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Cost-effectiveness Analysis of Active Surveillance Strategies for Men with Low-risk Prostate Cancer

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Abstract

Background: Active surveillance (AS) has become the recommended management strategy for men with low-risk prostate cancer. However, there is considerable uncertainty about the optimal follow-up schedule in terms of the tests to perform and their frequency.
Objective: To assess the costs and benefits of different AS follow-up strategies compared to watchful waiting (WW) or immediate treatment.
Design, setting, and participants: A state-transition Markov model was developed to simulate the natural history (ie, no testing or intervention) of prostate cancer for a hypothetical cohort of 50-yr-old men newly diagnosed with low-risk prostate cancer. Following diagnosis, men were hypothetically managed with immediate treatment, watchful waiting, or one of several AS strategies. AS follow-up was performed either with transrectal ultrasound-guided biopsy or magnetic resonance imaging (MRI) which was scheduled annually, biennially, every 3 yrs, according to the PRIAS protocol (yrs 1, 4, 7, and 10, and then every 5 yr) or every 5 yr. Diagnosis of higher-grade or -stage disease while on AS resulted in curative treatment.
Outcome measurements and statistical analysis: We measured discounted quality-adjusted life years (QALYs), discounted lifetime medical costs (2017 US$), and incremental cost-effectiveness ratios (ICERs).
Results and limitations: Compared to WW, MRI-based surveillance performed every 5 yr improved quality-adjusted survival by 4.47 quality-adjusted months and represented high-value health care at the Medicare reimbursement rate using standard cost-effectiveness metrics. Biopsy-based strategies were less effective and less costly than the corresponding MRI-based strategies for each testing interval. MRI-based surveillance at more frequent intervals had ICERs greater than $800 000 per QALY and would not be considered cost-effective according to standard metrics. Our results were sensitive to the diagnostic accuracy and costs of both biopsy modes in detecting clinically significant cancer.
Conclusions: Incorporation of MRI into surveillance protocols at Medicare reimbursement rates and decreasing the intensity of repeat testing may be cost-effective options for men opting for conservative management of low-risk prostate cancer.
Patient summary: Our study modeled outcomes for men with low-risk prostate cancer undergoing watchful waiting, immediate treatment, or active surveillance with different follow-up schedules. We found that conservative management of low-risk disease optimizes health outcomes and costs. Furthermore, we showed that decreasing the intensity of active surveillance follow-up and incorporating magnetic resonance imaging (MRI) into surveillance protocols can be cost-effective, depending on the MRI costs.

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1. Introduction

Nearly 50% of prostate cancers diagnosed are classified as low-risk according to the D'Amico risk stratification system (ie, T1–T2a, Gleason score ≤6, and prostate specific antigen [PSA] ≤10 ng/ml) [1] and are typically indolent with limited potential to progress [2–4]. Hence, in an attempt to quell overtreatment, active surveillance (AS) has become the recommended management strategy for men with low-risk prostate cancer [5]. The safety of this practice compared with local treatment has been demonstrated by two randomized trials [6,7]. In addition, several large cohorts of men with favorable- or intermediate-risk prostate cancer had high cause-specific survival rates and a low risk of metastases at 10 yr [8,9].

Despite the popularity of AS, there is considerable uncertainty about the optimal follow-up schedule in terms of which tests to perform and at what frequency. PSA and transrectal ultrasound-guided biopsy (TRUSB) have been the mainstay of AS follow-up protocols, but recent advances in magnetic resonance imaging (MRI) and MRI-guided biopsy (MRGB) have resulted in their incorporation into clinical practice. Conducting a randomized trial to compare the efficacy of multiple follow-up schedules would not be practical. However, decision analysis methodology can be used to project long-term outcomes associated with different follow-up strategies.

2. Materials and methods

2.1. Overview

We developed a state-transition Markov model with 6-mo cycles to simulate the downstream events for men diagnosed with low-risk prostate cancer (Gleason 6, stage ≤T2) in the absence of intervention. A percentage of these men will have misclassified disease at initial diagnosis, and over time can develop symptoms of their disease, progress in grade and/or stage, develop preclinical or clinical metastatic disease, or die from prostate cancer or other causes. We simulated conditions for these men under different AS strategies in which clinically significant preclinical disease could be identified and treated before becoming symptomatic (Supplementary Fig. 1). Detection of any disease of grade and/or stage higher than Gleason 3 + 3 = 6 and clinical stage T2 resulted in proceeding to treatment. Earlier detection of significant disease was associated with a higher probability that treatment occurred before the development of metastases. We evaluated follow-up AS strategies based on those used in the large AS cohort studies and alternative strategies endorsed by experts.

The primary outcomes evaluated were discounted lifetime medical costs and discounted quality-adjusted life years (QALYs). Secondary outcomes included the number of simulated individuals who developed metastatic disease or died from prostate cancer, the number of lifetime biopsies, and the percentage of men who underwent curative treatment. Costs were calculated from a health sector perspective. Both costs and outcomes were assessed over a lifetime horizon and discounted at 3% [10].

2.2. Diagnostic strategies

The strategies evaluated for men with low-risk prostate cancer included watchful waiting (WW), immediate treatment with radical prostatectomy, and alternative AS strategies. For WW, further investigation using TRUSB was initiated only by the onset of clinical symptoms. AS strategies were either MRI- or biopsy-based. For biopsy-based follow-up, systematic biopsies were performed at scheduled intervals. For MRI-based strategies, MRI scans were performed at the scheduled intervals and individuals with abnormal findings (Prostate Imaging-Reporting and Data System grade ≥3) underwent MRGB. We evaluated the following testing schedules: annually; every 2 yr; the PRIAS protocol (yrs 1, 4, 7, and 10, and then every 5 yr) [11]; and every 5 yr. We assumed that the mode of curative treatment for those found with grade or stage reclassification was radical prostatectomy and that simulated individuals with localized disease without preclinical metastases who underwent surgery were completely cured (ie, positive surgical margin rate of zero and postoperative PSA of zero). This assumption was made because there are no data describing the prevalence of underlying preclinical (undetected) metastases at the time of curative treatment. We performed sensitivity analyses on this parameter in our natural history model, which confirmed that this did not affect outcomes.

For AS strategies we assumed that all simulated individuals underwent a repeat biopsy or MRI within the 1st yr of follow-up to reflect real-world practice. A negative confirmatory biopsy decreased the risk of disease reclassification (risk ratio 0.41, 95% confidence interval 0.22–0.77) [12]. As part of the follow-up schedules, a PSA test was performed every 6 mo. We assumed that an abnormal PSA result, defined as a PSA doubling time of <3 yr, triggered further testing with a biopsy or MRI depending on the surveillance strategy, as is the current practice in a large contemporary AS cohort [13]. PSA kinetics were not used as a trigger to initiate treatment directly, as studies have demonstrated a lack of specificity [14,15]. To further reflect real-world clinical practice, we assumed that an individual who underwent a biopsy in a 6-mo period would not undergo another biopsy in the next 6-mo period, unless his PSA was abnormal or he developed symptoms of progression. We recognize that clinicians may use differing PSA parameters and cutoffs as the threshold for "abnormal" PSA, and hence it is the estimate of sensitivity that is important rather than the exact definition, and we performed sensitivity analyses on this estimate. Adherence rates to testing while on an AS program were derived from published sources and expert opinion (Table 1) [16]. AS ceased at age 75 yr.

2.3. Misclassification of disease eligible for AS

We superimposed a PSA screening mechanism on the natural history model (Supplementary material) to reflect the contemporary presentation of low-risk disease. We applied the sensitivity of TRUSB to determine misclassification (ie, percentage of patients with Gleason 6 cancer who have underlying Gleason ≥7 disease). We validated the model output via comparison to the grade distribution from the first round of the European Randomized Study of Screening for Prostate Cancer trial [17,18]. The base-case estimate of misclassification was 18.8% but increased with age, and sensitivity analyses were conducted on this parameter.

2.4. Quality of life

To calculate QALYs, each year of life spent in a health state was weighted by a value between 0 and 1 to reflect the health-related quality of life of that state, where 0 represents death and 1 represents perfect health. Utilities were obtained from the Cost-Effectiveness Analysis Registry [19]. We used a utility of 0.97 for patients on AS, which was derived by pooling estimates from published sources [20–24]. The disutility from morbidity due to treatment was applied for the duration of a single cycle, whereas the disutility from biopsy was only applied for 3 wk [20,25]. The disutility for treatment and side effects was estimated from published studies [26]. The utility reported for the terminal stage of prostate cancer was applied to the 6 mo before prostate cancer death [27].

Table 1 – Model parameters

Parameter	Estimate (range)	Source
Test characteristics		
TRUSB sensitivity for clinically significant cancer	0.67 (0.55–0.85)	[39,44,45]
TRUSB specificity clinically significant cancer	1.00	Assumption
MRI sensitivity for clinically significant cancer	0.94 (0.70-0.97)	[46–49]
MRI specificity clinically significant cancer	0.30 (0.20–0.80)	[46–49]
MRGB sensitivity clinically significant cancer	0.90 (0.78–0.98)	[39,40,45]
MRGB specificity clinically significant cancer	1.00	Assumption
PSA-DT sensitivity for clinically significant cancer	0.495 (0.20–0.70)	[50,51]
PSA-DT specificity for clinically significant cancer	0.508 (0.40–0.90)	[50,51]
Adherence		
Scheduled TRUSB	0.60 (0.00–1.00)	[16]
PSA-triggered TRUSB	0.30 (0.00–1.00)	[16]
Scheduled MRI	0.90 (0.00–1.00)	Assumption
PSA-triggered MRI	0.55 (0.00–1.00)	Assumption
MRGB	0.82 (0.50–1.00)	[52]
Costs		
Office visit	$74 ($37–$148)	Medicare [53]
PSA test	$43 ($21–$86)	
MRI	$591 ($295–$1182)	
TRUSB	$829 ($414–$1658)	
MRGB	$899 ($449–$1798)	
Curative treatment	$21 046 ($10 523–$42 092)	[28]
Biochemical recurrence treatment		[26]
No salvage treatment	$2074 ($1037–$4148)	
Androgen deprivation therapy	$2997 ($1499–$5994)	
Radiotherapy	$32 228 [16 114–64 456]	
Biochemical recurrence (continuing cost)	$2076 ($1038–$4152)	
Metastasis		
Initial cost	$19 123 ($9561–$38 246)	[26]
Continuing cost (annual)	$37 231 ($18 616–$74 462)	Unpublished data
Prostate cancer death	$46 636 ($23 318–$93 272)	[26]
Utilities (annual)		
Active surveillance	0.97 (0.90–1.00)	[20,24]
Post-treatment care	0.94–0.95 (0.85–0.96)	[20,26] [a]
Metastatic disease	0.58 (0.20–0.80)	[54]
Terminal cancer stage (6 mo before prostate cancer death)	0.25 (0.00–0.400)	[27]
Disutility from biopsy (for 3 wk)	0.004 (0.002–0.006)	[20]
Disutility from treatment (for one cycle, ie, 6 mo)	0.11 (0.05–0.22)	[25]

MRGB = MRI-guided biopsy; MRI = magnetic resonance imaging; PSA = prostate-specific antigen; PSA-DT = PSA doubling time; TRUSB = transrectal ultrasound-guided biopsy.
[a] Depending on the risk of recurrence.

2.5. Costs

The costs for an office visit and medical investigations were obtained from the Medicare physician fee schedule. The cost of radical surgery for disease progression included payments for hospital care, outpatient care, physician services, home health, hospice care, and medical equipment utilized in the 1st yr after treatment [28]. All costs were inflated to 2017 US$ using the Consumer Price Index published by the Bureau of Labor Statistics [29].

2.6. Analysis

The model was used to project discounted QALYs and discounted lifetime medical costs for each strategy. The incremental cost-effectiveness ratio (ICER) represents the cost of gaining an additional QALY and conveys the value of a health care intervention. The willingness-to-pay threshold (WTP) to determine cost-effectiveness is debated, but an ICER less than $100 000 has generally been considered to be cost-effective, although this threshold could be higher in different settings [30,31]. We performed deterministic and probabilistic sensitivity analyses to test the robustness of our results. Published sources and expert opinion were used to obtain ranges for test characteristics and utilities in the sensitivity analyses. Costs were varied between half and double the base-case estimates.

The model was programmed in TreeAge Pro (TreeAge Software, Williamstown, MA, USA) with calibration performed in R (R Foundation for Statistical Computing, Vienna, Austria).

3. Results

3.1. Base case: 50-yr-old man newly diagnosed localized low-grade prostate cancer

Model outputs were validated against observed clinical data (Supplementary material). Compared to WW, all strategies increased both costs and QALYs (Table 2). MRI-based surveillance was more effective and more costly than biopsy-based strategies at the same testing interval. For WTP thresholds between $100 000 and $200 000 per QALY, performing MRI every 5 yr was cost-effective. For a WTP of $50 000 per QALY, biopsy-based surveillance performed at 5 yr intervals was cost-effective.

Table 2 – Cost-effectiveness results for a 50-yr-old man with newly diagnosed low-risk prostate cancer[a]

Strategy	Total			Incremental		ICER
	Cost (US $)	Effectiveness (QALYs)	Life years (LYs)	Cost (US $)	Effectiveness (QALYs)	($/QALY)
Watchful waiting	11 446	17.199	17.815	–	–	–
Biopsy every 5 yr	15 292	17.523	18.090	3486	0.324	11 874
PRIAS biopsy schedule	15 848	17.528	18.096	–	–	ED
Biopsy every 3 yr	16 109	17.528	18.096	–	–	AD
Biennial biopsy	16 751	17.531	18.101	–	–	ED
Annual biopsy	18 676	17.534	18.111	–	–	ED
MRI every 5 yr	19 850	17.572	18.130	4559	0.050	92 068
PRIAS MRI schedule	20 812	17.574	18.132	962	0.001	817 058
MRI every 3 yr	21 238	17.573	18.132	–	–	AD
Immediate treatment	21 819	17.382	17.882	–	–	AD
Biennial MRI	22 349	17.574	18.134	$1,537	0.001	6 275 078
Annual MRI	25 693	17.573	18.139	–	–	AD

AD = absolute dominance; ED = extended dominance; ICER = incremental cost-effectiveness ratio, MRI = magnetic resonance imaging; QALY = quality-adjusted life year.

[a] Strategies that cost more and were less effective than another strategy were ruled out by simple dominance and strategies that were less effective than another but with a higher ICER were ruled out due to extended dominance. Reported costs, effectiveness, and life years are discounted.

Table 3 – Outcomes per 1000 individuals with low-risk prostate cancer

Strategy	Biopsies (*n*)	Men undergoing curative treatment (*n*)	Men with metastasis (*n*)	Prostate cancer deaths (*n*)
Watchful waiting	249	69	91	77
Immediate treatment	0	997	5	4
Biopsy-based AS				
Annual biopsy	12 572	299	21	18
Biennial biopsy	9217	289	23	20
Biopsy every 3 yr	8093	284	25	21
PRIAS biopsy schedule	7588	280	25	22
Biopsy every 5 yr	6705	270	27	23
MRI-based AS				
Annual MRI	10 709	312	17	14
Biennial MRI	8267	308	18	15
MRI every 3 yr	7451	306	18	16
PRIAS MRI schedule	7088	304	19	16
MRI every five years	6451	298	20	17

AS = active surveillance; MRI = magnetic resonance imaging.

WW had the highest incidence of metastasis and cancer-specific death (Table 3). All AS strategies increased the number of biopsies performed. MRI-based AS strategies reduced the number of biopsies relative to biopsy-based AS.

3.2. *Sensitivity analyses*

Our results were sensitive to the diagnostic performance of PSA, MRI, and both biopsy modes (Table 4). The sensitivity of MRI for clinically significant cancer had to be lower than 90.0% before biopsy-based strategies became cost-effective (Supplementary Fig. 3). Regarding biopsy accuracy, an MRI-based strategy every 5 yr represented better value when MRGB sensitivity was >87.1% or when TRUSB sensitivity was <68.9%. For an increase in PSA sensitivity for the detection of clinically significant cancer and clinician adherence to the recommendation to biopsy all patients with abnormal PSA, a biopsy-based AS strategy every 5 yr provided the most value.

The initial misclassification rate influenced the model outputs (Supplementary Fig. 4). If fewer than 2.6% of patients with intermediate- or high-risk disease were initially misclassified as low risk on primary biopsy, then WW would be the most cost-effective option. Our results were sensitive to MRI cost; MRI-based surveillance was cost-effective as long as the test cost was less than $640 (Supplementary Fig. 5). As the cost of MRI increased further, biopsy-based surveillance represented better value. The incremental cost and the minimal incremental gain in the accuracy of MRGB compared to TRUSB for MRI-based AS strategies to remain cost-effective are shown in Supplementary Figure 6. The model was robust to other cost and utility inputs.

On probabilistic sensitivity analysis, as the WTP threshold increased, there was an increase in the probability that MRI every 5 yr was the most cost-effective option (Fig. 1).

3.3. *Scenario analyses*

Neither advancing age at diagnosis (Supplementary Table 2), compliance with yr 1 confirmatory testing (Supplementary Fig. 7), nor the cost of local treatments (to reflect treatments other than surgery) changed the results (Supplementary Fig. 8). However, if perfect adherence to scheduled and PSA-

Table 4 – Results from one-way sensitivity analyses [a]

Strategy	ICER for model parameter limits ($/QALY)							
	PSA-DT SSY (base case 0.495)		MRGB SSY (base case 0.90)		MRI cost (base case $591)		MRGB cost (base case $899)	
	SSY 0.20	SSY 0.70	SSY 0.78	SSY 0.98	Cost $295	Cost $1182	Cost $499	Cost $1798
Watchful waiting	–	–	–	–	–	–	–	–
Biopsy every 5 yr	15 973	10 364	11 874	11 874	11 874	11 874	11 874	11 874
PRIAS biopsy schedule	25 064	Dominated	115 246	Dominated	Dominated	115 246	Dominated	115 246
Biennial biopsy	71 088	Dominated	Dominated	Dominated	Dominated	Dominated	Dominated	Dominated
MRI every 5 yr	Dominated	100 162	141 285	76 076	43 693	196 766	49 536	183 818
PRIAS MRI schedule	110 097	Dominated	507 539	1 269 045	598 324	1 254 515	625 089	1 200 998
Biennial MRI	204 244	Dominated	1 505 527	Dominated	4 572 317	9 680 601	4 780 956	9 263 321
Annual MRI	483 905	Dominated	3 930 872	Dominated	Dominated	Dominated	Dominated	Dominated

ICER = incremental cost-effectiveness ratio, MRGB = MRI-guided biopsy; MRI = magnetic resonance imaging; PSA-DT = prostate-specific antigen doubling time; QALY = quality-adjusted life year; SSY = sensitivity in detecting clinically significant prostate cancer.

[a] Results for the following strategies are not displayed because they were ruled out by extended or absolute dominance in all four reported one-way sensitivity analyses: immediate treatment, annual biopsy, biopsy every 3 yr, and MRI every 3 yr. Shaded cells denote strategies that are cost-effective strategies at a willingness-to-pay threshold of $100 000.

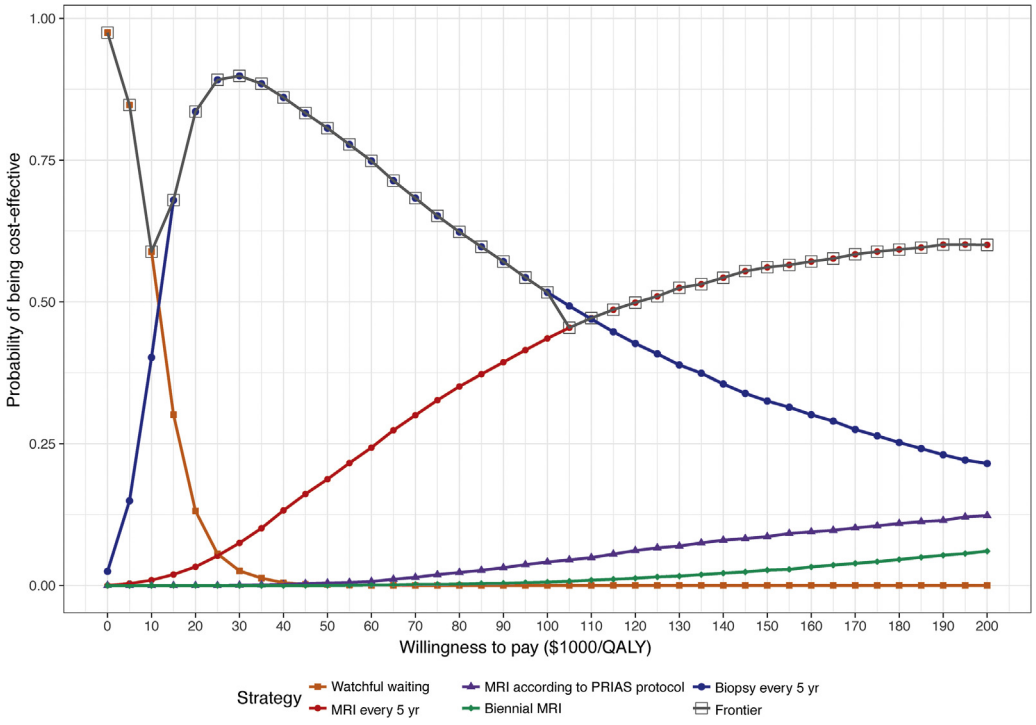

Fig. 1 – Cost-effectiveness acceptability curve for undominated strategies. MRI = magnetic resonance imaging; QALY = quality-adjusted life year.

triggered testing was assumed, AS using biopsy or MRI every 5 yr were cost-effective options. In addition, prolonging the AS duration increased the costs and decreased the incidence of secondary health outcomes.

If the institutional MRI charge ($1010) [32] was used instead of Medicare reimbursement rates, MRI-based surveillance was not cost-effective (Supplementary Table 3).

4. Discussion

We found that AS provides a high-value approach to managing disease for US men diagnosed with low-risk prostate cancer when compared with WW or immediate curative treatment. Our results are supported by both randomized trials and other decision models that have found AS to be an appropriate management strategy for low-risk prostate cancer [7,33–35]. Importantly, our study suggests that decreasing the intensity of surveillance strategies can optimize outcomes from an individual and economic perspective. Health outcomes for metastatic disease and cancer-specific death were improved across all surveillance strategies compared to WW, but were inferior to immediate treatment. Furthermore, life years gained was greatest with immediate treatment, but this

comes at the expense of reduced quality of life due to the short- and long-term side effects experienced with local treatment. Our findings highlight the importance of balancing cost and quality of life when determining the optimal management strategy.

Given the scarcity of high-quality evidence, the intensity of AS follow-up has been the subject of considerable debate. The current American Urological Association guidelines recommend routine surveillance with PSA testing, digital rectal examination, and confirmatory biopsy within the first 2 yr of diagnosis, but do not specify the frequency of surveillance biopsies thereafter [5]. The European Association of Urology recommends repeating biopsy at a minimum interval of 3–5 yr [36]. The variability in repeat biopsy frequency arises from the lack of data to inform this decision and anxiety regarding missing clinically significant disease and its window of curability. However, as the indolent nature of low-risk disease is increasingly evident, many experts believe that frequent surveillance is probably superfluous. A recent study reported that extending the interval between repeat biopsies after the confirmatory biopsy minimally delayed diagnosis of progression and was clinically acceptable [37]. Quality of life is also optimized as the morbidity associated with biopsy and curative treatment is delayed, if not completely avoided. Therefore, both clinicians and patients can be reassured that decreasing the intensity of surveillance does not significantly compromise health outcomes and represents higher-value health care.

MRI has been rapidly adopted in clinical practice as a diagnostic test for prostate cancer [38]. This practice is supported by a study that reported that MRI is more sensitive than TRUSB for the diagnosis of clinically significant cancer [39]. It has been suggested that the best use of MRI would be as a triage test to determine which patients require further investigation. Our findings support this by suggesting that MRI incorporation into AS protocols can improve QALYs by lowering the number of biopsies performed and the associated morbidity. Moreover, MRI provides the ability to identify areas of the prostate that are suspicious for cancer that can then be targeted during biopsy and improve diagnostic ability compared to random sampling during traditional systematic TRUSB [40]. Our results are consistent with a Dutch modeling study that reported that use of MRI and MRGB in AS reduced costs and improved outcomes compared to surveillance with TRUSB, but it should be noted that this study used a basic model that did not simulate the natural history of disease [41]. However, the MRI cost to the health sector had to remain at Medicare reimbursement rates rather than hospital charges in our model for cost-effectiveness to be maintained compared to a TRUSB-based surveillance protocol.

There are important study limitations that should be considered when interpreting the results. These limitations largely reflect the deficiencies in the literature and uncertainty in the underlying nature of disease (eg, progression rates). We needed to rely on inference and expert opinion for certain model inputs, but we did perform sensitivity analyses on these parameters to test the robustness of our results. We were also unable to model all the relevant factors involved in the decision-making process that trigger evaluation of individuals enrolled in surveillance programs. Therefore, the model findings should be interpreted conceptually for the index patient that the surveillance intensity can be decreased, rather than relying on the results as prescriptive. Correspondingly, the clinical targets used during the development of the natural history model were derived from white US men and may not be generalizable to other populations. For example, it has been shown that African-American men have more aggressive disease and may require more frequent surveillance to detect progression within an acceptable timeframe [42,43]. There are also methodological limitations, including the Markovian assumption that the probability of an event only depends on the current health state and is not impacted by past events, when this may not be the case in the real world, but we have modeled relevant factors affecting disease progression, such as grade and stage, independently.

5. Conclusions

Our simulation study revealed that conservative management of low-risk prostate cancer using AS improves QALYs compared to WW or immediate treatment. Furthermore, decreasing the intensity of AS testing improves the value of health care and maintains satisfactory health outcomes, but this decision needs to be tailored to the individual by considering their complete risk profile. Incorporation of MRI into AS protocols can be cost-effective if expensed at Medicare reimbursement rates.

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Author contributions: Badrinath R. Konety had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Study concept and design: Sathianathen, Konety, Lawrentschuk, Bolton, Kuntz.
Acquisition of data: Sathianathen, Alarid-Escudero, Konety, Kuntz.
Analysis and interpretation of data: All authors.
Drafting of the manuscript: All authors.
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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at https://doi.org/10.1016/j.eururo.2018.10.055.

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