Letter of rationale for treatment prepared for Blue Cross Blue Shield –NOT SENT

I acknowledge assistance from a similar letter of George W. Olney

Fairbanks, AK 99709
September 22, 1997

Blue Cross Blue Shield of …….

From a blood sample taken at a health fair on 4/27/97, I received a result of serum PSA of 61.4 ng/mL on 6/5/97. After reading several relevant articles in *JAMA* and *NEJM*, I found that the normal range for PSA is 0-4 ng/mL. So I consulted my primary care physician (Barbara Creighton, MD) who referred me to a urologist (George Jelinek, MD). On the basis of his biopsy (7/2/97), I was diagnosed with organ-confined cancer of the prostate (Prostatic Adenocarcinoma, Stage T1c; Gleason score 4 (2 + 2) in a small 17 gram prostate by Lester E. Wold, MD of the Mayo Clinic on July 10, 1997. PSA was 61.3-74.5; PAP 18, DRE, unremarkable. I obtained a second biopsy evaluation with the same diagnosis (Gleason score 6 (3+3), clear cell), from Thomas Stamey, MD and John McNeal, MD on September 9, 1997. My high PSA level suggests a high probability of extracapsular spread, but there is yet no direct evidence of metastases according to CT scan, bone scan, and laproscopic lymph node sampling. My full medical history can be found in Appendix 1.

I have consulted with the following physicians: Barbara Creighton, MD, Fairbanks, AK (primary care physician); George Jelinek, MD, Fairbanks, AK (urologist); Michael Albo, MD, University of California San Diego (urologist); Eric Saunders, MD, University of California San Diego (radiation oncologist); Michael Carroll, MD, Fairbanks, AK (medical oncologist); Richard Chung, MD, Anchorage, AK (radiation oncologist); Thomas Stamey, MD, Stanford University (urologist); Peter Grimm, DO, Swedish Medical Center, Seattle (radiation oncologist), and James Downey, MD, Swedish Medical Center, Seattle (urologist).

The treatment options (either singly or in combination) presented to me by these physicians were: radical prostatectomy, external beam irradiation, brachytherapy (seed implants), complete hormone blockade, and watchful waiting. Of these, watchful waiting was excluded on the basis of my age (61), general good health, and high PSA. This decision was reinforced by an article in the August 1997 issue of *Cancer* which showed that untreated prostate cancer in a Danish population inexorably progresses such that disease-specific survival rates at 5 and 10 years were 38% and 17% respectively. Overall, 62% of the diagnosed patients die of their prostate carcinoma (Borre et al., 1997). Chemotherapy was rejected since my histopathology indicates that I have a well- or moderately-differentiated tumor and there is no direct evidence of systemic disease. Thermotherapy and cryotherapy were not seriously considered since they are still largely investigational and other alternatives are quite viable.

The doctors explained to me that I must be the one to weigh the alternatives and choose the treatment that was right in terms of its impact on my longevity, quality of life, and emotional well-

being. I was told that in the end the decision was mine since I was the one who must live with the consequences. The alternative which I finally chose must take into account my small prostate, moderately differentiated tumor, and high PSA.

In my own evaluation of the treatment options, I used as my point of departure the full text of the American Urological Association Prostate Cancer Clinical Guidelines *Panel Report on the Management of Clinically Localized Prostate Cancer*, published in 1995, and referred to below as the AUA Report. [A summary of this report was published in the Journal of Urology (Middleton et al., 1995)] The AUA Report attempted to analyze the literature regarding the available methods for treating locally confined prostate cancer and to make policy recommendations accordingly. What the panel found is that available data, while extensive, differed too much with regard to age, tumor grade, etc. to make valid comparisons among the patient series and treatments. Instead of identifying any one treatment as more effective than another, the panel recommended that patients with newly diagnosed clinically localized prostate cancer should be informed of all commonly accepted treatment options. This is exactly how my physicians have presented the options to me.

I would like to explain the rationale behind my final choice of therapy. I am a cell biologist. For 16 years, I was Chair of Zoology (now Biology) at the University of Vermont. Because of our experience in biomedical research and our general familiarity with research literature, my wife and I have now spent several hundred hours (using Medline, the Internet, the libraries at the University of Alaska and at Stanford, and interlibrary loan) reading abstracts and full articles from the original medical literature on the cellular basis of prostate cancer, on treatment options and their likely sequelae, and on the morbidities associated with each. I have discussed the medical literature and its implications for me with my physicians. Although at first glance, each of the treatments appeared effective in producing remission (at least to 10 years), they differ in predicted morbidities.

The literature review for the AUA Report went through 1993 publications. On the basis of my own review of the literature, I concur with the AUA conclusions: 1) that it is very difficult to compare outcomes among the many studies because of differences in patient selection, therapeutic procedures, and outcome measures, and 2) the long term systematic follow-up needed to accurately record these data is exceptionally difficult.

Therapy Option 1: Radical Prostectomy (RP)

This is the classical gold standard for organ-confined disease. It was improved significantly in the decade 1982-1992, largely due to the work of Dr. Walsh and associates at Johns Hopkins. The results depend critically on the experience and skill of the surgeon. It is widely used; 9,263 patients were included in the T2 series reviewed in the AUA Report. The patient selection criteria are usually stringent, limiting this therapy to patients with a high probability of organ-confined disease.

The major advantage of radical prostatectomy is the potential for cure; lifetime freedom from the disease is possible if surgical margins are negative. However, if the surgical margins are positive,

radical prostatectomy must often be followed by external beam radiotherapy. The progression-free survival at five years after RP ranges from 45 to 92%. Pretreatment PSA is a predictor of success: Johns Hopkins University results at 5 years show that pretreatment PSA of 0-4 ng/mL yielded 92% PSA freedom from progression while with pretreatment PSA over 20 ng/mL, the freedom from progression was only 45% (Partin et al., 1993). Dr. Thomas Stamey, Professor of Urology at Stanford, told me that except for 5 cases with very large prostates and a primary tumor in the transition zone of the prostate, he has seen no surgical cures when the pretreatment PSA exceeded 23 ng/mL.

A major disadvantage of radical prostatectomy is potential morbidity, including bleeding, difficulty with the anastamosis of the bladder neck to the urethra, and rectal injury from the operation itself. Postoperative complications involve stress incontinence (range 4%-50%) and impotence (29-100%), as well as several less frequent problems. In an interesting post-treatment evaluation, Jønler and coworkers (1994) reported that surgical patients accepted these consequences quite well, apparently because they were well informed about the potential morbidities and chose the surgery none-the-less. My review of the literature since 1993 revealed no other pertinent new evaluative data since 1993, except for the increasing acceptance of hormone blockade for several months before surgery.

Therapy Option 2 - External Beam Radiotherapy (EBRT)

EBRT is a very widely used option; over 14,000 patients were included in the series reviewed in the AUA Report. The technology has rapidly evolved to the point that modern conformal EBRT uses computer technology to target the beam precisely to the prostate and seminal vesicles and thus conformal EBRT spares surrounding tissues much more than in the past. The five year progression-free survival ranges from 32-98% while ten year progression-free survival ranges from 44-88%. The wide range is due to differences in technical progress and also to differences in defining the progression statistics. The use of post-operative biopsy and recent widespread use of PSA has improved the consistency in these statistics. Recent data (Zagars, 1992; Zietman et al., 1995) show that a high pretreatment PSA (>15 ng/mL) is correlated with a high rate of failure with EBRT as a monotherapy. Morbidity complications include impotence (4-41%) and diarrhea (variable in incidence, usually grade 2 or less). In recent papers on the quality of life after radical prostatectomy and EBRT (Lim et al., 1995; Robinson et al., 1997), the authors conclude that the surgical group had worse sexual function and urinary incontinence and the EBRT group had worse bowel function. My review of the literature (e.g. Hanks et al., 1995) indicates that with steady progress in refining conformal techniques, the incidence of complications due to radiation damage to the rectum and urethra can be expected to decline.

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Therapy Option 3 - Brachytherapy

Brachytherapy is a widely used option; 4,891 patients were included in the series reviewed in the AUA Report. Patient selection criteria are similar to radical prostatectomy and EBRT. The AUA Report concluded that older retropubic seed implantation technique (1965-1985) gave good survival results for several surgical groups but showed slightly higher rates of incontinence and proctitis than did EBRT. On the basis of the data available in 1993, the AUA Report included brachytherapy in the list of approved and standard therapies for local disease. The newer ultrasound-guided transperineal computer-assisted seed implantation technique (largely practiced as an outpatient procedure), looked promising to the AUA panel, but no 5-year survival results for this treatment were available in 1993.

In 1997, there are much better data on both survival and morbidities for transperineal brachytherapy. Wallner et al., (1996) report on 92 patients treated at Memorial Sloan Kettering. They conclude that the 5-year biochemical freedom-from-progression rates from ^{125}I implantation are comparable with those achieved from prostatectomy and that the morbidity has decreased with increased physician experience. For high pretreatment PSA (>20 ng/mL), five year PSA freedom-from-progression data reveal success rates of 45% for surgery at Johns Hopkins (Partin et al., 1993) compared with a success rate of 80% in two brachytherapy series at Memorial Sloan Kettering (Wallner et al., 1996) and The Northwest Tumor Institute (Blasko et al., 1993).

The rate of complications following the early retropubic open procedure of seed implantation was of concern to the AUA panel in 1993. Since that time, new data on the success of the transperineal brachytherapy procedure has demonstrated that morbidity is sharply reduced in comparison with the retropubic procedure. The Seattle data (Grimm et al., 1996) show a high incidence of early minor urinary symptoms (RTOG grade 1-2) during the effective half-life of the isotope, but these are typically self-limited. Higher grade urinary complications are rare. The six year actuarial incontinence rate was 0% in patients with no prior TURP, and the loss of potency in those patients under 65 years of age was 15-20% (Blasko et al., 1995). In the Seattle series, the morbidity data for seed implantation monotherapy and for EBRT with a brachytherapy boost are almost indistinguishable (Grimm et al., 1996). Large prostate size, presence of a TURP, and obstructive symptomology at presentation identify patients with higher risk of complications for brachytherapy (Blasko et al., 1996).

In the present context, it is interesting to note that Dr. Charles Myers, MD, Director of the Cancer Center at the University of Virginia and an expert in prostate cancer chemotherapy, described brachytherapy as the “new gold standard” at the Prostate Cancer Symposium held in San Diego in September 1997.

Therapy Option 4 - Complete Hormone Blockade (CHB)

Complete hormone blockade is not addressed in detail in the AUA Report, since in 1993 CHB was largely regarded as a treatment to be used mostly for advanced prostate cancer. Recent papers show that pretreatment with CHB increases the success rates for radical prostatectomy (Labrie et al., 1997) and for EBRT (Bolla et al., 1997). The Bolla article has made a huge impact as it convincingly showed that that down-regulating the prostate with hormone blockade

significantly increased the rate of progression-free survival.

On the basis of my own case history, our thorough literature review and our discussions with the physicians, I have elected to down-regulate my tumor with several months of hormone blockade and then to proceed to beam irradiation boosted with radiation seed therapy. The logic follows from the review above.

The disease-free progression data is as good or better for seed therapy than for any other therapy at least out to 7 years (Ragde et al., 1997).

The morbidities and inconvenience after brachytherapy are less than those following surgery.

The disease-free progression data is distinctly better for seed therapy for a patient, like me, who has pretreatment PSA over 20 ng/mL than for EBRT alone or radical prostatectomy.

I have none of the patient characteristics (distant metastases, previous TURP, large volume gland, or extensive prostate calcification) that predict high risk with brachytherapy (Nag et al., 1997).

My high PSA argues for beam irradiation followed by a seed implantation boost since the beam is more likely to treat extracapsular extensions. According to the recent revision of the Partin tables for predicting pathological stage, I have a 49% chance of established capsular penetration (Partin et al., 1997).

Since several months of CHB increase the probability of progression-free survival for radiation therapy treatments (Bolla et al., 1997), I will use hormone blockade in conjunction with the radiation treatments.

Success also depends upon the skill and expertise of the practioner. To maximize the probability of disease control and to minimize the probability of morbidity, I have elected to have the seed implants in Seattle with Dr. Peter D. Grimm, one of the major figures in the highly successful development of modern transperineal brachytherapy.

The balance of my letter will focus on the question of whether brachytherapy is a standard and accepted therapy and thus should be covered by my health insurance.

It is my understanding that the insurance coverage for a treatment involves three issues: Is it effective? Are the morbidities serious? Is there sufficient experience with the treatment for it to have passed from an investigational therapy to a standard and accepted therapy?

I believe that the issues of effectiveness and morbidity have been adequately addressed above. The success rates for prostate-confined cancer is roughly similar for all three treatments, but there is no definitive study which allows rigorous comparisons of the success rates of the treatments,

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using a statistically similar population of patients and physicians. The effectiveness of surgery, EBRT, and brachytherapy are equivalent for most organ-confined disease at 5-7 years, and for PSA over 20 ng/mL, brachytherapy appears distinctly better. The morbidity from modern brachytherapy as performed by the Seattle group is much lower than that for surgery at major surgical centers.

Let me now directly address the question of whether brachytherapy is a standard and accepted therapy for prostate cancer or whether it is investigational.

Radiation seed therapy received FDA permission in 1987.

Brachytherapy is widely practiced. According to the listing of brachytherapists available on the Internet, seed implantation for prostate cancer is practiced in 37 of the 50 states (Vermont and Alaska are two of the 13 with no listed practitioners). Well over 5000 patients have been included in the series reported in refereed journal publication, as indicated by the AUA Report and other scientific papers since 1993.

Most nationally recognized medical policy-making entities endorse radiation seed therapy and consider it to be a standard treatment for early stage prostate cancer. The National Cancer Institute, a division of the National Institutes of Health (NIH), states that internal radiation is one of the standard treatments of early stage prostate cancer. The National Cancer Institute lists several other treatments for prostate cancer which it considers investigational, but does not place internal radiation in the investigational category. The American College of Radiology (ACR) endorses radioactive seed implantation as an effective treatment for prostate cancer and states that it should be a covered and reimbursable procedure. Finally as noted already, the American Urological Association (AUA) ranks brachytherapy treatment of the prostate as one of the three methods of urologic management of prostate cancer.

Brachytherapy has been covered by many insurance programs for several years. In addition to Medicare, these now include United HealthCare, CHAMPUS, Mutual of Omaha, Healthnet of Southern California, Kaiser, George Washington University Health Plan, Aetna, Cigna, BC/BS of Massachusetts Master Health PLUS, Alaska-Washington BC/BS, General Motors Retirement Plan, State Farm, Tufts HMO and Prudential.

In my view, the evidence overwhelmingly argues that brachytherapy is one of the standard and accepted therapies for prostate cancer and is particularly appropriate with my set of symptoms and test results. I therefore ask that Blue Cross Blue Shield of … approve payment for this therapy as part of my comprehensive plan.

George M. Happ

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