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Cost-comparison of prostate cancer screening versus not screening.

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COST-COMPARISON OF PROSTATE CANCER SCREENING VERSUS NOT SCREENING

By

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A.S., Jefferson Community College, 1975

A.Ap.S., Jefferson Community College, 1976

B.S., University of Louisville, 1981

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A Thesis Approved on

May 5, 2006

by the following Thesis Committee:

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Thesis Director

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DEDICATION

This thesis is dedicated to

my parents, my wife, my children, and my grandchildren

who have illuminated my life.

ACKNOWLEDGMENTS

I would like to thank Dr. Steven McCabe for his help and support. He is a most supportive and kind person. He has been my inspiration. I would like to thank Dr. Bill Rising for teaching me to think. I would like to thank Dr. Stephen Houghland for his clinical support. Finally, I would like to thank Dr. Charlene Mitchell for showing me the difference between perfect knowledge and human knowledge.

ABSTRACT

COST-UTILITY OF PROSTATE CANCER SCREENING

Bill Fell

May 13, 2006

Prostate cancer is a common form of cancer in men. In fact, prostate cancer has the highest incidence of any cancer in men. Prostate cancer is not only common, it carries a significant financial burden. The cost of prostate cancer is 11.3% of all cancer expenditures. If after a DRE the prostate is enlarged, or if the PSA is elevated, then a biopsy of the prostate would be recommended. Under the best of circumstances, cancer diagnoses will be missed and many will undergo unnecessary biopsy, etc.

The focus of this paper was the cost-utility of screening with the PSA test. The cost differences between screening and not screening was compared. A Markov analysis and a Monte Carlo simulation were utilized to provide a basis for conclusion.

The primary finding is that the costs associated with screening are much higher than those of not screening. Additional findings are that the specificity of the PSA test, the first year treatment costs, and the utility/outcomes of screening have an impact on the cost-utility of screening. The conclusion, however, is that the improvements in these factors would have to be significant to impact the case for screening. Until longitudinal studies are completed, it is not cost-effective to screen for prostate cancer.

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INTRODUCTION

Anatomy

The prostate is a cluster of glands located at the base of the bladder, centered between the base of the penis and the rectum (Figure 1)[1]. The prostate surrounds the urethra. The urethra, the tube through which urine travels from the bladder through the penis to be eliminated from the body, courses through the prostate. The primary function of the prostate is to produce the majority of seminal fluid. This fluid facilitates transport and nourishment of sperm. During ejaculation, the prostate squeezes fluid into the urethra.

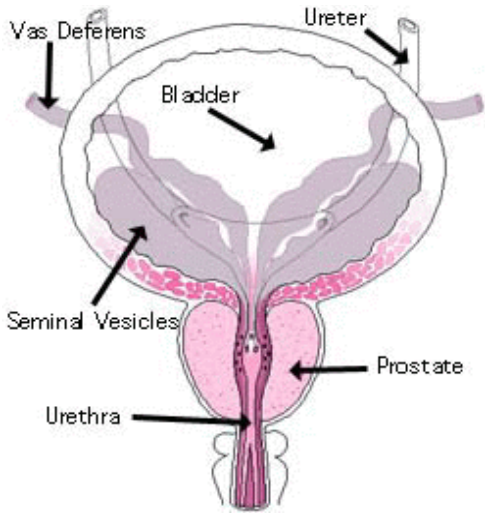


Figure 1. Male Genito-Urinary Anatomy

Prostate Diseases

There are three main diseases that can occur concerning the prostate.[2] The first is prostatitis. Prostatitis is the inflamation of the prostate gland. It can be caused by an infection or irritation of the prostate. The second is benign prostatic hyperplasia (BPH). BPH is the enlargement of the prostate. BPH manifests as men age and it may be a natural occurrence. From age 49 to age 80, the prevalence of BPH appears to increase linearly.[3] The third is prostate cancer, the growth of a tumor in the prostate gland. Other diseases such as prostatodynia (non-infection, non-inflamation prostatitis) and prostatic stones are less significant.

Prostate Cancer

Prostate cancer is a common form of cancer in men and is generally a slow growing cancer. Prostate symptoms often do not present themselves until the tumor is large in size, locally invasive, or until the cancer metastasises. The symptoms include difficulty urinating, a weak stream when urinating, frequent urge to urinate (especially during the night) painful or burning urination, and blood in the urine.[4] Unfortunately prostatitis and BPH share theses symptoms. If the cancer metastasises, the symptoms may come from the secondary site. The cancer may spread through the lymph nodes and blood stream to the secondary site. A common symptom of metastatic spread is lower back pain. This is caused by involvement of the lumbosacral spine.

In males, prostate cancer has the highest incidence of cancers. Additionally, prostate cancer trails only lung cancer in causes of death in men.[5] In 2005, it was estimated that 232,090 new cases of prostate cancer would be diagnosed and 30,350 men would die from it.[6] One in 6 will get the disease and one in 34 will die from the disease.

There are several risk factors associated with the incidence of prostate cancer.[7] They are age, African-American ethnicity, nationality, family history, diet, physical inactivity and obesity, and vasectomy. Of these, age and African-American ethnicity are the most significant. A majority (70%) of all new prostate cancers will be in men older than 65. The incidence for African-American men is 60% higher than the incidence for white American men. Family history is also a strong predictor. If one has a father or brother with prostate cancer, the probability of developing prostate cancer is higher. In fact, having a brother with prostate cancer carries a higher probability than having a father with the disease. Diet, physical activity and obesity, and vasectomy are not as strongly correlated as the others.

Economic Perspective

From a cost standpoint let us put this cancer in perspective. The Gross Domestic Product (GDP) for the United State was 2005 was $12,486 billion.[8] National healthcare expenditures for 2004 totaled $1,540 billion.[9] The direct annual medical cost of cancer care in the U.S. for 2004 was estimated at $72.1 billion.[10] This does not include any cost of lost productivity due to illness or death. The cost of prostate cancer was 11.1% of all cancer expenditures[11] or approximately $8.0 billion. This means that the cost of prostate cancer was approximately 0.064% of the U.S. GDP in 2005. Prostate Cancer treatment is moderately significant to other cancers in terms of cost.

Diagnosis

The diagnosis of prostate cancer can be accomplished in several ways.[12] Screening can be the initial step in the diagnostic process. The patient could be screened

by a digital rectal exam (DRE). During a DRE, a physician places a finger in the male's rectum and palpates the prostate gland for size and shape. If the size and/or shape are found to be irregular, a biopsy of the prostate would be performed. The biopsy is considered the "gold standard" for diagnosing prostate cancer.[13] Another screening modality is measuring the amount of prostate-specific antigen in the blood (PSA). PSA is a protein that is normally produced in the prostate gland.[14] The serum PSA level may become elevated if the normal structure is disturbed due to cancer, BPH, or prostatitis. If the PSA is elevated, then a biopsy of the prostate is often recommended depending on the clinical setting.[15]

When a patient presents with symptoms and has not been screened, the recommended practice is to perform the DRE and/or the PSA as part of the diagnostic work up and potentially continue to biopsy. Transrectal ultrasound (TRUS) is often used in conjunction with the biopsy. As the work up progresses other diagnostic imaging techniques may be employed, such as computerized tomography (CT scan) or magnetic resonance imaging (MRI).

Treatment

Treatment is essentially one of four modalities or a combination of the them. They are surgical, radiation, medical hormonal, or observation.[16] Surgical therapy is either a radical or partial prostatectomy. A radical prostatectomy involves removing the entire prostate. A partial prostatectomy removes only the affected area of the gland. The second treatment choice is radiation therapy. This can be accomplished by placing a radioactive "seed" in the prostate, or perhaps by using use of irradiation with an external beam radiation. A third option is medication therapy either through chemotherapy or

hormonal therapy. Finally, a treatment choice that has grown in popularity is the choice not to have treatment at all. This is sometimes called "watchful waiting." Many prostate cancers are very slow growing and organ confined. Therefore, some men elect to defer or decline treatment. Recognize this is not a passive process. The patient continues to undergo testing and biopsy until a final determination is made as to treat or not to treat.

The Issues

There are several issues that exist regarding the diagnosis and treatment of prostate cancer. The first issue to consider is that, for many men, prostate cancer is slow growing. Many males will go through life having prostate cancer, and they never have significant symptoms.[17] Compared to other cancers, the incidence in males is high.[18] The chance of a bad outcome does exist. There is the inherent difficulty in accurately predicting which affected person will be in the smaller percentage that has significant morbidity and mortality.

The second issue is that the DRE and the PSA test are good predictors of prostate cancer, but are not as accurate as we would like.[19] The best sensitivity and specificity for PSA is better than the DRE at 80% and 70% respectively.[20,21,22] What this means is that even under the best of circumstances, a cancer diagnosis will be missed in a fifth of males with disease. (Which is much worse than thought to be true.) This also highlights that about a third of the males that screen positive will undergo unnecessary biopsy and other testing. Diagnostic testing can be expensive, can be painful, and can produce undesirable side-effects.

Finally, the treatment options have inherent problems. The treatment of prostate cancer may not produce a 100% cure rate. In addition, the complications of treatment

can be devastating to a man. The treatments can leave a man incontinent or impotent or both. For this reason many are deciding to live with symptoms, with the potential for the onset of symptoms, or with the possibility of a bad outcome.

Focus

Since the PSA has better sensitivity and specificity than the DRE, we will consider the PSA to be the standard screening tool as compared to not screening at all. Serum PSA is the screening method recommended by established guidelines.[23] The paper was begun with the idea of focusing on the cost-utility of the PSA with respect to outcomes. As the literature search was undertaken, it was found that there were utility studies that look at the quality-adjusted life-years or other measures, available for prostate cancer and treatment. No connection was made between the improvement in these utilities due to screening.[24] Mortality and morbidity data are not available yet. It is expected that the utilities for the relationship between screening and outcomes will be available between now and 2010.[25] The focus of this paper is to study the factors that affect the relationship of screening to outcomes. The cost difference between "screening" and "not screening" will be compared. The aim is to develop a model for this comparison and to simulate changes in pertinent factors to determine their affect on the model. When the data becomes available, the model can be re-engineered to accommodate the updated information.

LITERATURE REVIEW

Prostate Cancer and the Progression of Disease

Prostate cancer continues to be a significant disease in the male population. Prostate cancer is the leading cancer diagnosis and is the second leading cancer cause of death in the United States in 2001, in men.[26] In 2004, the American Cancer Society estimated that prostate cancer would lead in new cancer diagnoses at 230,110. Prostate cancer would be the second leading cause of cancer death, second to lung, at 29,500 deaths.[27] This ranking remains true as the leader of new cancers with 232,090 prostate cancer cases for American males in 2005. The estimates of causes of cancer deaths for males for 2005 continue with the lung as number one and prostate as number two at 30,350 prostate cancer deaths.[28] This data supports the fact that prostate cancer is a common cancer diagnosis and a leading cause of cancer deaths in men.

Prostate cancer manifests in different ways. It is often a very slow growing tumor.[29] An individual may have this cancer for many years without symptoms. Lower urinary tract symptoms (LUTS) are generally part of the progress of the disease. These symptoms are listed in Table 1.[30] The symptoms can be of a flow restrictive nature or of a bladder capacity nature. LUTS can also be indicative of benign prostatic hyperplasia (BPH), bladder outlet obstruction (BOO), prostatic stones, and prostatodynia. BPH is a benign enlargement of the prostate that occurs as men age. BPH is so common it could be considered normal.[31] On autopsy, 50% of men in their 50's and 90% of men in their

90's have BPH.

Table 1.

Lower Urinary Tract Symptoms (LUTS)

Weak urinary stream
Abdominal straining
Hesitancy
Intermittency
Incomplete bladder emptying
Terminal and postmicturitional dribble
Dysuria
Frequency and repeated urination
Nocturia
Urgency
Incontinence
Bladder pain

The incidence rates of LUTS/BPH are in Table 2.[32] BOO can be prostatic in origin or from some other anomaly. Prostatic stones, mineral deposits in the prostate, can cause acute or chronic prostatitis. Prostatodynia is pain in the prostate of unknown origin.

Lower back pain can be a symptom of prostate cancer as a result of metastasis.[33] In this case, the prognosis is poor. The cancer originating in the prostate finds its way into bones of the pelvis and the lumbar spine. In fact, metastatic prostatic cancer should at least be considered in the differential diagnosis of back pain in men over the age of 50.

Table 2.
Incidence of LUTS/BPH

Incidence of LUTS/BPH	
Age (years)	**Incidence per 1000 man-years**
50 - 54	6.91
55 - 59	13.02
60 - 64	19.78
65 - 69	23.99
70 - 74	34.46
75 - 79	38.30
80 - 84	32.20

Finally, prostate cancer can result in death. However, because of the disease's slow growth, a man will probably die "with" prostate cancer rather than die "from" prostate cancer.[34] So, prostate cancer can manifest in a range from asymptomatic to death.

Screening

There are basically two methods for screening for prostate cancer. The digital rectal exam (DRE) and the prostate-specific antigen test (PSA).[35] The DRE is an exam where the physician palpates the male's prostate through the rectum. The exam is performed to detect enlargement, irregularity, and texture of the prostate that could indicate prostate cancer. PSA is a protein that is a normal product of the tissue in the prostate. The PSA test measures the level of prostate-specific antigen in the blood. An

elevated PSA can indicate prostate cancer, BPH, infection, or inflamation of the prostate.

The accuracy of the DRE and PSA tests is measured by the specific test's sensitivity and specificity. The sensitivity of a test is the number of true positive tests divided by the sum of the true positive tests and the false negative tests of who were tested. Expressed another way, the number of those that test positive and have the disease divided the total number that have the disease. The specificity of a test is the number of true negative tests divided by the sum of the true negative tests and the false positive tests of who were tested. In general terms, the number of those that test negative and do not have the disease divided the total number that do not have the disease.[36]

The sensitivity and the specificity of the DRE are not certain.[37] According to Coley, et al, the studies assessing the sensitivity and specificity are biased. No studies directly assessing the sensitivity and the specificity of the DRE in the last six years could be located within this literature search.

The studies focused on the sensitivity and the specificity of the PSA are summarized in the ranges 67.5% to 80% and 60% to 70%, respectively, at greater than 4 nanograms per milliliter (> 4ng/ml).[38] Clinically, a PSA range of 0 to 4 ng/ml is considered normal.[39] At values less than 4ng/ml, the sensitivity and specificity is generally low.[40] However, age specific ranges for the PSA concentration improve the sensitivity and specificity of the test.[41] The PSA specificity can vary with age, ethnicity, or national origin. In practice, 4ng/ml is the cut-off.[42] It is also important to consider that the higher the PSA the more strongly prostate cancer or prostatitis should be suspected.

Different, or variant methods of screening for prostate cancer have been, and are being, researched. One such is the ratio of serum complexed PSA (cPSA) to serum total PSA (tPSA).[43] Increased cPSA is indicative high risk. At lower levels of tPSA, detection

of cancer may be improved. In specific patients with co-morbidities such as end-stage renal disease, tPSA augmented by PSA density and transrectal ultrasound (TRUS) has shown improved detection.[44] In specific populations, the use of multiple biomarkers has shown some promise. In one study, the detection was reported improved using serum human glandular kallikrein 2 (jK2), tPSA, and free PSA (fPSA).[45] New methods such as PSA RapidScreen tests may improve availability and specificity of the screen.[46] Another tool that has been advocated is the PSA "velocity." This method evaluates the rate of increase of the serum PSA over time. The faster the rise the more suggestive of cancer. In fact, a doubling or tripling even withing the "normal" range can indicate an area of concern.[47] The amount of Medicare reimbursement for a PSA screen currently is $25.70.[48]

Diagnosis

A person enters the diagnostic phase by either screening positive or developing symptoms. Once either of these has occurred, as stated earlier, a biopsy is performed. The biopsy is considered the "gold standard." Unfortunately, as with any test, it is possible to obtain a false negative. When performing a sextant biopsy, there is a risk of between 15% and 34% false negative procedures.[49] For this reason, it is recommended that as many as 30 biopsies be performed. Nonetheless, biopsy is considered the standard. The average Medicare Part A and Medicare Part B reimbursement for a biopsy is approximately $900.00.[50]

Treatment

The breakdown of treatment preferences is not well documented. In a Louisiana study, the mix was 41.4% radical prostatectomy, 29.7% radiation therapy, 16.2% hormonal therapy, and 11.9% watchful waiting.[51] The spectrum of complications from any of these treatment choices includes lymphocele formation; injuries to the ureter, rectum, and urethra; prostatic necrosis; vesicourethral anastomotic leak and stricture; urethral stricture, necrosis, and fistula; radiation proctitis; transient bladder outlet obstruction; radiation-induced urethritis; urinary incontinence; and erectile dysfunction.[52] The average cost of the first year of treatment is $11,000.00.[53]

Recommendation

As of the latest update, September 12, 2005 to the Guidelines for Prostate Screening at the National Guideline Clearinghouse[54], the American Cancer Society (ACS), the University of Michigan Health System (UMHS), and the U.S. Preventative Services Task Force (USPSTF) provide the recommendations as follows:

Table 3
Comparison of Recommendations for Prostate Cancer Screening

Agency	Guideline
ACS (2001)	**Targeted screening/Screening tests/Informed decision-making** ACS recommends that both the PSA test and the DRE should be offered annually beginning at age 50, to men who have a life expectancy of at least 10 years. Men at high risk should begin testing at age 45. Information should be provided to patients about benefits and limitations of testing.

	Specifically, prior to testing, men should have an opportunity to learn about the benefits and limitations of testing for early prostate cancer detection and treatment. High-risk groups include men of African descent (specifically, sub-Saharan African descent) and men with a first-degree relative diagnosed at a young age. Risk increases with the number of first-degree relatives affected by prostate cancer.
UMHS (2004) New	**Modality.** PSA and DRE. Both have specificity limitations. **Initiate.** Clinicians who screen for prostate cancer should share decision making with patients, giving objective information about the potential risks and benefits of screening. ● Average risk. For men >age 50, consider initiating PSA screen. ● High-risk. For men with positive family history and for African Americans, consider starting PSA screening at age 40. **Frequency.** Annually **Terminate.** Stop when life expectancy is less than 10 to 15 years. There is considerable controversy surrounding screening for prostate cancer. Early detection and treatment may avert future prostate

	cancer-related illness, but treatment includes some risk of sexual dysfunction and incontinence and a small risk of treatment-induced mortality. At this time, no trials of sufficient power are available to document the benefit of aggressive treatment (e.g. surgery, radiation) versus conservative management and hormonal therapy. Similarly, there is no conclusive evidence that routine screening for prostate cancer is beneficial, and there is no consensus concerning the role of DRE and PSA testing in screening.
USPSTF (2002)	**Routine screening** USPSTF concludes that the evidence is insufficient to recommend for or against routine screening for prostate cancer using PSA testing or DRE. **I recommendation.** *The USPSTF found good evidence that PSA screening can detect early-stage prostate cancer but mixed and inconclusive evidence that early detection improves health outcomes. Screening is associated with important harms, including frequent false-positive results and unnecessary anxiety, biopsies, and potential complications of treatment of some cancers that may never have affected a patient's health. The USPSTF concludes that evidence is insufficient to determine whether benefits outweigh harms for a screened population.* **Clinical Considerations**

- PSA testing and DRE can effectively detect prostate cancer at early pathologic stages. There is insufficient evidence, however, that the currently available treatments (radical prostatectomy, radiation therapy, or hormonal therapy) reduce morbidity and mortality from early prostate cancer. Therefore, the benefit of screening for and treating early prostate cancer is unknown.

Informed decision-making/Targeted screening/Screening tests/Screening frequency

Clinical Considerations

- Despite the absence of firm evidence of effectiveness, some clinicians may opt to perform screening for other reasons. Given the uncertainties and controversy surrounding prostate cancer screening, clinicians should not order the PSA test without first discussing with the patient the potential but uncertain benefits (reduction of morbidity and mortality from prostate cancer) and the possible harms (false-positive results, unnecessary biopsies, and possible complications of treatment) of prostate cancer screening. Men should be informed of the gaps in the evidence, and they should be assisted in considering their personal preferences and risk profile before deciding whether to be tested.
- If early detection improves health outcomes, the population most

	likely to benefit from screening will be men aged 50-70 years who are at average risk, and men over age 45 who are at increased risk (African American men and men with a family history of a first-degree relative with prostate cancer). Benefits may be smaller in Asian Americans, Hispanics, and other racial and ethnic groups that have a lower risk of prostate cancer. Older men and men with other significant medical problems who have a life expectancy of fewer than 10 years are unlikely to benefit from screening. ● PSA testing is more sensitive than DRE for the detection of prostate cancer. PSA screening with the conventional cut-point of 4.0 ng/dl detects a large majority of prostate cancers; however, a significant percentage of early prostate cancers (10-20%) will be missed by PSA testing alone. Using a lower threshold to define an abnormal PSA detects more cancers at the cost of more false positives and more biopsies. ● The yield of screening in terms of cancer detected declines rapidly with repeated annual testing. If screening were to reduce mortality, biennial PSA screening could yield as much benefit as annual screening.

Cost-Utility

In the literature there are papers on the utilities of treatment, but there seems to be nothing currently demonstrating that outcomes are related to screening. No data is available, regardless of treatment, to demonstrate that the probabilities of mortality and morbidity are improved or not improved by screening. Within the next five years, data are expected to be coming from the European Randomized Study of Screening for Prostate Cancer (ERSPC).[55] This is a longitudinal study that spans over a decade. Data are being collected within this study with respect to the outcomes as affected by screening.

GOAL, OBJECTIVES, AND METHODS

Goal

The motive for this project is to answer the question of the cost-utility of screening for prostate cancer. A cost-utility considers the ratio of costs of diagnosis and treatment of prostate cancer to the utilities of outcomes. The cost-utility ratios of the course of the disease includes screening and the course of the disease that does not include screening will be compared. There is a problem with screening utilities and outcomes. There is documentation of the utilities of the outcome of treatment. However, to date, there is no documentation as to a difference in the outcomes when an individual is screened for prostate cancer and when he is not. Hence, the goal is to study the costs of diagnosis and treatment per person of screening versus costs of diagnosis and treatment per person of not screening. In addition, various parameters in the model will be studied to demonstrate the effects of these parameters on the costs per person. The model is constructed to accommodate utility data when the data becomes available.

Objectives

The specific objectives of this study are:

- to determine if there is a difference in the costs of diagnosis and treatment with respect to screening or not screening.
- to examine the relationship of the cost of treatment as a result of

screening to the cost of treatment as a result of not screening.

- to determine the effect of improvements in PSA test parameters (sensitivity and specificity) for the screening test.
- to determine the utility/effectiveness difference that favors screening with an "incremental cost-effectiveness ratio" less than $50,000 per quality adjusted life year (QALY).

Design

A decision-analysis model was developed to compare the costs associated with the diagnostic work-up and treatment following screening, and the diagnostic work-up and treatment following the presentation of symptoms. A cost analysis was used to differentiate the two alternatives. The costs involved will occur over time. To determine the costs over time a Markov model was utilized. In order to demonstrate the confidence that there is a difference in the alternatives, a Monte Carlo analysis of the Markov model was implemented. Most probability estimates were generated from the SEER and CDC databases. A few probability estimates were generated from data in the literature search. The most current years of data available at the time of publication were incorporated in the analysis. Sensitivity analyses were performed on the variables outlined in the objectives. The sensitivity analyses utilized ranges that were possible, but not necessarily probable. The calculations, Markov analysis, and Monte Carlo simulation were performed using TreeAge Pro Suite 2005, Release 0.8 (TreeAge Software, Inc., Boston, MA, 2004), a decision analysis software program. The statistical analysis was performed using R, Release 2.2.1 and SPSS for Windows, Release 8.0.0 (SPSS, Inc., 1997), a statistical software package.

The Model

The Cohort

The cohort is comprised of 50 year old males with no known cancer of the prostate. At this age the risk of developing prostate cancer increases significantly. The age range for this study was 50 to 85 years old. It is recommended that since prostate cancer is such a slow growing cancer, if the life expectancy is less than ten years, there is no need to screen, or perhaps even treat.

The States of Nature

When performing a Markov analysis, the states of nature must be identified. An initial bubble diagram was developed. (See Figure 2.) It included as states of nature: no cancer and no symptoms, no cancer and symptoms, cancer and no symptoms, cancer and symptoms, cancer and treatment, cancer and no treatment, death from prostate cancer, and death for other causes. Although these seemed to be the states appropriate to this model, some simplification was indicated. If there are no symptoms, then one would not know if there were cancer or not. Also, in the case known cancer, the state can be reduced to cancer with treatment and cancer with no treatment. And finally, death from prostate cancer or death from another cause can be pooled in just death. Figure 3 diagrams the model used in the Markov analysis.

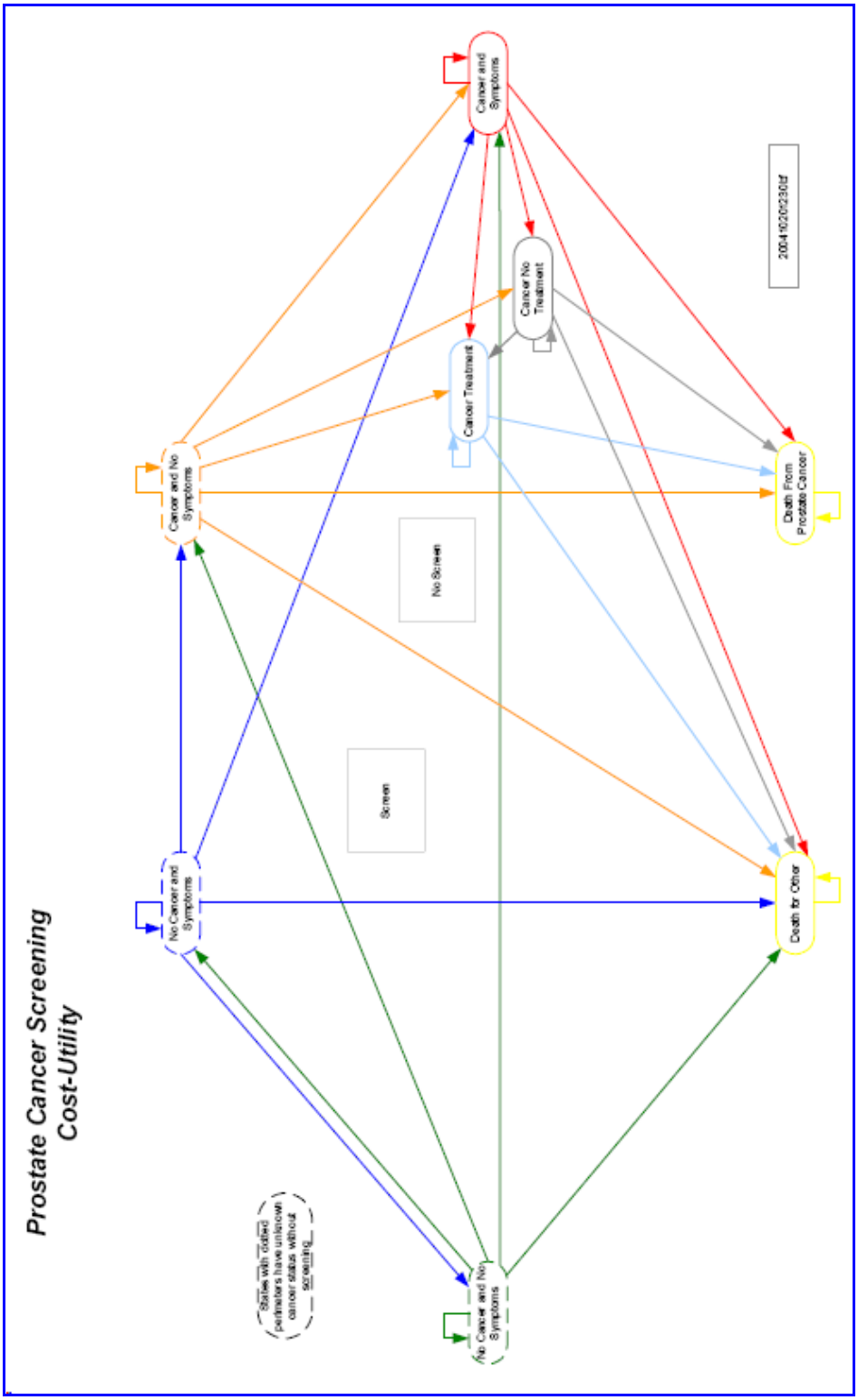


Figure 2. The initial bubble diagram demonstrates the complexity of the states of nature.

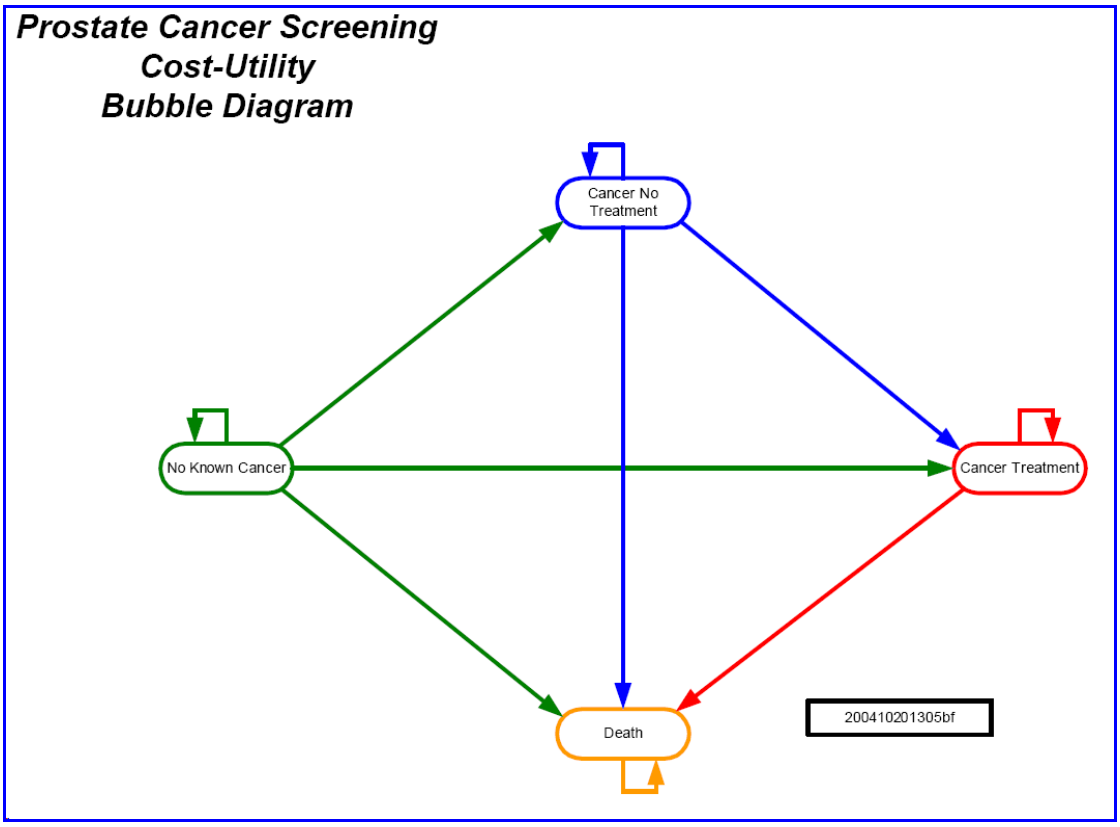


Figure 3. This bubble diagram illustrate the knowable states of nature and their relationships.

The Markov Model

The decision tree for the model is illustrated in figure 4. The Markov nodes are the decision to screen and the decision not to screen. See figure 5. The sub-trees beneath both these nodes branch into the four states of nature that the model is built upon. See figure 6. This is necessary in order to evaluate the Markov model for the four states of nature. Note that the box is the decision node, that the circles with the "M" in them are Markov nodes, that the open circles are chance nodes, and the triangles are terminal nodes. At the terminal nodes, the flow loops back to the designated state of nature.

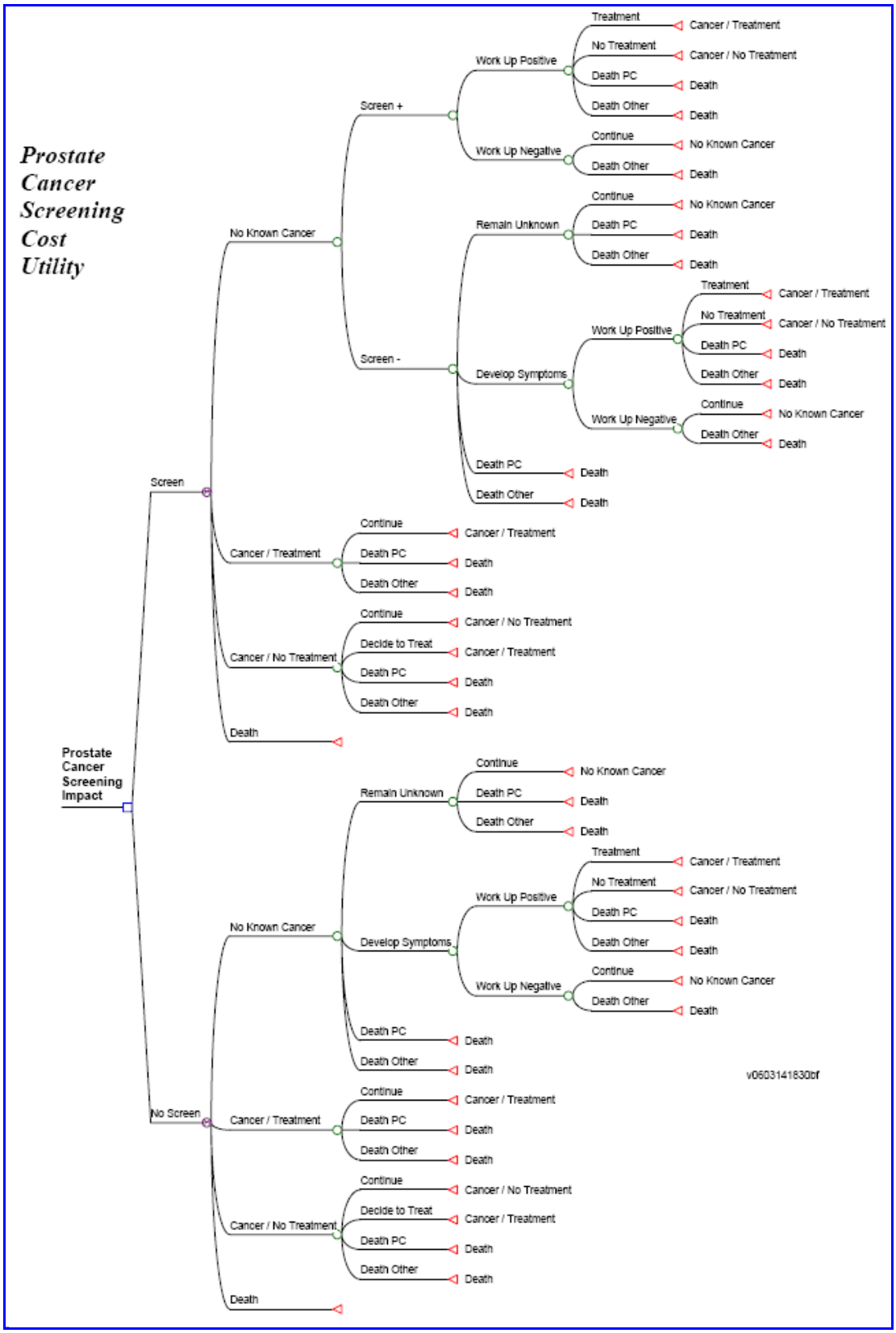


Figure 4. Cost-Comparison Markov Model.

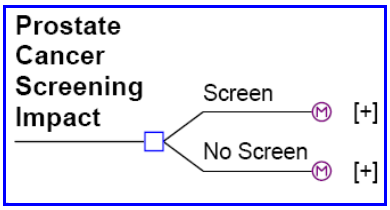


Figure 5. This is the initial decision in the model, the decision to screen or to not screen.

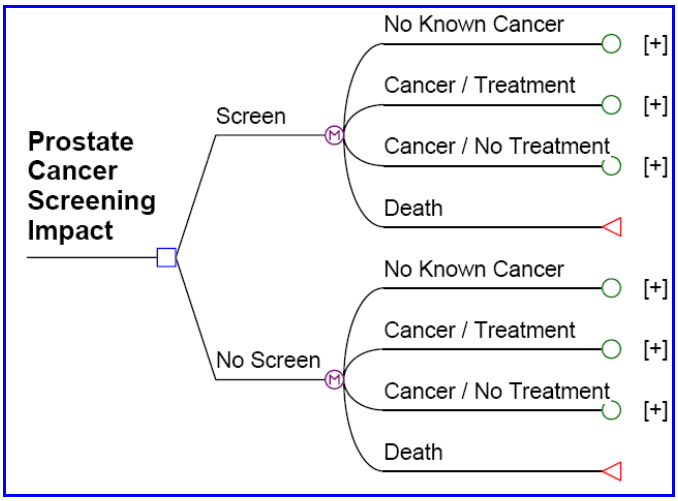


Figure 6. The states of nature are applied to each Markov node.

As illustrated in Figure 7, the branches from the nodes "Cancer/No Treatment" and "Cancer/Treatment" are identical for both "Screen" and No Screen" Markov nodes. A difference occurs in the "Screen/No Known Cancer Node." The node branches into "Screen +" and Screen -." See Figure 8. The "No Screen/No Known Cancer Node" and the "Screen/No Known Cancer Node/Screen -" have identical sub-trees which include "remain unknown," "develop symptoms," "death PC," and "death other." This is illustrated in Figure 9. In Figure 10 the "work-up" sub-branches are highlighted. These branches are a result of either screening positive or developing symptoms. Finally, the sub-tree displayed in Figure 11 is the portion of the model where the effect of screening

occurs.

Costs occur at the screening nodes, work-up nodes, and the treatment nodes. One cycle of the model is equivalent to one year elapsing. The analysis occurs over 35 years, ages 50 to 85. The reason the model ends at 85 years is that the data was not available to extrapolate the table used in the TreeAge® software.

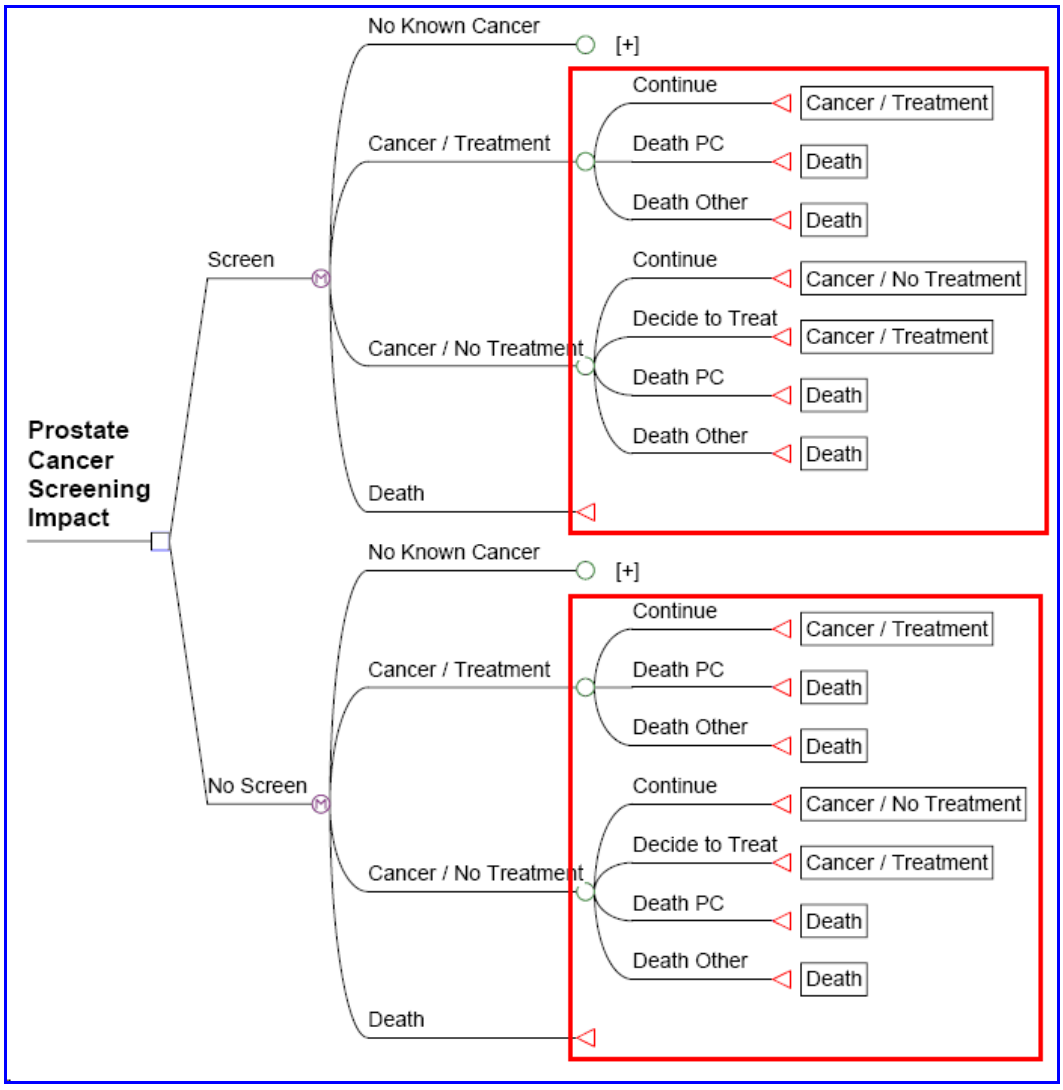


Figure 7. The sub-trees of Cancer/Treatment and Cancer/No Treatment are identical for both alternatives.

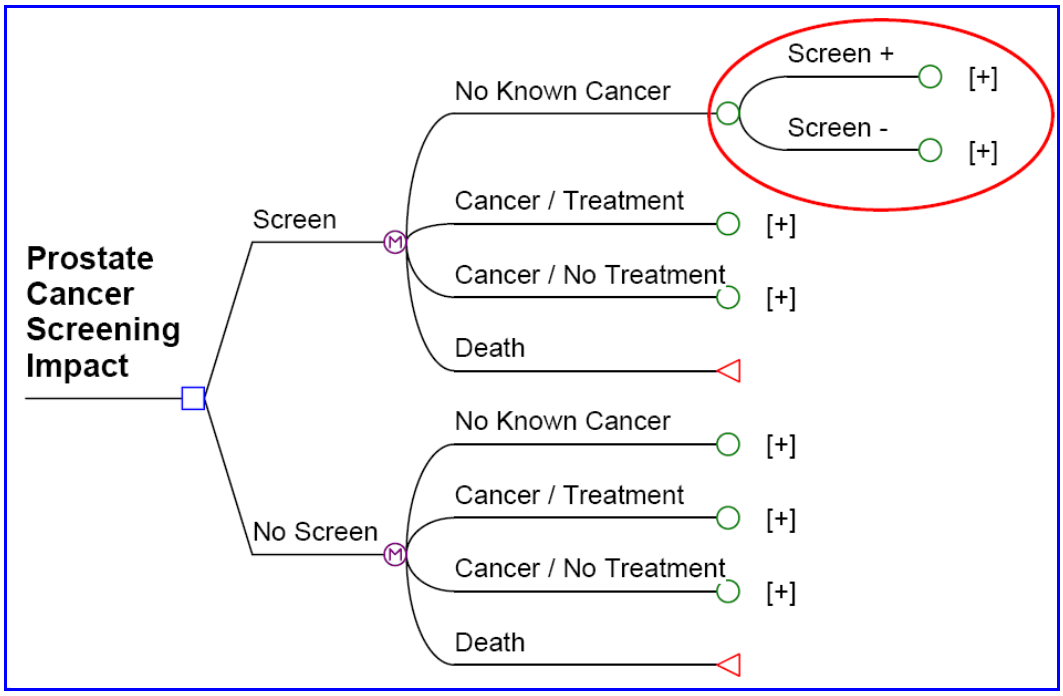


Figure 8. This figure illustrates the major difference in the sub-trees of the Markov nodes. The Screening chance node only exists in the Screen decision branch.

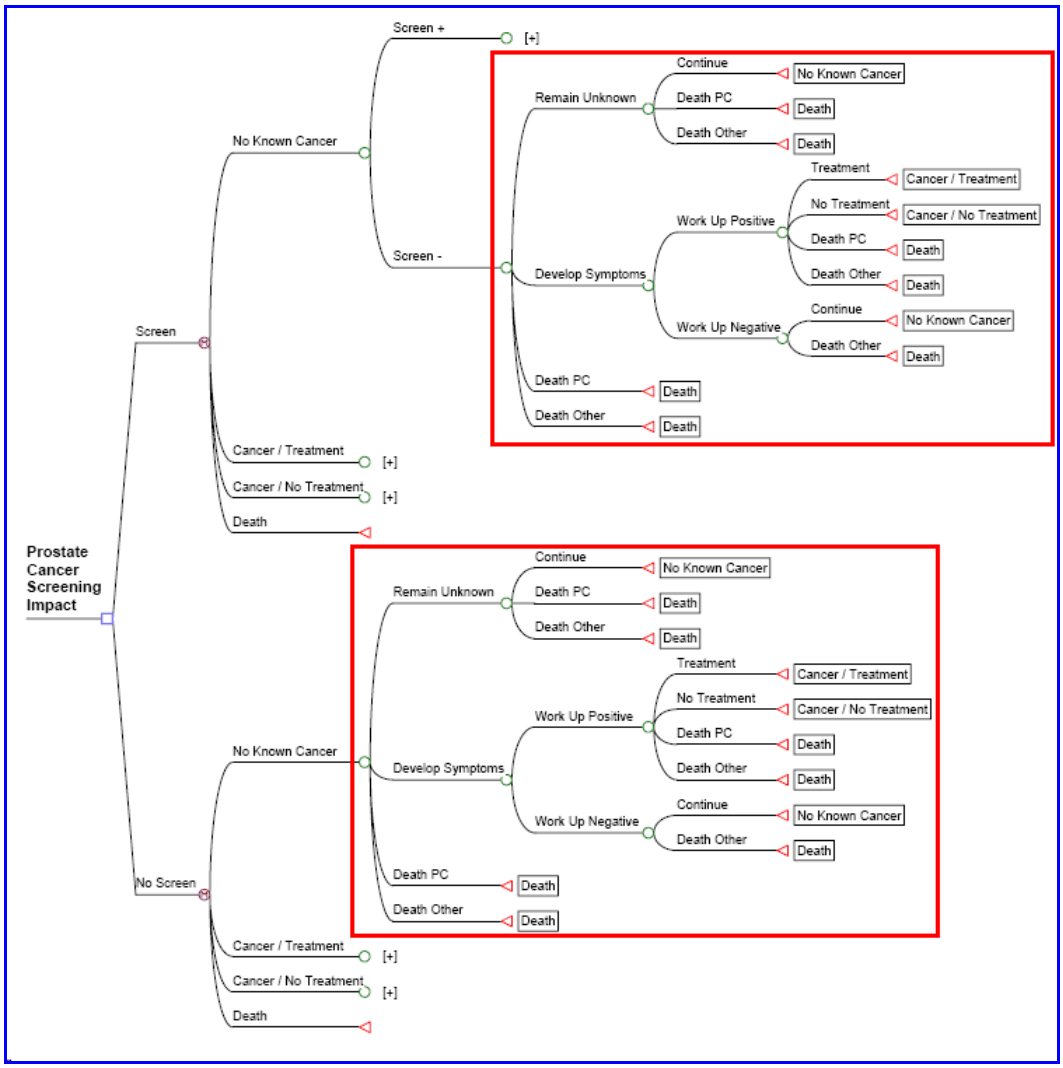


Figure 9. This figure illustrates the similarities in the sub-trees where the model is depending on symptoms to identify disease.

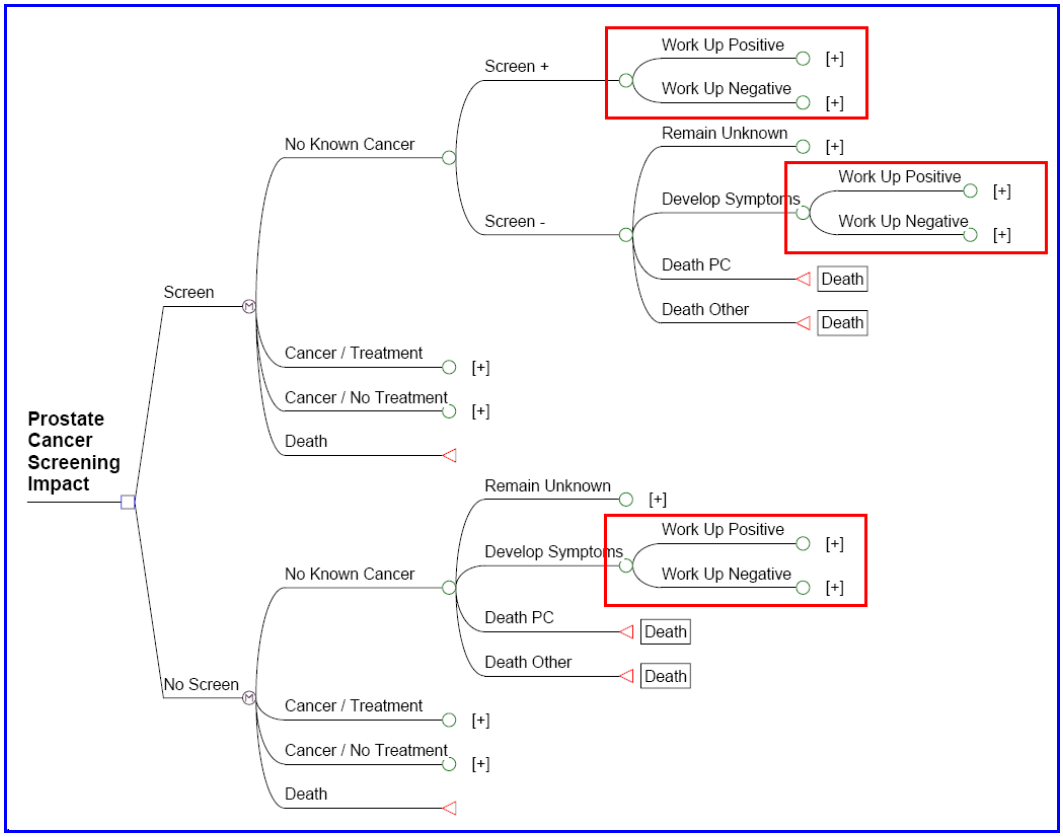


Figure 10. At these nodes in the model another similarity is found. The sub-trees at this level are focused on the results of the diagnostic work-up.

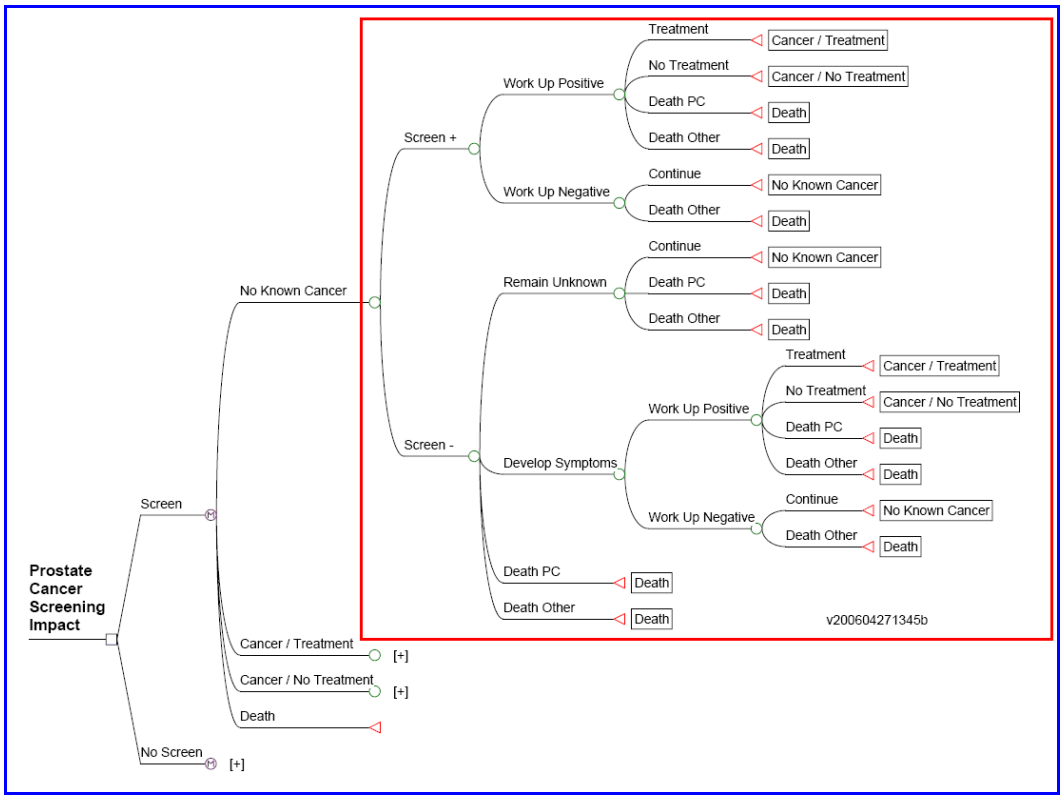


Figure 11. This figure details the branches for the state of nature of No Known Cancer of the decision node Screen.

Model Inputs

Incidence of Prostate Cancer

The incidence rates were obtained from the SEER database.[56] Table 4 contains the data obtained from the SEER database. The incidence rate changes with age. A table was used in the model in order to facilitate the changes in incidence as the cohort aged. The age-conditional probabilities of developing prostate cancer[57] in the table used in the model were extrapolated for each year by use of the hazard function. (See Appendix Bamd C.)

Table 4
SEER 13 Registries Incidence and Mortality (2004 Submission): Probability of Developing Prostate Cancer

Age Range	Probability of Developing Cancer
50 - 55	0..00765
55 - 60	0.01760
60 - 65	0.03051
65 - 70	0.04570
70 - 75	0.05396
75 - 80	0.05413
80 - 85	0.04582

Death Rates

Table 6 and Table 7contain each probability that someone entering the age group

at the lower age died before getting to the next age group. The data was obtained from the SEER data base. The overall death rates are in Table 7. The data for overall death rates came from the CDC mortality databases. Both tables list probabilities. The age-conditional probabilities of dying of prostate cancer[58] in the table used in the model were extrapolated for each year by use of the hazard function. (See Appendices B and C.) Being an incidence rate for the various age intervals, the overall probabilities of death in the analysis were extrapolated by an even distribution across the interval. The death rate for other causes was determined by subtracting the probability of dying from prostate cancer from the overall probability of death for that age interval.

Table 5.
SEER 13 Registries Incidence and Mortality (2004 Submission): Prostate Cancer Mortality Probability

Age	Probability of Dying of Prostate Cancer
50 - 54	0.00016
55 - 59	0.00046
60 - 64	0.00113
65 - 69	0.00245
70 - 74	0.00481
75 - 79	0.00875
80 - 84	0.01482

Table 6.
Overall Death Rate From All Causes

Age	Overall Probability of Death
50 - 54	0.006535
55 - 59	0.009618
60 - 64	0.014760
65 - 69	0.022659
70 - 74	0.035330
75 - 79	0.055227
80 - 84	0.086528

Other Inputs

The incidence of BPH was taken from Table 2, Incidence of LUTS/BPH. The data in this table is the incidence rate across the age intervals and is survival adjusted. The incidence rates of LUTS/BPH in the analysis were extrapolated across the intervals using the hazard function. (See Appendices B and C.) The screening cost was set at $25.70, the first year treatment cost was set at $11,000.00, the diagnostic work-up (biopsy) was set at $900.00, and the sensitivity and the specificity of the PSA test were 0.8 and 0.7, respectively. The initial values and the equations used to obtain the probabilities and payoffs within the decision tree are in Appendix A and Appendix B. The ranges used in the Markov sensitivity analyses are in Table 8.

Table 7.
Range of Values by Variable Used in the Sensitivity Analyses

Variable	Low	High
First Year Treatment Costs	11000	50000
Incidence Rate of Prostate Cancer	0.001	0.02
Treatment Factor	0	1
PSA Sensitivity	0.8	1.0
PSA Specificity	0.7	1.0

The "Treatment Factor" is introduced to simulate the relationship of the expected costs between "screening" and "not screening." The "Treatment Factor" (TF) is a multiplier that forces the first year treatment costs for "screening" to 0 as the first year treatment costs for "not screening" goes to double its original value. The assumption behind the TF is that if through screening more organ confined disease is found and the morbidities are decreased, then the first year treatment costs will be lower for screening than the first year treatment costs of without screening.

The incremental cost-effectiveness ratio (ICER) is the ratio of the difference in costs divided by the "willingness to pay" amount. The "willingness to pay" amount is $50,000. The ICER in this model is calculated by subtracting the "roll-back" cost associated with "no screen" from the "roll-back" cost associated with "screen," then divided by $50,000.

RESULTS

Baseline Analysis

Beginning at the baseline values listed in Appendix A and progressing through the Markov analysis using the changes due to age as listed in Appendix B, the results are listed in Table 9 and displayed in Figure 12. Utilities were not considered in this portion of the analysis. The Markov optimal cost was $252 which was the rollback amount for not screening. The screening cost was greater than the no screen cost at $10,717.

Table 8.
Markov Results

Decision	Rollback Cost
Screen	$10,717
Not Screen	$252

A Monte Carlo simulation was undertaken. The cohort was made up of 2,000,000 men from age 50 to 85 years. 1,000,000 men were screened and 1,000,000 men were not screened. The mean and standard deviation of the cost of those screened were $10,713 and $4,556, respectively. The mean and standard deviation of the cost of those not screened were $254 and $713, respectively. An analysis of variance was conducted on the data from the simulation. The F statistic was 5145997.2 with a significance of 0.000.

The distributions of screening and no screen are illustrated in graphs 1 and 2, respectively. The distribution of screening is slightly skewed, where as the distribution for not screening is strongly skewed.

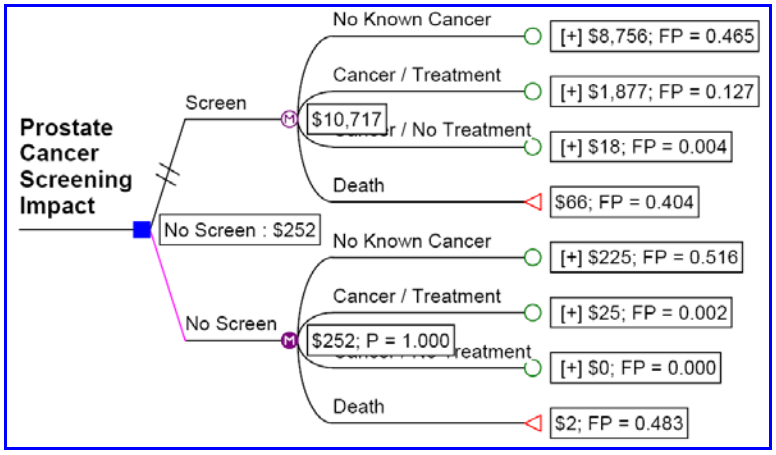
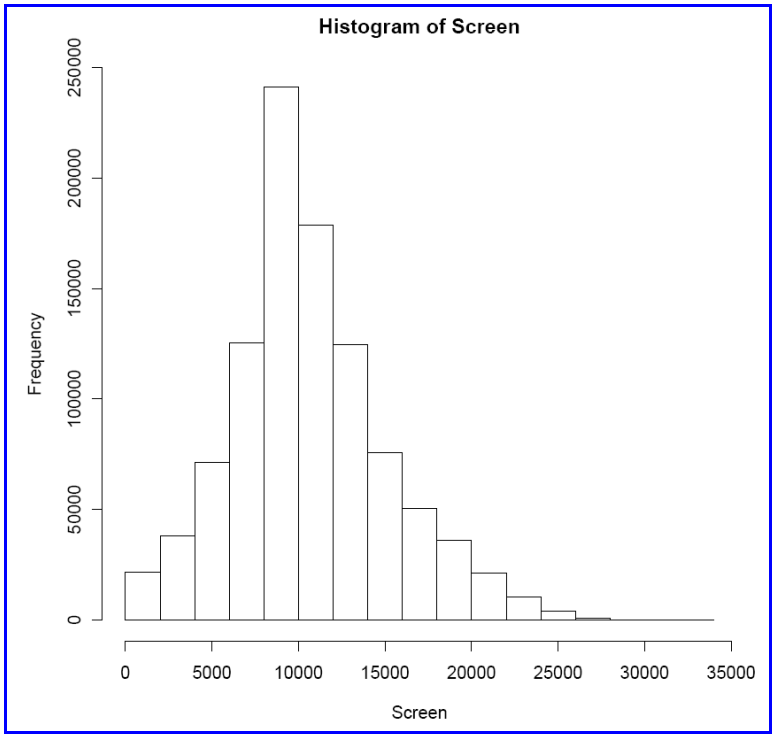
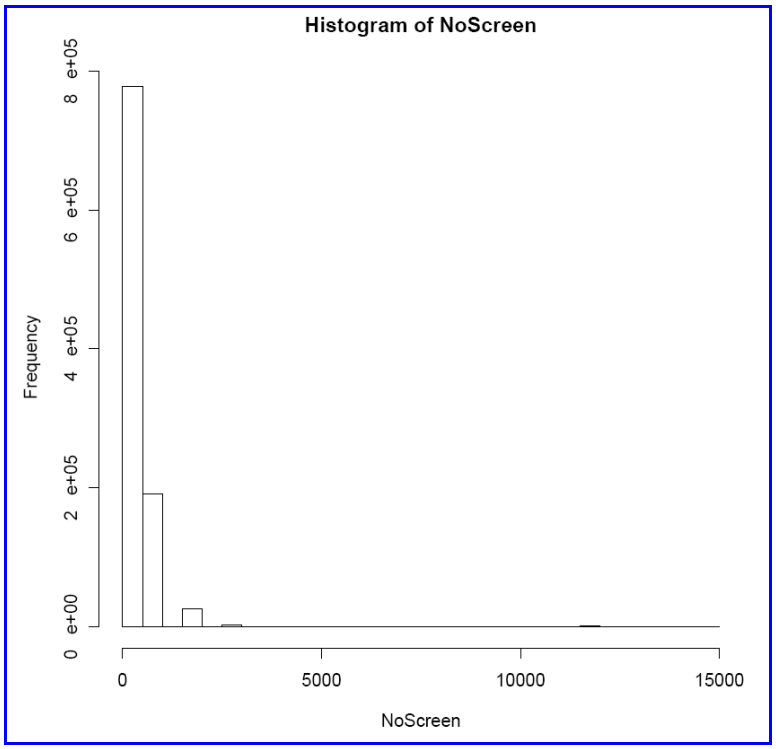


Figure 12. The Markov analysis roll-back indicates that at baseline, not screening is less costly. The “P = 1.000" is the probability of choosing “No Screen.”



Graph 1. Histogram of the cost per person results of the Monte Carlo simulation associated with screening by the frequency of occurrence of that cost for a Cohort of 1,000,000 Males.



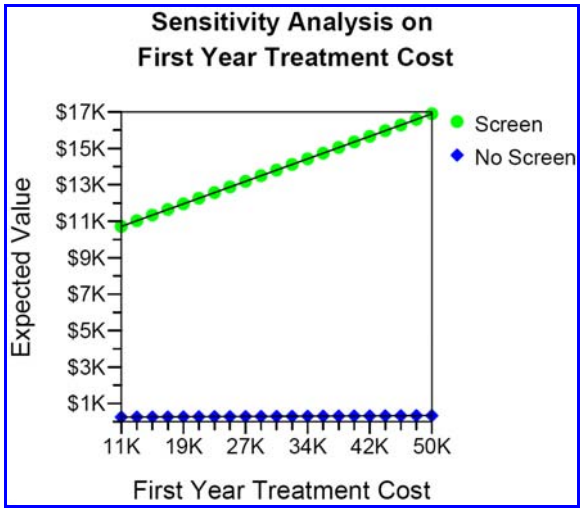
Graph 2. Histogram of the cost per person results of the Monte Carlo simulation associated with not screening by the frequency of occurrence of that cost for a Cohort of 1,000,000 Males.

One-Way Sensitivity Analyses

One-way sensitivity analyses were performed to explore the parameters that have an effect on the cost per person in the model. The sensitivity of the first year treatment costs (FYTC) was analyzed by increasing this cost incrementally from $11,000 to $50,000. The assumption here is that as the First Year Treatment Costs increase, the effect of the costs of screening and work-up is diminished. Table 10 and Graph 3 display the results. The resulting change in costs by alternative increased at different rates. The costs per person associated with screening rose from $10,717 to $16,896 and the costs per person associated with not screening rose from $252 to $335.

Table 9.
First Year Treatment Costs by Screening Associated Costs and Not Screening Associated Costs

FYTC	Screen	No Screen
11000	10717	252
12950	11026	256
14900	11335	260
16850	11644	264
18800	11953	268
20750	12262	273
22700	12571	277
24650	12880	281
26600	13189	285
28550	13498	289
30500	13807	293
32450	14115	297
34400	14424	302
36350	14733	306
38300	15042	310
40250	15351	314
42200	15660	318
44150	15969	322
46100	16278	326
48050	16587	330
50000	16896	335

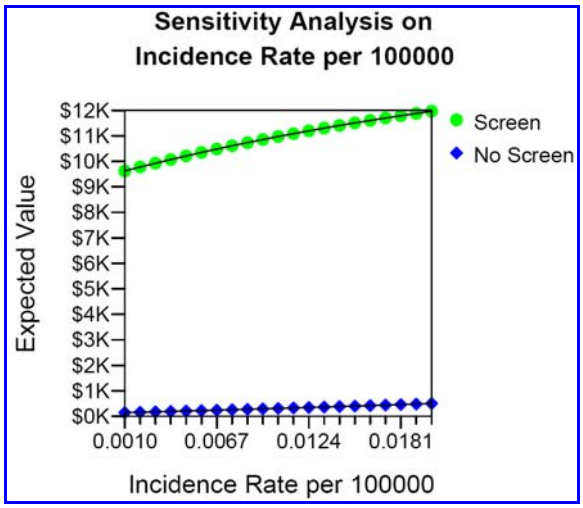


Graph 3. This is a graph of the of increases in first year treatment costs by the expected value of the total costs of screening and not screening.

Next, the sensitivity to increases in the incidence rate (IR) in terms probabilities were analyzed. If the IR is increased then it is assumed again that the increased treatment costs could reduce the effect of the screening and work-up costs. The IR was increased incrementally from 0.001 to 0.020. Table 11 and Graph 4 display the results. The resulting change in costs by alternative increased at different rates. The costs per person associated with screening rose from $9,847.43 to $12,200.10 and the costs per person associated with not screening rose from $150.79 to $517.25.

Table 10.
Incidence Rate expressed as a probability by Screening Associated Costs and Not Screening Associated Costs

IR	Screen	No Screen
0.00100	9621	145
0.00195	9775	160
0.00290	9925	176
0.00385	10070	192
0.00480	10211	207
0.00575	10348	224
0.00670	10480	240
0.00765	10609	257
0.00860	10734	274
0.00955	10855	292
0.01050	10972	309
0.01145	11086	327
0.01240	11196	346
0.01335	11302	364
0.01430	11406	383
0.01525	11506	402
0.01620	11603	421
0.01715	11697	441
0.01810	11788	461
0.01905	11877	481
0.02000	11962	502

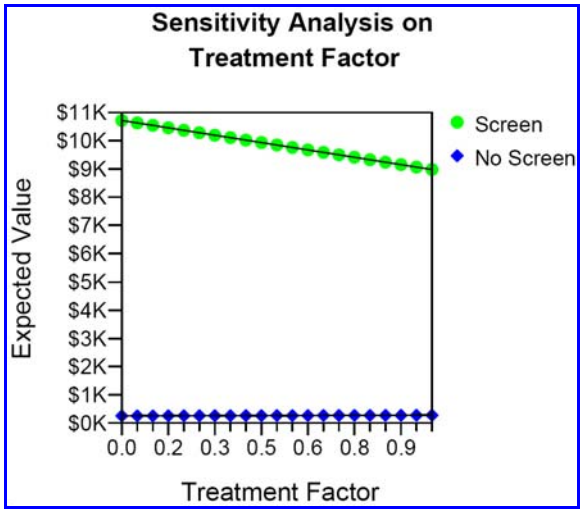


Graph 4. This is a graph of the of increases in incidence rates expressed as probabilities by the expected value of the total costs of screening and not screening.

The sensitivity of the treatment factor (TF) explores the effect of lowering the FYTC for screened persons at the same time increasing the FYTC for persons not screened. In effect the "screened" FYTC goes to zero as the "not screened" FYTC doubles. This assumes treatment cost would be lower if the disease is discovered earlier. The TF was increased incrementally from 0 to 1. Table 12 and Graph 5 display the results. The costs per person associated with screening declined from $10,717 to $8,974 and the costs per person associated with not screening rose from $252 to $275. There was no convergence before the FYTC of the costs associated with screening reached $0.00.

Table 11.
Treatment Factor by Screening Associated Costs and Not Screening Associated Costs

TF	Screen	No Screen
0.00	10717	252
0.05	10630	253
0.10	10543	254
0.15	10456	255
0.20	10368	257
0.25	10281	258
0.30	10194	259
0.35	10107	260
0.40	10020	261
0.45	9933	262
0.50	9846	264
0.55	9758	265
0.60	9671	266
0.65	9584	267
0.70	9497	268
0.75	9410	269
0.80	9323	271
0.85	9236	272
0.90	9148	273
0.95	9061	274
1.00	8974	275

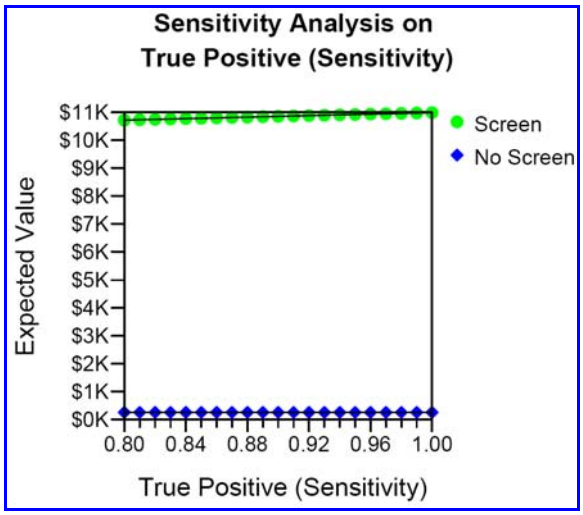


Graph 5. This is a graph of the of increases the treatment factor, that forces the costs associated with screening to zero and the costs associated with not screening to double, by the expected value of the total costs of screening and not screening.

The next sensitivity analyses is that of an improving PSA test sensitivity (TP). The sensitivity of a diagnostic test is the ratio of those that test positive and have the disease to the total of those that have the disease.[59] The true positive ratio was increased incrementally from 0.8 to 1.0. Table 13 and Graph 6 display the results. The costs per person associated with screening rose from $10,717 to $10,986, and the costs per person associated with not screening remained at $252.

Table 12.
True Positive by Screening Associated Costs and Not Screening Associated Costs

TP	Screen	No Screen
0.80	10717	252
0.81	10731	252
0.82	10745	252
0.83	10758	252
0.84	10772	252
0.85	10786	252
0.86	10799	252
0.87	10813	252
0.88	10826	252
0.89	10840	252
0.90	10853	252
0.91	10867	252
0.92	10880	252
0.93	10894	252
0.94	10907	252
0.95	10920	252
0.96	10933	252
0.97	10947	252
0.98	10960	252
0.99	10973	252
1.00	10986	252



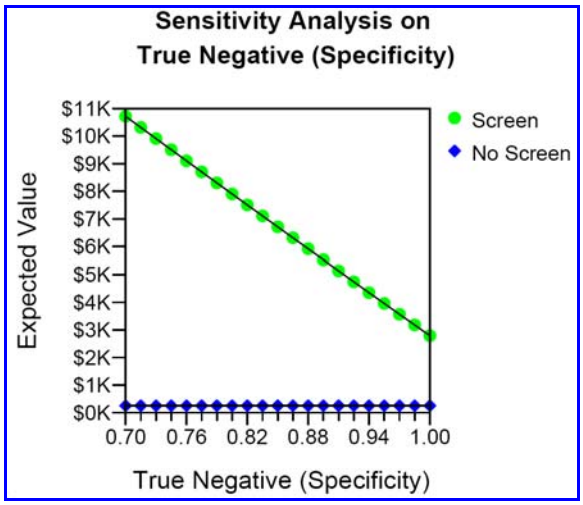
Graph 6. This is a graph of the of improvements in sensitivity of the screening test by the expected value of the total costs of screening and not screening.

The next sensitivity analyses is that of an improving PSA specificity (TN). The specificity of a lab test is the percentage of those that test negative and do not have the disease compared to the total of those that do not have the disease.[60] The true negative ratio was increased incrementally from 0.7 to 1.0. Table 14 and Graph 7 display the results. The costs per person associated with screening declined from $10,971.73 to $2,882.30 and the costs per person associated with not screening remained $261.75. There was no convergence before the TN reached 100%.

Table 13.
True Negative by Screening Associated Costs and Not Screening Associated Costs

TN	Screen	No Screen
0.700	10717	252
0.715	10312	252
0.730	9909	252
0.745	9506	252
0.760	9104	252
0.775	8703	252
0.790	8303	252

TN	Screen	No Screen
0.805	7903	252
0.820	7505	252
0.835	7107	252
0.850	6710	252
0.865	6314	252
0.880	5919	252
0.895	5525	252
0.910	5131	252
0.925	4739	252
0.940	4347	252
0.955	3956	252
0.970	3566	252
0.985	3176	252
1.000	2788	252



Graph 7. This is a graph of the of improvements in specificity of the screening test by the expected value of the total costs of screening and not screening.

Incremental Cost-Effectiveness Ratio

The incremental cost-effectiveness ratio calculation can describe the relationship between the utilities of the alternatives. The ICER is the difference in costs of the

alternatives divided by the differences in the utilities/effectiveness. The benchmark for the ICER is the amount that we are willing to pay for an additional QALY, or in other words the "willingness-to-pay" (WTP) amount for an additional QALY. The ICER is an important measure of medical ethics. It defines whether we ought to do something or not. With respect to this two-alternative model, the equation for the ICER is Figure 13. A corollary to this is illustrated in Figure 14. The difference between the effectiveness of one alternative and another is equal to the ratio of the cost difference to the WLP amount.

$$ICER = \frac{Cost_2 - Cost_1}{Effectiveness_2 - Effectiveness_1}$$

Figure 13. ICER Calculation

$$Effectiveness_2 - Effectiveness_1 = \frac{Cost_2 - Cost_1}{WTP}$$

Figure 14. Calculation of expected utility/effectiveness differences.

The differences in costs divided by the WTP in this model, before adjustments in any of the parameters, would be $\frac{\$10{,}717 - \$252}{\$50{,}000}$ or 0.209. Hence, the difference in the utilities/effectiveness must be greater than 0.209 in order to facilitate the ICER to be less than the WLP. An improvement in a parameter should lower this target ratio. It is anticipated that if the differences in costs are reduced, then this ratio decreases and the cost-effectiveness improves. In the sensitivity analysis of the treatment factor (TF), the cost per person of "screen" is $8,974 and the cost per person of "no screen" is $275. The ratio of cost difference to WTP is 0.174. The most significant parameter change is the improvement in the specificity of the PSA. the cost per person of "screen" is $2,788 and

the cost per person of “no screen” was $252. The ratio of cost difference to WTP is 0.051. As the utilities improve the cost difference to WTP improves making screening more cost-effective.

CONCLUSION AND DISCUSSION

Conclusion

At baseline, screening costs more than not screening. The estimates of cost and probabilities are conservative. With respect to the parameters examined in the model, marked improvement in all of them is required to facilitate a cost-effective case for screening. If in the future, as a result of the research currently being conducted in Europe it can be shown that the utilities are sufficiently higher, the first year treatment costs sufficiently lower, and the PSA specificity is sufficiently improved with respect to screening, then the cost-utility of screening would indicate that screening is the course of action.

Discussion

Prostate cancer is expensive. Prostate diseases in general are just about guaranteed if a man lives long enough. In the case of prostate cancer, a significant amount of the countries wealth is spent on this disease.

The screening and diagnostic procedures employed in the diagnosis of prostate cancer are not perfect. Using the example of the screened 1,000,000 man cohort and a PSA sensitivity of 0.8, at age 50 there were 307 false negatives, or men that have prostate cancer, but screened negative. Again using the cohort, there were 299,540 that screened positive when they didn't have the cancer. The costs associated with screening come

from the fact that the next step in the process is to have a biopsy. This means that 300,000 biopsies would be performed unnecessarily. In addition, if the sextant biopsy is performed, there are problems with its sensitivity, i.e. some false negatives.

An interesting point is the differences in thinking about treatment. Because all of the treatment modalities carry devastating complications, not all men are willing to be treated. Some elect to do "watchful waiting." This does not mean that they do nothing. They are followed via additional screening, biopsies, MRI, CT scans, etc.

The three groups that provide guidelines for screening, the American Cancer Society, the University of Michigan Health System, and the U.S. Preventive Services Task Force have different guidelines for screening. Only the American Cancer Society recommends routine annual screening. There is agreement that a man age fifty or greater should be educated about screening and its implications, both good and bad.

The data used in the model were conservative. $900 for the work-up cost only included the biopsy. Many times MRI and CT are included in the work. Sometime multiple biopsies are performed. The specificity and the sensitivity of the PSA test used in the model are the maximums reported. They vary by age, race, national origin, and ethnicity.

The model lends itself to further study. The model is set up to accept data from future research results. As the sensitivity and specificity of the screening test changes, the parameters in the model can be altered. The current optimal sensitivity and specificity for the PSA test were used in the model. The model was constructed to accommodate differences in these parameters for age. A utility function that considers the "willingness-to-pay" amount can easily be adapted. Cost-effectiveness can easily be extracted from the analysis. The model centers around age in men. However, the model

is also adaptable to high-risk groups of men who are differentiated by race, ethnicity, or national origin. The may be a better use of the model.

The results demonstrate that parameter improvements can effect the differences in utilities that are necessary to facilitate a case for screening cost-effectiveness. If screening can reduce the morbidities and mortality and thus reduce the cost of treatment, then the difference in utilities can be lower. It is demonstrated that the improvement in the screening test specificity can reduce the difference target by a large amount. In fact, improving specificity is the single best method of reducing the need for a large effectiveness difference. The most concrete conclusion that can be made is that screening costs more than not screening. Due to the unnecessary biopsies and work-ups, the costs are significantly different.

The cost-utility of prostate screening is questionable. The incremental cost-effectiveness can be improved by three things. The cost of treatment is going to have to be significantly lower for those that are screened. The specificity of screening must improve significantly. And, the utilities/QALYs for those screened will have to be higher than the utilities/QALYs for those not screened. Because of the negative outcomes of screening, this may or may not be the case. The European Randomized Study of Screening for Prostate Cancer will have data available to ascertain this information. In the absence of good outcome data, It may come down to a medically ethical or a moral decision to screen.

Limitations of Study

At this point, the only thing that is for certain is that screening costs more; the rest of the model is speculation. Without the outcomes data necessary to complete the analysis, the analysis merely sets goals for the data. Also, the actual data used in the model is conservative. The specifications for the utilities, the specificity, and the treatment costs are probably much tighter. The analysis does not take into consideration that the PSA specificity varies by age, race, and ethnicity. It is assumed in the model that cost will be lower for those that are screened. The literature shows that because one will probably die of something else before dying of prostate cancer, the lower cost of treatment may never be realized. With respect to the utilities, it is assumed that the large contingent of the cohort that is false positive and undergoes biopsy will continue to rate the utilities high. Good outcome and utility data will improve the integrity of the conclusions drawn from this model.

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Appendix A

Variable Definition Table

Name	Description	Formula	Value
Age	Age	_stage+SA	50
BPHS	BPH Symptom Incidence Rate	tPP[Age;7]	0.001386
CT	Completed Treatment Counter		0
DO	Death Rate All Other	tPP[Age;5]	0.001343
DP	Death Rate Prostate Cancer	tPP[Age;4]	0.000032
FN	False Negative	1-TP	0.2
FP	False Positive	1-TN	0.3
FYTC	First Year Treatment Cost		11,000
IR	Incidence Rate per 100000	tPP[Age;1]	0.001535
Neg	Negative Screen	((FN*IR)+(TN*(1-IR)))	0.699233
NT	No Treatment Rate	(1-DP-DO)*0.119	0.118844
NT1	No Treatment (1)	(1-DP-DO)/2	0.499347
Pos	Positive Screen	((TP*IR)+(FP*(1-IR)))	0.300767
SA	Starting Age		50
SC	Screening Cost	tPP[Age;6]	25.7
SDR	Symptom Development Rate	BPHS+(IR*0.5)	0.002153
TCN	Treatment Cost (No Screen)	FYTC+(TF*FYTC)	11,000
TCS	Treatment Cost (Screen)	FYTC-(TF*FYTC)	11,000
TF	Treatment Factor		0
TN	True Negative (Specificity)	tPP[Age;3]	0.7
TP	True Positive (Sensitivity)	tPP[Age;2]	0.8
TR	Treatment Rate	(1-DP-DO)-NT	0.879849
TR1	Treatment (1)	(1--DP-DO)/2	0.499379
WUC	Work Up Cost		900
WUNNS	Work Up Negative No Screen	(1-IR)	0.998465
WUNSN	Work Up Negative Screen Negative	(TN*(1-IR))/((FN*IR)+(TN*(1-IR)))	0.999561
WUNSP	Work Up Negative Rate Screen Positive	(FP*(1-IR))/((TP*IR)+(FP*(1-IR)))	0.995918
WUPNS	Work Up Positive No Screen	IR	0.001535
WUPSN	Work Up Positive Screen Negative	(FN*IR)/((FN*IR)+(TN*(1-IR)))	0.000439
WUPSP	Work Up Positive Rate Screen Positive	(TP*IR)/((TP*IR)+(FP*(1-IR)))	0.004082

Appendix B

Probability Table

Index	IR	TP	TN	DP	DO	SC	BPHS
50	0.001535	0.8	0.7	0.000032	0.001343	25.7	0.001386
51	0.001535	0.8	0.7	0.000032	0.001343	25.7	0.001386
52	0.001535	0.8	0.7	0.000032	0.001343	25.7	0.001386
53	0.001535	0.8	0.7	0.000032	0.001343	25.7	0.001386
54	0.001535	0.8	0.7	0.000032	0.001343	25.7	0.001386
55	0.003545	0.8	0.7	0.000092	0.002024	25.7	0.002618
56	0.003545	0.8	0.7	0.000092	0.002024	25.7	0.002618
57	0.003545	0.8	0.7	0.000092	0.002024	25.7	0.002618
58	0.003545	0.8	0.7	0.000092	0.002024	25.7	0.002618
59	0.003545	0.8	0.7	0.000092	0.002024	25.7	0.002618
60	0.006178	0.8	0.7	0.000226	0.003198	25.7	0.003988
61	0.006178	0.8	0.7	0.000226	0.003198	25.7	0.003988
62	0.006178	0.8	0.7	0.000226	0.003198	25.7	0.003988
63	0.006178	0.8	0.7	0.000226	0.003198	25.7	0.003988
64	0.006178	0.8	0.7	0.000226	0.003198	25.7	0.003988
65	0.009312	0.8	0.7	0.000490	0.005073	25.7	0.004845
66	0.009312	0.8	0.7	0.000490	0.005073	25.7	0.004845
67	0.009312	0.8	0.7	0.000490	0.005073	25.7	0.004845
68	0.009312	0.8	0.7	0.000490	0.005073	25.7	0.004845
69	0.009312	0.8	0.7	0.000490	0.005073	25.7	0.004845
70	0.011033	0.8	0.7	0.000964	0.008160	25.7	0.006989
71	0.011033	0.8	0.7	0.000964	0.008160	25.7	0.006989
72	0.011033	0.8	0.7	0.000964	0.008160	25.7	0.006989
73	0.011033	0.8	0.7	0.000964	0.008160	25.7	0.006989
74	0.011033	0.8	0.7	0.000964	0.008160	25.7	0.006989
75	0.011068	0.8	0.7	0.001756	0.013136	25.7	0.007780
76	0.011068	0.8	0.7	0.001756	0.013136	25.7	0.007780
77	0.011068	0.8	0.7	0.001756	0.013136	25.7	0.007780
78	0.011068	0.8	0.7	0.001756	0.013136	25.7	0.007780
79	0.011068	0.8	0.7	0.001756	0.013136	25.7	0.007780
80	0.009337	0.8	0.7	0.002982	0.021145	25.7	0.006525
81	0.009337	0.8	0.7	0.002982	0.021145	25.7	0.006525
82	0.009337	0.8	0.7	0.002982	0.021145	25.7	0.006525
83	0.009337	0.8	0.7	0.002982	0.021145	25.7	0.006525
84	0.009337	0.8	0.7	0.002982	0.021145	25.7	0.006525

Appendix C

Equation Used In Extrapolation

For developing prostate cancer:	p(developing disease that year) = 1 - (1 - p(developing the disease by the 5^{th} year)) ^ 0.2)
For dying from prostate cancer:	p(dying from the disease that year) = 1 - (1 - p(dying from the disease by the 5^{th} year)) ^ 0.2)
For dying from another cause:	p(dying from another cause that year) = 1 - ((1 - p(dying from any cause by the 5^{th} year) - (dying from the disease by the 5^{th} year)) ^ 0.2)
For developing LUTS/BPH:	p(developing disease that year) = 1 - (1 - p(developing the disease by the 5^{th} year)) ^ 0.2)

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