EUROPEAN UROLOGY xxx (xxxx) xxx–xxx

available at www.sciencedirect.com
journal homepage: www.europeanurology.com

European Association of Urology

Review – Prostate Cancer

VISION: An Individual Patient Data Meta-analysis of Randomised Trials Comparing Magnetic Resonance Imaging Targeted Biopsy with Standard Transrectal Ultrasound Guided Biopsy in the Detection of Prostate Cancer

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Article info

Article history:
Accepted August 12, 2024

Associate Editor:
Gianluca Giannarini

Keywords:
Magnetic resonance imaging
PRECISION
Prostate cancer

Abstract

Background and objective: The PRECISION and PRECISE trials compared magnetic resonance imaging targeted biopsy (MRI ± TB) with the standard transrectal ultrasound (TRUS) guided biopsy for the detection of clinically significant prostate cancer (csPCa). PRECISION demonstrated superiority of MRI ± TB over TRUS guided biopsy, while PRECISE demonstrated noninferiority. The VISION study is a planned individual patient data meta-analysis (IPDMA) comparing MRI ± TB with TRUS guided biopsy for csPCa diagnosis.

Methods: MEDLINE, EMBASE, Web of Science, Cochrane Central of Registered Trials, and ClinicalTrials.gov were searched on the November 12, 2023 for randomised controlled trials of biopsy-naïve patients with a clinical suspicion of prostate cancer undergoing

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https://doi.org/10.1016/j.eururo.2024.08.022

Please cite this article as: V. Kasivisvanathan, V. Wai-Shun Chan, K.D. Clement et al., VISION: An Individual Patient Data Meta-analysis of Randomised Trials Comparing Magnetic Resonance Imaging Targeted Biopsy with Standard Transrectal Ultrasound Guided Biopsy in the Detection of Prostate Cancer, Eur Urol (2024), https://doi.org/10.1016/j.eururo.2024.08.022

Prostate biopsy
Targeted biopsy
Transrectal ultrasound guided biopsy

MRI or standard TRUS. Studies were included if its participants with suspicious MRI underwent targeted biopsy alone and those with nonsuspicious lesion avoided biopsy. The primary outcome is the proportion of men diagnosed with csPCa (Gleason $\geq$3 + 4).

Key findings and limitations: Two studies, PRECISION and PRECISE (953 patients), were included in the IPDMA. In the MRI ± TB arm, 32.2% of patients avoided biopsy due to nonsuspicious MRI. MRI ± TB detected 8.7 percentage points (36.3% vs 27.6%; 95% confidence interval [CI] 2.8–14.6, p = 0.004) more csPCa than TRUS biopsy and 12.3 percentage points (9.6% vs 21.9%; 95% CI 7.8–16.9, p < 0.001) less clinically insignificant prostate cancer (cisPCa; Gleason 3 + 3). The overall risk of bias for the included studies were found to be low after assessment using the QUADAS-2, QUADAS-C, and ROB 2.0 tools.

Conclusions and clinical implications: The MRI ± TB pathway is superior to TRUS biopsy in detecting csPCa and avoiding the diagnosis of cisPCa. MRI should be included in the standard of care pathway for prostate cancer diagnosis.

ADVANCING PRACTICE

What does this study add?

This review provides the most up to date evidence on randomised trials comparing magnetic resonance imaging (MRI) targeted biopsy (without systematic biopsy) with the standard transrectal ultrasound biopsy. This individual patient data meta-analysis provides level 1a evidence to inform clinical practice and guidelines.

Clinical Relevance

This study is significant because it provides the highest-level evidence supporting the superior efficiency of a prostate cancer diagnostic pathway in biopsy-naïve men, where biopsies are performed only if prostate MRI shows suspicious lesions, with sampling targeted exclusively to the visible lesions, as opposed to the old standard of universal transrectal ultrasound-guided random biopsy. Notably, to achieve the benefits of this novel pathway, it is essential to ensure correct initial risk stratification, high-quality prostate MRI, and highly accurate targeting. The next task for future prospective trials is to evaluate whether combining targeted biopsy with perilesional sampling can further enhance the diagnostic performance, as recently suggested by the updated European Association of Urology Guidelines on Prostate Cancer.

Patient Summary

We reviewed all the literature and trials comparing the use of MRI prior to targeted biopsy and traditional transrectal systematic biopsy. Combining individual data from the two trials, we found the MRI diagnostic pathway to be superior to the traditional transrectal biopsy and concluded that patients should be offered MRI and targeted biopsy upfront.

1. Introduction

Prostate cancer (PCa) is the second most common cancer in men, with over 1 400 000 new diagnoses annually worldwide [1]. For the past three decades, the standard of care for diagnosing PCa in suspicious patients with raised prostate-specific antigen (PSA), abnormal digital rectal examination (DRE), and/or family history of PCa has traditionally been systematic transrectal ultrasound (TRUS) guided biopsy [2], in which ten to 12 cores are taken in a systematic fashion from the prostate. However, TRUS has poor sensitivity of 48% for the detection of clinically significant prostate cancer (csPCa) [3], resulting in many patients having csPCa missed and others being rebiopsied routinely multiple times [4]. Of all patients presenting in the PROMIS study with a suspicion of PCa, 78% (452/576) had clinically insignificant PCa (cisPCa) or no cancer on TRUS biopsy [3]. Thus, many patients have traditionally been biopsied unnecessarily and many have been treated for clinically insignificant cancer, despite randomised evidence showing that cisPCa does not benefit from treatment [5].

In the past 5 years, prebiopsy magnetic resonance imaging (MRI) and MRI targeted biopsy (MRI ± TB) have been advocated as an alternative standard of care for diagnosing localised PCa. In this pathway, patients presenting with a suspicion of localised PCa undergo prostate MRI. Patients with suspicious MRI undergo MRI ± TB to ascertain the presence of cancer and histology to guide further treatment, while patients with nonsuspicious MRI avoid a biopsy, unless other high-risk features are present.

Recent within-patient diagnostic test evaluation studies found that MRI ± TB alone can detect more csPCa and fewer cisPCa cases with higher sampling efficiency than TRUS biopsy [6]. However, the within-patient study design, where the patient undergoes both MRI ± TB and TRUS biopsy in the same sitting is subject to several biases [7].

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An incorporation bias is due to the potential knowledge of the location of MRI lesions during TRUS biopsy, which can influence where the standard cores are placed. In a recent systematic review, 87% of these studies were found to lack blinding [6]. Secondly, the within-patient design focuses on patients with an MRI lesion who undergo both techniques, so it cannot always be generalised to the patient group with a clinical suspicion of PCa with raised PSA, abnormal DRE, and family history of PCa, with some of the group having no MRI lesion.

As a result, the PRECISION [8] and PRECISE [9] trials were randomised trials, designed in parallel, to avoid the above biases [10]. Supplementary Figure 1 depicts the study design. The PRECISE trial was a multicentre trial conducted in Canada, and the PRECISION trial was a multicentre trial conducted in 11 different countries. The protocols were designed to be similar to permit a planned individual patient data meta-analysis (IPDMA), called VISION, by representatives from both trial groups after completion of the trials. Owing to the changing equipoise, it will be challenging in the future to reproduce the randomised designs of PRECISION and PRECISE; thus, this IPDMA was intended to be the definitive analysis to address the role of MRI ± TB compared with TRUS biopsy for the detection of csPCa and cisPCa.

2. Methods

This IPDMA is reported according to the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) statement [11] and relevant components of the IPDMA [12] and diagnostic test accuracy [13] extensions. A protocol [14] was published a priori and preregistered on PROSPERO (CRD42021249263).

2.1. Literature search

This systematic review is an update of a previously published review [6], with searches performed up to July 28, 2017; hence MEDLINE, EMBASE, Web of Science, Cochrane Central of Registered Trials (CENTRAL), and Clinical Trials.gov searches were restricted to between July 28, 2017 and November 12, 2023. A combination of medical subject heading (MeSH) terms and keywords were used. The full search strategy is presented in the Supplementary material. No language or other restrictions were imposed.

2.2. Selection criteria

The inclusion and exclusion criteria of the review are outlined in the patient, intervention, comparator, outcomes, and study type (PICOS) format below.

2.2.1. Population

Only studies evaluating biopsy-naïve men with a clinical suspicion of localised PCa (ie, raised PSA and/or abnormal DRE and/or a family history of PCa) and advised to have prostate biopsy were included. Studies focusing on patients with previous biopsies or treatment for PCa were excluded.

2.2.2. Intervention

MRI for PCa diagnosis was included in the study if those with suspicious MRI (Prostate Imaging Reporting and Data System version 2 [PIRADSv2]$\geq$ 3) underwent targeted biopsy alone (without systematic biopsy), and those with a nonsuspicious lesion avoided biopsy. There were no limitations to the approach for targeted biopsy (ie, both transrectal and transperineal targeted biopsies, and both cognitive and image-fusion registration were permitted).

2.2.3. Comparator

Studies with a standard ten to 12-core TRUS biopsy as a comparator were included.

2.2.4. Outcomes

The primary outcome of the study is the proportion of men diagnosed with csPCa (Gleason 3 + 4 or Gleason grade group [GGG] $\geq$2).

The secondary outcomes included the following:

1. Proportion of men diagnosed with cisPCa (Gleason 3 + 3 or GGG 1).
2. Proportion of men who avoided prostate biopsy following MRI.
3. Proportion of men with csPCa, cisPCa and no cancer by PIRADSv2 score.
4. Proportion of biopsy cores positive for cancer for MRI ± TB compared with systematic TRUS biopsy.
5. Proportion of men who get onto definitive local or systemic treatment for PCa.
6. Proportion of men with postbiopsy adverse events.
7. Health-related quality of life (QOL) scores.
8. Predictive factors for csPCa detection.
9. Proportion of men diagnosed with GGG $\geq$3 cancer.
10. Proportion of Gleason grade upgrading in men undergoing radical prostatectomy.

2.2.5. Study type

Only randomised controlled trials (RCTs) were included.

2.3. Study selection and data collection

The title and abstract of each record retrieved by the search were screened independently in duplicate by reviewers (V.W.S.C., K.D.C., A.N., and A.A.) using Covidence (Veritas Health Innovation, Melbourne, Australia) [15]. Conflicts were resolved by consensus between pairs of reviewers, and in the case of unresolved conflict, another author (V.K.) adjudicated. Full texts of potentially eligible papers were retrieved for further screening against the inclusion criteria in the same manner. Reviewers were not blinded to study authors, institution, publications journal, or year of publication.

After identification of trials meeting the eligibility criteria, both study-level and individual patient–level data were sought. A piloted data-extraction form was used for the extraction of study-level data by two independent authors. Where data were not reported, the study's corresponding author was contacted for further information. Similarly, authors of each study were also contacted to provide original patient-level data. Data extracted include the

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characteristics of the study and patients, their arms of investigation, and the outcomes stated above.

2.4. Data synthesis

2.4.1. Analysis of primary outcome

An intention-to-treat approach was used to compare the proportion of men diagnosed with csPCa in the MRI and TRUS biopsy arms. A sensitivity analysis was also performed using the per-protocol and modified intention-to-treat approaches (patients withdrawn prior to any fully completed diagnostic test were excluded). All randomised patients with outcome data were included in the analysis. A one-step IPDMA was performed using a three-level generalised linear mixed model to analyse all studies simultaneously, while accounting for the clustering of participants within centres within each study (random intercept used for both the study and the centre). The identity link function was used with a logistic regression model to allow for the estimation of the absolute difference in the proportion of men diagnosed with clinically significant cancer between the two arms. A sensitivity analysis was also performed using a two-stage IPDMA. In line with the PRECISION and PRECISE trials, a noninferiority margin of 5 percentage points was used to assess noninferiority, as determined at an expert consensus group meeting [16]. This implies that if the lower limit of the two-sided 95% confidence interval (CI) for the difference in the proportion of clinically significant cancer in the MRI arm relative to the TRUS biopsy arm was greater than –5 percentage points, then MRI would be considered noninferior to a TRUS biopsy alone; if the lower limit exceeded zero, superiority would be inferred.

A post hoc subgroup analysis was also performed by PSA density ($\geq$0.15 and <0.15 ng/ml/ml [clinically relevant threshold]), DRE (normal/abnormal), and family history (yes/no), to speculate the effect of these factors on the primary outcome. A subgroup analysis of PSA was not possible as patients with a PSA value of >20 ng/ml were excluded, meaning that the PSA measurements in the VISION study are not representative of men on whom the tests would be used in clinical practice.

2.4.2. Analysis of secondary outcomes

For the secondary outcomes comparing proportions in the MRI and TRUS biopsy arms, the one-step IPDMA method outlined above was used.

For the continuous secondary outcomes, such as health-related QOL, mean differences were meta-analysed using a linear mixed model with a random intercept. If data for particular outcomes were inadequate for a meta-analysis, these were presented descriptively using frequencies and percentages.

A random-effect logistic regression model was also fitted to investigate the associations between predefined covariates and clinically significant cancer detection in the MRI arm for the PRECISION and PRECISE data combined. Random effects were included for trial centre and study. The covariates included age, PSA, family history of PCa, DRE findings, PIRADSv2 score, and type of registration used (software or visual/cognitive).

2.4.3. Quality assessment of included studies

The individual studies included in the review were assessed for the risk of bias and applicability by two independent authors (V.W.S.C. and K.D.C.) using the relevant domains from QUADAS-2 and QUADAS-C tools [17,18]. The Cochrane risk of bias 2.0 tool for RCTs [19] was also used to assess the risk of bias of the included studies. Finally, the reporting of individual studies was assessed according to the START criteria for MRI ± TB studies [16] and relevant items from the STARD list for reporting diagnostic accuracy studies [20].

3. Results

3.1. Literature search results and IPD

The PRISMA flow chart is presented in Supplementary Figure 2. Of a total of 76 studies from the previously published review that were screened, only one study (PRECISION [8]) met the selection criteria for this study. A further 9754 records were identified from database searches, and 8124 remained after the removal of duplicates. After title and abstract screening, 8109 records were deemed irrelevant and excluded, with full reports sought for retrieval and full-text screening of 15 studies. Finally, 14 studies were excluded for having an intervention or study design that did not fit the eligibility criteria, therefore, only one study (PRECISE [9]) met the selection critiera for this study from the database searches. This leaves a total of two studies included for this review, the PRECISION and PRECISE studies [8,9].

Individual patient data were available for both trials—500 patients from the PRECISION study and 453 from the PRECISE study. All 953 patients were included in the IPDMA. The characteristics of both studies are outlined in Table 1. The features of MRI and TRUS biopsies are outlined in Table 2. As PRECISE used 3 T MRI scanners, software-assisted registration, and a transrectal approach for all patients, these subgroup analyses were not feasible. The experience of clinicians reporting scans, performing biopsies, and analysing pathological specimens are outlined in Supplementary Table 1, though part of the data were not available from the PRECISE study.

3.2. Risk of bias within studies

The risk of bias and applicability concerns are outlined in Supplementary Table 2. For QUADAS-2 and QUADAS-C, all domains were of a low risk of bias for PRECISION, while all domains but flow and timing were deemed to be of a low risk of bias for PRECISE. Flow and timing were deemed to have a high risk of bias for PRECISE due to a large difference in dropout rates between the MRI ± TB and TRUS arms. Utilising ROB 2.0, all domains but "bias in the measurement of the outcome" were of a low risk of bias; this is due to the potential of missing csPCa in patients who had negative MRI and did not undergo biopsy, suggesting a risk of bias in favour of the TRUS biopsy arm. The overall judgement of the risk of bias of the two studies remained low. The full summary of ROB 2.0 is shown in Supplementary Table 2.

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Table 1 – Details and characteristics of the two included studies

	PRECISION	PRECISE
Study design	Multicentre, randomised, noninferiority trial	Multicentre, randomised, noninferiority trial
Number of sites	25 sites in 11 countries	5 sites in 1 country
Included countries	Finland, Argentina, Italy, USA, UK, Germany, The Netherlands, France, Canada, Belgium, Switzerland	Canada
Inclusion criteria	1. Men at least 18 yr of age referred with clinical suspicion of prostate cancer who have been advised to have a prostate biopsy 2. Serum prostate-specific antigen ≤20 ng/ml 3. Suspected stage ≤T2 on rectal examination (suspected organ-confined prostate cancer) 4. Fit to undergo all procedures listed in protocol 5. Able to provide written informed consent	1. Men at least 18 yr of age referred with clinical suspicion of prostate cancer who have been advised to have a prostate biopsy 2. Serum prostate-specific antigen ≤20 ng/ml 3. ≥5% chance of high-grade prostate cancer, as calculated using individualised risk assessment of the prostate cancer calculator PCPTRC 2.0 4. Fit to undergo all procedures listed in protocol 5. Able to provide written informed consent
Exclusion criteria	1. Prior prostate biopsy 2. Prior treatment for prostate cancer 3. Contraindication to MRI (eg, claustrophobia, pacemaker, estimated GFR ≤50 ml/min) 4. Contraindication to prostate biopsy 5. Men in whom artefact would reduce the quality of the MRI 6. Previous hip replacement surgery, metallic hip replacement, or extensive pelvic orthopaedic metal work 7. Unfit to undergo any procedures listed in protocol	1. Prior prostate biopsy 2. Prior treatment for prostate cancer 3. Contraindication to MRI (eg, claustrophobia, pacemaker, estimated GFR ≤50 ml/min) 4. Men in whom artefact would reduce the quality of the MRI 5. Previous hip replacement surgery, metallic hip replacement, or extensive pelvic orthopaedic metal work 6. Unfit to undergo any procedures listed in protocol
Primary outcome	Proportion of men who received a diagnosis of clinically significant cancer (Gleason score ≥3 + 4	Proportion of men who received a diagnosis of clinically significant cancer (Gleason score ≥3 + 4)
Secondary outcome(s)	1. Proportion of men in each arm who received a diagnosis of clinically insignificant cancer (Gleason 3 + 3) 2. Proportion of men in the MRI targeted biopsy group who avoided biopsy 3. Proportion of men in whom mpMRI score for suspicion of clinically significant cancer was 3, 4, or 5, but no clinically significant cancer was detected 4. Proportion of men in each arm who go on to definitive local treatment (eg, radical prostatectomy, radiotherapy, brachytherapy) or systemic treatment (eg, hormone therapy, chemotherapy) 5. Cancer core length of the most involved biopsy core (maximum cancer core length, mm) in each arm 6. Proportion of men with postbiopsy adverse events 7. Health-related quality of life 8. Proportion of men with Gleason grade upgrading undergoing radical prostatectomy 9. Cost per diagnosis of cancer	1. Proportion of men in each arm who received a diagnosis of clinically insignificant cancer (Gleason 3 + 3) 2. Proportion of men in each arm detected with Gleason score ≥4 + 3 cancer 3. Proportion of men in the MRI-targeted biopsy group who avoided biopsy 4. Proportion of men in whom the PIRADS score for suspicion of clinically significant cancer was 3, 4, or 5, but no clinically significant cancer was detected 5. Proportion of men in each arm who go on to definitive local treatment (eg, radical prostatectomy, radiotherapy, brachytherapy) or systemic treatment (eg, hormone therapy, chemotherapy) 6. Cancer core length of the most involved biopsy core (maximum cancer core length, mm) in each arm 7. Total contiguous cancer core length of the most involved biopsy core (contiguous maximum cancer core length) excluding intervening normal regions 8. Proportion of men with negative MRI who develop positive MRI and/or Gleason score ≥7 cancer by 2 yr 9. Health-related quality of life 10. Proportion of men with Gleason grade upgrading undergoing radical prostatectomy
Recruitment period	February 2016–August 2017	April 2017–November 2019
Duration of follow-up and protocol	Participants were followed until the visit at which their treatment decisions were made or until their 30-d postintervention questionnaires were completed, whichever was later	Participants were given a 30-d postbiopsy questionnaire if they received a biopsy. All participants were followed up for up to 2 yr or until they had radical treatment
Funding information	NIHR and the European Association of Urology Research Foundation	Ontario Institute for Cancer Research and Prostate Cancer Canada

GFR = glomerular filtration rate; mpMRI = multiparametric MRI; MRI = magnetic resonance imaging; PCPTRC = Prostate Cancer Prevention Trial Risk Calculator; PIRADS = Prostate Imaging Reporting and Data System; NIHR = National Institute for Health and Care Research.

3.3. *Baseline characteristics*

The baseline characteristics of both the included studies and the IPDMA are outlined in Table 2. A total of 479 and 474 patients were randomised to the MRI ± TB and TRUS arms, respectively. All baseline characteristics were found to be similar between the two included studies and two intervention groups.

3.4. *Outcomes*

A total of 154 of 479 patients (32.2%) in the MRI ± TB arm had nonsuspicious MRI (PIRADSv2 ≤2) and hence avoided targeted biopsy. Amongst patients with suspicious MRI (PIRADSv2 ≥3), 16.1% had a PIRADSv2 score of 3, 31.8% a score of 4, and 17.5% a score of 5. The association of PIRADSv2 score with cancer outcomes is shown in Figure 1. The breakdown for individual studies is also outlined in Supplementary Figure 3. The pathological outcome for all patients is outlined in Table 3. The primary and secondary outcomes of the study are outlined in Table 4. Although stated in the protocol, due to the lack of some recorded data for the PRECISE trial, it was not possible to meta-analyse secondary outcomes such as cancer core length and proportion of patients with an upgraded Gleason grade at prostatectomy.

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Table 2 – Baseline characteristics of included patients and the features of MRI and TRUS biopsy

Baseline characteristic of included patients		PRECISION (n = 500)		PRECISE (n = 453)		Overall (n = 953)	
		MRI ± TB	TRUS	MRI ± TB	TRUS	MRI ± TB	TRUS
Number of patients		252 (50.4)	248 (49.6)	227 (50.1)	226 (49.9)	479 (50.3)	474 (49.7)
Age, mean (SD)		64.4 (7.5)	64.5 (8.0)	65.3 (7.6)	64.5 (8.8)	64.8 (7.5)	64.5 (8.4)
PSA, median (IQR)		6.8 (5.2, 9.4)	6.5 (5.1, 8.7)	6.7 (5.1, 9.1)	6.2 (4.7, 8.3)	6.7 (5.1, 9.3)	6.4 (4.9, 8.4)
Prostate volume, median (IQR)		46.0 (34.9, 62.0)	43.7 (33.3, 60.0)	47.5 (35.3, 70.4)	40.0 (33.5, 53.0)	46.0 (35.0, 66.0)	42.0 (33.3, 57.4)
PSA density, median (IQR)		0.14 (0.11, 0.21)	0.14 (0.10, 0.20)	0.14 (0.09, 0.20)	0.14 (0.10, 0.21)	0.14 (0.10, 0.21)	0.14 (0.10, 0.21)
Family history of PCa	No	204 (81.0)	208 (83.9)	152 (67.0)	134 (59.3)	356 (74.3)	342 (72.2)
	Yes	48 (19.1)	40 (16.1)	63 (27.8)	73 (32.3)	111 (23.2)	113 (23.8)
	Do not know	0 (0)	0 (0)	12 (5.3)	19 (8.4)	12 (2.5)	19 (4.0)
DRE Normal		216 (85.6)	210 (84.7)	163 (71.8)	165 (73.0)	379 (79.1)	375 (79.11)
Abnormal	Nodule >1.5 cm	36 (14.3)	38 (15.3)	12 (5.3)	8 (3.5)	95 (19.8)	97 (20.5)
	Nodule ≤1.5 cm			47 (20.7)	48 (21.2)		
	Both lobes			0 (0)	3 (1.3)		
Not Available		0 (0)	0 (0)	5 (2.2)	2 (0.9)	5 (1.0)	2 (0.4)
Risk of PCa	5–25%	Not reported	Not reported	204 (89.9)	203 (89.8)	Not applicable	Not applicable
	>25%	Not reported	Not reported	23 (10.1)	23 (10.2)	Not applicable	Not applicable
MRI features		PRECISION (n = 252, randomised) (n = 246, underwent MRI)		PRECISE (n = 227, randomised) (n = 221, underwent MRI)		Combined (n = 479, randomised) (n = 467, underwent MRI)	
Field strength of magnet, n (%)	1.5 T	62 (25.2)		0 (0)		62 (13.3)	
	3.0 T	184 (74.8)		221 (100)		405 (86.7)	
MRI sequences, n (%)	mpMRI	246 (100)		221 (100)		467 (100)	
	bpMRI	0 (0)		0 (0)		0 (0)	
MRI targeted approach, n (%)	Transperineal	25 (9.9)		0 (0)		25 (5.3)	
	Transrectal	227 (90.1)		221 (100)		448 (94.7)	
Type of registration used, n (%)	Visual	39 (23.1)		0 (0)		39 (8.4)	
	Software assisted	130 (76.9)		221 (100)		351 (73.3)	
MRI suspicion score (PIRADSv2) , n (%)	1–2	71 (28.9)		82 (37.3)		153 (32.8)	
	3, 4, or 5	175 (71.1)		138 (62.7)		313 (67.2)	
Suspicious lesions per patient, n (%)	No lesions	71 (28.9)		82 (37.3)		153 (32.8)	
	1 lesion	107 (43.5)		78 (35.3)		185 (39.6)	
	2 lesions	44 (17.9)		50 (22.6)		94 (20.1)	
	3 lesions	24 (9.8)		10 (4.5)		34 (7.3)	
Highest PIRADSv2 for men with suspicious lesions, n (%) [a]	3	51 (29.1)		26 (18.8)		77 (24.6)	
	4	70 (40)		82 (59.4)		152 (48.5)	
	5	54 (30.9)		30 (21.7)		84 (26.8)	
Maximum lesion diameter (mm), median (IQR)		12 (8, 15)		Not reported		Not applicable	
Lesion volume (ml), median (IQR)		0.6 (0.3, 1.2)		Not reported		Not applicable	
Number of biopsies taken, median (IQR) [b]		4 (3, 7)		5 (4, 8)		4 (4, 8)	
TRUS features		PRECISION (n = 248, randomised) (n = 228, underwent biopsy)		PRECISE (n = 226, randomised) (n = 202, underwent biopsy)		Combined (n = 474, randomised) (n = 430, underwent biopsy)	
TRUS volume of prostate (ml), median (IQR)		43.7 (33.3, 60.0)		40.0 (33.5, 53.0)		42.0 (33.3, 57.4)	
Number of biopsies taken (no.), median (IQR)		12 (12, 12)		12 (12, 12)		12 (12, 12)	
Length of procedure (min), median (IQR)		10 (9, 15)		Not reported		Not applicable	
Anaesthetics, n (%)	Local	196 (86.0)		Not reported		Not applicable	
	Sedation or general	32 (14.0)		Not reported		Not applicable	

bpMRI = biparametric MRI; DRE = digital rectal examination; IQR = interquartile range; mpMRI = multiparametric MRI; MRI = magnetic resonance imaging; PCa = prostate cancer; PIRADSv2 = Prostate Imaging Reporting and Data System version 2; PSA = prostate-specific antigen; SD = standard deviation; TB = targeted biopsy; TRUS = transrectal ultrasound.

[a] The denominator of reported percentage is based on the number of patients with a suspicious (PIRADS 3,4, or 5) lesion on MRI.

[b] Only patients undergoing biopsy were included.

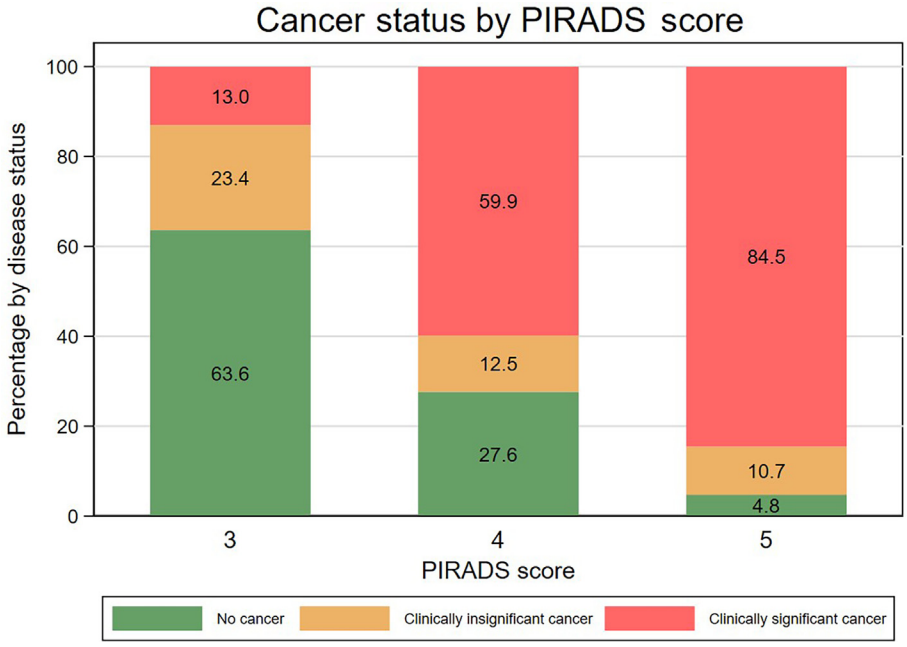

Fig. 1 – Association between PIRADSv2 score and cancer outcomes. In patients randomised to the MRI arm, the suspicion of cancer was scored according to PIRADSv2 in a scale of 1–5. A PIRADSv2 score of 5 represents the greatest likelihood of clinically significant cancer, a score of 3 suggests equivocal results, and a score of 1 represents the lowest likelihood of clinically significant cancer. The percentages of cisPCa (defined as Gleason 3 + 3 or GGG 1), csPCa (Gleason 3 + 4 or GGG ≥2), and noncancerous outcomes are outlined in the subgroups of PIRADSv2 score. Patients with PIRADSv2 3 are less likely to have csPCa (13%) and cisPCa (23.4%) than those with no cancer (63.6%). In patients with PIRADSv2 4, csPCa is the most likely outcome at 59.9%, followed by no cancer (26.6%) and cisPCa (12.5%). Finally, among those with PIRADS 5, the majority of patients (84.5%) have csPCa, 10.7% have cisPCa, and 4.8% have no cancer. cisPCa = clinically insignificant prostate cancer; csPCa = clinically significant prostate cancer; GGG = Gleason grade group; MRI = magnetic resonance imaging; PIRADSv2 = Prostate Imaging Reporting and Data System, version 2.

Table 3 – Pathological outcomes of included patients [a]

	PRECISION (n = 500)		PRECISE (n = 453)		Combined (n = 953)	
	MRI ± TB (n = 252, randomised) (n = 246, underwent MRI)	TRUS (n = 248, randomised) (n = 228, underwent biopsy)	MRI ± TB (n = 227, randomised) (n = 221, underwent MRI)	TRUS (n = 226, randomised) (n = 202, underwent biopsy)	MRI ± TB (n = 479, randomised) (n = 467, underwent MRI)	TRUS (n = 474, randomised) (n = 430, underwent biopsy)
Biopsy outcome						
Biopsy excluded by MRI	71 (28.2)	0 (0)	83 (36.6)	0 (0)	154 (32.2)	0 (0)
Benign	52 (20.6)	98 (39.5)	34 (15.0)	86 (38.1)	86 (18.0)	184 (38.8)
Atypical small acinar proliferation	0 (0)	5 (2.0)	–	–	0 (0)	5 (1.1)
High-grade prostatic intraepithelial neoplasia	4 (1.6)	10 (4.0)	–	–	4 (0.8)	10 (2.1)
Gleason score or grade group						
3 + 3/GG1	23 (9.1)	55 (22.2)	23 (10.1)	49 (21.7)	46 (9.6)	104 (21.9)
3 + 4/GG2	52 (20.6)	35 (14.1)	49 (21.6)	42 (18.6)	101 (21.1)	77 (16.2)
4 + 3/GG3	18 (7.1)	19 (7.7)	18 (7.9)	17 (7.5)	36 (7.5)	36 (7.6)
3 + 5/4 + 4/GG4	15 (6.0)	7 (2.8)	5 (2.2)	3 (1.3)	20 (4.2)	10 (2.1)
4 + 5/5 + 4/5 + 5/GG5	10 (4.0)	3 (1.2)	7 (3.1)	5 (2.5)	17 (3.6)	8 (1.7)
No biopsy	4 (1.6)	3 (1.2)	2 (8.8)	2 (0.9)	6 (1.3)	5 (1.1)
Withdrawal	3 (1.2)	13 (5.2)	6 (2.6)	22 (9.7)	9 (1.9)	35 (7.4)
Clinically significant PCa	95 (37.7)	64 (25.8)	79 (34.8)	67 (29.6)	174 (36.3)	131 (27.6)
Clinically insignificant PCa	23 (9.1)	55 (22.2)	23 (10.1)	49 (21.7)	46 (9.6)	104 (21.9)
Max core length, median (IQR)	7 (4, 12)	6 (2, 10)	–	–	–	–
Core positive for cancer, median (IQR)	3 (2, 4)	4 (2, 6)	4 (3, 5)	4 (2, 4)	4 (3, 4)	4 (2, 6)

GG = grade group; IQR = interquartile range; MRI = magnetic resonance imaging; PCa = prostate cancer; TB = targeted biopsy; TRUS = transrectal ultrasound.
[a] Number in parenthesis represents percentage unless otherwise stated.

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Table 4 – Primary and secondary outcomes of the study

	PRECISION (n = 500)		PRECISE (n = 453)		Overall (n = 953)	
	MRI ± TB (n = 252)	TRUS (n = 248)	MRI ± TB (n = 227)	TRUS (n = 226)	MRI ± TB (n = 479)	TRUS (n = 474)
Clinically significant cancer (Gleason 3 + 4 or GG ≥2), n (%)	95 (37.7)	64 (25.8)	79 (34.8)	67 (29.7)	174 (36.3)	131 (27.6)
Difference (95% CI; p value)	11.7 (3.6, 19.8; p = 0.005)		5.2 (–3.5, 13.8; p = 0.2)		8.7 (2.8, 14.6; p = 0.004)	
Clinically insignificant cancer (Gleason 3 + 3 or GG1), n (%)	23 (9.1)	55 (22.2)	23 (10.1)	49 (21.7)	46 (9.6)	104 (21.9)
Difference (95% CI; p value)	–13.1 (–19.3, –6.8; p < 0.001)		–11.6 (–18.2, –4.9; p < 0.001)		–12.3 (–16.9, –7.8; p < 0.001)	
GG ≥3 cancer, n (%)	43 (17.1)	29 (11.7)	30 (13.2)	25 (11.1)	73 (15.2)	54 (11.4)
Difference (95% CI; p value)	5.2 (–1.0, 11.4; p = 0.098)		2.2 (–3.9, 8.2; p = 0.5)		3.8 (–0.5, 8.2; p = 0.080)	
Definitive local or systemic treatment, n (%)	102 (40.5)	91 (36.7)	118 (52.0)	112 (49.6)	220 (45.9)	203 (42.8)
Difference (95% CI; p value)	3.2 (–5.3, 11.6; p = 0.5)		2.5 (–6.6, 11.6; p = 0.6)		2.9 (–3.3, 9.1; p = 0.4)	
Biopsy cores positive for cancer, n (%) [95% CI]	422/967 (43.6) [40.5, 46.8]	515/2788 (18.5) [17.0, 19.9]	466/852 (54.7) [51.4, 58.0]	527/2311 (22.8) [21.1, 24.5]	888/1819 (48.8) [46.5, 51.1]	1042/5099 (20.4) [19.3, 21.5]
Difference (95% CI; p value)	–		–		29.3 (26.7, 31.9; p < 0.001)	
Adverse events, n (%) [95% CI]	6 (2.4) [0.5, 4.3]	9 (3.6) [1.3, 6.0]	8 (3.5) [1.1, 5.9]	15 (6.6) [3.4, 9.9]	14 (2.9) [1.4, 4.4]	24 (5.1) [3.1, 7.0]
Difference (95% CI; p value) [a]	–		–		2.1 (–0.4, 4.6; p = 0.093)	
Avoided biopsy, n (%) [95% CI]	71 (28.2) [22.6, 33.7]	–	83 (36.6) [30.3, 42.8]	–	154 (32.2) [28.0, 36.3]	–

CI = confidence interval; GG = grade group; MRI = magnetic resonance imaging; TB = targeted biopsy; TRUS = transrectal ultrasound.
[a] Calculated using a two-level model with a random effect for study only due to low event numbers.

3.4.1. *Detection of clinically significant cancer*

MRI ± TB was shown to be superior to TRUS for the detection of clinically significant cancer (Gleason 3 + 4/GGG ≥2), with 36.3% and 27.6% of patients, respectively, in the MRI ± TB and TRUS groups found to have clinically significant cancer (difference: 8.7 percentage points, 95% CI 2.8–14.6, p = 0.004; Fig. 2). The results are similar across the per-protocol and modified intention-to-treat analyses (Supplementary Table 3).

3.4.2. *Detection of clinically insignificant cancer*

MRI ± TB was also shown to significantly reduce the rates of clinically insignificant cancer (Gleason 3 + 3 or GGG 1), as fewer patients undergoing MRI ± TB (9.6%) were found to have clinically insignificant cancer than those undergoing TRUS (21.9%; difference: –12.3 percentage points, 95% CI –16.9 to –7.8, p < 0.0001).

3.4.3. *Biopsy core positive for cancer*

Patients undergoing MRI ± TB had a significantly higher proportion of biopsy cores positive for cancer (48.8% vs 20.4%; difference: 29.3 percentage points, 95% CI 26.7–31.9, p < 0.0001).

3.4.4. *Proportion of patients avoiding biopsy in the MRI arm*

Of the patients, 32.2% (154/953; 95% CI 28.0–36.3%) avoided biopsy in the MRI arm.

3.4.5. *Rate of adverse events and complications*

MRI ± TB appears to be associated with lower rates of adverse events at 2.9% (95% CI 1.4–4.4%) in comparison with 5.1% (95% CI 3.1–7.0%) for patients undergoing TRUS. However, this difference was not statistically significant (difference: 2.1 percentage points, 95% CI –0.4 to 4.6, p = 0.093). The most common adverse event related to TRUS biopsy was sepsis, where seven cases were observed (1.5%), compared with one case (0.2%) with MRI ± TB. A full list of the adverse events and their incidences are outlined in Supplementary Table 4.

3.4.6. *QOL outcomes*

The mean difference in EQ-5D VAS score at baseline and after intervention was not significantly different (0 [95% CI –0.7 to 0.6]) between the MRI ± TB and TRUS arms. Similarly, when adjusted for baseline QOL scores, the mean difference in postintervention QOL scores between the MRI ± TB and TRUS arms was not significantly different (0.09 [95% CI –1.11 to 1.30], p = 0.88). The details of the QOL analysis are outlined in Supplementary Table 5.

3.4.7. *Other outcomes*

There was no statistically significant difference between MRI ± TB and TRUS for the detection of GGG ≥3 cancer (3.8 percentage points, 95% CI –0.5 to 8.2, p = 0.080) and the need for definitive local or systemic treatment (2.9 percentage points, 95% CI –3.3 to 9.1, p = 0.35). The percentage of men whose Gleason score was upgraded after radical prostatectomy were similar between the TRUS arm (28/65, 43.1%) and the MRI ± TB arm (33/77, 42.9%). Similarly, percentage of men whose Gleason score was downgraded after radical prostatectomy were similar between the two groups (12/77 [18.5%] vs 13/65 [16.9%]). Complete details of histology concordance after radical prostatectomy are outlined in Supplementary Table 6.

3.4.8. *Subgroup analyses*

Subgroup analyses were performed by PSA density. The primary outcome measure (detection of Gleason 3 + 4/GGG ≥2 PCa) was similar between patients with PSA density ≥0.15 ng/ml/ml and those with PSA density <0.15 ng/ml/

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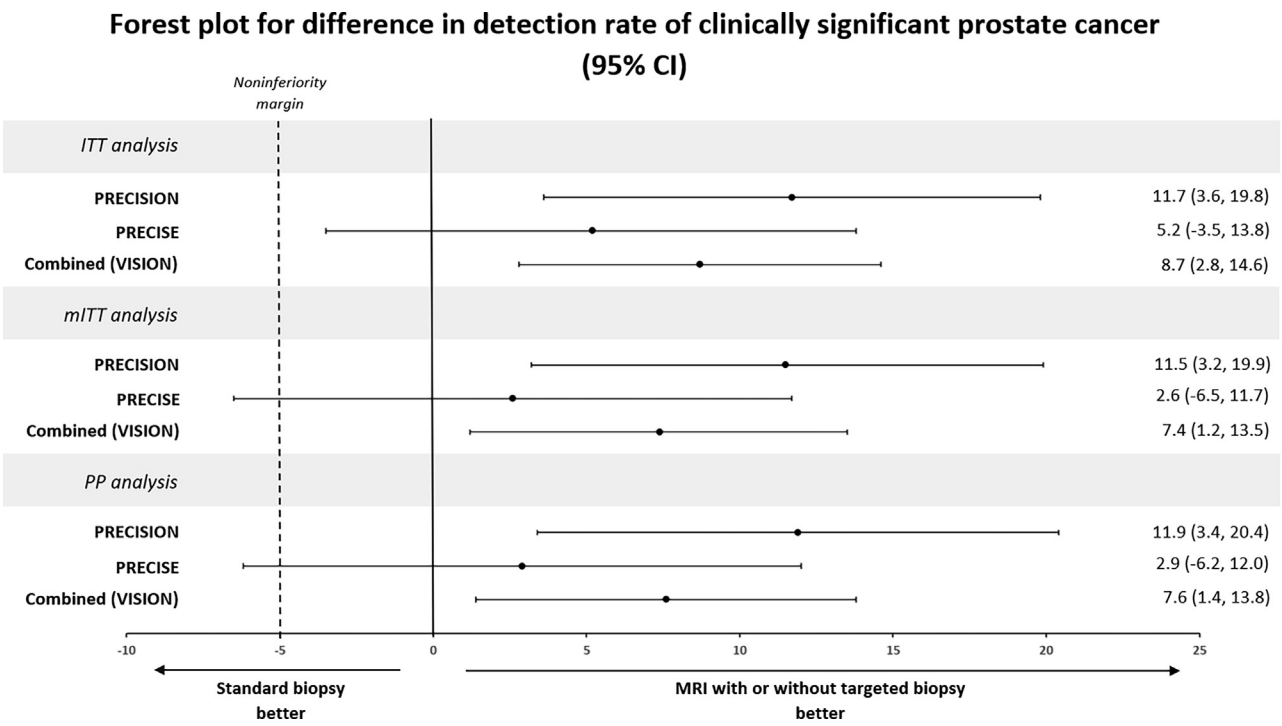

Fig. 2 – Forest plot of the difference in proportion of clinically significant cancer between MRI targeted biopsy and TRUS biopsy from the intention-to-treat (ITT), modified intention-to-treat (mITT), and per-protocol (PP) analyses. The absolute difference in csPCa detection between the MRI targeted biopsy group and the TRUS biopsy group is shown. The ITT analysis includes all patients who were randomised to the study. The PP analysis excludes all patients who did not undergo the randomised procedure as per the protocol. In the mITT analysis, patients withdrawn prior to any fully completed diagnostic test were excluded. If the lower boundary of the 95% confidence interval was greater than –5 percentage points (dashed line), noninferiority is suggested for MRI (with or without a biopsy) in comparison with a TRUS biopsy. Where the lower boundary of the 95% confidence interval was >0 percentage points (solid line), superiority is inferred. The individual trial (PRECISION and PRECISE) results are shown along with the combined results from the IPDMA. In both ITT and PP analyses, MRI with or without a biopsy is superior to the standard biopsy according to the IPDMA results. csPCa = clinically significant prostate cancer; CI = confidence interval; IPDMA = individual patient data meta-analysis; MRI = magnetic resonance imaging; TRUS = transrectal ultrasound.

ml. Subgroup analyses performed by DRE status (normal vs abnormal) and family history of PCa (family history vs no family history) also showed no differences between the subgroups (see forest plots in Supplementary Fig. 4). These results must be interpreted with caution and should be used only for hypothesis-generating purpose as a result of an underpowered post hoc subgroup analysis that was not prespecified in our protocol.

3.4.9. Prognostic factors for clinically significant cancer in patients undergoing preoperative MRI

On a multivariable analysis of the factors predictive of csPCa in patients undergoing MRI, only increased age (odds ratio [OR]: 1.05, 95% CI 1.01–1.09, p = 0.017), PSA (OR: 1.14, 95% CI 1.04–1.26, p = 0.007), and PIRADSv2 score were associated with increased odds of clinically significant cancer. Patients with PIRADSv2 scores of 4 (OR: 9.55, 95% CI 4.21–21.7, p < 0.001) and 5 (OR: 35.54, 95% CI 13.1–96.5, p < 0.001) were at significantly higher odds of detecting csPCa than those with a PIRADSv2 score of 3. Other factors, such as family history, DRE findings, registration method for MRI ± TB and coil strength of MRI had no significant effect on predicting csPCa. The full model, including breakdown for the PRECISION and PRECISE trials, is outlined in Supplementary Table 7.

4. Discussion

The principal findings of the VISION analysis were that in men with suspected PCa, a pathway of MRI ± TB was superior to TRUS biopsy for the detection of csPCa and the avoidance of cisPCa. In addition, just under a third of patients in the MRI ± TB arm avoided biopsy altogether, and there was good sampling efficiency and a low complication rate amongst those biopsied. The key drivers for csPCa detection in the MRI arm were the MRI score of suspicion (PIRADSv2 score), PSA, and age, whereas other traditionally associated factors such as DRE findings, family history, and MRI coil strength were not found to be associated with the detection of csPCa.

The PRECISION and PRECISE trials were landmark multicentre randomised trials comparing the MRI diagnostic pathway with the traditional TRUS biopsy pathway in the context of biopsy-naïve patients with a suspicion of localised PCa. The VISION analysis was planned from the outset of both trials, which were designed in parallel with deliberately similar protocols to allow an IPDMA once both trials were completed. Given the findings of the VISION analysis, it is unlikely that there will be equipoise to randomise patients to any further studies using a similar study design. The VISION study therefore provides unique insight into

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this cohort of patients and serves as the most robust evidence for defining the current best practice pathway for PCa diagnosis. Although the original studies differed slightly in their conclusions, with PRECISE showing noninferiority and PRECISION showing superiority of MRI ± TB over TRUS biopsy, the VISION analysis concluded that MRI ± TB was in fact superior to TRUS biopsy. Both studies had a low risk of bias, reflecting the high quality of evidence of this IPDMA. VISION confirms that MRI ± TB should be used routinely in patients with suspected PCa and should form the basis of international guidelines.

There are limitations of this analysis. This analysis compares the MRI ± TB and TRUS biopsy pathways. Other strategies, such as the addition of systematic biopsies to MRI biopsies, were not evaluated as part of the original design but have been suggested as adjuncts to MRI ± TB. Adding systematic biopsies only to men who are already undergoing MRI ± TB may improve the csPCa detection rate further in the range of 0–10% in well-designed studies, while providing further important information for staging and prognosis [21–24]. The addition of systematic biopsies also comes at the cost of increased detection of cisPCa in about 5% [25]. Avoiding the detection of cisPCa is particularly important in reducing overtreatment of men, which has been recognised as a major unmet need in PCa [26], and avoiding the "survivor" label and its attendant anxiety and QOL effects.

A strategy of avoiding biopsy in MRI-negative men resulted in about a third of men avoiding biopsy, which provides major health economic and environmental benefits [27,28]. However, a small proportion of these patients may harbour csPCa. Suggestions on minimising this proportion have included performing systematic biopsy in MRI-negative men in specific groups of patients at a high clinical risk, for example, with a high PSA density of >0.15 ng/ml/ml [29]. The majority of additional cancers identified in this way are likely to be MRI nonvisible Gleason 3 + 4 disease. These cancer have been shown to have a similar prognosis to cisPCa [30], supporting a hypothesis that the clinical significance of disease may be related to MRI visibility of the lesion independent of the Gleason grade [31]. Thus, early detection may be of limited value, despite the cancers being "clinically significant" by virtue of being GGG 2.

Although both PRECISION and PRECISE were designed using a similar protocol, there were still minor differences between the two studies. Although in both studies men were included if they had a suspicion of PCa based on PSA and abnormal DRE, PRECISE also required men to have a $\geq$5% chance of GGG 2 or PCa using the Prostate Cancer Prevention Trial Risk Calculator, version 2. However, this is a very low threshold and so does not provide a material difference between the studies. In addition, important patient characteristics such as PSA were quite similar between both trials, meaning that this difference is unlikely to be important.

VISION used a one-stage IPDMA as prespecified in the protocol. Another approach to conducting an IPDMA is to use a two-stage model. Whilst both approaches should (in most situations) give almost identical results, there is debate over which model is preferable. However, a sensitivity analysis was performed using a two-stage IPDMA, showing a very similar result for the primary outcome (8.6 percentage points, 95% CI 2.2–15.0; Supplementary Fig. 5). Further considerations should also be made regarding small sample corrections in the context of IPDMAs with a small number of studies.

Outside of the clinical trial context, as noted by the PRECISE study, there is significant difference in the performance of MRI ± TB between centres, with differences in positive MRI rates and targeted biopsy yields. Therefore, further work is needed to allow the universal adoption of these findings into global clinical practice. Whilst incorporation of MRI into PCa pathways has in the past few years been included in international guidelines [32,33], challenges remain in access and reimbursement. Given the massive demand for prostate MRI at present, addressing this challenge is particularly important. Strategies to overcome this using a streamlined, more cost-effective version of MRI such as biparametric MRI, seem promising and are being investigated in on-going multicentre studies [34,35].

The quality of MRI scans and expertise of staff reading MRI and performing MRI ± TB have also been proposed as barriers in universal adoption. Efforts to evaluate and optimise MRI quality are being made [36], and global education and quality improvement programmes should be prioritised [37,38]. There may also be a role for artificial intelligence in supporting MRI reading and MRI ± TB [39]. Further research is also on-going using other imaging modalities such as positron emission tomography in refining the ability to identify patients with csPCa and avoiding the detection of cisPCa within the framework of an MRI risk stratification pathway [40].

5. Conclusions

In conclusion, based on the level 1a evidence from the IPDMA, we conclude that the MRI ± TB diagnostic pathway for localised PCa is superior to traditional TRUS biopsy in detecting csPCa and avoiding the detection of cisPCa.

***Author contributions*:** Veeru Kasivisvanathan 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: Kasivisvanathan, Klotz, Moore.
Acquisition of data: Kasivisvanathan, Chan, Clement, Ng, Asif, Haider, Emberton, Pond, Takwoingi, Klotz, Moore.
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Drafting of the manuscript: Chan, Kasivisvanathan, Asif, Ng.
Critical revision of the manuscript for important intellectual content: All authors.
Statistical analysis: Agarwal, Scandrett, Takwoingi.
Obtaining funding: None.
Administrative, technical, or material support: Chan.
Supervision: Kasivisvanathan, Takwoingi, Klotz, Moore.
Other: None.

Financial disclosures: Veeru Kasivisvanathan certifies that all conflicts of interest, including specific financial interests and relationships and affili-

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ations relevant to the subject matter or materials discussed in the manuscript (eg, employment/affiliation, grants or funding, consultancies, honoraria, stock ownership or options, expert testimony, royalties, or patents filed, received, or pending), are the following: Veeru Kasivisvanathan receives funding from Prostate Cancer UK and the John Black Charitable Trust. Brooke Levis is funded by a Fonds de Recherche du Québec - Santé Postdoctoral Training Fellowship. Gregory Pond has received honorarium from AstraZeneca and Takeda, has received consulting fees from Merck and Profound Medical, and has a close family member who is an employee of Roche Canada and who owns stock in Roche Ltd. Yemisi Takwoingi is supported by the NIHR Birmingham Biomedical Research Centre. The views expressed are those of the author(s) and not necessarily those of the NIHR or the Department of Health and Social Care.

***Funding/Support and role of the sponsor*:** None.

Supplementary material

Supplementary data to this article can be found online at https://doi.org/10.1016/j.eururo.2024.08.022.

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Please cite this article as: V. Kasivisvanathan, V. Wai-Shun Chan, K.D. Clement et al., VISION: An Individual Patient Data Meta-analysis of Randomised Trials Comparing Magnetic Resonance Imaging Targeted Biopsy with Standard Transrectal Ultrasound Guided Biopsy in the Detection of Prostate Cancer, Eur Urol (2024), https://doi.org/10.1016/j.eururo.2024.08.022