

To: Member Appeals
Independence Blue Cross
Box 41820
Philadelphia, PA 19101-1820

From: Paul A. Morgan, Member
PO Box 244
Chester Springs, PA
Tel:
DOB:
Member ID No:
Health Plan: Keystone Health Plan East

Date: March 17, 2009

Subject: Pre-Service, Second-Level Grievance/Medical Necessity Appeal (File Ref: XXXX)

Review Committee:

This is my second appeal to coverage denials dated February 2, 2009 and February 17, 2009 for:

1. Services from the University of Florida Proton Therapy Institute for evaluation for proton beam therapy for prostate cancer, and
2. Proton beam therapy treatment at the University of Florida Proton Therapy Institute

In the letter dated February 17, 2009, the initial denial was upheld for the following reasons:

“The committee’s findings: The requested proton beam therapy is considered experimental or investigative. Review of the available published material concerning proton beam radiation therapy shows there is no convincing evidence that treatment results are superior to photon beam therapy (conformal radiation). There is limited clinical data comparing proton therapy to photon beam therapy in treatment of prostate cancer.”

“The committee’s conclusion: After reviewing all of the above information, the committee determined that the requested treatment of proton beam therapy is experimental and investigational based on the available scientific literature. Therefore, denial remains upheld as contract benefit exclusion. In addition, the request to go out of network for evaluation for this therapy is not medically necessary because this therapy is considered experimental/investigational.”

My Clinical Information

- 46-years-old: diagnosed with prostate cancer in December 2008
- Underwent a biopsy of the prostate secondary to elevated PSA levels (2.9)
- Biopsy was positive for Gleason 6 adenocarcinoma in 2 of 12 samples

Appeal Outline & Summary

I am appealing Keystone's coverage denial for proton beam therapy for the following reasons:

1) Proton beam therapy for prostate cancer is neither experimental nor investigational

- a) Proton beam therapy (PBT) is generally recognized by the medical community, as clearly demonstrated by Reliable Evidence, as effective and appropriate for the treatment of prostate cancer. Proton beam therapy is of proven benefit for the treatment of prostate cancer. Reliable Evidence exists that proton beam therapy for prostate cancer has a definite positive effect on health outcomes. Reliable Evidence exists that *over time*, proton beam therapy leads to improvement in health outcomes (i.e. the beneficial effects outweigh any harmful effects)
 - i) FDA approved; Medicare Policy (1997): PBT non-experimental, non-investigational
 - (1) **Medicare Bulletin 406** (April 13, 1997), "Proton Beam Radiation Therapy"
 - ii) The Loma Linda Experience: PBT effective and appropriate for prostate cancer
 - (1) **Slater, Jerry D., et al.** 2004. Proton Therapy for Prostate Cancer: The Initial Loma Linda University Experience. *International Journal for Radiation Oncology*, pp. Vol. 59 No. 2 pp. 348-352.
 - (2) **Slater, Jerry D.** 2006. Clinical Applications of Proton Radiation Treatment at Loma Linda University: Review of a Fifteen-year Experience. *Technology in Cancer Research and Treatment*. April 2006, Vol. 5, Number 2.
 - (3) **Rossi Jr., Carl J.** 2007. Conformal Proton Beam Radiation Therapy of Prostate Cancer. *Prostate Cancer Communication*. March 2007, Vol. 23, Number 1.
 - iii) Insurers have determined PBT to be non-experimental and non-investigational, including Independence Blue Cross

2) Reliable Evidence clearly demonstrates that proton beam therapy for prostate cancer is at least as effective in improving health outcomes as established technology. Moreover, there is convincing evidence that treatment results from PBT are superior to photon beam therapy (conformal radiation)

- a) **Metz, James.** 2006. Reduced Normal Tissue Toxicity with Proton Therapy. *OncoLink*. Abramson Cancer Center of the University of Pennsylvania (June 29, 2006).
- b) **Vargas, Carlos, et al.** 2008. Dose-Volume Comparison of Proton Therapy and Intensity-Modulated Radiotherapy for Prostate Cancer. March 1, 2008, *International Journal of Radiation Oncology*, pp. Vol. 70 Issue 3 pp. 744-751.
- c) **Chung CS, et al** "Comparative analysis of second malignancy risk in patients treated with proton therapy versus conventional photon therapy" *Int J Radiat Oncol Biol Phys* 2008; 72(1 Suppl):S8. Abstract 17.
- d) **Cella, L., et al.** 2001. Potential role of intensity modulated proton beams in prostate cancer radiotherapy. *International Journal of Radiation Oncology, Biology, Physics*. (January 1, 2001); 49(1): 217-23.
- e) Levin WP, et al. Proton Beam Therapy. *British Journal of Cancer* Vol. 93: 849-54, 2005.

- f) **Zietman, Anthony L, et al.** Comparison of Conventional-Dose vs High-Dose Conformal Radiation Therapy in Clinically Localized Adenocarcinoma of the Prostate, *The Journal of the American Medical Association*, September 15, 2005, Volume 294, Number 10.

3) There is sufficient clinical data comparing proton therapy to photon beam therapy in treatment of prostate cancer. It is *not generally* recognized by Reliable Evidence or the medical community that additional study on proton beam therapy's safety and efficacy for the treatment of prostate cancer is recommended. Reliable Evidence shows that the prevailing opinion among experts regarding proton beam therapy is that *studies or clinical trials* have determined its maximum tolerated dose, its toxicity, its safety, its efficacy or its efficacy as compared with a standard means of treatment for prostate cancer

i) RCTs comparing proton therapy to photon beam therapy in treatment of prostate cancer are unnecessary and may be unethical

(1) **Buckner, C.D.** 2002. Intensity Modulated Radiation Therapy (IMRT). *Current Topics in Oncology* 2002.

(2) **Suit, Herman, et al.,** 2008. Should positive phase III clinical trial data be required before proton beam therapy is more widely adopted? No. *Radiotherapy and Oncology : journal of the European Society for Therapeutic Radiology and Oncology* 2008;86(2):148-53.

(3) **Goitein, Michael & Cox, James D.** 2008. Should Randomized Clinical Trials Be Required for Proton Radiotherapy? *Journal of Clinical Oncology*, Vol. 26: No. 2 (2008) p. 175.

ii) Many more proton therapy centers are now available and under construction, at premier medical institutions, *because it is generally recognized by the medical community that proton beam therapy's safety and efficacy have been established.*

Proton Beam Therapy (PBT) for Prostate Cancer is Neither Experimental nor Investigational

Proton beam therapy (PBT) is generally recognized by the medical community, as clearly demonstrated by Reliable Evidence, as effective and appropriate for the treatment of prostate cancer. Proton beam therapy is of proven benefit for the treatment of prostate cancer. Reliable Evidence exists that proton beam therapy for prostate cancer has a definite positive effect on health outcomes.

Proton beam therapy has been in use for over 40 years, since treatments began at Harvard University in 1961. The therapy is well-established as efficacious, efficient, and preferred in light of the side effects of standard treatments. In the last 50 years, more than 60,000 patients have been treated world-wide using proton beam therapy. More than 300 peer-reviewed articles have documented the clinical efficacy of proton therapy in a wide variety of cancers including eye, lung, pediatric, gastrointestinal, head and neck, sarcoma, and brain tumors as well as prostate cancer.

There is virtually no debate in the scientific literature regarding the effectiveness of PBT to treat prostate cancer. Proton beam therapy is considered a reasonable and necessary form of treatment:

- Scientific data show that PBT is well recognized as an effective way to treat many cancers, including prostate cancer.
- PBT's inherent characteristics allow the physician to maximize the dose to the target while minimizing the dose to normal tissues outside the target. This is important because normal-tissue irradiation is the major limitation in tumor control.
- The ability to minimize dose to normal tissues allows for higher doses to be given to target volumes, thus promoting increasing rates of tumor control even as no increase occurs in rates of treatment-related toxicity. (Ruthita Fike, CEO, Loma Linda University Medical Center)

FDA approved; Medicare Policy 1997: PBT is non-experimental, non-investigational

Proton beam therapy is FDA approved. In 1997, more than ten years ago, Medicare concluded that proton beam therapy for prostate cancer was neither experimental nor investigational:

“Policy: Proton Beam Radiation Therapy for treatment of Prostate Cancer will no longer be considered investigational. Proton-beam radiation therapy is non-investigational in the treatment of malignancies. Proton-beam therapy may be medically necessary for the treatment of:

- Intraocular melanomas.
- Pituitary neoplasms.
- Small arteriovenous malformations.
- CNS lesions.
- Head and neck malignancies.
- Prostate malignancies.

Benefits will be provided when services are considered medically reasonable and necessary to treat the Prostate Cancer. Treatment with proton-beam radiation therapy should consider the characteristic absorption in a specified target volume and location that would likely result in superior clinical outcomes as compared to conventional (photons) or electron-beam radiotherapy.” **Medicare Bulletin 406** (April 13, 1997) – See attached document

The Loma Linda Experience: PBT is effective and appropriate for prostate cancer. Reliable Evidence exists that *over time*, proton beam therapy leads to improvement in health outcomes (i.e. the beneficial effects outweigh any harmful effects)

Slater, Jerry D., et al. 2004. Proton Therapy for Prostate Cancer: The Initial Loma Linda University Experience. *International Journal for Radiation Oncology*, pp. Vol. 59 No. 2 pp. 348-352.

Conclusion: “Conformal proton beam radiation therapy for prostate cancer can achieve excellent biochemical freedom-from-relapse rates with minimal treatment-related morbidity at the doses reported” (352).

Slater, Jerry D. 2006. Clinical Applications of Proton Radiation Treatment at Loma Linda University: Review of a Fifteen-year Experience. *Technology in Cancer Research and Treatment*. April 2006, Vol. 5, Number 2.

“Proton radiation therapy has been used at Loma Linda University Medical Center for 15 years Our cumulative experience has confirmed that protons are a superb tool for delivering conformal radiation treatments, enabling delivery of effective doses of radiation and sparing normal tissues from radiation exposure” (81).

Rossi Jr., Carl J. 2007. Conformal Proton Beam Radiation Therapy of Prostate Cancer. *Prostate Cancer Communication*. March 2007, Vol. 23, Number 1.

Conclusion: “Conformal proton beam therapy has clearly been shown to be a safe and effective treatment for prostate cancer. The unique physical properties of the proton beam allow for marked reductions in normal tissue radiation dose as compared with x-ray-based therapy and make further dose escalation feasible. The development and construction of dedicated medical treatment facilities have enabled this modality to progress from a laboratory curiosity to a mainstream therapy” (239-240).

Insurers have determined PBT to be non-experimental and non-investigational, including Independence Blue Cross

In addition to the FDA and Medicare, healthcare insurers throughout the United States have embraced proton beam therapy as non-experimental and non-investigational in the treatment of prostate cancer. “Proton therapy has an established history of reimbursement by Medicare and private healthcare payers. More than 150 insurance carriers, including Medicare, cover proton therapy” (MD Anderson Proton Cancer Center). Below is a *partial list* of the more than 150 insurers (including Independence Blue Cross) that do not consider PBT experimental or investigational. Following the list are the names of two men who were approved by Independence Blue Cross for proton beam therapy for prostate cancer, without appeal.

Anthem Blue Cross

http://www.anthem.com/ca/medicalpolicies/policies/mp_pw_a053258.htm

Blue Cross Blue Shield of Florida

<http://mcgs.bcbsfl.com/>

Empire Blue Cross Policy

http://www.empireblue.com/provider/noapplication/f2/s5/t9/pw_ad084931.pdf

Mountain State Blue Cross Blue Shield

<http://www.msbcbs.com/medpolicy/R-18-003.html>

Regence

<http://blue.regence.com/trgmedpol/medicine/med49.html>

Cigna

http://www.cigna.com/customer_care/healthcare_professional/coverage_positions/medical/mm_0252_coveragepositioncriteria_proton_beam_therapy_for_prostate_cancer.pdf

Blue Cross Blue Shield of North Carolina

http://www.bcbsnc.com/assets/services/public/pdfs/medicalpolicy/charged_particle_radio_therapy.pdf

Highmark Blue Shield

https://www.highmarkblueshield.com/pdf_file/prn/hbs-prn-8-05.pdf

Independence Blue Cross's PPO plan does not cover experimental or investigational procedures. Yet at least two men were approved for Proton Beam Therapy, without appeals. The first has been approved for treatment at the University of Florida Proton Institute beginning mid-March 2009, and has already completed pre-treatment consultations/preparations at the site:

XXXXXXXXXX
XXXXXXXXXX
Villanova, PA
Home: XXXXXXXX
Cell: XXXXXXXX
XXXXX

The second was treated at Loma Linda University Medical Center in 2005 and was also approved by Independence Blue Cross, without appeal, and with a PPO plan that excludes experimental/investigational treatments from coverage:

XXXXXXXXXX
XXXXXXX
XXXXXXX
XXXXXXXXX

Conclusion: Independence Blue Cross has already determined that there is sufficient Reliable Evidence in the scientific literature to approve proton beam therapy for prostate cancer as neither experimental nor investigational. Since this is fundamentally a question of evidence in the "available scientific literature", there is no scientific basis for proton therapy policy differences between the Personal Choice PPO plan and the Keystone HMO.

Based on the Reliable Evidence presented above, the first-level appeal committee incorrectly concluded that "the requested treatment of proton beam therapy is experimental and investigational based on the available scientific literature."

Reliable Evidence clearly demonstrates that proton beam therapy for prostate cancer is at least as effective in improving health outcomes as established technology. Moreover, there is *convincing* evidence that treatment results from PBT are *superior* to photon beam therapy (conformal radiation)

Proton beam therapy (PBT) has clear advantages over photon therapy when treating prostate cancer. PBT reduces the exposure and damage caused by radiation therapy to surrounding healthy tissue. Unlike photons, which scatter when entering the body and thus deliver the majority of their radiation in normal tissues upstream from the target volume, protons deliver their maximum radiation to the prostate. The physical properties of protons (i.e. mass, positive charge) allow them to scatter much less when entering tissue. Protons thus have a low entrance dose relative to the target, with the maximum dose occurring at a predetermined point, the Bragg Peak. This peak can be adjusted to conform precisely to the target volume and can be stopped within 2-3 mm of that volume. Hence there is no exit dose of radiation into normal tissues (see Levin, WP et. al., Proton Beam Therapy.) This phenomenon is not possible with photons; all individual photon beams deliver not only the greater part of their dose to normal tissues as they enter the body, but also irradiate normal tissues “downstream” from the target volume. (Ruthita Fike, CEO, Loma Linda University Medical Center)

PBT, as compared to IMRT, reduces the amount of harmful radiation to normal tissue

Radiation harms human cells. Data suggest that higher radiation doses to cells result in higher risks of cell death. No dose is considered “safe”. Therefore, the radiation oncologist seeks to irradiate normal cells as little as possible, and to avoid such radiation whenever possible. A major advantage of PBT over other forms of radiation therapy is its ability to minimize radiation exposure to normal cells, not only because of reduced scatter and the Bragg peak phenomenon, but also because PBT can deliver a highly conformal dose to the target volume with relatively few radiation portals. The result is a greater volume of normal tissues not exposed to any dose of radiation, and a minimal dose delivered to normal tissues that are exposed.

Advancements in conventional radiation therapy such as intensity-modulated radiation therapy (IMRT) use computerized x-ray accelerators to deliver radiation to the target volume with greater precision than traditional photon radiation allows. Some have claimed that IMRT is as effective as PBT. IMRT delivers radiation to the target via several portals—often many more than are used in standard x-ray therapy. IMRT uses computer assistance to vary the position of the portals and intensity of the beam, thus enabling it to reduce the dose to selected normal tissues near the target while still delivering a high dose to the target cells. The price paid for this target-volume conformality, however, is a larger volume of normal tissues exposed to radiation. In fact, the cumulative dose throughout this volume (the volume integral dose) is higher with IMRT than with standard photon radiation. The dose to most of the tissues in this larger volume is relatively low (albeit IMRT can have significantly more hot spots than are seen with protons or other forms of x-ray delivery), but it remains to be seen whether the greater volume exposed to radiation eventuates in long-term sequelae.

Thus, while both PBT and IMRT are effective in treating prostate cancer, PBT can be distinguished from IMRT based on both the volume of normal tissue treated by the radiation and the amount of radiation exposure to normal tissue. With the IMRT approach, instead of a single

volume of normal tissue receiving a high dose of radiation, multiple areas of normal tissue are exposed to lower doses of radiation. This exposure still can lead to a second malignancy or other unwanted side effects to the normal tissue, which may take years, perhaps decades, to develop. The end result is that patients receiving IMRT are exposed to two to three times more radiation to normal tissue than with PBT. (Ruthita Fike, CEO, Loma Linda University Medical Center)

PBT allows increased total doses of radiation per course of treatment

Because PBT minimizes both the dose delivered to normal tissues and the volume of normal tissues receiving radiation, PBT can provide dose escalation, while not harming normal tissues, in ways that photon radiation—whether delivered by IMRT or otherwise—does not permit. It is *generally agreed* among radiation oncologists that higher total doses increase the likelihood of disease control for most solid cancers, and in the case of localized prostate cancer, it has been demonstrated that an increased radiation dose delivered to the prostate decreases the chances of a recurrence (DeWeese, Theodore & Song, Danny Y. Radiation Dose Escalation as Treatment for Clinically Localized Prostate Cancer: Is More Really Better? *JAMA*, Vol. 294: No. 10 (2005) p. 1275). A study performed by researchers at Massachusetts General Hospital and Loma Linda University found that treating men with clinically localized prostate cancer with a high-dose combination therapy of conventional radiation along with PBT instead of just a conventional dose of external radiation therapy led to the patients being more likely to be free from increased prostate-specific-antigen (PSA) levels 5 years later, and less likely to have locally persistent disease (see **Zietman, Anthony L, et al.** Comparison of Conventional-Dose vs High-Dose Conformal Radiation Therapy in Clinically Localized Adenocarcinoma of the Prostate, *The Journal of the American Medical Association*, September 15, 2005, Volume 294, Number 10.)

Dose escalation with photon radiation, even with modern methods such as IMRT, is difficult to achieve because increasing the dose to the target volume also will increase the scattered and “downstream” dose to normal tissues. In contrast, because PBT can localize the dose to the target volume and minimize exposure to normal tissue, higher doses can be delivered without significantly increasing the toxicity and harmful side effects of the radiation (see **Slater, Jerry D. et. al.** 2004). Therefore, a major benefit of PBT over photon radiation is the ability to increase the total dose administered per course of treatment. (Ruthita Fike, CEO, Loma Linda University Medical Center)

Conclusion: PBT is effective in treating prostate cancer and protects normal tissues to a greater extent than is possible with photon irradiation.

Documentation

Metz, James. 2006. Reduced Normal Tissue Toxicity with Proton Therapy. *OncoLink*. Abramson Cancer Center of the University of Pennsylvania (June 29, 2006).

“Proton beams offer highly significant advantages over x-rays in the sparing of normal tissues. This is due to the physical characteristics of the proton beam compared to X-rays.”

“A significant proportion of patients treated in radiation oncology centers have prostate cancer. Side effects of treatment generally include gastrointestinal (GI) and genitourinary (GU) damage. Large numbers of patients experience urinary frequency and diarrhea during treatment, and long-term, may suffer impotence, incontinence, rectal fibrosis and bleeding, and extensive bowel fibrosis. These side effects may cause a reduction in the quality of life and result in delays of a typical radiation therapy treatment course. Tables 3 and 4 compare the acute and long-term complications of localized prostate cancer treated with protons, conventional X-rays, and radical prostatectomy, respectively.”

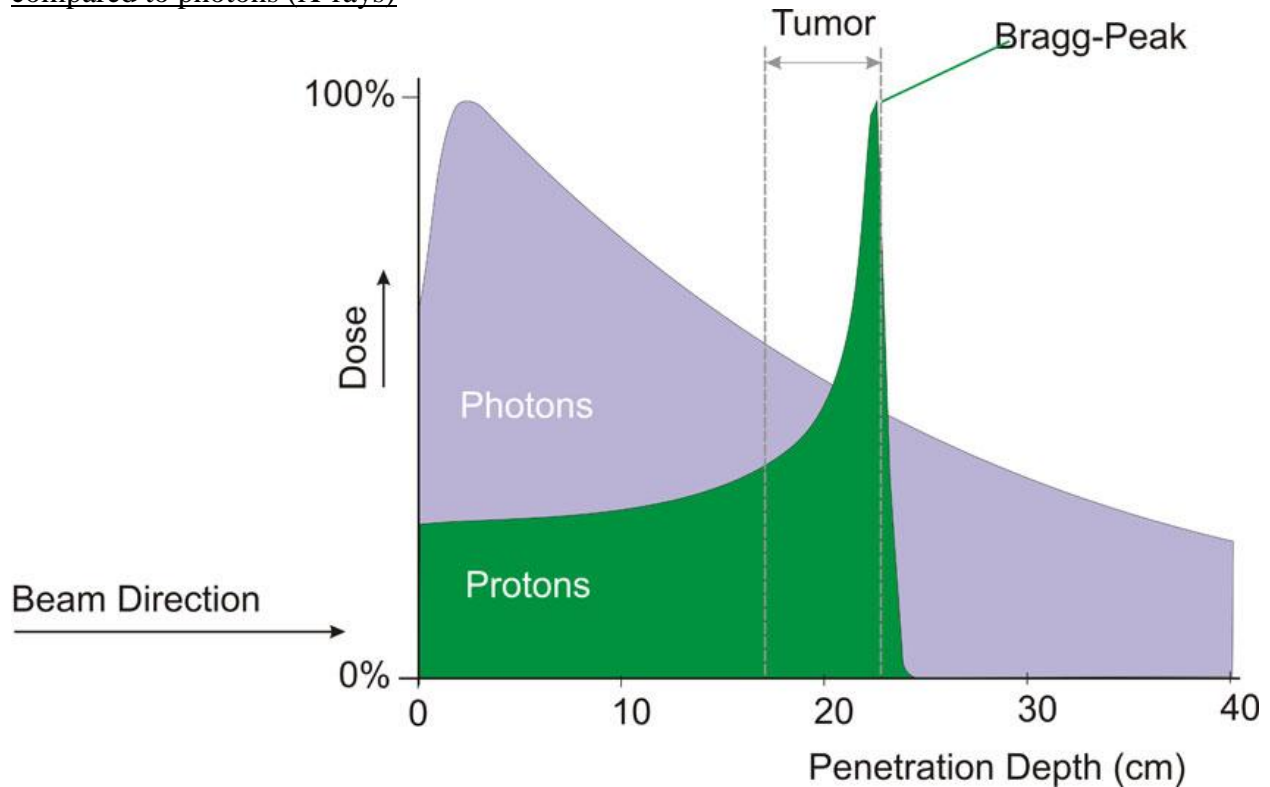
Table 3: Acute complications associated with the treatment of prostate cancer Acute Toxicity	Protons	Conventional Radiotherapy (Photons)	Prostatectomy
> Grade 2 GU toxicity (frequency, nocturia, dysuria)	0%	28%	N/A
> Grade 2 GI toxicity (diarrhea, rectal/abd pain)	0%	35%	N/A
Either GU or GI morbidity	0%	53%	N/A
Hospitalization	None	None	5-7 days
Absence from work	None	None	4-6 weeks
Death	0%	0%	0.3%
Pulmonary embolism / DVT	0%	0%	2.6%
Myocardial infarction or arrhythmias	0%	0%	1.4%
Wound Complications	None	None	1.3%
Lymphocele	None	None	0.6%
Surgical Rectal Injury	N/A	N/A	1.5%

Source: Reduced Normal tissue Toxicity With Proton Therapy; June 29, 2006; James Metz, MD – Assistant Professor of Radiation Oncology, The Abramson Cancer Center of the University of Pennsylvania

Table 4: Long-term complications associated with the treatment of prostate cancer Chronic Toxicity	Protons	Conventional Radiotherapy (Photons)	Prostatectomy
Impotence	30%	60%	60%
Incontinence requiring a pad	< 1%	1.5%	32%
Bladder Neck contracture	0%	3%	8%
Chronic Cystitis	0.4%	5%	N/A
Grade 3 GU toxicity Severe frequency q 1 hr dysuria	0.3%	2%	36%
Grade 3 GI toxicity rectal bleeding requiring transfusion severe pain (>70 Gy)	0%	7%	N/A
Rectal stricture	0%	0.5%	N/A

Source: Reduced Normal tissue Toxicity With Proton Therapy; June 29, 2006; James Metz, MD – Assistant Professor of Radiation Oncology, The Abramson Cancer Center of the University of Pennsylvania

The Figure below shows the reduction of normal tissue exposed to radiation with protons compared to photons (X-rays)



A study from the University of Florida Proton Therapy Institute (UFPTI) (**Vargas, Carlos, et al**, March 2008, *IJROBP*) compared proton therapy and IMRT plans for prostate cancer. This study demonstrated significant reductions in the volume of rectal tissue receiving doses from 10 Gy to 80 Gy.

Vargas, Carlos, et al. 2008. Dose-Volume Comparison of Proton Therapy and Intensity-Modulated Radiotherapy for Prostate Cancer. March 1, 2008, *International Journal of Radiation Oncology*, pp. Vol. 70 Issue 3 pp. 744-751.

“Conclusion: The results of our study have shown that proton radiotherapy dose delivery characteristics can be optimized to improve results seen with IMRT. The dose-sparing advantage was larger for the rectum, although the mean bladder doses were also decreased significantly. The PTV coverage was excellent with better homogeneity than with IMRT.”

Chung CS, et al "Comparative analysis of second malignancy risk in patients treated with proton therapy versus conventional photon therapy" *Int J Radiat Oncol Biol Phys* 2008; 72(1 Suppl):S8. Abstract 17.

“Conclusion: The results of our preliminary analysis indicate that the use of proton radiation therapy is associated with a significantly lower risk of a second malignancy compared to photon radiation therapy.”

Cella, L., et al. 2001. Potential role of intensity modulated proton beams in prostate cancer radiotherapy. *International Journal of Radiation Oncology, Biology, Physics*. (January 1, 2001); 49(1): 217-23.

“Conclusion: Both IM X-ray and proton beams were able to optimize the dose distribution and comply with the goal of delivering the highest dose to the target while reducing the risk of severe morbidity to acceptable levels. The main advantage compared to IM X-rays was that IM protons succeeded in significantly reducing the low-to-medium dose to the non-target tissues and achieved a small improvement in planning target volume (PTV) dose heterogeneity.”

Levin WP, et al. Proton Beam Therapy. *British Journal of Cancer* Vol. 93: 849-54, 2005.

“Conclusions: As discussed, the main benefit of proton therapy over photon beam radiotherapy is the absence of exit dose, which offers the opportunity for highly conformal dose distributions, while simultaneously irradiating less normal tissue. This technology therefore reduces irradiation to normal tissue, while permitting dose escalation to levels not achievable with standard techniques. Dose escalation with protons has been shown in a randomised clinical trial for prostate cancer to improve local tumour control; clinical experience with proton radiotherapy in phase II studies in other anatomic locations suggests that dose escalation in other sites results in improved local control.”

The Zeitman study accrued patients from 1996-99 and increased radiotherapy doses from 70.2 Gy to 79.2 Gy. In both dose groups, the initial 50.4 Gy was delivered with X-rays; following the X-ray treatment a proton boost was given of 19.8 Gy for a total dose of 70.2 Gy in the low radiation dose group or 28.8 Gy for a total dose of 79.2 Gy in the high radiation dose group. Thus approximately 28% of the total radiation dose was delivered with protons in the low dose treatment group and 36% with protons in the high dose group. This trial demonstrated a significantly lower risk of PSA failure rate with the higher radiation dose in both the intermediate risk prostate cancer patients, and, for the first time, in low risk prostate cancer patients. The 97% cure rate reported in low risk prostate cancer patients treated with the higher dose on the Zeitman trial has not been surpassed in any other randomized trial of radiation or other treatment modality in low risk prostate cancer. The rather compelling results of the study demonstrate that proton therapy is an extremely effective treatment for patients with localized prostate cancer. (Stuart Klein, Executive Director, University of Florida Proton Therapy Institute)

Zietman, Anthony L, et al. Comparison of Conventional-Dose vs High-Dose Conformal Radiation Therapy in Clinically Localized Adenocarcinoma of the Prostate, *The Journal of the American Medical Association*, September 15, 2005, Volume 294, Number 10.

“Conclusions: Men with clinically localized prostate cancer have a lower risk of biochemical failure if they receive high-dose rather than conventional-dose conformal radiation. This advantage was achieved without any associated increase in RTOG grade 3 acute or late urinary or rectal morbidity.”

Summary: “A salient shortcoming of photon radiation therapy for prostatic carcinoma is the damage to the urethra, rectum, and bladder that often arises when doses sufficiently high to control prostate cancer are delivered. Dose-volume relationships indicate, for example, that rectal bleeding occurs when the irradiation dose exceeds 70 Gy and the volume of return included is high (>25%) (see **Storey, M.R., et al.**, Complications from radiotherapy dose escalation in prostate cancer: preliminary results of a randomized trial. *International Journal of Radiation Oncology, Biology, Physics*. 2000 Oct 1;48(3):635-42.) Conversely, insufficient dose results in local failure and recurrence. The proton beam offers a delivery mechanism to administer the same qualitative ionizing radiation to the volume of interest, but to a much higher total dose. This heightens the chance of achieving biochemical as well as clinical disease-free control while avoiding the complications that interrupt and prevent delivery of a sufficient dose with photon beams. Proton beam therapy also avoids the large volume of normal pelvic tissues irradiated to low doses with IMRT.” (*Additional Supporting Documentation Regarding Proton Therapy Services*)

Based on the Reliable Evidence presented above, the first-level appeal committee incorrectly concluded that “published material concerning proton beam radiation therapy shows there is no convincing evidence that treatment results are superior to photon beam.”

There is sufficient clinical data comparing proton therapy to photon beam therapy in treatment of prostate cancer

It is *not generally* recognized by Reliable Evidence or the medical community that additional study on proton beam therapy’s safety and efficacy for the treatment of prostate cancer is recommended. Reliable Evidence shows that the prevailing opinion among experts regarding proton beam therapy is that *studies or clinical trials* have determined its maximum tolerated dose, its toxicity, its safety, its efficacy or its efficacy as compared with a standard means of treatment for prostate cancer.

Randomized Phase III Clinical Trials (RCTs) comparing proton therapy to photon beam therapy in treatment of prostate cancer are unnecessary and may be unethical

A randomized phase III clinical trial is unnecessary to prove the benefits of PBT for the treatment of prostate cancer. The benefits have already been documented. If PBT is at least as effective as conventional or IMRT photon irradiation in treating prostate cancer, and reduces radiation exposure to healthy surrounding cells, the simple conclusion is that PBT has a

beneficial role in the treatment of prostate cancer. The medical community has responded with a flurry of recently completed and planned proton beam therapy centers.

There are several reasons why there have not yet been any phase III trials comparing conventional photon radiation to PBT. One is that some in the field do not find any scientific need or benefit to conducting such phase III trials. (see **Suit, Herman et. al.**, Should Positive Phase III Clinical Trial Data Be Required Before Proton Beam Therapy Is More Widely Adopted? No. *Radiotherapy and Oncology*. Vol. 86 (2008) pp. 152-153). Another is that, in the judgment of some, conducting a phase III randomized clinical trial would be unethical. Given the demonstrated facts that dose distributions of proton beam therapy are superior to x-rays (photons), that proton therapy delivers two to three times less energy to normal, healthy tissue outside the prostate, that tissue response per unit does between protons and x-rays is virtually identical, and that radiation damages normal tissues, there are real ethical questions about whether RCTs comparing proton therapy to photon beam therapy in treatment of prostate cancer should be pursued. (see **Goitein, Michael & Cox, James D.** Should Randomized Clinical Trials Be Required for Proton Radiotherapy?, *Journal of Clinical Oncology*. Vol. 26: No. 2 (2008) p. 175).

Ethical concerns arise from the fact that the major clinical difference between modern photon irradiation (IMRT) and PBT lies in the volume of normal tissue exposed to radiation. The main point of a comparative trial would be to determine whether (if one assumes the same total dose delivered to the target volume) the difference in volume integral dose results in detectable clinical differences—presumably in side effects and second malignancies—over time. In order to conduct such a clinical trial, the study must be approved by institutional review boards, which are charged with ensuring that human research subjects are not harmed. Yet, a phase III study comparing photons to protons would require researchers to expose patients in the photon therapy group to normal-tissue radiation. Since there is overwhelming evidence that all radiation is harmful, how could one ethically design a study wherein half of the participants would be receiving two to three times more radiation to normal tissue with no expected clinical benefit? It would certainly be difficult to find patients willing to participate in such a study and to find an institutional review board willing to approve such an experiment. (see **Suit, Herman et. al.**, Should Positive Phase III Clinical Trial Data Be Required Before Proton Beam Therapy Is More Widely Adopted? No. *Radiotherapy and Oncology*, Vol. 86 (2008) pp. 149, 152-153)

A Double Standard

It is worth noting that, just as there have been no phase III trials comparing conventional photon radiation to PBT, there have been no phase III trials comparing conventional photon radiation to IMRT. Most proposals for a phase III trial call for a comparison between IMRT and PBT, on the assumption that IMRT is the most advanced form of photon radiation. Given the greater volume integral dose associated with IMRT, however, such an assumption may be premature. For this reason, as well as the demonstrated effectiveness of PBT in treating prostate cancer, the lack of phase III studies comparing IMRT to PBT is not an appropriate basis to deny coverage. (Ruthita Fike, CEO, Loma Linda University Medical Center)

In the field of radiation therapy, proton therapy is not unique in offering limited comparative evidence of one technology's superiority over another. For example, there is little, if

any, direct clinical evidence proving the superiority of IMRT over conformal three dimensional radiation therapy for the treatment of prostate cancer. Yet IMRT is a widely available technology that is offered by the vast majority of radiotherapy facilities.

“The current state of the art treatment modality, Intensity Modulated Radiation Therapy (IMRT), was widely adopted without comparative trials based on the same type of surrogate dose distribution modeling that supports the case for proton therapy. We believe that conducting randomized comparative clinical trials would do unnecessary harm to patients as this would expose the normal tissues to needlessly high levels of radiation. While we agree that clinical research on proton therapy needs to continue, the existence of well established surrogate models and published data has already been established. Therefore, we believe the development of comparative evidence through randomized clinical trials is an unnecessary and expensive undertaking.” (Robert L. Foote, MD; Professor of Radiation Oncology, Mayo Clinic)

Buckner, C.D. 2002. Intensity Modulated Radiation Therapy (IMRT). *Current Topics in Oncology* 2002.

“What is the data to support the use of IMRT over 3D-CRT? There have been no published randomized controlled trials comparing IMRT to 3D-CRT. The extended use of and enthusiasm for this technology rests on observations of phase II trials and simulation results where radiation to normal tissue was calculated to be less than for 3D-CRT under the same circumstances. Since this technology has apparently replaced 3D-CRT, it is unlikely that randomized trials will be performed in the future” (1-2).

“Summary: At the present time, it appears that IMRT will or has replaced 3D-CRT for the treatment of cancers where these are the appropriate choices. It is unlikely that there will be any significant number of formal randomized trials to confirm the superiority of IMRT over other technologies. Most major radiation oncology centers believe this technique to be superior and have already invested heavily in this technology” (4).

Suit, Herman, et al., 2008. Should positive phase III clinical trial data be required before proton beam therapy is more widely adopted? No. *Radiotherapy and oncology : journal of the European Society for Therapeutic Radiology and Oncology* 2008;86(2):148-53.

“**CONCLUSIONS:** Proton therapy provides superior distributions of low LET radiation dose relative to that by photon therapy for treatment of a large proportion of tumor/normal tissue situations. Our assessment is that there is no medical rationale for clinical trials of protons as they deliver lower biologically effective doses to non-target tissue than do photons for a specified dose and dose distribution to the target. Based on present knowledge, there will be some gain for patients treated by proton beam techniques. This is so even though quantitation of the clinical gain is less secure than the quantitation of reduction in physical dose. Were proton therapy less expensive than X-ray therapy, there would be no interest in conducting phase III trials.”

Goitein, Michael & Cox, James D. 2008. Should Randomized Clinical Trials Be Required for Proton Radiotherapy? *Journal of Clinical Oncology*, Vol. 26: No. 2 (2008) p. 175.

“It is therefore hard to imagine how any objective person could avoid the conclusion that there is, at the very least, a high probability that 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” (175).

Many more proton beam therapy centers are now available and under construction, at premier medical institutions, because it is generally recognized by the medical community that proton beam therapy’s safety and efficacy have been established.

Recent long-term reports of treatment history and results have generated a rapid proliferation of planned “Centers of Excellence” and primary medical institutions that are investing in the facilities to administer the Proton Beam Therapy. In 2005, there were only three primary proton beam medical facilities in the U.S. There are now five such centers with fully operational proton facilities that are currently treating cancer patients in a hospital environment: Loma Linda University Medical Center (LLUMC) at Loma Linda, California; Massachusetts General Hospital (MGH) in Boston; Midwest Proton Radiotherapy Institute at Indiana University, Bloomington; the M. D. Anderson Cancer Center in Houston, Texas; and the University of Florida Proton Therapy Institute at Jacksonville, Florida.

As of March 2008, the LLUMC Proton Center had treated well over 12,000 cancer patients with many types of cancer disease. More than half of these (approximately 65%) were treated for prostate cancer. The Texas and Florida centers have been in operation since mid-2006. There are minor variations at the different locations, depending on the facilities and doctors. However, the daily use of protons in the hospital environment has been proven (at LLUMC and the other active proton centers), and proton treatment protocols are well established.

Highlighting the growing recognition, progress, and degree of potential for proton beam treatment, there are several new centers either under construction or in the advanced planning stage within the U. S., most requiring an investment of \$120 million to \$200 million. The University of Pennsylvania is building a large facility near Philadelphia, which is being partly funded by The Dept. of Defense in partnership with Walter Reed Army Hospital. Construction of this facility is on schedule and proceeding. The cyclotron, built by IBA of Belgium, arrived in Philadelphia January 29, 2008.

Construction is in progress on a private, for-profit Proton Center in Oklahoma City that is planned to open in 2009. It is being built by ProCure Inc., the developers of the Bloomington, Indiana facility. Construction is well underway; the cyclotron was delivered in May 2008.

Hampton University in Hampton, Virginia, is planning a \$183 million facility that is scheduled to open in 2010, and will treat approximately 125 patients daily (over 2,000 patients per year). The Seattle Cancer Care Alliance is planning a \$120 million center in Seattle, Washington. A Letter of Intent was signed in February 2008; this facility will probably be on-line in late 2010 or 2011. In October 2006 Northern Illinois University announced plans to build a world-class cancer treatment and research center in Chicago that will provide state-of-the-art proton therapy. The facility will be known as the Northern Illinois Proton Treatment and Research Center. Central DuPage Hospital of Winfield, Illinois, a suburb of Chicago, is also pursuing development of a proton center.

Procure, Inc. is also planning a new proton center in south Florida, near Boca Raton. “The 58,000-square-foot center will be located in Broward or Palm Beach County with site selection near completion. The facility will be able to treat as many as 1,500 patients a year.” Barnes-Jewish Hospital in St. Louis, Missouri; Broward General at Ft. Lauderdale, and Orlando Regional at Orlando, Florida, are planning smaller units (\$20 million; see reference to MIT proton development below) to be brought on-line in 2009 and later. There are about fourteen others in the proposed, pre-planning, or design stage in the U. S. and worldwide. Experts foresee up to 100 U.S. proton centers within the next few decades. (Fuller C. Jones, Proton Beam Centers for Cancer Treatment: A Status Summary Update – July 2008)

Based on the Reliable Evidence presented above, the first-level appeal committee incorrectly concluded that there is a need for additional “clinical data comparing proton therapy to photon beam therapy in treatment of prostate cancer.”

Overall Conclusion

In light of the Reliable Evidence provided above and in the attached documents, I hereby request that Keystone Health Plan East approve for me the following:

1. Services from the University of Florida Proton Therapy Institute for evaluation for proton beam therapy for prostate cancer, and
2. Proton beam therapy treatment at the University of Florida Proton Therapy Institute

Sincerely,

Dr. Paul A. Morgan

Response to Dr. Edward D. Kim's Peer Review Report

(2/16/2009)

In his Peer Review Report of 2/16/2009, Dr. Edward D. Kim concludes that “The requested treatment is experimental and investigational based on the available scientific literature.” While I have addressed this conclusion in the accompanying document, Dr. Kim makes a number of specific claims and suggestions that require a rebuttal.

The document opens with the ominous statement that “only limited comparative clinical data are present and considerable concern has been aroused.” Again, the accompanying document thoroughly establishes the efficacy of proton beam therapy and explicitly addresses the issue of clinical data, but *who* exactly has expressed “considerable concern” and about what?

Any new treatment will have its critics, and they will come primarily from the ranks of those practicing the conventional, competing treatment options. It is easy to say, “more studies need to be done”, especially when proton beam therapy, with new centers springing up everywhere, is poised to revolutionize cancer treatment and make some conventional treatments obsolete – in large part because of its ability to limit side effects and preserve quality of life. There are almost no post-treatment prostate cancer patients expressing “considerable concern” about their choice of proton beam therapy, because as a lot they are overwhelmingly satisfied with the results. The attached **Patient Testimonials**, addressed to XXXXXX, are just a sampling.

As for the “potential additional risk for secondary malignancies” with proton beam therapy, a 2008 study turned the tables on photon radiation. C.S.Chung et al. conclude that “the use of proton radiation therapy is associated with a significantly lower risk of a second malignancy compared to photon radiation therapy.” Not only does this study deflate the “considerable concern” about proton beam therapy, it is more evidence that proton beam therapy is superior to conventional photon radiation. This abstract and accompanying text are included among the attached references (Chung CS, et al "Comparative analysis of second malignancy risk in patients treated with proton therapy versus conventional photon therapy" *Int J Radiat Oncol Biol Phys* 2008; 72(1 Suppl):S8. Abstract 17).

Dr. Kim goes on to reference D'Amico et al. in *Campbell-Walsh Urology* (9th edition), which is many years out-of-date in its status report on proton beam treatment facilities. It mentions only one free-standing facility, Loma Linda Medical Center, and suggests that proton beam therapy is an experimental treatment associated with physics labs. In fact, there are now five such free-standing centers in existence in the United States alone, there are others around the world, and many more are nearing completion and in development: “In 2005, there were only three primary proton beam medical facilities in the U.S. There are now five such centers with fully operational proton facilities that are currently treating cancer patients in a hospital environment: Loma Linda University Medical Center (LLUMC) at Loma Linda, California; Massachusetts General Hospital (MGH) in Boston; Midwest Proton Radiotherapy Institute at

Indiana University, Bloomington; the M. D. Anderson Cancer Center in Houston, Texas; and the University of Florida Proton Therapy Institute at Jacksonville, Florida” (from the accompanying documentation).

The Peer Review Report concludes with an unattributed three-sentence quotation that implies proton beam therapy is currently not safe: (sic)The same technical advances that allow delivery of improved photon therapy (conformal radiation) must be used by particle beam specialists. In time, it may be possible to deliver particle beams safely. . . .” This passage is also from D’Amico et al.’s article in *Campbell-Walsh Urology* [I checked], and this conclusion is as out-of-date as their status report on proton beam therapy facilities. Proton beam therapy has already been established as safe and efficacious in the treatment of prostate cancer.

With all due respect to Dr. Kim and others, it is evident – and even understandable – that not all urologists are up-to-date on the status of proton beam therapy as a safe, legitimate, superior, and preferable option for the treatment of prostate cancer. Dr. Edward D. Kim is a surgeon who has specialized in nerve grafting during radical prostatectomy (see his article titled, “Bilateral nerve grafting during radical retropubic prostatectomy: Extended follow-up”). He is not a radiation oncologist and is perhaps not in the best position to evaluate this relatively new form of treatment. Taken together, this rebuttal and the accompanying documents provide a much more thorough, up-to-date assessment of proton beam therapy’s efficacy and superiority over other available options for the treatment of prostate cancer.

In light of the Reliable Evidence provided above and in the attached documents, I request that Keystone Health Plan East approve for me the following:

3. Services from the University of Florida Proton Therapy Institute for evaluation for proton beam therapy for prostate cancer, and
4. Proton beam therapy treatment at the University of Florida Proton Therapy Institute

Sincerely,

Dr. Paul A. Morgan

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