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Optimization of Prostate Biopsy Referral Decisions

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Prostate cancer is the most common solid tumor in American men and is screened for using prostate-specific antigen (PSA) tests. We report on a nonstationary partially observable Markov decision process (POMDP) for prostate biopsy referral decisions. The core states are the patients' prostate cancer related health states, and PSA test results are the observations. Transition probabilities and rewards are inferred from the Mayo Clinic Radical Prostatectomy Registry and the medical literature. The objective of our model is to maximize expected quality-adjusted life years. We solve the POMDP model to obtain an age and belief (probability of having prostate cancer) dependent optimal biopsy referral policy. We also prove a number of structural properties including the existence of a control-limit type policy for the biopsy referral decision. Our empirical results demonstrate a nondecreasing belief threshold in age, and we provide sufficient conditions under which PSA screening should be discontinued for older patients. Finally, the benefits of screening under the optimal biopsy referral policy are estimated, and sensitivity analysis is used to prioritize the model parameters that would benefit from additional data collection.

Key words: partially observable Markov decision process; PSA screening; biopsy; control-limit policy; stopping time problem

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1. Introduction

Prostate cancer is the most common solid tumor in American men. The American Cancer Society (2010b) estimated that 217,730 new cases of prostate cancer would be diagnosed, and 32,050 deaths would occur in the United States in 2010. At its current level of prevalence, it is estimated that 16% of men will be diagnosed with prostate cancer during their lifetimes (National Cancer Institute 2009). Whereas the direct health impact is felt by men, the indirect social effects (emotional impact on a patient's family and friends) are felt by all. Therefore, prostate cancer is an important societal issue and preventive screening is an important consideration as part of the health service system.

Prostate cancer screening relies heavily on the prostate-specific antigen (PSA) test, a simple blood test that indicates the amount of PSA in the blood serum. PSA is a protein produced by the cells of the

prostate gland that varies in a continuous range. Men with a healthy prostate typically have a small amount of PSA present in the serum. PSA is often elevated in the presence of prostate cancer and in other prostate disorders. Thus, high PSA is correlated with the presence of prostate cancer. Patients with higher than normal PSA have a greater risk of prostate cancer; however, higher than normal PSA levels may occur for other reasons including natural variation over time, prostatic infections, and benign enlargement of the prostate gland. If a patient's PSA test result is classified as "suspicious," he may be referred for biopsy, which has a negligible false positive rate but a nontrivial false negative rate (about 20% according to Haas et al. 2007). In addition to providing imperfect information, biopsies are painful and carry the possibility of side effects. Therefore, from the patient's perspective, it is necessary to decide how best to use these tests to trade off the impact on quality of life

from screening with the long-term potential benefits of early detection and treatment of prostate cancer.

When should a patient be referred for a biopsy? How should a patient's age and PSA history (i.e., previous PSA test results) influence the referral decision? Surprisingly, there has been very little research on determining optimal decisions related to these questions. In this paper, we address these and other important questions related to prostate cancer screening. We focus on a population-based model and investigate biopsy referral policies that maximize a patient's expected quality-adjusted life years (QALYs). We chose QALYs as the criteria for our model because it is the most common criteria used in the medical decision-making literature to measure benefits of interventions to patients (for the examples of the use of QALYs for medical decision making, see Packer 1968, Fanshel and Bush 1970). Our model trades off the potential rewards from early detection and treatment of prostate cancer (additional QALYs) with the side effects of biopsy. To this end, we formulate a partially observable Markov decision process (POMDP) model for the biopsy referral decision process. The health states in our model are not directly observable, but can be probabilistically inferred from PSA test results and biopsy results. We use several data sources to calibrate our model including a large regional data set from Olmsted County in Minnesota.

We begin by presenting some relevant background on prostate cancer screening and a detailed mathematical formulation of our POMDP model. Next, we present several theorems illustrating generalizable insights into the structure of the optimal biopsy referral policy. For instance, we demonstrate under reasonable assumptions that the optimal biopsy referral decision follows a control-limit type policy with respect to a belief (probability of having prostate cancer) threshold. We show that the expected QALYs are nonincreasing with respect to belief, which is an important factor in computing bounds on the optimal policy. We provide conditions under which there is a finite age at which screening should be discontinued. Finally, we present empirical results for the optimal age dependent biopsy referral policy based on a data set for a large population from Olmsted County, Minnesota. Sensitivity analysis is used to identify which parameters most significantly affect the optimal biopsy policy and to provide guidance about how to prioritize further data collection through patient surveys and randomized controlled trials (RCTs) to develop more detailed future versions of our model.

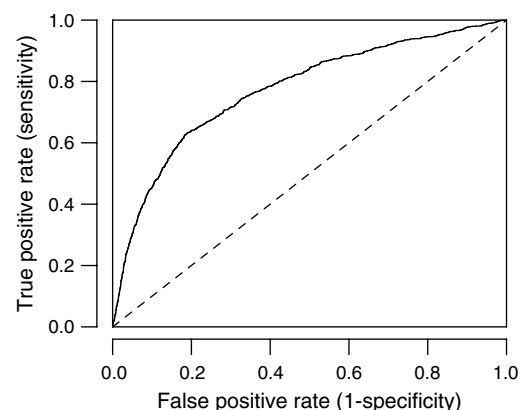
The remainder of this paper is organized as follows. Section 2 provides some background on prostate cancer. Section 3 reviews the related literature on prostate cancer screening and relevant literature on medical decision making in other contexts. Our POMDP

model is described in §4, and in §5 a number of structural properties are presented. Section 6 provides a detailed description of the data used to populate our model and presents numerical results illustrating the optimal policy and sensitivity analysis. In §7 we provide a brief synopsis of key findings, with particular emphasis on how the findings add to the current body of knowledge on prostate cancer screening. We also discuss limitations of our study and opportunities for future research.

2. Prostate Cancer Background

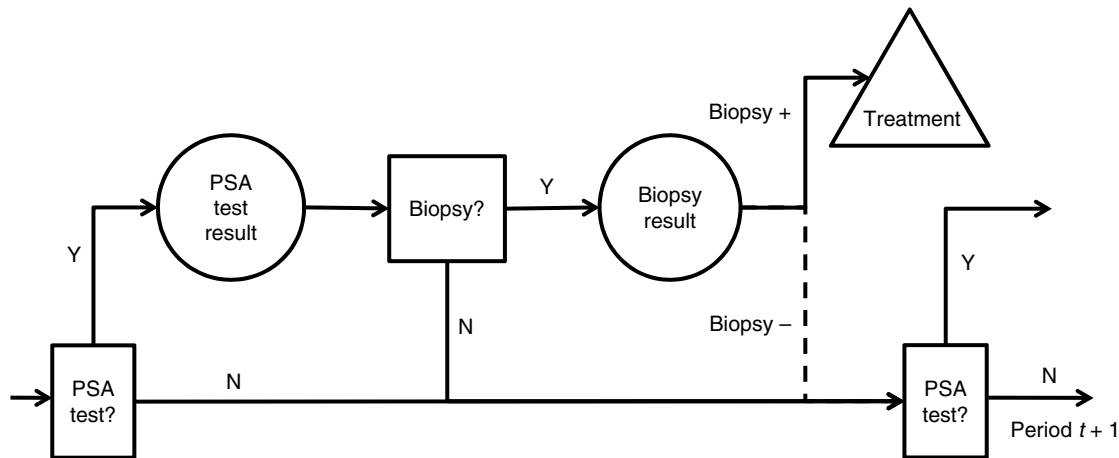
Prostate cancer is a disease in which malignant cancer cells form in the prostate gland. Because prostate tumors progress slowly, and at early stages there are usually no physical symptoms, screening with the PSA blood test is common. This blood test quantifies the amount of PSA that escapes into the blood from the prostate, measured typically in ng/mL. Patients with higher than normal PSA values have a greater risk of prostate cancer. However, a patient's PSA varies in a continuous range, and higher than normal levels may occur for a variety of other reasons. As a result, the definition of a "suspicious" test result versus a likely benign PSA test result is an open question. (Note that because PSA tests are imperfect, and PSA is a continuous measure, the term "suspicious" is used by clinicians rather than "positive" or "negative," which is common for other types of tests.) Figure 1 illustrates the imperfect nature of PSA testing using a receiver operating characteristic (ROC) curve based on our population data set described in §6.1. The ROC curve is with respect to the discrete 0/1 occurrence of prostate cancer. The area under the curve (AUC) of the ROC curve of PSA testing is 0.77. The sensitivity of a PSA test decreases and the specificity increases as the PSA threshold increases.

Figure 1 An ROC Curve That Illustrates the Imperfect Nature of PSA Tests for Diagnosing Prostate Cancer



Notes. The different points on the curve correspond to different PSA thresholds used to distinguish a suspicious and likely benign test. The curve was generated using the data set described in §6.1.

Figure 2 Illustration of the Typical Stages of Prostate Cancer Screening and Treatment Including PSA Screening, Biopsy, and Treatment



A screening process is illustrated in Figure 2 where the patient receives routine PSA tests at regular intervals (typically annually). If the test result is suspicious the patient is normally referred for biopsy, and if the biopsy indicates cancer the patient is referred for treatment. We use the dashed line in Figure 2 to represent the fact that patients with a previous negative biopsy result are considered differently from those without and may not go back to the primary screening process.

The biopsy procedure is ultrasound guided. Hollow needles are typically passed 12 times into the peripheral zone of the prostate gland to extract tissue. Each needle extricates a core of tissue to be analyzed by a pathologist. Biopsy is a fairly accurate detection method in the sense that the false positive rate is nearly zero. However, there is a non-trivial probability of a false negative biopsy, because biopsy involves sampling only a small portion of the prostate. More specifically, the sensitivity and specificity of biopsy are 0.8 and 1, respectively (Haas et al. 2007), compared to the sensitivity and specificity of 0.63 and 0.81 when, for example, the PSA threshold is 2.5 ng/mL and 0.44 and 0.91 when PSA threshold is 4 ng/mL (Inman et al. 2012). Although minimally invasive, biopsy is painful and carries nonnegligible short- and long-term risks for the patient.

The imperfect nature of the PSA test and biopsy, as well as the QALY decrements of biopsy and subsequent treatment, have raised questions about the most effective and efficient policies for prostate cancer screening. In some cases it is clearly not logical to perform such tests (e.g., screening a 90-year-old male, because his probability of dying from prostate cancer is generally much smaller than his risk of death from other competing causes such as heart disease). Furthermore, the imperfect sensitivity and specificity of the test illustrated in Figure 1 has led to criticism of the use of the PSA test for population screening

(Holmström et al. 2009) and the concern of over-diagnosis (Etzioni et al. 2002, Welch and Black 2010). The definition of a suspicious PSA test result, and the decision to refer a patient for biopsy must trade off the potential benefits from early detection with the side effects of biopsy and subsequent treatment.

Once detected with nonmetastatic prostate cancer, there are multiple options for treating prostate cancer. One option is radical prostatectomy (surgical removal of the prostate gland), which is one of the most common forms of treatment in the United States (Welch and Albertsen 2009). Other treatment options include active surveillance (monitoring prostate cancer progression through regular biopsies), brachytherapy (implantation of radioactive seeds in the prostate), external beam radiation therapy, and their combinations. All of these treatment options can have serious side effects (e.g., urinary, sexual, and gastrointestinal dysfunction), which impact the patient's future long-term quality of life. In the case of active surveillance, which has become more common in recent years, the patient may be subjected to hormone therapy and multiple future biopsies. In general, the disutility of a biopsy implies that it is optimal for the patients to get treated in some way if the biopsy result is positive.

In summary, there are many decisions involved in the design of screening and treatment policies for prostate cancer. These are complicated by the probabilistic progression of prostate cancer and the imperfect nature of the tests used to detect it. There have been recent advances in data collection and analysis for the progression of prostate cancer and its relationship to the biomarker PSA (see §3). There is also a growing literature on the study of treatment effects using RCTs. However, as we point out in the next section, the optimal policies for whether and when to biopsy, the topic of this paper, are not yet well understood. To our knowledge, ours is the first optimization study of prostate cancer screening that explicitly

treats the imperfect nature of PSA tests and prostate biopsies.

3. Literature Review

The medical community has recently focused considerable attention on the use of PSA tests for prostate cancer screening. The majority of family physicians and urologists in the United States use PSA tests to screen their patients, commonly initiating annual screening at age 50 (Woolf and Rothenich 1999). However, recently some have suggested that PSA screening should not be done routinely because it can result in unnecessary biopsies, potential harm to the patient, and increased treatment costs. The U.S. Preventive Services Task Force (2008), for instance, recommended a guideline for prostate cancer screening, stating that people older than 75 years should not be screened. The guideline made no specific recommendation for people younger than 75 years, citing insufficient evidence. Another guideline, from the American Urological Association (2009), recommended PSA screening starting at age 40, followed by future screening intervals based on previous results. A summary of current guidelines is provided in Table 1.

There have been a number of recent studies of the value of PSA screening for detecting prostate cancer (often with conflicting conclusions). Fall et al. (2007) evaluated the accuracy of changes in PSA as predictors of lethal prostate cancer outcomes. They analyzed a cohort of men with localized prostate cancer and found that PSA is a poor predictor of the number that will develop lethal cancer. The use of PSA kinetics (velocity or doubling time) instead of or combined with PSA in predicting the presence of prostate cancer is controversial. Some recent papers (Vickers et al. 2011, Inman et al. 2012) found that the PSA level is better than PSA velocity or doubling time in terms of predicting the presence of cancer. The controversy over PSA screening continued when the results of two large clinical trials were

reported in 2009. The U.S. Prostate, Lung, Colorectal, and Ovarian Cancer Screening Trial (Andriole et al. 2009) concluded that screening does not reduce mortality. On the other hand, the European Randomized Study of Screening for Prostate Cancer (ERSPC) Trial (Schröder et al. 2009) provided evidence of benefits from PSA screening, concluding that PSA screening reduced prostate cancer mortality by approximately 20%. Each of these studies reported serious problems in terms of bias calling into question the results of the trials (Barry 2009).

Uncertainty also exists about the optimal frequency of screening over the course of a patient's lifetime. van der Crujsen-Koeter et al. (2003) performed an RCT comparing screened and unscreened patients as part of the ERSPC. They concluded that sensitivity of the PSA test is high, and PSA testing detects the majority of cancer cases. Roobol et al. (2007) compared the incidence of prostate cancer between a Swedish and Dutch population that were screened at two-year and four-year intervals, respectively. They found no statistically significant difference in the incidence rate, suggesting that both screening intervals were of equal merit from a health outcomes perspective.

Some authors have developed simulation models to evaluate alternative prostate cancer screening policies. Ross et al. (2000) report on a simulation model to compare simple strategies (e.g., no screening, and screening intervals of one, two, and five years) based on performance measures including the number of PSA tests per 1,000 men and prostate cancer deaths prevented. Their model is based on a Markov process for progression of the disease. They consider two competing criteria, prostate cancer deaths prevented per 1,000 men and number of PSA tests per 1,000 men. Etzioni et al. (2008) used a simulation model to attempt to determine if declines in advanced stage prostate cancer can be attributed to PSA screening. They concluded that PSA screening has contributed in part to declines in incidence and resulting mortality.

The prostate biopsy process has received some attention in the operations research literature. For instance, the physical placement of needles based on imaging information is an important and complex decision that is part of the overall screening process. Haas et al. (2007) estimated the diagnostic accuracy of needle biopsy, to be approximately 80%. Sofer et al. (2003) studied the optimal number of samples, and placement of the individual needles. They formulated and solved a nonlinear integer programming problem to determine optimal placement of needles assuming the objective was to maximize the probability of cancer detection.

A wide range of operations research methodologies have been applied to modeling of disease screening decisions. For example, Lee and Pierskalla (1988)

Table 1 Comparisons of Published PSA Screening Guidelines

Guidelines	PSA cutpoint for biopsy
American Urological Association (2009) —Age adjusted	>4 ng/mL
American Urological Association (2009) —Age specific	40–50 >2.5 ng/mL 50–60 >3.5 ng/mL 60–70 >4.5 ng/mL 70+ >6.5 ng/mL
U.S. Preventive Services Task Force (2008)	<75: No recommendation; ≥75: Do not screen
American Cancer Society (2010a)	No routine screening recommended
European Association of Urology Guidelines (Aus et al. 2005b)	>3 ng/mL

proposed a mathematical programming model for contagious diseases with little or no latent periods. The objective was to minimize the average number of infected people in the population. The model was converted to a knapsack problem. The authors showed that the optimal screening policy has equally spaced screening intervals when the tests have perfect reliability. Schwartz et al. (1990) improved the performance of testing strategies for screening blood for the HIV antibody, and making decisions affecting blood donor acceptance. A decision tree, with the decisions probabilistically based on which screening test to use, and in what sequence, was used to minimize the number of HIV infected units of blood and blood products entering the nation's blood supply subject to a budget constraint. Brandeau et al. (1993) provided a cost benefit analysis of HIV screening for women of childbearing age based on a dynamic compartmental model incorporating disease transmission and progression over time. The model is formulated as a set of simultaneous nonlinear differential equations. Wein and Zenios (1996) proposed models for pooled testing of blood products for HIV screening. Optimization of pooled testing involves decisions such as transfusion, discarding of samples in the pool, and division of the pool into subpools. A dynamic programming model with a discretized state space and a heuristic solution algorithm are introduced to obtain near optimal solutions. Rubin et al. (2004) utilized a Bayesian network to assist mammography interpretation for breast cancer screening. The authors showed that their Bayesian network model may help to reduce variability and improve overall interpretive performance in mammography.

Markov decision processes (MDP) have been applied to several types of medical decisions. For instance, Alagoz et al. (2004) used an MDP model to study the structure of optimal policies for the timing of living-donor liver transplantation; Denton et al. (2009) used an MDP model to study optimal policies for initiating cholesterol lowering medication for patients with diabetes; and Shechter et al. (2005) used an MDP model to study the optimal time to initiate HIV therapy. Chhatwal et al. (2010) used a MDP to study the optimal policy for breast cancer biopsy based on mammography observations. In their model, states are defined by the probability of breast cancer at each epoch. A Bayesian network is used to estimate the probabilities. In all of these cases, the authors defined a discrete set of health states for a Markov process, and they computed the optimal policy to maximize expected future QALYs. QALYs are commonly employed in the health policy literature and are based on a decrement (from a nominal life year of 1.0) to represent the patient's perceived value of a year of life in a particular health state.

Gold et al. (2002) provide a review of QALYs, and Packer (1968) and Fanshel and Bush (1970) are early references on the use of QALYs in the operations research literature. We used QALYs as the criteria for our study because they are the standard used in the medical decision-making literature. Nevertheless, they have some limitations for evaluating screening decisions. For example, they are used to capture the impact of medical decisions on health years for a patient but they fail to capture other criteria related to the burden of screening and treatment, such as the impact of treatment on family members. Furthermore, estimates are challenging to obtain and may be subject to bias resulting from the survey methods used to estimate disutilities. We have used sensitivity analysis to mitigate this limitation; however, future studies that estimate QALYs related to biopsy and treatment will lead to more accurate models.

POMDPs have been used to study medical decisions in other contexts. Hu et al. (1993) considered the problem of choosing an appropriate drug infusion plan for the administration of anesthesia. Hauskrecht and Fraser (2000) applied a POMDP formulation to the problem of treating patients with ischemic heart disease. Maillart et al. (2008) used a partially observable Markov process to study breast cancer screening policies using mammography; they evaluated age-dependent screening policies and studied the trade-off between lifetime mortality risk of breast cancer and the expected number of mammograms. Ivy (2008) further studied a POMDP model of breast cancer screening; they considered the patient and third-party payer perspective by computing cost optimal screening policies subject to a patient-based utility constraint at each decision epoch.

Our study differs from the above referenced work in several respects. First, in contrast to the medical literature, which uses simulation to evaluate a small number of alternative screening policies, we study an optimization model that seeks to find the policy that maximizes expected QALYs for the patient. Second, we are unaware of any existing work addressing partial observability resulting from two stages of imperfect medical tests with a continuous serum biomarker such as PSA. For instance, for the breast cancer screening papers referenced above, mammogram results are discrete (normal or abnormal) and biopsy is perfect resulting in significantly different models. Third, we identify a number of interesting structural properties of our model that provide insight into the optimal screening policy. These properties are not obvious based on well-known sufficient conditions (see, for example, Albright 1979, White 1980, Lovejoy 1987) because of the nonstationary core state process, effects of competing cause mortality, and lack of a stochastic ordering of the core states. Finally, we calibrate

our model with a data set based on a large regional population that includes all screening and treatment events. Other studies using standard statistical methods or simulation have used data sets for high-risk patients or patients under study in RCTs, which can result in selection bias.

4. Partially Observable Markov Decision Process

In this section we describe our POMDP model for prostate biopsy referral decisions. The objective in our model is to maximize expected QALYs for the patient. QALYs are estimated by decrementing a normal life year as a result of various events including (a) occurrence of biopsy, (b) treatment upon detection of cancer, (c) long-term complications resulting from treatment, and (d) symptoms from metastasis and its treatment. Note that there is no disutility associated with undetected prostate cancer because it is typically nonsymptomatic. The benefit of early detection is in preventing patients' health state from metastasis and further prostate cancer related death. The optimal policy for biopsy therefore trades off the long-term benefits from early detection of prostate cancer with the short-term negative impact of biopsy and long-term side effects of treatment.

In our model patients progress through (unobservable) health states and (observable) PSA intervals. PSA intervals are defined by clinically relevant ranges (e.g., $[0, 1)$, $[1, 2.5)$, $[2.5, 4)$, $[4, 7)$, $[7, 10)$, and ≥ 10). The PSA intervals determine a conditional probability that the patient has prostate cancer. At each decision epoch the patient's PSA is measured, and a decision is made to refer the patient for biopsy, or to defer the referral decision until the next decision epoch. If a patient receives a positive biopsy result he is assumed to be treated. Radical prostatectomy, active surveillance, external beam radiation therapy, and brachytherapy (Lee et al. 1999) are all common forms of treatment that can be considered in our model. Following is a description of our model.

Time Horizon. PSA screening is performed annually, $t = \{40, 41, 42, \dots, \infty\}$. In this infinite horizon problem, biopsy decisions are made until \hat{N} , which corresponds to an upper bound on the age that screening is discontinued because of the risk of treatment being greater than the benefits. In our computational experiments in this paper, $\hat{N} = 95$. An infinite horizon Markov process is used beyond age \hat{N} to estimate remaining expected QALYs in the absence of screening. Although no further decisions are made after \hat{N} , the Markov process is used to evaluate the remaining lifetime QALYs, which is standard practice in medical decision-making models for evaluating long-term costs and benefits. (Note that we provide a way to estimate \hat{N} in §5.)

Table 2 Detailed Explanations of Cancer States *OC*, *EP*, *LN*, and *M*

Abbreviation	Description	Meaning
<i>OC</i>	Organ confined	Cancer is confined to the prostate gland and has not spread to any other site.
<i>EP</i>	Extra prostatic	Cancer has grown and is no longer confined to the prostate but has invaded outside of the prostate into structures immediately adjacent to the prostate.
<i>LN</i>	Lymph node positive	Cancer has spread to the regional lymph nodes. This is early metastatic disease.
<i>M</i>	Metastasis	Cancer has spread to distant organ sites. This is late metastatic disease.

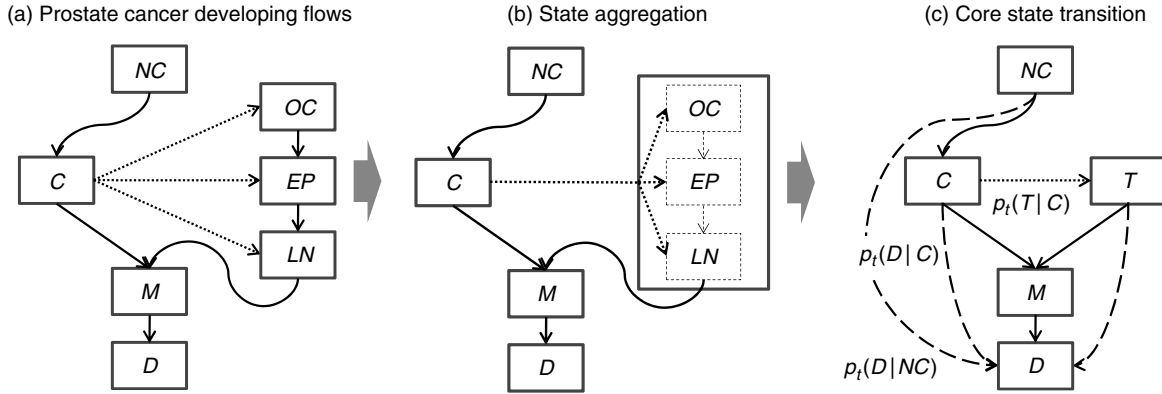
Actions. Action, $a_t \in \{B, W\}$, denotes the decision to perform a biopsy (B) or defer the biopsy decision (W) until the next decision epoch, $t + 1$.

States. At each decision epoch a patient is in one of several health states including no cancer (NC), non-metastatic prostate cancer present but not detected (C), organ confined cancer detected (OC), extraprostatic cancer detected (EP), lymph node-positive cancer detected (LN), metastasis (M), and death from prostate cancer and all other causes (D). Cancer states *OC*, *EP*, *LN*, and *M* are explained in more detail in Table 2. The states *NC* and *C* are not directly observable, but the other health states are assumed to be completely observable. The possible transitions among states are illustrated in Figure 3(a). Figure 3 illustrates how the model can be simplified by aggregating the three observable cancer stages (*OC*, *EP*, and *LN*) into a single state in which nonmetastatic prostate cancer has been detected and treated (*T*). Note that the state aggregation does not cause a loss of accuracy in our model, because the reward for state *T* is the expected discounted future rewards, which are independent of the actions. Once patients enter state *T*, they will discontinue screening and have no further biopsies; therefore, state *T* is an absorbing state. In our POMDP model, we use the set of core states $S = \{NC, C, T, M, D\}$ illustrated in Figure 3(c).

Observations. At each decision epoch, the patient is observed in one of a set of observable states including PSA intervals, *T*, *M*, or *D*, indexed by $l_t \in O = \{1, 2, 3, \dots, m, T, M, D\}$, where m is the number of discretized PSA intervals. Note that state *M* is observable because patients with metastases are treated palliatively, almost never receiving surgery or radiation for their prostate. Upon entering state *M* patients are identified within a very short time because of symptoms.

Information Matrix. Conditional probabilities relate the underlying core states to the observations. We let $q_t(l_t | s_t)$ denote the probability of observing $l_t \in O$

Figure 3 Illustration of the POMDP Model Simplification That Involves Aggregating the Three Nonmetastatic Prostate Cancer States After Detection Into a Single Core State T



Notes. The box surrounding states OC , EP , and LN in (b) denotes the aggregation of the states into a single treatment state. Solid lines denote the transitions related to prostate cancer; dotted lines denote the action of biopsy and subsequent treatment; dashed lines in (c) denote death from other causes (for simplicity these are omitted from (a) and (b)).

given he is in health state $s_t \in S$ and let $Q_t(l_t | s_t)$ be its matrix form. Note that $Q_t(l_t | s_t)$ is independent of the actions, B and W , because actions are only taken for patients in state C or NC , and these actions do not influence the PSA test results.

Belief States. The belief state (or belief vector), $\pi_t = (\pi_t(NC), \pi_t(C), \pi_t(T), \pi_t(M), \pi_t(D))$, defines the probability the patient is in one of the five health states at epoch t . Note that, if a patient has a positive biopsy result, his belief state is $\pi_t(T) = 1$, and if a patient has an observation of M , his belief state is $\pi_t(M) = 1$. We point out that the five-state POMDP model includes two partially observable states (C and NC) and three absorbing states (T , M , D). Thus, the complexity of the model is similar to that of a two-dimensional POMDP. We present the complete five-state model to allow a detailed description of the model inputs and computational results in §6. For a patient without a positive biopsy result, his belief state can be represented as $\pi_t = (1 - \pi_t(C), \pi_t(C), 0, 0, 0)$. Therefore, we use $\pi_t(C)$, the first component of vector π_t as a concise representation of belief in the remainder of this paper.

Transition Probabilities. The core state transition probabilities $p_t(s_{t+1} | s_t, a_t)$ denote the core state transition probability from health state s_t to s_{t+1} at epoch t given action a_t .

Rewards. The reward $\tilde{r}_t(s_t, a_t)$ is the immediate reward (measured in QALYs) given the patient is in core state s_t and action a_t is taken at decision epoch t . Thus, the belief state immediate reward is $r_t(\pi_t, a_t) = \sum_{s_t \in S} \tilde{r}_t(s_t, a_t) \pi_t(s_t)$.

The goal of our model is to determine the biopsy referral policy that maximizes expected discounted QALYs over the patient's lifetime. It is well known that POMDPs can be converted into an equivalent completely observable Markov decision process on

the continuous belief states π_t (Astrom 1965, Sondik 1971, Monahan 1982). The optimal value function and the corresponding optimal action for our model can be written as

$$v_t(\pi_t) = \max_{a_t \in \{W, B\}} \left\{ r_t(\pi_t, a_t) + \lambda \sum_{l_{t+1} \in O} v_{t+1}(\pi_{t+1}) \cdot p_t(l_{t+1} | \pi_t, a_t) \right\}, \quad \forall \pi_t \in \Pi, \quad (1)$$

and

$$a_t^*(\pi_t) = \arg \max_{a_t \in \{W, B\}} \left\{ r_t(\pi_t, a_t) + \lambda \sum_{l_{t+1} \in O} v_{t+1}(\pi_{t+1}) \cdot p_t(l_{t+1} | \pi_t, a_t) \right\}, \quad \forall \pi_t \in \Pi,$$

where

$$p_t(l_{t+1} | \pi_t, a_t) = \sum_{s_{t+1} \in S} q_{t+1}(l_{t+1} | s_{t+1}) \sum_{s_t \in S} p_t(s_{t+1} | s_t, a_t) \pi_t(s_t),$$

and $\lambda \in [0, 1]$ is the discount factor. Bayesian updating is used to revise the patient's belief state over time as PSA observations are obtained. Bayesian updates are defined by the following transformation of the belief state:

$$\pi_{t+1}(s_{t+1}) = \frac{q_{t+1}(l_{t+1} | s_{t+1}) \sum_{s_t \in S} p_t(s_{t+1} | s_t, a_t) \pi_t(s_t)}{\sum_{s_{t+1} \in S} q_{t+1}(l_{t+1} | s_{t+1}) \sum_{s_t \in S} p_t(s_{t+1} | s_t, a_t) \pi_t(s_t)}, \quad (2)$$

where $\pi_{t+1}(s_{t+1})$ is the component of the belief vector, and π_{t+1} is a function of l_{t+1} , a_t , and π_t . Thus, (2) updates the belief state of a patient based on their prior

Table 3 Detailed Description of Model Parameters Defining Transition Probabilities and Rewards for the Core State Process

	Description
w_t	Annual probability of prostate cancer incidence
d_t	Annual probability of death from other causes
b	Annual probability of developing metastasis for patients in state T
e	Annual probability of developing metastasis for patients in state C
z_t	Annual probability of prostate cancer death excluding death from other causes for patients in state M
f	Biopsy detection rate for patients with prostate cancer (sensitivity)
μ	One-time utility decrement associated with biopsy
ϵ	Annual utility decrement of living in state T
γ	Annual utility decrement of living in state M

belief state and their most recent observed PSA interval. The sequence of probabilities $\{\pi_t, t = 1, \dots, \infty\}$ has been shown to follow a Markov process (Monahan 1982), and therefore (1) defines a continuous state MDP. Note that when using the model, it is not necessary to have annual PSA test results. Belief at any age can be estimated based on available information.

Transition probability matrices and reward vectors are shown in Appendix A in the online supplement (available at <http://dx.doi.org/10.1287/msom.1120.0388>). Table 3 defines the parameters used to construct the core state transition probability matrices and the rewards in our model. All the parameters in Table 3 are nonnegative and not greater than 1 by definition.

5. Structural Properties

In this section we discuss the structure of our model and prove several structural properties that give insights into the optimal policy for biopsy referral. For example, insights include that the optimal biopsy referral policy is of control-limit type and that biopsy referral and even PSA screening should be discontinued for older patients. In our model we focus on primary screening, assuming that patients have at most one biopsy. In reality, about 7%–12% of men undergoing biopsy have had a previous negative biopsy (Nguyen et al. 2010, Thompson et al. 2006). This is likely because the 10–12 cores obtained in a standard office prostate biopsy miss cancer in some men (Haas et al. 2007). Importantly, however, a prior negative prostate biopsy is an indicator of the absence of prostate cancer and therefore decreases the probability that the patient will have cancer detected at rebiopsy (Thompson et al. 2006, Ashley et al. 2008). In rebiopsy situations, the technique of biopsy also changes, with more cores being sampled to ensure that a “hidden” cancer is not missed again (Rabets et al. 2004, Chon et al. 2002). Fortunately, when a cancer is found at rebiopsy, it is often a low-risk tumor and frequently clinically insignificant (Epstein et al. 2005, Bastian et al. 2004, Master et al. 2005). It can be surmised from these data that the deci-

sion to rebiopsy a man is inherently different than the decision to biopsy him for the first time, and for this reason we have opted to focus on the first biopsy decision because it informs about 90% of biopsy decisions. From the perspective of our model, this can be interpreted to mean that once patients are biopsied they leave the system. This assumption has also been made in previous cancer screening studies (Maillart et al. 2008, Chhatwal et al. 2010).

Assuming a single biopsy, the optimality Equation (1) can be rewritten as

$$v_t(\pi_t) = \max \left\{ r_t(\pi_t, W) + \lambda \sum_{l_{t+1} \in O} v_{t+1}(\pi_{t+1}) \cdot p_t(l_{t+1} | \pi_t, W), R_t(\pi_t) \right\}, \quad \forall t, \forall \pi_t \in \Pi, \quad (3)$$

where $R_t(\pi_t)$ is the expected discounted future reward given $a_t = B$ at decision epoch t , which can be written as

$$R_t(\pi_t) = -\mu + (1 - \pi_t(C))\bar{R}_t(NC) + \pi_t(C)((1 - f)\bar{R}_t(C) + f\bar{R}_t(T)), \quad (4)$$

where μ is the QALY decrement of biopsy; f is the biopsy detection rate; and $\pi_t(C)$, a component of vector π_t , is the probability the patient is in state C . We let $\bar{R}_t(NC)$, $\bar{R}_t(C)$, $\bar{R}_t(T)$, and $\bar{R}_t(M)$ denote the expected discounted future rewards under the policy of never referring the patient for biopsy after age t for states NC , C , T , and M , respectively, which can be written as

$$\begin{aligned} \bar{R}_t(NC) &= \bar{r}_t(NC, W) + \lambda(p_t(NC | NC, W)\bar{R}_{t+1}(NC) \\ &\quad + p_t(C | NC, W)\bar{R}_{t+1}(C)), \\ \bar{R}_t(C) &= \bar{r}_t(C, W) + \lambda p_t(C | C, W)\bar{R}_{t+1}(C) \\ &\quad + \lambda p_t(M | C)\bar{R}_{t+1}(M), \\ \bar{R}_t(T) &= \bar{r}_t(T) + \lambda p_t(T | T)\bar{R}_{t+1}(T) \\ &\quad + \lambda p_t(M | T)\bar{R}_{t+1}(M), \\ \bar{R}_t(M) &= \bar{r}_t(M) + \lambda p_t(M | M)\bar{R}_{t+1}(M). \end{aligned} \quad (5)$$

We let $\bar{R}_t(\pi_t)$ denote the expected discounted future QALYs given the patient is never referred for biopsy, and is in belief state π_t , in decision epoch t . It can be written as

$$\bar{R}_t(\pi_t) = (1 - \pi_t(C))\bar{R}_t(NC) + \pi_t(C)\bar{R}_t(C). \quad (6)$$

To simplify the notation in later proofs related to (3), we define

$$v_t(\pi_t, W) = r_t(\pi_t, W) + \lambda \sum_{l_{t+1} \in O} v_{t+1}(\pi_{t+1})p_t(l_{t+1} | \pi_t, W). \quad (7)$$

Formulation (3) can be viewed as a partially observable optimal stopping time problem. At each decision epoch, the decision maker selects between the expected reward associated with biopsy, $R_t(\pi_t)$, or deferral of the decision to biopsy for one more decision epoch.

Because PSA involves only a simple blood test, and because no QALY decrement associated with a PSA test has been reported in the literature, we assume there is no direct utility loss associated with the test because PSA tests are normally ordered as part of a larger panel of blood tests when patients have an annual exam (thus, the PSA test itself does not typically result in an additional lab visit or blood test). Furthermore, most medical decision-making studies assume no disutility of blood tests. An estimate in the literature based on blood tests for infants suggests a conservative upper bound of 0.0002 QALYs (Madsen et al. 2006), which is negligible compared to the impact of biopsy and treatment in our model.

When there is no QALY decrement associated with a PSA test, it can be shown that any additional PSA test provides nonnegative benefit in total expected QALYs. We formalize this concept with the following proposition.

PROPOSITION 1. *The incremental benefit of an additional PSA test is nonnegative.*

Proposition 1 is presented without a formal proof. It follows trivially from the fact that a patient cannot have a worse outcome given the availability of additional information. An immediate corollary to the above proposition is the following.

COROLLARY 1. *Annual PSA screening is optimal when decisions to perform PSA tests are made not more frequently than annually.*

Proposition 1 and Corollary 1 shed light on the controversy of whether frequent PSA testing is the cause of overdiagnosis (Etzioni et al. 2002). They imply that PSA screening should be done as frequently as reasonably possible to maximize the expected QALYs from the patient perspective. Thus, in the context of screening based on belief of prostate cancer, a high frequency of PSA tests does not lead to an increase in unnecessary biopsies and treatments, rather it provides greater ability to discriminate between patients with and without prostate cancer. Therefore, because annual screening is the highest frequency of screening generally supported in the medical literature (U.S. Preventive Services Task Force 2008, American Urological Association 2009, American Cancer Society 2010b), in the results that follow in §6, we assume that patients are screened at each of a set of annual decision epochs.

Several structural properties can be proved about the optimal biopsy referral policy under the assumption of annual screening and reasonable assumptions

about the model parameters. Lemmas and detailed proofs for the lemmas and theorems, can be found in Appendix B in the online supplement. We begin by stating several important assumptions before presenting our main theoretical results.

ASSUMPTION 1. *The probability of prostate cancer incidence satisfies the condition that $w_t \leq Kb$, $\forall t$, where $K = (\bar{R}_{t+1}(NC) - \bar{R}_{t+1}(M)) / (\bar{R}_{t+1}(NC) - \bar{R}_{t+1}(C))$.*

Assumption 1 means that the annual probability of prostate cancer incidence is not more than K times the prostate cancer metastasis probability for patients in state T . Lemmas 1 and 2 in Appendix B in the online supplement together imply that the coefficient K is greater than or equal to 1. Therefore, Assumption 1 is consistent with published mortality and incidence data for prostate cancer, which we discuss in §6.

ASSUMPTION 2. *The annual probability of death from other causes, d_t , is monotonically nondecreasing in t .*

Assumption 2 means the annual probability of death from other causes, d_t , is nondecreasing in age. This is consistent with the fact that age is recognized as a risk factor for most diseases, including prostate cancer as well as all-cause mortality. This assumption is also empirically consistent with published U.S. life tables (Arias 2010).

ASSUMPTION 3. *The annual probability of death from metastatic prostate cancer, z_t , is monotonically nonincreasing in t .*

Assumption 3 means the annual probability of death from metastatic prostate cancer excluding death from other causes, z_t , is nonincreasing in age. Note that, z_t is defined as the number of people who die from metastatic prostate cancer divided by the number of people who do not die from all other causes at age t . This is consistent with the fact that metastatic prostate cancer is more deadly for younger patients. This assumption is also empirically consistent with the Surveillance Epidemiology and End Results (SEER) data (National Cancer Institute 2009).

In the remainder of this section we present our main theoretical results that provide general insight into the optimal policy for biopsy referral decisions. Theorem 1 provides a monotonicity result for our POMDP model.

THEOREM 1. *Under Assumptions 1, 2, and 3, the optimal biopsy referral policy is of control-limit type with $\pi_t^*(C)$ such that*

$$a_t^*(\pi_t) = \begin{cases} W & \text{if } \pi_t(C) \leq \pi_t^*(C), \\ B & \text{if } \pi_t(C) > \pi_t^*(C). \end{cases}$$

Theorem 1 implies that the optimal policy is of control-limit type under the above assumptions. The existence of a control-limit type policy means the

optimal decisions on the belief space are separated by the threshold, $\pi_i^*(C)$. This is important for two reasons. First, the introduction of partial observability and the fact that the underlying health states are not ordered (state C and T are not ordered in that the reward of being in state C is greater than in state T , but the annual probability of developing metastatic prostate cancer from state C is higher than state T) makes the proof of the structural properties novel relative to existing literature (e.g., Albright 1979, White 1980, Lovejoy 1987). Second, such policies are intuitive and much easier to implement in practice, which is particularly important in an already challenging clinical environment. Although the result in Theorem 1 is intuitive there are counter examples demonstrating that intuition can be misleading. For instance, Lovejoy (1987) presents an example of a simple POMDP, which counter to intuition, does not have a threshold policy.

Next, we provide a sufficient and necessary condition for the existence of the stopping time policy in our POMDP model in Theorem 2 and Corollary 2.

THEOREM 2. *Under Assumptions 2 and 3, there exists a finite age, N , at which it is optimal to discontinue biopsy referral if and only if the following condition is satisfied:*

$$\bar{R}_N(T) - \bar{R}_N(C) \leq \mu/f.$$

Theorem 2 provides a general result for a partially observable stopping time problem that is potentially relevant to other medical decision-making problems in which the patient's health state is not known without invasive and imperfect testing. Discontinuing biopsy referral at age N means $a_t^*(\pi_t) = W$, $\forall \pi_t \in \Pi$, $\forall t \geq N$. Note that this implies that PSA screening should be discontinued, which we state formally as the following corollary.

COROLLARY 2. *If $a_t^*(\pi_t) = W$, $\forall \pi_t \in \Pi$, $\forall t \geq N$, PSA screening should be discontinued.*

PROOF. This corollary is a direct result of Theorem 2.

In words, Corollary 2 states that if the incremental benefit of treatment is not greater than the ratio of disutility of biopsy to the biopsy detection rate, it is no longer optimal to screen. Intuitively this means that reducing the negative impact of biopsy or increasing the biopsy detection rate will increase the age at which screening should be discontinued. Furthermore, improving the benefit of treatment will also increase the age at which screening is discontinued. Note that, although Proposition 1 guaranteed any additional PSA test will provide nonnegative incremental benefit, Corollary 2 implies that PSA screening should be discontinued if an additional PSA test cannot provide positive incremental benefit.

Theorem 2 and Corollary 2 provide an insight into published clinical recommendations that prostate can-

cer screening should be terminated for older patients when their risk of dying of prostate cancer becomes low relative to other causes of death (e.g., heart disease). Estimating the stopping time N is useful for two reasons. First, it provides a foundation for guidelines such as those of the U.S. Preventive Services Task Force (2008), which recommend terminating screening for older patients. Second, it provides a means to improve computational efficiency in solving the POMDP because it defines a finite horizon beyond which the policy is fixed. Thus, it informs the choice of \hat{N} in the POMDP model formulation.

6. Computational Results

In this section we present results based on our POMDP model. We describe the data used to estimate our model parameters and details about how we estimated model parameters based on the medical literature. We present sensitivity analysis based on variation of the model parameters, and we present estimates of the benefits of annual PSA screening. Finally, we discuss insights that can be drawn from the results of our numerical experiments. For instance, the biopsy referral threshold on the probability of having prostate cancer is nondecreasing as age increases, the optimal biopsy referral policy is the most sensitive to the disutility of treatment, the optimal expected QALYs is the most sensitive to the other cause mortality probability and the probability of prostate cancer incidence, and both the optimal policy and the expected QALYs are insensitive to the biopsy detection rate.

6.1. Data Description

The data we used for parameter estimation in our model consists of 11,872 patients from Olmsted County, Minnesota. It includes PSA values, biopsy information (if any), diagnosis information (if any), and the corresponding ages for patients recorded from 1993 through 2005. This regional data set includes all patients in Olmsted County irrespective of their prostate cancer risk. We use it to estimate prostate cancer probabilities conditional on PSA level for a general population. To our knowledge, it is the largest data set of its kind for a North American population.

Among the patients in our data set, 1,140 patients have at least one biopsy prior to detection during their lifetime, and 739 patients (81.4%) have exactly one biopsy. Because we focus on the prostate biopsy referral policy for primary screening, we do not consider PSA records after cancer treatment. Based on expert opinion, we removed abnormal PSA records such as the following. Suppose there are three consecutive PSA tests for any patient; the first one and the third one are lower than 2.5 ng/ml; the second one is

greater than 4.0 ng/ml and two times higher than the first and third. Then we assume the second PSA value is abnormal (likely caused by infections or data entry error), and remove it from the data set. This method eliminates a total of 94 abnormal PSA records.

6.2. Estimating Parameters

Because some patients in the data set likely have prostate cancer that has not yet been diagnosed, the information matrix, $Q_t(l_t | s_t)$, is subject to bias. Patients without any biopsy result and with a false negative biopsy result may be a source of bias. To adjust for this, we randomly selected 20% of negative biopsy results to be positive. To adjust the bias caused by patients without any biopsy result, we used the methods proposed by Begg and Greenes (1983) to correct for this bias. We use biopsy as the confirmative test. This is consistent with its use as the confirmative test for outcome prediction based on PSA test results in other studies (Punglia et al. 2003). Thus, we assume that patients who have positive biopsies are true cancer patients, and those who have negative biopsy are true no cancer patients. We first separate the patients into different groups according to their PSA values ($[0, 1)$, $[1, 2.5)$, $[2.5, 4)$, $[4, 7)$, $[7, 10)$, and ≥ 10) and ages ($[40, 50)$, $[50, 60)$, $[60, 70)$, $[70, 80)$, and ≥ 80). Within each group, we assume patients without a confirmative test (biopsy) have the same probability of prostate cancer as patients who have had a confirmative test. The resulting information matrix is

$$Q_t(l_t | s_t) = \begin{pmatrix} 0.471 & 0.337 & 0.101 & 0.059 & 0.015 & 0.017 & 0 & 0 & 0 \\ 0.319 & 0.287 & 0.142 & 0.135 & 0.056 & 0.061 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 & 1 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 & 0 & 1 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 1 \end{pmatrix}, \quad \forall t.$$

The rows of $Q_t(l_t | s_t)$ correspond to states NC, C, T, M, and D, respectively; the columns correspond to PSA intervals $[0, 1)$, $[1, 2.5)$, $[2.5, 4)$, $[4, 7)$, $[7, 10)$, $[10, \infty)$, T, M, and D, respectively. Our choice of the PSA intervals is based on clinically meaningful cut points identified by a urologist involved in this study. Our choice balances the density of samples in each PSA interval and is consistent with the PSA intervals chosen in other prostate cancer research (Partin et al. 1997, Thompson et al. 2004, Makarov et al. 2007). (Finer PSA intervals were tested in numerical experiments, and the optimal policy and the expected QALYs were found to be insensitive to an increase in the number of PSA intervals.) The information matrix, $Q_t(l_t | s_t)$, is fixed for all the ages in this empirical study because our preliminary numerical experiments

showed that changes in $Q_t(l_t | s_t)$ with respect to age do not significantly influence the optimal policy.

In the results we present, we assume patients detected with nonmetastatic prostate cancer are treated by radical prostatectomy. Radical prostatectomy is historically the most common treatment (Burkhardt et al. 2002, Kawachi et al. 2010, Hamilton et al. 2011) and reported to be the best treatment in terms of expected QALYs for all the ages (Sommers et al. 2007). It is also the only form of treatment for which the patients' cancer stages can be understood by pathological examination of the removed organ. To estimate the annual probability of developing metastasis for patients in state T, b, we use the weighted average of the probability of developing metastasis from three nonmetastatic prostate cancer stages using Mayo Clinic Radical Prostatectomy Registry survival data. In our base case $b = 0.006$.

We estimated the annual death probability for metastasis from the five-year death probabilities for patients' age < 65 and ≥ 65 from the SEER data (National Cancer Institute 2009). Based on our estimates the disease-specific annual death probability of metastatic prostate cancer is $z_t = 0.074$ for $t < 65$ and $z_t = 0.070$ for $t \geq 65$. The disease-specific metastasis probability from cancer not detected is estimated using the weighted sum of the grade-specific metastasis probability (Scardino et al. 1994) and the probabilities of grades upon detection (Ghani et al. 2005). The base case estimate is $e = 0.069$ for all ages.

In our base case, we use a decrement of $\mu = 0.05$ in the year of biopsy to estimate quality adjustment in the year a patient has a biopsy. Because no estimates of utility decrement exist yet for prostate biopsy, this is an estimate based on a similar choice of parameters for a recent bladder cancer study for the occurrence of surveillance cystoscopy (Kulkarni et al. 2009) and a breast cancer biopsy study (Chhatwal et al. 2010). In our base case, the disutility of metastasis is $\gamma = 0.24$ (Bremner et al. 2007). We assume that the annual QALY in years after treatment via prostatectomy is the mean of two extremes: (a) the most severe (metastasis) and (b) minor (mild sexual dysfunction) symptoms according to patient surveys reported in Bremner et al. (2007). Hence, annual QALYs of being in state T, $1 - e$, equals 0.855, which is the midpoint of 0.76 and 0.95.

The annual probability of prostate cancer incidence, w_t (shown in Table 4), is estimated from an autopsy review study (Bubendorf et al. 2000) that provides

Table 4 Age-Specific Values of the Annual Probability of Prostate Cancer Incidence, w_t

t	40–50	50–60	60–70	70–80	≥ 80
w_t	2.32×10^{-3}	4.70×10^{-3}	7.02×10^{-3}	6.17×10^{-3}	1.17×10^{-2}

Table 5 Age-Specific Annual Probability of Death from Other Causes, d_t

t	40–44	45–49	50–54	55–59	60–64	65–69	70–74	75–79	80–84	85–89	90–94	95–99
d_t	0.003	0.004	0.006	0.009	0.013	0.019	0.030	0.049	0.081	0.129	0.200	0.297

Table 6 Parameters, Their Sources, and Specific Values Used in Our Base Case Analysis

Parameter	Source	Value
w_t	Bubendorf et al. (2000)	Age specific
d_t	National Cancer Institute (2009), Arias (2010)	Age specific
b	Mayo Clinic Radical Prostatectomy Registry	0.006
e	Scardino et al. (1994), Ghani et al. (2005)	0.069
z_t	National Cancer Institute (2009)	Age specific
f	Haas et al. (2007)	0.8
μ	Kulkarni et al. (2009), Chhatwal et al. (2010)	0.05
ϵ	Bremner et al. (2007)	0.145
γ	Bremner et al. (2007)	0.24

estimates of prostate cancer prevalence in the general population in ten-year age intervals.

The mortality probability from other causes, d_t (shown in Table 5), is age specific and based on the general mortality probability from the National Vital Statistics Reports (Arias 2010) minus the prostate cancer mortality probability from the National Cancer Institute (2009). Note that because the National Cancer Institute reports a single annual probability of prostate cancer incidence for ages greater than 95 and the National Vital Statistics Reports (Arias 2010) reports a single annual probability of all-cause mortality for ages greater than 95, we assume that d_t are fixed after the age of 95, i.e., $\hat{N} = 95$ in our numerical experiment. Our base case biopsy detection rate is 0.8 (Haas et al. 2007).

A summary of all of the parameter values and their sources are provided in Table 6. It is worth noting that these parameter estimates satisfy Assumptions 1, 2, and 3 in §5. Thus, they validate our assumptions empirically. In §6.3 we use sensitivity analysis to evaluate the influence of changes in each of these parameters on the optimal biopsy referral policy.

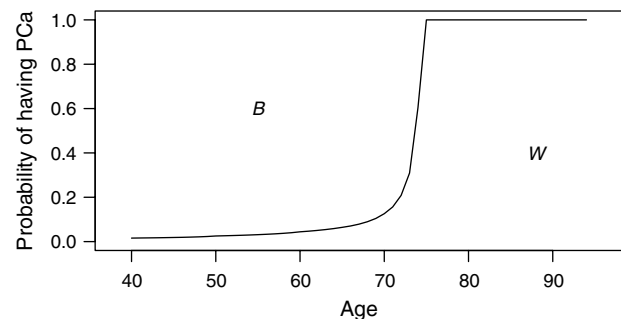
6.3. Computational Experiments and Sensitivity Analysis

POMDP models are often computationally intractable, however, because of the low dimensionality of the belief state instances of our model, the POMDP can be solved exactly in a reasonable computation time using incremental pruning (Zhang and Liu 1996, Cassandra et al. 1997). All the experiments in this study were completed on a 64-bit Intel Xeon 2.5 GHz CPU with 6 MB of cache. All instances were solved in less than six minutes.

Results of the base-case parameter settings are presented in Figure 4. The optimal policy, denoted by

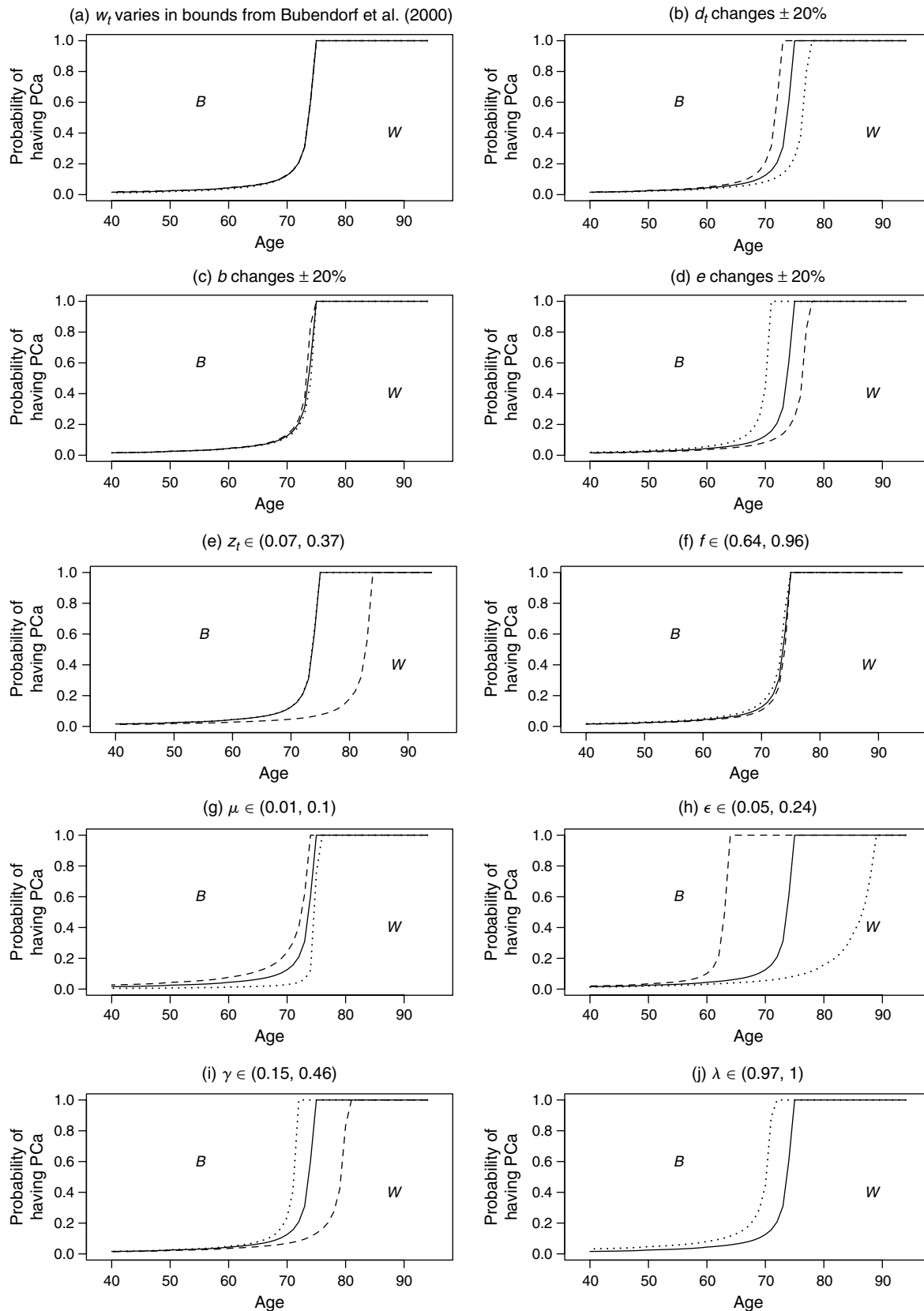
the belief threshold between biopsy and wait, is illustrated in the figure. There are several interesting properties of the optimal policy. First, as expected from Theorem 1, the optimal policy is control-limit type. Second, there is a stopping time for screening at age 74, and thus the optimal policy is consistent with Theorem 2. Finally, we note that the threshold is increasing in age; thus, as patients age, their probability of having prostate cancer must be higher for a biopsy referral to be optimal. This is consistent with increases in all-other-cause mortality that occurs as patients age, and the general consensus in the medical community that because of the low risk of death from prostate cancer, treatment becomes less beneficial as age increases. The biopsy threshold increases rapidly around the biopsy stopping age primarily because of the significant increase in risk of death from other causes for older patients. This trend is observed in Table 5, which provides probabilities of death from other causes based on Centers for Disease Control and Prevention life tables (Arias 2010). When death from other causes becomes large relative to death from prostate cancer, the expected benefit of treatment decreases significantly, resulting in a rapid change in the biopsy threshold.

Some of the parameters in our model are subject to variation either because they differ among patients because of differences in preferences (e.g., the perceived impact of biopsy, μ) or differences in physiology (e.g., anticipated recovery from surgery, ϵ). Furthermore, there is variation in reported estimates such as the annual probability of prostate cancer incidence, w_t (Bubendorf et al. 2000). Therefore, in Figure 5 we present the results of a one-way sensitivity analysis for the model parameters that define the core process and reward function. In several cases, parameters were varied between lower and upper

Figure 4 Optimal Biopsy Referral Policy

Note. The solid line denotes the optimal threshold for the base case, and PCa is an abbreviation for prostate cancer.

Figure 5 One-Way Sensitivity Analysis for Parameters: w_t , d_t , b , e , z_t , f , μ , ϵ , γ , and λ



Note. Solid lines denote the base-case optimal policy, dashed lines denote the optimal policies for the upper bound of the parameter estimates, dotted lines denote the optimal policies for the lower bound of the parameter estimates, and PCa is an abbreviation for prostate cancer.

Table 7 Bounds on w_t Derived from Bubendorf et al. (2000) for One-Way Sensitivity Analysis

(a) Lower bounds of w_t					
t	40–49	50–59	60–69	70–79	≥ 80
w_t	2.00×10^{-4}	1.51×10^{-3}	2.43×10^{-3}	5.22×10^{-3}	7.12×10^{-3}
(b) Upper bounds of w_t					
t	40–49	50–59	60–69	70–79	≥ 80
w_t	5.01×10^{-3}	4.91×10^{-3}	8.52×10^{-3}	1.51×10^{-2}	1.10×10^{-2}

bound based on published estimates in the literature, when such estimates were available. In other cases, parameters were varied by $\pm 20\%$ from the baseline values provided in §6.2. We discuss some of the interesting observations and general insights that can be drawn below.

Figure 5(a) is a one-way sensitivity analysis for w_t , in which the upper and lower bounds on w_t (shown in Table 7) are based on the lowest and highest estimates of the annual probability of prostate cancer incidence reported in autopsy studies (Bubendorf et al. 2000). The figure illustrates the optimal policy for the base case, and the lower and upper bounds on w_t (note that the solid line denotes the base case, the dashed line denotes the upper bound, and the dotted line the lower bound in all figures). We observe that optimal threshold is insensitive to changes in w_t , based on the fact that the lines in Figure 5(a) are nearly overlapping. This is intuitive because w_t is directly related to the probability of prostate cancer, and the nature of the policy, which is defined by the belief, automatically compensates for this fact. As we show later, the value function itself is quite sensitive to changes in w_t .

The optimal policy was also found to be relatively insensitive to the annual probability of developing metastasis from state T , b , and the biopsy detection rate, f . Although the effects are small, we observed that the threshold for screening is decreasing in b . Thus, the probability threshold at which biopsy is recommended goes up as the probability of developing metastasis goes up. This is intuitive because the change represents less aggressive biopsy referral decisions to compensate for the higher likelihood of disease progression following treatment. We also observe that the threshold is decreasing in f , indicating that the likelihood of prostate cancer must be higher to warrant biopsy as the accuracy of detection decreases. Although the direction of the changes is intuitive, it is interesting to note that the magnitude of the changes is very small for these parameters, indicating that changes in their estimates are unlikely to substantially effect the optimal policy.

The optimal policy was found to be particularly sensitive to the disutility parameters for biopsy, μ , treatment, ϵ , and metastasis, γ , as illustrated in Figures 5(g)–5(i). Figure 5(g) is a one-way sensitivity anal-

ysis of varying the disutility of biopsy, μ , from 0.01 to 0.1 (a wide range was used in this case to reflect potentially significant variation among patient preferences for biopsy). As μ increases, we observe that the threshold for biopsy goes up, consistent with the greater impact of the test on quality of life. Figure 5(h) shows the one-way sensitivity analysis for the utility decrement after prostatectomy, ϵ , which has lower bound $\epsilon = 0.05$ (consistent with mild urinary problem after prostatectomy) and upper bound $\epsilon = 0.24$ (consistent with metastasis), which are taken from Bremner et al. (2007). The threshold increases with respect to ϵ , reflecting the decreased benefits of screening represented by a higher disutility of treatment. Figure 5(i) is the one-way sensitivity analysis for the disutility of metastasis, γ , with lower bound $\gamma = 0.15$ from Krahn et al. (2003) and upper bound $\gamma = 0.46$ from Sandblom et al. (2004). As illustrated in Figure 5(i), when γ was decreased to 0.15, the optimal biopsy threshold increased, implying that patients should be subjected to less aggressive prostate cancer screening, and vice versa when γ was perturbed to 0.46.

The optimal policy is also sensitive to change in the prostate cancer death probability, z_t . The one-way sensitivity analysis for z_t is illustrated in Figure 5(e), where the lower bound, 0.07, is an estimate from Messing et al. (2006) and the upper bound, 0.37, is an estimate from Aus et al. (2005a). When z_t was perturbed to 0.37, the optimal biopsy threshold moved considerably lower, which implies that patients should be subjected to more aggressive prostate cancer screening if the outcome of having metastatic cancer is worse, and vice versa when z_t was perturbed to 0.07. In Figure 5(b) the all-otherwise mortality, d_t , was perturbed by $\pm 20\%$. The results imply that patients should be subjected to more aggressive prostate cancer screening if their probability of dying from other causes is lower, and vice versa when d_t is higher. The changes are intuitive because increasing probability of death from other causes naturally decreases the relative benefits of detecting and treating prostate cancer, since the patient's expected lifespan following treatment will be lower. Thus, the results for d_t imply that comorbidities (e.g., heart disease, diabetes, other cancers) should be considered when making screening decisions for individual patients.

The optimal policy was also found to be fairly sensitive to e , the annual probability of developing prostate cancer metastasis of patients in state C. Figure 5(d) shows the one-way sensitivity analysis of e . The results imply that patients should be subjected to less aggressive prostate cancer screening if the outcome of state C is better (lower probability of developing metastasis without treatment), and vice versa when e is higher. In other words, the benefits of

screening decrease as the probability of dying from untreated prostate cancer goes down.

Figure 5(j) shows the one-way sensitivity analysis on the discount factor, λ , with a baseline value of 1. In the sensitivity analysis, the lower bound of λ takes 0.97, the most commonly used value in the health economics literature for cost effectiveness studies (Gold et al. 2002) (note that no upper bound is evaluated in this case). When λ reduced to 0.97, the optimal biopsy threshold increased significantly, implying more aggressive prostate cancer screening when a greater discount applies to the future QALYs. This is consistent with the fact that discounting decreases the benefit of future life years, i.e., the expected value to go, in favor of immediate rewards. Thus, the long-term benefits of early detection and treatment of prostate cancer are decreased by discounting.

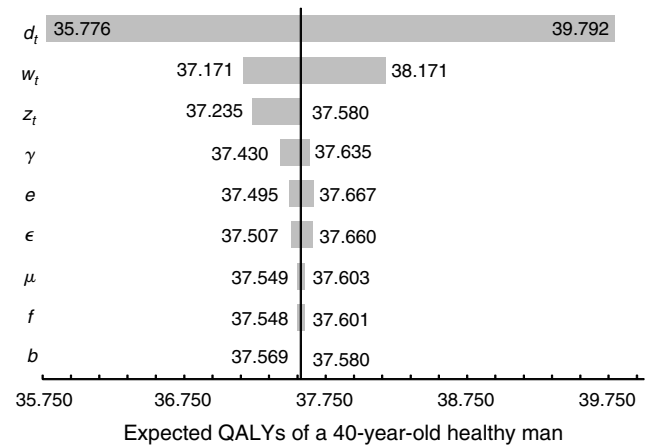
In summary, from Figure 5 we can see that the optimal policy is most sensitive to the utility decrements, ϵ and γ , which are the factors affecting the reward function. The optimal policy is also quite sensitive to d_t , e , z_t , λ , and μ . On the other hand, it is less sensitive to the annual probability of prostate cancer incidence, w_t , the annual probability of developing metastasis of state T , b , and the biopsy detection rate, f .

Note that the results in Figure 5 differ from the recommended guidelines summarized in Table 1 in several ways. First, all but one of the guidelines in Table 1 are independent of age, whereas the optimal policy based on our model is highly dependent on the patient's age. Second, our results suggest that the decision to biopsy is dependent on a number of factors including a patient's all-other-cause mortality, disutility of biopsy and treatment, and the annual probability of prostate cancer death, none of which are considered by the guidelines in Table 1.

Figure 5 illustrates the sensitivity of the optimal policy to changes in model parameters. In contrast, Figure 6 illustrates the changes to the optimal value function at age 40 given that the parameters are varied in the same ranges used in Figure 5. We found that the value function is most sensitive to the annual probability of death from other causes, d_t , and the annual probability of prostate cancer incidence, w_t . It is also very sensitive to the utility decrement of treatment, ϵ .

Although not illustrated in Figure 6, we found that changing the discount factor λ from 1 to 0.97 will make the optimal value function decrease more than 10 QALYs. In this sense, the optimal value is the most sensitive to λ . The use of a discount factor, particularly over long time frames, has been a highly debated topic for decades (for a discussion of this, see Gold et al. 2002). From Figure 6, d_t and w_t are the parameters affecting expected QALYs the most; from Figure 5, the parameters defining the reward function, ϵ and γ are among the ones with greatest influence

Figure 6 One-Way Sensitivity Analysis on Optimal Values for Model Parameters



Note. d_t (annual probability of death from other causes), w_t (annual probability of prostate cancer incidence), z_t (annual probability of death from metastatic prostate cancer), γ (annual disutility of having metastasis), e (annual probability of developing metastasis from state C), ϵ (annual disutility of treatment), μ (disutility of biopsy), f (biopsy detection rate), and b (annual probability of developing metastasis from state T).

on the optimal policy. Both the optimal policy and the expected QALYs were found to be insensitive to the biopsy detection rate, f . Note that the main reason for biopsy referral is that the benefit of treatment is greater than no treatment when a positive biopsy result is observed. The benefits of treatment are primarily influenced by the disutility of treatment, which results in a long-term permanent change in a patient's annual quality of life. Because the biopsy detection rate, f , does not directly influence the outcome trade-off between treatment and no treatment, and because the disutility of biopsy is a one-time loss and therefore dominated by the influence of treatment disutility, variation in f does not significantly affect the decision to biopsy.

6.4. Benefits of Prostate Cancer Screening

We measured the total estimated benefit of prostate cancer screening by estimating how much the value function at age 40, i.e., the expected QALYs for a 40-year-old patient with no prostate cancer, improves when the optimal policy is adopted versus no PSA screening ($a_t = W, \forall t, \forall \pi_t \in \Pi$). In Table 8 the optimal objective values are provided for our base case along with several choices of model parameters, λ , ϵ , and μ . The benefits of prostate cancer screening are most significant for cases in which μ and ϵ , the factors that define the effect of screening and treatment on the patients quality of life, are minimized. For $\lambda = 1$, the base-case benefit of screening is 0.102 QALYs per person for the male population regardless of their risk of prostate cancer. For the case that is most favorable for the benefits of prostate cancer screening and treatment ($\epsilon = 0.05$, $\mu = 0.01$), the benefit is 0.217 QALYs per person.

Table 8 Sensitivity Analysis for Expected QALYs for a 40-Year-Old Patient Assuming $\pi_{40}(C) = 0$ Comparing the Optimal Policy to the Case of No Screening, Allowing at Most One Biopsy over One's Lifetime

λ	ϵ	μ	Expected QALYs under optimal biopsy referral policy	Improvements over no screening (QALYs)	Percentage improvement
0.97	0.05	0.01	21.861	0.069	0.317
		0.05	21.845	0.053	0.244
		0.1	21.831	0.039	0.180
	0.145	0.01	21.826	0.034	0.157
		0.05	21.812	0.020	0.093
		0.1	21.803	0.011	0.052
	0.24	0.01	21.798	0.006	0.029
		0.05	21.793	0.001	0.006
		0.1	21.792	0.000	0.001
1	0.05	0.01	37.689	0.217	0.574
		0.05	37.660	0.188	0.498
		0.1	37.629	0.157	0.416
	0.145	0.01	37.603	0.131	0.347
		0.05	37.574	0.102	0.270
		0.1	37.549	0.077	0.204
	0.24	0.01	37.531	0.059	0.156
		0.05	37.507	0.035	0.092
		0.1	37.493	0.021	0.055

Note. Base-case values are shown in bold.

In Table 9 we compare our optimal policy to the widely adopted American Urological Association (AUA) age-adjusted guideline described in Table 1. This guideline calls for annual PSA screening with 4.0 ng/mL threshold for biopsy. Comparing Tables 8 and 9, we see that the AUA age-adjusted guideline is worse than no screening at moderate and higher disutility values.

To put our results in a different context, we evaluated the benefits of screening for patients who ultimately develop cancer between the age of 40 and 50. Based on our experiments we find that the expected incremental benefit is about 1.56 QALYs per person for the base case parameter setting and ranges from

0.26 to 2.90 based on varying the disutilities ϵ and μ in the ranges used in Table 8.

7. Conclusions

The U.S. Preventive Services Task Force (2008, p. 185) provides the following recommendation: "Current evidence is insufficient to assess the balance of benefits and harms of screening for prostate cancer in men younger than age 75 years. Do not screen for prostate cancer in men age 75 years or older." Our theoretical results in §5 provide a foundation for the concept of stopping screening at older ages. Our base case results from our empirical study in §6 estimate the optimal stopping time at 74 years of age, which is surprisingly close to the U.S. Preventive Services Task Force recommended stopping time. However, based on our sensitivity analysis, we find that the decision is highly dependent on a number of factors that may vary among patients. Based on our sensitivity analysis, we find that it may be optimal to discontinue screening as early as age 63 if the quality of life after treatment is expected to be very low.

The partially observable nature of cancers, such as a prostate cancer, make it challenging to estimate model parameters. Our sensitivity analysis provides a basis to help prioritize research on the collection of data to better estimate model parameters. For example, from our sensitivity analysis, we observed that the referral threshold is most sensitive to utility decrements of QALYs, but not very sensitive to the biopsy detection rate. Thus, it appears that improvements in prostate biopsy technology are not likely to significantly influence the expected QALYs of the optimal

Table 9 Sensitivity Analysis for Expected QALYs for a 40-Year-Old Patient Assuming $\pi_{40}(C) = 0$ Comparing the Optimal Policy to Annual PSA Screening with 4.0 ng/mL Threshold for Biopsy, Allowing at Most One Biopsy over One's Lifetime

ϵ	μ	Expected QALYs under optimal biopsy referral policy	Improvement over the guideline (QALYs)	Percentage improvement
0.05	0.01	37.689	0.178	0.472
	0.05	37.660	0.188	0.499
	0.1	37.629	0.207	0.550
0.145	0.01	37.603	0.104	0.277
	0.05	37.574	0.115	0.306
	0.1	37.549	0.140	0.373
0.24	0.01	37.531	0.045	0.120
	0.05	37.507	0.060	0.160
	0.1	37.493	0.096	0.256

Note. Base-case values are shown in bold.

biopsy referral policy. On the other hand, methods for estimating disutilities, an area in which very little research has been done, are very important for measuring the benefit of PSA screening in individual patients. Furthermore, reducing the disutilities of treatment and biopsy could significantly influence the optimal policy, and incorporating individual characteristics of a patient (body mass index and medical history) could help better inform biopsy and treatment decisions.

Our results in §6 shed light on the recent controversy about PSA screening (Andriole et al. 2009, Schröder et al. 2009). For instance, we quantify the benefits of annual PSA screening. The results in Table 8 illustrate the benefits are significantly greater than the benefit per person of some well-known population-based prevention programs such as vaccination against measles and rubella, which has an estimated benefit per person of 0.008 QALYs (Wright and Weinstein 1998). Therefore, our results indicate that there is a potentially significant benefit from PSA screening policies based on the risk of prostate cancer relative to other public health interventions.

Heterogeneity plays an important role in personalized medicine. To achieve a more personalized biopsy referral decision, more information about the individual patient is needed. For example, our results suggest that personalized utility assessment, consideration of comorbidity, and family history of prostate cancer are particularly important directions for future research because we have shown that the optimal policy is highly sensitive to these factors. Once such information is available, it will be easy to obtain personalized screening policy by updating parameter estimation.

There are some limitations of our study, which present opportunities for future research. First, prostatectomy was assumed to be the only treatment because it is one of the most common treatments, and because prostatectomy data was readily available for our study. Our model could be easily adapted to consider other treatment options such as radiation therapy, brachytherapy, and active surveillance, if data on expected quality adjusted survival after such treatments becomes available. Second, we have not considered physical screening through digital rectal examination (DRE). There are several reasons for choosing to omit DRE from the model: (a) accurate DRE data is typically not available in large population-based data sets such as ours; (b) DRE is a highly subjective test (what is worrisome for one physician may not be for another); (c) the large majority of patients that are referred for biopsy are referred based on PSA elevations alone. It is worth noting, however, that if DRE data were available, we could factor it into our model by considering it as an additional observation, without any changes to the structure of our model. Third, we did not consider the

decision to select among multiple treatment options, i.e., we assume the choice of treatment for a given patient is known prior to screening. Fourth, factors such as sexual activity may cause a minor (typically less than 1.0 ng/milliliter), transient (gone within 48 hours) increase in PSA levels (Tchetgen et al. 1996, Herschman et al. 1997). Patients are normally told by their physician not to have sexual activity within 48 hours prior to a scheduled PSA test. However, there could be variation in PSA resulting from imperfect adherence to this recommendation. Our model captures this as a factor influencing the random nature of PSA. Finally, our study is based on a single regional population in Olmsted County, Minnesota. Future work based on a more diverse population could reveal insights about the role of race as a risk factor in prostate biopsy referral decisions.

Our findings in this paper motivate the potential benefits of developing decision support systems to help patients and physicians make decisions about biopsy referral. Many organizations (e.g., the Mayo Clinic, Cardiff University, and the Centers for Disease Control and Prevention), have already developed decision aids for patients facing prostate cancer screening decisions (O'Connor et al. 2009). However, these decision aids do not provide individualized recommendations based on a patient's history of PSA test results, risk factors, or other factors that are likely to influence decisions such as disutility of biopsy and treatment, and all-cause mortality. Our model provides the necessary foundation for implementing such a decision support system.

Electronic Companion

An electronic companion to this paper is available as part of the online version at <http://dx.doi.org/10.1287/msom.1120.0388>.

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