

Cost-effectiveness of magnetic resonance imaging and targeted fusion biopsy for early detection of prostate cancer

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Objective

To determine how best to use magnetic resonance imaging (MRI) and targeted MRI/ultrasonography fusion biopsy for early detection of prostate cancer (PCa) in men with elevated prostate-specific antigen (PSA) concentrations and whether it can be cost-effective.

Methods

A Markov model of PCa onset and progression was developed to estimate the health and economic consequences of PCa screening with MRI. Patients underwent PSA screening from ages 55 to 69 years. Patients with elevated PSA concentrations (>4 ng/mL) underwent MRI, followed by targeted fusion or combined (standard + targeted fusion) biopsy on positive MRI, and standard or no biopsy on negative MRI. Prostate Imaging Reporting and Data System (PI-RADS) score on MRI was used to determine biopsy decisions. Deaths averted, quality-adjusted life-years (QALYs), cost and incremental cost-effectiveness ratio (ICER) were estimated for each strategy.

Results

With a negative MRI, standard biopsy was more expensive and had lower QALYs than performing no biopsy. The optimum screening strategy (ICER \$23 483/QALY) recommended combined biopsy for patients with PI-RADS score ≥ 3 and no biopsy for patients with PI-RADS score < 3 , and reduced the number of screening biopsies by 15%. Threshold analysis suggests MRI continues to be cost-effective when the sensitivity and specificity of MRI and combined biopsy are simultaneously reduced by 19 percentage points.

Conclusions

Our analysis suggests MRI followed by targeted MRI/ultrasonography fusion biopsy can be a cost-effective approach to the early detection of PCa.

Keywords

#pcsm, #ProstateCancer, magnetic resonance imaging, Markov model, cost-effectiveness analysis, biopsy

Introduction

Concerns about the poor sensitivity and specificity of the PSA test have led to recommendations to discontinue prostate cancer (PCa) screening in the USA [1]. A key factor leading to this recommendation is that PSA does not distinguish between likely indolent and potentially lethal PCa [2]. As a result, many men who undergo PSA screening receive biopsies, with negative results, which are associated with pain, anxiety and the potential for infection [3]. Eliminating screening spares patients from unnecessary biopsies; however, it also results in late detection of intermediate- and high-grade cancers, potentially leading to poor outcomes for these patients [4].

Recently, MRI has been proposed as a way to achieve early detection of high-grade cancer in a minimally invasive way.

This would potentially reduce overtreatment by preferentially detecting intermediate- and high-grade cancers [5–8]; however, MRI is costly and there is limited evidence for its effectiveness as an intermediate test in patients being screened for PCa. Moreover, there are multiple ways to use MRI in a screening setting, and it is not clear which is best. For example, if an MRI does not detect lesions suspicious for PCa, either no biopsy or a standard biopsy (which randomly samples cores of tissue from the entire prostate gland) can be performed. If an MRI detects suspicious lesions, a targeted MRI/ultrasonography fusion biopsy (i.e. targeted fusion biopsy) can be performed in which the images from MRI are used with real-time ultrasonography to sample cores of tissue directly from suspicious lesions; alternatively, a combined approach can be used in which both standard and targeted fusion biopsies are performed during a single biopsy session.

As there are multiple ways to implement MRI in a screening setting, the optimal clinical pathway is unknown.

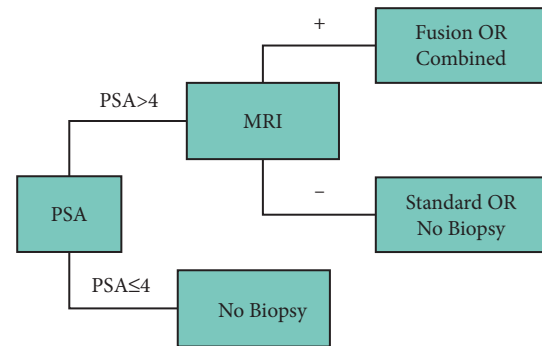
We used a Markov model to evaluate the cost-effectiveness of MRI in a screening setting. We used the model to predict outcomes based on simulation for five screening strategies and report the results on the basis of 1 000 men. The frequency of screening for each strategy was based on the AUA guideline for PSA screening. The first strategy included the standard biopsy for men with elevated PSA concentrations (>4 ng/mL) [9]. The other four strategies involved performing MRI on men with elevated PSA concentrations, and the results were used to decide whether the men should be referred for no biopsy, standard biopsy, targeted fusion biopsy, or combined (standard + targeted fusion) biopsy. We estimated the number of deaths averted, quality-adjusted life-years (QALYs) gained, and the total cost for each strategy. Additionally, we estimated the incremental cost-effectiveness ratios (ICERs).

Methods

We extended a recently validated partially observable Markov model to estimate outcomes for MRI-based screening strategies [10]. The extended Markov model included five pretreatment states that are not directly observable, including no PCa, organ-confined PCa based on Gleason score (<7 , 7 , >7), and extraprostatic or lymph node-positive cancer. This established model simulates the onset and progression of PCa from age 40 years until end-of-life, and has been validated in Barnett et al. [10]. We incorporated the five biopsy strategies and updated the annual metastasis rate to calibrate our model based on estimates from the literature [11]. Our revised model estimates for expected life-years gained and QALYs gained from PSA screening have external validity relative to another recent cost-effectiveness study of PSA screening [12]. For each strategy, we used 30 000 000 samples of biopsy-naïve men who were screened every 2 years from age 55 to 69 years according to the AUA guideline. In strategy 1, a standard biopsy was recommended for elevated PSA concentration (>4 ng/mL). The decision rule diagram for strategies 2–5 is shown in Fig. 1. Each strategy from 2 to 5 recommended MRI for elevated PSA concentration, while actions based on the MRI results depended on the strategy as defined in Table 1. Our model focused on initial biopsy decisions; thus, the screening strategy terminates after the patient receives an initial biopsy or two negative MRI results. However, the patient continues to make state transitions in the absence of screening until all-other-cause mortality or clinical detection of and subsequent mortality from PCa.

The model comprised discrete health states based on Gleason score, which are not directly observable but can be inferred from PSA and MRI subject to published estimates of sensitivity and specificity. In our model, we considered clinically

Fig. 1 Decision rule diagram for screening strategies 2–5. All of the decision rules were compared to no screening and the case of standard biopsy for PSA greater than 4 ng/mL.



significant disease to be any Gleason score ≥ 7 . For standard biopsy, the results were randomly sampled as either positive or negative for any PCa, assuming a sensitivity of 80.0% [13]. If the biopsy result was positive, the probability that the biopsy provides an incorrect grading at diagnosis was based on data reported by Epstein et al. [14]. For targeted fusion and combined biopsy, we used the values of sensitivity and specificity for high-grade cancer (high-volume Gleason $3 + 4$ or \geq Gleason $4 + 3$) reported in Siddiqui et al. [5] of 77.0% and 68.0%, respectively, for targeted fusion biopsy, and 85.0% and 49.0%, respectively, for combined biopsy. Based on Medicare infection rates reported in Loeb et al. [15], 1.1% of biopsies performed led to hospitalization for post-biopsy infection [3].

In addition to detection of PCa through routine screening, the model incorporated the clinical detection of symptomatic PCa. For each patient, we randomly sampled a lead time from an elevated PSA measurement of ≥ 3 ng/mL to clinical diagnosis of PCa from a distribution developed by Savage et al. [16]. If a patient had PCa and a PSA score ≥ 3 ng/mL for their lead time and had not yet been diagnosed with PCa in the model, it was assumed the patient was clinically detected as a result of symptoms.

Treatment

Patients with PSA concentration >20 ng/mL or a Gleason score ≥ 8 received a bone scan and a CT scan for staging [17,18]. Patients with a biopsy result of Gleason score ≥ 7 underwent radical prostatectomy. Based on practice patterns reported in Liu et al. [19], we assumed that 48.5% of patients diagnosed with Gleason score 6 PCa underwent active surveillance, while the rest underwent radical prostatectomy. If a patient was clinically detected to have PCa after age 80 years, we assumed they received watchful waiting.

Patients on active surveillance received an annual PSA test and a biopsy every 2 years and continued to progress through the natural history of the disease. If any biopsy indicated

Table 1 Definitions of five screening strategies.

Screening strategy	PSA > 4 ng/mL	Positive MRI	Negative MRI
1	Standard biopsy	–	–
2	MRI	Targeted fusion biopsy	Standard biopsy
3	MRI	Targeted fusion biopsy	No biopsy
4	MRI	Combined biopsy	Standard biopsy
5	MRI	Combined biopsy	No biopsy

progression in Gleason score, the patient received radical prostatectomy. For patients with no indication of progression within 10 years, survival was consistent with survival for men with untreated PCa [10]. Patients treated via radical prostatectomy had survival consistent with a treated population [20], with the potential for progression to metastatic PCa and PCa mortality. Other-cause mortality was based on estimates from Centers for Disease Control and Prevention life tables [21].

PSA and MRI Sensitivity and Specificity

A published statistical model from the PCa prevention trial was used to sample age-dependent and cancer onset-

dependent PSA scores [22]. The outcome of MRI was based on Prostate Imaging Reporting and Data System (PI-RADS) scores, between 1 and 5, with an increasing score indicating an increasing likelihood of the presence of clinically significant cancer [23]. We considered two PI-RADS thresholds to trigger biopsy: 3 and 4. A PI-RADS threshold of ≥ 3 had a sensitivity and specificity to clinically significant PCa (i.e. cancer core involvement of ≥ 6 mm or the presence of any Gleason pattern 4) of 96.5% (95% CI: 86.8–99.4) and 59.7% (95% CI: 51.2–67.7), respectively, and a PI-RADS threshold of ≥ 4 had sensitivity and specificity values of 78.9% (95% CI: 65.8–88.2) and 78.9% (95% CI: 69.9–84.1), respectively [24].

Costs and Quality of Life

We estimated the difference in costs and QALYs for each combination of the five screening strategies and the two PI-RADS score thresholds. Cost and QALY estimates with their sources are shown in Table 2 and our assumptions were similar to those of previous studies [25–27]. The post-recovery period for radical prostatectomy was assumed to last 9 years [27]. Li et al. [28] reported the disutility for

Table 2 Costs considered in our cost-effectiveness analysis and annual disutilities for health states.

Intervention	Unit costs in \$	Source
PSA screening	33.86	Medicare data
MRI	964.21	Medicare data
Standard prostate biopsy*	2 953.67	Medicare data
Targeted fusion prostate biopsy †	3 018.35	Medicare data
Combined prostate biopsy †	3 018.35	Medicare data
Post-biopsy infection-related hospitalization	6 361.31	Adibi et al. [44] Gonzalez et al. [3]
Staging	1 059.28	Medicare data
Active surveillance–standard biopsy (per year)‡	1 642.58	Medicare data
Active surveillance–targeted biopsy (per year) ‡	1 674.92	Medicare data
Active surveillance–combined biopsy (per year) ‡	1 674.92	Medicare data
Radical prostatectomy	15 752.37	Aizer et al. [25]
Distant-stage initial treatment	17 831.29	Roth et al. [26]
Distant-stage management (per year)	2 500.65	Roth et al. [26]
Other cause of death	5 975.15	Mariotto et al. [45]
Prostate cancer death (age <65 years)	103 884.24	Mariotto et al. [45]
Prostate cancer death (age ≥ 65 years)	69 256.16	Mariotto et al. [45]
Health state	Annual disutility (range)	Source
PSA screening	0.00019 (0.0–0.00019)	Heijnsdijk et al. [27]
MRI	0.00077 (0.00038–0.0012)	Grann et al. [29] Heijnsdijk et al. [27]
Biopsy	0.00577 (0.00346–0.0075)	Heijnsdijk et al. [27]
Post-biopsy infection	0.0161 (0.00969–0.0291)	Li et al. [28] Heijnsdijk et al. [27]
Diagnosis	0.0167 (0.0125–0.0208)	Heijnsdijk et al. [27]
Radical prostatectomy	0.247 (0.0917–0.323)	Heijnsdijk et al. [27]
Post-radical prostatectomy recovery	0.05 (0.0–0.07)	Heijnsdijk et al. [27]
Active surveillance	0.03 (0.0–0.15)	Heijnsdijk et al. [27]
Palliative therapy	0.4 (0.14–0.76)	Heijnsdijk et al. [27]
Terminal illness	0.3 (0.3–0.38)	Heijnsdijk et al. [27]

Costs from the literature have been updated to 2016 US dollars based on inflation. *Includes professional, technical, and facility fees, pathology costs, and office visit. †Includes professional, technical, and facility fees, pathology costs, office visit, and three-dimensional reconstruction. ‡Assumed to include an annual office visit, annual PSA test, and a biopsy every 2 years.

hospitalization attributable to post-biopsy infection to be 0.28, which we assumed lasted for 3 weeks [27]. Grann et al. [29] reported the disutility for MRI as 0.04, which we assumed lasted for 1 week [27].

Cost-Effectiveness

Future costs and QALYs were discounted to net present value using an annual discount rate of 3% [30]. We identified the efficient strategies by removing dominated strategies (i.e. strategies that are more expensive and less effective than another strategy), as well as strategies ruled out by extended dominance (i.e. strategies that have higher ICERs than a more effective strategy) [31]. The ICERs of the efficient policies were calculated as the incremental costs divided by the incremental health gains compared with the next most effective strategy. If the ICER was under \$100 000/QALY, the screening strategy was considered cost-effective [32].

Sensitivity Analysis

To evaluate the robustness of our results, we performed one-way sensitivity analysis on the net costs per QALY gained relative to no screening for the optimal screening strategy. Ranges of the QALY disutilities appear in Table 2. Cost estimates and other-cause mortality rates [21] were varied by $\pm 20\%$. The sensitivity and specificity of PI-RADS threshold 3 were varied using the 95% CIs reported in Grey et al. [24]. The annual metastasis rate for patients with undiagnosed PCa was varied within the 95% CI reported in Johansson et al. [11]. Finally, we varied the annual PCa incidence rate within the 95% CI reported in Haas et al. [13]. Threshold analysis was also performed on the sensitivity and specificity of MRI and combined biopsy under the optimal strategy. Base-case values of the sensitivity and specificity of MRI were 96.5% and 59.7%, respectively, and base-case values of the sensitivity and specificity of combined biopsy were 85.0% and 49.0%, respectively. During threshold analysis, we simultaneously

reduced the sensitivity and specificity of MRI and combined biopsy until it was no longer cost-effective to use MRI for screening.

Results

Base-case Analysis

Table 3 shows the deaths averted, life-years and QALYs gained, and number of screening biopsies for each screening strategy. The largest 95% CI for QALY and cost per patient reflecting Monte Carlo statistical error was <1% of the corresponding sample mean point estimate. Strategy 5 with a PI-RADS threshold of 3 maximized expected QALYs and number of PCa deaths averted. For every strategy, a PI-RADS threshold of 3 gained more QALYs than a PI-RADS threshold of 4. This difference was statistically significant for strategies 3–5. Additionally, performing a combined biopsy after positive MRI (strategies 4 and 5) resulted in additional QALY gains compared to performing a targeted fusion biopsy alone (strategies 2 and 3), and these differences were statistically significant.

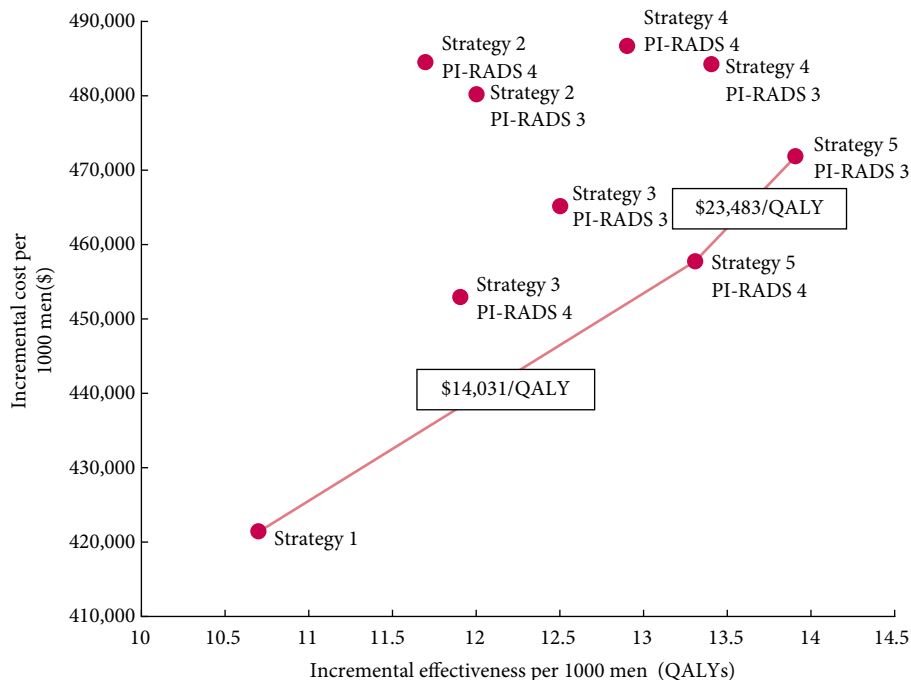
Figure 2 shows the discounted incremental effectiveness in QALYs vs the discounted incremental cost for each strategy relative to no screening. Dominated strategies were simultaneously more expensive and less effective than at least one other strategy. Interestingly, all four schemas that performed a standard biopsy after a negative MRI (strategies 2 and 4, with PI-RADS thresholds of 3 or 4) were dominated by strategies that performed no biopsy after negative MRI (strategies 3 and 5). The efficient strategies were strategy 1, strategy 5 with PI-RADS threshold of 4 and with an ICER of \$14 031/QALY, and strategy 5 with PI-RADS threshold of 3 and with an ICER of \$23 483/QALY. Thus, we found strategy 5 (i.e. MRI if PSA >4 ng/mL, combined biopsy if MRI-positive, no biopsy if MRI-negative) with a PI-RADS threshold of 3 to be optimal under a willingness-to-pay threshold of \$100 000/QALY. This strategy performed 15% fewer screening biopsies than the strategy that uses PSA alone (strategy 1).

Table 3 Predicted effects for various screening strategies per 1 000 men. Screening strategies are defined in Table 1.

Screening strategy	PCa deaths averted*	Life-years gained*	QALYs gained* (95% CI)	Number of screening biopsies
Strategy 1	4.7	58.7	47.8 (47.2–48.3)	151
Strategy 2, PI-RADS ≥ 3	5.2	64.1	53.0 (52.4–53.5)	151
Strategy 2, PI-RADS ≥ 4	5.1	63.0	51.9 (51.3–52.5)	151
Strategy 3, PI-RADS ≥ 3	5.2	64.3	53.9 (53.3–54.5)	128
Strategy 3, PI-RADS ≥ 4	4.9	60.3	50.9 (50.3–51.4)	107
Strategy 4, PI-RADS ≥ 3	5.8	71.4	59.2 (58.6–59.8)	151
Strategy 4, PI-RADS ≥ 4	5.5	68.7	56.8 (56.2–57.5)	151
Strategy 5, PI-RADS ≥ 3	5.9	72.6	60.7 (60.1–61.3)	128
Strategy 5, PI-RADS ≥ 4	5.5	67.8	57.2 (56.6–57.8)	107

Effects are shown without discount. In 2016 US dollars. PCa, prostate cancer; PI-RADS, Prostate Imaging Reporting and Data System; QALY, quality-adjusted life-year. *Compared with no screening.

Fig. 2 Incremental health benefits and costs associated with alternative screening strategies relative to no screening. Costs and quality-adjusted life-years (QALYs) are discounted at a rate of 3%. Each point is labeled with the screening strategy and Prostate Imaging Reporting and Data System (PI-RADS) score threshold. Screening strategies are defined in Table 1. Lines connecting points representing two efficient screening strategies indicate the incremental cost-effectiveness ratio.



Sensitivity Analysis

Figure 3 shows the one-way sensitivity analysis on the net costs per QALY gained relative to no screening for strategy 5 with a PI-RADS threshold of 3. We performed one-way sensitivity analysis on all model variables; Fig. 3 shows the variables that changed the net costs per QALY gained by at least \$5 000/QALY when using the low and high values. The three model variables that had the greatest impact were: (i) the metastasis rate for undiagnosed PCa; (ii) the annual QALY disutility for the 9-year post-radical prostatectomy recovery period; and (iii) the annual QALY disutility for living with metastasis. In the sensitivity analysis, the only scenario that has a cost per QALY gained relative to no screening over \$100 000/QALY is the case with a substantially lower risk of developing metastases compared to the base case, suggesting that our results are robust for most patients and cost-effective under a willingness-to-pay threshold of \$100 000/QALY. Threshold analysis showed that strategy 5 with a PI-RADS threshold of 3 remained cost-effective under a willingness-to-pay threshold of \$100 000/QALY when sensitivity and specificity of MRI and combined biopsy to high-grade cancer were all simultaneously reduced by 19 percentage points. In particular, it was still cost-effective when sensitivity and specificity of MRI were $\geq 77.5\%$ and $\geq 40.7\%$, respectively,

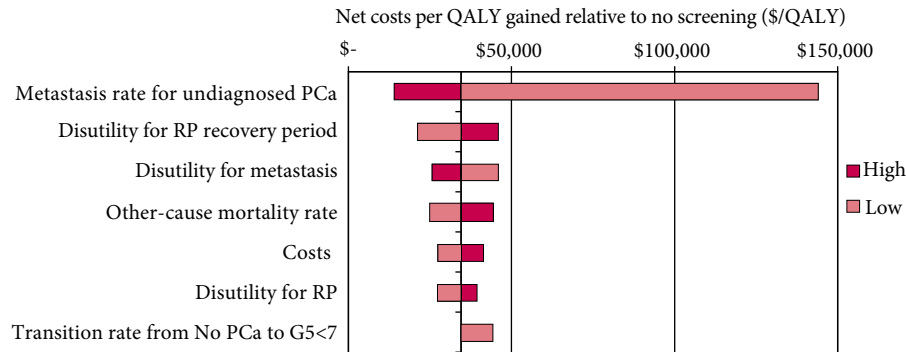
and sensitivity and specificity of combined biopsy were $\geq 66.0\%$ and $\geq 30.0\%$, respectively.

Discussion

Based on our study, MRI as an intermediate test in the screening of men for PCa is cost-effective assuming a willingness-to-pay threshold of \$100 000/QALY threshold. The most efficient strategy was the use of MRI if PSA concentration was >4 ng/mL, followed by combined biopsy if MRI was positive and no biopsy if MRI was negative, using a PI-RADS threshold of 3 to indicate a positive MRI. These results were robust over a range of sensitivity analyses and were maintained even if the sensitivity and specificity of MRI and combined biopsy were reduced by 19 percentage points. Additionally, this MRI strategy reduced the number of screening biopsies by 15% compared with using PSA alone to trigger standard biopsy.

Although MRI has recently been proposed as an effective way to achieve early detection of PCa, evidence in support of the use of MRI for early detection of PCa in biopsy-naïve men is sparse. Ahmed et al. [33] showed that MRI could be effective from a clinical perspective by reducing primary biopsy and clinically insignificant cancer diagnoses, but did

Fig. 3 Tornado diagram of one-way sensitivity analysis on the net costs per quality-adjusted life-year (QALY) gained of strategy 5 with a Prostate Imaging Reporting and Data System (PI-RADS) score threshold of 3 relative to no screening. Costs and QALYs are discounted at a rate of 3%. PCa, prostate cancer; RP, radical prostatectomy; GS, Gleason score.



not consider the cost-effectiveness. Willis et al. [34] performed clinical decision analysis and de Rooij et al. [35] performed cost-effectiveness analysis; however, both studies assumed a fixed sensitivity and specificity of MRI and assumed that positive MRI was automatically followed by a targeted fusion biopsy, while negative MRI automatically results in no biopsy. Thus, they evaluated one clinical pathway compared with the standard of care. In the present study we evaluated strategies that performed targeted fusion biopsy or combined biopsy on positive MRI, as well as the option to perform a standard biopsy or no biopsy on negative MRI. Thus, our study evaluated eight MRI-based clinical pathways (two PI-RADS thresholds for each of the four MRI-based strategies) compared with screening with PSA alone, allowing us to estimate the effects of varying PI-RADS thresholds and biopsy techniques on the cost-effectiveness of using MRI for PCa screening. More recently, Pahwa et al. [36] performed cost-effectiveness of using MRI in biopsy-naïve men; however, this study is a decision tree that did not consider various PI-RADS scores and did not account for sequential PSA testing or progression of cancer over time. Additionally, their study does not incorporate other-cause mortality, which is an important consideration when studying a disease like PCa, which can be slow-growing. Finally, to our knowledge, the present study is the first to focus on the use of MRI in a screening setting in combination with PSA and incorporates lifetime costs and health outcomes, rather than assessing short-term outcomes. Including long-term costs and health impacts enabled us to assess the potentially negative impact of detecting low-risk cancers related to harm from biopsy/biopsies and overtreatment. Previous studies did not account for the costs and harms associated with biopsy complications, resulting in an overestimation of the benefit from screening and an underestimation of the costs.

Heijnsdijk et al. [12] evaluated the cost-effectiveness of several PSA screening policies in the absence of MRI, and our

models produced similar expected outcomes for PSA screening. The net cost per QALY gained reported in the present study for PSA screening was lower than the results reported in Heijnsdijk et al. [12] because we included more costs in our model, including the significant cost of a PCa-related death. Faria et al. [37] recently published a cost-effectiveness study based on the Prostate MR Imaging Study (PROMIS) based in the UK and found that performing multiparametric MRI followed by up to two targeted TRUS-guided biopsies was a cost-effective approach to early detection of PCa, reaching a similar conclusion to that of the present study.

Using MRI for PCa screening resulted in health benefits for the patient compared with both no screening and screening using PSA alone. For example, the screening strategy whereby men with a PI-RADS score ≥ 3 were recommended for combined biopsy (i.e. strategy 5) resulted in 5.9 deaths from PCa averted, 60.7 QALYs gained, and 72.6 life-years gained per 1 000 men compared with no screening. For every screening strategy, a PI-RADS threshold of 3 outperformed a threshold of 4 in terms of QALYs. Our results also suggest that performing a combined biopsy after a positive MRI outperforms performing a targeted fusion biopsy in terms of QALYs; however, there does not appear to be a benefit to performing standard biopsy on negative MRI, because it results in additional costs and disutility to the patient without added health benefits. This conclusion has been supported in the literature. For example, Hansen et al. [38] concluded that biopsies may not be necessary for men with elevated PSA and non-suspicious MRI because the negative predictive value for excluding Gleason score ≥ 7 disease on MRI was very high. The present study adds additional evidence in support of this conjecture.

The results are sensitive to the choice of disutility estimates used to compute QALYs. Because we assumed patients undergoing definitive treatment would have surgery, the

results do not necessarily apply to those patients who may receive radiation treatment. This is because disutility estimates for radiation treatment are not readily available; however, other authors have noted the similarity in the disutility for these alternative treatment options [39].

It is important to note that the cost figures used in the present study are from the USA and the cost and ICER threshold used to define willingness to pay will vary depending on the specific healthcare setting. For example, in the UK the threshold is typically £20 000–£30 000 per QALY gained [40].

Given the wide variability in the quality of radiology reporting and interpretation of MRI results, we performed threshold analysis on the sensitivity and specificity of MRI and combined biopsy. These analyses found this approach to be a cost-effective method of early detection even if the sensitivity and specificity were substantially lower than estimates reported in the literature, suggesting that our results may be relevant in a community setting where sensitivity and specificity may be lower than in specialized medical centres where most previous MRI studies have been conducted. Despite these encouraging findings, minimizing variation in radiologist reporting remains a critical unmet need [41,42]. The minimum thresholds we found for sensitivity and specificity of MRI in our sensitivity analysis were within the range of clinical possibility. Prospective tracking of outcomes data stratified by indication and PI-RADS v2 scoring is necessary to ensure performance within the range of values we studied can be achieved.

Our model was based on available evidence but there are a number of noteworthy limitations. One potential limitation is that there was the potential for bias in the data we used to estimate MRI results because the population used included patients with previous negative biopsies in addition to biopsy-naïve patients; however, by using the estimates based on the larger patient population we were able to obtain better estimates of sensitivity and specificity. Our sensitivity analysis further confirms our conclusions are not sensitive to this assumption. Another possible limitation is the inconsistent definition of clinically significant PCa in the literature. For example, Siddiqui et al. [5] defined clinically significant disease as high-volume Gleason 3 + 4, or Gleason $\geq 4 + 3$, while Grey et al. [24] defined it as cancer core involvement ≥ 6 mm or the presence of any Gleason pattern 4. In our model, we considered clinically significant disease to be any Gleason score ≥ 7 . Additionally, the only curative treatment included in our model was radical prostatectomy, because it is the most common curative treatment, and patients undergoing radiation therapy have similar health outcomes [43]. Our model uses many different sources of data; however, given the long-term evaluation period needed for PCa screening,

randomized trials are unlikely to be able to assess long-term QALYs and costs. We considered multiple ways of using MRI for early detection, but MRI may also play an important role in active surveillance. We have not attempted to incorporate this aspect of MRI into the model because of the complexity of decisions and evidence related to the use of MRI for active surveillance. These limitations notwithstanding, we believe the present study provides important evidence in support of the use of MRI for early detection of PCa in biopsy-naïve men, both from a health benefit and cost perspective.

Our results show that incorporating MRI into PCa screening in biopsy-naïve men is cost-effective under a willingness-to-pay threshold of \$100 000/QALY. The strategies that performed a standard biopsy on negative MRI were more expensive and less effective than strategies that performed no biopsy on negative MRI. The screening strategy where men with PI-RADS score ≥ 3 were recommended for combined biopsy, while men with PI-RADS score < 3 were recommended for no biopsy was optimal and cost-effective with an ICER of \$23 483/QALY. Our results were also robust with respect to sensitivity analysis. MRI appears, therefore, to be a viable approach for early detection of PCa from a cost-effectiveness perspective.

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Conflict of Interest

None declared.

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Abbreviations: ICER, incremental cost-effectiveness ratio; PCa, prostate cancer; PI-RADS, Prostate Imaging Reporting and Data System; QALY, quality-adjusted life-year.