Magnetic Resonance Imaging (MRI) for prostate cancer diagnosis in primary care

Volume 2 of 2

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I certify that all material in this thesis which is not my own work has been identified and that no material has previously been submitted and approved for the award of a degree by this or any other University.

Signature: 

Appendices

Papers relating to the PhD

1.1 Published paper from Chapter 2

Merriel, S. W. D., Hardy, V., Thompson, M., Walter, F. M., & Hamilton, W. (2020). Patient-Centered Outcomes From Multiparametric MRI and MRI-Guided Biopsy for Prostate Cancer: A Systematic Review. *Journal of the American College of Radiology*, *September*. Apr; 17(4):486-495 https://doi.org/10.1016/j.jacr.2019.08.031

Patient-Centered Outcomes From Multiparametric MRI and MRI-Guided Biopsy for Prostate Cancer: A Systematic Review

SA-CME

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Abstract

Objective: To identify and characterize patient-centered outcomes (PCOs) relating to multiparametric MRI (mpMRI) and MRI-guided biopsy as diagnostic tests for possible prostate cancer.

Methods: Medline via OVID, EMBASE, PsycInfo, and the Cochrane Central register of Controlled Trials (CENTRAL) were searched for relevant articles. Hand searching of reference lists and snowballing techniques were performed. Studies of mpMRI and MRI-guided biopsy that measured any PCO were included. There were no restrictions placed on year of publication, language, or country for study inclusion. All database search hits were screened independently by two reviewers, and data were extracted using a standardized form.

Results: Overall, 2,762 database search hits were screened based on title and abstract. Of these, 222 full-text articles were assessed, and 10 studies met the inclusion criteria. There were 2,192 participants featured in the included studies, all of which were conducted in high-income countries. Nineteen different PCOs were measured, with a median of four PCOs per study (range 1-11). Urethral bleeding, pain, and urinary tract infection were the most common outcomes measured. In the four studies that compared mpMRI or MRI-guided biopsy to transrectal ultrasound biopsy, most adverse outcomes occurred less frequently in MRI-related tests. These four studies were assessed as having a low risk of bias.

Discussion: PCOs measured in studies of mpMRI or MRI-guided biopsy thus far have mostly been physical outcomes, with some evidence that MRI tests are associated with less frequent adverse outcomes compared with transrectal ultrasound biopsy. There was very little evidence for the effect of mpMRI and MRI-guided biopsy on emotional, cognitive, social, or behavioral outcomes.

Key Words: mpMRI, MRI biopsy, patient-centered outcomes, prostate cancer

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INTRODUCTION

The current diagnostic tests for prostate cancer have important limitations, which can impact patients. Prostate biopsy via the transrectal (TRUS) or transperineal route under ultrasound guidance carry a risk of adverse effects [1], and both have a significant false-negative rate leading to potential underdiagnosis [2]. In recent years there has been increasing interest in the potential utility of multiparametric MRI (mpMRI) as a new diagnostic test for prostate cancer. mpMRI could avoid the need for up to 28% of men to undergo a prostate biopsy for possible prostate cancer if used as a prebiopsy triage test [3]. MRI-guided biopsy has been shown to increase the diagnostic accuracy for clinically significant prostate cancer and reduce the numbers of patients diagnosed with clinically insignificant prostate cancer [4,5].

Mortality benefits, diagnostic accuracy, and adverse effects are all important clinical outcomes of diagnostic tests, but they are not the only elements that need to be considered. The Agency for Healthcare Research and Quality Effective Healthcare Program White Paper series on diagnostic test evaluation proposed that, in addition to the clinical outcome, a medical test can have emotional, social, cognitive, and behavioral outcomes for patients. These outcomes can be positive or negative, and they are not restricted to the medical test itself, but the entire diagnostic pathway [6].

Outcomes that are considered to have most importance or meaning to patients are often referred to as patient-centered outcomes (PCOs), although a precise definition of PCOs has not yet been reached [7]. The Patient-Centered Outcomes Research Institute (PCORI) has been established to support and conduct research into the comparative effectiveness of health care interventions to inform patient and clinical decision making. PCOs have three domains [8]:

1. Assessment of harms and benefits to inform decision making, highlighting comparisons and outcomes that matter to people
2. A focus on outcomes that people notice and care about
3. The incorporation of a wide variety of settings and diversity of participants

Among the PCORI portfolio, there is some ongoing work exploring the most important outcomes for patients from diagnostic tests [9].

This systematic review aims to summarize and compare the current evidence relating to PCOs for mpMRI or MRI-guided biopsy as a diagnostic test in men suspected of having prostate cancer.

METHODS

The protocol for this systematic review has been published on PROSPERO [10].

In summary, databases including Medline via OVID, EMBASE, PsycInfo, and the Cochrane Central register of Controlled Trials (CENTRAL) were selected to search for relevant articles. The Cochrane Collaboration recommends combining the test(s) of interest with the specific condition to refine searches [11]. This approach was merged with pretested search filters developed by the Scottish Intercollegiate Guidelines Network [12] for "diagnostic studies" and "patient issues" to achieve balance between the sensitivity and precision of the search strategy (see e-only Appendix 1). Hand searching and snowballing techniques from reference lists of systematic reviews and key references were performed to identify potentially relevant studies not captured by database searches.

The inclusion criteria were: (1) studies of MRI-guided biopsy or mpMRI for possible prostate cancer diagnosis and (2) PCOs included as an outcome measure in the study (as primary or secondary outcomes).

There were no limits set on date of publication, language, or study design. All database search hits were assessed independently against the inclusion criteria by two reviewers (S.M., V.H.). Disagreements were resolved with a third reviewer (W.H.). Full-text articles were reviewed, and data were extracted from full-text studies using a standardized form piloted in three studies and iteratively developed to capture all possible PCOs. Study quality for randomized controlled trials (RCTs) was assessed with the Cochrane Risk of Bias tool [13], and the MINORS checklist [14] was used for nonrandomized studies. A narrative approach was used to synthesize findings due to significant study heterogeneity. This manuscript was written following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses statement [15] (see e-only Appendix 2).

RESULTS

In all, 2,762 records were identified through database and hand searching. After removal of duplicates and screening of titles and abstracts, 222 full-text articles were assessed. Ten publications were included in the systematic review. A full breakdown of study selection and reasons for full-text exclusions is in Figure 1.

Study Characteristics

Seven of the included studies were performed in European countries, two in the United States and one in Australia. Mean ages for participants in included studies ranged from 63 to 66 years, and the numbers of participants ranged from 8 to 576. Studies varied widely in terms of design, participant numbers, and outcomes measured. Table 1 contains full details of all included studies. Of the 10 included

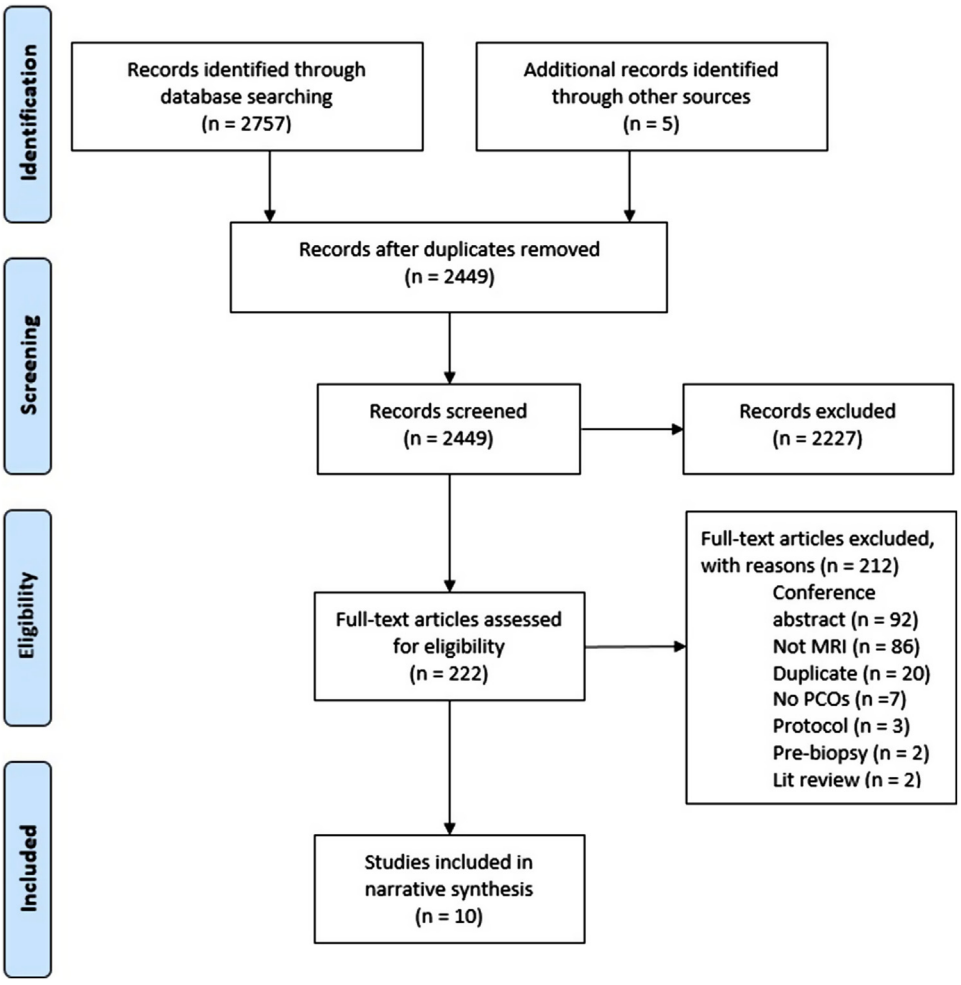

Fig 1. Preferred Reporting Items for Systematic Reviews and Meta-Analyses flow diagram (from Moher et al [37]).

studies, 4 [5,16-18] were assessed as having a low risk of bias (see Table 2).

Nineteen different outcomes were measured across the 10 included studies, measuring an average of 4.9 outcomes per study. The number of outcomes measured in individual studies varied from 1 to 11. Included publications very seldom justified the selection of outcomes measured (see Table 3 for further information on outcomes measured).

Physical Effects

Bleeding. Bleeding after investigation was the most commonly measured outcome. Bleeding was categorized as urethral bleeding, rectal bleeding, hematospermia, or hematoma. Bleeding was measured through self-report from patients via survey or interview in all studies (one unreported), and reporting occurred between 7 and 56 days after biopsy. The proportion of patients reporting some type of bleeding after biopsy varied between studies from 0% to 88.4% [6,16,17,19-22].

Pain. Pain was measured in five studies: three utilized a 10-point visual analogue scale [6,17,23], two relied on patient self-report [16,20], and one measured the presence of pain 4 days after biopsy [17]. Pain was measured between 0 and 56 days postprocedure. Kasivisvanathan et al found a mean visual analogue scale of 1 for MRI-guided biopsy and 2 for TRUS biopsy, though without performing significance testing [5]. Egbers et al found a significantly lower pain score from patients undergoing MRI-guided biopsy compared with TRUS biopsy (median visual analogue scale 2 versus 3, $P < .005$) [17].

Infection. Urinary tract infection and urosepsis are also important potential adverse effects from undergoing a prostate biopsy and were measured in five publications. A mixture of measures, including recorded fever, urine culture, clinical notes review, and patient self-report, were utilized to asses for signs of infection. Sepsis (0.4%-1.6%) [6,16,19] occurred less commonly than urinary tract infection (1%-9.2%) [6,16,21,20,24] across the individual studies, which measured this outcome.

Table 1. Details of included studies

Author (Year) [Reference]	Country	Study Design	Participants	Mean Age (y)	Diagnostic Test(s)	Follow-up (days)	Outcomes Measured
Ahmed et al (2017) [16]	UK	Prospective cohort	576	63.4	mpMRI, MRI-GB, and TRUS-GB in same patient	30	Physical
Egbers et al (2015) [17]	Germany	Cross-sectional	54	68 (median)	MRI-GB after negative TRUS-GB	7	Physical
Hadaschik et al (2011) [24]	Germany	Prospective	106	66	mpMRI and fusion MRI–TRUS biopsy	1	Physical
Kasivisvanathan et al (2018) [5]	Multiple	RCT	500	64.4	mpMRI ± MRI-GB or TRUS-GB	30	Physical, QoL
Kuru et al (2013) [21]	Germany	Prospective	347	65	Fusion MRI–TRUS biopsy	28	Physical
Miah et al (2018) [20]	UK	Prospective	249	63.7	mpMRI and TTPM	56	Physical, QoL
Pokorny et al (2014) [18]	Australia	Prospective	223	63	mpMRI, MRI-GB and TRUS-GB in same patient		Physical
Powell et al (2014) [23]	USA	Prospective	30	Unreported	mpMRI with colorectal or prostatic coil	0	Physical
Stanley et al (2016) [28]	Ireland	Case-control	8	49 (median)	MRI		Emotional, QoL
Tilak et al (2015) [22]	USA	Retrospective-prospective	99	66.01	Manual or robotic MRI-guided TTPM		Physical

mpMRI = multiparametric MRI; MRI-GB = MRI-guided biopsy; QoL = quality of life; RCT = randomized controlled trial; TRUS = transrectal ultrasound biopsy; TRUS-GB = TRUS-guided biopsy; TTPM = transperineal temple prostate mapping biopsy.

Urinary Retention. Four studies [6,16,20,25] assessed whether patients went into acute urinary retention after undergoing a prostate biopsy, measured 30 to 56 hours after the biopsy. Consistent with most other outcomes, this was mostly measured by patient self-report. In the study by Miah et al [20], which used MRI-guided transperineal template mapping biopsy, 22.6% (56 of 249) of men suffered urinary retention, whereas it was much less common in the other studies that used TRUS-guided biopsy (1%-10%) or MRI-TRUS fusion biopsy (1.9%).

Erectile Dysfunction. Problems achieving or maintaining erection after prostate biopsy are recognized as a potential adverse effect [26]. One study measured this using the International Index of Erectile Function [20]; and three used self-report [5,16,27]. Follow-up time for this outcome was also longer than for others (median 30 days, range 28-56). Erectile dysfunction occurred in between 10.8% and 26.3% of men.

Lower Urinary Tract Symptoms. Symptoms such as waking frequently in the night to pass urine, passing urine often, and having a poor stream are among a group of symptoms commonly referred to as lower urinary tract symptoms (LUTS). LUTS usually occur due to diseases of the prostate or the bladder, though they can also occur after prostate biopsy. Miah et al measured LUTS using the International Prostate Symptoms Score [20], and showed a small increase in the presence of LUTS post-biopsy (10.93 ± 6.77 prebiopsy versus 11.76 ± 6.56 postbiopsy, $P = .024$).

Emotional Effects

Stanley et al was the only study to specifically measure anxiety relating to undergoing an MRI scan and found that there was no difference whether patients received an intervention aimed at reducing anxiety or not. In both the intervention and control groups, 39% of participants reported preprocedure anxiety [28].

Table 2. Study quality assessment

Author (Year) [Reference]	Randomization	Deviation	Missing Data	Measurement	Selection	Overall
Randomized studies*						
Kasivisvanathan et al (2018) [5]	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk
Powell et al (2014) [23]	Low risk	Medium risk	Low risk	High risk	Low risk	Some concerns

Author (Year) [Reference]	Aim	Consecutive Pts	Prospective Data	End-points	Unbiased Assess	Fup Appropriate	Loss to Fup	Size Calc	Subtotal	Adequate Control	Contem-porary	Equal Groups	Analysis	Total
Nonrandomized studies†														
Ahmed et al (2017) [16]	2	2	2	2	2	0	2	2	14‡					
Egbers et al (2015) [17]	2	2	2	2	2	1	2	0	13‡					
Hadaschik et al (2011 [24])	2	1	0	2	0	0	0	0	5§					
Kuru et al (2013) [21]	2	1	1	1	1	1	0	0	7‖					
Miah et al (2018) [20]	1	2	2	2	2	1	2	0	12‖					
Pokorny et al (2014) [18]	2	2	2	2	1	1	2	0	12‖	2	2	2	2	20‡
Stanley et al (2016) [28]	2	1	2	1	0	1	0	0	7‖	1	2	1	1	12‖
Tilak et al (2015) [22]	2	1	1	1	0	1	0	0	6§	1	1	1	2	11‖

Calc = calculation; Fup = follow-up; Pts = patients.
*Risk of bias assessment for included randomized controlled trials [13].
†Study quality assessment of nonrandomized studies (two reported and adequate; one reported, not adequate; zero not reported; subtotal of 16; total of 24.
‡High quality [14].
§Low quality.
‖Medium quality.

Table 3. PCOs from all included studies

	Studies of mpMRI or MRI-Guided Biopsy and TRUS				Studies of mpMRI or MRI-Guided Biopsy Only					
PCO (Measure)	Ahmed et al (2017) [16]	Egbers et al (2015) [17]	Kasivisvanathan et al (2018) [5]	Pokorny et al (2014) [18]	Hadaschik et al (2011) [24]	Kuru et al (2013) [21]	Miah et al (2018) [20]	Powell et al (2014) [23]	Stanley et al (2016) [28]	Tilak et al (2015) [22]
Physical outcomes										
Pain	64%	2 of 10 (VAS)	1 of 10 (VAS)				61.8%	2.7 of 10 (VAS)		
Dysuria	46%									
Urethral bleeding	67%	51%	30.2%	0		50.6%	88.4%			5.92%
Hemato-spermia	55%	36%	32.1%							
Rectal bleeding		16%	14.2%							
Hematoma					0.94% (unreported)	13%	54.6%			16.07%
Acute urinary retention	10%		1.4%		1.9% (unreported)		22.55%			
UTI	6%		5.4%		0 (unreported)	1%	9.2%			
Fever		2.2%	4.2%							
Sepsis	1%		0.4% (notes review)	0						
Erectile dysfunction	14%		10.8%			26.3%	9.02 (IIEF)			
LUTS							0.83 (IPSS)			
Urinary incontinence			6.1%							
Vasovagal				0.45%						
Quality of life outcomes										
Quality of life			−0.004 (EQ5-D)				0.19 (IPSS QoL)			
Satisfaction									1.67 (4-point Likert scale)	
Emotional outcomes										
Anxiety									39%	

Outcomes were measured through self-report unless otherwise stated, and were presented as proportions who reported the outcome. EQ5-D = EuroQol-5 Dimensions; IIEF = International Index of Erectile Function; IPSS = International Prostate Symptom Score; ISS = International Prostate Symptom Score; LUTS = lower urinary tract symptoms; mpMRI = multiparametric MRI; PCO = patient-centered outcome; QoL = quality of life; TRUS = transrectal ultrasound; Unreported =– authors did not report outcome measure; UTI = urinary tract infection; VAS = visual analogue scale.

Table 4. Adverse PCOs from studies comparing mpMRI and MRI-guided biopsy to TRUS-guided biopsy

Author (Year) [Reference]	Pain	Urethral Bleeding	Hematospermia	Rectal Bleeding	Urinary Retention	Fever	UTI	Urosepsis	ED	Incontinence	QoL	Vasovagal
Ahmed et al (2017) [16]	*	‡	‡	‡	‡	‡	‡	‡	‡	‡	‡	‡
Egbers et al (2015) [17]	*	*	†	*	‡	*	‡	‡	‡	‡	‡	‡
Kasivisvanathan et al (2018) [5]	*	*	*	*	†	*	†	*	*	†	*	‡
Pokorny et al (2014) [18]	‡	*	‡	‡	‡	‡	‡	*	‡	‡	‡	‡

ED = erectile dysfunction; mpMRI = multiparametric MRI; QoL = quality of life; TRUS = transrectal ultrasound; UTI = urinary tract infection.
*Less frequent from mpMRI or MRI-guided biopsy
†Less frequent from TRUS-guided biopsy.
‡Patient-centered outcome not measured

Quality of Life

Kasivisvanathan et al assessed patients undergoing prostate biopsy for changes in quality of life using the EuroQol-5 Dimensions and demonstrated a nonsignificant difference after TRUS-guided biopsy (−0.27; 95% confidence interval [CI] −1.88 to 1.33) compared with MRI-guided biopsy (−0.0004; 95% CI −0.028 to 0.020) [5]. Miah et al measured quality of life using a subsection of the International Prostate Symptoms Score involving one question with a 7-point Likert scale (7 being low), showing a mean score of 1.76 (±1.39) postbiopsy [20].

mpMRI/MRI Guided Biopsy Versus TRUS-Guided Biopsy

Four studies included mpMRI or MRI-guided biopsy and TRUS-guided biopsy. Kasivisvanathan et al randomized patients to mpMRI, with MRI-guided biopsy if a lesion was detected or TRUS-guided biopsy [5] for a multicenter, randomized, noninferiority trial in 11 countries. Two studies (one in the UK and one in Australia) compared mpMRI with subsequent MRI-guided biopsy to TRUS-guided biopsy in the same patients in prospective cohort studies [16,18] and one in a cross-sectional study in Germany [17]. Table 4 shows a comparison of the outcomes measured between MRI- and TRUS-guided biopsy.

DISCUSSION

Key Findings

This systematic review of PCOs associated with mpMRI and MRI-guided biopsy for prostate cancer found wide variation in study quality, PCOs measured, tools used for measurement, follow-up of patients, and outcomes. In the four studies that compared mpMRI and subsequent MRI-guided biopsy with TRUS-guided biopsy, most adverse PCOs were less frequent with MRI testing. Pain and bleeding were the most commonly measured PCOs. In contrast, there were no published studies measuring any cognitive, social, or behavioral outcomes of mpMRI or MRI-guided biopsy. Meta-analysis was not possible due to significant heterogeneity.

Comparison With Existing Literature

This is the first systematic review of PCOs associated with mpMRI and MRI-guided biopsy for prostate cancer, as far as the authors are aware. Glaser et al performed a literature review of the effects of prostate biopsy on urinary symptoms, erectile function, and anxiety after early reports in the field [26]. The authors looked at TRUS-guided biopsy only and considered the relationship of these outcomes with factors such as analgesic approaches and type of approach to

TRUS-guided biopsy. They found evidence suggesting a transient increase in LUTS, and a relationship between TRUS-guided biopsy and erectile dysfunction in the short term. The authors considered that the impact on erectile dysfunction needed further research to determine the etiology of this effect. There was limited justification for choosing to focus on these outcomes, or why others were omitted.

Efficace et al undertook a systematic review of health-related quality of life measurements performed in RCTs relating to prostate carcinoma treatments [29]. The authors found a range of health-related quality of life assessments; however, some studies had methodological limitations that could have affected the measurement of health-related quality of life. The same authors assessed the methodological quality of patient-reported outcomes in RCTs with prostate cancer patients in 2014 [30]. The quality of patient-reported outcomes improved over time, and approximately 20% of the assessed patient-reported outcomes were deemed to collate sufficient detail to inform clinical practice and health policy. These two systematic reviews focused only on studies of conventional prostate cancer treatments, excluding any other interventions such as diagnostic testing or alternative therapies.

There is growing recognition of the importance of PCOs for diagnostic tests within radiology, especially in the United States, after the establishment of the PCORI [31]. There have been methodological challenges in identifying and measuring PCOs relating to diagnostic tests that are still being overcome. Many of the direct effects on patients from undergoing an imaging test are short term in nature, and not easily captured with existing measures used in research [32]. The relationship between these short-term effects and the ultimate patient outcome may be tenuous, because diagnostic testing makes up just one element in a patient's illness journey [33].

This review found very little evidence of patient involvement in identifying outcomes to measure in studies of prostate cancer diagnostic tests. This finding is consistent with Mathers et al, who showed that, up until 2006, there was minimal patient engagement to determine the important patient outcomes for radiology research [34]. A recent study of outcomes in primary care for imaging tests interviewed patients who had undergone x-ray, CT scan, MRI, or ultrasound in the previous 12 months. The four key themes for outcomes that were identified from patients were knowledge gained from the test, test contribution to overall health care journey, physical experiences during the test, and impacts of the testing process on emotions [35]. Studies in this systematic review considered only the latter two patient priorities, but omitted the knowledge gained or the impact of MRI- or TRUS-guided biopsy on the overall patient journey.

Strengths and Limitations

This study followed a systematic and comprehensive methodological approach to understand which PCOs have been measured in studies of diagnostic tests for prostate cancer. Published high-quality search strategies were adapted for the purposes of this study. The search strategy and definition used for PCOs were deliberately broad to identify as many relevant studies as possible to obtain a clear picture of all current research. Some recent studies comparing mpMRI and MRI-guided biopsy to TRUS-guided biopsy were obtained, allowing tentative conclusions to be drawn between the two diagnostic tests regarding their comparative effectiveness.

However, this systematic review has some important limitations affecting the generalizability of the results. PCO measures have not yet been clearly defined, and designing a systematic search strategy to capture all studies measuring PCOs was problematic. It is possible some studies that could have been included were missed despite our thorough search methodology. The included studies varied widely in a number of areas, making meta-analysis between PCOs for mpMRI or MRI-guided biopsy and TRUS-guided biopsy impossible. Most studies included in the study had at least some risk of bias based on the quality assessment, and there were few data reported on PCOs other than physical outcomes of undergoing testing.

Implications for Policy and Practice

Within the limited evidence currently available, there is some indication that mpMRI and MRI-guided biopsy may perform better than TRUS-guided biopsy in terms of PCOs. TRUS-guided biopsy is the current standard diagnostic test for prostate cancer, despite its known limitations [1]. Following on from the PROMIS [16] and PRECISION [5] trials showing the higher diagnostic accuracy of mpMRI and MRI-guided biopsy for prostate cancer, the National Institute for Health and Care Excellence in the UK has recently updated guidelines for prostate cancer to include a recommendation for prebiopsy mpMRI in all patients with possible prostate cancer [36]. MRI-based diagnostic pathways for prostate cancer need further investigation to determine the best design and the economic impacts of these pathways. Integration of PCOs into this research would provide more robust evidence to determine whether mpMRI and MRI-guided biopsy truly do outperform TRUS-guided biopsy in key domains other than diagnostic accuracy.

TAKE-HOME POINTS

- Studies of mpMRI and MRI-guided biopsy for prostate cancer have mostly measured physical PCOs, with very limited evidence about the emotional, cognitive, behavioral, and social effects of testing.
- Some evidence suggests mpMRI and MRI biopsy are associated with fewer adverse PCOs compared with TRUS biopsy.
- There is no evidence of patient engagement or involvement in the selection of PCOs for studies of mpMRI and MRI biopsy for possible prostate cancer.

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DATA ACCESS STATEMENT

The research data supporting this publication are provided within this article.

ADDITIONAL RESOURCES

Additional resources can be found online at: https://doi.org/10.1016/j.jacr.2019.08.031.

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1.2 Published paper from Chapter 5

SWD Merriel, L Pocock, E Gilbert, S Creavin, FM Walter, A Spencer, W Hamilton ‘Systematic review & meta-analysis of the diagnostic accuracy of prostate specific antigen (PSA) for the detection of prostate cancer in symptomatic patients’ *BMC Medicine* (2022) 20:54 https://doi.org/10.1186/s12916-021-02230-y

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BMC Medicine

RESEARCH ARTICLE Open Access

Systematic review and meta-analysis of the diagnostic accuracy of prostate-specific antigen (PSA) for the detection of prostate cancer in symptomatic patients

Samuel W. D. Merriel*, Lucy Pocock, Emma Gilbert, Sam Creavin, Fiona M. Walter, Anne Spencer and Willie Hamilton

Abstract

Background: Prostate-specific antigen (PSA) is a commonly used test to detect prostate cancer. Attention has mostly focused on the use of PSA in screening asymptomatic patients, but the diagnostic accuracy of PSA for prostate cancer in patients with symptoms is less well understood.

Methods: A systematic database search was conducted of Medline, EMBASE, Web of Science, and the Cochrane library. Studies reporting the diagnostic accuracy of PSA for prostate cancer in patients with symptoms were included. Two investigators independently assessed the titles and abstracts of all database search hits and full texts of potentially relevant studies against the inclusion criteria, and data extracted into a proforma. Study quality was assessed using the QUADAS-2 tool by two investigators independently. Summary estimates of diagnostic accuracy were calculated with meta-analysis using bivariate mixed effects regression.

Results: Five hundred sixty-three search hits were assessed by title and abstract after de-duplication, with 75 full text papers reviewed. Nineteen studies met the inclusion criteria, 18 of which were conducted in secondary care settings with one from a screening study cohort. All studies used histology obtained by transrectal ultrasound-guided biopsy (TRUS) as a reference test; usually only for patients with elevated PSA or abnormal prostate examination. Pooled data from 14,489 patients found estimated sensitivity of PSA for prostate cancer was 0.93 (95% CI 0.88, 0.96) and specificity was 0.20 (95% CI 0.12, 0.33). The area under the hierarchical summary receiver operator characteristic curve was 0.72 (95% CI 0.68, 0.76). All studies were assessed as having a high risk of bias in at least one QUADAS-2 domain.

Conclusions: Currently available evidence suggests PSA is highly sensitive but poorly specific for prostate cancer detection in symptomatic patients. However, significant limitations in study design and reference test reduces the certainty of this estimate. There is very limited evidence for the performance of PSA in primary care, the healthcare setting where most PSA testing is performed.

Keywords: Prostate-specific antigen, PSA, Lower urinary tract symptoms, LUTS, Prostate cancer, Diagnostic accuracy, Primary care, Secondary care

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Background

Prostate-specific antigen (PSA) is a commonly used test for the detection of prostate cancer, identifying patients that may require a diagnostic test [1]. PSA testing is usually performed for one of two reasons: assessing a patient presenting to their general practitioner (GP) or primary care physician with lower urinary tract symptoms (LUTS) [2] or screening for a patient who is asymptomatic but concerned about their risk of prostate cancer [3, 4]. Patients with an elevated PSA are usually referred to a urologist for diagnostic testing, which may include magnetic resonance imaging (MRI) of the prostate and/or a prostate biopsy [5]. Very large randomised controlled trials of PSA-based prostate cancer screening have been performed; these are summarised in a recent systematic review in 2018 that showed a small potential reduction in prostate cancer specific mortality with no change in all-cause mortality and an increased risk of complications from biopsy, overdiagnosis of clinically insignificant prostate cancer, and overtreatment [6–8]. However, uncertainty remains about the diagnostic accuracy of PSA for prostate cancer in patients with LUTS [9].

The most recent systematic review of the diagnostic accuracy of PSA was published by Harvey et al. in 2009 [10]. A range of estimates for the accuracy of PSA was found amongst the ten included studies. That review presented limited information on their methods; crucially, it was unclear whether the included studies were assessing PSA in symptomatic or asymptomatic patients nor was it clear whether any were relevant to primary care populations. Just et al. published a brief review of the literature in 2018, highlighting that the paucity of research in this area applicable to primary care, where a significant proportion of PSA testing is performed, still remains [9].

This systematic review aimed to determine the diagnostic accuracy of PSA for the detection of prostate cancer in patients, focusing on studies where the included patients (or a subset of included patients) had at least one symptom that could relate to an undiagnosed prostate cancer. Given the findings by Just et al., this review considered studies from primary and secondary care settings.

Methods

Types of studies

We included cross-sectional and cohort studies that reported paired data on the diagnostic accuracy of PSA for the detection of prostate cancer in symptomatic men, verified with the use of a reference test (prostate biopsy). We excluded studies if it was not possible to extract data for a complete two-by-two table for the target condition or if the patient cohort was only asymptomatic patients (i.e. a screening cohort). We did not restrict studies by publication date, country, or clinical setting.

Participants

The study population of interest was any patient with symptoms of a possible prostate cancer, with no history of the disease. We defined symptoms of prostate cancer as at least one of LUTS (nocturia, hesitancy, poor stream, incomplete voiding, double voiding, terminal dribbling, urgency, incontinence, frequency), haematuria, erectile dysfunction, or lower back pain. Symptoms may have been identified by a standardised tool, such as the International Prostate Symptom Score (IPSS), clinical coding, or through patient self-report. We did not exclude studies based on age of participants or study setting. Where studies included groups of both asymptomatic and symptomatic men, we included men in the symptomatic group.

Index test

The index test was prostate-specific antigen (PSA) in a peripheral blood sample, measured in nanograms per millilitre (ng/mL). We did not set an a priori PSA threshold for prostate cancer detection but instead extracted data based on the PSA thresholds used in each study.

Target condition

The target condition was prostate cancer, regardless of Gleason grade or clinicopathological stage.

Reference test

The reference test was a biopsy of the prostate with histological examination. We did not set an inclusion criteria on the basis of prostate biopsy approach used in studies, but this was recorded as part of the data extraction.

Electronic searches

Medline Ovid, EMBASE, the Cochrane Central Register of Controlled Trials (CENTRAL), and Web of Science databases were utilised to identify relevant studies. Key search terms, informed by the Scottish Intercollegiate Guidelines Network (SIGN) search strategies and pre-existing systematic reviews in the field of prostate cancer, were combined with MeSH terms for each database search. Hand-searching of reference lists from included studies and snowballing techniques were performed to locate any other possibly relevant studies. Please see Additional file 1 for the search strategy used in this review.

Data collection and analysis

Selection of studies

Search hits from each database were downloaded and combined into a review database managed in Mendeley Desktop. Each search hit was screened against the inclusion/exclusion criteria by SM and a 2nd investigator (LP, SC, or EG) independently, based on title and abstract. Full text articles were reviewed if a reviewer was unclear on the basis of title and abstract. Any discrepancies of study inclusion were adjudicated by a third reviewer (WH or AS).

Data extraction

A pre-prepared proforma for data extraction was used to collate relevant data from each included study, including two by two tables for the index and reference tests. SM extracted the data from all included studies. A second investigator extracted data from a random sample of 10% of included studies for verification of accuracy of data extraction. Any discrepancies were adjudicated by a third reviewer (WH or AS).

Quality assessment

Risk of bias and applicability of all included studies was assessed by SM using the QUADAS-2 [11] tool, with a second investigator independently assessing 10% of included studies and discussed any discrepancies with SM.

Meta-analysis

Raw data extracted from included papers on PSA result and prostate cancer diagnoses were extracted and combined into 2 × 2 tables to assess diagnostic accuracy. Measures of pooled diagnostic accuracy were intended to be determined for the following outcomes using bivariate mixed effects regression [12]:

Any prostate cancer diagnosis

Clinically significant prostate cancer diagnosis (Gleason Grade Group ≥ 2)

The majority of included studies used a fixed PSA threshold of 4 ng/mL, and this was also used as the threshold for meta-analysis. No included studies reported sufficient information to Meta-analyse age-adjusted thresholds.

Heterogeneity

Heterogeneity was assessed for visually, using Forest plots of sensitivity and specificity.

All analyses were performed using Stata Version 16 (StataCorp, http://www.stata.com)

Protocol publication

The protocol for this systematic review and meta-analysis was registered with PROSPERO (CRD42021257783).

PRISMA reporting guidelines

This systematic review was conducted following the PRISMA reporting guidelines for systematic reviews and meta-analyses [13]. A completed PRISMA checklist can be found in Additional file 2.

Results

Database searching identified 631 potentially relevant studies, and a further 42 studies were identified through reference list checking and snowballing techniques from initial search hits and key papers. Following de-duplication, 563 search hits were assessed by two reviewers independently, and 75 papers selected for full text assessment. Nineteen papers were ultimately included. Details of full-text exclusions can be found in Fig. 1.

Risk of bias assessment using the QUADAS-2 tool demonstrated a number of potential areas of bias in the included studies (see Table 1 and Fig. 2). None of the studies were assessed as having a low risk of bias with regards to the reference standard test, which was almost always a transrectal ultrasound-guided (TRUS) biopsy. TRUS biopsy suffers from a significant risk of false negative or misclassification of prostate cancer diagnosis owing to the random nature of sampling of the prostate [14]. The reference standard was performed with knowledge of the index test (PSA) in 16 of 19 studies. Patient populations were drawn from hospital urology clinics in all but one study, affecting applicability to other clinical settings. Limited information with regards to patient selection was available in eight studies, and the majority had a low risk of bias with regards to the conduct of the index test.

Table 2 summarises the features of the included studies. There was a wide range of countries and study sizes. One study focused on a symptomatic cohort within a population screening study, and the remainder were set in hospital urology clinics. No study was performed in a primary care population. Five studies gathered stage and grade data. All but one study used TRUS biopsy as a reference test, with three studies also gathering diagnostic data from transurethral resection of the prostate (TURP) or other urological surgical procedures involving the prostate.

Table 3 shows the measures of diagnostic accuracy calculated using reported data in 14 included studies featuring 14,489 patients that considered a PSA level of greater than or equal to 4 ng/mL as abnormal. The remaining five studies focused on populations in a specific part of the PSA range; either a low or raised PSA level. Meta-analysis showed an estimated combined sensitivity of a PSA greater than or equal to 4 ng/mL for any prostate cancer of 0.93 (95% CI 0.88, 0.96) and a combined specificity of 0.20 (95% CI 0.12, 0.33) (see Fig. 3). There was significant

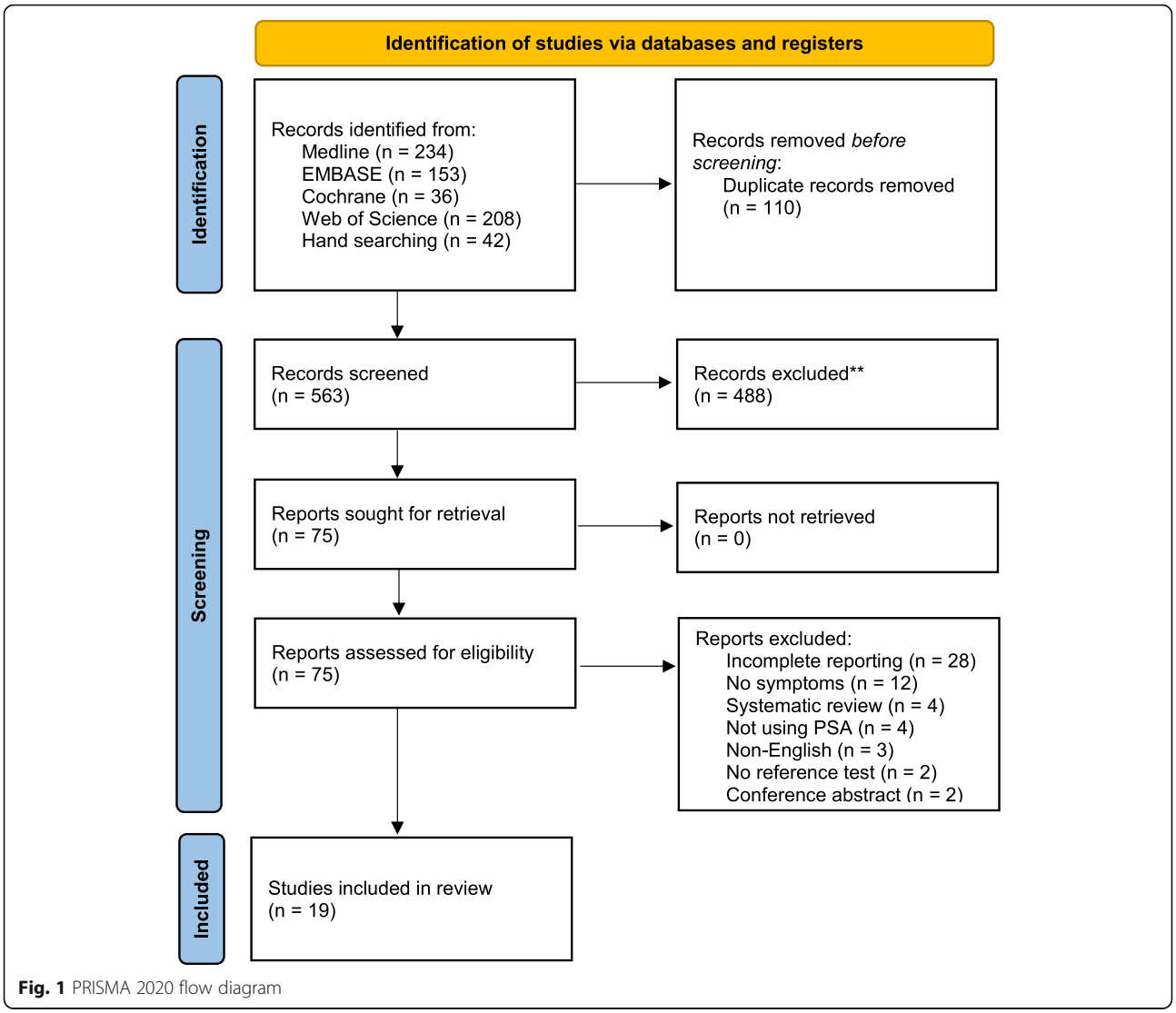

Fig. 1 PRISMA 2020 flow diagram

heterogeneity between included studies (sensitivity I^2 98.97, specificity I^2 99.61). Hierarchical summary receiver operator curve (HSROC) analysis showed an AUC of 0.72 (95% CI 0.68, 0.76) (see Fig. 4). A Fagan plot can be found in Additional File 3.

Three studies included in the meta-analysis collected stage and grade data for prostate cancer cases; however, none of these studies reported data for clinically significant prostate cancer diagnoses at a PSA cut-off of ≥ 4 ng/mL. Chang et al. [18] did not report the accuracy of PSA but showed a statistically significant difference in free to total PSA ratio for a Gleason Score of seven or more compared to Gleason Score of six or lower (11.69 ± 0.98 vs 16.47 ± 2.25, p = 0.029). Richie et al. [29] did not report the Gleason Score data collected but found higher PSA levels and increasing age were associated with a higher risk of metastatic prostate cancer. Shahab et al. [31] identified a PSA cut-off of 6.95 ng/mL for differentiating moderate versus high Gleason Score (which was not defined).

Discussion

Summary of findings

Published studies assessing the diagnostic accuracy of PSA in symptomatic patients reported high sensitivity and low specificity for the detection of prostate cancer. Eighteen of the included studies were undertaken in hospital urology outpatient populations, with one study focused on a symptomatic cohort within a population screening study. Importantly, there were no studies assessing the performance of PSA in a primary care population. Insufficient data was available to assess the diagnostic accuracy of PSA for clinically significant prostate cancer. Furthermore, all included studies had a high risk of bias in at least one QUADAS domain.

Table 1 Risk of bias assessment of included studies using QUADAS-2 tool

Study	RISK OF BIAS				APPLICABILITY CONCERNS		
	PATIENT SELECTION	INDEX TEST	REFERENCE STANDARD	FLOW AND TIMING	PATIENT SELECTION	INDEX TEST	REFERENCE STANDARD
Abdrabo *et al*	?	?	☹	☹	☹	☺	☹
Agnihotri *et al*	☹	☺	☹	☹	☹	☺	☹
Aragona *et al*	☺	☺	☹	☹	☹	☺	☹
Chang *et al*	☹	?	☹	☹	☹	?	☹
Chavan *et al*	☹	☺	☹	☹	☹	☺	☹
Galic *et al*	☺	☺	?	☹	☺	☺	☺
Hofer *et al*	☹	☺	☹	☹	☹	☺	☹
Lee *et al*	?	☺	☹	☺	☹	☺	☹
Magistro *et al*	?	?	?	?	☹	?	☺
Meigs *et al*	?	☺	☹	☹	☹	☺	☹
Nordstrom *et al*	☺	☺	☹	☹	☺	☺	☹
Patel *et al*	?	☺	☹	☹	☹	☺	☹
Pepe *et al*	?	☺	☹	☹	☹	☺	?
Rashid *et al*	?	☺	☹	☹	☹	☺	☹
Richie *et al*	☺	☺	☹	☹	☺	☺	☹
Seo *et al*	☺	☺	☹	☹	☹	☺	☹
Shahab *et al*	?	☺	☹	☹	☹	☺	☹
Tauro *et al*	☺	☺	☹	☺	☹	☺	☹
Wymenga *et al*	☹	☺	☹	☹	?	☺	☹

☺ Low Risk ☹ High Risk ? Unclear Risk

Comparison to existing literature

Harvey et al. [10] published a systematic review of the diagnostic accuracy of PSA for prostate cancer in European populations, focused on studies published between 1998 and 2008. Individual study level data from 10 included papers was reported, though without estimating a combined level of accuracy. They considered the accuracy of PSA for all prostate cancer types overall and showed a range of accuracy estimates similar to this study. Over half of the studies included in this review were published since the review by Harvey et al. A review of clinical features of prostate cancer in primary care by Young and colleagues [34] in 2015 identified one study from 1989 of 287 patients referred from primary

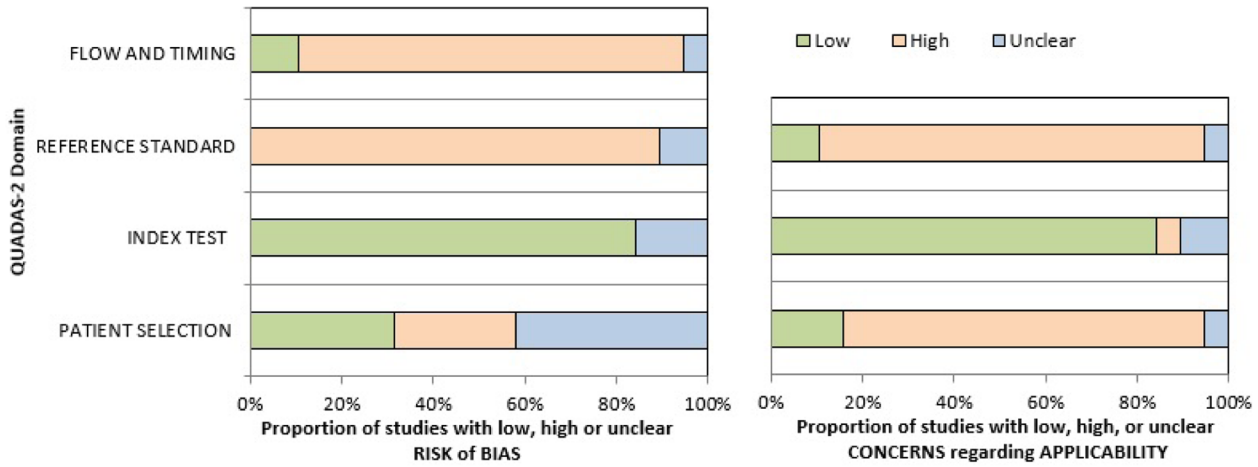

Fig. 2 Summary of QUADAS-2 risk of bias assessments

care with bladder outlet obstruction, of whom 211 had a PSA test. High levels of sensitivity (89.5%) and specificity (90%) were reported, but Young and colleagues considered the true level of accuracy was likely to be lower given few patients with a normal PSA level had the reference test for prostate cancer.

Strengths and weaknesses

This study benefited from a rigorous, focused, methodological approach in conducting the review. All clinical settings were eligible, ensuring we found as many relevant studies as possible. Most included studies employed PSA in a similar manner, using similar indications and diagnostic thresholds, allowing for cross-study comparisons.

The evidence for the association between lower urinary tract symptoms and prostate cancer, particularly clinically significant prostate cancer, is equivocal. A number of secondary care studies suggest that symptoms do not discriminate well between prostate cancer and benign prostatic hypertrophy [35, 36]. This assumption is largely untested in primary care populations and contrasts with studies showing that the majority of patients diagnosed with prostate cancer present to their GP with LUTS prior to diagnosis [37–40]. This controversy also means that LUTS and other relevant symptoms may not be reported or be the focus of some potentially relevant studies of PSA for prostate cancer and may have limited the sensitivity of the search strategy employed. However, key papers were picked up by the database searches and the majority of PSA studies will likely be focused on screening in asymptomatic populations.

All included studies employed TRUS biopsy as a reference test, with some also including pathological data obtained from urological procedures on the prostate. TRUS biopsy is recognised as having poor sensitivity as a diagnostic test [41], owing to the inability to visualise lesions within the prostate resulting in a random sampling of the gland, and thus misclassification bias. Reporting of histological classification of prostate cancers was only included in three studies, and each presented this data differently. Insufficient data was available to determine a relationship between PSA and clinically significant prostate cancer, which is a crucial consideration for the optimal use of PSA for prostate cancer detection. Most included studies only performed the reference test on patients with a raised PSA or abnormal prostate examination, introducing partial verification bias. Therefore, the true sensitivity of PSA in symptomatic patients is unknown and likely to be lower than reported.

Implications for research and practice

PSA is a commonly used test to assess for the presence of prostate cancer, mostly in a primary care setting, and is recommended as part of the assessment of patients with LUTS in national guidelines [42–44]. The lack of primary care evidence for the use of PSA to detect prostate cancer is known and is not the only condition for which secondary care evidence has been applied to primary care guidance [45]. Even so, this is a major gap in knowledge, as spectrum bias means that secondary care data (or screening data) do not translate to primary care. High-quality studies in primary care populations are needed to fill this gap, and future studies should report not just on prostate cancer per se but on clinically significant cancer as well. The introduction of more accurate diagnostic tests for prostate cancer, including multiparametric magnetic resonance imaging [41], increases the need for better understanding of the role of PSA in the early detection of symptomatic prostate cancer. PSA performance could also be enhanced by

Table 2 Details of included studies

First author	Year	Country	Number of patients	Mean age (range)*	Setting	PSA range	Stage/grade data	Reference test
Abdrabo et al. [15]	2011	Sudan	118	70 years (56–83)	One hospital urology clinic	2.5–10 ng/mL	No	TRUS biopsy
Agnihotri et al. [16]	2014	India	875 biopsied (of 4702 patients)	66 years (50–75)	One hospital urology clinic	Any	No	TRUS biopsy
Aragona et al. [17]	2005	Italy	3171 biopsied (of 16,298 patients)	62 years (40–75)	15 hospital urology clinics	Any	Clinical TNM staging	TRUS biopsy
Chang et al. [18]	2015	Taiwan	225	PCa 72 years; BPH 67 years	One hospital urology clinic	Any	TNM stage and Gleason Score	TRUS biopsy
Chavan et al. [19]	2009	India	440 biopsied (of 922 patients)	64 years (40–95)	One tertiary hospital urology clinic	Any	No	TRUS biopsy
Galic et al. [20]	2003	Croatia	88 biopsied (of 944 patients)	≥ 50 years	Recruited from two villages to attend hospital clinic	Not stated	No	TRUS biopsy
Hofer et al. [21]	2000	Germany	188	PCa 70 years; BPH 68 years	One hospital urology clinic	Any	No	TRUS biopsy/TURP/non-cancer surgery
Lee et al. [22]	2006	Korea	201	63 years	One hospital urology clinic	< 4 ng/mL	No	TRUS biopsy
Magistro et al. [23]	2020	Germany	1125	70 years	One hospital urology clinic	Any	TNM stage and Gleason Score	HoLEP (+ mpMRI with targeted and systemic biopsy for some patients)
Meigs et al. [24]	1996	USA	1524	50-79 years	One hospital urology clinic + two BPH study cohorts	Any	Clinical T stage	TRUS biopsy/TURP/non-cancer surgery
Nordstrom et al. [25]	2021	Sweden	1554	64 years (50–69)	Population-based screening study cohort	> 3 ng/mL	TNM stage and Gleason Score	TRUS biopsy
Patel et al. [26]	2009	UK	647 biopsied (of 3976 patients)	65 years (15–91)	One hospital urology clinic	Any	No	TRUS biopsy
Pepe et al. [27]	2007	Italy	403 biopsied (of 13,294 patients)	62 years (40–75)	Two hospital urology clinics	< 4 ng/mL	Pathological T stage	TRUS biopsy
Rashid et al. [28]	2012	Bangladesh	206	> 50 years	One hospital urology clinic and one nursing home	> 2.5 ng/mL	No	TRUS biopsy
Richie et al. [29]	1993	USA	1167 biopsied (of 6630 patients)	63 years (50–96)	Six medical centres	Any	TNM stage and Gleason Score	TRUS biopsy
Seo et al. [30]	2007	Korea	4967	66 years (40–96)	25 hospital urology clinics	Any	No	TRUS biopsy
Shahab et al. [31]	2013	Indonesia	404	64 years (34–84)	One hospital urology clinic	Any	TNM stage and Gleason Score	TRUS biopsy
Tauro et al. [32]	2009	India	100	68 years	One hospital urology clinic	Any	No	TRUS biopsy
Wymenga et al. [33]	2000	The Netherlands	716	Not reported	Two hospital urology clinics	Any	Clinical T stage	TRUS biopsy/TURP/prostatectomy

PSA prostate-specific antigen, *TRUS* transrectal ultrasound-guided biopsy, *PCa* prostate cancer, *BPH* benign prostatic hypertrophy, *TNM* tumour-node-metastasis, *TURP* transurethral resection of the prostate, *HoLEP* holmium laser enucleation of the prostate, *mpMRI* multiparametric magnetic resonance imaging
*Age range and/or mean not present in table if not reported

Table 3 Diagnostic accuracy of PSA ≥ 4 ng/mL for prostate cancer detection in symptomatic patients

Author	Year	Sensitivity	Specificity	Positive predictive value	Negative predictive value
Abdrabo	2011	0.92	0.24	0.35	0.87
Agnihotri	2014	0.99	0.05	0.59	0.80
Aragona	2005	0.92	0.15	0.38	0.76
Chang	2015	0.89	0.09	0.19	0.76
Chavan	2009	0.96	0.03	0.18	0.79
Galic	2003	0.91	0.32	0.47	0.85
Hofer	2000	0.92	0.29	0.46	0.85
Meigs	1996	0.61	0.74	0.34	0.89
Rashid	2012	0.72	0.46	0.28	0.85
Richie	1993	0.82	0.48	0.31	0.90
Seo	2007	0.98	0.04	0.33	0.87
Shahab	2013	0.98	0.19	0.13	0.98
Tauro	2009	1.00	0.38	0.40	1
Wymenga	2000	0.95	0.16	0.44	0.82

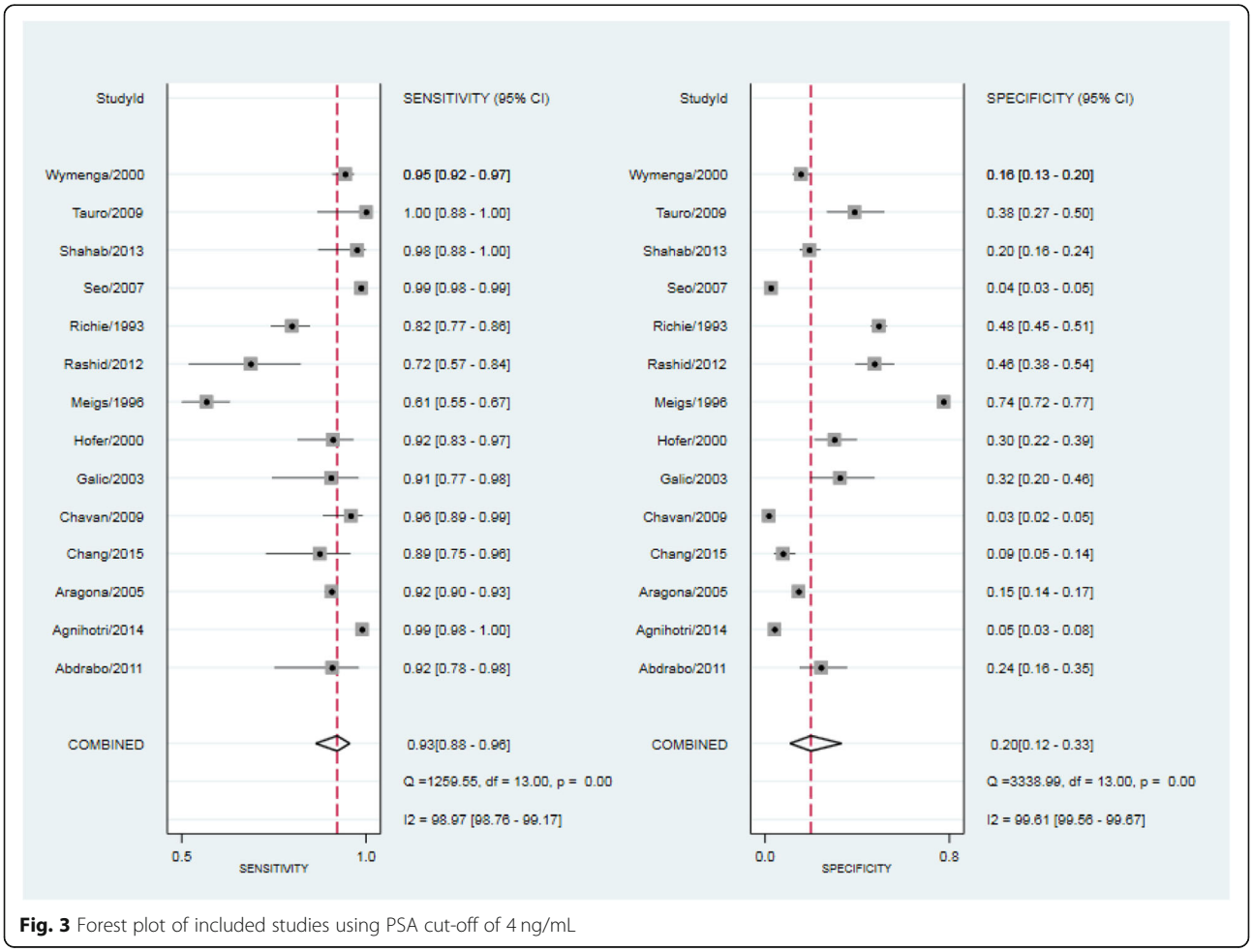

Fig. 3 Forest plot of included studies using PSA cut-off of 4 ng/mL

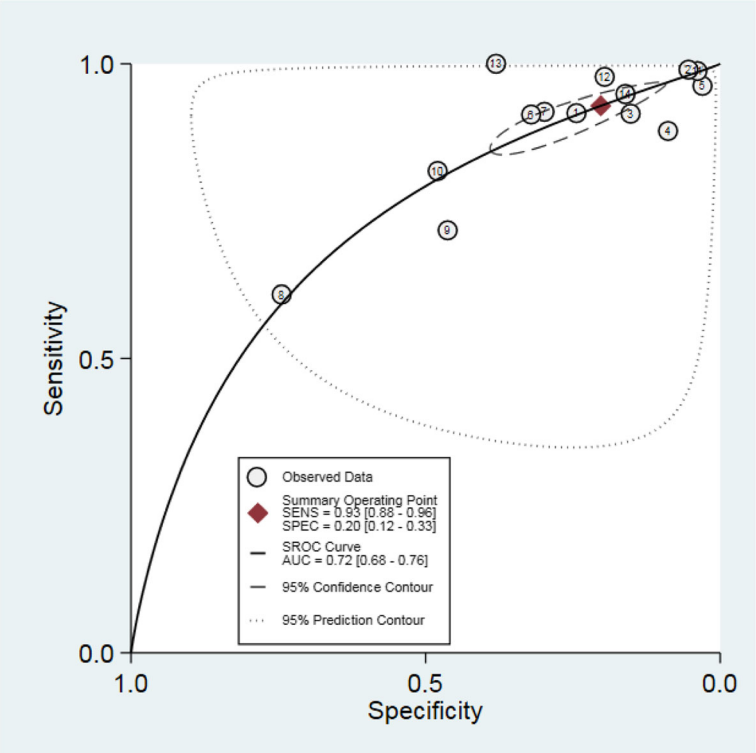

Fig. 4 Hierarchical summary receiver operator curve (HSROC) of included studies using PSA cut-off of 4 ng/mL

incorporating additional relevant clinical data in multivariable risk models [46], although only one has been validated in primary care [47].

Primary care clinicians are generally aware of the limitations of PSA testing [48], and clinical guidelines encourage a balanced discussion with patients of the potential benefits and harms of relying on PSA to detect prostate cancer [3, 49]. The findings of this review suggest this is a pragmatic approach in providing care to patients with LUTS. False-positive PSA results can also occur from non-cancer conditions affecting the prostate such as benign prostatic hypertrophy or prostatitis, further limiting the clinical utility of the test for prostate cancer detection. Alternative tests to PSA have been extensively researched [50, 51], and some show promise of improving the level of confidence in detecting prostate cancer, though none has entered primary care practice as yet.

Conclusions

Published evidence from almost entirely secondary care based studies suggests that PSA has high sensitivity and low specificity for the diagnosis of prostate cancer in symptomatic patients. Published studies suffer from a number of biases, which probably overestimate the accuracy of PSA, and there were no included studies assessing the accuracy of PSA in a primary care population. The utility of PSA for the diagnosis of clinically significant prostate cancer in primary care remains unclear and needs urgent study. A major focus of such a study would be to identify patients with clinically significant cancer, warranting radical treatments, whilst avoiding exacerbating the issue of overdiagnosis of clinically insignificant prostate cancer.

Abbreviations

AUC: Area under the curve; BPH: Benign prostatic hypertrophy; CI: Confidence interval; GP: General practitioner; HoLEP: Holmium laser enucleation of the prostate; HSROC: Hierarchical summary receiver operator curve; IPSS: International prostate symptom score; LUTS: Lower urinary tract symptoms; mpMRI: Multiparametric magnetic resonance imaging; MRI: Magnetic resonance imaging; ng/mL: Nanograms per millilitre; PCa: Prostate cancer; PSA: Prostate-specific antigen; SIGN: Scottish intercollegiate guidelines network; TNM : Tumour-node-metastasis; TRUS: Transrectal ultrasound-guided biopsy; TURP: Transurethral resection of the prostate

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s12916-021-02230-y.

Additional file 1. Database search strategy.

Additional file 2. PRISMA 2020 Checklist.

Additional file 3. Supplementary figure 1—Fagan plot of included studies using PSA cut-off of 4ng/mL.

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Authors' contributions

SWDM, WH, FMW, and AS conceived the study. SWDM drafted the protocol, and all authors read and approved the final protocol. SWDM performed the database searches. SWDM, EG, SC, and LP performed database search hit screening. SWDM extracted data from the included studies and assessed study quality, with LP checking extraction and quality assessment for a random sample of 10% of included studies. SWDM performed the meta-analysis. SWDM drafted the manuscript. All authors read and approved the final manuscript.

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Availability of data and materials

All data were extracted from published research articles. The study protocol is available on PROSPERO and database search strategy is attached as an additional file.

Declarations

Ethics approval and consent to participate

Ethical approval was not sought for this study, and there were no participants to seek consent from.

Consent for publication

No content in this manuscript requires consent for publication.

Competing interests

The authors declare that they have no competing interests.

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Publisher's Note

1.3 Submitted paper from Chapter 3 currently under peer review following revisions

SWD Merriel, S Archer, A Forster, D Eldred-Evans, J McGrath, HU Ahmed, W Hamilton, FM Walter 'Experiences of 'traditional' and 'one-stop' MRI-based prostate cancer diagnostic pathways in England: a qualitative study with patients and GPs' *BMJ Open* UNDER PEER REVIEW

Experiences of ‘traditional’ and ‘one-stop’ MRI-based prostate cancer diagnostic pathways in England: a qualitative study with patients and GPs

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Keywords: Prostate cancer, diagnostic pathway, primary care

Abstract

Objectives

This study aimed to understand and explore patient and GP experiences of 'traditional' and 'one-stop' prostate cancer diagnostic pathways in England.

Design

Qualitative study using semi-structured interviews, analysed using inductive thematic analysis

Setting

Patients were recruited from National Health Service (NHS) Trusts in London and in Devon; GPs were recruited via National Institute for Health Research (NIHR) Clinical Research Networks. Interviews were conducted in person or via telephone.

Participants

Patients who had undergone a magnetic resonance imaging (MRI) scan of the prostate as part of their diagnostic work-up for possible prostate cancer, and GPs who had referred at least one patient for possible prostate cancer in the preceding 12 months.

Results

22 patients (aged 47 – 80 years) and 10 GPs (6 female, aged 38 – 58 years) were interviewed. Patients described three key themes: cancer beliefs in relation to patient's attitudes towards prostate cancer; communication with their GP and specialist having a significant impact on experience of the pathway; and pathway experience being influenced by appointment and test burden. GP interview themes included: the challenges of dealing with imperfect information in the current pathway; managing uncertainty in identifying patients with possible prostate cancer, and sharing this uncertainty with them, and other social, cultural and personal contextual influences.

Conclusions

Patients and GPs reported a range of experiences and views of the current prostate cancer diagnostic pathways in England. Patients valued 'one-stop' pathways integrating prostate MRI and diagnostic consultations with specialists over the more traditional approach of several hospital appointments. GPs remain uncertain how best to identify patients needing referral for urgent prostate cancer testing due to the lack of accurate triage and risk assessment strategies.

Article summary

Strengths and limitations

- Patient experiences of two very different prostate cancer diagnostic pathways compared and contrasted
- Patient sample feature a broad range of ages, geographical regions, and cancer investigation journeys to generate rich data
- First study to explore GP experience and understanding of new prostate cancer diagnostic pathways incorporating magnetic resonance imaging (MRI)
- Limited knowledge of prostate MRI curtailed interviews with some GP participants

Introduction

Patient experience of healthcare has developed as an important marker of quality of care in recent decades. However, measuring and understanding patient experience of diagnostic pathways and services is underexplored and poorly prioritised compared to other aspects of healthcare such as access or treatments[1]. Assessment of the impact of variations in pathway design between health services may also identify elements associated with better patient experiences that could be implemented more widely.

Cancer diagnostic pathways are prioritised for urgent access to diagnostic tests in many healthcare systems as early-stage diagnosis is associated with increased survival[2]. Not only do shorter diagnostic intervals improve outcomes for patients, but patients also report better experiences of care[3]. The National Health Service (NHS) in England has a Two Week Wait (2WW) urgent cancer referral pathway system, where any patient with symptoms or signs of a potential undiagnosed cancer referred by their General Practitioner (GP) should have a specialist review for further investigation within two weeks[4]. Significant variation in cancer diagnostic pathways between NHS Trusts and regions in England exists, most markedly for prostate cancer[5]. Identifying patients for 2WW prostate cancer referral in primary care is also challenging for GPs owing to limitations of existing tests, including prostate specific antigen (PSA), which can impact on doctor-patient communication and patient experience of the early stages of the prostate cancer diagnostic pathway[6,7].

National Institute for Health and Care Excellence (NICE) guidance for diagnosing prostate cancer in England was updated in 2019 to recommend pre-biopsy magnetic resonance imaging (MRI) for men suspected of having prostate cancer[8]. In response, Cancer Alliances and Hospital Trusts in the NHS have updated local prostate cancer diagnostic pathways, with significant variation in the implementation of MRI[9]. Despite the potential benefits prostate MRI brings in terms of more accurate prostate cancer diagnosis[10], adding further testing into the prostate cancer diagnostic pathway could lengthen the diagnostic interval, adversely impacting patient experience. Experiences of the prostate cancer diagnostic pathway for patients and GPs since the advent of prostate MRI is unknown. The aim of this study was to elicit the experience of patients and GPs following two prostate cancer diagnostic pathways

that incorporate pre-biopsy MRI in different ways. In the context of the Model of Pathways to Treatment, a key theoretical framework in cancer diagnostic pathways, this study focuses on the 'Help-seeking' and 'Diagnostic' intervals and explores the perspectives of both patient and clinician[11,12].

Methods

This qualitative study used semi-structured interviews to explore the experiences of patients referred from primary care with possible prostate cancer who had undergone an MRI, and GPs who have referred men with possible prostate cancer for further investigation. A constructivist approach was adopted to access the data and understand the experiences of patients and GPs[13] based on their individual experiences (past and present) and the socio-cultural context[14,15].

Participants

This study recruited participants from two populations;

- Patients with possible prostate cancer who had undergone an MRI as part of their diagnostic workup.
- GPs who had referred at least one patient for investigation for possible prostate cancer within the preceding 12 months.

Patients who were undergoing MRI for active surveillance or watchful waiting for a previously diagnosed prostate cancer were not eligible, as the focus of this study was on the role of MRI in the diagnosis of prostate cancer rather than management.

Recruitment

Patients were recruited from two NHS Trusts in England: The Royal Devon & Exeter NHS Foundation Trust in Exeter and the Imperial College Healthcare NHS Trust in London. The Royal Devon & Exeter Hospital use separate outpatient appointments in the South West (SW) Prostate Cancer Diagnostic Pathway for a prostate MRI, consultant review, and prostate biopsy (if required), as shown in Figure 1. Imperial College employ the RAPID pathway, where patients undergo a prostate MRI scan, receive their MRI result, and potentially undergo a prostate biopsy on the same day at a single outpatient attendance (see Figure 2). These Trusts were selected as prostate MRI has been implemented in very different ways, creating the opportunity to explore and compare patient and clinician experiences in different clinical contexts. Research staff at the Trusts identified potentially eligible men and contacted them within days of undergoing an MRI to discuss this study and offer the men a Patient Information Leaflet (PIL). The lead investigator and local recruitment leads were in regular contact throughout recruitment to identify any under-represented groups of men and focus

recruitment where needed. Travel costs for patient participants to attend a face-to-face interview were reimbursed, and participants were also offered a gift voucher in recognition of contributing their time.

Figure 1

Figure 2

GPs were recruited through two National Institute for Health Research (NIHR) Clinical Research Networks (CRNs) in the same regions as the hospital sites: Northwest London CRN and the South-West Peninsula CRN. The CRNs promoted the study to local practices, and GPs expressed their interest to the CRNs. Eligibility and basic demographics were checked to assist with purposive sampling. GPs chosen for invitation into the study were given a PIL to review prior to the arrangement of an interview. GP practices were reimbursed for the GP's time to participate in the study.

A purposive sampling approach was used, in order to obtain a diverse group of participants with a wide range of geographical locations, ages, genders (GPs) and MRI results (patients).

Data collection

One-to-one interviews were conducted with all participants in this study between July and November 2019 by SM (a male GP). Patient participants were either interviewed face-to-face in their own home or via telephone, while all GP participant interviews were conducted via telephone. Formal written consent was obtained from all participants, and patient's partners if present (n=2), prior to commencement of the interview. A semi-structured approach was followed, with separate interview topic guides for patient and GP interviews to support discussions (See supplementary file 1 and 2). The topic guide was developed to incorporate all aspects of the revised prostate cancer diagnostic pathway and was used flexibly within the interviews to ensure that no key aspects of the diagnostic pathway experience were missed. An encrypted audio recording device was employed to record all interviews, and written

notes were taken during and immediately following the interviews. Interview times ranged between 15-45 minutes each. Interview recordings were transferred securely to an independent transcribing service, and transcribed verbatim.

Data analysis

An inductive thematic analysis was conducted to understand the experiences of participants[16], using the conceptual framework of the Model of Pathways to Treatment[11,12]. The researchers initially immersed themselves in the data through reading and re-reading individual transcripts and listening back to the audio recordings of the interviews. A selection of early interviews were coded, and this initial coding framework was reviewed and refined by SM, SA and FW. The remaining interview transcripts were coded inductively from the entirety of the data. The codes were reviewed and arranged into themes through an iterative process, returning to the original data as needed. Patient and GP transcripts were analysed separately. Within and between themes, the experiences of participants following different diagnostic pathways were compared and contrasted. Recruitment ceased when no new themes emerged in analysis. Transcripts were imported into NVivo v12 to manage the data for the analysis. A study summary report was sent to all study participants after completion of data analysis.

Patient & Public (PPI) Involvement statement

Eight men were recruited via the People in Health West of England (PHWE) initiative to contribute to the research: these men had a range of ages, locations, ethnic backgrounds and experiences with prostate cancer. PPI group members reviewed the plain English summary and all patient participant documents and gave feedback prior to submission as part of the ethical approval application. PPI group members also gave input into the interview topic guides and the expected burden of involvement for participants. One of the anonymised patient interview transcripts was shared with the group at a meeting and discussed to explore themes emerging from the text.

Ethical approval

Ethics committee approval was received from the NHS HRA South-West Frenchay research ethics committee (REC reference 19/SW/0040).

COREQ reporting guidelines

This manuscript has been written in accordance with the consolidated criterion for reporting qualitative research (COREQ) checklist[17]. Further detail regarding the methods can be found in the study protocol (see Supplementary file 3).

Results

Participants

Twenty-two patients were interviewed; two with their wives present and involved in the interview: participant ages ranged from 47 – 80 years. Ten GPs were interviewed: most were female (n = 6), with an age range of 38 – 58 years (See table 1). Five further potential (three patients and two GPs) participants were approached but declined to participate.

	Patients (n = 22)		**GPs (n = 10)**
Age		**Age**	
<65	8	31-40	3
65+	14	41-50	6
		50+	1
Location		**Location**	
London	10	London	4
Devon	12	Devon	6
Ethnicity		**Gender**	
White	19	Male	4
BME	3	Female	6
PIRADS v2*		**Role**	
1-2	6	Partner	8
3-5	15	Salaried	2
Unknown	1		

Table 1 – Patient and GP demographics

* PIRADS – Prostate Imaging-Reporting And Data System v2 score of 1-2 suggest clinically significant prostate cancer is unlikely and biopsy not indicated. A PIRADS score of 3-5 indicates at least one suspicious area of the prostate that warrants biopsy.

Patient experiences of the prostate cancer diagnostic pathway

We identified three main themes with interlinking sub-themes (see figure 3): Cancer beliefs, Communication, and Pathway experience.

Figure 3

Cancer beliefs

The decision for patients to see their doctor about potential prostate problems was not undertaken in isolation (*Outside influences*). The experiences of family members and friends shaped the patients' expectations, and family members and partners often encouraged men to be tested:

> *"Obviously back then he [dad] was in his mid to late 60s. And I think I didn't really know about it until he'd gone for his MRI and got the results and everything, and then all of a sudden he sat me down and told me all about it." P20 (London, <65)*

Most patients' attitudes towards the possibility of a diagnosis of cancer (*Attitude to diagnosis*) were fairly relaxed. Many seemed philosophical about the prospect:

> *"it is what it is" P03 (Devon, <65)*

The reactions of patients who had a diagnosis of prostate cancer (*Reaction to findings*) were mixed, ranging from despondence to quick acceptance:

> *"Not fair. No, it's... it's not fair on... on anyone, not just me. It isn't fair on anyone." P01 (Devon, 65+)*

Communication

The absence of the use of the word cancer ('*C word*') was evident in interviews with many patients. Patients also reported a reluctance from clinicians to raise cancer specifically as a possibility during a consultation, even if they were referred for urgent tests to rule out a diagnosis of prostate cancer:

> *"And then this developed." P01 (Devon, 65+)*

"For me, my... my dad had it roughly about eight, nine years... eight to ten years ago, I suppose. He had it." P20 (London, <65)

"The only thing that I found was you were given leaflets that mention a lot about cancer but no one actually really, sort of like said to me, you know, there's a possibility that you could have cancer or you know, that you're just being given leaflets and such, and no one really explained to you that there is a possibility. " P25 (Devon, <65)

The mode of communication to the patient from clinicians (*personal contact*) appeared to directly affect their experiences of the pathway. Most London patients sat down with their consultant and reviewed their MRI results together, whereas many patients in Devon received their results via a letter:

"I think it was interesting to see this sort of slightly darker little, ti… little circular area that he thought might be cancerous and… and also explain that they would need to take some samples from another area which… which was more the normal colour of the whole gland for comparison." P13 (London, 65+)

"Most of the letters go to the GP and I just get a copy." P23 (Devon, 65+)

Communicating the meaning (*conveying significance*) of the results of the MRI and other tests performed was very important to help patients and their partners understand what the results mean for them as an individual:

"Yeah, so apparently, because this is mid-rank they said that if you just got the first circle, the first ones in, they probably wouldn't have done anything about it and you could have had a lot of years where you just monitor that. But because P03 was mid-stage, they said we have to do something." P03's partner (Devon, <65)

Despite most of the patients having undergone a prostate MRI by the time of their interview, there were still limited understanding of the MRI results for some patients (*Gaps in understanding*). More patients from Devon reported these gaps, which often

appeared to be a result of communication breakdown between the patient and the doctor:

> *"Umm… I think, all I know is those letters passed to and fro between the urologist and my GP, and I'm copied in on these things and there was some mention of an abnormality on the left hand side or somewhere or other on the prostate. That's all I know." P23 (Devon, 65+)*

Pathway experience

Patients entered the pathway in different ways, with varied length of time and diagnostic work-up prior to urgent suspected cancer referral (*Mixed routes*). For patients in Devon, the prostate cancer pathway required a number of individual appointments, whereas most patients in London received their MRI results on the same day or soon after which was well received (*Appointments burden*):

> *"I had a PSA of, I think it was 4.03, which was fractionally above the four limit. Then they gave me two additional PSAs every three months, so I went back three months later did another PSA and then I think it was about 3.84. Then another one three months later was 4.08. So then I saw a urologist at Exeter and as a precaution they gave me an MRI and the MRI identified an area of concern if you like [inaudible]. Then I had a biopsy and what that identified was that the area of concern that the MRI identified, there was no cancer, but there was cancer in another area." P04 (Devon, 65+)*

"so… the scan, you get the result within minutes, and even though I had to wait perhaps an hour before I actually saw the doctor but that's a lot less than three months." P05 (London, 65+)

Patient interviewees were generally positive about undergoing investigations for possible prostate cancer, including blood tests and MRI. Most, but not all, patients reported that undergoing an MRI of the prostate was not a significant undertaking (*Test acceptability*):

"I'd go for any scan, anything like that. Needles don't bother me, scans don't bother me." P21 (Devon, 65+)

GP Experiences of the prostate cancer diagnostic pathway

We identified three main themes: Imperfect information, Managing uncertainty, and Contextual influences (see figure 4).

Figure 4

Imperfect information

GPs spoke at length about the limitations of the current primary care diagnostic pathway for prostate cancer, and about having imperfect information on which to base their clinical decisions.

A few GPs described a sense of inevitability about patients presenting with lower urinary tract symptoms at some point as they entered their later years (*Non-specific presentation*):

"It's a bit of a grey area so you're kind of waiting for patients to develop symptoms and come to see you" GP03 (Male, London, 31-40)

As described earlier, GPs experienced men refusing to have a prostate examination when prostate cancer is suspected (*Examination acceptance*). GPs reported different reasons for this, and perceived that patients may still be worried even if the prostate feels normal:

"I've had patients before who even will have got a high PSA decline, a rectal examination because they've previously had some, kind of, you know, traumatic experience or whatever." GP04 (Female, Devon, 41-50)

GPs from both regions did not hold back in sharing their opinions about the PSA blood test, and its usefulness (or lack thereof) in helping them make clinical decisions about which men to refer for further testing for possible prostate cancer (*GP test limitations*):

> *"I think if there's one test you could un-invent, I think PSA would be that…" GP02 (Male, Devon, 31-40)*

GPs working in the NHS cannot currently order an MRI of the prostate; the request must come from a secondary or tertiary care clinician. London GPs were more likely to be positive about the concept of a prostate MRI:

> *"I think it will be a really useful idea" GP03 (Male, London, 31-40)*
> *"Well, it's great, but it's not available to me. It's not something I decide on." GP05 (Female, Devon, 41-50)*

<u>Managing uncertainty</u>

GPs made efforts to share their diagnostic dilemma with patients where possible and consulted guidelines and their local urology specialists in managing uncertainty in their decisions about which men to refer to secondary care. Prior to referral, GPs tried to make their patients understand the limitations of the current diagnostic pathway (*counselling patient*):

> *"But I always would tell patients that it's not 100% and that both my examinations, whether it's a digital rectal or a PSA, are not 100% and it can be raised even without having cancer." GP03 (Male, London, 31-40)*

Whilst most GPs reported feeling satisfied with their local urology service (see *health service & guidance* below), some Devon GPs reported inconsistencies in the advice and management plans for their patients that came back from hospital specialists (*seeking advice*):

"I mean, we try to follow the guidelines but, as I say, we find mystifying as to the variation in the urology advice that comes back in terms of who to follow and who not to…" GP04 (Female, Devon, 41-50)

Contextual influences

A spectrum of broader influences had an effect on when patients chose to present to their GP with concerns about prostate cancer, and the consultation itself (*Gender, society & culture*). Some GPs noted a reticence of men to seek healthcare:

"I think men don't... it's such a sweeping statement but men don't like coming to the doctor" GP07 (Female, London, 31-40)

Consistent with the patient interviews (*outside influences*), the GPs reported that it was often the wives and partners encouraging male patients to seek help and advice:

"…the majority of men I see who mention prostate cancer it's because their wives have asked them to come and they're worried." GP07 (Female, London 31-40)

Cultural and ethnic norms relating to the patient and their partners also influenced the consultation and acceptance of prostate examination, which were more commonly reported by GPs working in London:

"And over here I notice there are some patients of south Indian descent where, it's [DRE] almost like a taboo really." GP03 (Male, London, 31-40)

GPs in both regions were aware of the influence of news and media stories relating to prostate cancer that were encouraging patients with symptoms or concerns to see their GP and get tested:

"…there was a lot in the media recently with prostate and testicular cancer, actually which is a good thing, because we had a… I had suddenly quite a few men coming in requesting the blood test." GP09 (Female, London, 41-50)

GPs felt that most patients were aware of prostate cancer and that tests were available for it. Awareness of MRI of the prostate was lower than for the PSA blood test (*Patient awareness*):

> *"Lots of people are aware of the PSA" GP07 (Female, London, 31-40)*
> *"I think a few of them might have said, "I've heard there's a new test around." I don't think anyone's come in and said, "I'd like to have that MRI test." GP04 (Female, Devon, 41-50)*

The decision-making of GPs was also affected by their own experiences in their personal and professional lives (*Personal & professional experience*). GPs demonstrated an awareness of how these experiences shaped their approach:

> *"…my dad has prostate cancer that was picked up with a raised PSA. And my stepfather has prostate cancer which was picked up by a raised PSA. Both completely asymptomatic. So I think that also affects how you... how you practice and you know, as clinicians we do take on our life experiences and we can't help but have that shape how... how we work." GP07 (Female, London, 31-40)*

The health service context in which GPs practise was another significant influence on their approach to patients with possible prostate cancer (*Health services & guidelines*). They often rely on guidance from a number of sources, including national guidelines and local urology services:

> *"I think we've got some, you know, very good local colleagues who offer good pragmatic advice and are very approachable." GP02 (Male, Devon, 31-40)*

Discussion

Principal findings

Patients' experiences of more traditional and 'one-stop' prostate cancer diagnostic pathways incorporating MRI showed some key similarities and differences. The communication between patients and healthcare teams significantly affected the patients' overall experience and their understanding of MRI results. MRI appeared to be an acceptable and low burden test for patients. Compared to patients attending a 'one-stop' clinic, patients following more traditional diagnostic pathways felt that longer waits for tests, more appointments to attend, and increased travel requirements all impacted on their pathway experience. GPs faced challenges in dealing with uncertainty and the perceived limitations of symptoms, examination and tests available to them for diagnosing prostate cancer with confidence. GP awareness, understanding and access relating to MRI was limited in both regions, and they reported some variation in local guidelines and specialist urology advice.

Strengths and weaknesses

Participants in this study were recruited from two regions with contrasting prostate cancer diagnostic pathways in terms of number of appointments, length of diagnostic interval, and integration of prostate MRI. This enabled identification of key similarities and differences in the experiences of patients and GPs engaging with the different pathways.

The influence of the researcher on data collection and analysis is important to consider in qualitative research. Participants were aware that SM was a clinician, and that may have given some level of respectability and authority to the interviewer and the study. Some patients and GPs reported that men were less comfortable seeing a female GP about problems relating to the prostate, so having a male interviewer may have helped patient participants be more comfortable and open in the interviews. GP participants may have been more comfortable in talking to a peer in these interviews; peer discussions are a common part of professional practice for GPs in the form of Balint groups[18] and annual appraisal by a fellow GP[19].

MRI is a new test for prostate cancer and has only recently been integrated into diagnostic pathways. GPs are not currently able to request an MRI of the prostate, and access to MRI for other indications varies across the NHS. Some GPs were reluctant to engage in any discussion about prostate MRI as they felt it was outside their current scope of practice and may have been focused on the more traditional (pre-MRI) prostate cancer pathway. In this context, data gathered from GP participants was not as rich as the data collected from the patients.

Relation to published literature

This is the first study the authors are aware of to explore experiences of the modern pre-biopsy MRI prostate cancer diagnostic pathway from the perspective of patients and GPs. Similar studies with patients or GPs have been conducted before MRI emerged as a diagnostic test for prostate cancer. Ruseckaite *et al* interviewed 10 GPs from metropolitan Melbourne and a regional part of Victoria, Australia regarding their perceptions of prostate cancer care. In line with the findings of this study, most men were willing to have a PSA blood test, and some GPs had to grapple with inconsistent guidance from specialist bodies[20]. Evans *et al* assessed men's experience of PSA testing in primary care in Wales, and also found that social networks and media stories influenced patient demand for testing. In contrast to the views of GPs in this study, the men in the study by Evans *et al* felt decision-making about testing was doctor-centred rather than shared or patient-centred[21].

A number of qualitative studies have explored patient and GP experiences of diagnostic pathways for other cancer types, including lung[22,23], haematological[24], and breast or bowel cancer[25]. Lung, breast and bowel cancer patients expressed a desire to progress through the diagnostic pathway as fast as possible, which was valued by London patients in this study attending the 'one-stop' clinic. Consistent with GP's concerns about non-specific presentations of prostate cancer, patients and clinicians in studies of other cancer types also report presenting with 'intermittent, vague' symptoms[25] and facing 'uncertainty' through their experience of the diagnostic pathway[23]. This reflects the challenge of making an early diagnosis of cancer in some cases for a range of cancers.

Implications for clinicians and health service design

Men's experiences of the prostate cancer diagnostic pathway are influenced by the appointment burden they face to receive a diagnosis; the mode of communication used by GPs and specialists to communicate test results; and requirements for travel to attend clinic appointments and tests. Significant challenges remain for GPs owing to the limitations of the current clinical signs and tests they rely on to identify possible prostate cancer cases. Men seemed broadly positive about MRI as a new test for prostate cancer, whereas GPs were equivocal owing to a lack of awareness and access. Cancer alliances and health service designers should consider the implications of how MRI is integrated into prostate cancer diagnostic pathways in terms of patient access to MRI, outpatient appointment burden, and communication of clinical guidelines for prostate cancer diagnostic testing and results to patients.

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Competing interests

HA was a paid medical consultant for Sophiris Biocorp in the previous 3 years. The remaining authors have no conflicts of interest to declare.

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Contributors

SWDM, WH and FMW conceived the study. SWDM developed the research protocol with contributions from FMW, AF, and SA. HA, JM and DE-E were local investigators who supervised recruitment into the study. SWDM undertook all interviews. SWDM, FMW, AF and SA performed the analysis. SWDM drafted the first version of the manuscript. All authors contributed to the development of the manuscript, and approved the final submitted version.

Ethics approval

Ethics committee approval was received from the NHS HRA South-West Frenchay research ethics committee (REC reference 19/SW/0040).

Patient consent for publication

Patient consent for publication of anonymised individual remarks was obtained at the time of recruitment into the study.

Data sharing statement

All data requests should be submitted in writing to the corresponding author

Disclaimer

The views expressed in this publication are those of the author(s) and not necessarily those of the NIHR or the Department of Health and Social Care.

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Figure 1 – South West Prostate Cancer Diagnostic Pathway, NHS Cancer Alliances in South-West Peninsula and Somerset, Wiltshire, Avon & Gloucester (SWAG)
mpMRI – multiparametric magnetic resonance imaging; TRUS – transrectal ultrasound guided biopsy; MDT – multidisciplinary team

Figure 2 – RAPID pathway, Imperial College Healthcare NHS Trust, London
2WW – Two Week Wait pathway; mpMRI – multiparametric magnetic resonance imaging; MRI – magnetic resonance imaging

Figure 3 – Thematic diagram from patient participant interviews

Figure 4 – Thematic diagram from GP participant interviews

1.4 Paper I co-authored related to the PhD

M Elwenspoek, A Sheppard, SWD Merriel, M McInness, E Rowe, J Donovan, R Bryant, P Whiting 'Comparison of multiparametric magnetic resonance imaging and targeted biopsy with systematic biopsy alone for the diagnosis of prostate cancer: a systematic review and meta-analysis' *JAMA Network Open* 2019; 2(8): e198427 doi:10.1001/jamanetworkopen.2019.8427

I provided clinical input into the interpretation of the data gathered, assisted with manuscript preparation, and reviewed final draft of manuscript.

JAMA Network Open

Original Investigation | Imaging

Comparison of Multiparametric Magnetic Resonance Imaging and Targeted Biopsy With Systematic Biopsy Alone for the Diagnosis of Prostate Cancer

A Systematic Review and Meta-analysis

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Abstract

IMPORTANCE The current diagnostic pathway for patients with suspected prostate cancer (PCa) includes prostate biopsy. A large proportion of individuals who undergo biopsy have either no PCa or low-risk disease that does not require treatment. Unnecessary biopsies may potentially be avoided with prebiopsy imaging.

OBJECTIVE To compare the performance of systematic transrectal ultrasonography–guided prostate biopsy vs prebiopsy biparametric or multiparametric magnetic resonance imaging (MRI) followed by targeted biopsy with or without systematic biopsy.

DATA SOURCES MEDLINE, Embase, Cochrane, Web of Science, clinical trial registries, and reference lists of recent reviews were searched through December 2018 for randomized clinical trials using the terms "prostate cancer" and "MRI."

STUDY SELECTION Randomized clinical trials comparing diagnostic pathways including prebiopsy MRI vs systematic transrectal ultrasonography–guided biopsy in biopsy-naive men with a clinical suspicion of PCa.

DATA EXTRACTION AND SYNTHESIS Data were pooled using random-effects meta-analysis. Risk of bias was assessed using the revised Cochrane tool. Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) guidelines were followed. All review stages were conducted by 2 reviewers.

MAIN OUTCOMES AND MEASURES Detection rate of clinically significant and insignificant PCa, number of biopsy procedures, number of biopsy cores taken, and complications.

RESULTS Seven high-quality trials (2582 patients) were included. Compared with systematic transrectal ultrasonography–guided biopsy alone, MRI with or without targeted biopsy was associated with a 57% (95% CI, 2%-141%) improvement in the detection of clinically significant PCa, a 33% (95% CI, 23%-45%) potential reduction in the number of biopsy procedures, and a 77% (95% CI, 60%-93%) reduction in the number of cores taken per procedure. One trial showed reduced pain and bleeding adverse effects. Systematic sampling of the prostate in addition to the acquisition of targeted cores did not significantly improve the detection of clinically significant PCa compared with systematic biopsy alone.

(continued)

Key Points

Question Is prebiopsy magnetic resonance imaging combined with targeted biopsy associated with improved detection of clinically significant prostate cancer compared with transrectal ultrasonography–guided systematic prostate biopsy alone?

Findings This systematic review and meta-analysis of 7 randomized clinical trials (2582 patients) demonstrates that prebiopsy magnetic resonance imaging combined with targeted biopsy is associated with improved detection of clinically significant prostate cancer and reduced numbers of biopsy cores per procedure, while potentially avoiding unnecessary biopsies.

Meaning These findings support the introduction of prebiopsy magnetic resonance imaging into the diagnostic pathway for biopsy-naive men with suspected prostate cancer.

+ Invited Commentary

+ Supplemental content

Author affiliations and article information are listed at the end of this article.

Abstract (continued)

CONCLUSIONS AND RELEVANCE In this meta-analysis, prebiopsy MRI combined with targeted biopsy vs systematic transrectal ultrasonography–guided biopsy alone was associated with improved detection of clinically significant PCa, despite substantial heterogeneity among trials. Prebiopsy MRI was associated with a reduced number of individual biopsy cores taken per procedure and with reduced adverse effects, and it potentially prevented unnecessary biopsies in some individuals. This evidence supports implementation of prebiopsy MRI into diagnostic pathways for suspected PCa.

JAMA Network Open. 2019;2(8):e198427. doi:10.1001/jamanetworkopen.2019.8427

Introduction

Prostate cancer (PCa) is the most commonly diagnosed cancer in men and the second leading cause of cancer-associated death among men in the United States.[1] Despite this statistic, a large number of PCas are not clinically significant and are unlikely to lead to problems if left untreated.[2] Distinguishing high-risk from low-risk PCa remains difficult,[3] leading to overdiagnosis and, for some men, unnecessary invasive treatments and treatment-associated morbidity.[4] There is, therefore, an unmet clinical need to develop tests that can detect clinically significant PCa (csPCa) while reducing overdiagnosis of low-risk disease.

Clinical findings of possible PCa include elevated prostate-specific antigen (PSA) levels and/or abnormal digital rectal examination findings. The US Preventive Services Task Force,[5] European Association of Urology,[6] and UK National Institute for Health and Care Excellence[7] recommend transrectal ultrasonography (TRUS)–guided biopsy as a standard investigation in the diagnosis of PCa. Transrectal ultrasonography is primarily used for anatomical guidance during biopsy, with approximately 10 to 14 individual biopsy cores taken systematically from the prostate (depending on the gland volume). However, a TRUS-guided systematic biopsy predominantly samples the peripheral zone of the prostate gland, so some PCa foci may be missed or undersampled, leading to disease misclassification and/or underdiagnosis.[8]

A recent development in the diagnostic pathway for suspected PCa involves prebiopsy magnetic resonance imaging (MRI) using 2 or more parameters to identify suspicious areas. Multiparametric MRI (mpMRI) uses T2-weighted, dynamic contrast-enhanced, and diffusion-weighted imaging, whereas biparametric MRI only uses T2-weighted and diffusion-weighted imaging. These MRI-visualized lesions are graded using the Prostate Imaging Reporting and Data System[9] and can be specifically targeted at biopsy. This method offers potential advantages over a pathway where only peripheral zone cores are taken systematically without prior imaging, including more-accurate detection of csPCa using targeted biopsy, the possibility of reducing the need for a biopsy in some individuals with normal MRI findings, and a potential reduction in the number of biopsy cores taken per procedure. Avoiding unnecessary biopsies may reduce serious adverse events associated with this procedure, such as bleeding, sepsis, and, rarely, death.[10] Fewer biopsy cores being taken per procedure could reduce the total procedure time and may reduce the risk of adverse effects, making it a more acceptable investigation for patients.[11] Previous studies[12] have suggested that using prebiopsy mpMRI to guide biopsies may increase the sensitivity to detect higher-grade PCa appropriate for treatment. Prebiopsy mpMRI has recently been recommended in the United Kingdom as the standard of care for biopsy-naive patients with suspected PCa.[13]

Evidence supporting the value of introducing MRI into the diagnostic pathway for suspected PCa is increasing. Several randomized clinical trials (RCTs) have been conducted comparing a systematic TRUS-guided biopsy pathway (ie, systematic biopsy alone) with pathways including a prebiopsy MRI. We conducted a systematic review of these RCTs and investigated 2 different prebiopsy MRI pathways: (1) prebiopsy MRI followed by a targeted biopsy only (ie, MRI plus targeted biopsy pathway) and (2) prebiopsy MRI followed by a biopsy obtaining both targeted and systematic biopsy cores (ie, MRI plus targeted and systematic biopsy pathway) (**Figure 1**). Our main outcome

was the detection rate of csPCa. Secondary outcomes were the detection rate of any-grade PCa, the number of biopsy procedures potentially avoided, the number of any-grade PCa missed by MRI, and complications.

Methods

This review followed recommended methods for systematic reviews[14,15] and is reported according to the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) reporting guideline. We expanded the data extraction and analysis, as described elsewhere,[16] to differentiate between the 2 prebiopsy MRI pathways and to include the secondary outcome of PCa missed by MRI.

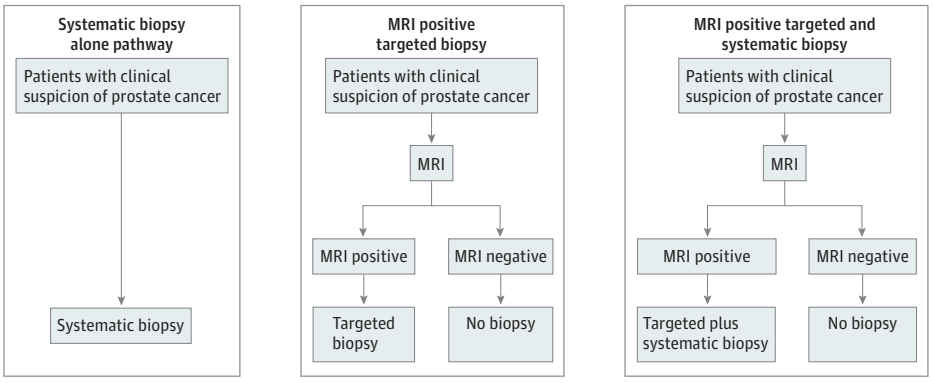
Data Sources and Study Selection

Randomized clinical trials including biopsy-naive men with clinical suspicion for PCa that compared a 2-step MRI pathway (prebiopsy MRI group) with TRUS-guided systematic biopsy (systematic biopsy alone group) were eligible for inclusion. Eligible MRI pathways consisted of prebiopsy MRI using 2 or more parameters, followed by a targeted biopsy with or without systematic sampling based on the MRI results (MRI plus targeted biopsy or MRI plus targeted and systematic biopsy). MEDLINE, Embase, Cochrane, and Web of Science were searched through December 2018 using the terms "prostate cancer" and "MRI" and an RCT filter.[16] Trial registries and reference lists of recent reviews were also searched. Abstracts and full texts were independently screened by 2 reviewers using Rayyan.[17] Any discrepancies between the reviewers were resolved through discussion or referral to a third reviewer.

Data Extraction and Risk of Bias Assessment

Data were extracted by 1 author and checked by a second author using standardized data extraction forms. Data on patient characteristics, study design, imaging, and biopsy protocols were extracted according to the Standards of Reporting for MRI-Targeted Biopsy Studies recommendations.[3] We investigated 2 hypothetical prebiopsy MRI pathways and extracted data that allowed analysis of these pathways (Figure 1): (1) where prebiopsy MRI–positive patients undergo targeted biopsy alone (MRI plus targeted biopsy pathway), or (2) where prebiopsy MRI–positive patients undergo biopsy including targeted and systematic cores (MRI plus targeted and systematic biopsy pathway). In RCTs that investigated the MRI plus targeted and systematic biopsy pathway, but also reported data that allowed deduction of outcomes for MRI plus targeted biopsy (ie, trials that reported results for the targeted and systematic cores separately), data were extracted for both potential prebiopsy MRI pathways. We extracted the number of patients with a diagnosis of csPCa or clinically insignificant PCa according to the definition of clinical significance used in each RCT (eTable 1 in the Supplement).

Figure 1. Three Diagnostic Pathways Used to Detect Clinically Significant Prostate Cancer



Flowcharts show, from left to right, a transrectal ultrasonography–guided systematic biopsy alone pathway (control), in which all patients with clinical suspicion of prostate cancer undergo this procedure; a magnetic resonance imaging (MRI) plus targeted biopsy pathway, in which individuals with a positive prebiopsy MRI undergo a transrectal ultrasonography–guided targeted biopsy alone; and an MRI plus targeted and systematic biopsy pathway, in which individuals with positive prebiopsy MRI findings undergo a transrectal ultrasonography–guided targeted biopsy combined with a systematic biopsy. In both hypothetical MRI pathways, individuals with negative MRI findings do not undergo a prostate biopsy procedure.

The number of patients with negative MRI findings was extracted to determine the number of biopsy procedures that could potentially have been avoided. We also extracted information on those cancers missed according to the systematic TRUS-guided biopsy or a reference standard, such as prostatectomy or saturation biopsy. These numbers were used to calculate percentages of cancers missed by MRI (ie, when the MRI findings were negative, but a cancer was subsequently identified at systematic biopsy, prostatectomy, or saturation biopsy) or by targeted biopsy alone (ie, when the targeted cores did not sample the cancer, but when the malignant neoplasm was identified within systematic cores). Risk of bias was assessed using the revised Cochrane tool (RoB 2.0 tool).[18] Authors were contacted to provide missing information.

Data Synthesis and Analysis

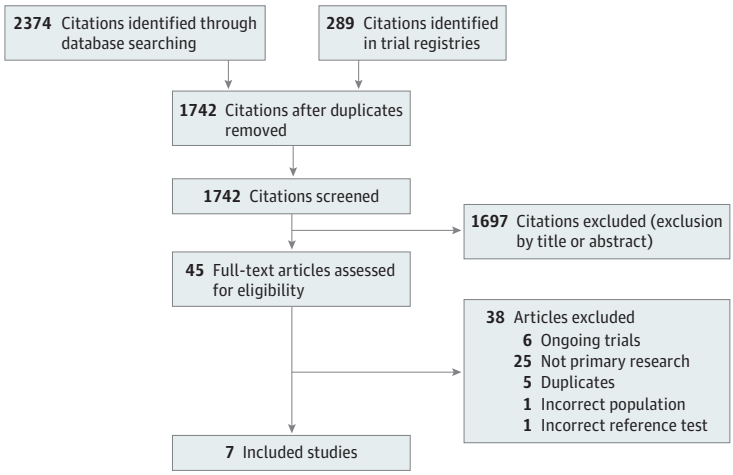
Random-effects meta-analysis models were used to estimate summary effect estimates (risk ratios and percentages) and to allow for variation among studies using the method of DerSimonian and Laird.[19] Heterogeneity was assessed using the I^2 statistic.[20] Ninety-five percent confidence intervals around risk ratios were calculated using the Woolf method, and 95% confidence intervals around percentages were calculated using the exact binomial (Clopper-Pearson) procedure.[21] A $P < .05$ was regarded as statistically significant (1-sided χ^2 test). All analyses were performed in Stata statistical software version 15.1 (StataCorp)[22] using the metan and metaprop commands.[23,24]

Summary risk ratios were estimated to compare the proportion of csPCas detected for each prebiopsy MRI pathway (MRI plus targeted and systematic biopsy and MRI plus targeted biopsy) compared with the systematic biopsy alone group. We stratified the analysis by biparametric MRI and mpMRI given the fundamental differences in these MRI techniques. We also estimated the summary percentage of patients with negative MRI findings (ie, potential biopsies avoided) with any-grade PCa and csPCa cases missed by prebiopsy MRI or targeted biopsy alone.

Results

The literature searches identified 1742 records, of which 7 RCTs fulfilled the inclusion criteria (**Figure 2**): 6 original investigations[25-30] and 1 conference abstract[31] including 2582 patients in total. In 5 RCTs,[25-28,31] the clinical suspicion of PCa was based on elevated PSA levels, abnormal digital rectal examination findings, or both. In 2 RCTs,[29,30] patients with abnormal digital rectal examination findings were excluded. Two RCTs[25,29] applied an age restriction excluding patients older than 75 years. There were no significant differences in age, prostate volume, or prebiopsy PSA levels

Figure 2. Diagram of Inclusion Criteria for Randomized Clinical Trials



between individuals in the prebiopsy MRI pathways and those in the systematic biopsy alone group, although 1 trial[27] did not report these measures (**Table**).

Several prebiopsy MRI pathways were used in the studies included in this analysis (**Figure 3**). In all RCTs, individuals with a clinical suspicion of PCa were randomly allocated to either the systematic biopsy alone group or to a prebiopsy MRI group. In all but 1 RCT,[26] individuals with negative prebiopsy MRI findings proceeded to undergo a systematic biopsy, with this procedure being identical to that performed in the systematic biopsy alone group because there was no visible MRI lesion to be sampled by a targeted approach. In 2 RCTs,[26,29] individuals with positive MRI findings underwent a targeted procedure alone (MRI plus targeted biopsy pathway), whereas in the other RCTs,[25,27,28,30,31] individuals with positive MRI findings underwent a combined procedure incorporating both targeted and systematic cores (Figure 3). For 3 of the MRI plus targeted and systematic biopsy RCTs,[25,28,30] it was possible to extract sufficient data regarding the content of the targeted cores. In 2 RCTs,[25,28] targeted cores were also taken in patients within the systematic biopsy alone group if suspicious lesions were visible at ultrasonography or palpable during digital rectal examination (Figure 3), which may have increased PCa detection in the control group of these RCTs compared with the systematic biopsy alone group of other RCTs.

Two RCTs[25,29] used a 1.5-T MRI scanner, 4 RCTs[27,28,30,31] used a 3.0-T MRI scanner, and 1 RCT[25] included data from both 1.5- and 3.0-T MRI scanners. Three RCTs[26,27,29] used a phased-array coil with or without an endorectal coil, 1 RCT[30] used body and spine matrix surface coils, 1 RCT[31] used a transrectal coil, 1 RCT[25] did not use a coil, and 1 RCT[28] did not report whether a coil was used. One RCT[25] used biparametric MRI, whereas the other RCTs used mpMRI. Different definitions were used to define a positive MRI, including a Prostate Imaging Reporting and Data System score of 3 or higher,[25,26,29] Prostate Imaging Reporting and Data System score of 4 or higher,[31] or any lesion detected at MRI without the use of a standardized reporting system (eTable 2 in the Supplement).[27,28,30] The images were interpreted by at least 1 experienced radiologist[25,26,31] or were assessed in consensus by 2 radiologists[27,28,30] or 3 radiologists[29] (eTable 1 in the Supplement).

Individuals in the prebiopsy MRI group with positive MRI findings underwent a targeted biopsy. The number of cores sampled during this targeted procedure varied considerably among RCTs (eTable 1 in the Supplement). For example, in 2 RCTs,[25,27] a maximum of 2 cores were taken per targeted biopsy, whereas in another RCT,[26] a maximum of 4 cores were obtained from a maximum of 3 areas, resulting in 1 to 12 cores per targeted procedure. The individuals randomized to the systematic biopsy alone group underwent a standard TRUS-guided prostate biopsy systematically sampling the peripheral zones of the prostate gland (eTable 1 in the Supplement) with 12 cores,[25,29] 14 cores,[27] or 10 to 12 cores[26,28,30] taken during the procedure. Most trials used only the transrectal approach to perform targeted prostate biopsies;[25,27,28,30,31] however, 2 trials[26,29] used either the transrectal or transperineal approach depending on local expertise or the anatomic location of the radiological lesion. Transperineal approaches were used only in the MRI group of these studies, whereas in the systematic biopsy alone group, all biopsies were performed using the transrectal approach. Furthermore, the manner in which the prebiopsy MRI findings were used to guide the targeted biopsy varied among RCTs. Four RCTs[25,26,29,31] used MRI-ultrasonography image fusion, 3 RCTs[26,28,30] used cognitive guidance, and 1 RCT[27] did not report the method of biopsy guidance.

Individuals received a diagnosis of csPCa, clinically insignificant PCa, or no PCa, depending on the biopsy pathologic results. The characterization of biopsy-detected PCa as being clinically significant or insignificant depended on the Gleason sum score (≥6 or 7), maximum cancer core length (≥3 or 5 mm), and/or the number of positive cores. (With the Gleason scoring system, pathologists grade the cell patterns in the biopsy sample from 1 to 5, where grade 1 cells resemble normal prostate tissue and grade 5 are high-risk cancerous cells. The Gleason score is calculated by adding the grade of the most predominant pattern with the second-most predominant pattern, such as 3 + 4.) However, no 2 studies used the same definition of csPCa (eTable 1 in the Supplement).

Five RCTs[25,26,29,30] were judged to have a low overall risk of bias (eTable 3 in the Supplement). Two RCTs[27,31] were judged to have some concerns regarding the randomization process, one of

Table. Study Characteristics

Source	Dates of Recruitment	Inclusion Criteria	Exclusion Criteria	Men Randomized, No.			Age, y			Prostate Volume, mL			Prebiopsy PSA Level, ng/mL		
				Total	MRI[a]	Standard[b]	Overall	MRI[a]	Standard[b]	Overall	MRI[a]	Standard[b]	Overall	MRI[a]	Standard[b]
Baco et al,[25] 2016 Norway	Sep 2011-Jun 2013	Age <75 y; clinical suspicion of PCa, based on verified PSA level increase to 4-20 ng/mL, abnormal DRE findings, or both	Previous prostate biopsy or MRI of the prostate; contraindication to MRI	183	90	93	65 (59-69)[c]	64 (58-69)[c]	65 (59-69)[c]	42 (30-59)[c]	45 (33-60)[c]	40 (29-52)[c]	7.3 (5.5-9.9)[c]	6.9 (5.2-9.2)[c]	7.6 (5.9-10.4)[c]
Kasivisvanathan et al,[26] 2018 United Kingdom	Feb 2016-Aug 2017	Clinical suspicion of PCa, based on elevated PSA level, abnormal DRE findings, or both; PSA level ≤20 ng/mL	Previous prostate biopsy or treatment for prostate cancer; DRE findings that suggest extracapsular disease; contraindications to biopsy or MRI	500	252	248	64.4 (7.8)[d]	64.4 (7.5)[d]	64.5 (8.0)[d]	Not reported				6.75 (5.16-9.35)[c]	6.50 (5.14-8.65)[c]
Panebianco et al,[27] 2015 Italy	Oct 2011-Mar 2014	Symptoms highly suggestive of PCa; total PSA level >4 ng/mL; PSA density >0.15; PSA velocity >0.75 ng/mL/y; free/total PSA ratio <0.10 when total PSA level was 4-10 ng/mL	Previous prostate biopsy	1140	570	570	64 (51-82)[e]			Not reported			Not reported		
Park et al,[28] 2011 Korea	Jul 2008-Dec 2009	Clinical suspicion of PCa, based on high PSA level or abnormal DRE findings	Previous prostate biopsy or treatments for prostate cancer	103	54	49	62 (37-92)[e]	63 (40-82)[e]	61 (37-92)[e]	37 (15-94)[e]	37 (17-94)[e]	38 (15-87)[e]	5.8 (2.9-9.9)[e]	6.1 (4.0-9.7)[e]	5.6 (2.9-9.9)[e]
Plata-Bello et al,[31] 2018 Spain	Feb 2015-Oct 2017	Clinical suspicion of PCa, based on elevated PSA level (4-20 ng/mL), abnormal DRE findings, or both	Previous prostate biopsy	303	182	121		67.9 (8.5)[d]	67.6 (8.8)[d]		47.5 (26.0)[d]	53.5 (25.5)[d]		6.48 (2.60)[d]	7.74 (6.87)[d]
Porpiglia et al,[29] 2017 Italy	Nov 2014-Mar 2016	Aged ≤75 y; clinical suspicion of PCa; PSA level ≤15 ng/m findings; negative DRE findings	Previous prostate biopsy or surgery; previous prostate MRI; contraindication to MRI	223	111	112		64 (58-70)[c]	66 (60-70)[c]		46.2 (34.5-71.6)[c]	45.7 (34.6-65.0)[c]		5.9 (4.8-7.5)[c]	6.7 (5.5-8.5)[c]
Tonttila et al,[30] 2016 Finland	Apr 2011-Dec 2014	Clinical suspicion of PCa, based on elevated PSA level (PSA<20 ng/mL or free-to-total PSA ratio ≤0.15 and PSA<10 ng/mL in repeated measurements); no evidence of PSA level increase due to noncancerous factors (ie, urinary tract infection); negative DRE findings	Previous prostate biopsy or surgery; contraindication to MRI	130	65	65		63 (60-66)[c]	62 (56-67)[c]		27.8 (23.5-36.6)[c]	31.8 (26.1-44.3)[c]		6.1 (4.2-9.9)[c]	6.2 (4.0-10.7)[c]

Abbreviations: DRE, digital rectal examination; MRI, magnetic resonance imaging; PCa, prostate cancer; PSA, prostate-specific antigen.

SI conversion factor: to convert PSA to µg/L, multiply by 1.0.

[a] MRI pathway (intervention group).

[b] Standard pathway (comparator group).

[c] Values are median (interquartile range).

[d] Values are mean (SD).

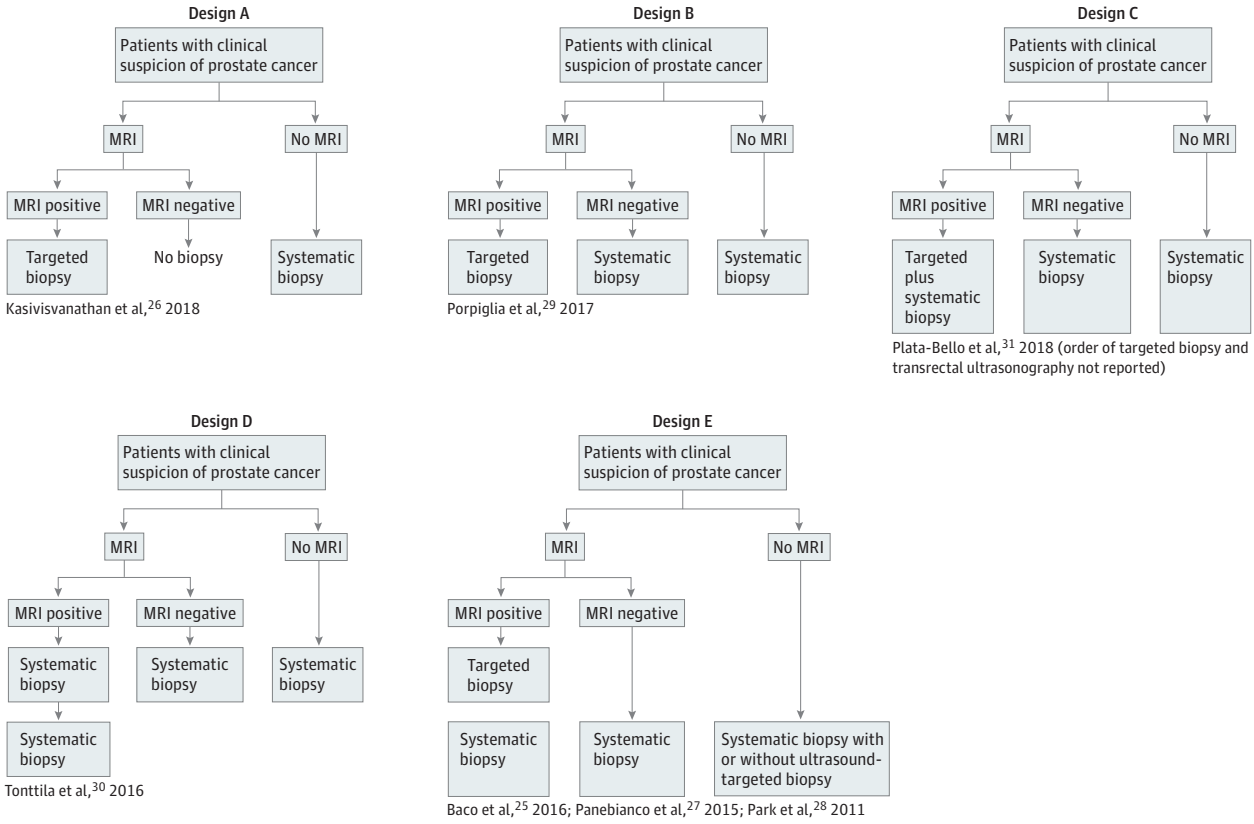
[e] Values are mean (range).

which[27] did not report methods of randomization, allocation concealment, or baseline characteristics of each group; the other RCT[31] did not report sufficient information to asses randomization.

Data from 5 RCTs[24,27,28,30,31] contributed to the analysis of the MRI plus targeted and systematic biopsy pathway, and data from 5 RCTs[25,26,28-30] were used to analyze the MRI plus targeted biopsy pathway (**Figure 4**). In 1 study,[25] the use of prebiopsy biparametric MRI did not significantly improve the detection of csPCa compared with the use of systematic biopsy alone (risk ratio, 0.78; 95% CI, 0.55-1.09). However, in 4 of the RCTs,[26,28-30] the MRI plus targeted biopsy pathway improved the detection of csPCa by 57% (95% CI, 2%-141%; risk ratio, 1.57; [95% CI, 1.02-2.41]; I^2 = 71%) compared with systematic biopsy alone. Compared with systematic biopsy alone, the MRI plus targeted and systematic biopsy pathway did not significantly improve the detection of csPCa (risk ratio, 1.36; 95% CI, 0.79-2.34; I^2 = 87%) in 4 RCTs.[27,28,30,31]

Direct comparison between the 2 prebiopsy MRI pathways, using the 3 RCTs[25,28,30] that evaluated the MRI plus targeted and systematic biopsy pathway and reported separate data for the targeted and systematic cores regarding PCa detection, showed mixed results. In 2 of these RCTs,[25,28] the additional acquisition of systematic cores did not identify additional csPCa cases beyond those detected in the targeted cores alone. However, in the study by Tonttila et al,[30] 4 csPCa cases would have been missed if only a targeted approach had been used (ie, the MRI plus targeted

Figure 3. Study Designs of the Included Randomized Clinical Trials



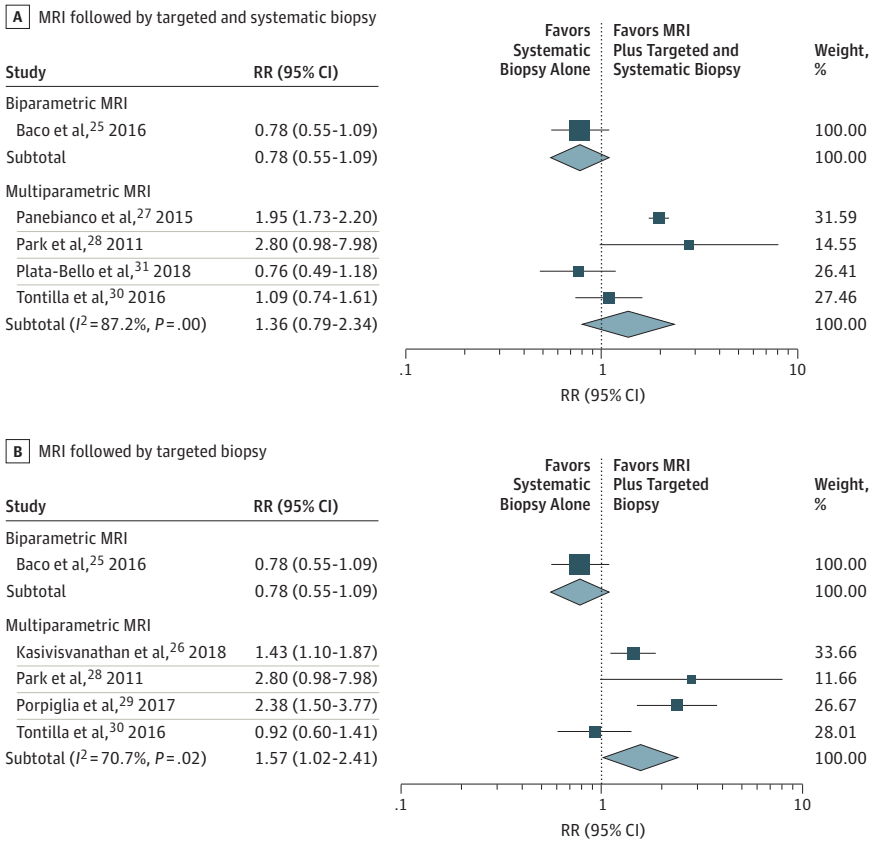
Designs A and B allowed for sufficient data extraction to analyze the systematic biopsy alone pathway vs the magnetic resonance imaging (MRI) plus targeted biopsy pathway. Design C allowed for sufficient data extraction of the systematic biopsy alone and the MRI plus targeted and systematic biopsy pathways, but not the MRI plus targeted biopsy pathway because separate data were not reported for the content of targeted and systematic biopsy prostate cores. Designs D and E allowed for sufficient data extraction of the systematic biopsy alone, MRI plus targeted and systematic biopsy, and MRI plus targeted biopsy pathways, except for the study by Panebianco et al,[27] which did not separately report the content of targeted and systematic biopsy prostate cores. Randomized clinical trials with design E performed targeted biopsies on the basis of digital rectal examination or ultrasonography findings, which may have resulted in an improved prostate cancer detection in the systematic biopsy alone pathway compared with other study designs.

biopsy pathway), which would have resulted in underdiagnosis in 10% of patients with positive MRI findings.

In most RCTs, it was not possible to assess the risk of complications associated with the targeted biopsy procedure compared with systematic TRUS-guided biopsy, because the individuals in the prebiopsy MRI group underwent systematic sampling during the targeted biopsy procedure. In only 2 RCTs[26,29] was the acquisition of targeted cores not combined with systematic sampling. However, the RCT by Porpiglia et al[29] is ongoing, and there are plans to report on complications in future publications. Kasivisvanathan et al[26] reported fewer overall complications for individuals in the prebiopsy MRI group compared with individuals in the systematic biopsy alone group. The frequency of hematuria (30% vs 63%), hemoejaculate (32% vs 60%), rectal bleeding (14% vs 22%), erectile dysfunction (11% vs 16%), and pain at the site of the procedure (13% vs 23%) were each reported to be lower in individuals in the prebiopsy MRI pathway compared with the systematic biopsy alone group.[26] However, in the prebiopsy MRI pathway, this RCT used both transperineal and transrectal approaches and only transrectal biopsies in the systematic biopsy alone group, which may account for the reduced complications in the MRI pathway. Moreover, approximately one-half of individuals in the prebiopsy MRI group did not undergo a biopsy at all (in the context of the MRI findings being negative); therefore, this would naturally have reduced the risk of complications in this group of the study.

We calculated the percentage of individuals for whom a biopsy was avoided, or could theoretically have been avoided, if the men with mpMRI-negative findings had not undergone prostate biopsy. The percentage of men who may have avoided a biopsy procedure ranged from 23%[27] to 55%,[31] with an overall estimate of 33% for all 7 RCTs[25-31] (95% CI, 23%-45%; I^2 = 91.8; eFigure 1 in the Supplement). In 6 RCTs,[25-30] the MRI plus targeted biopsy pathway would also

Figure 4. Detection Rate of Clinically Significant Prostate Cancer



Risk ratios (RRs) are represented by boxes, with the size of each box representing its weight. Horizontal lines represent 95% CIs. Diamonds represent combined-effect estimates and their 95% CIs. MRI indicates magnetic resonance imaging.

theoretically have reduced the number of biopsy cores taken per procedure by 77% (95% CI, 60%-93%) compared with the systematic biopsy alone group. The median number of targeted cores ranged from 1 to 6, compared with a mean number of systematic biopsy cores in the systematic biopsy alone group ranging from 11 to 12.

Overall, 31% (95% CI, 15%-49%; I^2 = 87%) of PCa cases were not visualized at prebiopsy mpMRI in 5 RCTs[27-31] (eFigure 2A in the Supplement), and most were classified as clinically insignificant (according to a systematic biopsy[28-31] or saturation biopsy[27]). In these 5 RCTs,[27-31] the risk of a patient having csPCa and a negative MRI findings ranged between 0% and 23% (eFigure 2B in the Supplement).

Discussion

This systematic review and meta-analysis demonstrates that the use of prebiopsy mpMRI combined with a targeted biopsy is superior to a systematic biopsy alone in diagnostic pathways for PCa. This improvement is seen in terms of increased detection of csPCa and a reduced number of biopsy cores obtained during a biopsy procedure, potentially preventing unnecessary biopsies and possibly reducing the overall burden of adverse effects from the invasive biopsy procedure. This observation adds to the evidence suggesting that the incorporation of prebiopsy MRI should be recommended for diagnostic pathways for suspected PCa. Obtaining systematic cores in addition to the targeted cores during a biopsy procedure did not seem to improve detection of csPCa, and only a few PCas were missed. However, data in this area were sparse, and studies may have been underpowered to test this, whereas some level of misclassification could not be ruled out.

To our knowledge, this is the first systematic review to compare 2 MRI pathways (MRI plus targeted and systematic biopsy and MRI plus targeted biopsy) with a pathway including systematic biopsy alone. The main strength of this review is that the inclusion criteria were limited to RCTs, which permits direct comparison between 2 diagnostic pathways with clinically relevant outcomes, as opposed to diagnostic cohort studies that can only inform us about test accuracy measures. Furthermore, all included trials were of high quality with low risk of bias, and there were sufficient data to conduct a meta-analysis on each MRI pathway. Extracting data for both MRI pathways from within the MRI plus targeted and systematic biopsy group of some RCTs allowed for direct comparisons between these pathways, even though none of the RCTs was designed to compare these 2 pathways per se.

Limitations

Limitations of this meta-analysis include the fact that we were unable to assess publication bias or perform a meta-regression analysis to test for variables associated with PCa detection because of insufficient data. The design of the included studies did not allow for calculation of test properties, such as sensitivity and specificity, because most patients did not undergo a reference standard procedure (ie, saturation biopsy or prostatectomy). Test accuracy measures were beyond the scope of this review, but a systemic review will be published soon.[32]

Two RCTs[27,29] did not use identical biopsy approaches for all patients in both study groups. Some patients in the prebiopsy MRI group underwent biopsy using a transperineal approach, whereas all patients in the systematic biopsy alone group underwent biopsy using a transrectal approach. The transrectal approach can be less adequate than the transperineal approach in terms of sampling the apex and anterior regions of the prostate. Some of the MRI-guided biopsies were performed through the transperineal approach, which permits better sampling of the apex and anterior regions of the prostate gland. This may have inflated the cancer detection rates in the prebiopsy MRI group. However, because of the limited number of RCTs included, it was not possible to perform a sensitivity analysis on the type of biopsy approach used.

An important limitation of the included RCTs was that each study used a different definition of csPCa, and it was not possible to extract sufficient data for a standardized definition. This may

explain the high degree of heterogeneity among studies, which means that results should be interpreted with some caution. Another source of variation was the guidance method used during the biopsy procedure itself. Cognitive guidance is potentially more error prone than MRI-ultrasonography image fusion guidance,[33] and the 2 RCTs[28,30] using cognitive guidance missed the highest percentage of csPCa. Only 1 RCT[26] reported data on complications associated with biopsy; therefore, we have very limited data for this important outcome. None of the RCTs reported long-term follow-up data to capture screening-relevant outcomes, such as time to mortality or cancer-associated mortality.

There have been concerns about the financial costs of MRI, but these have reduced over time, and 2 recent studies[34,35] based on US and UK data have demonstrated that incorporating MRI can be cost-effective, especially because doing so may avoid some unnecessary biopsies and reduce the burden of overtreatment. Another concern has been the availability of the necessary expertise to interpret MRI scans and perform MRI-guided biopsies. Training is necessary for radiographers to perform high-quality mpMRI scans and for radiologists and urologists to interpret the images and perform targeted biopsies. Standardized reporting has reduced variation in the interpretation of MRI scans among radiologists, but this variation is still significant.[36] Inaccurate sampling has been identified as a contributor to reduced MRI performance, even in those individuals undergoing MRI-ultrasonography fusion prostate biopsy.[37]

Conclusions

A key issue in the diagnosis and treatment of PCa remains the need to identify clinically significant disease that requires intervention and to avoid the unnecessary diagnosis of low-risk, low-volume disease. This systematic review and meta-analysis suggests that introducing prebiopsy mpMRI followed by a targeted biopsy into a PCa detection pathway may lead to the performance of fewer biopsies than a pathway using systematic biopsy alone. Such an approach may increase the likelihood of detecting csPCa, while reducing the detection of low-risk tumors. Introducing prebiopsy MRI, therefore, has the potential to transform practice. One RCT[26] has demonstrated that this may lead to fewer complications, and further studies have indicated that this may be a useful cost-effective strategy. There remain concerns that some csPCa cases may be missed in individuals with an increased age-specific PSA level and negative MRI findings. Combining the MRI results with other measures, such as PSA density (ie, PSA levels adjusted for prostate volume), can potentially decrease the risk of missing these csPCa cases,[38] but there are few studies in this area, and this requires further investigation. Moreover, there is no evidence regarding the impact of a delayed diagnosis of csPCa after a decision not to perform a biopsy is made on the basis of normal MRI findings in the context of an increased PSA level. The availability of mpMRI and radiologists and urologists trained to use it appear to be the only hurdles to overcome in establishing mpMRI and targeted biopsy with standardized reporting as the recommended diagnostic pathway for men with suspected PCa.

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Acquisition, analysis, or interpretation of data: All authors.

Drafting of the manuscript: Elwenspoek, Sheppard.

Critical revision of the manuscript for important intellectual content: All authors.

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Obtained funding: Donovan.

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SUPPLEMENT.

eFigure 1. The Percentage of Patients in the Prebiopsy MRI Arm With a Negative MRI Result
eFigure 2. Prostate Cancers Missed by Prebiopsy MRI Pathways
eTable 1. Definitions Used for Clinically Significant Prostate Cancers and Biopsy Methods in Reported Studies
eTable 2. Multiparametric Magnetic Resonance Imaging
eTable 3. Risk of Bias Assessment

Chapter 2

2.1 Database search terms

Medline

1. (prostat* adj3 (cancer* or carcinoma* or malignan* or tumo?r* or neoplas* or adeno*)).tw.
2. Exp Prostatic neoplasms/
3. Exp Prostatic Intraepithelial Neoplasia/
4. Exp prostate/
5. OR/1-4
6. exp "Sensitivity and Specificity"/
7. sensitivity.tw.
8. specificity.tw.
9. ((pre-test or pretest) adj probability).tw.
10. post-test probability.tw.
11. predictive value$.tw.
12. likelihood ratio$.tw.
13. OR/6-12
14. “multiparametric magnetic resonance imaging”.mp
15. mpMRI.mp
16. “magnetic resonance imaging”.mp
17. MRI.mp
18. OR/14-18
19. “prostate biopsy”
20. TRUS
21. Transrectal
22. 19 AND 21
23. Transperineal
24. 19 AND 23
25. Mapping.tw
26. 19 AND 25
27. Template.tw
28. 19 AND 27
29. 19 OR 20 OR 22 OR 24 OR 26 OR 28
30. “patient-focus*”.mp
31. “patient-centred”.mp

32. “patient-centered”.mp
33. “patient reported”.mp
34. PROM
35. PROMS
36. Patient outcome assessment/
37. “patient experience”.tw
38. “quality of life”.tw
39. QoL.tw
40. OR/30-39
41. 5 AND 13 AND 40
42. 5 AND 29 AND 40

EMBASE

1. (prostat* adj3 (cancer* or carcinoma* or malignan* or tumo?r* or neoplas* or adeno*)).tw.
2. Exp prostate/
3. Or/1-3
4. “multiparametric magnetic resonance imaging”
5. “multiparametric MRI”
6. mpMRI
7. “magnetic resonance imaging”
8. MRI
9. Or/4-9
10. “prostate biopsy”.tw
11. TRUS
12. Transrectal
13. 10 AND 12
14. Transperineal
15. 10 AND 14
16. Mapping
17. 10 AND 16
18. Template
19. 10 AND 18
20. 10 OR 11 OR 13 OR 15 OR 17 OR 19
21. “patient-focused”.tw

22. “patient-centred”.tw
23. “patient-centered”.tw
24. “patient reported outcome”
25. PROM
26. PROMS
27. Outcome assessment/
28. Health status indicator/
29. Outcomes research/
30. ((patient* or self or client* or subject* or participant* or lived or personal or consumer* or “service user” or “service users”) NEAR/3 (report* or relate* or view* or expectation* or perception* or perspective* or experience*or measure* or impact* or effect*)).tw
31. Or/21-29
32. 3 AND 9 AND 31
33. 3 AND 20 AND 31

PSYCINFO

1. Prostate.af
2. (prostat* adj3 (cancer* or carcinoma* or malignan* or tumo?r* or neoplas* or adeno*)).af
3. 1 or 2
4. mpMRI.af
5. mri.af
6. “multiparametric magnetic resonance imaging”.af
7. “multiparametric mri”.af
8. “magnetic resonance imaging”.af
9. 4 or 5 or 6 or 7 or 8
10. TRUS.af
11. “prostate biopsy”.af
12. Transrectal.af
13. Transperineal.af
14. Mapping.af
15. Template.af
16. 11 and 12
17. 11 and 13

18. 11 and 14
19. 11 and 15
20. 10 or 11 or 16 or 17 or 18 or 19
21. “quality of life”.af
22. “health related quality of life”.af
23. “patient outcome$”.af
24. “patient reported outcome$”.af
25. “patient centred”.af
26. “patient centered”.af
27. “patient centred outcome$”.af
28. “patient centered outcome$”.af
29. PRO.af
30. PROM.af
31. PROMs.af
32. Qol.af
33. Hrqol.af
34. Hrql.af
35. PREM.af
36. “patient experience”.af
37. 21 or 22 or 23 or 24 or 25 or 26 or 27 or 28 or 29 or 30 or 31 or 32 or 33 or 34 or 35 or 36
38. 3 and 9 and 37
39. 3 and 20 and 37

CENTRAL

#1 Prostat*(cancer or neoplasm* or carcin* or tumour* or tumor* or malignan* or neoplasia or adenocarcinoma*): ti,ab,kw
#2 MeSH descriptor: [Prostatic neoplasms] explode all trees
#3 MeSH descriptor: [Prostatic Intraepithelial Neoplasia] explode all trees
#4 MeSH descriptor: [Prostate] explode all trees
#5 #1 or #2 or #3 or #4
#6 “patient-centred”:ti,ab,kw
#7 “patient-centered”:ti,ab,kw
#8 PCO
#9 “patient-focused”:ti,ab

#10 PROMS
#11 “patient reported outcome*”
#12 ((patient* or self or client* or subject* or participant* or lived or personal or consumer* or “service user” or “service users”) NEAR/3 (report* or relate* or view* or expectation* or perception* or perspective* or experience*or measure* or impact* or effect*)):ti,ab
#13 MeSH descriptor: [Patient Reported Outcome Measures] explode all trees
#14 MeSH descriptor: [Patient Outcome Assessment] explode all trees
#15 #6 or #7 or #8 or #9 or #10 or #11 or #12 or #13 or #14
#16 “multiparametric magnetic resonance imaging”:ti,ab,kw
#17 “multiparametric MRI:ti,ab,kw
#18 mpMRI
#19 “magnetic resonance imaging”:ti,ab,kw
#20 MRI
#21 #16 or #17 or #18 or #19 or #20
#22 TRUS
#23 “prostate biopsy”:ti,ab,kw
#24 transrectal
#25 transperineal
#26 mapping
#27 template
#28 #23 and #24
#29 #23 and #25
#30 #23 and #26
#31 #23 and #27
#32 #22 or #23 or #28 or #29 or #30 or #31
#33 #5 and #15 and #21
#34 #5 and #15 and #32

2.2 Published protocol on PROSPERO

Citation

Sam Merriel, Victoria Hardy, Matthew Thompson, Willie Hamilton. Patient-centred outcomes of diagnostic tests for prostate cancer: a systematic review and narrative synthesis. PROSPERO 2018 CRD42018116244 Available from: https://www.crd.york.ac.uk/prospero/display_record.php?ID=CRD42018116244

Review question

What are the patient centred outcomes (PCOs) reported for ultrasound guided prostate biopsy and/or multiparametic MRI (mpMRI) as a diagnostic test for possible prostate cancer?

Searches [1 change]

MEDLINE Ovid, EMBASE, PsyINFO, and the Cochrane Central Register of Controlled Trials (CENTRAL) databases will be utilised to identify relevant studies. Key search terms, informed by the Scottish Intercollegiate Guidelines Network (SIGN) search strategies and pre-existing systematic reviews in the field of prostate cancer, will be combined with MeSH terms for each database search. Hand-searching and snowballing of references from search hits will be performed to locate any other possibly relevant studies. Studies will be limited to those published in English language. There will be no restrictions on search dates or study design.

Types of study to be included [1 change]

Case reports, conference abstracts, protocols, letters, editorials or commentaries will be excluded.

Condition or domain being studied

Prostate cancer diagnostic tests.

Participants/population

Men suspected of having prostate cancer that are referred for diagnostic testing.

Intervention(s), exposure(s)

mpMRI or ultrasound guided biopsy as a diagnostic test.

Comparator(s)/control

Standard diagnostic test, or no testing.

Context

Main outcome(s) [1 change]

Any patient-centred outcome as specified by the studies.

Measures of effect

The effect measure will depend on the PCOs from included studies

Additional outcome(s) [1 change]

Any patient-reported outcome measure or patient-report experience measure.

Measures of effect

The effect measure will depend on the PCOs from included studies

Data extraction (selection and coding)

A pre-prepared proforma for data extraction will be used to collate data from each included quantitative

study. For included qualitative studies, patient experiences will be unpacked from the data presented to identify PCOs that are important to patients.

SM will extract the data from all included studies. VH will extract data from a random sample of 10% of included studies for verification of accuracy of data extraction. Any discrepancies will be adjudicated by a 3rd author (WH or MT). Corresponding authors will be contacted if there is insufficient data in the manuscript to complete all fields in the data extraction.

Risk of bias (quality) assessment [1 change]

Multiple study types will be potentially be included in this systematic review. Randomised controlled trials will be evaluated using the Cochrane Risk of Bias tool 2.0. Non-randomised studies will be assessed using the MINORS checklist.

Strategy for data synthesis

If the included quantitative studies are mostly of a similar design without significant heterogeneity, a meta-analysis will be conducted. In the case of a range of study designs and significant heterogeneity, a narrative synthesis approach will be taken to compare individual studies and the outcomes measured, and synthesise the key overall findings.

Analysis of subgroups or subsets

PCOs from included quantitative studies will be combined and analysed on an individual PCO level, if there are numerous studies measuring the same outcome(s).

Contact details for further information

Sam Merriel
s.w.d.merriel@exeter.ac.uk

Organisational affiliation of the review

University of Exeter Medical School

Review team members and their organisational affiliations [1 change]

Dr Sam Merriel. University of Exeter Medical School
Miss Victoria Hardy. Primary Care Unit, University of Cambridge
Professor Matthew Thompson. University of Washington
Professor Willie Hamilton. University of Exeter Medical School

Type and method of review [1 change]

Diagnostic, Narrative synthesis, Systematic review

Anticipated or actual start date

01 December 2018

Anticipated completion date

31 August 2019

Funding sources/sponsors

Dr Merriel and Miss Hardy are research fellows funded by CanTest, a Cancer Research UK Catalyst Award Programme. Prof Thompson is a co-investigator for CanTest. Prof Hamilton is co-PI for CanTest.

Conflicts of interest

None known

Language

English

Country

England

Stage of review [3 changes]

Review Completed published

Details of final report/publication(s) or preprints if available [1 change]

Samuel W.D. Merriel, Victoria Hardy, Matthew J. Thompson, Fiona M. Walter, Willie Hamilton. Patient-Centered Outcomes From Multiparametric MRI and MRI-Guided Biopsy for Prostate Cancer: A Systematic Review. Journal of the American College of Radiology (JACR). Volume 17, ISSUE 4, P486-495, April 01, 2020

Published:September 18, 2019. DOI:https://doi.org/10.1016/j.jacr.2019.08.031

https://www.jacr.org/article/S1546-1440(19)31032-4/fulltext

Subject index terms status

Subject indexing assigned by CRD

Subject index terms

Diagnostic Tests, Routine; Humans; Male; Narration; Outcome Assessment (Health Care); Prostatic Neoplasms

Date of registration in PROSPERO

21 November 2018

Date of first submission

09 November 2018

Stage of review at time of this submission [3 changes]

Stage	Started	Completed
Preliminary searches	Yes	Yes
Piloting of the study selection process	Yes	Yes
Formal screening of search results against eligibility criteria	Yes	Yes
Data extraction	Yes	Yes
Risk of bias (quality) assessment	Yes	Yes
Data analysis	Yes	Yes

Revision note

The systematic review is completed and published

The record owner confirms that the information they have supplied for this submission is accurate and complete and they understand that deliberate provision of inaccurate information or omission of data may be construed as scientific misconduct.
The record owner confirms that they will update the status of the review when it is completed and will add publication details in due course.

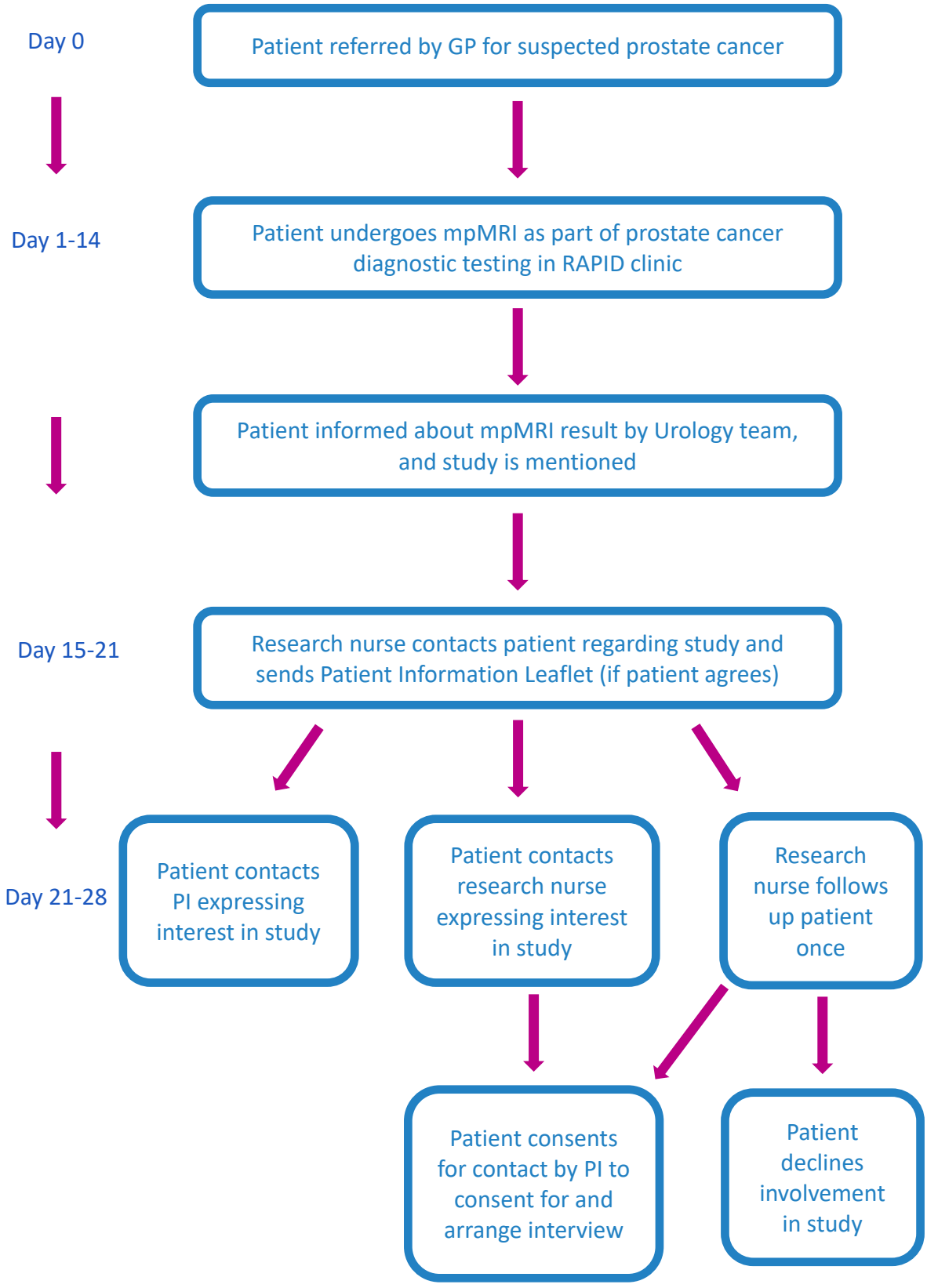
Versions

21 November 2018
13 December 2018
04 April 2019
28 July 2020

Chapter 3

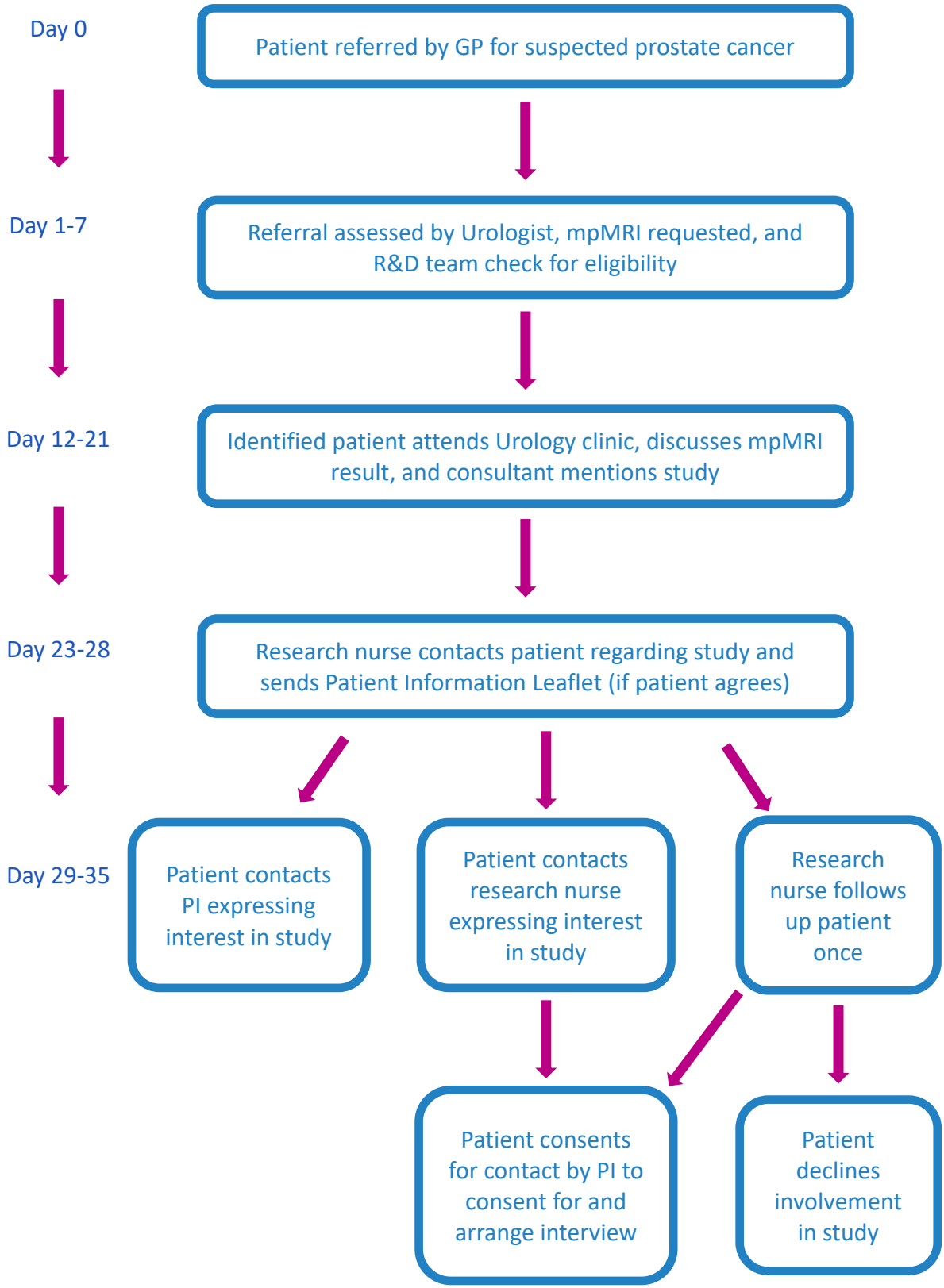
3.1 Patient participant recruitment flow diagram – Royal Devon & Exeter NHS Trust

STUDY FLOW CHART 1 – Patient participant recruitment at Imperial College Healthcare



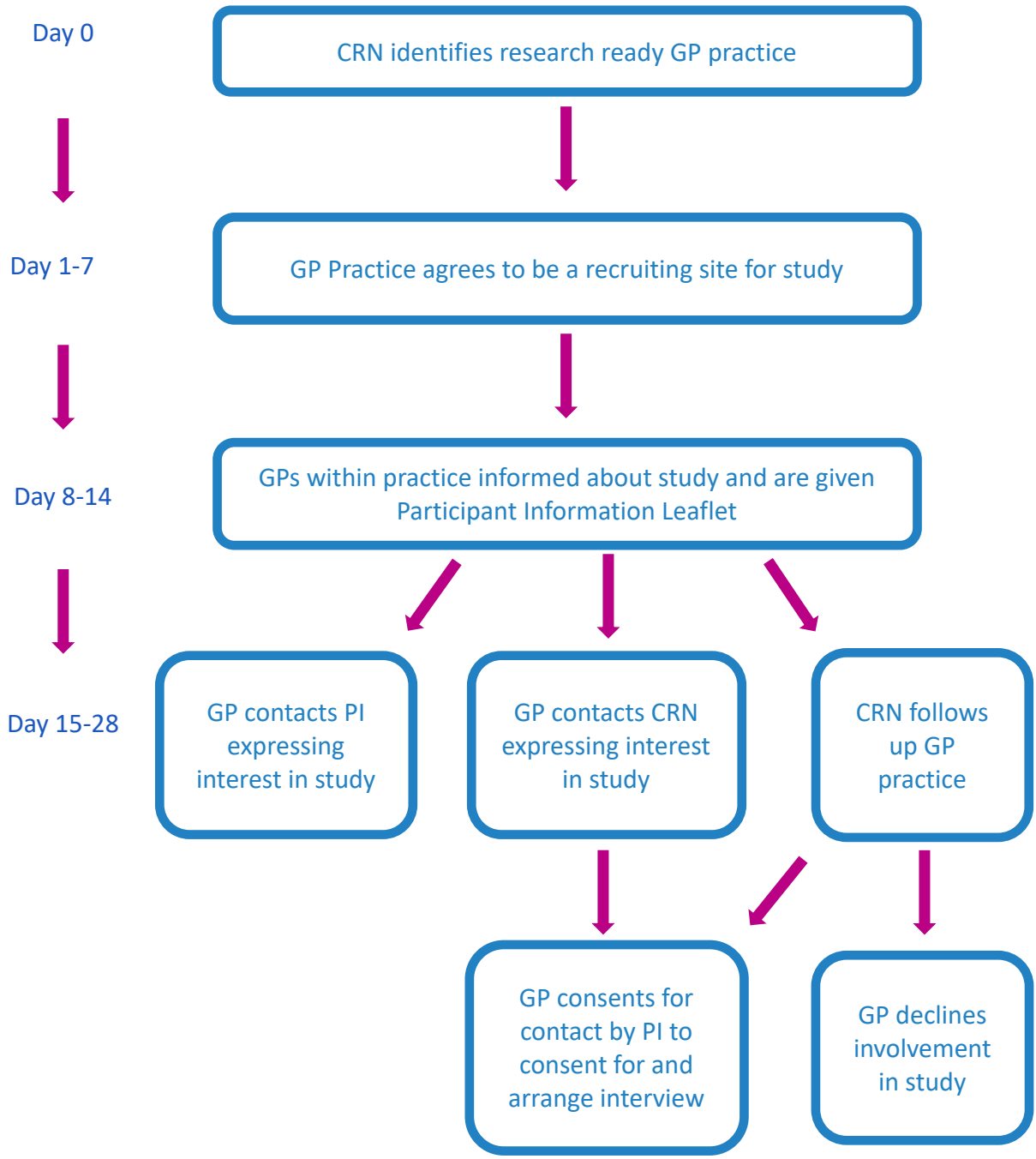
3.2 Patient participant recruitment flow diagram – Imperial College Healthcare NHS Trust

STUDY FLOW CHART 2 – Patient participant recruitment at Royal Devon & Exeter



3.3 GP participant recruitment flow diagram

STUDY FLOW CHART 3 – GP participant recruitment via Clinical Research Networks



3.4 Patient participant information leaflet

Participant Information Sheet

Patients

Title of Project: 'Acceptability, understanding and experience of diagnostic tests for prostate cancer: a qualitative study with patients and GPs'

Researcher name: Dr Sam Merriel

Invitation and brief summary:
A new technique for scanning the prostate for signs of cancer, called Multiparametric Magnetic Resonance Imaging (or mpMRI for short), is increasingly being used by hospital specialists when they see patients referred by their GP who may be showing symptoms/signs of prostate cancer. Studies of mpMRI suggest that if a scan shows no sign of prostate cancer, the chances of a cancer being missed are low, so mpMRI could potentially be used as a 'rule out' test to avoid some patients having to undergo a prostate biopsy. The researchers conducting this study are interested whether mpMRI could be used by a patient's GP for the same purpose.

We would like to invite you to take part in our research study. Before you decide we would like you to understand why the research is being done and what it would involve for you. Talk to others about the study if you wish. Please ask us if there is anything that is not clear.

Purpose of the research:
This study aims to understand patient's experiences of undergoing mpMRI as a test to diagnose prostate cancer. It forms part of a PhD for Dr Merriel, which is registered with the University of Exeter.

Why have I been approached?
You have been invited to participate as you have undergone an mpMRI because your doctor has suspected you may have prostate cancer.

Do I have to take part?
It is up to you to decide whether you wish to take part or not in the study. Please read this information sheet carefully. If you agree to take part, we will then ask you to give your consent. You are free to withdraw at any time, without giving a reason.

What would taking part involve?

You will be invited to give consent for an interview about your experiences of undergoing tests for possible prostate cancer, including mpMRI. Approximately 20 patient participants will be interviewed as part of this study. Interviews will be arranged either in person or over the phone/Skype (whatever is more convenient for you). They will be conducted by a member of the research team and should last no longer than 45 minutes. The interviews will be recorded using an encrypted audio recording device.

What are the possible benefits of taking part?
There may be no direct benefit for you as an individual for taking part in this study. However, we hope to understand whether mpMRI is an acceptable test for patients and GPs to rule out prostate cancer. Your participation will help us to gather evidence to guide GPs and specialists about the best way to use mpMRI from a patient's perspective.

What are the possible disadvantages and risks of taking part?
The researchers feel there is a low risk of harm for you by taking part in this study. Talking about cancer and health-related issues to do with the prostate can make some men uncomfortable or upset. If at any stage in your participation of this study you feel distressed, please inform the researcher immediately, whereupon the interview will cease, and the researcher may offer information about accessing support if needed.

What will happen if I don't want to carry on with the study?
You can withdraw from the study at any time without giving a reason. However, your rights to access, change or move your information are limited, as we need to manage your information in specific ways in order for the research to be reliable and accurate. If you withdraw from the study, we will keep the information about you that we have already obtained. To safeguard your rights, we will use the minimum personally identifiable information possible.

How will my information be kept confidential?
Due to recent regulatory changes in the way that data is processed (General Data Protection Regulation 2018 and the Data Protection Act 2018) the University of Exeter's lawful basis to process personal data for the purposes of carrying out research is termed as a 'task in the public interest'. Health and care research should serve the public interest, which means that we have to demonstrate that our research serves the interests of society as a whole. We do this by following the UK Policy Framework for Health and Social Care Research.

The University, which is the sponsor of this study, will endeavour to be transparent about its processing of your personal data and this information sheet should provide a clear explanation of this. If you do have any queries about the University's processing of your personal data that cannot be resolved by the research team, further information may be obtained from the University's Data Protection Officer by emailing dataprotection@exeter.ac.uk or at www.exeter.ac.uk/dataprotection. If you have any concerns about how the data is controlled and managed for this study then you can also contact the Sponsor Representative, Pam Baxter, Senior Research Governance Officer, whose details are at the end of the information sheet. If you are not satisfied with our response or believe we are processing your personal data in a way that is not lawful you can complain to the Information Commissioner's Office (ICO).

For the purposes of this study we will also use consent to protect your confidentiality and provide you with choice in your participation. All information collected in this study will be kept strictly confidential and stored either on an encrypted password protected computer, or in a locked cabinet at the University which can only be accessed by the researchers. You will be allocated a unique participant number, which will ensure the information from your interview will be protected. Individuals from the University of Exeter and regulatory organisations may look at your research records to check the accuracy of the research study. The only people in the University of Exeter who will have access to information that identifies you will be people who need to contact you if they need to audit the data collection process. The people who analyse the information will not be able to identify you and will not be able to find out your name or contact details. Any personally identifiable information will be stored separately and securely from information obtained from the research, including your name and contact details, and will be securely destroyed 12 calendar months after the interview has been conducted. All data collected for this study will be archived on University of Exeter servers and in locked filing cabinets in University offices for five years, and then destroyed.

Will I receive any payment for taking part?

Reasonable travel costs for any travel incurred to participate in an interview will be reimbursed. In addition, you will be offered a £20 gift voucher at the conclusion of the interview in recognition of your time taken to participate in this study.

What will happen to the results of this study?
The authors intend to publish the findings of this study in peer-reviewed journals and present the results at relevant conferences. You will not be identified in any way in these activities.

Where is data intended to or likely to be used for future research?
When you agree to take part in a research study, the information from the interviews may be provided to researchers running other research studies in this organisation and in other organisations. These organisations may be universities, NHS organisations or companies involved in health and care research in this country or abroad. Your information will only be used by organisations and researchers to conduct research in accordance with the UK Policy Framework for Health and Social Care Research**.**

This information will not identify you and will not be combined with other information in a way that could identify you. The information will only be used for the purpose of health and care research and cannot be used to contact you. It will not be used to make decisions about future services available to you, such as insurance.

Who is organising and funding this study?
Dr Sam Merriel from the Institute for Health Research at the University of Exeter is the lead researcher for this study. The authors have received funding from Cancer Research UK through the CanTest Catalyst Award (www.cantest.org).

Who has reviewed this study?
The NHS Research Ethics Committee and Health Research Authority Approval programme have reviewed the research and provided HRA Approval. The University of Exeter Research Ethics Committee have also reviewed the research.

Further information and contact details
If you have any further questions or concerns, please feel free to contact Dr Sam Merriel via telephone 01392 726002 or email s.w.d.merriel@exeter.ac.uk or Professor William Hamilton (main supervisor) via telephone 01392 726097 or email w.hamilton@exeter.ac.uk

If you have any concerns you don't want to discuss with the researchers, or wish to make a formal complaint about this study, please contact Ms Pam Baxter (details below)

Ms Pam Baxter
Senior Research Governance Officer
University of Exeter
Research Ethics and Governance Office
Lafrowda House
St Germans Road
Exeter
EX4 6TL
Tel: 01392 723588
Email: p.r.baxter2@exeter.ac.uk

Thank you for your interest in this study.

3.5 GP participant information leaflet

Participant Information Sheet

General Practitioners

Title of Project: 'Acceptability, understanding and experience of diagnostic tests for prostate cancer: a qualitative study with patients and GPs'

Researcher name: Dr Sam Merriel

Invitation and brief summary:
A new technique for scanning the prostate for signs of cancer, called Multiparametric Magnetic Resonance Imaging (mpMRI), is increasingly being used by hospital specialists when they see patients referred by their GP who may be showing symptoms/signs of prostate cancer. Studies of mpMRI suggest that if a scan shows no sign of prostate cancer, the chances of a cancer being missed are low, so mpMRI could potentially be used as a 'rule out' test to avoid some patients having to undergo a prostate biopsy. The researchers conducting this study are interested whether mpMRI could be used by a patient's GP for the same purpose.

We would like to invite you to take part in our research study. Before you decide we would like you to understand why the research is being done and what it would involve for you. Talk to others about the study if you wish. Please ask us if there is anything that is not clear.

Purpose of the research:
This study aims to understand GP's experience, knowledge and attitudes regarding mpMRI as a potential diagnostic test for prostate cancer. It forms part of a PhD for Dr Merriel, which is registered with the University of Exeter.

Why have I been approached?
You have been invited to participate as you have referred at least one patient for suspected prostate cancer to secondary care in the last 12 months.

Do I have to take part?
It is up to you to decide whether you wish to take part or not in the study. Please read this information sheet carefully. If you agree to take part, we will then ask you to give your consent. You are free to withdraw at any time, without giving a reason.

What would taking part involve?
You will be invited to give consent for an interview about your experiences, knowledge and understanding of diagnostic tests for possible prostate cancer, including mpMRI. Approximately

10 GP participants will be interviewed as part of this study. Interviews will be arranged either in person or over the phone/Skype (whatever is more convenient for you). They will be conducted by a member of the research team and should last no longer than 45 minutes. The interviews will be recorded using an encrypted audio recording device.

What are the possible benefits of taking part?
There may be no direct benefit for you as an individual for taking part in this study. However, we hope to understand whether mpMRI is an acceptable test for patients and GPs to rule out prostate cancer. Your participation will help us to gather evidence to guide GPs and specialists about the best way to use mpMRI.

What are the possible disadvantages and risks of taking part?
The researchers feel there is a low risk of harm for you by taking part in this study. Talking about cancer and related issues can make some research participants, including doctors, uncomfortable or upset. If at any stage in your participation of this study you feel distressed, please inform the researcher immediately, whereupon the interview will cease, and the researcher may offer information about accessing support if needed.

What will happen if I don't want to carry on with the study?
You can withdraw from the study at any time without giving a reason. However, your rights to access, change or move your information are limited, as we need to manage your information in specific ways in order for the research to be reliable and accurate. If you withdraw from the study, we will keep the information about you that we have already obtained. To safeguard your rights, we will use the minimum personally identifiable information possible.

How will my information be kept confidential?
Due to recent regulatory changes in the way that data is processed (General Data Protection Regulation 2018 and the Data Protection Act 2018) the University of Exeter's lawful basis to process personal data for the purposes of carrying out research is termed as a 'task in the public interest'. Health and care research should serve the public interest, which means that we have to demonstrate that our research serves the interests of society as a whole. We do this by following the UK Policy Framework for Health and Social Care Research.

The University, which is the sponsor of this study, will endeavour to be transparent about its processing of your personal data and this information sheet should provide a clear explanation of this. If you do have any queries about the University's processing of your personal data that cannot be resolved by the research team, further information may be obtained from the University's Data Protection Officer by emailing dataprotection@exeter.ac.uk or at www.exeter.ac.uk/dataprotection. If you have any concerns about how the data is controlled and managed for this study then you can also contact the Sponsor Representative, Pam Baxter, Senior Research Governance Officer, whose details are at the end of the information sheet. If you are not satisfied with our response or believe we are processing your personal data in a way that is not lawful you can complain to the Information Commissioner's Office (ICO).

For the purposes of this study we will also use consent to protect your confidentiality and provide you with choice in your participation. All information collected in this study will be kept strictly confidential and stored either on an encrypted password protected computer, or in a locked cabinet at the University which can only be accessed by the researchers. You will be allocated a unique participant number, which will ensure the information from your interview will be protected. Individuals from the University of Exeter and regulatory organisations may look at your research records to check the accuracy of the research study. The only people in the University of Exeter who will have access to information that identifies you will be people who need to contact you if they need to audit the data collection process. The people who analyse the information will not be able to identify you and will not be able to find out your name or contact details. Any personally identifiable information will be stored separately and securely from information obtained from the research, including your name and contact details, and will be securely destroyed 12 calendar months after the interview has been conducted. All data collected for this study will be archived on University of Exeter servers electronically for five years, and then destroyed.

Will I receive any payment for taking part?

Reasonable travel costs for any travel incurred to participate in an interview will be reimbursed. In addition, your practice will be reimbursed at the conclusion of the interview in recognition of your time taken to participate in this study.

What will happen to the results of this study?
The authors intend to publish the findings of this study in peer-reviewed journals and present the results at relevant conferences. You will not be identified in any way in these activities.

Where is data intended to or likely to be used for future research?
When you agree to take part in a research study, the information from the interviews may be provided to researchers running other research studies in this organisation and in other organisations. These organisations may be universities, NHS organisations or companies involved in health and care research in this country or abroad. Your information will only be used by organisations and researchers to conduct research in accordance with the UK Policy Framework for Health and Social Care Research**.** However, we will ask for your consent to do so.

This information will not identify you and will not be combined with other information in a way that could identify you. The information will only be used for the purpose of health and care research and cannot be used to contact you.

Who is organising and funding this study?
Dr Sam Merriel from the Institute for Health Research at the University of Exeter is the lead researcher for this study. The authors have received funding from Cancer Research UK through the CanTest Catalyst Award (www.cantest.org).

Who has reviewed this study?
The NHS Research Ethics Committee and Health Research Authority Approval programme have reviewed the research and provided HRA Approval. Local approval will be sought from GP Practices involved in the study before the research commences. The University of Exeter Research Ethics Committee have also reviewed the research.

Further information and contact details
If you have any further questions or concerns, please feel free to contact Dr Sam Merriel via telephone 01392 726002 or email s.w.d.merriel@exeter.ac.uk or Professor William Hamilton (main supervisor) via telephone 01392 726097 or email w.hamilton@exeter.ac.uk

If you have any concerns you don't want to discuss with the researchers, or wish to make a formal complaint about this study, please contact Ms Pam Baxter (details below)

Ms Pam Baxter
Senior Research Governance Officer
University of Exeter
Research Ethics and Governance Office
Lafrowda House
St Germans Road
Exeter
EX4 6TL
Tel: 01392 723588
Email: p.r.baxter2@exeter.ac.uk

Thank you for your interest in this study.

3.6 Participant consent form

Participant Identification Number:

CONSENT FORM

Title of Project: **'Acceptability, understanding and experience of diagnostic tests for prostate cancer: a qualitative study with patients and GPs'**

Name of Researcher: **Dr Sam Merriel**

1. I confirm that I have read the information sheet dated..... (version no.....) for the above project. I have had the opportunity to consider the information, ask questions and have had these answered satisfactorily. ☐

2. I understand that my participation is voluntary and that I am free to withdraw at any time without giving any reason and without my medical care or legal rights being affected. I acknowledge that withdrawal of my interview data may not be possible after anonymisation, which will occur one calendar month after the interview has been completed. ☐

3. I understand that relevant sections of the data collected during the study may be looked at by members of the research team, and/or individuals from the University of Exeter, where it is relevant to my taking part in this research. I give permission for these individuals to have access to these records. ☐

4. I understand that my participation in an interview for this study will involve audio recordings of my voice, that will be transcribed verbatim and de-identified direct quotations from an interview I participate in may appear in publications related to the study. ☐

5. I agree to take part in the above project. ☐

Name of Participant	Date	Signature
Name of researcher taking consent	Date	Signature

When completed: 1 copy for participant; 1 copy for researcher/project file

3.7 Patient participant interview topic guide

Introduction (5mins)

Thank you for agreeing to participate in this interview.

Introduce myself and my role.

This study seeks to understand your knowledge and understanding of diagnostic tests for prostate cancer, and your experiences of the current prostate cancer diagnostic pathway in the region where you live. It is part of my PhD at the University of Exeter. This study has been funded by Cancer Research UK and has ethical approval from the NHS Health Research Authority and the University of Exeter.

As we've talked about with the consent form, participating in this study is voluntary and you can stop at any time. We want to know about your experiences and what you think, so there are no right or wrong answers.

This interview is being recorded for the purposes of qualitative analysis by the researchers. You can ask for the recording to be stopped at any time. What you say will be kept confidential and anonymous, unless we discuss something that suggests there is a significant risk to yourself or someone else. Everyone being interviewed will be asked the same questions, so if you don't have an answer to any of the questions that's fine, just say so and we can move on.

This interview study if focused on your experience of diagnostic test for prostate cancer. However, if you have a partner, family member or significant other who you wish to be present that's fine. Ideally, we would start the interview without them, and then invite them in later on. If you and they are happy for them to participate, they would need to complete a consent form as well.

Ensure participant has copy of participant information sheet

Answer any questions

Ensure consent form is completed correctly

Commence audio recording

Basic demographics (5 minutes)

"To start with, can you tell me a little bit about yourself and your background"

Check - Age, Ethnicity, City/town lived in

Prostate cancer diagnosis journey [Prior to test] (5-10 minutes)

"Now I would like to talk a bit about how you came to have tests for possible prostate cancer."

When did you first notice symptoms (if any)? Which symptoms were they?

How long until consulted you consulted your GP? What affected that decision?

How did GP assess? PSA? DRE?

Decision to refer – what do you remember about that discussion?

mpMRI for prostate cancer [Having test] (10-15 minutes)

"I would now like to ask some questions about having an MRI scan for possible prostate cancer."

What did you understand about having an MRI and why it is used?

What was your experience of having an MRI?

mpMRI result [After test] (10 minutes)

"If you are happy to discuss, I would like to ask a few questions about the results of your MRI scan and the next steps."

What was the result of your mpMRI? Did you understand it?

How much did you trust the findings?

How were the results communicated? Did you have any questions as a result?

What were you told about the results' meaning?

What else did you discuss with the specialist?

Doctor(s) involved in cancer diagnosis (5 minutes)

"Finally, I would like to ask about your thoughts or feedback about being investigated for possible prostate cancer."

What do you think the role of the GP should be?

Interview close (2 minutes)

Thank you for participating in this interview. The data you have provided will be transcribed under a pseudonym and analysed by the research team. You will be sent a final study report after the analysis has been completed.

If you have any questions or concerns about the study, please contact Ms Pam Baxter at the Research Ethics and Governance Office at the University of Exeter on 01392 723588 or via email p.r.baxter2@exeter.ac.uk Her details are on your patient information leaflet.

3.8 GP participant interview topic guide

Introduction (5mins)

Thank you for agreeing to participate in this interview.

Introduce myself and my role.

This study seeks to understand your knowledge and understanding of diagnostic tests for prostate cancer, and your experiences of the current prostate cancer diagnostic pathway in the region where you work. It is part of my PhD at the University of Exeter. This study has been funded by Cancer Research UK and has ethical approval from the NHS Health Research Authority and the University of Exeter.

As we've talked about with the consent form, participating in this study is voluntary and you can stop at any time. We want to know about your experiences and what you think, so there are no right or wrong answers.

This interview is being recorded for the purposes of qualitative analysis by the researchers. You can ask for the recording to be stopped at any time. What you say will be kept confidential and anonymous, unless we discuss something that suggests there is a significant risk to yourself or someone else. This interview is not assessing your clinical competence, and we want to hear about your approach and experiences. Everyone being interviewed will be asked the same questions, so if you don't have an answer to any of the questions that's fine, just say so and we can move on.

This interview study if focused on your experience of diagnostic test for prostate cancer. However, if you have a partner, family member or significant other who you wish to be present that's fine. Ideally, we would start the interview without them, and then invite them in later on. If you and they are happy for them to participate, they would need to complete a consent form as well.

Ensure participant has copy of participant information sheet

Answer any questions

Ensure consent form is completed correctly

Commence audio recording

Basic demographics (5 minutes)

"To start with, can you tell me a little bit about yourself and your background"
Age, Gender, Years of GP experience, Main CCG area you work in

Decision to refer for suspected prostate cancer (10-15 minutes)

"I would like to now move on to your current practice around referring men with suspected prostate cancer for further investigation"

"What symptoms/signs do you enquire about when assessing a man for suspected prostate cancer? How do they affect your decision to refer?"

PSA use – When would you offer it to a man? What are the important points you make about PSA when counselling a man about the test? What do you do with a negative PSA?

"What other factors, if any, affect your decision to refer a man for further investigation?"

"What are the key points you discuss with men when making a referral?"

Diagnostic testing for prostate cancer (15-20 minutes)

"Now I would like to ask some questions about diagnostic tests for prostate cancer."

> What is your experience of the prostate cancer diagnosis pathway in your region?
> What do you know about current diagnostic tests? How accurate do you believe current diagnostic tests are for prostate cancer?

Do you feel incorporating mpMRI into the prostate cancer diagnosis pathway would be beneficial for patients? Do you believe it could be cost effective?

What would be the characteristics of an ideal diagnostic test for prostate cancer?

Men diagnosed with prostate cancer (5-10 minutes)

"Finally, I would like to ask about any of your patients who have been diagnosed with prostate cancer"

Are you aware of any of your patients diagnosed with low-grade prostate cancer?

If so, what has been the impact of the diagnosis on patient?

Are you aware of any of your patients being put on active surveillance – what is your experience of interacting with these men after diagnosis?

Interview close (2 minutes)

Thank you for participating in this interview. The data you have provided will be transcribed under a pseudonym and analysed by the researchers. You will be sent a final study report after the analysis has been completed. If you have any questions or concerns about the study, please contact Ms Pam Baxter at the Research Ethics and Governance Office at the University of Exeter on 01392 723588 or via email p.r.baxter2@exeter.ac.uk

3.9 Confirmation of ethical approval

Dr Samuel W D Merriel
Clinical Senior Research Fellow
1.18 College House
St Luke's Campus, University of Exeter
Heavitree Road, Exeter
EX1 2LU

Email: hra.approval@nhs.net
Research-permissions@wales.nhs.uk

16 May 2019

Dear Dr Merriel

HRA and Health and Care Research Wales (HCRW) Approval Letter

Study title:	**'Acceptability, understanding and experience of diagnostic tests for prostate cancer: a qualitative study with patients and GPs'**
IRAS project ID:	**259602**
Protocol number:	**1819/03**
REC reference:	**19/SW/0040**
Sponsor	**University of Exeter**

I am pleased to confirm that HRA and Health and Care Research Wales (HCRW) Approval has been given for the above referenced study, on the basis described in the application form, protocol, supporting documentation and any clarifications received. You should not expect to receive anything further relating to this application.

How should I continue to work with participating NHS organisations in England and Wales?
You should now provide a copy of this letter to all participating NHS organisations in England and Wales, as well as any documentation that has been updated as a result of the assessment.

Participating NHS organisations in England and Wales **will not** be required to formally confirm capacity and capability before you may commence research activity at site. As such, you may commence the research at each organisation 35 days following sponsor provision to the site of the local information pack, so long as:

- You have contacted participating NHS organisations (see below for details)
- The NHS organisation has not provided a reason as to why they cannot participate
- The NHS organisation has not requested additional time to confirm.

You may start the research prior to the above deadline if the site positively confirms that the research may proceed.

If not already done so, you should now provide the local information pack for your study to your participating NHS organisations. A current list of R&D contacts is accessible at the NHS RD Forum website and these contacts MUST be used for this purpose. After entering your IRAS ID you will be able to access a password protected document (password: **Redhouse1**). The password is updated on a monthly basis so please obtain the relevant contact information as soon as possible; please do not hesitate to contact me should you encounter any issues.

Commencing research activities at any NHS organisation before providing them with the full local information pack and allowing them the agreed duration to opt-out, or to request additional time (unless you have received from their R&D department notification that you may commence), is a breach of the terms of HRA and HCRW Approval. Further information is provided in the "*summary of assessment*" section towards the end of this document.

It is important that you involve both the research management function (e.g. R&D office) supporting each organisation and the local research team (where there is one) in setting up your study. Contact details of the research management function for each organisation can be accessed here.

How should I work with participating NHS/HSC organisations in Northern Ireland and Scotland?
HRA and HCRW Approval does not apply to NHS/HSC organisations within the devolved administrations of Northern Ireland and Scotland.

If you indicated in your IRAS form that you do have participating organisations in either of these devolved administrations, the final document set and the study wide governance report (including this letter) has been sent to the coordinating centre of each participating nation. You should work with the relevant national coordinating functions to ensure any nation specific checks are complete, and with each site so that they are able to give management permission for the study to begin.

Please see IRAS Help for information on working with NHS/HSC organisations in Northern Ireland and Scotland.

How should I work with participating non-NHS organisations?
HRA and HCRW Approval does not apply to non-NHS organisations. You should work with your non-NHS organisations to obtain local agreement in accordance with their procedures.

What are my notification responsibilities during the study?
The document "*After Ethical Review – guidance for sponsors and investigators*", issued with your REC favourable opinion, gives detailed guidance on reporting expectations for studies, including:

- Registration of research
- Notifying amendments
- Notifying the end of the study

The HRA website also provides guidance on these topics, and is updated in the light of changes in reporting expectations or procedures.

I am a participating NHS organisation in England or Wales. What should I do once I receive this letter?
You should work with the applicant and sponsor to complete any outstanding arrangements so you are able to confirm capacity and capability in line with the information provided in this letter.

The sponsor contact for this application is as follows:

Name: Ms Pam Baxter
Email: p.r.baxter2@exeter.ac.uk

Who should I contact for further information?
Please do not hesitate to contact me for assistance with this application. My contact details are below.

Your IRAS project ID is **259602.** Please quote this on all correspondence.

Yours sincerely

Thomas Fairman
HRA Assessor

Email: hra.approval@nhs.net

Copy to: *Ms Pam Baxter, University of Exeter, (Sponsor Contact)*

List of Documents

The final document set assessed and approved by HRA and HCRW Approval is listed below.

Document	*Version*	*Date*
Costing template (commercial projects) [Primary care costings]	1.0	30 January 2019
Covering letter on headed paper [Cover letter]	1.0	30 January 2019
Evidence of Sponsor insurance or indemnity (non NHS Sponsors only) [Professional indemnity]	1.0	30 January 2019
HRA Schedule of Events [CRN]	1.0	21 February 2019
HRA Schedule of Events [Hospitals]	1.0	21 February 2019
HRA Statement of Activities [CRN]	1.0	21 February 2019
HRA Statement of Activities [Hospitals]	1.0	21 February 2019
Interview schedules or topic guides for participants [GP interview schedule]	1.0	30 January 2019
Interview schedules or topic guides for participants [Patient interview schedule]	1.0	30 January 2019
Interview schedules or topic guides for participants [GP Interview Schedule]	1.1	09 April 2019
Interview schedules or topic guides for participants [Patient Interview Schedule]	1.1	09 April 2019
IRAS Application Form [IRAS_Form_31012019]		31 January 2019
IRAS Application Form XML file [IRAS_Form_31012019]		31 January 2019
Letter from sponsor [Letter from sponsor]		08 January 2019
Participant consent form [GP consent form]	1.0	30 January 2019
Participant consent form [Patient consent form]	1.0	30 January 2019
Participant consent form [Patient Significant Other Consent Form]	1.0	30 January 2019
Participant information sheet (PIS) [Patient PIS]	1.0	30 January 2019
Participant information sheet (PIS) [GP PIS]	1.1	08 April 2019
Participant information sheet (PIS) [Patient PIS]	1.1	08 April 2019
Participant information sheet (PIS) [Patient Significant Other PIS]	1.1	08 April 2019
Referee's report or other scientific critique report [Peer review feedback]		19 February 2018
Referee's report or other scientific critique report [Peer review feedback]		19 February 2018
Research protocol or project proposal [Research protocol]	1.0	30 January 2019
Summary CV for Chief Investigator (CI) [Dr Sam Merriel CV]		
Summary CV for student [Dr Sam Merriel CV]		
Summary CV for supervisor (student research) [Prof Willie Hamilton CV]	1.0	30 January 2019
Summary CV for supervisor (student research) [Dr Fiona Walter CV]	1.0	30 January 2019
Summary CV for supervisor (student research) [Dr Alice Forster CV]	1.0	30 January 2019
Summary, synopsis or diagram (flowchart) of protocol in non technical language [Lay summary]	1.0	30 January 2019

Summary of assessment

The following information provides assurance to you, the sponsor and the NHS in England and Wales that the study, as assessed for HRA and HCRW Approval, is compliant with relevant standards. It also provides information and clarification, where appropriate, to participating NHS organisations in England and Wales to assist in assessing, arranging and confirming capacity and capability.

Assessment criteria

Section	Assessment Criteria	Compliant with Standards	Comments
1.1	IRAS application completed correctly	Yes	No comments
2.1	Participant information/consent documents and consent process	Yes	No comments
3.1	Protocol assessment	Yes	No comments
4.1	Allocation of responsibilities and rights are agreed and documented	Yes	There are two site types participating in the study CRN sites and Hospital Sites. A statement of activities has been submitted for each site type and the sponsor is not requesting and does not expect any other site agreements to be used. Although formal confirmation of capacity and capability is not expected of all or some organisations participating in this study, and such organisations would therefore be assumed to have confirmed their capacity and capability should they not respond to the contrary, we would ask that these organisations pro-actively engage with the sponsor in order to confirm at as early a date as possible. Confirmation in such cases should be by email to the CI and Sponsor confirming participation based on the

Section	Assessment Criteria	Compliant with Standards	Comments
			relevant Statement of Activities and information within this letter.
4.2	Insurance/indemnity arrangements assessed	Yes	Where applicable, independent contractors (e.g. General Practitioners) should ensure that the professional indemnity provided by their medical defence organisation covers the activities expected of them for this research study
4.3	Financial arrangements assessed	Yes	External study funding has been secured from Cancer Research UK. No study funding will be provided to sites, as detailed in the HRA Statement of Activities.
5.1	Compliance with the Data Protection Act and data security issues assessed	Yes	No comments
5.2	CTIMPS – Arrangements for compliance with the Clinical Trials Regulations assessed	Not Applicable	No comments
5.3	Compliance with any applicable laws or regulations	Yes	No comments
6.1	NHS Research Ethics Committee favourable opinion received for applicable studies	Yes	No comments
6.2	CTIMPS – Clinical Trials Authorisation (CTA) letter received	Not Applicable	No comments
6.3	Devices – MHRA notice of no objection received	Not Applicable	No comments
6.4	Other regulatory approvals and authorisations received	Not Applicable	No comments

Participating NHS Organisations in England

This provides detail on the types of participating NHS organisations in the study and a statement as to whether the activities at all organisations are the same or different.

The following site types participating in the study.

CRN Sites – NIHR CRN sites (South West Peninsula, and North West London) will promote the study to research active GP practices in their regions, and identify potential GP practices from which to recruit GPs to participate. The practices will contact the CI if they are interested in participating.

Hospital Sites – Hospital sites (Royal Devon & Exeter NHS Foundation Trust, and Imperial College Healthcare NHS Trust) will identify potentially eligible patient participants and introduce the study to the patients.

The Chief Investigator or sponsor should share relevant study documents with participating NHS organisations in England and Wales in order to put arrangements in place to deliver the study. The documents should be sent to both the local study team, where applicable, and the office providing the research management function at the participating organisation. Where applicable, the local LCRN contact should also be copied into this correspondence.

If chief investigators, sponsors or principal investigators are asked to complete site level forms for participating NHS organisations in England and Wales which are not provided in IRAS or on the HRA or HCRW websites, the chief investigator, sponsor or principal investigator should notify the HRA immediately at hra.approval@nhs.net, or HCRW at Research-permissions@wales.nhs.uk. We will work with these organisations to achieve a consistent approach to information provision.

Principal Investigator Suitability

This confirms whether the sponsor position on whether a PI, LC or neither should be in place is correct for each type of participating NHS organisation in England and the minimum expectations for education, training and experience that PIs should meet (where applicable).

A Local Collaborator should be appointed at study sites participating in this study.

GCP training is not a generic training expectation, in line with the HRA/HCRW/MHRA statement on training expectations.

HR Good Practice Resource Pack Expectations

This confirms the HR Good Practice Resource Pack expectations for the study and the pre-engagement checks that should and should not be undertaken

As a non-commercial study undertaken by local staff, it is unlikely that letters of access or honorary research contracts will be applicable.

Where arrangements are not already in place, researchers undertaking any of the research activities listed in A18 of the IRAS form would be expected to obtain a Letter of Access. This would be on the basis of a Research Passport (if university employed) or an NHS to NHS confirmation of pre-engagement checks letter (if NHS employed). These should confirm DBS checks and occupational

health clearance.

Where researchers involvement is limited to working with staff (with no involvement of patients/service users as participants), who will participate in interviews and focus groups held in non-clinical areas, no research specific access arrangements are required and no additional pre-engagement checks are necessary.

Other Information to Aid Study Set-up

This details any other information that may be helpful to sponsors and participating NHS organisations in England to aid study set-up.

The applicant has indicated that they do intend to apply for inclusion on the NIHR CRN Portfolio.

Chapter 4

4.1 Full database search strategy and hits

Medline

	Search term	Hits
1.	(prostat* adj3 (cancer* or carcinoma* or malignan* or tumo?r* or neoplas* or adeno*)).af.	187609
2.	prostatic neoplasms.af.	128153
3.	exp Prostatic Intraepithelial Neoplasia/	1365
4.	exp PROSTATE/	35905
5.	or/1-4	204278
6.	Economics/	27917
7.	exp "costs and cost analysis"/	236393
8.	Economics, Dental/	1911
9.	exp economics, hospital/	24514
10.	Economics, Medical/	9077
11.	Economics, Nursing/	3999
12.	Economics, Pharmaceutical/	2938
13.	(economic$ or cost or costs or costly or costing or price or prices or pricing or pharmacoeconomic$).ti,ab.	794486
14.	(expenditure$ not energy).ti,ab.	29812
15.	value for money.ti,ab.	1692
16.	budget$.ti,ab.	29253
17.	or/6-16	946393
18.	((energy or oxygen) adj cost).ti,ab.	4104
19.	(metabolic adj cost).ti,ab.	1416
20.	((energy or oxygen) adj expenditure).ti,ab.	25027
21.	or/18-20	29566
22.	17 not 21	939546
23.	letter.pt.	1087262
24.	editorial.pt.	533922
25.	historical article.pt.	358935
26.	or/23-25	1960536
27.	22 not 26	903243
28.	exp animals/ not humans/	4712329
29.	27 not 28	846074
30.	bmj.jn	79957
31.	"cochrane database of systematic reviews".jn.	14876
32.	health technology assessment winchester england.jn.	1321
33.	or/30-32	96154
34.	29 not 33	839828
35.	"biparametric MRI".mp.	69
36.	bpMRI.mp.	48
37.	exp Diffusion magnetic resonance imaging/	27681
38.	35 or 36 or 37	27757
39.	multiparametric magnetic resonance imaging.mp.	1386

40. mpMRI.mp. [mp=title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, organism supplementary concept word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]	1041
41. magnetic resonance imaging.mp. [mp=title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, organism supplementary concept word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]	514658
42. mri.mp. [mp=title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, organism supplementary concept word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]	248691
43. or/39-42	572044
44. 38 or 43	575878
45. 5 and 34 and 44	325

EMBASE

	Search term	**Hits**
1.	Health Economics.af	70688
2.	Exp Economic Evaluation/	305387
3.	exp Health Care Cost/	290365
4.	pharmacoeconomics/	7301
5.	1 or 2 or 3 or 4	558324
6.	(econom$ or cost or costs or costly or costing or price or prices or pricing or pharmacoeconomic$).ti,ab.	1063793
7.	(expenditure$ not energy).ti,ab.	40291
8.	(value adj2 money).ti,ab.	2430
9.	budget$.ti,ab.	38479
10.	6 or 7 or 8 or 9	1099995
11.	5 or 10	1340159
12.	letter.pt.	1120824
13.	editorial.pt.	656739
14.	note.pt.	801764
15.	12 or 13 or 14	2579327
16.	11 not 15	1236647
17.	(metabolic adj cost).ti,ab.	1507
18.	((energy or oxygen) adj cost).ti,ab.	4318
19.	((energy or oxygen) adj expenditure).ti,ab.	31676
20.	17 or 18 or 19	36399
21.	16 not 20	1229225
22.	animal/	1459554
23.	exp animal experiment/	2559977
24.	nonhuman/	6213893

25. (rat or rats or mouse or mice or hamster or hamsters or animal or animals or dog or dogs or cat or cats or bovine or sheep).ti,ab,sh.	5710948
26. 22 or 23 or 24 or 25	8911462
27. exp human/	21024838
28. human experiment/	500972
29. 27 or 28	21026436
30. 26 not (26 and 29)	6511540
31. 21 not 30	1116161
32. 0959-8146.is.	61726
33. 1469-493X or 1366-5278).is.	22875
34. 1756-1833.en.	33354
35. 32 or 33 or 34	106843
36. 31 not 35	1108855
37. conference abstract.pt.	3816855
38. 36 not 37	903809
39. (prostat* adj3 (cancer* or carcinoma* or malignan* or tumo?r* or neoplas* or adeno*)).tw.	213809
40. Prostate.sh.	46299
41. 39 or 40	239670
42. "multiparametric magnetic resonance imaging".tw.	1753
43. mpMRI.tw.	2353
44. "magnetic resonance imaging".tw.	274646
45. mri.tw.	414342
46. "multiparametric mri".tw.	2511
47. 42 or 43 or 44 or 45 or 46	561594
48. bpmri.mp.	58
49. exp diffusion weighted imaging/	41638
50. "biparametric mri".mp.	82
51. "biparametric magnetic resonance imaging".mp.	46
52. 48 or 50 or 51	118
53. 47 or 52	561595
54. 47 or 49 or 52	577791
55. 38 and 41 and 54	310

PsycINFO

	Search term	**Hits**
1.	Prostate.af.	21759
2.	(prostat* adj3 (cancer* or carcinoma* or malignan* or tumo?r* or neoplas* or adeno*)).af.	19267
3.	1 or 2	22019
4.	mpMRI.af.	1
5.	mri.af.	130514
6.	"multiparametric magnetic resonance imaging".af.	45
7.	"multiparametric mri".af.	235
8.	"magnetic resonance imaging".af.	147502
9.	4 or 5 or 6 or 7 or 8	192087
10.	"costs and cost analysis"/	16711

11. "Cost Containment"/	611
12. (economic adj2 evaluation$).ti,ab.	1725
13. (economic adj2 analy$).ti,ab.	1549
14. (economic adj2 (study or studies)).ti,ab.	811
15. (cost adj2 evaluation$).ti,ab.	342
16. (cost adj2 analy$).ti,ab.	3736
17. (cost adj2 (study or studies)).ti,ab.	878
18. (cost adj2 effective$).ti,ab.	15432
19. (cost adj2 benefit$).ti,ab.	3514
20. (cost adj2 utili$).ti,ab.	1280
21. (cost adj2 minimi$).ti,ab.	374
22. (cost adj2 consequence$).ti,ab.	116
23. (cost adj2 comparison$).ti,ab.	188
24. (cost adj2 identificat$).ti,ab.	26
25. (pharmacoeconomic$ or pharmaco-economic$).ti,ab.	315
26. Or/10-25	35113
27. (task adj2 cost$).ti,ab,id.	648
28. (switch$ adj2 cost$).ti,ab,id.	1356
29. (metabolic adj cost).ti,ab,id.	103
30. ((energy or oxygen) adj cost).ti,ab,id.	287
31. ((energy or oxygen) adj expenditure).ti,ab,id.	2734
32. or/27-31	4836
33. (animal or animals or rat or rats or mouse or mice or hamster or hamsters or dog or dogs or cat or cats or bovine or sheep or ovine or pig or pigs).ab,ti,id,de.	354985
34. editorial.dt.	44086
35. letter.dt.	22468
36. dissertation abstract.pt.	498253
37. or/33-36	897583
38. (0003-4819 or 0003-9926 or 0959-8146 or 0098-7484 or 0140-6736 or 0028-4793 or 1469-493X).is.	13343
39. 26 not (32 or 37 or 38)	30075
40. 3 and 9 and 39	14

Web of Science

	Search term	**Hits**
1.	TOPIC:(prostate) Indexes=SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH, ESCI Timespan=All years	275543
2.	TS=(cancer OR malignancy OR neoplas$ OR tumour OR adenocarcinoma) Indexes=SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH, ESCI Timespan=All years	3538950
3.	#1 and #2	230656
4.	TS=(MRI OR mpMRI OR "Magnetic Resonance Imaging" OR "Multiparametric MRI" OR "Multiparametric magnetic resonance imaging" OR bpMRI OR "Biparametric MRI") Indexes=SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH, ESCI Timespan=All years	445352

5. TS=(economic* or cost or costs or costly or costing or costed or price or prices or pricing or priced or discount or discounts or discounted or discounting or ration* or expenditure or expenditures or budget* or afford* or pharmacoeconomic or pharmaco-economic*) Indexes=SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH, ESCI Timespan=All years	3562854
6. TS=(markov* or monte carlo) Indexes=SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH, ESCI Timespan=All years	414269
7. TS=(decision near/2 (tree* or analy* or model*)) Indexes=SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH, ESCI Timespan=All years	97099
8. TS=(survival near/3 analys*) Indexes=SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH, ESCI Timespan=All years	66737
9. TS=(qol* or qoly or qolys or hrqol* or qaly or qalys or qale or qales) Indexes=SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH, ESCI Timespan=All years	63953
10. TS=((sensitivity analys*) or ("willingness to pay") or (quality-adjusted life year*) or (quality adjusted life year*) or (quality-adjusted life expectanc*) or (quality adjusted life expectanc*)) Indexes=SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH, ESCI Timespan=All years	467563
11. TS=utilit* Indexes=SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH, ESCI Timespan=All years	396051
12. TS=(valu*) Indexes=SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH, ESCI Timespan=All years	4564549
13. #4 or #5 or #6 or #7 or #8 or #9 or #10 or #11 or #12	8672201
14. #3 and #4 and #13	3804

CINAHL

Search term	**Hits**
1. MH “Economics+”	937591
2. MH "Financial Management+"	71012
3. MH "Financial Support+"	600298
4. MH "Financing, Organized+"	162919
5. MH "Business+"	171536
6. 2 or 3 or 4 or 5	935931
7. 1 not 6	111670
8. MH "Health Resource Allocation"	10004
9. MH "Health Resource Utilization"	20689
10. 8 or 9	30117
11. 7 or 10	132757
12. TI (cost or costs or economic* or pharmacoeconomic* or price* or pricing*) OR AB (cost or costs or economic* or pharmacoeconomic* or price* or pricing*)	247144
13. 11 or 12	326671
14. PT editorial	323566
15. PT letter	361775

16. PT commentary	369669
17. 14 or 15 or 16	816600
18. 13 not 17	302970
19. MH "Animal Studies"	138648
20. (ZT "doctoral dissertation") or (ZT "masters thesis")	26300
21. 18 not (19 or 20)	299343
22. Prostate	39569
23. 21 and 22	1483

Cochrane library

	Search term	Hits
1.	Prostate.ti.ab.kw.	19947
2.	mri.ti.ab.kw.	22387
3.	1 and 2	688

EconLIT

	Search term	Hits
1.	Prostate	111

ISRCTN

	Search term	Hits
1.	prostate.af.	350
2.	mri.af.	1015
3.	1 and 2	64

CRD Database

	Search term	Hits
1.	prostate.af.	1057
2.	mri.af.	610
3.	1 and 2	27

4.2 Published protocol on PROSPERO

Citation

Sam Merriel, Rebekah Hall, Willie Hamilton, Anne Spencer. Systematic review and narrative synthesis of economic evaluations of pre-biopsy magnetic resonance imaging (MRI) based prostate cancer diagnostic pathways. PROSPERO 2020 CRD42020182573 Available from: https://www.crd.york.ac.uk/prospero/display_record.php?ID=CRD42020182573

Review question

What is the evidence for the cost effectiveness of prostate cancer diagnostic pathways that include pre-biopsy multiparametric magnetic resonance imaging (mpMRI)?

Searches [1 change]

Bibliographic databases and other sources of publications that will be searched include MEDLINE, PubMed, the Cochrane Library, EMBASE, PsycINFO, CINAHL, PLoS, Web of Science, Scopus, BioMed Central, ClinicalTrials.gov, University of York CRD database, and Current Controlled Trials

Proven search strategies for clinical trials and systematic reviews from SIGN (http://www.sign.ac.uk/methodology/filters.html#random) will be used for MEDLINE, EMBASE and CINAHL

Search terms and MeSH headings will include MRI OR mpMRI OR “Magnetic Resonance Imaging” OR “Multiparametric MRI” OR “Multiparametric magnetic resonance imaging OR bpMRI OR “Biparametric MRI” AND prostate AND cancer OR malignancy OR neoplas$ OR tumour OR adenocarcinoma AND cost OR “cost effectiveness” OR “health economics” OR economics

Technical reports relating to prostate cancer will also be searched for on the National Institute for Health and Care Excellence (NICE) website

References will also be obtained by hand searching for relevant papers in the bibliographies of papers and reviews selected, along with citation searching via Science Citation Index

No limits will be set on date, language or country of publication

Types of study to be included

Included studies

Full economic evaluations

Excluded studies

Partial economic evaluations

Conference abstracts

Case series

Letters to the editor

Commentary pieces

Condition or domain being studied

Prostate cancer

Participants/population

Adult males with symptoms of a possible prostate cancer

Intervention(s), exposure(s)

Prostate cancer diagnostic pathway that incorporate pre-biopsy magnetic resonance imaging (MRI)

Comparator(s)/control

Prostate cancer diagnostic pathway that does not incorporate pre-biopsy MRI

Main outcome(s)

Cost effectiveness of pre-biopsy MRI-based diagnostic strategies compared to diagnostic strategies that do not include pre-biopsy MRI

Measures of effect

QALYs

Additional outcome(s)

Costs of MRI based pathway

Difference in quality life years gained

Diagnostic accuracy

Reduction in unnecessary biopsies

Measures of effect

Cost per QALY gained from diagnostic strategies incorporating MRI

ICER

QALYs from each pathway

Costs for each pathway

False negative rate

Proportion of biopsies avoided

Data extraction (selection and coding) [1 change]

Title and abstract of potentially relevant papers will then be screened by the principle researcher (SM) and a second reviewer (RH) independently using the inclusion/exclusion criteria. In the event of disagreement between reviewers of study eligibility on basis of title and abstract, the full paper will be reviewed and a decision reached by consensus with a third author (WH or AS).

Full paper review of all studies included on initial screening of title and abstract will be performed by SM and RH independently, with any disagreements resolved through discussion with a third author (WH or AS).

Data will be extracted from papers selected using a standardised form by the primary researcher (SM). A random selection of 10% of included full-text papers will be reviewed by a second reviewer (RH) to confirm accuracy of data extraction.

Basic study and methods data (first author, year of publication, country, study population, setting, modelling approach, time horizon, data sources, currency, discounting, and methods to address uncertainty) will be extracted from each included paper.

Modelled pathway characteristics will be extracted including items such as patient selection criteria, tests done, MRI approach (multiparametric or biparametric), biopsy approach (TRUS, MRI-guided, fusion) thresholds for diagnostic test, and non-MRI pathways used for comparison.

Primary and secondary outcome measures, including cost effectiveness measures in terms of ICERs or QALYs, will be extracted from each study.

The specified contact author of primary studies will be contacted in the event that additional data is required for the analysis. Disagreements will be resolved by consensus discussion, involving a third author (WH or AS)

Risk of bias (quality) assessment

Quality assessment of included economic evaluations associated with trials will be performed using the Critical Appraisal Skills Programme (CASP) checklist for Economic Evaluation.

Quality assessment of included economic evaluations using modelling will be performed using the framework developed by Philips et al.

Strategy for data synthesis [1 change]

A formal narrative synthesis of data extracted from included studies will be undertaken. The key parameters, assumptions, and outcome measures of the models used to estimate the cost-effectiveness of an MRI-based prostate cancer diagnosis pathway from each included study will be analysed and compared in tabular format to understand how the models differed. Estimated costs per QALY and/or ICERs from each study will also be analysed and compared, in the context of the different models used to make the estimates of cost effectiveness of MRI-based pathways for prostate cancer diagnosis.

A transferability assessment will be performed to estimate the relevance of the data available to a primary care patient population.

Analysis of subgroups or subsets [1 change]

Further analysis will be performed comparing the primary outcomes of MRI-based pathways that use the following investigation types for a diagnosis of prostate cancer =

1. Pre-biopsy MRI techniques - Multiparametric vs Biparametric

2. Biopsy technique - TRUS, MRI-guided, fusion

Contact details for further information

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Organisational affiliation of the review

University of Exeter Medical School

Review team members and their organisational affiliations

Dr Sam Merriel. University of Exeter Medical School
Miss Rebekah Hall. University of Exeter
Professor Willie Hamilton. University of Exeter
Assistant/Associate Professor Anne Spencer. University of Exeter

Type and method of review

Cost effectiveness, Diagnostic, Narrative synthesis, Systematic review

Anticipated or actual start date

18 May 2020

Anticipated completion date

31 August 2020

Funding sources/sponsors
SM and RH are supported by the CanTest Collaborative, which is funded by Cancer Research UK. WH is co-director of CanTest, and AS is an associate director.

Grant number(s)

State the funder, grant or award number and the date of award

C8640/ Q37A23385

Conflicts of interest
None known

Language
English

Country
England

Stage of review
Review Ongoing

Subject index terms status
Subject indexing assigned by CRD

Subject index terms
Biopsy; Cost-Benefit Analysis; Humans; Magnetic Resonance Imaging; Male; Prostatic Neoplasms

Date of registration in PROSPERO
29 June 2020

Date of first submission
13 May 2020

Stage of review at time of this submission
The review has not started

Stage	Started	Completed
Preliminary searches	No	No
Piloting of the study selection process	No	No
Formal screening of search results against eligibility criteria	No	No
Data extraction	No	No
Risk of bias (quality) assessment	No	No
Data analysis	No	No

The record owner confirms that the information they have supplied for this submission is accurate and complete and they understand that deliberate provision of inaccurate information or omission of data may be construed as scientific misconduct.
The record owner confirms that they will update the status of the review when it is completed and will add publication details in due course.

Versions

29 June 2020

Chapter 5

5.1 Full database search strategy

Medline

1. (prostat* adj3 (cancer* or carcinoma* or malignan* or tumo?r* or neoplas* or adeno*)).tw.
2. Exp Prostatic neoplasms/
3. Exp Prostatic Intraepithelial Neoplasia/
4. Exp prostate/
5. OR/1-4
6. exp "Sensitivity and Specificity"/
7. sensitivity.tw.
8. specificity.tw.
9. ((pre-test or pretest) adj probability).tw.
10. post-test probability.tw.
11. predictive value$.tw.
12. likelihood ratio$.tw.
13. diagnos*.tw
14. accura*.tw
15. OR/6-14
16. “prostate specific antigen”.mp
17. PSA.mp
18. OR/16-17
19. 5 AND 15 AND 18 Hits = 15,673 (05/02/21)
20. LUTS.tw
21. “lower urinary tract symptoms”.tw
22. 20 or 21
23. 19 and 22 Hits = 234 (05/02/21)

EMBASE

1. (prostat* adj3 (cancer* or carcinoma* or malignan* or tumo?r* or neoplas* or adeno*)).tw.
2. Exp prostate/
3. 1 or 2
4. “prostate specific antigen”

5. PSA
6. 4 or 5
7. Sensitive:.tw.
8. Diagnostic accuracy.sh.
9. Diagnostic.tw.
10. 7 or 8 or 9
11. 3 and 6 and 10 Hits = 13429 (05/02/21)
12. LUTS.tw.
13. “lower urinary tract symptoms”.tw.
14. 12 or 13
15. 11 and 15 Hits = 153 (05/02/21)

CENTRAL

#1 MeSH descriptor: [Prostate] explode all trees

#2 MeSH descriptor: [Prostatic neoplasms] explode all trees

#3 MeSH descriptor: [Prostatic Intraepithelial Neoplasia] explode all trees

#4 Prostat*(cancer or neoplasm* or carcin* or tumour* or tumor* or malignan* or neoplasia or adenocarcinoma*): ti,ab,kw

#5 #1 or #2 or #3 or #4

#6 “prostate specific antigen”:ti,ab,kw

#7 (PSA) :ti,ab,kw

#8 #6 AND #7

#9 MeSH descriptor: [Diagnosis] explode all trees

#10 #5 AND #8 AND #9 Hits = 1418 (05/02/21)

#11 (LUTS):ti,ab,kw

#12 (“lower urinary tract symptoms”):ti,ab,kw

#13 #11 OR #12

#14 #10 AND #13 Hits = 36 (05/02/21)

Web of science

#1 TS = (Prostate)

#2 TS = (cancer OR malignancy OR neoplas$ OR tumour OR adenocarcinoma)

#3 #1 AND #2

#4 TS = (PSA)

#5 TS = “prostate specific antigen”

#6 #4 OR #5

#7 TS=(diagnos* or accura* or sensitivit* or specificit* or likelihood or "positive predictive value" or PPV or "negative predictive value" or PPV or precision)

#8 #3 AND #6 AND #7 Hits = 15,041 (05/02/21)

#9 TS = LUTS

#10 TS = “lower urinary tract symptoms”

#11 #9 OR #10

#12 #8 AND #11 Hits = 208 (05/02/21)

Full search Total hits = 45,561

+ LUTS search = 631

5.2 Published protocol on PROSPERO

Citation

Sam Merriel, Lucy Pocock, Sam Creavin, Emma Gilbert, Anne Spencer, Willie Hamilton. Systematic review of the diagnostic accuracy of prostate specific antigen (PSA) for prostate cancer detection in symptomatic patients. PROSPERO 2021 CRD42021257783 Available from: https://www.crd.york.ac.uk/prospero/display_record.php?ID=CRD42021257783

Review question

What is the evidence for the diagnostic accuracy of prostate specific antigen (PSA) for the detection of prostate cancer in males with symptoms possibly relating to an undiagnosed prostate cancer?

Searches

MEDLINE Ovid, EMBASE, the Cochrane Central Register of Controlled Trials (CENTRAL) and Web of Science databases will be utilised to identify relevant studies. Key search terms, informed by the Scottish Intercollegiate Guidelines Network (SIGN) search strategies and pre-existing systematic reviews in the field of prostate cancer, will be combined with MeSH terms for each database search. Hand-searching and snowballing of references from included studies will be performed to locate any other possibly relevant studies.

There will be no limits set on date of publication, language or study type for this review

Types of study to be included

Diagnostic accuracy studies

Condition or domain being studied

Prostate cancer

Participants/population

Male patients with no history of prostate cancer and lower urinary tract symptoms

Intervention(s), exposure(s)

Prostate specific antigen

Comparator(s)/control

Prostate biopsy (as reference standard)

Main outcome(s)

Prostate cancer diagnosis (any)

Clinically significant prostate cancer diagnosis (Gleason score ?7 / Gleason Grade Group ? 2)

Measures of effect

Sensitivity, Specificity, Positive Predictive Value, Negative Predictive Value

Additional outcome(s)

None

Data extraction (selection and coding)

Search hits from each database will be downloaded and combined into a review database managed in Mendeley Desktop. Each search hit will be screened against the inclusion/exclusion criteria by SM and LP reviewer independently based on title and abstract. Full text will be reviewed if a reviewer is unclear on the basis of title and abstract. Any discrepancies of study inclusion will be adjudicated by a 3rd author (WH or AS).

A pre-prepared proforma for data extraction will be used to collate data from each included study in the following fields: First author, Year of publication, Country(s), Patient population, Patient demographics,

type/number of symptoms, threshold for prostate cancer detection number of PSA tests performed, PSA result, definitions of diagnosis number of cancers diagnosed, cancer type, Gleason score / Grade Group, TNM stage, Sensitivity, Specificity, PPV, NPV

Risk of bias (quality) assessment
Risk of bias and applicability of all included studies will be assessed using the QUADAS-2 tool.

Strategy for data synthesis
Raw data extracted from included papers on PSA result and prostate cancer diagnoses will be extracted and combined into 2 x 2 tables to assess diagnostic accuracy. Measures of diagnostic accuracy will be determined for the following outcomes using bivariate mixed-effects regression:

Any prostate cancer diagnosis

Clinically significant prostate cancer diagnosis (GS ?7 / GGG ? 2)

Diagnostic accuracy measures for these outcome groups will be stratified by symptom type and PSA thresholds.

Analysis of subgroups or subsets
Not applicable

Contact details for further information
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Organisational affiliation of the review
University of Exeter Medical School

Review team members and their organisational affiliations
Dr Sam Merriel. University of Exeter Medical School
Dr Lucy Pocock. University of Bristol
Dr Sam Creavin. University of Bristol
Ms Emma Gilbert. University of Bristol
Professor Anne Spencer. University of Exeter
Professor Willie Hamilton. University of Exeter

Type and method of review
Diagnostic, Meta-analysis, Systematic review

Anticipated or actual start date
01 May 2021

Anticipated completion date
30 November 2021

Funding sources/sponsors
CanTest Collaborative (Cancer Research UK Catalyst Award)

Grant number(s)

State the funder, grant or award number and the date of award

C8640/a23385

Conflicts of interest

Language
English

Country
England

Stage of review
Review Ongoing

Subject index terms status
Subject indexing assigned by CRD

Subject index terms
Humans; Male; Prostate-Specific Antigen; Prostatic Neoplasms

Date of registration in PROSPERO
28 May 2021

Date of first submission
28 May 2021

Stage of review at time of this submission

Stage	Started	Completed
Preliminary searches	Yes	No
Piloting of the study selection process	Yes	No
Formal screening of search results against eligibility criteria	Yes	No
Data extraction	No	No
Risk of bias (quality) assessment	No	No
Data analysis	No	No

The record owner confirms that the information they have supplied for this submission is accurate and complete and they understand that deliberate provision of inaccurate information or omission of data may be construed as scientific misconduct.
The record owner confirms that they will update the status of the review when it is completed and will add publication details in due course.

Versions
28 May 2021