 2018. Only one patient experienced acute grade 3 toxicity. Late toxicities observed in 4 patients (neuropathy, cognitive disturbance, optic nerve disorder, and seizure), all occurred above 40 Gy. No grade 4+ toxicities observed. Median PFS was 13.9 months and median OS was 14.2 months after PBT-reirradiation. MVA revealed that prior surgery was associated with a 91.3% decreased hazard of death. Conclusion indicates PBT offers efficacy rates comparable to photon-reirradiation and is well-tolerated.
Radiotherapy and Oncology, Vol. 133	2019	"Are further studies needed to justify the use of proton therapy for paediatric cancers of the central nervous system? A review of current evidence.	Huynh et al.	CNS	Huynh et al. completed a literature analysis from which they gathered that "proton therapy for treatment of paediatric cancers of the CNS was found to provide survival and tumor control outcomes comparable, and frequently superior, to photon therapy." Most the publications reviewed in the article are retrospective observational studies instead of clinical trials. "There are no phase III trial reports on proton therapy for paediatric CNS tumors to clearly elucidate the immediate and also the long-term biological effects of these particles." There is epidemiological and radiobiological evidence that there's risk of second cancers after photon treatment and, at the same time, there's scientific consent on the unlikelihood of higher risks from protons.
International Journey of Radiation Oncology, Biology, Physics 104(4) December 2018	2019	"Insurance Approval for Proton Beam Therapy and its Impact on Delays in Treatment"	Gupta et al.	General	444 patients were considered for PBT treatment: 77% were supported for coverage by the American Society for Radiation Oncology's model policy. Of adults requiring PA, 64% were initially denied and 32% remained denied after appeal. The most common diagnoses to be considered for PBT were breast cancer (17%), low- or high-grade glioma (11%), and benign histology (93% of which were in the central nervous system) (10%). The most common diagnoses to be initially denied were prostate cancer (80%), lymphoma (77%), breast cancer (69%), and primary liver cancer (69%). The average time to authorization for adults requiring PA was 22.5 days. For patients approved upfront, after appeal, and then denied, the average and range were 13.4 days (0-50 days), 26.2 days (3-100 days), and 29.0 days (1-79 days). The average time to authorize pediatric patients was 7.9 days, including an average and range of 7.4 days (0-22 days) and 13.0 days (5-26 days) for patients approved upfront and after appeal, respectively.
Miami Cancer Institute (Proton Collaborative Group)	2019	"Reduced acute toxicity after proton versus photon chemoradiation for anal cancer: outcomes from the Proton Collaborative Group REG001-09 Trial"	Chuong et al.	GI	Definitive chemoradiation (CRT) is a standard of care for anal squamous cell carcinoma, cures the majority of patients, but causes significant morbidity. Acute grade 2+ toxicity is common (chances often greater than 70% for area such as skin and blood). 45 anal cancer patients treated with definitive CRT (28 PBT vs 17 IMRT). Toxicity was 88.3% for IMRT and 75% for PBT in skin. Acute grade 2 or 3 toxicity was 35.7% and 58.8% for PBT and IMRT respectively for gastrointestinal treatment.
Acta Onocologica vol. 59, Issue 2	2019	"Minimal acute toxicity from proton beam therapy for major salivary gland cancer"	Chuong et al.	Head & Neck	105 patients across 7 institutions were included, 90 had parotid and 15 had submandibular gland tumors, treated most commonly in post-op setting (70.5%) although some treated definitively (29.5%). Acute grade 2 or higher toxicity included nausea (1.5%), dysgeusia (4.8%), xerostomia (7.6%), mucositis (10.5%) and dysphagia (10.5%) after a follow up (median 14.3 months). Most common grade 2 (58%) or grade 3 (11%) toxicity was dermatitis. There was no significant difference in toxicity based on treatment with PBS or uniform scanning.
UW Medicine PCG	2017	"Proton Therapy Patterns of Care Among Pediatric and Adult Patients with CNS Tumors"	Tseng et al.	CNS	In this study, 1295 patients with a brain tumor diagnosis were treated with PBT. PBT was used more frequently at initial diagnosis (67.3%) than recurrence (32%). Primary brain tumor patients are younger with the majority under 40. No comparison was completed to evaluate the efficacy against RT.

Source	Year Published	Title	Author	Type of Cancer	Conclusion
Proton Collaborative Group	2019	"Clinical Outcomes Following Proton Beam Therapy for Locally Advanced Non-Small Cell Lung Cancer: Analysis of a Multi-Institutional Prospective Registry"	Jongen et al.	Lung	195 patients were included in analysis: PBT was given to 93% of patients with a median dose of 63.8 Gy(RBE). PBS used in 20% of treatments. Treatment-related grade 3 AEs were rare (1 pneumonitis, 2 dermatitis, 3 esophagitis). No grade 4 events reported. Two grade 5 occurred, both cardiological (likely unrelated to PBT). Median follow up was 13.6 months and median OS was 19 months. MVA indicated that PBS and increased EQD2 were associated with decreased mortality. Conclusion is that PBT appears to yield low rates of AEs with encouraging OS for the treatment of LA-NSCLC.
2019 Jul;58(7):1036-1040	2019	"Proton therapy for thymic malignancies: multi-institutional patterns-of-care and early clinical outcomes from the proton collaborative group and the university of Florida prospective registries"	Mercado et al.	Lymphoma	30 total patients. 22 thymoma patients received a median RT dose of 54 Gy (RBE) either postoperatively (91%) or definitively (9%). 8 thymic carcinoma patients received median RT dose of 60 Gy delivered postoperatively (75%) or definitively (25%); 50% received chemotherapy. Median follow up for all was 13 months. 5 patients relapsed, one locally (3%). 3 patients died of disease progression (two thymomas and one thymic carcinoma). 1 patient with thymic carcinoma and 1 with thymoma were alive and with disease. At baseline, patients most commonly experienced grade 1 fatigue (27%) and cough (20%). Two patients had grade 3 dyspnea. At follow-up during or after PT treatment, the most common grade 1 side effects were dermatitis (43%), fatigue (37%), and skin pain (40%). The most common grade 2 side effects were dermatitis (37%), cough (13%), and esophagitis (10%). No patients (de novo) experienced grade 3 or greater toxicities after PT. The patient who was treated with reirradiation for a recurrent thymoma developed grade 3 radiation pneumonitis two months after completing PT. Conclusion is that early results for PBT demonstrate an acceptable rate of recurrence with a tolerable toxicity profile.
NAPT	2018	"The Clinical Benefits of Proton Therapy - NAPT"	NAPT	General	Proton therapy delivers less radiation to brain stem, eyes, and healthy tissue than conventional radiation, lowering likelihood of side effects while allowing potentially higher dosages. For Nasopharynx Cancer there is a 60% chance of decreases associated with PBT: 50% decrease for Oropharynx cancer. Benefits for breast cancer include improved cosmetic results and decreased toxicities. survival rates for hepatocellular (58% higher 2 year), intrahepatic Cholangio (54% higher 4 year), lung (32% higher 3 year) and prostate (14% to 29% 5 year) cancer are also higher. For chordomas, there is 49% to 56% higher cancer disease control. There were also decreases in lung complications (41% and hospitalization rates (20%) for esophagus cancer, fewer severe lung complications (57%) for lung cancer, and severe rectal toxicity (32 - 69%) and moderate big bowel problems (50%) for prostate cancer. PBT is highly recommend for children due to chances of developing secondary cancer later in life.
Journal of Clinical Oncology, Vol. 26, Issue 2	2008	"Should Randomized Clinical Trials Be Required for Proton Radiotherapy?"	Goitein & Cox	General	“For each proton beam, virtually no dose is administered distal to the target volume and substantially less dose is administered than x-rays proximal to the target volume”; “There is virtually no difference in tissue response per unit dose between protons of therapeutic energies as compared with x-rays, so that the only relevant differences are physical”; “Radiation delivered to normal tissues causes damage to them, just as it does to tumors, and the severity of that damage increases with increasing dose”; Therefore, “protons can provide superior therapy to that possible with x-rays in almost all circumstances. It is primarily for this reason that the practitioners of proton beam therapy have found it ethically unacceptable to conduct RCTs comparing protons with x-rays.”
Journal of Clinical Oncology, Vol. 26, Issue 2	2008	"Should Randomized Clinical Trials Be Required for Proton Radiotherapy?"	Goitein & Cox	General	"Goitein and Jermann have analyzed the relative costs of proton beam therapy and high-technology x-ray therapy. They conclude that, with some foreseeable improvements, the ratio of costs is likely to be about 1.7. Although this represents an appreciable cost increment, it is substantially less than the costs of, for example, some expensive systemic therapies. Moreover, the recent surge of interest in acquiring proton beam facilities will almost certainly reduce the costs of proton therapy equipment through free market competition, the design of smaller and less expensive facilities, and a normalization of reimbursement rates based on the real costs of proton treatments."
Proton Collaborative Group	2017	"Outcomes of Atypical Teratoid Rhabdoid Tumors (ATRT) Treated with Proton Therapy"	Shin et al.	CNS	ATRT are highly malignant tumors of the CNS seen primarily in pediatric patients. Treatment involves multimodality regimes. This study retrospectively identified 14 patients with curative intent and prospectively enrolled in a nationwide registry. There was no G4 or above toxicity. Acute G2 AEs include alopecia (85.7%), RD (35.7%), nausea (14.3%), vomiting (14.3%), weight loss/anorexia (7.1%), fatigue (28.6%), blurred vision (7.1%), insomnia (7.1%), ataxia (14.3%), dysarthria (7.1%), and muscle weakness (28.6%). One patient presented with G3 thrombocytopenia.
Proton Collaborative Group; Journal of Clinical Oncology	2017	"Proton Beam Therapy for Liver Cancer is Well Tolerated: Outcomes from the Proton Collaborative Group REG001-09 Trial"	Chuong et al.	GI	This prospective trial studies the outcomes of PBT for the treatment of liver cancer using multi-institutional data. Forty-three patients were included, most of whom had hepatocellular carcinoma (48.8%) or cholangiocarcinoma (25.6%). Median dose prescribed was 58.05 Gy (RBE). US was used in 72.1% patients and PBS was used in 4.7% of patients. Median follow-up was 4.4 months. Seven percent of patients experienced intrahepatic recurrence, 4.6% developed distant metastasis, and 23.3% of patients died. The worst acute toxicity was G2 in 37.2% of patients consisting of anorexia, fatigue, nausea/vomiting, and RD.
Proton Collaborative Group	2017	"Multi-Center Experience of Proton Beam Therapy in the Treatment of H&N Cancer"	Petras et al.	Head & Neck	This study prospectively collected data from 8 PBT centers in the United States. RT was delivered from 2010 to 2017. After exclusions, 230 patients were included. Results showed acute G3 toxicity in n=41. Late toxicity was experienced by n=6 patients. In the reRT cohort, acute G3 toxicity in n=21 and late toxicity was observed in n=2. Minimal G3 toxicity and no late G4 toxicity was observed.

Source	Year Published	Title	Author	Type of Cancer	Conclusion
International Journal of Radiation Oncology, Vol. 99, Issue 2	2017	"Clinical Outcomes of Patients with Recurrent Lung Cancer Re-irradiated with Proton Therapy on the Proton Collaborative Group Prospective Registry Trial"	Badiyan et al.	Lung	This study observed the outcomes of treating recurrent lung cancer with PBT. It included 67 patients reRT with PBT from 2010-2016 at 6 PVG centers. Survival was estimated using Kaplan Meier and log rank statistics. Median PFS was 7.9 months. One and 2-year PFS was 26% and 3%. Median PFS for patients receiving a definitive dose of PBT was 9.4 months vs. 3.4 months for patients receiving a palliative dose. One and 2-year PFS was 27% and 4% for patients receiving a definitive dose and 18% and 0% for patients receiving a palliative dose, respectively. Median OS was 13.2 months. One and 2 year OS 51% and 13%. Median OS for patients receiving a definitive dose of PBT was 13.9 months and 10.1 months for palliative dose patients. One and 2-year OS was 52% and 17% for patients receiving a definitive dose and 46% and 0% for patients receiving a palliative dose, respectively.
Proton Collaborative Group	2017	"Machine Learning Analysis for Predicting Survival in Stage III Non-Small Cell Lung Cancer Patients Receiving Definitive Chemotherapy and Proton Radiation Therapy"	Kunaprayoon et al.	Lung	Standard line of treatment for non-small cell lung cancer (NSCLC) is chemoradiation. PBT can spare OAR. This study uses machine learning to analyze what factors are predictive of survival. The study design was retrospective; 179 consecutive stage III NSCLC patients enrolled from 2010-2017. The predictive algorithm's input variables were patient demographics, treatment parameters, and tumor parameters. The researchers used Naive Bayes, Logistic Regression, Neural Network, Support vector machine, and random forest. Tables of 6 mos. OS and 1-year OS show the predictors of survival using each type of predictive model.
Annals of Oncology	2017	"Consolidative proton therapy after chemotherapy for patients with Hodgkin lymphoma"	Hoppe et al.	Lymphoma	The researchers studied the early clinical outcomes of patients receiving PBT after chemotherapy for Hodgkin lymphoma (HL). From 6/2008 to 8/2015, 138 patients enrolled and received consolidative PT. The 3-year relapse free survival rate was 92% for adults and 87% for pediatric patients. Ten recurrences developed. The researchers evaluated the patients with a positron emission tomography/computed tomography scan response at the end of chemotherapy, and patients with a partial response had worse 3-year PFS compared with other patients (78% vs. 94%). No late G3 toxicities occurred, unsurprising given that decades of follow-up are needed to observe significant late toxicities. G2 esophagitis was expected and occurred; however, there was a lack of G2 pneumonitis.
International Journal of Radiation Oncology, Vol. 99, Issue 2	2017	"Proton Therapy for Lymphoma: A Multi-institutional Patterns of Care Study"	Mohindra et al.	Lymphoma	The researchers evaluated 139 consecutive patients with HL or NHL treated with PBT within 7 PCG institutions between 2010 and 2016. Disease diagnosis was 60% HL and 40% NHL. Chemotherapy was administered to 83% of patients prior to PBT. The median dose of PBT was 30.6 Gy (RBE). The median PT dose was 30.6 Gy(RBE) (range, 19-54). The median PT dose in the three age-cohorts; the three stage groups (I/II, III/ IV and relapsed/refractory) was 30.6, 30 and 36.3 Gy(RBE), and diagnosis (HL, NHL) was 30.6 and 36 Gy(RBE), respectively. In their multivariate regression analysis, older age, NHL diagnosis, and relapsed/refractory (R/R) stage predicted for higher PBT dose with no impact on enrollment date or gender.
International Journal of Radiation Oncology, Vol. 99, Issue 2	2017	"Rates of Toxicity and Outcomes After Mediastinal Proton Therapy for Relapsed/Refractory Lymphoma"	Tseng et al.	Lymphoma	The researchers reviewed 51 R/R HL and aggressive NHL patients treated with mediastinal PBT. Most patients were treated for HL (73%) followed by NHL (25%). Median RT dose and dose/fraction to the mediastinum was 36 Gy(RBE) (range, 25.2-54) and 1.8 Gy, respectively. The median follow-up was 21.2 months, during the follow-ups it was assessed that 6 (12%) patients developed symptomatic pneumonitis (all G2 toxicity). No G3 or higher late toxicity has occurred. Two-year OS and PFS were 87% and 69%, respectively, which was higher among the HL cohort compared to the NHL cohort.
Northwestern Medicine Chicago Proton Center	2017	"Rectal Toxicity for Patients Treated with Proton Beam Radiation Diagnosed with Prostate Cancer Using Free Rectal Water, Water Filled Rectal Balloon or Interstitial Hydrogel for Rectal Immobilization"	Casablanca & Hartsell	Prostate	837 patients: 308 given free rectal water, 309 rectal balloon, 220 implanted tissue expander (hydrogel). Hydrogel had the fewest adverse events (80) follower by free water (192) and then the balloon (219). No grade 3 in water, but 3 in balloon and 1 in hydrogel. fewer than 20% had grade 2 toxicities across all treatments (fewer than 10% hydrogel). Over 50% of hydrogel patients had no toxicity, while about 38% of water and 20% of balloon patients had no toxicities.
Acta Oncologica, Vol. 57, Issue 3 (368-374)	2017	"Minimal Toxicity After Proton Beam Therapy for Prostate and Pelvic Nodal Irradiation: Results from the Proton Collaborative Group REG001-09 Trial"	Chuong et al.	Prostate	85 patients with exclusive PBT treatment. Acute grade 1,2, and 3 GI toxicity rates were 16.4%, 2.4%, and 0% respectively. Acute grade 1,2, and 3 GU toxicity rates were 60%, 34.1%, and 0% respectively. Most patients were treated with pencil beam scanning (PBS) (68.2%); the remainder was treated with uniform scanning (US) (31.8%). Of note, 5 of the 6 patients with node-positive disease experienced acute grade 2 GU toxicity despite their low median baseline IPSS of 3.5 (range, 0–23).
Northwestern Medicine Chicago Proton Center	2017	"An Evaluation of Prostate Volume and Proton Therapy-Related Toxicities"	Krcik et al.	Prostate	Study examined 688 prostate cancer patients (70.0 Gyat 2.5 Gyper fx, OR 79.2 Gyat 1.8 Gyper fx). Most patients had prostate size of 26-50 cc (418) or 51-75 (155). Very few high grade toxicities overall. Most proton therapy-related toxicities exhibit no significant relationship with prostate size (although significant correlation between size and incidence of low grade hematuria).
Hampton University Cancer Research Center	2017	"Utilization of Machine Learning and Proton Collaborative Group Data to Develop a Model for Predictive Prostate Cancer Proton Radiotherapy Response"	Ricks-Santi et al.	Prostate	Primary Gleason Score was mostly 3 (1762 patients) or 4(795 patients) in a sample of size 2617. Prior androgen suppression and age were highly correlated with biochemical recurrence (1.40 points) while a prior rectal prostatectomy (-1.98 points) and decrease in time between treatment and follow-up were highly associated with a decrease in biochemical recurrence.

Source	Year Published	Title	Author	Type of Cancer	Conclusion
University of Florida	2017	"Proton Therapy for Thymic Malignancies: Multi-institutional Patterns-of-Care and Early Clinical Outcomes from the Proton Collaborative Group Registry & UF"	Mercado et al.	Thymus	Thymoma and thymic carcinoma are rare malignancies arising in the anterior mediastinum from the thymus (median diagnosis age of 40-60 years). Treatment is usually surgery and occasionally RT as well as chemo. If unresectable chemoRT is used. As long-term survival is common (5yr 95%, 10yr 86% with RT), concerns of radiotherapy related side effects are common. PT lowers dosage to OARs, decreasing long-term toxicity (studies have shown significant reductions in heart, lung, and esophagus dose). Study examined 30 patients who received post-operative or definitive proton therapy for thymoma or thymic carcinoma. 18 with thymoma and 6 with thymic carcinoma received post-op RT. Median follow-up was 22 months, with local recurrence in 2 thymoma and 1 thymic carcinoma patient (3 patient deaths due to, locally recurrent thymic carcinoma, metastatic disease, or intercurrent disease). No patient experienced grade 3 or greater toxicity. At 3 years, regional control 96%, distant control 74%, OS 94% (results comparable to studies at UPenn, and UF/PCG).
PCG ASTRO	2016	"Low Levels of Acute Toxicity Associated with Proton Therapy for Low Grade Gliomas: A Proton Collaborative Group Study"	Wilkinson et al.	CNS	The PCG prospective database was queried for the treatment of low-grade gliomas (LGG). Fifty eight primary CNS tumors were included in the study. No acute G3 AE were found. RD was found in 81% and fatigue was found in 78%; these were shown to have interval improvement by the 3 month follow-up. Other AEs include: Alopecia (84%; its grade did not show a significant change at 3 mos.), Nausea (30%; may be due to concurrent chemoradiation), seizures decreased from baseline 25% over the course of treatment to 8%.
International Journal of Radiation, Vol. 96, Issue 2	2016	"Limited Toxicity After Proton Beam Therapy for Esophageal Cancer: Outcomes from the Proton Collaborative Group"	Chuong et al.	Esophagus	A total of 77 patients were enrolled in this multi-institutional study evaluating the toxicity of PBT when treating esophageal cancer (42.9% were from a single institution). Pencil beam scanning was reported starting in 2015 and completed for 8 patients, otherwise uniform scanning was completed (at times the techniques were not reported). Acute G3 toxicities were reported in 15.6% of the patients. There were no G4 and above toxicities. Long follow-up needed to address late toxicity.
Proton Collaborative Group	2016	"Proton Therapy Posterior Beam Approach with PBS for Esophageal Cancer: Clinical Outcome, Dosimetry, & Feasibility"	Zeng et al.	Esophagus	Twelve patients were included in this study using trimodality therapy (chemoradiation and surgery). The pathologic complete response (pCR) rate was 25%. The same pCR rate was seen in both uniform scanning (US) and pencil beam scanning (PBS). No G4 and above toxicity was observed in chemoradiation. AEs included: Neutropenia (G3 13% US), Thrombopenia (G2 13% US), Anemia (G2 40% PBS; 25% US), Nausea (G2 20% PBS; 25% US; G3 13% US), Fatigue (G2 20% PBS; G2 25% US), RD (G2 20% PBS; G2 50% US), Esophagitis (G2 38% US). Median PFS and OS not reached.
Proton Collaborative Group; Journal of Clinical Oncology	2016	"Postoperative proton therapy for pancreatic cancer patients enrolled on the Proton Collaborative Group (PCG) registry"	Nichols et al.	GI	This study uses the Proton Collaborative Group's (PCG) multicenter registry for patients receiving PBT for postoperative resected pancreatic cancer. From 2/2013 to 6/2015 12 patients were identified. 1 year survival was 54%. PBT was well tolerated without significant toxicity or treatment interruption.
Radiotherapy and Oncology, Vol. 120, Issue 1	2016	"Intensity modulated proton beam therapy (IMPT) versus Intensity modulated photon therapy (IMRT) for oropharynx cancer patients – a case matched analysis"	Blanchard et al.	Head & Neck	This study compared IMPT to IMRT for oropharynx cancer patients in a case matched analysis. Patient data came from a single institute during the period 2010 to 2014. Patients were matched by the following characteristics unilateral/bilateral treatment, disease site, HPV status, T and N stages, smoking status and receipt of concomitant chemotherapy. Fifty IMPT and 100 IMRT patients were included. The median follow-up time was 32 months. Statistically significant differences were not shown in OS or in PFS. There were no significant differences in acute G3 or higher RD or mucositis. The median duration of G-tube placement was 2.8 months and 4.8 in the IMPT and IMRT patients respectively. The age-adjusted OR for the use of a G-tube during treatment and at 3 months post-treatment were respectively 0.53 during treatment and 0.43 at 3 months. IMPT is associated with a reduction of G-tube rates during the acute, 3-mos., and 12-mos. endpoints.
International Journal of Radiation Oncology, Vol. 96, Issue 2	2016	"Clinical Outcomes of Patients with Stage II-III Non-Small Cell Lung Cancer Treated with Proton Beam Therapy on the Proton Collaborative Group Prospective Registry Trial"	Badiyan et al.	Lung	Badiyan et al. (2016) evaluated the outcomes of patients enrolled in the PCG registry trial with stage IIA-IIIB NSCLC when treated with PBT. The researchers included 96 consecutive patients between 2010-2015 with a curative intent at 4 PCG centers. Freedom from recurrence (FFR) and OS were estimated using the Kaplan-Meier method. Patients had stage IIA (14%), IIB (8%), IIIA (54%), or IIIB (24%) disease. Patients received definitive (83%) or adjuvant (17%) treatment. A median dose of 70 Gy(RBE) in 35 fractions was administered. "The estimated median 1- and 2-year OS were 13.2 mos., 53.4%, and 39.4%, respectively. Estimated median and 1-year FFR were 13.1 months and 51.8%, and 39.1% respectively. Acute grade 3 and 4 toxicities occurred in 6% (dyspnea, dehydration, radiation dermatitis, skin pain, esophagitis and fatigue) and 1% (myocardial infarction), respectively." Late G3 toxicity occurred in 3% of the patients.
Acta Oncologica, Vol. 55, Issue 11	2016	"Proton Therapy Patterns-of-Care and Early Outcomes for Hodgkin Lymphoma: Results from the Proton Collaborative Group Registry"	Hoppe & Hartsell	Lymphoma	Hoppe & Hartsell (2016) evaluated patients that were administered PBT for HL. The researchers identified 40 patients between 2008 and 2015. Pediatric patients received a median dose of 21 Gy (RBE) and adult patients received a median dose of 30.6 Gy (RBE). The median follow-up was 21 mos. The 2-year PFS was 85%. There were no G3 toxicities. "Consolidative proton therapy following standard chemotherapy in HL is primarily used in young patients with bulky mediastinal disease." In order to assess late toxicities, longer follow-up is required.
Northwestern Medicine Chicago Proton Center; PTCOG-NA	2017	"Dosimetric Comparison of IMPT versus IMRT using VMAT and HRT for Salvage Radiation Post Prostatectomy"	Chang et al.	Prostate	Chang et al. compared the dosimetric differences of IMPT to two types of IMRT for the treatment of prostate cancer. They evaluated the effects on the target and OARs. The researchers included 15 patients that were treated at the Northwestern Proton Center. The patients were treated with IMPT to 70.2 Gy(RBE). Dose volume histograms were compared with a one-tailed T-test. The 98% planning target volume coverage (PTV) was statistically similar to all three modalities; however, the average dose to 95% of the PTV was a little higher in the IMRT plans. "IMPT seems to have a dosimetric advantage over IMRT in several categories for the bowel and bladder."

Source	Year Published	Title	Author	Type of Cancer	Conclusion
Northwestern Medicine Chicago Proton Center	2016	"Assessment of Acute Toxicity in Prostate Cancer Patients using Hydrogel Spacer During Proton Therapy"	Conterato	Prostate	Conterato assessed the acute toxicity outcomes in prostate cancer patients treated with definitive PBT with a hydrogel spacer (HS) in place. The study conducted a retrospective review of 63 consecutive patients during 2015-2016. The most common G2 genitourinary (GU) toxicities were urinary frequency, retention, and urgency. Two patients experienced G3 toxicity (urinary tract pain and retention that required treatment). Two patients experienced G2 Gastrointestinal (GI) toxicities (fecal incontinence and rectal hemorrhage). The use of HS resulted in acceptable low rates of GI and GU toxicity. Additional follow-up is required for late toxicities.
Northwestern Medicine Chicago Proton Center	2016	"Reduction in Rectal Dose in Prostate Cancer Patients Using Hydrogel Spacer During Proton Therapy"	Conterato	Prostate	Conterato compared the reduction of rectal dose using HS versus daily endo-rectal balloons when being treated with PBT. The study retrospectively reviewed 63 consecutive patients with HS in place undergoing PBT at a single center from 2015-2016. The patients received two types of PBT: PBS and uniform scanning. "HS patients, averaged across all PBT targets, experienced a significant reduction in both Rectum Eval V50 and V70." The HS cohort experienced significant reduction in average Rectum Eval V70 compared to the rectal balloon cohort, regardless of PBT delivery method.
Journal of Medical Radiation Sciences	2016	"Dosimetric and radiobiological impact of intensity modulated proton therapy and RapidArc planning for high-risk prostate cancer with seminal vesicles"	Rana et al.	Prostate	10 high-risk cancers cases included in retrospective study. The dosimetric impact of the treatment technique was more distinct in the case of OARs, especially in the low-dose (V30) and medium-dose (V50) regions. For the bladder, the V30 and V50 were consistently lower in IMPT plans (23.2% and 16.6%) when compared to RapidArc plans (50.9% and 25.1%). The mean doses of the rectum and bladder were found to be significantly lower in IMPT plans (16.9 Gy (RBE) and 17.5 Gy (RBE) respectively) when compared to RapidArc plans (41.9 Gy and 32.5 Gy respectively) mean dose. Conclusion is that IMPT produced better dosimetric results in low, medium, and high dose regions as well as lower NTCP compared to RapidArc. For the Bladder, the NTCP and dosimetric results were comparable for both plans in the high dose region whereas IMPT had better results in the low and medium dose regions.
Reports of Practical Oncology and Radiotherapy 21 (2016) 207-212	2016	"Image-guided Hypofractionated Proton Beam Therapy for Low-Risk Prostate Cancer: Analysis of Quality of Life and Toxicity, PCG GU 002"	Vargas et al.	Prostate	Study examined 82 patients. .For urinary functions, statistically and clinically significant change was not seen. Urinary QOL scores did not show statistically and clinically significant change at any end point. Bowel QOL scores showed small but statistically and clinically significant change at 6, 12, 18, and 24 months. Sexual scores showed small but statistically and clinically significant change at 24 months. No AE grade ≥3 was seen. Overall only 17 grade urinary and 6 bowel grade 2 symptoms were present over the 2 year period.

APPENDIX 3: LITERATURE REVIEW – COMPARATIVE EFFICACY

Appendix Table 3: Literature Review – Comparative Efficacy

Source	Year Published	Title	Author	Type of Cancer	Merits of Alternative Therapies	Type of Source	Conclusion
Academic Press	2019	Proton beam therapy for oligodendroglioma	Williams et Al	Brain	RCTs comparing proton versus photon therapy in the treatment of CNS tumors is lacking in the pediatric population. Therefore, dosing of proton therapy is not well defined like it is for photon therapy.	Comparative Efficacy	The key concern with patients with oligodendroglioma is the quality of life once treatment is complete. Treatments can achieve prolonged life expectancy; however, conventional radiation therapy causes cognitive side effects. These include memory loss, difficulty with executive function, and attention deficit problems. One study presented data with dosimetric comparisons between proton and photon therapy for low-grade gliomas. The researchers found that the mean excess risk of secondary malignancy was 106 per 10,000 cases for IMRT versus 47 per 10,000 cases for proton plans. Another study investigated proton therapy vs. photon therapy in pediatric population modeled dose characteristics in 4 different CNS tumors. The researchers found better sparing of smaller OARs when they were further away from the PTV. Larger structures received less low and intermediate-dose radiation which resulted in clinically significant IQ differences. Neurocognitive outcomes were studied in a meta-analysis where verbal and nonverbal cognitive deficits were one full standard deviation below the mean when comparing protons to XRT. Proton therapy represents promising way of reducing the long-term toxicities of radiation therapy in the treatment of CNS tumors.
International Journal of Radiation Oncology	2018	National Cancer Institute Workshop on Proton Therapy for Children: Considerations Regarding Brainstem Injury	Haas-Kogan et Al	Brain	No discussion of photon therapy.	Comparative Efficacy	There is widespread consensus that proton therapy should be used to treat pediatric brain tumor patients to avoid critical CNS structures. However, there has also been recent reports of brainstem necrosis after PBT. These incidences have "raised concerns over the potential biological differences among radiation modalities." The 3 largest U.S. pediatric PBT centers gathered the incidences of symptomatic brainstem injury as well as treatment details for 671 children with focal posterior fossa tumors treated with protons from 2006 to 2016. The analysis of the data showed there was an average of 2.38%. "The actuarial rate of grade ≥2 brainstem toxicity was successfully reduced from 12.7% to 0% at one center after adopting modified radiation guidelines."
International Journal of Radiation Oncology	2018	Risk of Visual Toxicity Following Fractionated Proton vs Photon Radiation Therapy for Patients with Meningiomas	Tran et Al	Brain	There were less patients who developed late visual toxicity if treated with IMRT (PBT n=10 vs. IMRT n=3).	Comparative Efficacy	The purpose of this study was to compare the visual toxicity associated with treatment from photon therapy versus proton therapy for patients with tumors involving the base of the skull. The researchers reviewed records of 136 patients treated with RT for meningioma at MD Anderson center between 2000 and 2014. 55% patients received IMRT and 45% received PBT. 64% of the patients had tumors involving the base of the skull (60% PBT vs. 68% IMRT). "There was no difference in the incidence of acute visual toxicity between PBT (15%) and IMRT (8%) with the 2 most common being eye irritation (n=6) and diplopia (n=4)." 6% of patients experienced grade 1 visual toxicity and grade 2, with no differences between photon therapy and PBT. 27% of patients had at least one late toxicity (65% grade 1-2). 10% of the developed a late visual toxicity (PBT n=10 versus IMRT n=3). The risk of developing a high grade toxicity is low following RT for patients with meningioma. "However, for patients with BOS tumors, there's a risk of decreased visual acuity and/or optic neuropathy that is not correlated with Dmax."
Spring Nature 2018	2018	Proton Beam Therapy (For CNS Tumors)	Yerramilli et Al	Brain		Comparative Efficacy	In general, the efficacy of radiation therapy is limited by the dose constraints of normal tissue, which is the primary determinant for unacceptable radiation-related toxicity. Malignancies may require high doses to control tumors, and proton therapy can allow for dosage increases in ways that weren't previously possible. Proton therapy can offer some advantages, compared to photon based therapies with regards to toxicity, such as that the volume of normal tissue exposed to low doses of radiation therapy can be reduced. One study demonstrated that patients with skull base chordomas who received proton therapy to doses between 77.4 Gy(RBE) and 79.4 Gy(RBE) showed that local control at 2 years was 86% and OS was 92%, with grade 2 toxicity of hearing loss in 18% and no grade 2 or higher toxicities observed for optic structures or brainstem. This suggests that proton therapy is effective for dosing and local control. In the long term, follow up showed that 7-year local control rates of 70.9% for patients with chordoma and 93.6% of patients with chondrosarcoma with mean delivered dose of 72.5 Gy(RBE).Another study of 191 patients found fantastic control rates with 98% eye preservation in the SRS group and 95% in the PBT group. However, proton therapy had higher preservation of visual acuity among group members (45% of group vs 65% of group).
International Journal of Radiation Oncology	2017	Brainstem Injury in Pediatric Patients With Posterior Fossa Tumors Treated With Proton Beam Therapy and Associated Dosimetric Factors	Gentile et Al	Brain	The 5-year cumulative incidence of brainstem injury post-irradiation is 2%, which is comparable with patients who are treated with photon therapy.	Comparative Efficacy	PBT is widely utilized in pediatric patients with brain tumors due to the dosimetric advantage which potentially decreases both early and late side effects. However, there is controversy regarding the rates of symptomatic brainstem injury when compared to photon therapy. This study included 216 consecutive patients that were treated between 2000 and 2015 at MGH. The crude rate of the injury was 2.3% in all patients; while the 5-year cumulative incidence of the injury was 2.0% (95% CI, .7%-4.8%). This incidence is comparable to the rate found in the photon therapy setting. The researchers show that when D_{max} and V_{55} are kept below 55.8 GY radiobiological effectiveness (RBE) and ≤6.0%, respectively, the 5-year rate of symptomatic brainstem injury would be less than 2%.
International Journal of Radiation Oncology	2019	Quantification of Acute Skin Toxicities in Patients With Breast Cancer Undergoing Adjuvant Proton versus Photon Radiation Therapy: A Single Institutional Experience	DeCesaris et Al	Breast	Both proton and photon treatment are correlated with incidence of grade >=2 RD. However, due to the dose distribution of protons there was a significantly higher rate of grade >=2 RD.	Comparative Efficacy	Radiation dermatitis (RD) is a common side effect for patients undergoing breast irradiation. In this study, a retrospective database was created of patients with invasive breast cancer who were treated with adjuvant radiation with either protons (PBS) or photons. 86 patients that underwent adjuvant radiation therapy to the breast with either PBS (n=39) or photon (n=47) radiation therapy within a single institution were included. A significantly higher rate of grade ≥2 radiation dermatitis was observed in patients treated with protons. Grade ≥2 RD was present in 69.2% versus 29.8% of patients receiving proton and photon therapy, respectively. 74.4% of the proton cohort and 87% of the photon cohort had clinical follow-up by a radiation oncologist within 8 weeks of treatment. In the multivariate analysis, only the use of proton RT and increasing total RT dose was predictive of grade ≥2 RD. There is a likelihood of radiobiologic differences in the dose distribution of protons that cannot be accounted for within the currently available treatment planning system. Acute RD is an expected toxicity experienced by patients being treated for breast cancer with RT.

Source	Year Published	Title	Author	Type of Cancer	Merits of Alternative Therapies	Type of Source	Conclusion
International Journal of Radiation Oncology	2017	Predicted Rate of Secondary Malignancies Following Adjuvant Proton Versus Photon Radiation Therapy for Thymoma	Vogel et Al	Chest		Comparative Efficacy	10 patients were examined in a double-scattered proton beam study (median age 65 years, 6 men). There were no differences in coverage, but large reductions in dosage for lung, heart, and esophagus in DS-PBT compared with IMRT. 5 excess malignancies could be treated by using protons instead of photons. In addition, proton therapy can reduce late complications. Proton and photon plans provided similar PTV coverage, but protons had greater sparing of OARs, such as lung (5.5 Gy vs 9.6 Gy), heart (7.4 Gy vs 19.4 Gy), and esophagus (27.5 Gy vs 49.6 Gy). Protons were more effective than IMRT in preventing secondary cancers per 10,000 in lungs (1.1 vs 3.9), esophagus (0.4 vs 1.2), breasts (0.8 vs 1.8), skin (0.2 vs 1.6), stomach (less than 0.01 vs 1.8), and thyroid (0.3 vs 0.8). In total, this amounts to 17.3 excess SMNs per 10,000 for IMRT vs 2.8 for DS-PBT (difference of 14.5). Photons also have 5 more SMNs per 100 for patients with life expectancy 35 years from treatment.
Acta Oncologica	2017	Risk of major cardiac events following adjuvant proton versus photon radiation therapy for patients with thymic malignancies	Vogel et Al	Chest	Adjuvant radiation therapy has been shown to reduce the risk of local recurrence and improve survival in high risk patients. Radiation dosage to the heart is associated with increased risk of ischemic heart disease, pericarditis, and valvular disease in patients with breast cancer and Hodgkin's lymphoma. Pencil beam scanning would allow more normal tissue to be spared via modulation of intensity than PBT, which relies on physical scattering of foils. Additionally, double scattering-PT and PBS are less robust than IMRT for dose distribution along the depth direction. Developing tools to properly calculate beam margins and mitigate the interplay effects with PBS-PT would be needed to derive greater benefits from proton therapy for thoracic tumors. Additionally, it is unclear what clinical benefits exist for reducing dosage to the heart with proton therapy.	Comparative Efficacy	Twenty-two consecutive patients were evaluated. DS-PBT resulted in statistically significant decreases in dose to the heart, lungs, left ventricle, esophagus, and spinal cord. The increase in risk of MCEs from 0 to >= 20 years was lower with PBT (74% versus 135%). Because of its dose deposition, PBT may reduce dose to thorax and anterior mediastinum while sparing OARs. Coverage of CTV and PTV did not vary by modality: compared with photon radiation, proton radiation resulted in statistically significant improvements in the mean lung, heart, and esophagus dose. DS-PBT was also expected to have lower risk of major cardiac events than IMRT every year post-treatment. Ultimately, proton beam therapy results in decreased dose to OARs and may reduce risk of MCEs compared with IMRT.
CMAJ	2019	Proton beam therapy for cancer	Tsang et Al	General	Radiotherapy is the conventional treatment used for the treatment of cancer in the treatment of one-third of cancer patients.	Comparative Efficacy	Proton beam therapy can effectively treat cancer by targeting the specific tumor and minimizing the volume of normal tissues exposed to radiation. Children and young adults are subgroups of the population that will benefit from this form of therapy due to the fact minimizing the dose to normal tissues leads to less long term adverse effects. Due to reduced irradiated normal tissue, PBT may reduce the incidence of secondary, radiation-induced malignant neoplasms. Economic evaluation studies point to PBT as a cost-effective treatment for pediatric brain tumors (US$21,716-$26,419 per quality-adjusted life year depending on the study) and some head-and-neck cancers (ICER US$4254-$143,229 per QALY) below the common WTP threshold of $150,000 per QALY.
MDPI	2019	The Radiobiological Effects of Proton Beam Therapy: Impact on DNA Damage and Repair	Vitti et Al	General	The studies that the authors reviewed showed that there is DNA damage caused by both PBT and photons; however, the quality of DNA damage may vary (e.g. clustered/complex DNA damage) between PBT and photons. There are no clear differences in double-strand DNA damage. Some results are shown in Table 1.	Comparative Efficacy	PBT is characterized by a "low entrance dose and maximum energy deposition" in a targeted region. This range where the dose peaks is known as the Bragg peak; the Bragg peak can spare surrounding tissues and organs at risk compared to conventional RT using photons due to drop in energy shortly after the peak. Several modulated proton beams can produce a wider peak (spread-out Bragg peak or SOPB) allowing larger tumor irradiation. The authors of this paper explore the collateral damage that occurs to DNA during the linear energy transfer (LET) at the distal fall-off of the Bragg Peak and if the body has the ability to repair the damage caused by the LET. There is little information on the biological effectiveness of PBT. Researchers do not know if the LET of proton beams cause double-strand DNA or single-strand DNA damage nor do they know complete information about the pathways that the cells follow for the damage response. The authors suggest that future research should use 3D spheroid models to study DNA damage from LET of PBT.
Clinical and Translation Radiation Oncology	2018	Relative biological effectiveness in proton beam therapy – Current knowledge and future challenges	Luhr et Al	General		Comparative Efficacy	Brainstem injury is a rare complication of radiation therapy for both photons and protons. Substantial dosimetric data have been collected for brainstem injury after proton therapy, and established guidelines to allow for safe delivery of proton radiation have been defined. Linear electron therapy optimization is a less complex problem to address and therefore will likely be an early step in the process, optimizing plans to ensure that LET hot spots remain outside normal tissues. To move forward requires acceptance of the following: (1) the physical dose does not necessarily reflect the biologically effective dose in particle therapy; and (2) we have not developed our treatment algorithms to adequately reflect normal tissue tolerance in photon or proton therapy. Thus, the biologically correct calculation of dose in proton therapy might exceed the normal tissue tolerances.
Molecular and Clinical Oncology	2018	The evolution of proton beam therapy: Current and future status (Review)	Tian et Al	General	Controversy has arisen overusing PBT to treat prostate cancer compared, where it is more costly and offers no proven advantage over conventional IMRT. Additionally, further studies will be needed to ensure that the precision advantages of PBT can be applied properly in a clinical setting.	Comparative Efficacy	There have been controversies surrounding PBT regarding costs, routine application to certain cancers, and insufficient technology/clinical trials to monitor its effects. The greater mass of protons allows for localized surgery while sparing normal organs through concentrated energy deposition followed by no further dosage (Bragg peak). Literature suggests that PBT is particularly effective for treating head and neck cancers. More critically, PBT has been demonstrated to reduce toxicity rates while producing a survival benefit compared with photon beam therapy and 3DCRT: its advantage in dose escalation also lowers risk of recurrence, severe toxicity, intensifies chemotherapy, and prolongs survival rates. Additionally, PBT has been found to be more cost-effective for breast, intracavitary, and interstitial cancers than conventional x-ray/electron beam treatment. Similarly, concerns over the long-term effects of RT can be ameliorated via PBT in pediatric applications, where its lower dosages could mitigate developmental side effects of treatment, including secondary RT-related cancers.

Source	Year Published	Title	Author	Type of Cancer	Merits of Alternative Therapies	Type of Source	Conclusion
Seminars in Radiation Oncology	2017	Proton Therapy for Head and Neck Cancers	Blanchard et Al	Head and Neck	The majority of treatment plans for head and neck cancers are employing external beam photon therapy. IMRT and proton therapy have emerged to address challenges in treatment conformality and reduction of high doses to OARs.	Comparative Efficacy	The main theoretical superiority of proton therapy against photon therapy relies on "the absence of exit dose beyond the target and the sharper lateral dose distribution secondary to protons' heavier mass relative to photons." There are two types of PBT: passive scattering (less flexible, labor intensive, generates secondary neutrons, and limits the capacity for adaptive replanning in case of tumor or anatomical changes during treatment) and IMPT (more advanced and more widely used form of PBT).
Radiotherapy and Oncology Journal	2016	Intensity-modulated proton beam therapy (IMPT) versus intensity-modulated photon therapy (IMRT) for patients with oropharynx cancer – A case matched analysis	Blanchard et Al	Head and Neck	IMRT favors younger patients in terms of toxicity and late feeding tubes.	Comparative Efficacy	Fifty IMPT and 100 IMRT patients were included. The median follow-up time was 32 months. There were no imbalances in patient/tumor characteristics except for age (mean age 56.8 years for IMRT patients and 61.1 years for IMPT patients). Statistically significant differences were not observed in overall survival (hazard ratio (HR) = 0.55) or in progression-free survival (HR = 1.02). The age adjusted odds ratio (OR) for the presence of a gastrostomy (G)-tube during treatment for IMPT vs IMRT were OR = 0.53 and OR = 0.43 at 3 months after treatment. When considering the pre-planned composite endpoint of grade 3 weight loss or G-tube presence, the ORs were OR = 0.44 at 3 months after treatment and OR = 0.23 at 1 year after treatment. IMPT associated with reduced rates of feeding tube dependency and severe weight loss without jeopardizing outcome. IMRT group had twice as many recurrences post-treatment than the IMPT group. IMPT may achieve toxicity reduction while preserving tumor control compared with IMRT. Additionally, IMPT exhibits similar cure rates to IMRT by OS and disease control measures post-treatment and a reduction in feeding tube rates and weight loss.
Radiotherapy and Oncology Journal	2019	Differential inflammatory response dynamics in normal lung following stereotactic body radiation therapy with protons versus photons	Li et Al	Lung	SBRT is a conventionally used to treat early-stage NSCLC as it is safe and effective treatment option. It results in "excellent local control and low rates of symptomatic pulmonary toxicity." The effects of protons that give high total doses to the normal lung on the other hand are undefined as the time and dose dependence are unknown.	Comparative Efficacy	There is an emerging body of evidence that though protons may have superior tumor cell kill, and there are also unexpected normal tissue reactions or toxicity in a subset of patients. The effects seen may be the result of an increased relative biological effectiveness "at the end of a single passively scattered proton beam." This study compares the time-dependent changes in lung parenchyma of early-stage non-small cell lung carcinoma (NSCLC) patients after targeted radiation to the tumor while minimizing radiation to adjacent normal tissue (stereostatic body therapy). The two techniques compared are stereotactic body radiation therapy (SBRT) and stereotactic body proton therapy (SBPT). The researchers retrospectively matched patients treated with SBPT with patients treated with SBRT by patient, tumor, and treatment characteristics and conducted the quantitative analysis using Wilcoxon's signed rank tests to assess for statistically significant differences in the dose-response curves (DRC) between SBPT and SBRT patients. The researchers also used the Spearman's rank correlation for finding the correlation between the severity of the response (expressed by the DRC) and the qualitative radiology assessment. Results showed that SBPT patients showed slightly more inflammatory responses, however not significantly (21.7% of {SBPT patients vs. 13% of SBRT patients, defined as 6HU/Gy). SBRT patients on the other hand, "the severity of response significantly increased from early to late time period follow-ups." Though there was no significant difference in the maximum response after both types of treatments, the data suggests SBPT could induce more (asymptomatic) inflammation than SBRT. Sample size is too small to draw definitive conclusions.
Spring Nature 2018	2018	Proton Therapy in Non-small Cell Lung Cancer	Mesko et Al	Lung	Radiation therapy is a critical component of the treatment plan for patients with non-small cell lung cancer (NSCLC). Though it is widely used, 25% of patients experience isolated locoregional recurrences and toxicity has been proven to be another concern.	Comparative Efficacy	PBT has emerged as an alternative therapy that could prove to provide better clinical outcomes for NSCLC. Due to the sharp build-up and drop-off, "which is particularly important in lung cancer where nearby structures include the heart, spinal cord, esophagus, and uninvolved lung." RCTs have not shown significant differences in toxicity and local control between photon and proton therapy; however, with the newer PBT techniques emerging there may be increased toxicity and tumor control benefits. Notably, there may be certain subpopulations that would benefit from proton therapy more such as central early stage tumors, previously irradiated tumors, and locally advanced tumors, while others may be better fit for photon therapy. There are 2 methods of PBT: passive scatter (PSPT) and intensity-modulated proton therapy (IMPT; e.g. pencil beam). PSPT "allows for more confidence in where the dose will be delivered," however is limited by its ability to match the shape of the tumor. IMPT, on the other hand, can accurately match the shape of the tumor, but it is sensitive to the motion of the patient or the tumor. The majority of studies conducted investigating early-stage and locally advanced NSCLC have found improved or comparable local control, toxicity, QOL, and survival when using PBT. In one study employing the national cancer database, the researchers found "significantly better survival on multivariate and propensity-matched analysis in NSCLC patients who were treated with proton therapy, and this improvement was further amplified in stage II and stage III cases." Although there is a clear dosimetric benefit in several scenarios, early RCT results show that there is no difference comparing proton therapy to IMRT in locally advanced disease. In the most recent phase II RCT showed that "treatment delivery with PBT improved over time" (31% PSPT and 13% IMRT).

Source	Year Published	Title	Author	Type of Cancer	Merits of Alternative Therapies	Type of Source	Conclusion
International Journal of Radiation Oncology	2016	National Cancer Database Analysis of Proton Versus Photon Radiation Therapy in Non-Small Cell Lung Cancer	Higgins et Al	Lung	This analysis demonstrates an improvement in survival with proton therapy in NSCLC compared with photon-based radiation. The present study is the largest study to date evaluating proton versus photon radiation therapy. The analysis found improved survival for patients treated with proton radiation therapy, including the subset of patients with stage II and III NSCLC. Of the photon-based modalities, 5-year survival was highest with IMRT treatment. The clinical experience with proton therapy in lung cancer is still developing, and data such as these support further use of proton therapy as a means to protect normal tissues when delivering thoracic radiation.	Comparative Efficacy	A total of 243,822 patients (photon radiation therapy: 243,474; proton radiation therapy: 348) were included in the analysis. Analysis was conducted using data from the National Cancer Database, which includes data from more than 1,500 facilities and captures 70% of all newly diagnosed cancer cases annually. Of the patients treated with photons, the modalities were: IMRT, 22,346 (9%); Photons, 140,035 (57%); 3D Conformal, 36,406, (15%); and External Beam NOS, 44,687 (18%). Patients treated with proton therapy had significantly better overall survival compared with those treated with non-proton therapy, with a 5-year overall survival rate (23.1% vs 13.5%). Proton therapy was also associated with a better 5-year OS rate for all modalities (except for IMRT) when compared with 3D Conformal (14.7%), External Beam NOS (13.5%), IMRT (17.2%), and Photons (12.6%). There was no significant difference in 5-year OS for stage IV patients between modalities. Proton radiation therapy (nZ309) was associated with better 5-year overall survival compared with non-proton radiation therapy (nZ1549) (22% vs 16%). For stage II and III patients, non-proton radiation therapy was associated with worse survival compared with proton radiation therapy (hazard ratio 1.35). Patients in later stages (except for stage IV) also had lower survival rates using non-proton therapy.
Japanese Journal of Clinical Oncology	2016	Dosimetric comparison between proton beam therapy and photon radiation therapy for locally advanced non-small cell lung cancer	Wu et Al	Lung	Proton beam therapy for patients with stage III non-small cell lung cancer was feasible and was superior to three-dimensional conformal radiotherapy for several dosimetric parameters.	Comparative Efficacy	33 patients with stage III non-small cell lung cancer were treated with proton beam therapy. In comparison to the intensity-modulated radiotherapy plan, proton beam therapy also achieved dose reduction in the normal lung. None of the patients experienced grade 4 or worse non-hematological toxicities. The results of this study indicated that PBT with chemotherapy might be an effective treatment option for patients with locally advanced NSCLC, based on a comparison of the dosages for PBT and 3DCRT. PBT: Regarding the toxicity grades, the grades of radiation pneumonitis were as follows: 28 patients (85%) had grade 0, three patients (9%) had grade 1 and two patients (6%) had grade 2 (0% grade 3). The grades of esophagitis were: five patients (15%) had grade 0, 17 patients (52%) had grade 1, nine patients (27%) had grade 2 and two patients (6%) had grade 3, respectively (0% grade 4). The grades of dermatitis were: one patient (3%) had grade 0, 24 patients (73%) had grade 1 and eight patients (24%) had grade 2 (0% grade 3). None of the patients experienced other severe toxicities (grade 3 or worse). 3DCRT: Dummy plans for 3DCRT at a radical dose could not be generated in 10 patients because of an undesirable spatial relationship between the extent of disease and the spinal cord. All the PBT dosimetric variables regarding lung dose were significantly lower than those of the dummy plan for 3DCRT. In terms of the normal lung V20 Gy, the dosimetric parameters of two patients exceeded the constraints (V20 Gy < 35%) in the dummy plans for 3DCRT. The mean heart dose and the heart V40 GyE of PBT were both significantly lower than those of the dummy plans for 3DCRT. The mean esophageal dose of the PBT was slightly lower than that of the photon dummy plans (21.8GyE vs. 23.4 Gy), with no significant difference observed between them. The maximum spinal cord dose associated with PBT was significantly lower than that of the photon dummy plan. IMRT: Dummy IMRT plans were generated and a dosimetric analysis was performed for the ten patients who were regarded as 'off-cord impossible' with 3DCRT. 6 of the 10 were regarded as suitable to be treated with IMRT in curative intent. A dosimetric comparison between PBT and IMRT were then performed in these six patients (Table 6). All the normal lung doses of PBT were significantly lower than those of IMRT.
International Journal of Radiation Oncology	2018	Cognitive and Adaptive Outcomes After Proton Radiation for Pediatric Patients With Brain Tumors	Pulsifer et Al	Pediatric Brain	Overall, no significant change was found in adaptive functioning after PBT, and adaptive outcome was not significantly related to age or PBT field. The rates of impairment in adaptive functioning were comparable to population-based norms (15%) at baseline and actually improved (to 12%) at follow-up.	Comparative Efficacy	The study included 155 patients that were treated at MGH Francis H. Burr Proton Center for a primary brain tumor. The patients underwent baseline cognitive and adaptive tests. 4 different standardized measures were used to evaluate baseline and follow-up cognitive function. All measures generate age-based standard scores, with a mean of 100 and SD of 15. Lower scores suggest lower functioning or greater problems. The researchers employed a one-way ANOVA to study the cognitive and adaptive functioning among the 4 age-by radiation field groups. Patients under 6 years of age treated with craniospinal irradiation (CSI; 13% □ = 94.6 IQ) exhibited a significantly greater decline in IQ than did patients treated with focal PBT (22% □ = 104.5 IQ) and older patients (CSI: 28.9% □ = 98.8 IQ; PBT 35% □ 107.3). Processing speed and working memory skills were significantly lower at follow-up for patients treated with CSI, regardless of age. In conclusion, the results indicated that cognitive function in young children who received large-volume CSI performed poorly; however, no significant cognitive change was found in younger children who received focal treatment or for older children with either CSI or focal PBT.
Journal of Clinical Oncology	2016	Comparing Intelligence Quotient Change After Treatment With Proton Versus Photon Radiation Therapy for Pediatric Brain Tumors	Kahalley et Al	Pediatric Brain	There was no statistically significant IQ decline for PBRT or XRT for patients who received craniospinal irradiation. IQ slopes did not differ between PBRT and XRT for patients who received craniospinal irradiation or focal RT.	Comparative Efficacy	Study compared change in intelligence quotient (IQ) over time in pediatric patients with brain tumors treated with PBRT versus XRT using scores from 150 patients. XRT treatment plans included three-dimensional conformal (8.3%), IMRT (45.0%), and three-dimensional conformal plus IMRT tumor bed (TB)/margin boost (46.7%). The majority of PBRT-treated patients received passive scatter (90.0%) versus scanning beam proton therapy (10.0%). In the PBRT group, no change in IQ over time was identified, whereas in the XRT group, IQ declined by 1.1 points per year. IQ slopes did not differ between groups. IQ was lower in the XRT group (by 8.7 points) versus the PBRT group. IQ was lower in the XRT group (by 12.5 points) versus the PBRT group. In the focal subgroup, IQ scores remained stable in the PBRT group but declined significantly in the XRT group by 1.57 points per year. PBRT was not associated with IQ decline or impairment, yet IQ slopes did not differ between the PBRT and XRT groups. It remains unclear if PBRT results in clinically meaningful cognitive sparing that significantly exceeds that of modern XRT protocols. Additional long-term data are needed to fully understand the neurocognitive impact of PBRT in survivors of pediatric brain tumors.

Source	Year Published	Title	Author	Type of Cancer	Merits of Alternative Therapies	Type of Source	Conclusion
Clinical and Translation Radiation Oncology	2019	Proton beam therapy delivered using pencil beam scanning vs. passive scattering/uniform scanning for localized prostate cancer: Comparative toxicity analysis of PCG 001-09	Mishra et Al	Prostate	Limitation includes lack of data on dosimetric correlates with toxicity that may have an effect on toxicity profiles. The results of the studies raise concern of clinically significant differences between the two common forms of PBT, which warrant further investigation. The merits of photons to treat prostate cancer were not discussed.	Comparative Efficacy	There is increasing controversy in treating cancer patients; patient benefits from proton therapy versus photon therapy are uncertain. ASTRO actively recommends against use of PBT for prostate cancer outside of clinical trial or prospective registry study. There is a pivotal RCT of protons vs. photons for the treatment of prostate cancer in progress; however, since then two different modes of PBT delivery have emerged: passive scattering/uniform scanning (PS/US) and pencil beam scanning (PBS). This study introduces toxicity evidence comparing these two modes of delivery utilizing chi-squared analysis. There were a total of 1343 patients included in the study. PBS delivered to 238 patients and 1105 received PS/US. A significantly higher proportion of the PBS group (21.9% and 15.1%, respectively; P<0.01) experienced grade ≥ 2 acute genitourinary (GU) toxicity than the PS/US group; however, the incidence of gastrointestinal (GI) toxicity did not differ significantly and was low in both groups. Additionally, there were no significant differences in the cumulative incidence of late GI and GU toxicities.
Prostate Cancer and Prostatic Diseases	2018	Proton versus photon-based radiation therapy for prostate cancer: emerging evidence and considerations in the era of value-based cancer care	Kamran et Al	Prostate	Although there are theoretical advantages to using PBT on prostate cancer, it is not clear if its enhanced precision will create better clinical outcomes for prostate cancer patients. Currently, patients with bilateral hip prostheses are generally not eligible for proton beam treatment. Anterior oriented beams have tried to ameliorate this problem, and a study demonstrated that after median follow-up of 6.4 months, acute grade 2 urinary toxicity was 40%, grade 2 erectile dysfunction occurred in two patients, one patient developed late grade 2 rectal proctitis, and 25% of patients experienced hip pain. Proton beams are sensitive to tissue density and heterogeneity, which can create complications due to the amount of bone, muscle, and fat in the pelvis. Variance of dose can be significant with organ motion, or inadequate immobilization. There is concern about generation of high-energy neutrons from the head of proton machines, which have high radiobiological effects and increased risk of causing secondary cancers compared with standard photon treatment.	Comparative Efficacy	IMRT's usage of multiple beams creates a low-dosage "radiation bath". Reducing exposure is key to preventing secondary malignancies, a potentially deadly long-term side effect of treatment. Computer models have shown that proton therapy reduces this risk by 40% compared with IMRT. Studies have demonstrated mixed results regarding the long-term effects of PBT's higher RBE, where GI toxicity has been lower and higher across 2 different studies. In a study of 693 men who received PBT were matched to 3,645 who received IMRT, it was found that men treated with proton therapy had a lower risk of composite urinary toxicity (33 vs 42%) and erectile dysfunction (21 vs 28%) but a higher risk of bowel toxicity (20 vs 15%). Mean radiation costs were almost twice as high for PBT patients vs IMRT ($115,501 vs $59,012).
Reports of Practical Oncology and Radiotherapy	2017	Morbidity dynamics in proton–photon or photon radiation therapy for locally advanced prostate cancer	Khmelevsky et Al	Prostate	Newer techniques of pencil beam scanning therapy and IMRT have been shown to "work better for further escalation of a fractional dose of an overall local dose due to their precision in irradiation that allows an increase in the dose."	Comparative Efficacy	In this RCT, 289 patients with prostate cancer were included in the study. The two comparator groups were 116 patients who underwent combined proton-photon therapy and the control group that consisted of 173 patients who had undergone standard photon therapy. Treatment efficacy was measured by overall and recurrence-free survival and locoregional progression rate. The actuarial survival and locoregional progression rate were calculated by the Kaplan-Meier method. Lastly, the "identification of independent prognostic factors and post irradiation injuries were performed with the Cox regression model of proportional risks." Acute GI toxicity of maximum grade 2 severity was less prevalent in the main group after combined therapy than in the control group (54.4 ± 5.4% vs. 69.2 ± 5.7%; p<0.01). No difference was found in the frequency and severity of acute GU injuries in the two groups. The main result in this paper is the difference in late toxicity. Late grade 2 GI injuries were seen 3 times less often in the combined therapy group. However, GU injuries were seen with commensurate frequency in the two groups. There were no differences in 5-year survival rates between the two groups (60.0 ± 5.4% and 61.9 ± 4.4%; 10-year survival 45.5 ± 8.5% and 42.8 ± 7.1%).
Scientific Reports	2019	Increased elasticity of melanoma cells after low-LET proton beam due to actin cytoskeleton rearrangements	Jasinska-Konior et Al	Skin	The effect of photon therapy on elasticity and migration of cells was dependent on the cell line. In this paper, PBT was shown to have significantly better long-term inhibitory properties when compared to photon therapy.	Comparative Efficacy	The authors in this paper have shown PBT increased cellular elasticity to a greater extent than photon therapy in melanoma cells, i.e. this is strongly correlated with cancer invasion and migration during metastasis. Additionally, both types of radiation caused changes in actin cytoskeleton organization. It was found that low-LET PBT eliminated more highly-proliferating colonies of cells long-term than photons. 20 and 40 days after treatment both Mel270 and BLM cell lines showed decreased proliferation for low LET proton beam therapy. Photons showed similar results at 20 days but at 40 days a stimulation of Mel270 proliferation was overserved. Higher elasticity of a cell is considered to be connected to increased invasiveness because it is thought that the softer and more malleable a cancer cell is, the more likely it will invade different tissue barriers; however, in the study the researchers showed that along with changes in elasticity of the cells there was disruption of actin cytoskeleton. Actin cytoskeleton is one of the most important components of cell migration. Proton beam therapy proves to indicate long-term inhibitory properties; however, pathways need to be further investigated.

Source	Year Published	Title	Author	Type of Cancer	Merits of Alternative Therapies	Type of Source	Conclusion
International Journal of Radiation Oncology	2017	Comparative Outcomes After Definitive Chemoradiotherapy Using Proton Beam Therapy Versus Intensity Modulated Radiation Therapy for Esophageal Cancer: A Retrospective, Single-Institutional Analysis	Xi et Al	Throat	3-dimensional conformal radiation therapy is the conventional radiation technique employed to treat EC. Newer techniques such as IMRT have demonstrated superiority in improving dose conformity and normal tissue sparing. However, this study shows the clear benefits of PBT when evaluating relative biological effectiveness and toxicity outcomes between the two modalities.	Comparative Efficacy	In this retrospective study, the researchers evaluated 343 patients with esophageal cancer (EC) from 2007 to 2014 who received definitive chemoradiotherapy with either PBT (n=132) or IMRT (n=211). The measures evaluated were overall survival, recurrence, and treatment toxicity and a Cox proportional hazards regression model was completed to test the relationship between patient/treatment variables and survival. The variables were well-balanced, except for age and race. At five years, PBT had significantly better overall survival (OS; 41.6% vs 31.6%, p=0.011), progression-free survival (PFS; 34.9% vs. 20.4%, p=0.011), distant metastasis-free survival (DMFS 64.9 vs. 49.6%, p=0.031), and marginally better locoregional failure-free survival (LRFFS; 41.7% vs. 33.3%). These rates were calculated using the Kaplan-Meier method. However, there were no significant differences in treatment-related toxicities between the two groups. PBT may be correlated with improved OS, PFS, and LRFFS.
Medical Dosimetry	2016	Pencil beam scanning proton therapy vs rotational arc radiation therapy: A treatment planning comparison for postoperative oropharyngeal cancer	Apinorasethkul et Al	Throat	RA plans offered better sparing to the brain stem, spinal cord, esophagus, larynx, ipsilateral middle ear, and ipsilateral parotid gland. Additionally, one could consider a mixed proton-photon plan to compensate for deficiencies in either treatment, especially since protons are advantageous for normal organs but unable to meet constraints for critical ones.	Comparative Efficacy	Seven patients were planned with both proton and photon modalities. The planning goal for both modalities was achieving the prescribed dose to 95% of the planning target volume (PTV). Dose-volume histograms were compared in which all cases met the target coverage goals. Mean doses were significantly lower in the proton plans for the oral cavity (1771 cGy photon vs 293 cGy proton), contralateral parotid (1796 cGy photon vs 1358 proton), and the contralateral submandibular gland (3608 cGy photon vs 3251 cGy proton). Average total integral dose was 9.1% lower in proton plans. In terms of OARs, Proton therapy for oral cavity, contralateral submandibular gland, contralateral parotid glands, contralateral middle ear, visual structures, and temporal lobes resulted in significant sparing. Overall dosages were significantly lower, especially for oral cavity, contralateral submandibular gland, contralateral parotid glands mean doses compared to photon radiotherapy. The average total integral dose for proton plans was 9.1% lower as well. Lower dosages may lead to reduced weight loss, pain, taste changes, and dry mouth. The sparing of these organs will likely result in higher quality of life and nutritional outcomes, producing meaningful clinical benefit. PBS' lower mean dosage is hypothesized to result in less oral mucositis and dysgeusia compared to patients treated with photon RA.

APPENDIX 4: AUTHORS' CURRICULUM VITAES

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2006-2018	Compass Lexecon, Senior Vice President (Compass Lexecon is an FTI Consulting sub-entity)
1993-2006	The CapAnalysis Group, LLC. (formerly Capital Economics)
1992-1993	U.S. International Trade Commission, Office of the Commissioner, Senior Economics Advisor
1988-1992	The CapAnalysis Group, LLC. (formerly Capital Economics)
1980-1988	Dames & Moore, Inc.
1978-1980	Potomac Electric Power Company, Rates and Regulatory Practices

Representative Cases

Case List

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Assessment of market demand and five-year demand forecast for King Edward VII private hospital in London, UK.

Application support for Delivery Service Reform Incentive Payment Project (DSRIP) in New York State, on behalf of Niagara Falls Memorial Medical Center.

Economic analysis of the need for and potential viability of a proposed proton beam therapy center in Western U.S., with focus on estimating patient volumes, potential patient draw area, reimbursements, and competitive alternatives. Prepared for confidential academic medical center client.

WellStar Health System's acquisition of Tenet Health's Atlanta facilities. Assessment of competitive effects, changes in consumer choice decision making, and consumer benefits of integrating healthcare delivery systems in adjoining service areas. Before the U.S. Federal Trade Commission. Regulatory expert.

Highmark's affiliation with West Penn Allegheny Hospital System and establishment of an Integrated Delivery Network, on behalf of the Pennsylvania Insurance Department.

Rochester General Hospital System and Unity Health System merger.

Capella Health System's acquisition of Mercy Health System's St. Joseph's Hospital in Hot Springs, AR. Before the U.S. Federal Trade Commission.

Pennsylvania Department of Insurance regulatory review and approval of Highmark's acquisition of Blue Cross of Northeast Pennsylvania (BCNEPA).

Valitas (PHS) merger with America Service Group, Inc. (CMS), involving healthcare services to Federal and State prisons and local jails.

Joint Venture between two large healthcare systems in the Southeastern United States. Assessment of competitive effects and consumer benefits of integrating healthcare delivery systems in adjoining service areas. Regulatory expert.

Analysis of the population healthcare effects and re-configuration of hospital and outpatient facilities in Brooklyn NY pending failure of two local hospitals.

Assessment of economic and patient welfare benefits to the Charlotte NC metropolitan statistical area of operating Novant hospitals and care facilities in the Charlotte area.

Federal Trade Commission v. OSF Healthcare System and Rockford Health System, United States District Court for the Northern District of Illinois, Western Division, Civ. No: 11-CV-50344. Testifying economics expert on merger efficiencies. Testifying expert.

In the Matter of ProMedica Health System, Inc., Before the U.S. Federal Trade Commission. Docket No. 9346. Non-testifying expert.

In the Matter of Lisa Reed and Cindy Digiannantonio v. Advocate Health Care, et al., in the Northern District of Illinois Eastern Division, Civil Action No. 06 C 3337. Non-testifying expert.

Wendy Fleishman and Cindy Cullen, on Behalf of Themselves and All Others Similarly Situated v. Albany Medical Center, Ellis Hospital, Northeast Health, Seton Health System, and St. Peter's Health Care Service, In the United States District Court for the Northern District of New York, Civil Action No. 06-CV-0765/ TJM/ DRH. Non-testifying expert.

Monopsony claims against health insurers involving purchases of hospital services in Louisiana, *Louisiana Health Services and Indemnity Company d/b/a Blue Cross and Blue Shield of Louisiana v. Rapides Healthcare Systems, et.al.*, Civ. Action 00-694-D-M2, in the United States District Court for the Middle District of Louisiana. Non-testifying expert.

Monopsony claims against health insurers involving purchases of hospital services in Pennsylvania in re *The Chester County Hospital v. Independence Blue Cross, QCC Insurance Company, Keystone Health Plan East, and Keystone Mercy Health Plan*, U.S. District Court, Eastern District Pennsylvania, Case No, 02-CV-02746. Non-testifying expert.

In the Matter of Certain Recombinantly Produced Human Growth Hormones, Investigation No. 337-TA-358, on behalf of Respondent BTG. Testifying expert.

Mergers and Acquisitions/Antitrust Litigation (Selected Matters)

Economic analysis in support of antitrust litigation, including preparation of expert witness and evidentiary testimony in both private and public claims. Selected matters include:

Continental Guest Services Corp. v. IBS, Twin America, et.al., Before the Supreme Court of the State of New York, County of New York, No. 600643/10.

Woolworths Ltd. and The Warehouse Group v. The Commerce Commission, High Court of New Zealand, Wellington Registry, CIV 2007-485-1255 (hearing on the appeal from the determination of the NZ Commerce Commission)

Ryan Rodriguez, et.al. v. West Publishing Corporation, et. al., in the United States District Court for the Central District of California, Case No. CV 05-3222 R(MCx).

Budget Pest Prevention, Inc., et. al. v. Bayer Corporation, Bayer CropScience, L.P., and BASF Corporation, In the United States District Court for the Western District of North Carolina Asheville Division, Case No. 1:05-CV-90

National Recycling, Inc. v. Waste Management of Massachusetts, Inc., Browning-Ferris Industries, Inc., and SEMASS Partnership LP, United States District Court for the District of Massachusetts, Case No. 03-12174-NMG

American Express Travel Related Services Company, Inc. v. Visa U.S.A. Inc., et al, United States District Court Southern District of New York, Civil Action No. 1:04-CV-08967.

Enron Coal Services Limited (In Liquidation) and English Welsh & Scottish Railway Limited, Before the Competition Appeal Tribunal, Case No. 1106/5/7/08.

Examination of loyalty discounting and bundling pricing practices for a client involving on-highway truck transmissions.

Price fixing litigation re baby food on behalf of H.J. Heinz.

FTC v. Arch Coal, Inc., et.al. Clayton Act challenge involving coal for electric utility generation, on behalf of defendant.

DOJ price fixing investigation into white pan bread in Texas.

Louisa Coca-Cola Bottling Company v. PepsiCo, Inc. monopolization and unfair competition case, relating to category management practices, brought by a Coca-Cola bottler in the Eastern District of Kentucky.

Godix Equipment Export Corp. v. Caterpillar, Inc. violation of antitrust laws, fraud, and tortious interference were alleged.

Waste Services Inc. v. Waste Management Inc., et. al., Sherman § 2 antitrust injury and damages.

Northland Cranberries, Inc. *v. Ocean Spray Cranberries*, U.S. District Court, D. Mass., 382 F. Supp. 2d 221 alleging unlawful restraints on competition and anticompetitive conduct.

Economic analysis in support of mergers and acquisitions filed under the Hart-Scott-Rodino Act requiring approval from the U. S. Department of Justice, Antitrust Division, the U.S. Federal Trade Commission, and foreign commissions. Selected matters include:

ISI's acquisition of ADS's septic chamber division, presenting evidence to the FTC on competitive effects and efficiencies.

CitySights and Stagecoach Group PLC and Coach USA formation of joint venture involving double-decker tour buses. Before the Surface Transportation Board, STB Docket No. MC-F-21035.

Various consultations with large pet food manufacturer of product acquisitions.

Coca-Cola acquisition of a foreign beverage producer and distributor.

Monsanto's acquisition of DPL and divestiture of Stoneville involving genetically-modified cotton seed.

Quantum acquisition of ADIC involving backup, recovery and archiving storage media.

Verizon acquisition of MCI involving telephony.

AO Smith's acquisition of American involving water heaters.

National Oilwell acquisition of Varco International involving capital drilling equipment, before the United States Department of Justice and Norway Minister of Modernisation.

Quantum acquisition of Certance involving data storage media

PepsiCo acquisition of Quaker Oats.

Oracle's hostile takeover of PeopleSoft involving enterprise applications software before the Department of Justice.

Heinz acquisition of Lea & Perrins involving steak sauces before the Federal Trade Commission and OFT.

Nestle's acquisition of Ralston Purina.

Seneca Foods Corporation acquisition of Dole canned vegetables.

Analysis of potential acquisitions and joint ventures in tin mill products market.

Divestiture analysis of Nestle's acquisition of Garoto in Brazil involving chocolates.

Nestle acquisition of Dreyer's Ice Cream.

Arch Coal acquisition of Triton involving coal for electric utility generation.

Sub-HSR economics analysis Westway Holdings Corp. acquisition of United Molasses involving industrial molasses

Dana Corporation divestiture of engine parts sold in the aftermarket.

Dana Corporation's defense against hostile takeover by ArvinMeritor involving automotive and truck parts.

H.J. Heinz acquisition of True Soups.

Ames acquisition of True Temper Hardware involving lawn and garden tools.

Anheuser-Busch partial ownership acquisition of Grupo Modello involving Mexican beer.

Anheuser-Busch joint venture distribution with Redhook.

Cargill acquisition of Pillsbury flour mills.

Caterpillar Inc. acquisition of VarityPerkins involving diesel engines.

Cyprus Minerals acquisition of competitor's ball clay operations.

Dana Corporation acquisition of Eaton axle business.

Dana Corporation divestiture of aftermarket engine parts business.

Dana Corporation antitrust defense against hostile bid by Arvin Meritor.

Evenflo acquisition of Huffy's Gerry baby products division.

Earthgrains acquisition of various white pan bread manufacturers.

Federal Signal acquisition of Peabody street cleaning trucks.

General Mills/3M acquisition of household sponges operations.

H.J. Heinz acquisition of Quaker's pet food operations.

Ingersoll Rand acquisition of Newman door hardware.

PepsiCo acquisition of General Cinema Beverages, Grand Metropolitan and other bottling operations (1988 through 2001).

Pre-acquisition antitrust analysis of acquisition of competitor by major OEM automotive parts supplier

Rockwell Corporation acquisition of ICOM involving industrial software.

Rockwell Corporation acquisition of Reliance Electric involving industrial AC and DC drives.

Economic analysis in other non-litigated antitrust and other matters.

DOJ investigation involving on-line music on behalf of third party.

Examination of loyalty discounting and bundling pricing practices for a client involving on-highway truck transmissions.

Analysis of gray market imports of heavy duty construction equipment from the European Union.

Analysis of vertical restraints business justification involving heavy duty construction equipment.

Damages Estimation

Economic analysis and formulation of lost profit and restitution damage for plaintiffs and defendants, including those related to antitrust, intellectual property going-concern value, and breach of contract. Selected matters include:

Price fixing liability and estimation of damages involving white rock on behalf of defendants.

Antitrust, tortious interference, and fraud damages analysis in *Godix Equipment Export Corp. v. Caterpillar Inc.*, 948 F. Supp. 1570, 1996 U.S. Dist. LEXIS 18551 (S.D. Fla. 1996), aff'd mem., 144 F.3d 55, 1998 U.S. App. LEXIS 12264 (11th Cir. 1998), on behalf of defendant.

Estimation of price fixing damages involving white pan bread in Texas on behalf of defendant.

Estimation of Lanham Act damages in *The Joint Stock Society v. UDV North America*, Inc., 53 F. Supp. 2d 692 (D. Del. 1999), aff'd, 266 F.3d 164 (3d Cir. 2001) involving vodka on behalf of defendant.

Intellectual Property Litigation

Economic analysis of liability, economic damages, and remedies in Federal District court actions and USITC Section 337 litigation (non-healthcare related). Selected matters include:

Testifying economic expert *In the Matter of Certain Baseband Processor Chips and Chipsets, Transmitter and Receiver (Radio) Chips, Power Control Chips, and Products Containing Same, Including Cellular Telephone Handsets*, Investigation No. 337-TA-543, on behalf of Respondent Qualcomm Inc. on issues of downstream product remedies and the public interest.

Non-testifying economic expert on Lanham Act liability claims in *The Joint Stock Society v. UDV North America, Inc.*, 53 F. Supp. 2d 692 (D. Del. 1999), aff'd, 266 F.3d 164 (3d Cir. 2001) involving vodka, on behalf of defendant.

Non-testifying economic expert In the Matter of Mechanical and Digital Phonorecord Delivery Rate Adjustment Proceeding, Testimony before the Copyright Royalty Board of the Library of Congress, Washington, DC, Docket No. 2006-3 CRB DPRA.

Non-testifying economic expert In the matter of United States v. ASCAP Application of America Online, Inc.; United States v. ASCAP, Application of RealNetworks, Inc. and United States v. ASCAP, Application of Yahoo! Inc., United States District Court Southern District of New York, Civil Action No. 41-1395 (WCC). May 4, 2007.

International Trade (Selected Matters)

Expert economics testimony in Sunset Review of antidumping orders on purified carboxymethycellulose from Finland, Mexico, Netherlands, and Sweden, on behalf of Akzo Nobel.

Expert economics testimony in Sunset Review of antidumping orders on sugar from Belgium, France, Germany, and Canada and countervailing duty order on sugar from the European Union.

Expert economics testimony in Sunset Review of countervailing duty orders on softwood lumber from Canada, on behalf of the Maritime Provinces.

Economic analysis on the effects of sampling as a means of determining dumping margins in Section 751 Review, in support of respondent before the International Trade Administration

Material injury and causation economic analyses in support of petitioner in nitrile rubber anti-dumping case before the International Trade Commission.

Material injury and causation economic analysis and testimony in support of respondent in ball bearing antidumping petition before the International Trade Commission.

Expert economics testimony on material injury and causation economic analysis and testimony in support of respondent re potassium hydroxide anti-dumping case before the International Trade Commission.

Material injury and causation economic analysis in support of respondent in antifriction bearings antidumping case before the International Trade Commission.

Expert economics testimony on material injury and causation economic analysis in support of respondent in nitrocellulose antidumping petition before the International Trade Commission.

Expert economics testimony on serious injury and causation in Section 201 proceeding re lamb meat.

Expert economics testimony on material injury and causation in support of respondents re liquid sulfur dioxide.

Expert economics testimony on material injury and causation in support of petitioner re PET resin.

Other

Testifying economic expert in temporary restraining order and preliminary injunction in *Center for Food Safety, et al, v. Thomas J. Vilsack*, United States District Court for the Northern District of California, San Francisco Division, Case No. C-08-0484, involving genetically modified sugarbeet seed.

Analysis of demographic "baby boom" issues affecting the demand for automobiles, on behalf of a major foreign automaker

Admissions and Associations

Professional Associations

- American Bar Association, Associate Member, Antitrust Section
- American Economic Association, Member

Publications and Speeches

Articles

- Maki, Jen, Susan H. Manning, John Maruyama, "Issues in Equity, Cost-Effectiveness and Utilisation Relating to Digital Health", International Comparative Legal Guides, Digital Health 2020.
- Manning, Susan Henley, "Measuring the Future of Healthcare," FTI Journal, forthcoming 2016.
- Manning, Susan Henley, Delivery Reform Panel, U.S. Chamber of Commerce 2nd Annual Health Care Summit, "Harnessing Efficiencies to Increase Value and Improve Outcomes," October 30, 2013.
- Manning, Susan H. and Jonathan S. Bowater, "The Effects of Bundled Discounts on Entry in the Market for Pediatric Vaccines," 2011, Working Paper.
- Orszag, Jonathan M. and Susan H. Manning, "An Economic Assessment of Regulating Credit Card Fees and Interest Rates, Commissioned by the American Bankers Association, September 2007.
- Manning, Susan H. and Eileen Reed, "Multijurisdictional Merger Control: Relevant Economic Evidence," *The 2005 Handbook of Competition Economists* (June 2005).
- Manning, Susan H., Gauri Prakash-Canjels, and Eileen Reed, "Economic Issues in Antitrust: 2004-5," *The Antitrust Review of the Americas 2006* (September 2005).
- Manning, Susan H. and Mark Glueck. "Economic Issues in Antitrust: 2003-2004," *The Antitrust Review of the Americas 2005* (September 2004).
- Manning, Susan H. and James F. Rill and Nils von Hinten-Reed. "The Use of Economics in Merger Control Analysis," *Global Counsel Competition Law Handbook*, (2002).
- Manning, Susan H. and C. E. Mann, and D. Olsen. "Coal Slurry Pipeline Costs," *Fieldston Coal Transportation Manual 1984-1985*, (1985). Fieldston Company.
- Manning, Susan H. and et. al.. "Integrated Fuel and Investment Planning: Methods and Process," *Energy Markets in the Longer Term: Planning Under Uncertainty*, (1985). Brookhaven National Laboratory.

Speeches and Presentations

- “Hospital Consolidation,” Federation of American Hospitals Podcast, August 7, 2019.
- “The Economics of Healthcare Consolidation,” SheppardMullin, Nota Bene Podcast Episode 49, September 11, 2019.
- “Import Injuries and Private Trade War Remedies at the U.S. International Trade Commission,” Nota Bene podcast, SheppardMullin, Episode 9, October 31, 2018.
- “Payor/Provider Considerations,” 2016 Health Care Services Private Equity Symposium, Moderator, March 10, 2016.
- “Data Trends in Pain Management”, The Business of Pain Medicine: 21st Century Challenges and Solutions, National Spine and Pain Center Conference, October 8-10, 2015.
- “Weighing the Public Health and Welfare in Downstream Product Exclusions,’ ITC Litigation & Enforcement Conference, American Conference Institute’s Second Expert Forum, February 2010.
- “Refusals to License Intellectual Property,” 15th Annual Conference on Intellectual Property Law and Policy, Fordham University, School of Law, April 2007.
- “IP and Competition Policy on Parallel Trade,” 15th Annual Conference on Intellectual Property Law and Policy, Fordham University, School of Law, April 2007
- “Effective Use of Economic Evidence in Litigation,” Before the Irish Competition Authority, 2005
- “Measuring Trademark and Copyright Value in Licensing and Litigation,” AIPLA Spring Meeting, 2002
- “Using Empirical Evidence to Define Relevant Markets,” Howrey & Simon presentation, May 1995.
- “Economics and Title VII Injury Investigations before the U.S.I.T.C.,” International Trade Committee ABA Workshop, March 16, 1994.
- "Coal Transportation Contracting Analysis," Coal Transportation Costing and Modeling Seminar, Electric Power Research Institute, December 1986.
- "Cogeneration Planning for Utilities and PUCs," Energy Technology Conference, April 1985.
- "Systems Approach to Regional-Perspective Energy Planning," ORSA Conference, June 1983 (with H.S. Gill).
- Susan H. Manning, "Cogeneration and Project Financing Alternatives," Northeast Utilities Cogeneration Seminars, Fall 1982.

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EDUCATION:

Ph.D.: Economics, Texas A&M University, 2013
B.S.: Chemical Engineering, University of Illinois Urbana-Champaign, 2006

DISSERTATION:

Title	"Ownership in the Healthcare Sector: The Impacts of Different Ownership Types"
Committee	Dr. Li Gan (Chair), Dr. Thomas Saving, Dr. Stephanie Houghton, Dr. Tim Gronberg, Dr. Joanna Lahey

PROFESSIONAL EXPERIENCE:

2013- Present	Center for Healthcare Economics and Policy at FTI Consulting
2010-2013	Private Enterprise Research Center
2006-2008	Intel Integration Engineer

REPRESENTATIVE PROJECTS

- Health Care Policy Analysis
  - Reviewing health care policies such as Medicare for All, Public Option
  - Conducting new analysis on effects of these policies on coverage, costs, workforce
  - Producing Issue Briefs to explain and report results
- Large Pharmaceutical Company Class Action Lawsuit
  - Supporting expert witness
  - Reviewing and assessing arguments and analysis from other experts and putting forward affirmative arguments and analysis
- South Africa Healthcare Inquiry
  - Review and assess econometric modeling identifying sources of increased expenditures
  - Review and assess econometric modeling of relationship between supply and demand
  - Design and lead analysis of South African healthcare market to determine and address any areas for improvement
  - Testified on the market and results of analysis
- Ballad Health
  - Providing and directing analysis of hospital market in Eastern Tennessee
- West Essex/Princess Alexandria Hospital
  - Develop a financial model for provision of COPD care and savings from interventions
  - Design application of that model that adjusts to user modifications
- Millennium PPS
  - Analysis supporting Community Needs Assessment for WNY

    - Evaluation of the healthcare of Medicaid beneficiaries in area using more advanced metrics
- King Edward VII Hospital
    - Medium-term forecast of demand
    - Medium-term forecast of revenues
- Academic Medical Center
    - 10-year forecast of cancer prevalence
    - demand for cancer treatment
    - potential revenues based on demand and historical payments
- Damage Analysis
    - Evaluation of discrete choice model used to estimate damages
    - Creation of alternative model
    - Preparation of expert witness
- Anti-Trust Analysis
    - Application of Willingness to Pay model for several cases

SKILLS

- Methodologies
    - Microsimulation Using ModGen
    - Propensity Score Matching
    - Stochastic Frontier Analysis
    - Discrete Event Simulation
    - Consumer Discrete Choice Modeling
    - Demand Forecasting

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EDUCATION

1976	A.B., Economics, Brown University
1979	M.P.A., (Masters in Public Affairs), Woodrow Wilson School of Public and International Affairs, Princeton University

PROFESSIONAL EXPERIENCE

2012-present	President, Center for Healthcare Economics and Policy and Senior Managing Director, FTI Consulting, Inc.
2012-2/2019	Senior Consultant, Compass Lexecon (continue as Senior Consultant on selected matters)
2008-2012	Vice Chairman and Senior Managing Director, Compass Lexecon (formerly Competition Policy Associates)
2003-2008	President, Competition Policy Associates (As of January 2006, also Senior Managing Director, FTI Consulting Inc.)
1994-2003	Principal, Economists Incorporated
1990-1994	Assistant Chief, Economic Regulatory Section, Economic Analysis Group, Antitrust Division, U.S. Department of Justice
1987-1990	Senior Economist, Economists Incorporated
1986-1987	Director of Analytical Resources Unit, Economic Analysis Group, Antitrust Division
1985-1986	Economist, Economic Analysis Group, Antitrust Division, U.S. Department of Justice
1982-1985	Economist, Financial Structure Section, Division of Research and Statistics, Board of Governors of the Federal Reserve System
1979-1982	Economist, Economic Policy Office, Antitrust Division, U.S. Department of Justice

1976-1977	Research Associate, Energy Economics Group, Arthur D. Little, Inc.

TEACHING EXPERIENCE

1984	Adjunct Lecturer, Institute of Policy Sciences, Duke University
1984-1989	Executive Education for Top State Managers, conducted by The Institute of Policy Sciences, Duke University
1983	Lecturer, Board of Governors of the Federal Reserve System and American Institute of Banking
1979	Teaching Assistant, Princeton University

TESTIMONIES

Investigation into the Competitive Marketing of Air Transportation, CAB.

Arbitration Between First Texas Savings Association and Financial Interchange Network.

In Re "Apollo" Air Passenger Computer Reservation System (CRS) MDL DKT. No. 760 M-21-49-MP.

U.S. v. Ivaco, Inc.; Canron, Inc.; and Jackson Jordan, Inc.

Consent Order Proceeding before the Competition Tribunal, Canada Between The Director of Investigation and Research and Air Canada, Air Canada Services, Inc., PWA Corporation, Canadian Airlines International, and the Gemini Group Automated Distribution Systems Inc.

In the Matter of an Application by the Director of Investigation and Research under Section 79 of the Competition Act and in the Matter of certain practices by the D & B Companies of Canada Ltd. (Respondent), before the Competition Tribunal.

Beville v. Curry, et al.; Comanche County District Court, Case No. CJ-95-115.

U.S. v. Northshore Health System, et al.

Testimony before Committee on Banking and Financial Services, U.S. House of Representatives (April 29, 1998)
Easy Gardener, Inc. v. Dalen Products, Inc.

Trigen – Oklahoma City Energy Corporation v. Oklahoma Gas & Electric Company.

State of California v. Sutter Health; Alta Bates; and Summit Medical Center.

Ernest T. Smith, III et al. v. N. H. Department of Revenue Administration, et al.

St. Luke's Hospital v. California Pacific Medical Center; Sutter Health System.

In Re: Cigarette Antitrust Litigation and related cases, *Holiday Wholesale Grocery Co., et al. v. Philip Morris Inc., et al*., MDL Docket No.: 1342 Civil Action No.: 1:00-cv-0447-JOF and *Artemio Del Serrone, Steven Ren, Heather Snay, Jon Ren, Keith Pine, and Bill Reed, on behalf of themselves and all others similarly situated v. Philip Morris Inc., R.J. Reynolds Tobacco Co., Brown & Williamson Tobacco Corp., Lorillard Tobacco Co., Liggett Group, Inc., and Brooke Group, Ltd.,* Case No. 00-004035 CZ, State of Michigan in the Circuit Court for the County of Wayne.

In Re: Vitamin Antitrust Litigation; Misc. No. 99-197 (THF) MDL No. 1285.

Economic Report in Response to European Commission's Statement of Objections Dated 22 May 2003.

European Commission Hearing, Case No Comp/E-2/37.533-Choline Chloride.

Report of Robert D. Willig and Margaret E. Guerin-Calvert to the NZCC *An Economic Analysis of the Consumer Benefits and Competitive Effects of the Proposed Alliance Between Qantas Airways and Air New Zealand* .

Report of Robert D. Willig and Margaret E. Guerin-Calvert to the NZCC *An Economic Assessment of Professor Tim Hazledine's Model of the Proposed Alliance Between Qantas and Air New Zealand.*

Presentations by Robert D. Willig and Margaret E. Guerin-Calvert to the NZCC *An Economic Analysis of the Consumer Benefits and Competitive Effects of the Proposed Alliance Between Qantas Airways and Air New Zealand; Consumer Benefits*.

Erol Riza, M.D. et al., Plaintiffs v. Mercy Health System Physician Hospital Organization, et al, Defendants, Case No. CO199904796/Case NO.CI0200104455.

Federal Trade Commission, et al. v. Arch Coal, Inc., et al. Case No.1:04CV00534 (JDB).

Comments of Margaret E. Guerin-Calvert, Competition Policy Associates, Inc., Washington, DC on Revision of Regulation (EEC) 2299/89 on a code of conduct for computerized reservation systems (CRS), July 8, 2004.
In the Matter of an Appeal from Determinations of the Commerce Commission, Between Air New Zealand Limited and Qantas Airways Limited and Commerce Commission, High Court of New Zealand, CIV 2003 404 6590.

Economic Assessment of Issues in FERC NOPR for the Alaska Natural Gas Pipeline, December 17, 2004.

In Re: DRAM Antitrust Litigation, Master File No. M-02-1486PJH, MDL No. 1486, United States District Court, Northern District of California.

In Re: Carbon Black Antitrust Litigation, MDL Docket No. 1543, No. 03-CV-10191-DPW (D. Mass.)

Ryan Rodriguez, et.al. v. West Publishing Corporation, et. al., Central District of California, Case No. CV 05-3222 R(MCx).

Neotonus, Inc. v. American Medical Association and American Urological Association, In the United States District Court for the Northern District of Georgia Atlanta Division Civil Case No. 1: 04-CV-2050.

Budget Pest Prevention, Inc., et. al. v. Bayer Corporation, Bayer CropScience, L.P., and BASF Corporation, In the United States District Court for the Western District of North Carolina Asheville Division, Case No. 1:05-CV-90.

National Recycling, Inc. v. Waste Management of Massachusetts, Inc., Browning-Ferris Industries, Inc., and SEMASS Partnership LP, United States District Court for the District of Massachusetts, Case No. 03-12174-NMG.

In the Matter of Mechanical and Digital Phonorecord Delivery Rate Adjustment Proceeding, Testimony before the Copyright Royalty Board of the Library of Congress, Washington, DC, Docket No. 2006-3 CRB DPRA.

In the matter of *United States v. ASCAP Application of America Online, Inc.; United States v. ASCAP, Application of RealNetworks, Inc.* and *United States v. ASCAP, Application of Yahoo! Inc.,* United States District Court Southern District of New York, Civil Action No. 41-1395 (WCC). May 4, 2007.

Lockheed Martin Corporation, Plaintiff, v. *L-3 Communications Corporation*, *Mediatech, Inc*., Kevin Speed, Steve Flemming, and Patrick St. Romain, Defendants. *L-3 Communications Corporation*, Counterclaim and Third-Party Plaintiff, v. *Lockheed Martin Corporation,* Counterclaim Defendant, and Jack Kelly, Thomas Dorsey, Michael Homan, and Thomas Hull, Third-Party Defendants. US District Court for the Middle District of Florida, Orlando Division, Case Nc. 6:05-cv- 1580-Orl-31KRS, Expert Report August 15, 2007.

Abbott Laboratories, an Illinois corporation, *Fournier Industrie et Sante*, a French corporation, and *Laboratoires Fournier, S.A.*, a French corporation, Plaintiffs, v. *Teva Pharmaceuticals USA, Inc.*, a Delaware corporation, Defendant; Civil Action No. 02-1512 (KAJ); *Teva Pharmaceuticals USA, Inc.*, a Delaware corporation, *Teva Pharmaceutical Industries, Ltd.*, an Israeli corporation, and *Novopharm, Ltd.*, a Canadian Corporation, Counterclaim Plaintiffs, v. *Abbott Laboratories*, an Illinois corporation, *Fournier Industrie et Sante*, a French corporation, and *Laboratoires Fournier, S.A.*, a French corporation, Counterclaim Defendants; *Abbott Laboratories*, an Illinois corporation, *Fournier Industrie et Sante*, a French corporation, and *Laboratoires Fournier, S.A.*, a French corporation, Plaintiffs, v. *Impax Laboratories, Inc.*, a Delaware corporation, Defendant; Civil Action No. 03-120-KAJ; *Impax Laboratories, Inc*., a Delaware corporation, Counterclaim Plaintiff, v. *Abbott Laboratories*, an Illinois corporation, *Fournier Industrie et Sante*, a French corporation, and *Laboratoires Fournier, S.A.*, a French corporation, Counterclaim Defendants.; *in re TriCor direct purchaser antitrust litigation*; Civil Action No. 05-340 (KAJ); *in re TriCor indirect purchaser antitrust litigation*; Civil Action No. 05-360 (KAJ).

State of California ex rel. Lockyer et al., Plaintiffs *v. Infineon Technologies AG et al.*, Defendants. Case No. C-06-04333 PJH US District Court for the Northern District of California, San Francisco Division.

Natchitoches Parish Hospital Service District, on behalf of itself and all others similarly situated, Plaintiff, v. Tyco International, Ltd., Tyco International, (U.S.), Inc., Tyco Healthcare Group, L.P., The Kendall Healthcare Products Company, Civil Action No. 05-12024 PBS.

Daniels Sharpsmart, Inc. v. Tyco International, (US) Inc., Tyco Healthcare Group, L.P., Becton Dickinson and Company, Novation, LLC, VHA, Inc., Premier Inc., Premier Purchasing Partners, and Consorta, Inc., United States District Court for the Eastern District of Texas, Texarkana Division, Civil Action No. 5:05-cv-169.

In re Wellbutrin SR antitrust litigation (direct purchaser actions), Civil Case no. 2:04-cv-5525 (E.D. Pa.); *Sheet Metal Workers Local 441 Health and Welfare Plan, et al. v. GlaxoSmithKline, plc, et al. (indirect purchaser actions),* Civil Case no. 2:04-cv-5898 (E.D. Pa.); *Medical Mutual of Ohio, Inc. v. GlaxoSmithKline, plc, et al.,* Civil Case no. 2:05-cv-396 (E.D. Pa.)

In the Matter of the Form A Application by The Doctors Company, An Interinsurance Exchange, with Respect to the Acquisition of American Healthcare Indemnity Company, Hearing before the Insurance Commissioner of the State of Delaware, Docket No. 678.

L-3 Communications Integrated Systems, LP, Plaintiff v. Lockheed Martin Corporation, Defendant, United States District Court for the Northern District of Texas, Dallas Division, Civil Action No. 3-07CV0341.

DataTreasury Corporation v. Wells Fargo & Company, et al., Defendants, United States District Court for the Eastern District of Texas, Marshall Division, Civil Action No. 2:06CV-72(DF).

Federal Trade Commission and The State of Ohio v. ProMedica Health System, Inc., United States District Court for the Northern District of Ohio, Western Division, Case No. 3:11-cv-00047-DAK.
Testimony before Pennsylvania Insurance Department regarding proposed affiliation between Highmark, Inc. and the West Penn Allegheny Health System (April 17, 2012) and Report (Economic Analysis Of Highmark's Affiliation with WPAHS and Implementation of an Integrated Healthcare Delivery System), April 2013.

Highmark Inc.'s Acquisition of Control of Blue Cross of Northeastern Pennsylvania and Subsidiaries, Pennsylvania Insurance Department.

In re: Cathode Ray Tube (CRT) Antitrust Litigation (United States District Court Northern District of California San Francisco Division).

Commonwealth of Massachusetts, Plaintiff, v. Partners Healthcare System, Inc., South Shore Health and Educational Corp., and Hallmark Health Corp., Defendants, Civil Action No. 14-2033-BLS, Expert Declaration of Robert D. Willig and Margaret E. Guerin-Calvert.

Methodist Health Services Corporation v. OSF Healthcare System, United States District Court for the Central District of Illinois, Peoria Division, Case No: 13-cv-1054.

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"ATM and Bank Electronic Networks: Competitive Issues and Technological Change," for presentation at the 71st Annual WEA International Conference, June 29, 1996.

"Assessing the Implications of Kodak for Franchise Market Power Issues," before the American Bar Association, Antitrust Law Section, Spring Meeting, Washington, DC, March 27, 1996.

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OTHER PROFESSIONAL ACTIVITIES

Co-Chair, NASEM's Action Collaborative on Business Engagement in Building Healthy Communities

Co-Chair, Special Operations Team, Section of Antitrust Law, American Bar Association

Associate Member, Section of Antitrust Law, American Bar Association and its Committees, including Healthcare and Pharmaceuticals

Member, American Economics Association

Member, AcademyHealth

Member, American Health Lawyers Association

Member, Brown University – The Warren Alpert Medical School's Advisory Council on Biology and Medicine

Member, NASEM Roundtable on Population Health Improvement

Member, NASEM Action Collaborative on Obesity Solutions

PAST PROFESSIONAL ACTIVITIES

Chair, Interagency Task Force on Bank Competition (at the U.S. Department of Justice, Antitrust Division)

Co-Chair, Economics Task Force, Member, Technology and Financial Resources Task Force, Chair of the Membership Committee, Transition Task Force Member, Chair of the Exemptions and Immunities Task Force, Council Member, Chair, Financial Markets and Institutions Committee, Member Advisory Board on Section Reserves, International Task Force, Member Long Range Planning Committee, Section of Antitrust Law, American Bar Association

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