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Award Number: W81XWH-09-1-0512

TITLE: Decision Analysis of the Benefits and Costs of Screening for Prostate Cancer

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REPORT DATE: August 2012

TYPE OF REPORT: Annual Summary

PREPARED FOR: U.S. Army Medical Research and Materiel Command
                         Fort Detrick, Maryland 21702-5012

REPORT DOCUMENTATION PAGE

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1. REPORT DATE	2. REPORT TYPE	3. DATES COVERED
August 2012	Annual Summary	27 July 2011 – 26 July 2012

4. TITLE AND SUBTITLE

Decision Analysis of the Benefits and Costs of Screening for Prostate Cancer

5a. CONTRACT NUMBER

5b. GRANT NUMBER
W81XWH-09-1-0512

5c. PROGRAM ELEMENT NUMBER

6. AUTHOR(S)

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5d. PROJECT NUMBER

5e. TASK NUMBER

5f. WORK UNIT NUMBER

7. PERFORMING ORGANIZATION NAME(S) AND ADDRESS(ES)

Dana-Farber Cancer Institute
Boston, MA 02115

8. PERFORMING ORGANIZATION REPORT NUMBER

9. SPONSORING / MONITORING AGENCY NAME(S) AND ADDRESS(ES)
U.S. Army Medical Research and Materiel Command
Fort Detrick, Maryland 21702-5012

10. SPONSOR/MONITOR'S ACRONYM(S)

11. SPONSOR/MONITOR'S REPORT NUMBER(S)

12. DISTRIBUTION / AVAILABILITY STATEMENT
Approved for Public Release; Distribution Unlimited

13. SUPPLEMENTARY NOTES

14. ABSTRACT

PURPOSE/SCOPE: Observation has emerged as a strategy to avoid overtreatment in men with screen-detected low-risk prostate cancer (CaP). This analysis examines the cost-effectiveness of observation with watchful waiting (WW) or active surveillance (AS), radical prostatectomy (RP), radiation therapy (IMRT), and brachytherapy (BT) in these men. METHODS: A Markov Monte Carlo model was constructed: adverse effects (AE) of treatment were included. Main outcomes were costs (2008US$), quality-adjusted life-years (QALYs), and incremental cost-effectiveness ratios (ICERs) for men 65, 55, and 75 years of age. RESULTS: In 65 year old men, AS was associated with the greatest QALE but at $35,201 was more expensive than brachytherapy(ICER $15,420/QALY); RP and IMRT were dominated. In 55 and 75 year old men these ICERs were $8,374/QALY and $8,671/QALY, respectively. When costs of treatment of adverse effects were doubled, AS became least expensive in all men. When the PIVOT trial was simulated, WW was cost-saving compared with AS and RP and remained less expensive and associated with improved QALE over a wide range of cost and utilities, including if the risk of CaP-specific death on AS was 50% the risk on WW. CONCLUSIONS: In this model, observation is a cost-effective alternative to initial treatment and is underutilized in these men.

15. SUBJECT TERMS
Prostate cancer, screening, cost-effectiveness analysis

16. SECURITY CLASSIFICATION OF:			17. LIMITATION OF ABSTRACT	18. NUMBER OF PAGES	19a. NAME OF RESPONSIBLE PERSON USAMRMC
a. REPORT	b. ABSTRACT	c. THIS PAGE			19b. TELEPHONE NUMBER *(include area code)*
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INTRODUCTION

This annual report details the progress that has been made between July 2011 and July 2012, the third year of the Physician Research Training Award entitled "Decision analysis of the benefits and costs of screening for prostate cancer". Of note, I was on maternity leave from January 25 to April 25, 2012, as I communicated in a letter sent in May in which I also apologized for not having communicated my plans prior to January. The goal of the proposed research is to develop a decision analytic model of PSA screening for prostate cancer. This model will permit the analysis of the effect of various PSA screening strategies on life expectancy (LE), quality-adjusted LE (QALE), and the cost-effectiveness of screening. The comparator will be a natural history model of unscreened, conservatively-treated prostate cancer based on primary data unique in its duration of follow up and inclusion of Gleason scores from the modern era. It is hypothesized that the optimal screening strateg(ies) for prostate cancer will be dependent not only upon mortality benefit, but also upon the value patients place on health states and costs.

This report will summarize the accomplishments that have been made in undertaking the tasks outlined in the Statement of Work. Due to difficulties that have arisen in conducting Task 1, previously reported and, the majority of the work conducted to date has been on Task 3. The portion of the model described in Task 3 assesses the life expectancy, quality-adjusted life expectancy, and cost-effectiveness of treatment in screened vs. unscreened men with prostate cancer. Over the past three years, a model has been constructed comparing first the effectiveness, then the cost-effectiveness of treatment strategies for low-risk, clinically localized prostate cancer. The strategies previously modeled included active surveillance, radical prostatectomy, brachytherapy, intensity-modulated radiation therapy, and proton beam therapy. It was found that active surveillance is the most effective strategy of these, or associated with the greatest quality-adjusted life expectancy, but brachytherapy is the least expensive treatment. Active surveillance remained cost-effective under all scenarios constructed and in men aged 55 to 75. Results of this model have been published in the *Journal of the American Medical Association*[1], presented at annual meetings of professional societies, discussed in a teleconference sponsored by the Institute for Healthcare Improvement and *JAMA*, and discussed at the Cancer Intervention and Surveillance Modeling Network's (CISNET) Annual Conference at the National Institutes of Health. A second manuscript arising from this model incorporating costs and including an analysis of watchful waiting based on data recently published from the PIVOT trial[2], is currently being revised for resubmission to *Annals of Internal Medicine*, and a third is being written.

This report will also summarize the training accomplishments achieved over the past year. As planned, I have continued to receive training in the construction and population of a Markov Monte Carlo model, and I have participated and presented in institutional conferences. I have participated in meetings with my mentors as planned. Although my travel has been limited this year, I resume presentation and attendance at professional society annual meetings this month.

Although the order in which the work is being conducted has changed due to circumstances beyond my control, the tasks outlined in the original statement of work will be performed as originally planned. I look forward to the opportunity to continue working on this timely and important work.

BODY

TASK 1: Develop a Markov Monte Carlo disease model of the natural history of prostate cancer.

Methods. We will create a Markov Monte Carlo disease model of the natural history of prostate cancer. Individuals will progress from a disease-free state to preclinical disease to clinically-detectable prostate cancer; each individual will have a PSA value and, in those with prostate cancer, a Gleason score. Men with disease will progress from clinically localized to regional to metastatic disease and death of prostate cancer; they may also progress between Gleason scores. Death of other causes can occur from any health state.

Task 1.1 Utilizing data from the published literature, create a model of the preclinical development of prostate cancer. Estimates of age-specific prevalence of preclinical prostate cancer, correlation of the presence of preclinical disease with serum PSA, and evaluation of PSA rise in the serum of patients subsequently diagnosed with prostate cancer will be obtained from the published literature. This data will be combined using regression analysis to estimate the preclinical incidence and progression of disease based on Gleason score and PSA.

Task 1.2 Utilizing data from the control arm of the ERSPC, create a model of the characteristics of prostate cancer at diagnosis in a contemporary, unscreened population. We will utilize data provided by investigators from the ERSPC to model tumor and patient characteristics of clinically-diagnosed prostate cancer in the modern era, including age, stage at diagnosis, and Gleason score,

Task 1.3 Utilizing data from a database of men diagnosed in the pre-PSA era, create a model of the progression of clinically localized, conservatively-treated prostate cancer. We have created a database of such men in collaboration with investigators from Örebro, Sweden, that will be used to develop transition probabilities between model health states described in Task 1.1. We will collaborate with Dr. D'Amico in interpretation and analysis of the data, particularly with regard to modeling PSA kinetics.

Task 1.4 Calibrate the model using data from published studies of the natural history of conservatively-treated prostate cancer and recent clinical trials. We will calibrate the model to reproduce target outputs within 5% of pre-selected values. Sources of calibration data for our model will include incidence data from the control arm of the ERSPC and the published literature.

Timeline: The collection and analysis of data from the ERSPC and the Örebro cohort and from the published literature will take 9 months. Construction and calibration of the natural history model will take 15 months. Two manuscripts will be generated: the first will reflect findings from the primary data, and the second will describe the natural history model. I will also take a course during the fall of the first year in order to acquire skills necessary to develop transition probabilities from the published literature.

Outcomes: This task will result in the creation of a natural history model of unscreened, conservatively-treated prostate cancer that will provide data on characteristics of patients at clinical diagnosis and at progression, rates of progression, and prostate cancer specific- and all cause mortality.

Progress report:

The construction of this portion of the model is crucially dependent upon data obtained from the Örebro cohort, as described in Task 1.3. This model will be unique in that it will be able to trace the natural history of prostate cancer in men diagnosed in the pre-PSA era whose prostate cancer has been regraded in the modern era, hence avoiding the concern raised by the fact that Gleason scores have shifted higher over the past 20 years. As described in previous progress reports, during analysis of the data from Örebro during the first 9 months of the grant period, I realized that in our cohort, Gleason score did not correlate with prostate cancer-specific survival. This finding is at odds with the published literature and prompted me to question the accuracy of the Gleason grading performed. A representative selection of pathologic samples was obtained from Örebro and regraded by a pathologist at Massachusetts General Hospital. It was realized that serious errors in Gleason scoring had been made and that as a result, this data was unusable. Therefore, the decision has been made to have all the samples in the cohort regraded. However, in the interim, in working with colleagues in Örebro and at the Harvard School of Public Health, additional patients have been

identified to be added to the patient population. We are therefore still in the process of regrading Gleason samples; although last year it was anticipated that this regrading would be completed by December 2011, this date has been pushed back. It is now hoped that we will have corrected Gleason scoring in the next few months (I am currently awaiting an update from my coinvestigators with a more exact date, but as it is August in Sweden and they are away, I have not yet had a response). The timeline for both Tasks 1 and 2 will therefore be shifted forward by approximately 24 months. Since the discovery of this complication, my research efforts have therefore been primarily focused on Task 3, as described below.

TASK 2: Compare the clinical effectiveness, cost and cost-effectiveness of PSA screening strategies.

Methods. *Task 2.1 Vary the biopsy threshold for screening PSA, the interval between screening events, and establish the effect of PSA kinetics prior to diagnosis on screening strategies.* We will first assess the effect of annual screening varying PSA biopsy thresholds. We will then vary the interval between PSA screening events using these thresholds. These two variables will then be modified simultaneously to identify the screening strategy that maximizes LE. Subsequent analyses will focus on identifying the optimal screening strategy once a PSA velocity has been established. The model will vary PSA velocity, biopsy threshold, and subsequent screening interval simultaneously. Similar analyses will be performed using PSA doubling time.

Task 2.2 For each strategy, establish the lead time and effect on prostate cancer incidence. To quantitate lead time, the difference in time between screen diagnosis and clinical diagnosis of prostate cancer will be calculated. To estimate incidence and overdiagnosis rates, incidence in the presence and absence of screening will be compared.

Task 2.3 Extend the model to include quality of life adjustments (utilities) and costs and use the model to estimate the clinical effectiveness, cost, and cost-effectiveness of each screening strategy.
We will run the model using both community and patient-elicited utilities from the published literature and unpublished results provided by Dr. Murray Krahn[30-33]. Dr. Swan will assist in analysis of these utilities and their incorporation into the model. Costs will be estimated from a societal perspective[48-50]. Costs and QALYs will be discounted. Total cost will be the sum of direct medical costs. Costs will be calculated using data from the medical literature or local institutional cost data and will be expressed in 2008 dollars.
The model will estimate the QALE and costs associated with each screening strategy. The model results will estimate the magnitude of benefit for intermediate and long-term outcomes, costs of care, and incremental cost-effectiveness.

Task 2.4 Identify model parameters likely to cause a shift in model results using sensitivity analysis. We will perform sensitivity analysis on parameters likely to have a significant effect on LE in our model. The model will be run across a literature-derived plausible range of probabilities for selected variables.

Timeline: Modification of the model to assess screening strategies, model calibration, and the calculation of lead time, incidence, and overdiagnosis rates will take approximately one year. Identification of costs, analysis and incorporation of utilities, cost-utility analysis and sensitivity analysis are projected to take nine months. I will take several courses at HSPH during the first two years to acquire the skills necessary for this task. One manuscript will be generated after completion of the screening model to describe the effect of screening on LE in conservatively-treated patients and the lead time and overdiagnosis associated with screening; the second at the completion of the CEA.

Outcomes: This task entails the creation of a PSA screening model that will compare outcomes in screened versus unscreened conservatively-treated men. Outcomes will include LE, QALE, and cost-effectiveness for each strategy and identification of the strategy that maximizes each of these outcomes; secondary outcomes will include lead time, incidence, and overdiagnosis rates for each strategy.

Progress report:
This task, originally planned to be undertaken during months 18-42, will be conducted months 42-60.

TASK 3: **Modify the model created in Task 2 to include modern treatment practices to evaluate the clinical effectiveness, cost, and cost-effectiveness of the PSA screening strategies described above.**
Methods. *Task 3.1 Extend the model created in Task 2 to include modern treatment practices.* We will incorporate modern treatment practices into the model to determine the effect of screening and treatment of screen-diagnosed disease on LE, QALE, and its cost-effectiveness. Treatments and outcomes will be obtained from the published literature and expert opinion, and sensitivity analysis will be performed[7,53,54].
Task 3.2 Extend the model to include quality of life adjustments (utilities) and costs and use the model to estimate the effectiveness, cost, and cost-effectiveness of each screening strategy. In treated men, utilities and costs will be calculated, and effectiveness and cost-effectiveness of each screening strategy will be estimated, as described in Task 2.3.
Task 3.3 Explore the role of future, as-yet-undeveloped diagnostic tests in screening for prostate cancer to establish the test characteristics required in order to identify men with clinically significant disease. The creation of a natural history model will enable us to identify the characteristics of prostate cancer most predictive of outcomes. Decision analytic modeling will highlight predictors of adverse outcomes in our model and will enable us to use them to characterize an "ideal" screening test.
Timeline: Modification of the model to include modern treatment practices and its calibration will take one year. Identification of costs, analysis and incorporation of utilities, cost-utility analysis and sensitivity analysis are projected to take nine months; analysis and comparison of these results with those obtained in Task 2 will take 3 months. Two manuscripts will be produced: the first describing the effect of screening on LE in treated vs. untreated men, the second at the completion of the CEA. Courses I will take to acquire skills necessary for this task will be taken during the second and third years. I will attend seminars and national meetings and continue clinical work with prostate cancer patients throughout the award period.
Outcomes: Outcomes for this task will include LE, QALE, and cost-effectiveness for each screening strategy in men treated for prostate cancer and identification of the screening strategy that maximizes each of these outcomes.

Progress report:
In a previous progress report, we described the Markov Monte Carlo model comparing active surveillance to treatment at diagnosis with radical prostatectomy or radiation therapy using brachytherapy, intensity-modulated radiation therapy, or proton beam therapy. Briefly, a societal perspective was taken with a lifetime horizon. A systematic review of the literature was performed to establish transition probabilities for disease outcomes and for the probabilities of incurring complications of surgery and adverse effects (erectile dysfunction, urinary incontinence, gastrointestinal dysfunction)[3-5]. Utilities were obtained from literature review and from personal communication[6-8], (personal communication, Stewart). Outcomes included QALEs, used for comparative effectiveness analysis, previously described and published in *JAMA*[1].

The model has also been utilized to produce cost-effectiveness data. Costs for the model have been obtained from Medicare reimbursement schedules and include costs of initial treatment, treatment of side effects, and patient time costs. We submitted a manuscript of our cost-effectiveness analysis to *Annals of Internal Medicine* in April and received a request for revision from that journal at the end of May. This analysis compares the cost-effectiveness of active surveillance, brachytherapy, intensity-modulated radiation therapy, and radical prostatectomy. We are also conducting analyses for this manuscript comparing these approaches to watchful waiting. Recently, results of the PIVOT study comparing watchful waiting to radical prostatectomy were published – the first randomized controlled trial in a screened population - that

demonstrated no mortality benefit to radical prostatectomy compared to watchful waiting after 10 years of follow up, and indeed a trend towards harm in men with low-risk disease treated with surgery[2]. Watchful waiting, with its non-curative, non-interventionist approach, would be expected to provide less benefit than active surveillance compared to treatment, so these results raise important questions regarding the optimal surveillance approach to take.

This manuscript will be resubmitted within the next month. Changes to our model in response to reviewer comments include
1) structural changes to account for competing mortality,
2) incorporation of discussion of different types of radical prostatectomy,
3) and a simulation of the PIVOT study (published in July)[2].
4) We have also updated our review of the literature, in particular to reflect recent publication of key articles on active surveillance (for example the REDEEM study)[9].

We have demonstrated that active surveillance is cost-effective when compared to initial treatment in men aged 55-75. However, when the model is modified to reflect the population and outcomes of the PIVOT trial, watchful waiting is both more effective and less expensive than either active surveillance or watchful waiting. This finding holds true even if the risk of death on active surveillance compared to watchful waiting is reduced by 50%. The current intensity of approach to active surveillance, with frequent follow up and surveillance biopsies, is therefore called into question.

Completed abstracts and manuscripts are listed in the Reportable Outcomes section of this report.

The completed model described above is specific to men with low-risk prostate cancer (Gleason $\leq$ 3+3; clinical stage $\leq$T2a, PSA <10 ng/mL). Modifications necessary to generalize this model to all men treated after screening will include a review of the literature to establish prostate cancer-specific outcomes for men with intermediate and high-risk disease, outcomes that are expected to be reflected in shorter life expectancies for men with higher-risk disease. It is anticipated that these modifications to the model will require 6 months to complete and will take place from months 54-60 of the grant period, as originally planned.

Over the course of this year, I have continued to analyze practice patterns for the treatment of men with biochemical recurrence of prostate cancer after definitive treatment and with metastatic disease using our institutional CRIS (Prostate Cancer Research Information System) database at Dana-Farber Cancer Institute. A manuscript of these analyses is currently being written. The next step in this project will be to analyze the costs of these treatments. This analysis, will provide information regarding costs incurred by patients from recurrence of their disease after treatment to death for use to address Task 3.2[10].

KEY RESEARCH AND TRAINING ACCOMPLISHMENTS

Research Accomplishments:

In summary, work completed on this grant proposal to date has demonstrated that
   a) in screen-detected men with low-risk prostate cancer, active surveillance is a cost-effective alternative to initial treatment with radical prostatectomy or radiation therapy (with brachytherapy, intensity-modulated radiation therapy, or proton beam therapy), for men between 55 and 75 years of age at diagnosis.
   b) the quality-adjusted life expectancy benefit of active surveillance seen in these men is robust but depends upon the patient preferences, or utilities, associated with being on active surveillance and with having been treated.
   c) observation with watchful waiting as practiced in the PIVOT study is associated with improved QALE and is cost saving compared to either active surveillance or initial treatment.

Training accomplishments:

   a) I have built a Markov Monte Carlo model, acquiring skills including model design, the derivation of probabilities to populate the model, utilities, and costs through regular instruction by my mentor Dr. Michael Barry, Dr. James E. Stahl, Dr. Pamela McMahon.
   b) Completion of the Society for Medical Decision Making's Meta-Analysis Course, October 2010
   c) Attendance at
       ITA Core Seminar, a weekly seminar at ITA with didactic lectures focusing on study design, analysis, and grant-writing, and presentations of ongoing research including decision analysis, cancer outcomes, technology and quality of life assessment.
       Lank Center for GU Oncology Seminar, a bi-monthly lecture series during which basic research and recent developments in the diagnosis and treatment of GU cancers are presented.
       Lank Center for GU Oncology Journal Club, a monthly presentation of critical articles in genitourinary cancer basic and clinical research.
       Dana-Farber/Harvard Cancer Center Outcomes Research Seminar, a weekly seminar at DFCI focusing on study design and analysis and critical review of work in progress.
   d) I have continued my clinical training under the guidance of Dr. Philip Kantoff through seeing patients 1.5 days/week and case discussions in both formal and informal settings.

REPORTABLE OUTCOMES

Manuscripts:

Hayes JH, Ollendorf DA, Pearson SD, et al. Active surveillance compared with initial treatment for men with low-risk prostate cancer: a decision analysis. *JAMA*. Dec 1 2010;304(21):2373-2380.

Hayes JH, Ollendorf DA, Pearson SD, Barry MJ, Kantoff PW, Lee PA, McMahon PM. Active surveillance vs. Initial treatment for men with low-risk prostate cáncer: A cost-effectiveness analysis. Revising for resubmission to *Annals of Internal Medicine*.

An analysis evaluating the cost-effectiveness of new technologies such as IMRT, proton beam therapy, and robot-assisted laparascopic radical prostatectomy is in progress.

Abstracts:

Hayes JH, Ollendorf DA, Pearson SD, McMahon PM. Cost-effectiveness analysis of therapeutic options for low-risk prostate cancer. ASCO Genitourinary Cancers Symposium. 2010; abstr 170.

Hayes JH, Ollendorf DA, Barry MJ, Pearson SD, McMahon PM. Therapeutic options for low-risk prostate cancer: A cost-effectiveness analysis. J Clin Oncol 28:7s, 2010 (suppl; abstr 6012).

Hayes JH, Ollendorf DA, Barry MJ, Pearson SD, McMahon PM. A Cost-effectiveness analysis of therapeutic options for low-risk prostate cancer. Med Decis Making, January/February 2011; vol. 31, 1: p.E100.

Presentations:

Hayes JH, Ollendorf DA, Barry MJ, Pearson SD, McMahon PM. Therapeutic options for low-risk prostate cancer: A cost-effectiveness analysis. J Clin Oncol 28:7s, 2010 (suppl; abstr 6012).
Juried Poster Presentation

Hayes JH, Ollendorf DA, Barry MJ, Pearson SD, McMahon PM. A cost-effectiveness analysis of therapeutic options for low-risk prostate cancer. Abstract 5418.
Oral presentation, Society for Medical Decision Making Annual Meeting, October 2010

Hayes, JH. Active Surveillance vs. Initial Treatment for Low-Risk Clinically Localized Prostate Cancer. Invited Speaker, Cancer Intervention and Surveillance Modeling Network Annual Meeting. NIH, Bethesda, MD. December 2010.

Hayes, JH. Author in the Room Teleconference: Active Surveillance Compared With Initial Treatment for Men With Low-Risk Prostate Cancer: A Decision Analysis. Invited

Speaker, Institute for Healthcare Improvement and Journal of the American Medical Association, Chicago, IL. January 2011.

Patents and licenses applied for/issued:

     None

Degrees obtained that are supported by this training grant:

     None

Development of cell lines, tissue or serum repositories:

     None

Informatics such as databases and animal models:

     None

Funding applied for based on work supported by this award:

     Prostate Cancer Foundation Young Investigators Award.
     Applied for and received, grant period July 2010 to July 2013.
     The funds from this award are used to pay the salary of a computer programmer
     who is assisting in the development of the natural history model.

Employment or research opportunities applied for and/or received based on experience/training supported by this grant

     None

CONCLUSIONS

In screen-detected men with low-risk prostate cancer, observation appears to be a safe and effective alternative to initial treatment. In our model comparing active surveillance (AS) to initial treatment, the quality of life advantage associated with AS is robust, reflecting the deferred and substantially lower incidence of side effects of treatment experienced by men on AS. AS is associated with significant improvements in QALE even in analyses in which the probability of dying of prostate cancer or of developing progressive disease on AS is increased. However, our finding that the optimal strategy is sensitive to utility weights is evidence that the decision whether to pursue AS must be individualized. In future, models incorporating individual patient utilities may be available to assist patients and their caregivers to estimate the risks and potential benefits of AS prior to making this decision.

Active surveillance is also a cost-effective therapeutic approach in men between the ages of 55 and 75. In this model, active surveillance was associated with an ICER of only $$15,420/QALY for 65 year old men as compared to brachytherapy, the next most effective strategy, well below the traditional willingness-to-pay threshold of $50-75,000/QALY. The cost-effectiveness of active surveillance as compared to initial treatment is maintained over sensitivity analyses including probability of adverse effects, progressive disease on active surveillance, and utilities.

Watchful waiting has also emerged as an intriguing alternative both to initial treatment and to the more interventionist active surveillance. When the results of the PIVOT study were modeled, it was found that watchful waiting was both more effective and less expensive than either active surveillance or initial treatment, even if the risk of dying of prostate cancer on active surveillance is half that of watchful waiting. Observation for low-risk prostate cancer is a promising strategy both on an individual and on a societal level, and it is hoped that increasing utilization of this approach will counteract the overtreatment resulting from PSA screening.

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