BMJ Open

Prostate MRI versus PSA screening for prostate cancer detection (the MVP Study): a randomised clinical trial

Robert Nam,[1] Chirag Patel,[2] Laurent Milot,[2] Amanda Hird ![ORCID],[1] Christopher Wallis,[3] Patrick Macinnis,[1] Mala Singh,[1] Urban Emmenegger,[4] Christopher Sherman,[5] Masoom A Haider[2]

[1]Division of Urology, Sunnybrook Health Sciences Centre, Toronto, Ontario, Canada
[2]Division of Medical Imaging, Sunnybrook Health Sciences Centre, Toronto, Ontario, Canada
[3]Division of Urology, Mount Sinai Hospital, Toronto, Ontario, Canada
[4]Division of Medical Oncology and Hematology, Sunnybrook Health Sciences Centre, Toronto, Ontario, Canada
[5]Division of Anatomic Pathology, Sunnybrook Health Sciences Centre, Toronto, Ontario, Canada

Correspondence to
Dr Robert Nam;
robert.nam@utoronto.ca

ABSTRACT

Objectives Our objective was to compare prostate cancer detection rates between patients undergoing serum prostate-specific antigen (PSA) vs magnetic resonance imaging (MRI) for prostate cancer screening.

Design Phase III open-label randomised controlled trial.

Setting Single tertiary cancer centre in Toronto, Canada.

Participants Men 50 years of age and older with no history of PSA screening for ≥3 years, a negative digital rectal exam and no prior prostate biopsy.

Interventions Patients were recommended to undergo a prostate biopsy if their PSA was ≥2.6 ng/mL (PSA arm) or if they had a PIRADS score of 4 or 5 (MRI arm). Patients underwent an end-of-study PSA in the MRI arm.

Primary and secondary outcome measures Adenocarcinoma on prostate biopsy. Prostate biopsy rates and the presence of clinically significant prostate cancer were also compared.

Results A total of 525 patients were randomised, with 266 in the PSA arm and 248 in the MRI arm. Due to challenges with accrual and study execution during the COVID-19 pandemic, the study was terminated early. In the PSA arm, 48 patients had an abnormal PSA and 28 (58%) agreed to undergo a prostate biopsy. In the MRI arm, 25 patients had a PIRADS score of 4 or 5 and 24 (96%) agreed to undergo a biopsy. The relative risk for MRI to recommend a prostate biopsy was 0.52 (95% CI 0.33 to 0.82, p=0.005), compared with PSA. The cancer detection rate for patients in the PSA arm was 29% (8 of 28) vs 63% (15 of 24, p=0.019) in the MRI arm, with a higher proportion of clinically significant cancer detected in the MRI arm (73% vs 50%). The relative risk for detecting cancer and clinically significant with MRI compared with PSA was 1.89 (95% CI 0.82 to 4.38, p=0.14) and 2.77 (95% CI 0.89 to 8.59, p=0.07), respectively.

Conclusions Prostate MRI as a stand-alone screening test reduced the rate of prostate biopsy. The number of clinically significant cancers detected was higher in the MRI arm, but this did not reach statistical significance. Due to early termination, the study was underpowered. More patients were willing to follow recommendations for prostate biopsy based on MRI results.
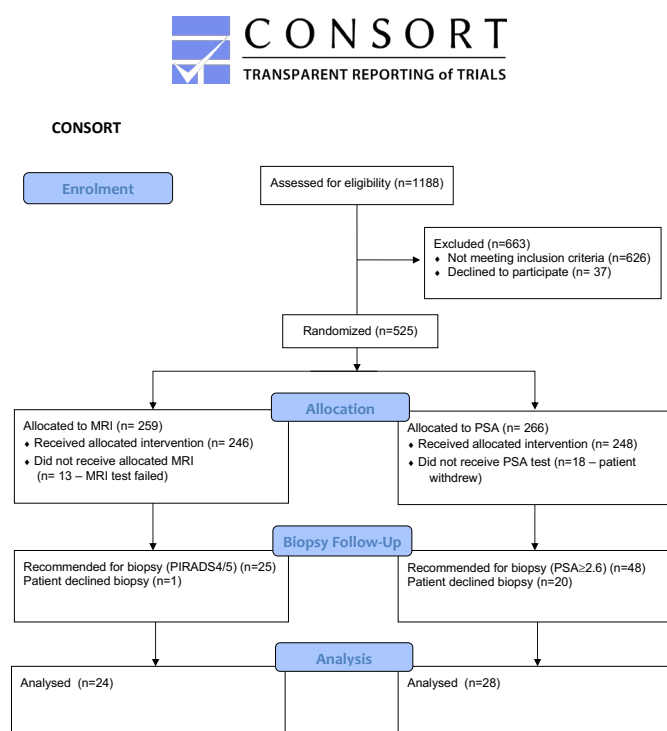
Trial registration number NCT02799303.

STRENGTHS AND LIMITATIONS OF THIS STUDY

⇒ This is the first randomised trial to directly compare serum prostate-specific antigen (PSA) testing and prostate MRI for prostate cancer screening purposes.

⇒ Participants in each arm did not undergo the reciprocal test at the time of randomisation.

⇒ Limitations of the current study include the conduct of the trial at a single centre and the higher drop-out rate seen in the PSA arm.

⇒ The study was terminated prematurely due to accrual challenges and difficulties accessing MRI resources and PSA follow-up data due to resource limitations and patient reluctance during the COVID-19 pandemic; as a result, the study was underpowered.

⇒ Nevertheless, this randomised trial confirms the utility and public acceptance of the use of MRI in this setting.

screening after randomised clinical trials demonstrated some improvement in prostate cancer mortality rates.[1 2] Several serological and imaging tests have been evaluated to improve its predictive value. Prostate multiparametric MRI (mpMRI) has been examined as an adjunct test to PSA to better identify patients who require a prostate biopsy for the presence of aggressive forms of prostate cancer.[3] Randomised clinical trials have shown that mpMRI can improve the predictive value for the presence of clinically significant prostate cancer, compared with PSA alone.[3]

Although prostate MRI can improve the predictive value of PSA, it is still dependent on the pitfalls of interpreting the initial PSA test. To our knowledge, no randomised controlled trial has directly compared the efficacy between PSA and stand-alone prostate MRI testing (without the influence of PSA) for prostate cancer detection among an unselected cohort of men for prostate

INTRODUCTION

The prostate-specific antigen (PSA) blood test continues to be used for prostate cancer

Figure 1. CONSORT Diagram

Figure 1 CONSORT diagram. CONSORT, Consolidated Standards of Reporting Trials; PSA, prostate-specific antigen; PIRADS, Prostate Imaging-Reporting and Data System.

cancer screening. It would be important to characterise the predictive value of MRI for the presence of prostate cancer as a stand-alone test without the potential biases that PSA introduces in assessing prostate cancer risk. Thus, we conducted a randomised, phase 3 study comparing prostate cancer detection rates between MRI versus PSA—the MVP study.

MATERIALS AND METHODS
Study design
We conducted a single centre, phase 3, randomised open-label controlled trial comparing MRI of the prostate vs serum PSA testing among eligible men who had not undergone a previous prostate cancer screening evaluation.

The study was registered under ClinicalTrials.gov (NCT02799303, 14 June 2016) and followed the Consolidated Standards of Reporting Trials guidelines (figure 1). Patients or the public were not involved in the design, or conduct, or reporting, or dissemination plans of our research.

Participants
Participants were recruited from newspaper and radio advertisements approved by the REB calling for volunteers from the Greater Toronto Area who had not undergone a prostate cancer screening evaluation by their primary physician. Volunteers had to be 50 years or older with a life expectancy of at least 10 years, have

no history of any prostate biopsy even if remote, no serum PSA measurement within the last 3 years and no urinary difficulty symptoms (ie, asymptomatic). Subjects who answered the advertisements were invited to be further screened at Sunnybrook Health Sciences Centre. Following informed consent, we accessed the personal province-wide electronic medical record to verify whether each volunteer had previously undergone a PSA test (electronic records report province-wide laboratory records) or a prostate biopsy. Where relevant testing was identified, these individuals were excluded. Patients were further excluded if they had a history of prostate cancer in one or more first degree relatives diagnosed <50 years of age, a urinary International Prostate Symptom Score of ≥8, any prior or current use of 5-alpha reductase inhibitor medications (finasteride or dutasteride), or if they had a history of claustrophobia or other medical indication which would preclude undergoing an MRI. After all exclusions were considered, subjects then underwent digital rectal examination (DRE) and any subjects with an abnormal DRE were excluded and referred to their primary physician for further management. The DRE was completed by a medical doctor at Sunnybrook Health Sciences Centre with expertise in treating prostate cancer. Given the expertise of the staff, we do not expect any bias to be caused by the performance of the DRE by different providers as this is a standard part of assessment of all patients.

Randomisation and masking
Patients were randomised in a 1:1 ratio using a computerised random generator and the group assignment was revealed once a patient was deemed eligible and had provided written informed consent.

PSA arm
Patients randomised to the PSA arm underwent a PSA blood test performed by provincially licensed laboratories. All provincial laboratories in Ontario are regulated by the province to ensure they meet quality standards. PSA tests were not centrally performed. Patients with PSA levels of≥4.0 ng/mL were recommended to undergo a transrectal ultrasound (TRUS)-guided prostate biopsy with a minimum of 12 needle-core biopsy template. A total of 12 cores were taken for all systematic biopsies. If the physician completing the biopsy noted a lesion on TRUS, this could be sampled and was at the discretion of the treating provider. Patients with a PSA level between 2.6 ng/mL and 4.0 ng/mL were offered TRUS-guided prostate biopsy based on past studies showing a significant prevalence of prostate cancer among that range.[4] A biopsy was not mandated for this range since the largest North American randomised PSA screening study used a PSA cut-off level of 4.0 ng/mL as the standard-of-care.[1] Patients with a normal PSA underwent annual PSA testing for 3 years.

MRI Arm

Patients randomised to the MRI arm underwent biparameteric prostate MRI (bpMRI) testing at our centre (see online supplemental appendix 1). No PSA test was performed. Prostate MRI examination was performed on a 3T Siemens Magnetom Prisma Scanner Software V.E11 (Siemens Healthcare, Erlangen, Germany) without an endorectal coil. All exams were performed on the same scanner and software version. No intravenous contrast or other medication was administered for the MRI study. Multiparametric MRI is a combination of T2-weighted imaging, diffusion-weighted imaging (DWI) and dynamic contrast-enhanced imaging (DCEMRI). Biparametric MRI where no contrast agent is given and only T2 and DWI are performed is advocated as a more cost-efficient approach in prebiopsy scenarios[5] and was used in this study. In cases where there was a poor-quality exam precluding interpretation of DWI, the patient was called back and the exam repeated.

The bpMRI was read by one uroradiologist (MAH) with 20 years of experience interpreting prostate MRI. The presence or absence of up to four cancer targets was scored on a 5-point scale using the Prostate Imaging-Reporting and Data System (PIRADS) V.2.1 guidelines modified for bpMRI interpretation[6] with one being 'clinically significant disease is highly unlikely to be present' and five being 'clinically significant disease is highly likely to be present' determined by a composite of T2 and DWI appearances. As DCEMRI only affects the composite PIRADS score by potentially increasing the score from 3 to 4 when there is a PIRADS 3 DWI lesion, lesions with a PIRADS 3 score on DWI were simply kept as 3. The scoring scheme was otherwise identical to PIRADS as used in mpMRI.

The study protocol was amended prior to enrolment to require biopsy only among men in the MRI arm with PIRADS 4 or 5 lesion(s) (previously 3, 4 or 5). Patients with significant lesions were recommended for targeted biopsy using ultrasound-MRI fusion directed biopsies using a biopsy fusion system (Artemis, Eigen, Grassy Valley, California, USA) in addition to systematic 12-core prostate biopsy. Four cores were performed for the primary target and up to 4 cores were allowed for secondary targets, which was at the discretion of the physician performing the biopsy based on size, position and expertise in whether the lesion had been appropriately sampled. All patients were followed in the same urology clinic where the accrual process had been completed by the same provider on an annual basis for clinical assessment. An end-of-study PSA was recommended to all patients in the MRI arm.

Outcomes

The primary endpoint was the presence of adenocarcinoma on prostate biopsy (International Society of Urological Pathology [ISUP] grade group 1 and above). The presence of clinically significant cancer was defined as patients with a Gleason score of 7 or greater (ISUP grade group 2 and above). All prostate biopsies were read by genitourinary cancer pathologists to assign a Gleason score pattern. Gleason score was assigned based on a combination of the most common and highest Gleason score on prostate biopsy. All cores (systematic and targeted if the patient was in the MRI group) were considered together and not separately. All biopsy discussions took place between the patients and a single physician expert with over 20 years of experience in treating prostate cancer. All patients diagnosed with prostate cancer were referred for consultation with a urologist and a radiation oncologist for subsequent management.

Statistical analysis

Based on our previous pilot study,[7] we anticipated 14% of patients in the PSA group and 21% of those in the MRI group would be diagnosed with cancer. Based on an alpha=0.05 and beta=0.20 (power=0.80) and a superiority design, we estimated that 918 patients in total (459 in each arm) would be required and allowing for a 10% drop-out rate, we needed to recruit a total of 1010 patients.

A planned interim analysis was conducted by the study's lead coprincipal investigators (RN and MAH) when half of the expected accrual was completed. The study had to be closed prematurely due to accrual challenges and difficulties accessing MRI resources and PSA follow-up data due to resource limitations and patient reluctance during the COVID-19 pandemic. As a result, the study was underpowered.

Baseline distributions of PSA levels and MRI PIRADS scores were examined. Baseline characteristics that were continuous were presented as mean with SD and compared using the Student's t-test. Categorical variables were compared by using the χ^2 test. Patients who dropped out of the study because they declined to undergo a prostate biopsy based on PSA or MRI results were included as part of an intent-to-treat analysis when comparing cancer detection rates between each arm. To estimate relative risks and 95% CIs for our primary and secondary outcomes, a 2×2 comparison was performed between the PSA and MRI groups. A p<0.05 was used to indicate statistical significance for a two-tailed comparison. All analyses were performed by using the SAS V.9.

RESULTS

A total of 1188 subjects volunteered to participate in the study and were assessed for eligibility. On screening with a review of their electronic medical record, 663 were excluded (figure 1), leaving 525 subjects for randomisation. Of the 266 patients randomised to the PSA arm, 18 patients withdrew after being informed they would not get an MRI, leaving 248 (93%) patients for analysis. Of the 259 patients randomised to the MRI arm, the MRI test was not completed on 13 patients due to claustrophobia, leaving 246 (95%) for analysis.

The baseline characteristics between patients in the PSA and MRI arms were similar (table 1). Of the 248 patients

Table 1 Comparison of baseline characteristics between PSA and MRI arms

Characteristic	PSA arm (n=248)	MRI arm (n=246)
Age (years) (mean±SD deviation)	67.5±7.8	67.7±7.3
Ethnic background (%)		
White	211 (85.1)	207 (84.2)
Black	4 (1.6)	1 (0.4)
Asian	9 (3.6)	19 (7.7)
Other	24 (9.7)	19 (7.7)
PSA distribution (%)		
<2.6 ng/mL	200 (80.6)	
2.6–4.0 ng/mL	30 (12.1)	
4.1–10.0 ng/mL	15 (6.0)	
10.1–20.0 ng/mL	3 (1.2)	
MRI PIRADS score distribution (%)		
1		6 (2.4)
2		183 (74.4)
3		32 (13.0)
4		22 (8.9)
5		3 (1.2)

.PIRADS, Prostate Imaging-Reporting and Data System; PSA, prostate-specific antigen.

in the PSA arm, the median PSA level was 1.26 ng/mL (IQR 0.72–2.16 ng/mL). Most patients had a PSA level of <2.6 ng/mL (n=200, n=80.6%) (table 1), while 48 (19.4%) had a PSA ≥2.6 ng/mL. Of the 48 patients with PSA≥2.6 ng/mL, 28 (58%) agreed to undergo a prostate biopsy. Of the 246 patients in the MRI arm, most patients had a PIRADS score of 1, 2 or 3 (n=221, 89.8%). A total of 25 patients (10.1%) had a PIRADS score of 4 or 5 and were recommended prostate biopsy (table 1), and 24 (96%) agreed to undergo a biopsy. The relative risk for MRI to recommend a prostate biopsy was 0.52 (95% CI 0.33 to 0.82, p=0.005) compared with PSA.

The positive predictive value of PSA was significantly lower than MRI on per protocol (8/28 (28.6%) vs 15/24 (62.5%), p=0.019) and intention-to-treat analysis (8/48 (16.7%) vs 15/25 (60.0%), p<0.001). The proportion of patients diagnosed with prostate cancer who had ISUP grade group 2 or higher disease was greater among the patients in the MRI arm compared with the PSA arm (73.3% vs 50.0%) (table 2). The relative risk for detecting cancer with MRI was 1.89 (95% CI 0.82 to 4.38, p=0.14) while the relative risk for detecting clinically significant cancer (ISUP grade group 2 or more) with MRI was 2.77 (95% CI 0.89 to 8.59, p=0.07) vs PSA.

We obtained end-of-study PSA tests among patients in the MRI arm. However, due to COVID-19 pandemic-related restriction, we obtained PSA results on only 117 of the 246 in the MRI arm. Patients who had a higher

PIRADS score on MRI were more likely to have had an end-of-study PSA (93/221 of patients with a PIRADS 1–3 lesion had an end-of-study PSA vs 24/25 of patients with a PIRAD 4–5 lesion, p<0.001).

When we examined the distribution of PSA categories by MRI PIRADS scores, there were significant discordances of which patients were considered normal or abnormal by the PSA or MRI categories (table 3). Among patients in the MRI group considered to have normal PSA level (<2.6 ng/mL), 13.3% had a PIRADS score 4 or 5 lesion and 61.8% patients considered to have an abnormal PSA level had a PIRADS score of 1–3 (p<0.002) (table 3). Of the 11 patients who had a PSA <2.6 ng/mL and a PIRADS score of 4 or 5, three patients (27%) had cancer; two patients had Gleason score 7 and the other had Gleason score 6 disease. If we use MRI as the reference to undergo a prostate biopsy, the relative risk of PSA potentially missing a prostate cancer was 1.69 (95% CI 1.6 to 10.4) and the relative risk of unnecessary biopsy based on PSA was 2.40 (95% CI 1.4 to 4.1).

DISCUSSION

Statement of principal findings

From this randomised controlled study where patients underwent a stand-alone PSA or prostate MRI test for prostate cancer screening, we found that patients in the MRI screening arm were less likely to be recommended to undergo prostate biopsy (relative risk 0.52, 95% CI 0.33 to 0.82). Despite a lower biopsy rate in the MRI group, there was a trend towards higher prostate cancer and clinically significant prostate cancer detection, although this did not reach statistical significance. Further, among the subgroup of patients in the MRI arm who had an end-of-study PSA test, recommendations based on a single screening PSA test would have both potentially missed patients with cancer and conversely, unnecessarily recommended prostate biopsy.

Strengths and weaknesses of the study

To our knowledge, this is the first randomised trial to directly compare serum PSA testing and prostate MRI for prostate cancer screening purposes. A major strength of our study is that each arm did not undergo the reciprocal test at the time of randomisation. More specifically, patients in the MRI arm did not have a PSA test at the time of randomisation. Thus, the potential bias introduced with a PSA test with the MRI could have led to violations in the study protocol with misleading results. The end-of-study PSA tests among patients in the MRI clearly showed how PSA levels could have affected biopsy and cancer detection rates.

Limitations of the current study include the conduct of the trial at a single centre and the higher drop-out rate seen in the PSA arm. Given the nature of the interventions, blinding was not possible. Biparametric MRI was used in this trial; however, bpMRI has been shown to have similar sensitivity and specificity compared with mpMRI and may be more cost-effective.[5][8] The Siemens Prisma

Table 2 Distribution of prostate biopsy grade by PSA and MRI arm

Histology grade	PSA arm			MRI arm	
	2.6–4.0	4.1–10.0	10.1–20.0	PIRADS 4	PIRADS 5
Gleason score 6		4		4	
Gleason score 7					
(3+4)	1		1	3	3
(4+3)	1			3	
Gleason score 8–10		1		2	

.PIRADS, Prostate Imaging-Reporting and Data System; PSA, prostate-specific antigen.

system 1 is one of the highest performance gradient systems for MRI. This can help improve the quality of DWI compared 3T gradient systems used in routine clinical practice. Given MRI interpretation was done by a single experienced reader on a high-performance system, our results may be optimistic if compared with multiplatform and reader performance.

Given that both systematic and targeted biopsy were used in combination in the MRI arm, this may introduce detection bias. Nevertheless, this represents the first randomised trial to compare PSA vs MRI for prostate cancer screening and confirms the utility and public acceptance of the use of MRI in this setting.

Given the occurrence of the COVID-19 pandemic during the trial, our study was terminated early and thus we were likely underpowered to show significance in our primary and secondary outcomes. The conduct of this trial during a global pandemic highlights an important consideration for future clinical trials. Consideration should be given to alternative means of study completion, for example, use of telephone or virtual assessment and the use of local labs and imaging centres when feasible. These strategies may not only enhance participant safety, but also facilitate easier completion of study assessments. In our study, access to prostate MRI and prostate biopsy were tied to our primary study site and required in person assessment. Other study designs and interventions may be more conducive to a hybrid in-person and remote assessment protocol.

Table 3 Distribution of end-of-study PSA and MRI PIRADS score among MRI arm

	PSA category (ng/mL)			
MRI PIRADS score	< 2.6	2.6–4.0	4.1–10.0	10.1–20.0
1–3	72 (86.8%)	12 (92.3%)	7 (36.8%)	2 (100%)
4–5	11 (13.2%)	1 (7.7%)	12 (63.2%)	0 (0%)

PIRADS, Prostate Imaging-Reporting and Data System; PSA, prostate-specific antigen.

Strengths and weaknesses in relation to other studies

PSA-based prostate cancer screening is limited by the lack of a concrete cut-off value and the poor specificity of the test. Although a serum PSA cut-off of 4.0 ng/mL has been suggested, as many as 25% of prostate cancers may present with a PSA less than this threshold. Indeed, in the MRI arm of the current trial, 18% of patients with diagnosed with clinically significant prostate cancer had a PSA <4.0 ng/mL. Thus, PSA-based prostate cancer screening lacks both sensitivity and specificity to identify men with aggressive prostate cancer. MRI offers several advantages including sparing biopsy in approximately one-third of patients, greater acceptance of the recommendation for prostate biopsy if the test is abnormal, much higher negative predictive value with targeted biopsy versus standard TRUS-guided biopsy, and the potential for this screening strategy to reduce the over diagnosis of clinically insignificant prostate cancer.

Eldred-Evans et al prospectively compared rates of cancer among 408 patients who had an ultrasound, MRI and PSA test in a blinded fashion—the IP1-PROSTAGRAM study.[9] If any one of the three tests was positive, the patient underwent systematic biopsy with ultrasound-MRI fusion biopsy as necessary. They showed a higher rate of clinically significant cancer with MRI using a PIRADS threshold of 4 or 5, compared with using a PSA threshold of >3.0 ng/mL for prostate biopsy. However, the blinding could have been revealed at the time prostate biopsy since MRI-based lesions would be revealed.

In our study, we estimate that the use of screening MRI for prostate cancer screening could reduce the need for prostate biopsy by approximately 48%. This is consistent with estimates from clinical trials examining prostate MRI among patients with abnormal PSA levels where 27% to 37% of patients could avoid prostate biopsy in the context of an elevated PSA test but negative MRI studies.[3 10 11] Recently, Eklund et al showed that MRI-based biopsy detected lower rates of insignificant cancer and higher rates of clinically significant cancer, but did not examine patients with PSA levels below 3.0 ng/mL.[12] Our study showed that among men randomised to the MRI arm, approximately 18% (2/11) of patients with clinically significant cancer had a normal PSA.

Meaning of the study

Other important observations from our study include the compliance rate of patients in the PSA arm. First, at the time of randomisation to PSA, 7% of patients dropped out of the study citing that they had wished to be randomised for an MRI. Second, when a biopsy was recommended by the PSA test, only about half of the patients agreed to undergo a biopsy, while 96% of patients agreed to undergo a biopsy in the MRI arm. Thus, the public perception of the effectiveness of PSA screening has waned. This perception may be warranted, given that there was a trend towards higher clinically significant cancer detection among patients in the MRI arm versus the PSA arm.

Unanswered questions and future research

While MRI has proven to be a useful clinical tool for prostate cancer risk stratification, the feasibility and cost-effectiveness of widespread population-based prostate MRI is a challenge in many clinical landscapes. A recent microsimulation model assessed the cost-effectiveness of PSA with MRI and MRI-guided biopsy for prostate cancer detection.[13] MRI-based prostate cancer screening resulted in more years of life gained and quality-adjusted life-years (QALY) by 3 and 3.5 years per 1000 men invited for screening, respectively. In the integrated cost-effectiveness analysis, MRI-based screening was associated with a cost of just over €11 000 per QALY gained compared with PSA-screening, suggesting MRI-based screening is cost-effective. In their analysis, compliance rates were assumed to be the same for both PSA-based and MRI-based screening. However, as demonstrated in this study, greater public acceptance of MRI-based screening may further increase the benefit of integrating MRI into prostate cancer screening practices. Indeed, imaging-based cancer screening approaches for breast (mammography), lung (low-dose CT) and colon (CT colonography) have been considered.

CONCLUSION

Stand-alone biparametric prostate MRI further reduces rates of unnecessary biopsy compared with PSA-based screening, while identifying patients with clinically significant forms of prostate cancer that would have been missed with serum PSA screening alone. More patients are willing to follow recommendations for prostate biopsy based on MRI results compared with PSA.

ORCID iD
Amanda Hird http://orcid.org/0000-0002-2549-6079

REFERENCES

1 Andriole GL, Crawford ED, Grubb RL, *et al*. Mortality results from a randomized prostate-cancer screening trial. *N Engl J Med* 2009;360:1310–9.
2 Schröder FH, Hugosson J, Roobol MJ, *et al*. Screening and prostate-cancer mortality in a randomized European study. *N Engl J Med* 2009;360:1320–8.
3 Kasivisvanathan V, Rannikko AS, Borghi M, *et al*. MRI-Targeted or standard biopsy for prostate-cancer diagnosis. *N Engl J Med* 2018;378:1767–77.
4 Catalona WJ, Smith DS, Ornstein DK. Prostate cancer detection in men with serum PSA concentrations of 2.6 to 4.0 ng/mL and benign prostate examination. enhancement of specificity with free PSA measurements. *JAMA* 1997;277:1452–5.
5 Porter KK, King A, Galgano SJ, *et al*. Financial implications of biparametric prostate MRI. *Prostate Cancer Prostatic Dis* 2020;23:88–93.
6 Boesen L, Nørgaard N, Løgager V, *et al*. Assessment of the diagnostic accuracy of Biparametric magnetic resonance imaging for prostate cancer in Biopsy-Naive men: the Biparametric MRI for detection of prostate cancer (BIDOC) study. *JAMA Netw Open* 2018;1:e180219.
7 Nam RK, Wallis CJD, Stojcic-Bendavid J, *et al*. A pilot study to evaluate the role of magnetic resonance imaging for prostate cancer screening in the general population. *J Urol* 2016;196:361–6.
8 Alabousi M, Salameh J-P, Gusenbauer K, *et al*. Biparametric vs multiparametric prostate magnetic resonance imaging for the detection of prostate cancer in treatment-naïve patients: a diagnostic test accuracy systematic review and meta-analysis. *BJU Int* 2019;124:209–20.
9 Eldred-Evans D, Burak P, Connor MJ, *et al*. Population-Based prostate cancer screening with magnetic resonance imaging or ultrasonography: the IP1-PROSTAGRAM study. *JAMA Oncol* 2021;7:395–402.
10 Ahmed HU, El-Shater Bosaily A, Brown LC, *et al*. Diagnostic accuracy of multi-parametric MRI and TRUS biopsy in prostate cancer (PROMIS): a paired validating confirmatory study. *Lancet* 2017;389:815–22.

11 Klotz L, Chin J, Black PC, *et al*. Comparison of multiparametric magnetic resonance Imaging-Targeted biopsy with systematic transrectal ultrasonography biopsy for Biopsy-Naive men at risk for prostate cancer: a phase 3 randomized clinical trial. *JAMA Oncol* 2021;7:534–42.

12 Eklund M, Jäderling F, Discacciati A, *et al*. MRI-Targeted or standard biopsy in prostate cancer screening. *N Engl J Med* 2021;385:908–20.

13 Getaneh AM, Heijnsdijk EA, de Koning HJ. Cost-Effectiveness of multiparametric magnetic resonance imaging and MRI-guided biopsy in a population-based prostate cancer screening setting using a micro-simulation model. *Cancer Med* 2021;10:4046–53.