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

Volume 1 of 2

Submitted by Samuel William David Merriel to the University of Exeter
as a thesis for the degree of
Doctor of Philosophy in Medical Studies
In December 2021

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: 

Abstract

Background

Detection of prostate cancer in primary care relies on Digital Rectal Examination (DRE) and Prostate Specific Antigen (PSA), both of which have significant limitations. Magnetic Resonance Imaging (MRI) has emerged as a diagnostic test for prostate cancer that is more accurate than existing tests but is currently only used in secondary care. This PhD aimed to examine the potential impact of prostate MRI on the diagnosis of prostate cancer in primary care.

Methods

I performed systematic reviews with narrative syntheses to examine the evidence on patient centred outcomes (PCOs) from diagnostic tests for prostate cancer, including MRI, and the cost-effectiveness of prostate cancer diagnostic pathways that incorporate pre-biopsy MRI. I undertook a qualitative study employing one-to-one interviews of patients who had undergone prostate MRI and GPs who had recently referred men with suspected prostate cancer for diagnostic testing to explore the acceptability of prostate MRI as a diagnostic test and experiences of the prostate cancer diagnostic pathway. I completed an early economic evaluation of primary care prostate cancer diagnostic pathways incorporating prostate MRI using decision analytic modelling informed by a linked data approach.

Results

Prostate MRI and MRI-guided biopsy have more favourable PCOs compared to standard prostate biopsy techniques. Prostate MRI met most key constructs of acceptability for patients, whilst GPs had a spectrum of knowledge and understanding of prostate MRI as a diagnostic test for prostate cancer. Published evidence suggests MRI-based prostate cancer diagnostic pathways are cost-effective, although no studies incorporated primary care data. Modelling suggests implementing prostate MRI in primary care could reduce costs involved with prostate cancer diagnosis, without a significant utility detriment for patients.

Conclusion

Incorporating MRI into primary care as a diagnostic test for prostate cancer could reduce costs for the NHS and is acceptable to patients. Prior to implementation in primary care, feasibility, comparable diagnostic accuracy, GPs' clinical knowledge, and improved outcomes for patients must be demonstrated.

Acknowledgements

There are a number of people I need to thank for helping me along my journey in completing this PhD.

First and foremost, I want to sincerely thank my supervisors.

> Willie, you are a truly great mentor, a supportive senior colleague, and a friend (despite the constant jibes about my antipodean roots). If I turn out to be half as successful as you are in my career and my life, I will be a very lucky man.
>
> Fiona, you are an inspirational woman. Your drive and your passion shine through in everything you do. Your critical eye and constant urging to think of the next steps and the long game have kept pushing me to strive to be better.
>
> Anne, you are a very thoughtful and supportive person. You go above and beyond for all those around you, and I particularly appreciate all your efforts to help me enter the brave new world of health economics in the midst of a pandemic.

Thank you to the men who formed the patient & public involvement and engagement group that guided this PhD. Your humble insights and your personal stories helped shape this research, and your encouragement through the pandemic certainly helped get this PhD over the line.

Paul Greensmith	Robert Griffin
Fred Miller	Peter Buttle
Alan Cleverley	Dave Butterworth
Nick Taylor	Tony Wellingham

Thank you to all my fellow academics that assisted with different aspects of my PhD. I'm so grateful for each of you giving your precious time to help shape this thesis.

Matthew Thompson	Victoria Hardy
Stephanie Archer	Alice Forster
John McGrath	David Eldred-Evans
Hashim Ahmed	Rebekah Hall
Lucy Pocock	Sam Creavin
Emma Gilbert	Sarah Price

I must say thank you to my family. My wife, Abi, for your love and support. My boys, William and Edward, for making life fun. My parents and siblings for being so encouraging. The Smith family for accepting me as one of your own and helping Abi and I pursue our careers.

And thank you, for taking the time to read this PhD. I hope you learn something.

Table of contents

List of tables

List of figures

Abbreviations

2WW – Two Week Wait

AHRQ – Agency for Healthcare Research and Quality

AI – Artificial Intelligence

AMSTAR – A Measurement Tool to Assess systematic Reviews

AS – Active Surveillance

ASIR – Age-standardised incidence rate

AUC – Area Under the Curve

AUD – Australian Dollars

BME – Black and Minority Ethnic

BPH – Benign Prostatic Hypertrophy

bpMRI – Biparametric Magnetic Resonance Imaging

CAD – Canadian Dollars

CADTH – Canadian Agency for Drugs and Technology in Health

CAP – Cluster randomised trial of PSA testing for prostate cancer

CASP – Critical Appraisal Skills Programme

CCG – Clinical Commissioning Group

CEA – Cost effectiveness analysis

CG27 – Clinical Guideline 27

CI – Confidence Interval

CINAHL – Cumulative Index of Nursing and Allied Health Literature

COREQ – Consolidated criteria for reporting qualitative research

CPRD – Clinical Practice Research Datalink

CRD – Centre for Reviews and Dissemination

CRN – Clinical Research Network

CRPC – Castration Resistant Prostate Cancer

CRUK – Cancer Research UK

CS – Clinically significant

CT – Computerised Tomography

DCE – Dynamic Contrast-Enhanced

DI – Diagnostic Interval

DRE – Digital Rectal Examination

DSA – Deterministic Sensitivity Analysis

DWI – Diffusion Weighted Imaging

EAPC – Estimated annual percentage change

EE – Economic Evaluation

EED – Economic Evaluations Database

EEPRU – Policy Research Unit in Economic Evaluation of Health and Care Interventions

EPIC – Expanded Prostate Index Composite

EQ-5D – EuroQol

FHx – Family History

GA – General anaesthetic

GADS – Generalised Anxiety Disorder Scale

GBD – Global Burden of Disease

GBP – Great Britain Pounds

GI – Gastrointestinal

GP – General Practitioner

HADS – Hospital Anxiety and Depression Scale

HoLEP – Holmium Laser Enucleation of the Prostate

HRA – Health Research Agency

HRQoL – Health Related Quality of Life

HSROC – Hierarchical Summary Receiver Operator Curve

HTA – Health Technology Assessment

ICER – Incremental Cost Effectiveness Ratio

IIEF – International Index of Erectile Function

IPSS – International Prostate Symptoms Score

IQR – Interquartile Range

ISAC – Independent Scientific Advisory Committee

ISPOR-SMDM – International Society for Pharmacoeconomics and Outcomes Research & Society for Medical Decision Making

ISRCTN – International Standard Randomised Controlled Trial Number

ISSG – Information Specialists Sub-Group

ISUP – International Society of Urological Pathology

LA – Local anaesthetic

LR – Likelihood Ratio

LUTS – Lower Urinary Tract Symptoms

MDT – Multidisciplinary Team

MeSH – Medical Subject Heading

MHRA – Medicines and Healthcare products Regulatory Agency

MINORS – Methodological Item for Non-Randomised Studies

mL – millilitre

mpMRI – Multiparametic Magnetic Resonance Imaging

MRI – Magnetic Resonance Imaging

MRI-GB – Magnetic Resonance Imaging Guided Biopsy

MRSI – Magnetic resonance spectroscopy imaging

MRTB – Magnetic resonance imaging targeted biopsy

MSU – Mid-Stream Urine

Mx – Management

NCDA – National Cancer Diagnosis Audit

ng/mL – nanograms per millilitre

NG12 – NICE guidance 12

NG12 – NICE guideline 12

NHB – Net Health Benefit

NHS – National Health Service

NICE – National Institute for Health and Care Excellence

NIHR – National Institute for Health Research

NPV – Negative Predictive Value

OECD – Organisation for Economic Cooperation and Development

PCa – Prostate Cancer

PCA3 – Prostate Cancer Antigen 3

PCO – Patient Centred Outcome

PCORI – Patient Centred Outcome Research Institute

PCRMP – Prostate Cancer Risk Management Programme

PET – Positron Emission Tomography

PhD – Doctor of Philosophy

PHQ – Patient Health Questionnaire

PICO – Patient, Intervention, Comparison, Outcome

PIL – Patient Information Leaflet

PIRADS – Prostate Imaging Reporting And Data System

PPI – Patient & Public Involvement

PPV – Positive Predictive Value

PREM – Patient Reported Experience Measure

PRISMA – Preferred Reporting Items for Systematic Reviews & Meta-Analysis

PRO – Patient Reported Outcome

ProbSA – Probabilistic Sensitivity Analysis

PROM – Patient Reported Outcome Measure

PSA – Prostate Specific Antigen

PSAD – Prostate Specific Antigen Density

PSMA – Prostate Specific Membrane Antigen

QALY – Quality Adjusted Life Year

QoL – Quality of Life

QUADAS – Quality Assessment of Diagnostic Accuracy Studies

RCT – Randomised Controlled Trial

REC – Research Ethics Committee

RoB – Risk of Bias

SD – Standard Deviation

SIGN – Scottish Intercollegiate Guidelines Network

SR-EE – Systematic Review of Economic Evaluations

SWAG – Somerset, Wiltshire, Avon and Gloucester

T2 – T2 weight imaging

TFA – Theoretical Framework of Acceptability

TNM – Tumour Node Metastasis

TP – Transperineal

TPMB – Template Prostate Mapping Biopsy

TPUSGB – Transperineal Ultrasounds Guided Biopsy

TRUS – Transrectal Ultrasound

TRUS-GB – Transrectal Ultrasound Guided Biopsy

TURP – Transurethral Resection of the Prostate

UI – Uncertainty Interval

UICC – Union for International Cancer Control

UK – United Kingdom

USA – United States of America

USD – United States Dollars

USPSTF – United States Preventive Services Taskforce

UTI – Urinary Tract Infection

VACURG – Veterans Administration Cooperative Urological Research Group

VAS – Visual Analogue Scale

WOS – Web of Science

WTP – Willingness to pay

WW – Watchful Waiting

Chapter 1 – Introduction

1.1 Structure of thesis

This Doctor of Philosophy (PhD) thesis is written in six chapters, followed by appendices. Chapter 1 introduces the current challenges in prostate cancer diagnosis and the justification for the focus of this PhD on magnetic resonance imaging for prostate cancer and its potential impact in primary care. Chapters 2-5 outline the context, methods and results of the four studies conducted as part of the PhD, with a brief discussion of the main findings and strengths and weaknesses specific to each study. Chapter 6 summarises the main findings of the PhD research overall, comparing them with existing literature, and exploring key discoveries and research gaps that could subsequently be pursued. Appendices 1.1 – 1.4 are peer review research papers stemming from or related to the PhD. Appendices 2 – 5 are additional content related to the relevant chapters.

1.2 Epidemiology of prostate cancer

Prostate cancer presents a significant and increasing challenge for the National Health Service (NHS) in the United Kingdom (UK), as well as healthcare systems and societies around the world. According to the Global Burden of Disease (GBD) study 2017, prostate cancer is the second most common cancer in males and the fifth most common cause of cancer death worldwide. 1.33 million incident cases of prostate cancer were diagnosed in 2017 (95% uncertainty interval [UI] 1.17million – 1.69million). Between 1990 and 2017, global age-standardised incidence rates (ASIR) of prostate cancer increased from 30.49 per 100,000 (95% UI 22.79 – 33.69) to 37.86 per 100,000 (95% UI 33.03 – 47.99). This summary statistic masks a wide variation in changes in ASIR over this time period, ranging from an estimated annual percentage change (EAPC) of -0.82% in North America (95% confidence interval [CI] -1.08 – -0.56) to 2.96% (95% CI 2.76 – 3.16) in Eastern Europe. Global age-standardised death rates (ASDR) from prostate cancer fell from 1990 to 2017 from 15.19 per 100,000 (95% UI 11.93 – 16.91) to 13.11 per 100,000 (95% UI 11.18 – 15.33). Similarly, there was significant variation between regions and

countries with a mostly inverse relationship between prostate cancer mortality and the wealth of the nation(1).

52,580 patients were diagnosed with prostate cancer in England and Wales in 2017-18(2), making it the most common cancer type diagnosed in males in the UK(3). One in eight UK males will be diagnosed with prostate cancer in their lifetime. Similar to the GBD study findings, prostate cancer incidence in the UK increased between 1993 and 2017, although the increase was higher than the global change (41% vs 24.2%). Prostate cancer stage at diagnosis has not significantly changed in recent years in the UK, with 54.6% of patients diagnosed at an early stage (Stage I or II) in 2018(4). Prostate cancer incidence rises with increasing age over 50 years, peaking between 75 and 79 years. Just over half of patients diagnosed with prostate cancer in the UK are 70 years or older (54% in 2017-18). There are variations in prostate cancer incidence and mortality between ethnic groups in the UK. Estimates using English national cancer registry data showed that Black men were twice as likely to be diagnosed and twice as likely to die from prostate cancer compared to White men(5).

1.3 Prostate cancer biology and classification

The prostate gland in males is located just under the bladder, with the urethra passing through the middle of the gland (see figure 1.1). It is made up of two lobes on either side of the urethra. The prostate produces fluid that mixes with sperm to make semen. It also produces a substance called prostate specific antigen (PSA), which makes semen more watery. The prostate gland is divided into three zones: a central, transition, and peripheral zone. The peripheral zone is where most prostate cancers arise.

Almost all prostate cancers are adenocarcinoma; rarer tumour types originating in the prostate include transitional cell, squamous cell, or small cell carcinoma. Prostate cancer development is driven by a combination of inherited and acquired genetic mutations, microenvironmental factors, and chronic inflammation. Heritability accounts for 57% of prostate cancer risk (95% CI 51-63%)(6). The majority of prostate cancers are multifocal, meaning that the prostate gland contains multiple deposits of tumour cells simultaneously.

Recent advances in the understanding of the molecular biology of prostate cancer have demonstrated that different tumour deposits within the same prostate gland often have different genetic alterations and metastatic potential(7).

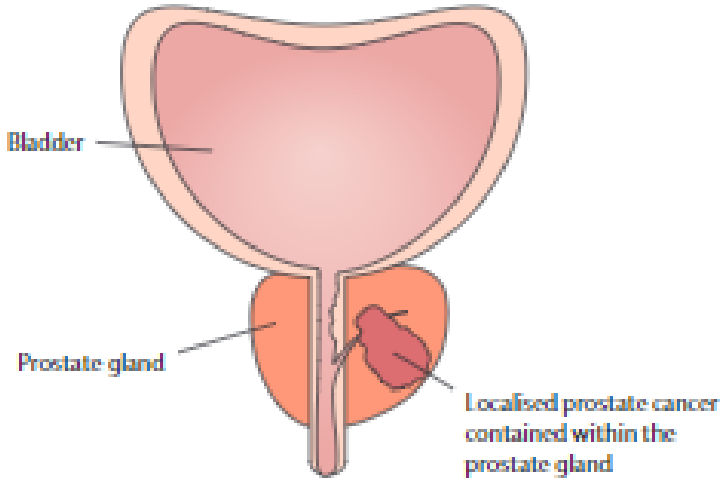


Figure 1.1 – Prostate gland with T2bN0M0 localised prostate cancer from Sandhu *et al* (2021)(7)

There are a number of different tumour classification and staging systems for prostate cancer used in the scientific literature and clinical practice. The 8th edition of the Union for International Cancer Control (UICC) Tumour, Node, Metastasis (TNM) classification of malignant tumours is used in many countries, including the UK, and outlines the definitions of stage I-IV prostate cancer and how that relates to TNM classification(8) (see Tables 1.1 and 1.2). TNM classification can be based on clinical information, such as examination findings (cTNM), radiological investigations (rTNM) and/or pathological staging (pTNM).

Primary Tumour (T)	
Tx	Primary tumour cannot be assessed
T0	No evidence of primary tumour
T1	Clinically inapparent tumour not palpable or visible on imaging
T1a	Tumour incidental finding in 5% or less of tissue resected
T1b	Tumour incidental finding in more than 5% of tissue resected
T1c	Tumour identified by needle biopsy
T2	Tumour confined within the prostate gland
T2a	Tumour involves one half of one lobe or less
T2b	Tumour involves more than one half of one lobe, but not both lobes
T2c	Tumour involves both lobes
T3	Tumour extends through the prostate capsule
T3a	Extraprostatic extension
T3b	Tumour invades seminal vesicle(s)
T4	Tumour is fixed or invades adjacent structures
Regional lymph nodes	
Nx	Regional lymph nodes cannot be assessed
N0	No regional lymph node metastasis
N1	Regional lymph node metastasis
Distant metastasis	
M0	No distant metastasis
M1	Distant metastasis

Table 1.1 – UICC TNM classification of prostate cancer (8th edition)(8)

Stage 1	T1 – T2a	N0	M0
Stage 2	T2b – T2c	N0	M0
Stage 3	T3 – T4	N0	M0
Stage 4	Any T Any T	N1 N0	M0 M1

Table 1.2 – UICC Prostate cancer staging system(8)

The Gleason histologic grading system for prostate cancer was developed by the Veterans Administration Cooperative Urological Research Group

(VACURG) based on studies conducted between 1960 and 1975 in the United States of America (USA). Gleason grading of tumours is performed using histopathological analysis of prostate tissue samples retrieved by biopsy, and grades cells from one (normal appearance of prostatic cells) to five (poorly differentiated carcinoma) (see figure 1.2). Gleason scores range from two to ten (six to ten being classed as prostate cancer) and consists of two numbers; the first number being the most common grade of cells seen and the second number being the next most common grade of cells visible. For example, a biopsy sample with mostly Gleason grade 4 cells with some Gleason grade 3 cells would have a Gleason score of 4 + 3 = 7, or if only grade 3 cells were seen in a sample the Gleason grade would be 3 + 3 = 6. The VACURG studies demonstrated that the higher the Gleason score, the greater the likelihood of prostate cancer mortality(9). The Gleason grading system has undergone many iterations since its original publication, the most recent of which being the 2019 International Society of Urological Pathology (ISUP) Consensus Conference on Grading of Prostatic Carcinoma. Modern iterations of prostate cancer grading systems have reconfigured Gleason score into Gleason Grade Groups, as the prognosis for patients with a Gleason score of 3 + 4 = 7 is different from those with a Gleason score of 4 + 3 = 7(10) (see table 1.3).

Figure 1.2 – Gleason scoring system based on histopathological diagnosis(9)

Gleason score	*Gleason Grade Group*
Gleason 3 + 3 = 6	Group 1
Gleason 3 + 4 = 7	Group 2
Gleason 4 + 3 = 7	Group 3
Gleason 4 + 4 = 8	Group 4
Gleason = 9 or 10	Group 5

Table 1.3 – Comparison of Gleason score and Gleason Grade Group

A further method for classifying tumours localised to the prostate is differentiating clinically significant from clinically insignificant prostate cancer. The importance in making this distinction lies in whether a patient is then recommended to receive radical treatments to prevent serious morbidity or mortality (such as surgery or radiotherapy), active surveillance with regular monitoring of the tumour for signs of clinical progression in order to delay or avoid radical treatments, or watchful waiting where no treatment is commenced at all. There is no universally agreed definition of clinically significant prostate cancer, and the definition has evolved in recent decades with advancements in

prostate cancer diagnostics and treatments. Determination of clinically significant prostate cancer can be made on the basis of radiological, pathological or molecular findings. The simplest definition of clinically significant prostate cancer is a Gleason score of seven or more, but other proposed methods incorporate biopsy, imaging, and/or surgical data, and PSA levels(11).

National Institute for Health and Care Excellence (NICE) guidelines for prostate cancer diagnosis and treatment recommend diagnostic and staging investigations to determine PSA level, Gleason score, and clinical tumour stage, which is then used to risk stratify patients with localised prostate cancer. Patients with localised prostate cancer are classified into low, intermediate or high risk (see table 1.4), and this determines which treatment options are recommended by NICE to be discussed with the patient(12). This approach is based on a validated system of prostate cancer risk stratification first proposed by D'Amico *et al* in 1998(13).

Level of risk	*PSA*		*Gleason score*		*Clinical stage*
Low	<10ng/mL	and	≤ 6	and	T1 – T2a
Intermediate	10 – 20 ng/mL	or	7	or	T2b
High	> 20 ng/mL	or	8-10	or	≥ T2c

Table 1.4 – NICE risk stratification of patients with localised prostate cancer(12)

1.4 Diagnosis of prostate cancer

The role of symptoms for prostate cancer diagnosis in primary care is equivocal owing to limited evidence(14), but the majority of patients with prostate cancer report that they experience symptoms that likely relate to the cancer prior to their diagnosis(15). Symptoms associated with prostate cancer include lower urinary tract symptoms (LUTS), urinary retention (inability to empty the bladder), haematuria (visible blood in the urine), or erectile dysfunction(16). LUTS is a broad group of urinary symptoms that includes frequency (passing urine more often than usual), hesitancy (taking longer to start passing urine), nocturia (waking multiple times in the night to pass urine), poor stream (slow urine stream), and urgency (sudden urge to pass urine). Unexplained weight loss and/or lower back pain can be presenting symptoms of late-stage prostate

cancer. The diagnosis of symptomatic prostate cancer is challenging for a number of reasons. The more common symptoms associated with prostate cancer (LUTS and erectile dysfunction) are very common in the same age groups that are at higher risk of prostate cancer (older males) and are more often due to benign prostatic hypertrophy (BPH), detrusor muscle instability, or psychological causes than prostate cancer. Symptoms of prostate cancer also have poor discriminatory power between malignant and benign conditions affecting the prostate. A significant proportion of patients with prostate cancer, particularly early-stage cancer, are thought to have no symptoms and some will not develop symptoms until their cancer has progressed to advanced and/or metastatic disease(14,17).

Prostate cancer can also be detected through digital rectal examination (DRE) of the prostate. A 'normal' prostate on examination is smooth with a central sulcus between the two lobes. Prostate cancer that can be palpated is described as a hard lump in one lobe, a rough feeling prostate, or prostatic asymmetry. A recent systematic review of four studies that examined the diagnostic accuracy of DRE for prostate cancer in symptomatic patients showed a sensitivity of 28.6%, specificity of 90.7%, and a positive predictive value (PPV) of 42.3%(18). The conclusions from the review suggested DRE still plays a role in prostate cancer diagnosis, owing to the high PPV, but should not be relied upon alone given the poor sensitivity of examination.

PSA measurements from a blood sample is another method of diagnosing prostate cancer that is used in primary and secondary care settings. PSA levels can be raised in patients with prostate cancer; but can also be elevated for other reasons such as BPH, lower urinary tract infection, recent ejaculation or vigorous exercise. PSA levels can be normal in patients with prostate cancer and artificially lowered by medications such as 5-alpha reductase inhibitors(19). The most recent systematic review of the diagnostic accuracy of PSA for prostate cancer, published in 2009, showed a range of reported sensitivities (78% – 100%) and specificities (6% - 66%). This review did not report whether the diagnostic accuracy of PSA differed in patients with prostate cancer presenting with symptoms compared to those without any symptoms, nor did it report whether studies had compared the ability of PSA to differentiate between

clinically significant and clinically insignificant prostate cancer. All included studies for the review were conducted in secondary care patient cohorts(20).

PSA testing for prostate cancer in high income countries became widespread in the late 1980s and resulted in a significant increase in the number of patients being diagnosed with prostate cancer. In the USA, prostate cancer incidence doubled between 1986 and 1992(21), and a similar increase in prostate cancer incidence in the 1990s was seen in the UK(3). This phenomenon is thought to be largely due to quasi-PSA screening in patients without symptoms concerned about possibly having prostate cancer, which was widespread in many countries although very few have formal, national screening programmes. Several very large clinical trials of PSA screening with long-term follow-up have demonstrated a probable small reduction in prostate cancer mortality, but no reduction in overall mortality and increased risks of complications from invasive diagnostic testing, overdiagnosis of clinically insignificant prostate cancer, and overtreatment(22). The US Preventative Services Task Force's (USPSTF) most recent recommendations on PSA screening state patients aged 55-69 years should only undergo a PSA screening test after discussing the potential benefits and harms of the test, and PSA screening is not recommended for patients aged 70 years and above(23).

The NICE *Suspected cancer: recognition and referral (2015)* guideline outlines symptoms, signs and clinical investigation results for which General Practitioners (GPs) in the NHS should refer patients on an urgent suspected cancer pathway to be seen by a specialist for further assessment within two weeks, commonly known as the Two Week Wait (2WW) pathway. NICE guidance recommends patients presenting to their GP with new onset of LUTS, haematuria, or erectile dysfunction should undergo a DRE and PSA blood test. If either the DRE is abnormal or the PSA is above recommended age-specific reference ranges, then a 2WW referral is recommended(24). The UK Prostate Cancer Risk Management Programme (PCRMP) and the UK National Screening Committee do not recommend formal PSA screening, but guidance does allow for opportunistic PSA screening for patients who have made an informed decision taking into account the potential benefits and harms(25).

The gold standard diagnostic test for patients who are suspected of having prostate cancer is a prostate biopsy. This procedure involves taking multiple tissue samples of the prostate using a needle, followed by microscopic examination of the tissue samples by a pathologist for signs of prostate cancer as described above(26). Prior to the advent of magnetic resonance imaging (MRI) of the prostate, prostate biopsies have been performed under ultrasound guidance using either a transrectal or transperineal approach. A Transrectal ultrasound guided (TRUS) biopsy taking between 6 and 12 samples of the prostate has been a standard diagnostic test for patients referred to a Urologist. Whilst TRUS biopsy is generally well tolerated by patients with minor side effects such as pain, haematuria or LUTS, the procedure carries a risk of infection requiring hospitalisation of approximately 3%. Patients can be given antibiotic prophylaxis to reduce the risk of infection, but rates of antimicrobial resistance associated with TRUS biopsy procedures are rising(27).

A further challenge with TRUS biopsy as a diagnostic test for prostate cancer relates to the diagnostic accuracy of the test. Ultrasound guided biopsy of the prostate, irrespective of the approach, is essentially random sampling of the prostate because ultrasound as an imaging modality is not accurate enough to identify areas of tumour within the prostate. The ultrasound images are mainly used to locate the prostate. Coupled with the fact that prostate cancer is often multifocal (see above), this results in ultrasound guided prostate biopsies carrying a risk of false negatives (if the tumour is not sampled at all) or misclassification (if a lower grade tumour is sampled and a higher-grade focus is missed) (see figure 1.3)(28) . A Cochrane review of prostate MRI and systematic biopsy found TRUS biopsy had a pooled sensitivity of 63% (95% CI 19%, 93%) and a pooled specificity of 100% (95% CI 91%, 100%) based on four included studies with a low certainty of evidence(29).

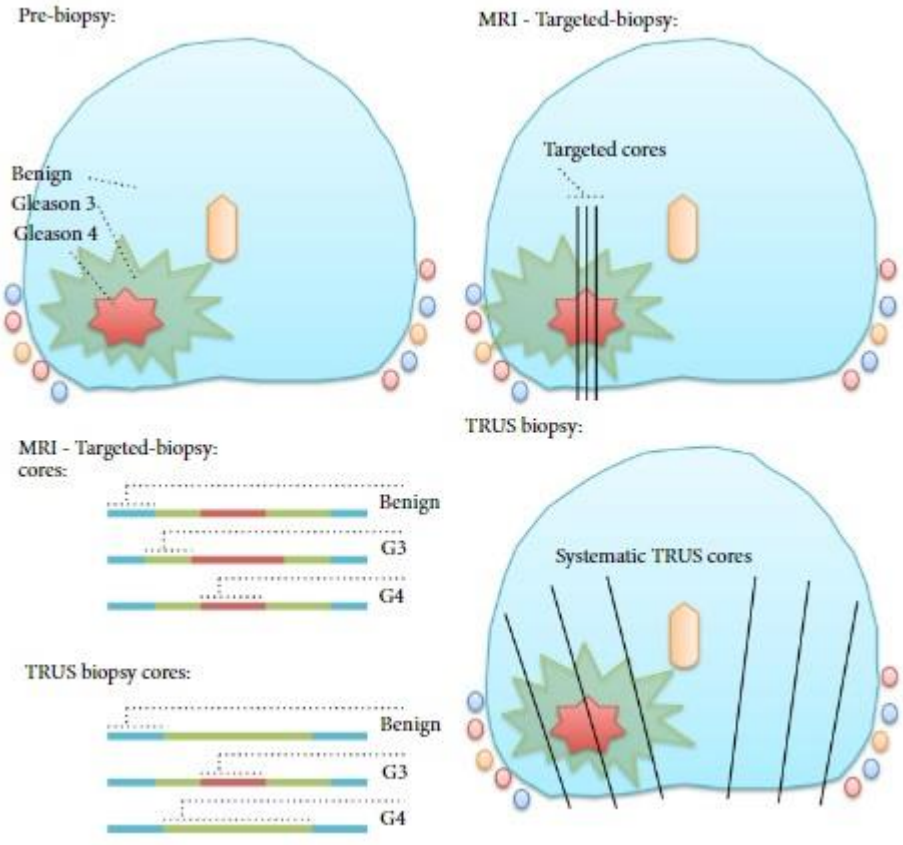


Figure 1.3 Differences between systematic (ultrasound-guided) and targeted (MRI-guided) prostate biopsy(28)

Accurate and timely diagnosis of prostate cancer remains a significant clinical challenge. The utility of symptoms associated with prostate cancer for the early detection of clinically significant prostate cancer in primary care is unclear. The current tests available in primary care in terms of DRE and PSA have limitations in detecting the majority of prostate cancer among the many patients who present with symptoms. The benefits for patients of asymptomatic PSA screening have not been shown to clearly outweigh the harms, and ultrasound-guided biopsy of the prostate as a diagnostic test has a high false negative rate. These factors affecting the prostate cancer diagnostic pathway have driven a search for new tests to detect prostate cancer more accurately.

1.5 Magnetic resonance imaging of the prostate

Magnetic resonance imaging of the prostate has recently emerged as a more accurate diagnostic test for prostate cancer with multiple potential applications. Research into the potential role for MRI in prostate cancer in the 1980s was initially focused around improving the accuracy of staging investigations after a

diagnosis had been made. As MRI technology and techniques improved over the years, other potential applications were explored, leading to trials and diagnostic accuracy studies in recent years for the detection of prostate cancer at an earlier stage(30).

Evaluation of the prostate with MRI uses multiple different imaging techniques to identify abnormal areas within the gland. The main MRI sequences used to examine the prostate are(30) =

T2-weighted imaging (T2) – this sequencing technique reflects the water content of tissue and provides high quality views of the prostate that are able to distinguish between the zones within the gland. Tumours in the transition zone of the prostate are more difficult to visualise using T2-weighting.

Diffusion weighted imaging (DWI) – this sequencing technique quantifies the amount of random movement of water molecules within a tissue. Water molecules move more freely in normal prostate tissue compared to cancer cells, helping with identification of prostate tumours in the transition zone. This sequence can be used to calculate a diffusion coefficient map of the prostate.

Dynamic contrast-enhanced imaging (DCE) – this sequencing technique uses an intravenous contrast agent (usually Gadolinium) to assess the vasculature within the gland. Prostate tumours tend to appear sooner in the imaging sequence owing to their increased blood supply compared to the surrounding tissue.

Magnetic resonance spectroscopy imaging (MRSI) – this sequencing technique visualises the pattern of the expressions of different metabolites by cells within the prostate. Certain metabolites, such as citrate or choline, are expressed either more or less by prostate cancer cells compared to normal tissue. This technique is less commonly used in prostate imaging.

Reporting of prostate MRI is undertaken by radiologists and reporting each scan can take a significant amount of time owing to the number of images generated. Images taken using the various sequences are examined for any

sign of abnormal signal that could relate to a prostate cancer. The radiologist summarises the report with an overall estimation of the likelihood of the presence of prostate cancer. This can be done on a simple Likert scale from one to five; one meaning the prostate appears to be normal through to five suggesting there are significant abnormalities that are likely to be prostate cancer. A more formalised reporting and grading system is the Prostate Imaging Reporting and Data System (PIRADS) version 2.1. This standardised approach gives guidance to radiologists on the various features of a prostate MRI to assess and report and is also summarised with a five-point scale similar to the simple Likert scale(31). Additional training is often required for radiologists to accurately report prostate MRI scans, and greater experience with prostate MRI has been shown to result in more accurate reporting(32).

The most common approach to prostate MRI for the detection of prostate cancer is called multiparametric MRI (mpMRI). This method involves the use of T2 imaging, DWI and DCE of the prostate, as these imaging techniques can complement each other to improve the diagnostic accuracy for prostate cancer detection (see Figure 1.4). A typical mpMRI scan can take up to 45 minutes to perform and requires intravenous access to give the patient a contrast agent just prior to the scan being performed(33). An alternative approach to mpMRI is called biparametric MRI (bpMRI), which involves T2 imaging and DWI without the use of DCE. The advantages of this approach include lower cost, shorter scan time, not requiring a recent blood test for renal function, and avoiding the risks associated with contrast agent use, such as anaphylaxis. Whilst mpMRI is the current standard of care for prostate MRI in UK(12) and European(34) guidelines, studies suggest that bpMRI is not significantly inferior to mpMRI in terms of diagnostic accuracy for clinically significant prostate cancer(35).

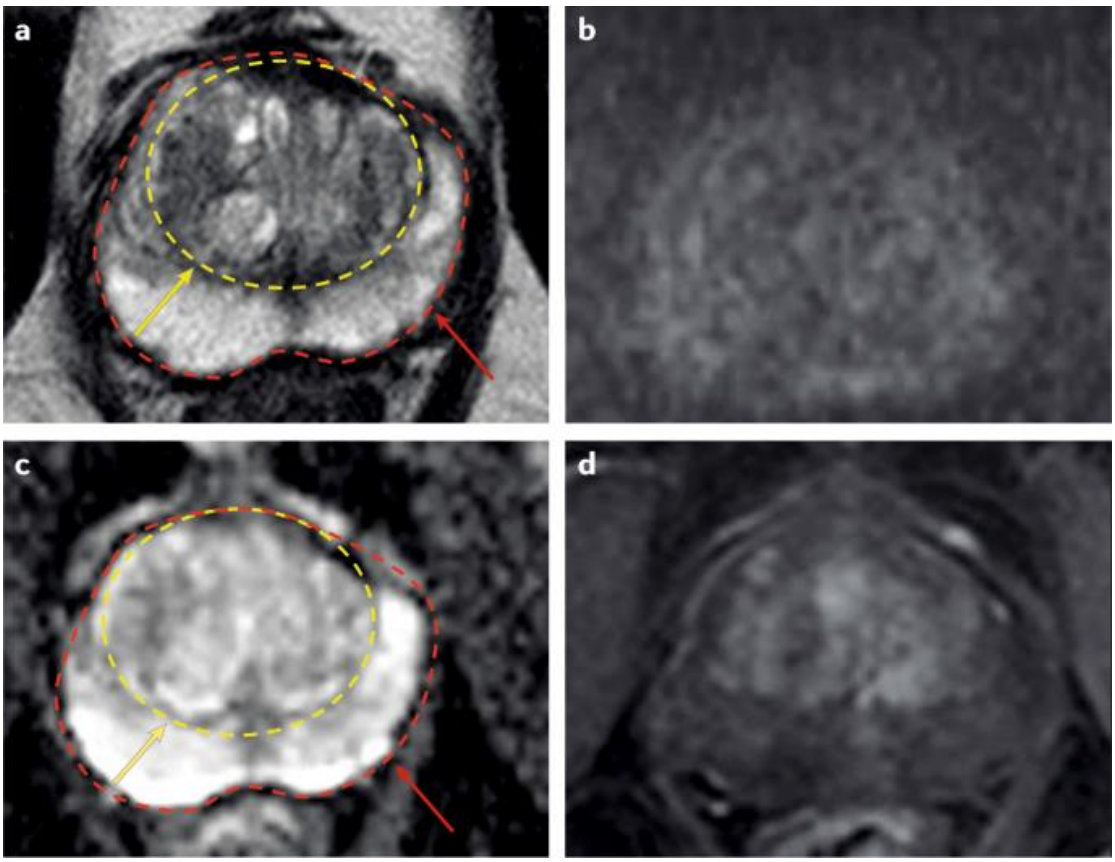


Figure 1.4 – Multiparametic MRI scan images of a patient without prostate cancer(30). Yellow circle indicates the border of the transitional zone. Red border indicates the edge of the peripheral zone.
a T2 weighted imaging **b** Diffusion weighted imaging **c** Diffusion coefficient map **d** Dynamic contract-enhanced imaging

Prostate MRI has multiple roles in the diagnosis of prostate cancer. For patients with a suspicion of prostate cancer, either due to an abnormal DRE or raised PSA, an MRI of the prostate can be performed prior to a prostate biopsy. This approach can identify patients with a suspicious region (or regions) of the prostate that warrants further investigation with a biopsy (PIRADS 3-5), and patients with a normal appearing prostate gland (PIRADS 1-2). Patients referred due to a suspicion of prostate cancer but who have a normal prostate on MRI scan may be able to safely avoid a biopsy after consultation with a urologist(12). A pre-biopsy MRI approach has been subject to a number of clinical trials and diagnostic accuracy studies, usually compared to TRUS biopsy. Diagnostic accuracy of pre-biopsy prostate MRI for clinically significant prostate cancer is estimated to have a pooled sensitivity of 91% (95% CI 83%, 95%) and a pooled specificity of 37% (95% CI 29%, 46%). These studies estimate that pre-biopsy

MRI reduces the number of patients undergoing biopsy by 31%, reduces the number of patients subsequently diagnosed with clinically insignificant prostate cancer by 8%, and increases detection of clinically significant cancer by 3%(29,36).

Prostate MRI images can also be used to guide prostate biopsy in a more targeted manner because the tumour (or tumours) in the prostate can be visualised. There are a number of different methods for using prostate MRI to guide biopsy, including cognitive (the operator reading images and aiming to biopsy the target region) and fusion (using real-time ultrasound merged with the MRI images to guide biopsy) techniques(37). Regardless of the methods used, targeted MRI-guided biopsy has been shown to detect more patients with clinically significant prostate cancer (detection ratio 1.16 95% CI 1.09, 1.24) and fewer patients with clinically insignificant prostate cancer (detection ratio 0.66 95% CI 0.57, 0.76) compared to systematic TRUS biopsy. Targeted biopsy also resulted in a higher proportion of positive biopsy samples for prostate cancer (see Figure 1.3), suggesting more accurate sampling of the tumour(38). Targeted prostate biopsy still risks missing some clinically significant prostate cancer, leading to a combination of systematic and targeted biopsies being used in some settings(39).

1.6 Implementation of new diagnostic tests

Prior to the implementation of a new diagnostic test in a health service for any disease, such as MRI for prostate cancer, it should ideally have undergone thorough evaluation to understand the optimal use of the test within the relevant diagnostic pathways and the likely patient outcomes in clinical practice. The performance of the test should be known in the population of interest, to reduce the spectrum effect(40), whereby test performance differs in different populations. In addition to assessing the diagnostic accuracy and the cost effectiveness of a newly developed test, the emotional, cognitive, behavioural and social effects on patients should be explored(41). Numerous frameworks for the development and evaluation of new diagnostic tests have been proposed, some being more specific to certain types of tests (e.g. imaging or genetics) and others taking a more general approach. A more recently developed approach, called the CanTest framework (see Figure 1.5), sought to

define a comprehensive methodological framework covering the spectrum of test development from conceptualisation and development to trialling the impact on patients and clinical practice. The CanTest framework consists of five phases through which evaluation of a new test can cycle from initial measurement of performance in a selected population to implementation and evaluation of the impacts of the test at a population level(42).

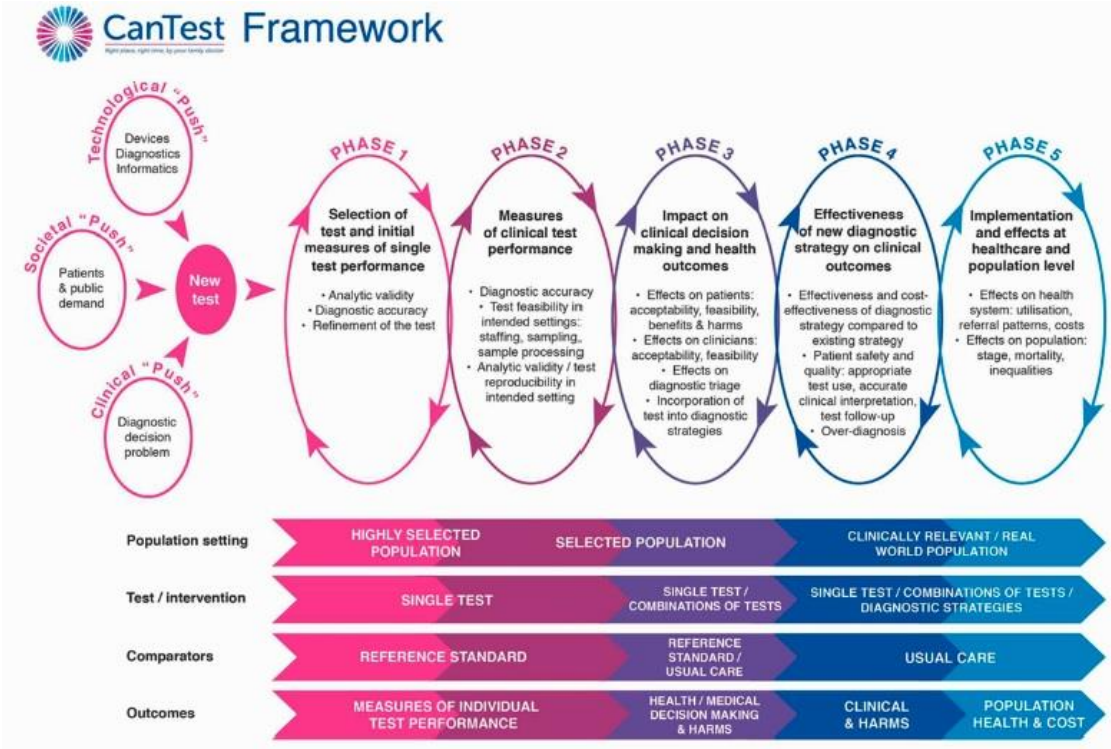


Figure 1.5 – The CanTest framework(42)

With reference to the CanTest framework, there is published evidence for most of the phases of test development for prostate MRI as a test for cancer. MRI sequences for the prostate have been developed and refined over recent decades(30) (CanTest phase 1), and trial evidence and real-world studies have been published to demonstrate feasibility and analytic validity in secondary care settings(29) (CanTest phase 2). A number of cost-effectiveness studies for integrating prostate MRI into prostate cancer diagnostic pathways have been published(43,44) (CanTest Phase 4), although no systematic review in this area has been published to date. There are no published studies examining patient or clinician acceptability for prostate MRI to date(45) and no uniform or agreed optimal prostate cancer diagnostic pathway incorporating prostate MRI (CanTest Phase 3), which impacts on the understanding of diagnostic workforce

and MRI scanner requirements to implement prostate MRI widely(30) (CanTest Phase 5).

1.7 Prostate cancer diagnosis in the NHS

Improving cancer diagnosis and outcomes for patients is a strategic priority for the NHS in England. A clear target in the recent NHS Long Term Plan has been set to increase the proportion of patients diagnosed with cancer at an early stage (Stage I or II) in England to 75% by 2028(46), as early-stage diagnosis is associated with higher 1-year, 5-year and 10-year cancer survival. The NHS Faster Diagnosis Standard sets a target for all NHS services to achieve a diagnosis of cancer (or ruling out cancer) within 28 days of a patient being referred on a 2WW pathway(47), enabling quicker access to treatment for those with a new diagnosis of cancer. These targets apply to prostate cancer, alongside all other cancer types. Significant improvements would be needed in terms of early-stage prostate cancer diagnosis and timeliness of diagnosis to meet these targets for prostate cancer diagnostic pathways in the NHS.

Following publication of the NHS Faster Diagnosis Standard in 2018 and updated NICE *Prostate cancer: Diagnosis and management* guidelines in 2019, NHS Cancer alliances and Trusts have been integrating prostate MRI into local prostate cancer diagnostic pathways. Where, when and how prostate MRI is integrated into local pathways varies widely, with some services following a more traditional approach of multiple outpatient appointments (see Figure 1.6) and others shortening the pathway to deliver a ‘one-stop’ approach incorporating specialist outpatient review, prostate mpMRI, and plan for biopsy into the one clinic visit (see Figure 1.7).

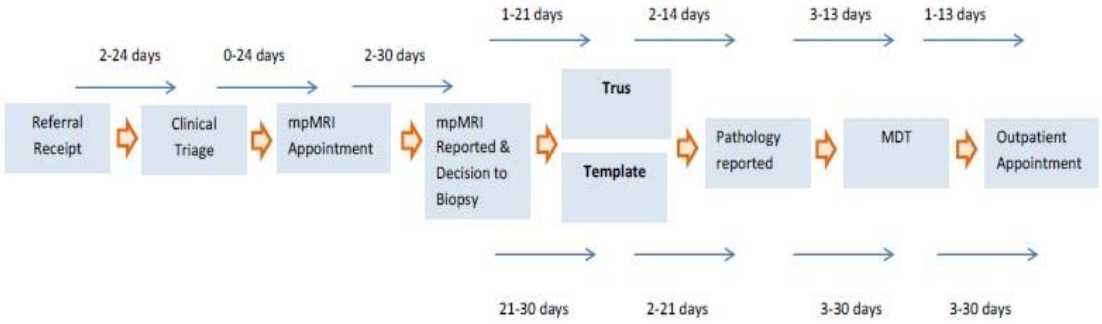


Figure 1.6 – South West Prostate Cancer Diagnostic Pathway, NHS Cancer Alliances in South-West Peninsula and Somerset, Wiltshire, Avon & Gloucester (SWAG)

mpMRI – multiparametric magnetic resonance imaging; TRUS – transrectal ultrasound guided biopsy; MDT – multidisciplinary team

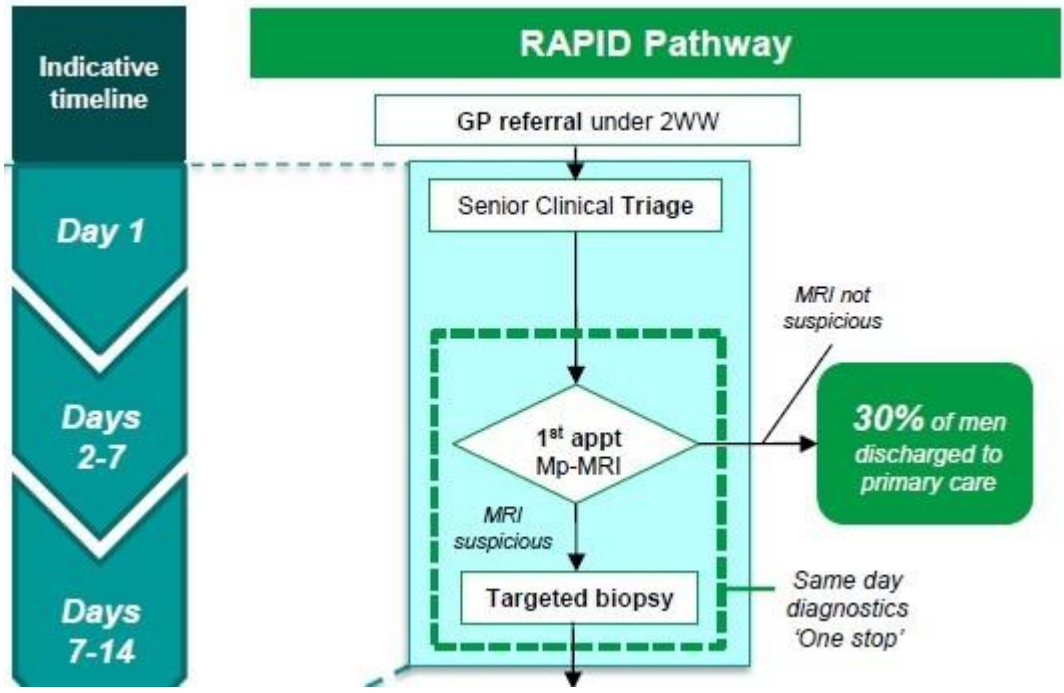


Figure 1.7 – RAPID pathway, Imperial College Healthcare NHS Trust, London

2WW – Two Week Wait pathway; mpMRI – multiparametric magnetic resonance imaging; MRI – magnetic resonance imaging

Integration of prostate MRI into prostate cancer diagnostic pathways presents some significant challenges for healthcare service delivery. The NHS prostate cancer diagnostic pathway was already resource intensive prior to the updated NICE guidelines, and the proportion of patients reviewed, investigated, diagnosed and started on management or discharged within specified timed targets for prostate cancer pathways was lower relative to other cancer

pathways before recommendations for integration of pre-biopsy prostate MRI(48). Increasing the number of MRI scans being performed has implications for pressure on MRI scanner capacity and diagnostic workforce requirements in terms of radiographers to perform the scans and radiologists to report them.

A potential alternative application of prostate MRI as a pre-biopsy triage test for patients with suspected prostate cancer could be within primary care. Prostate MRI for suspected prostate cancer is not currently available for direct access from primary care in the UK, or any other country. Prostate MRI can only currently be ordered and acted upon by specialists working in secondary or tertiary centres. Direct access for cancer diagnostic testing in primary care is established for other cancer types, such as colonoscopy for suspected lower gastrointestinal cancer, or urgent brain imaging for a suspected brain tumour. Available evidence outlined in a recent systematic review suggests that there is no significant difference in the pooled cancer conversion rate for direct access cancer diagnostic testing between GPs and specialists, except for gastroscopy; time from referral to testing was shorter for referrals from a GP; and patient and GP satisfaction with direct access testing was consistently high(49). The proposed benefit of prostate MRI in reducing rates of unnecessary prostate biopsies could be further improved by reducing urology referrals as well if pre-biopsy prostate MRI was performed in primary care and referral decisions were made on the basis of the MRI result. Prostate MRI also outperforms currently available tests in primary care for prostate cancer detection through better identification of clinically significant prostate cancer compared to PSA or DRE.

1.8 Aim & Objectives for PhD

Aim

To examine whether magnetic resonance imaging (MRI) can be utilised in primary care to improve prostate cancer diagnosis

PhD objectives

1. Critically appraise existing evidence for improved patient outcomes and cost effectiveness of MRI as a diagnostic test for prostate cancer
2. Understand the acceptability of MRI as a diagnostic test for prostate cancer amongst medical professionals and patients

3. Evaluate the cost-effectiveness of direct access MRI testing for primary care patients with possible prostate cancer
4. Develop possible new primary care diagnostic pathways to incorporate MRI for patients with possible prostate cancer

The objectives for this PhD have been set to further develop the evidence base for prostate MRI in the diagnosis of prostate cancer, and evaluate whether piloting, implementing and evaluating direct access to prostate MRI in primary care is worth pursuing. Given that prostate MRI is not currently used at all in primary care for prostate cancer detection in the UK or overseas, I decided to focus on areas within the CanTest framework (see Figure 1.5) where evidence for prostate MRI is lacking. Chapters two and three focus mainly on patients in terms of impacts of prostate MRI and acceptability of the test. Chapters four and five focus more on how prostate MRI could be implemented into the primary care element of the diagnostic pathway and modelling what the impact on the health service might be.

Chapter two outlines the conduct and findings of a systematic review and narrative synthesis of patient centred outcomes reported in the published literature relating to diagnostic tests for prostate cancer. Prior to implementing prostate MRI in an entirely new clinical setting (primary care), it is beneficial to understand clearly how prostate MRI compares to alternative diagnostic tests in terms of patient outcomes. Diagnostic tests can have a wide range of impacts on patients, and if prostate MRI was not found to compare favourably to alternative tests then implementation in primary care may not be worth pursuing. This chapter addresses objective one of the PhD.

Chapter three outlines the findings of a qualitative interview study of patients and GPs exploring the acceptability and understanding of prostate MRI for diagnosing prostate cancer. The acceptability of a diagnostic test for patients and clinicians is important to understand before implementing the test, as outlined above in the CanTest framework (see Section 1.6). The acceptability of prostate MRI for investigating suspected prostate cancer amongst patients and GPs is currently unknown. This chapter addresses objective two of the PhD.

Chapter four outlines a systematic review and narrative synthesis of full economic evaluations that compare prostate cancer diagnostic pathways incorporating pre-biopsy prostate MRI with existing diagnostic pathways relying on TRUS biopsy. Before embarking on my own early economic evaluation of integrating prostate MRI into primary care triage for prostate cancer detection, it is vital to assess the existing evidence in this area and assess how the primary care elements of the prostate cancer diagnostic pathway are incorporated into existing cost-effectiveness studies. This chapter addresses objective one of the PhD and provides some evidence to inform objectives three and four.

Chapter five outlines an early economic evaluation of incorporating prostate MRI into primary care in the prostate cancer diagnostic pathway, comparing this to currently recommended practice in NICE guidelines. Early economic evaluations of new diagnostic tests or new uses of existing tests generates estimates around the potential cost-effectiveness of the test in the proposed way, and can be used to guide decisions about further research in implementation and evaluation. There are no published studies modelling the use of prostate MRI in primary care for prostate cancer detection, so this chapter fills another evidence gap. This chapter addresses objectives three and four of the PhD.

Chapter six is a summary discussion chapter for the PhD as a whole. It considers how the key findings of the PhD relate to each other and their place the context of recent and potential developments in prostate cancer diagnosis. All the PhD objectives are revisited in light of the new evidence generated from this PhD, and future directions for research in this area are proposed.

Chapter 2 – Systematic review and narrative synthesis of patient centred outcomes from diagnostic tests for prostate cancer

Chapter one presented a discussion of the major challenges in prostate cancer diagnosis and the recent advent of prostate MRI to address some of these challenges. In order to inform the decision about whether to implement and evaluate prostate MRI in primary care, a clear understanding about the impact of prostate MRI on outcomes that are important to patients would be beneficial. This chapter outlines a systematic review of the evidence for patient centred outcomes from prostate MRI, and includes a comparison with existing alternative diagnostic tests to determine whether prostate MRI is associated with more favourable patient outcomes. This chapter addresses objective one of the PhD.

2.1 Introduction

The current tests available for prostate cancer can have a significant impact on patients. Concerns remain about whether Prostate Specific Antigen (PSA)-based screening programmes have greater benefits to patients, through reduced prostate cancer mortality, or greater harms, through false negatives(22) and overdiagnosis of clinically insignificant tumours(50). The US Preventive Services Taskforce(51), the UK National Screening Committee(25), and the European Association of Urology(52) all currently recommend against national screening programmes, but opportunistic screening still occurs in many countries. PSA is also used in clinical practice as part of the diagnostic workup in symptomatic patients. A raised PSA level in symptomatic or asymptomatic patients usually results in referral to a urologist for consideration of a prostate biopsy via the transrectal or transperineal route under ultrasound guidance (TRUS). This mode of biopsy also has significant adverse effects(27) and suffers from misdiagnoses(51). In recent years there have been an increasing number of studies assessing the potential utility of pre-biopsy magnetic resonance imaging (MRI) of the prostate and MRI-guided prostate biopsy as new diagnostic tests for prostate cancer(53–55). The most common prostate

MRI methods used are multiparametric MRI (mpMRI) and biparametric MRI (bpMRI).

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. In the Agency for Healthcare Research and Quality (AHRQ) Effective Healthcare Program White Paper series on diagnostic test evaluation, Bossuyt and McCaffery identify that, in addition to the clinical outcome, a medical test can have emotional, social, cognitive, and behavioural effects on patients. These effects can be positive or negative, and they are not restricted to the medical test itself, but the entire diagnostic pathway(41). Bossuyt and McCaffery also highlight that the relative importance of particular outcomes for clinicians and patients differ.

The recent movement towards making health research relevant and responsive to patients and the public has resulted in more patient-centred care and research, and great effort has been put into defining patient-centred outcomes (PCOs) and improving the methodology around collecting and analysing this data(57). In the USA, the Patient-Centred Outcomes Research Institute (PCORI) was established in 2010 to conduct patient-centred outcome research for the evaluation of comparative effectiveness of clinical care(57). PCORI defines PCOs as having three domains(58):

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

Numerous other patient-centred measures are used in healthcare research, including patient-reported outcome measures (PROMs) and patient-reported experience measures (PREMs)(59). Patient-reported outcomes (PROs) come from the patient without interpretation from another person, and tend to refer to a health outcome (e.g. functional status) and quality of life (QoL) measures that patients identify as being important(60); thus, many PROs are also PCOs.

PCOs were chosen as the outcome for this review as they are broader than other measures of patient outcomes.

Much of the debate surrounding diagnostic testing for prostate cancer has focused on the diagnostic accuracy for transrectal/transperineal ultrasound guided prostate biopsy and MRI/MRI guided biopsy. Comparison of the impact of these tests and their effects from the patient's perspective is less well understood. This systematic review aims to summarise and compare the current evidence relating to patient-centred outcomes for ultrasound guided prostate biopsy and prostate MRI. The review focuses on PCOs as we are comparing diagnostic tests for prostate cancer, however PROMs and PREMs will also be considered given these are measures of outcomes important to and identified by patients.

2.2 Methods

Databases

Medline via OVID, EMBASE, PsycInfo and the Cochrane Central register of Controlled Trials (CENTRAL) were selected to search for relevant articles. These databases are key resources for health and medical research and were assumed to include the vast majority of papers that were relevant for this systematic review.

Search strategy

Studies of diagnostic tests can be difficult to identify in systematic searches of databases due to variation in methods reporting in title and abstracts and indexing terms(61). The Cochrane Handbook for Systematic Reviews of Diagnostic Test Accuracy recommends combining the test(s) of interest with the specific condition to refine searches(62). This approach was combined with pre-tested search filters developed by the Scottish Intercollegiate Guidelines Network (SIGN) for 'diagnostic studies' and 'patient issues' to attempt to achieve balance between the sensitivity and precision of the search strategy. Initial searches were still returning too many search hits to feasibly screen, so additional terms were added to focus the searches on patient centred outcomes(63). See Appendix 2.1 for database search terms used.

In addition to online database searching, hand-searching of reference lists from systematic reviews identified in the searches and snow-balling techniques from reference lists in key papers were performed to identify potentially relevant studies not captured by database searches.

Inclusion criteria

Search hits were included in this systematic review based on the following criteria:

1. Studies of ultrasound-guided prostate biopsy, MRI-guided biopsy, and/or mpMRI or bpMRI for prostate cancer diagnosis. This includes re-biopsy strategies after initial negative testing.
2. Patient-centred outcome(s) included as an outcome measure in the study (primary or secondary)

Exclusion criteria

Search hits were excluded if they featured any of the following criteria:

1. Screening tests for prostate cancer
2. Studies of outcomes associated with treatments for prostate cancer, including active surveillance and re-biopsy of patients to test for treatment effect
3. Case reports, conference abstracts, protocols, letters, editorials or commentaries
4. Studies with non-human subjects

There were no limits set on date of publication, language or study design for this review to try to increase the sensitivity of the database searches.

Screening search hits

Search hits from each database were downloaded and combined into a review database managed in a shared folder in Mendeley Desktop (Version 1.19.4, Mendeley Ltd). Each search hit was screened against the inclusion/exclusion criteria by me and a 2nd reviewer (Victoria Hardy, PhD student, University of Cambridge) independently based on title and abstract. Full text papers were reviewed if a reviewer was unclear on the basis of title and abstract. Any discrepancies of study inclusion between the two independent screeners were adjudicated by a PhD supervisor (WH).

Quality assessment

Consistency in quality assessment of included studies in a systematic review allows comparison between included studies to better judge the weight of evidence provided. Given there was no limitation on study design in the inclusion/exclusion criteria for this systematic review, a single quality assessment tool for each included study was not able to cover for the various designs. After reviewing the available tools and methodological literature, separate quality assessment tools were selected for randomised controlled trials, non-randomised studies, and qualitative studies.

The Cochrane Collaboration risk of bias tool 2.0(64) was used to assess included randomised controlled trials (RCTs). The Cochrane risk of bias tool

includes five key domains for potential bias in studies, with a range of sub-areas for each domain rated on a 5-point Likert scale. Based on the scores for the five domains, an overall judgement regarding the risk of bias for the study is made (high risk; some risk; low risk).

The Methodological item for non-randomised studies (MINORS) checklist(65) was applied to non-randomised trials and observational studies, featuring eight items for non-comparative studies and an additional four items for comparative studies. Each item is scored on an unweighted 3-point scale, and studies were considered low quality with a global score of 0-6 (non-comparative) or 0-10 (comparative); medium quality studies scored 7-12 (non-comparative) or 11 – 18 (comparative); high quality studies scored 13-16 (non-comparative) or 19-24 (comparative).

Quality assessment of qualitative studies is much less straight forward relative to quantitative research. Qualitative research can take a wide range of methodological approaches, and whilst there are some elements that have been identified as necessary for transparent and more representative results, these studies are more disparate in their conduct. There is on-going debate about whether quality assessment can even be performed(66,67), and there is no agreed approach(68). Majid and Vanstone's recent review identified some of the key appraisal tools for qualitative evidence synthesis. The Critical Appraisal Skills Programme (CASP) Qualitative checklist is the most commonly used qualitative study appraisal tool and has been judged to be easy to administer(68). It involves two screening questions, and eight appraisal questions on domains such as research design, recruitment strategy and ethical issues(69). Feder et al used the CASP checklist with equal weighting of the various domains and with alternative approaches weighting the domains differently but found no significant difference between these methods in terms of the overall rating of the studies. For this study an unmodified CASP checklist was used.

Data extraction

Data were extracted from the included studies using a pre-prepared proforma under the following headings: Study details, Participants, Diagnostic test,

Patient-Centred Outcome(s). The proforma was iteratively developed after initial data extraction for 10 papers, with the addition of further sub-headings under the Patient-Centred Outcome(s) section to include all PCOs measured.

Narrative synthesis

It was anticipated that there would be a small number of MRI studies measuring patient centred outcomes, given that MRI is a relatively new test for prostate cancer diagnosis. Transrectal and transperineal biopsy techniques under ultrasound guidance have been used in clinical practice for much longer than MRI, so more studies of these tests were expected from the database searches. No limits were placed on the study design in the inclusion/exclusion criteria, therefore observational and non-randomised studies were likely to be included, as well as RCTs. Meta-analyses tend to be limited to RCTs, given the higher levels of heterogeneity between non-randomised and observational studies. There are currently no agreed methods for performing a meta-analysis of observational studies(70), and some bodies, such as the Centre for Reviews and Dissemination at the University of York(71), recommend against attempting it in most situations. Therefore, a narrative synthesis was performed to summarise and compare the included studies.

PRISMA reporting guidelines

The Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement(72) is one of the most widely cited reporting guidelines for systematic reviews and is followed by numerous peer-reviewed published systematic reviews. This chapter has been written with reference to the PRISMA statement.

Protocol publication

The protocol for this systematic review has been published on PROSPERO, an international prospective register of systematic reviews hosted by the University of York (See Appendix 2.2)

2.3 Results

2,762 records were identified for screening through database and hand searching. After removal of duplicates and screening of title & abstract, 220 full text articles were assessed, and 96 papers were included in the systematic review. A full breakdown of study selection and reasons for full text exclusions can be found in figure 2.1.

PRISMA 2009 Flow Diagram(72)

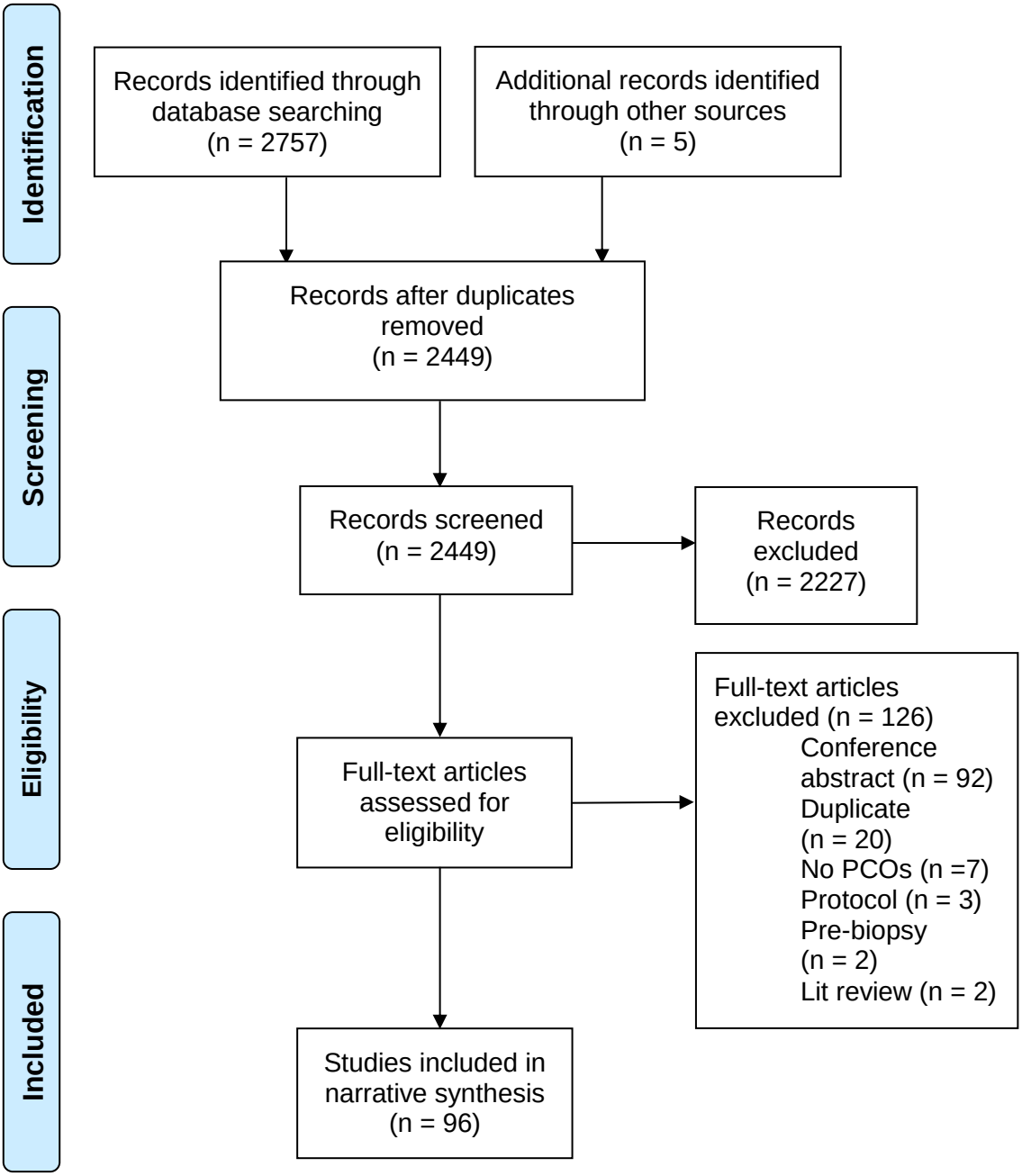


Figure 2.1 – 2009 PRISMA diagram outlining the number of studies identified, screened and included in this systematic review

Study quality

Randomised studies

38 randomised studies were included in this systematic review. The risk of bias for each study, based on the five criteria in the Cochrane Collaboration Risk of Bias tool v 2.0, is shown in table 2.1. The majority of included RCTs (26/38, 68.42%) were judged to be at high risk of bias. Four studies were considered low risk(54,73–75).

Author	Year	Randomisation	Deviation	Missing data	Measurement	Selection	Overall
Adamakis	2004						High risk
Aktoz	2010						High risk
Alam	2017						Some concerns
Bruyere	2007						Some concerns
Cazarim	2018						Low risk
Damiano	2004						High risk
Doganca	2015						High risk
Fabiani	2016						High risk
Feltes-Ochoa	2006						High risk
Fink	2005						High risk
Ghafoori	2015						High risk
Giannarini	2009						Low risk
Giovanni	2009						High risk
Hara	2008						Some concerns
Horinaga	2006						High risk
Imani	2015						High risk
Iremashvili	2010						Some concerns
Jones	2004						High risk
Kang	2011						High risk
Kasivisvanthan	2018						Low risk
Kilciler	2007						High risk
Klein	2010						High risk
Kucur	2015						Some concerns
Lodeta	2012						High risk

Martella	2009						High risk
Naughton	2001						High risk
Novac	2013						High risk
Ooi	2013						Some concerns
Ozcan	2017						High risk
Powell	2014						Some concerns
Song	2011						High risk
Song	2006						High risk
Stirling	2002						High risk
Stravodimos	2007						High risk
Udeh	2015						High risk
Wu	2001						Low risk
Yang	2016						High risk
Zargar	2015						Some concerns

Table 2.1 – Risk of bias assessment for included RCTs. Green (low); Yellow (medium); Red (High)(64)

Author	Year	Aim	Consecutive pts	Prospective data	Endpoints	Unbiased assess	Fup appropriate	Loss to fup	Size calc	**Subtotal**	Adequate control	Contemporary	Equal groups	Analysis	**Total**
Ahmed	2017	2	2	2	2	2	0	2	2	14					
Aktas	2014	2	1	1	2	0	1	2	1	10	1	1	2	2	16
Al Rumaihi	2012	2	2	1	2	0	0	0	0	7	1	0	2	1	11
Avci	2003														
Awsware	2008	2	0	0	2	2	2	0	0	8					
Bulbul	2002	2	0	0	1	0	0	2	0	5	1	1	0	1	8
Cai	2017	2	2	1	2	2	2	0	0	11	1	1	1	2	16
Crundwell	1999	2	1	0	1	2	1	1	0	8					
Dowrick	2016	2	1	2	2	0	2	1	0	10					
Egbers	2015	2	2	2	2	2	1	2	0	13					
Gaylis	2016	2	1	1	2	0	2	1	0	9					
Gomez-Gomez	2015	2	0	1	2	0	1	0	0	6					
Gu	2015	2	1	0	2	0	1	0	0	6					
Hadaschik	2011	2	1	0	2	0	0	0	0	5					
Helfand	2013	2	1	2	2	0	1	1	0	9					
Hou	2015	2	0	2	2	0	1	2	0	9					

Irani	1997	1	0	0	1	0	1	0	0	3					
Jhan	2018	2	0	1	2	0	0	0	0	5					
Kahriman	2011	2	1	0	2	0	1	1	0	7					
Kim	2015	2	2	2	2	2	1	1	0	12	1	2	2	2	19
Koprulu	2012	1	0	0	2	0	2	0	0	5	1	0	1	1	8
Kuru	2011														
Kuru	2013	2	1	1	1	1	1	0	0	7					
Larsson	1999	2	2	1	2	1	1	0	0	9					
Lee	2015	2	1	1	2	1	1	0	0	8					
Linden-Castro	2016	2	2	0	2	0	2	2	0	10					
Losa	2013	2	0	2	2	0	2	0	0	8					
Lu	2017	2	2	1	1	0	1	0	0	7					
Makinen	2002	2	1	2	1	0	1	2	0	9					
Matin	2009	2	2	1	1	1	1	2	0	10					
Medd	2005	2	2	2	2	2	1	2	0	13					
Merrick	2016	1	1	1	2	0	2	0	0	7					
Miah	2018	1	2	2	2	2	1	2	0	12					
Nafie	2017	2	0	1	1	0	0	0	1	5					
Oba	2014	2	2	2	2	0	2	1	2	13					
Ozveri	2004	2	1	2	2	1	2	1	0	11	1	1	1	2	16
Pal	2012	1	1	0	1	0	0	0	0	3					
Pepe	2016	1	0	2	2	0	2	2	0	9	1	2	0	1	13

Pepe	2013	1	0	1	1	0	1	2	0	6	1	2	1	1	11
Pokorny	2014	2	2	2	2	1	1	2	0	12	2	2	2	2	20
Raaijmakers	2002	1	2	2	2	1	1	2	1	12					
Rietbergen	1997	2	2	2	1	1	2	0	0	10					
Ristau	2018	1	1	2	1	0	0	1	0	6					
Robins	2018	2	1	2	2	0	0	2	2	11	1	2	1	2	17
Rosario	2012	2	1	2	2	1	2	1	1	12					
Saracoglu	2012	2	1	2	2	0	1	1	0	9					
Sarkar	2016	1	1	2	2	1	1	1	0	9					
Schwarzman	2018	2	2	1	2	0	2	1	0	10					
Song	2017	2	1	2	2	2	1	1	1	12	2	2	1	2	19
Spajic	2006	0	1	0	1	0	1	0	0	3					
Stanley	2016	2	1	2	1	0	1	0	0	7	1	2	1	1	12
Tilak	2015	2	1	1	1	0	1	0	0	6	1	1	1	2	11
Vasudeva	2015	2	1	2	1	0	2	2	0	10					
Wadhwa	2017	2	1	2	2	0	1	0	0	8					
Wang	2018	2	2	1	1	0	0	0	0	6					

Table 2.2 – Study quality assessment of observational studies (2 reported and adequate; 1 reported, not adequate; 0 not reported; Red ‘low quality’; yellow ‘medium quality’; green ‘high quality’)(65)

Author	Year	Aims	Methods	Design	Recruitment	Collection	Relationship	Ethics	Analysis	Findings	Value
Avery	2008										
Chapple	2007										
Oliffe	2004										

Table 2.3 – Study quality assessment of qualitative studies (Red 'not considered'; yellow 'considered to some degree'; green 'well performed')(69)

Non-randomised and observational studies

55 studies using non-randomised or observational designs met the inclusion criteria. The assessment of quality for each study using the MINORS checklist(65) is presented in table 2.2. The majority of included non-randomised and observational studies were of medium quality (40/59, 67.8%). Six studies were considered to be of high quality(53,76–80).

Qualitative studies

Three qualitative studies were included from the database searches. The quality assessment for these included studies based on the CASP checklist is in table 2.3. All three studies generally presented sufficient detail and justification for the aims, methods and study design. None of the three papers included discussions about reflexivity and the role of the researcher in the data collection or analysis, and discussion about ethical issues was generally absent or limited.

Study characteristics

50 (52.08%) of the included studies were conducted in Europe and Central Asia, with the remainder mostly in the East Asia & Pacific region (21/96, 21.88%) and North America (13/96, 13.54%). The vast majority (76/96, 79.17%) of studies were conducted in high-income countries. Mean ages for participants in included studies ranged from 43.4 – 71.5 years, and numbers of participants ranged from 8 to 5,676.

10 studies included mpMRI or MRI guided biopsy (MRI-GB) as a diagnostic test being assessed, and they varied widely in terms of study design, participant numbers, and PCOs measured. No studies employing bpMRI that measured PCOs met the inclusion criteria. Four studies included mpMRI/MRI-GB and TRUS-GB. Kasivisvanthan et al randomised patients to mpMRI, with MRI-GB if a lesion was detected, or TRUS-GB(54) in a multi-centre, randomised, non-inferiority trial. Three studies compared mpMRI with subsequent MRI-GB to TRUS-GB in the same patients(53,79,80). All four studies were assessed as having a low risk of bias. Table 2.4 (below) shows a comparison for the PCOs measured between MRI and TRUS-GB.

90 studies included TRUS-GB as a diagnostic test for prostate cancer. Most of these studies were comparing two or more approaches to reduce pain from the biopsy procedure, using interventions such as different methods of pain relief, patient position, or probe/needle gauge. The three qualitative studies included in this review all interviewed men who had undergone TRUS-GB to understand their experiences of the test.

Patient centred outcomes

23 different PCOs were measured across the 96 included studies. Studies involving mpMRI/MRI-GB measured an average of 4.9 PCOs, with TRUS biopsy studies measuring 3.3 PCOs per study. The number of PCOs measured in individual studies varied from 1 to 11. Included papers very seldom justified their selection of PCOs to measure.

Further discussions of individual PCOs measured follows below.

Pain

Pain was the most commonly measured PCO across all included studies. 54 (56.25%) studies measured pain; 46 (85.19%) of which utilised a visual analogue scale (VAS). The majority of studies measured pain within hours of the procedure being performed (median 0 hrs, range 0 – 168hrs). Participants in arms of the mpMRI/MRI-GB studies reported a smaller and narrower range of pain scores on a 10-point scale (VAS 0-2.7) compared to the TRUS-GB studies (VAS 0.28 – 8.02).

Author	Year	Pain	Urethral bleeding	Haematospermia	Rectal bleeding	Urinary retention	Fever	UTI	Urosepsis	ED	Incontinence	QoL	Vasovagal
Ahmed	2017												
Egbers	2015												
Kasivisvanthan	2018												
Pokorny	2014												

Table 2.4 – PCOs from studies comparing mpMRI/MRI-GB to TRUS-GB (Blue favours mpMRI/MRI-GB; Orange favours TRUS-GB; Black PCO not measured)

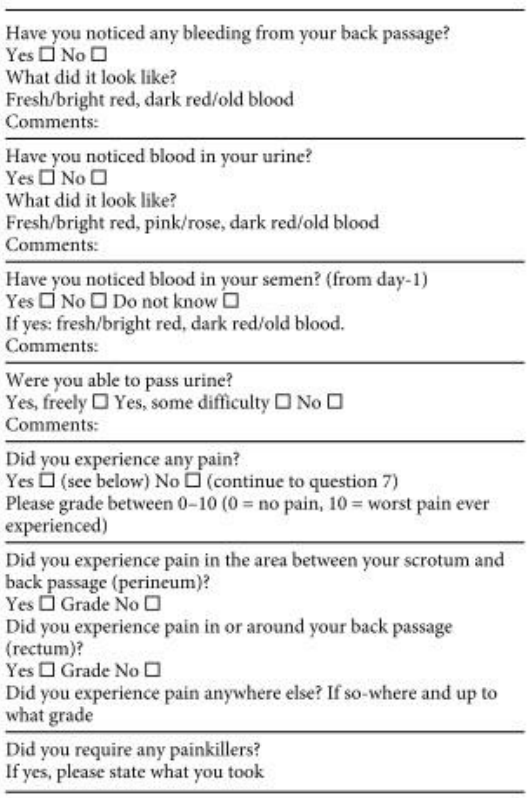
Bleeding

Bleeding following investigation was the other PCO that was commonly measured and was included in 48 (50%) studies. Bleeding was categorised as urethral bleeding, rectal bleeding, haematospermia, or haematoma. The proportions of patients reporting bleeding after biopsy varied widely between studies, and the range of values reported in the mpMRI/MRI-GB studies (0.94% – 88.4%) and TRUS-GB studies (0.07% – 91.8%) were broadly similar.

Bleeding was measured through self-report from patients via survey or interview in all but six studies. Sarkar et al measured patient reported experience using a questionnaire (see Figure 2.2) the authors had developed for transperineal template guided saturation biopsy in the absence of an appropriate validated questionnaire(81). Rosario *et al* developed and validated a patient reported outcome measure survey (the ProBE questionnaire) to assess short-term outcomes of prostate biopsy performed for men in a PSA screening trial(82), which was adapted and used by Wadhwa et al(83).

Infection

Urinary tract infection (UTI) and urosepsis are also important adverse effects from undergoing a prostate biopsy and were measured in 29 (30.21%) included papers. A mixture of more objective measures, such as a recorded fever, urine culture, or clinical notes review, and patient self-report were utilised to assess for signs of infection. Sepsis (0.4% - 1.6%) occurred less commonly than UTI (1% - 9.2%) across the studies which measured this outcome.



Have you noticed any bleeding from your back passage?
Yes ☐ No ☐
What did it look like?
Fresh/bright red, dark red/old blood
Comments:

Have you noticed blood in your urine?
Yes ☐ No ☐
What did it look like?
Fresh/bright red, pink/rose, dark red/old blood
Comments:

Have you noticed blood in your semen? (from day-1)
Yes ☐ No ☐ Do not know ☐
If yes: fresh/bright red, dark red/old blood.
Comments:

Were you able to pass urine?
Yes, freely ☐ Yes, some difficulty ☐ No ☐
Comments:

Did you experience any pain?
Yes ☐ (see below) No ☐ (continue to question 7)
Please grade between 0–10 (0 = no pain, 10 = worst pain ever experienced)

Did you experience pain in the area between your scrotum and back passage (perineum)?
Yes ☐ Grade No ☐
Did you experience pain in or around your back passage (rectum)?
Yes ☐ Grade No ☐
Did you experience pain anywhere else? If so-where and up to what grade

Did you require any painkillers?
If yes, please state what you took

Figure 2.2 – PREM from Sarkar *et al*(81)

Urinary retention

23 studies (23.96%) assessed whether patients went into acute urinary retention after undergoing a prostate biopsy. This PCO was mostly measured within weeks of undergoing the biopsy (median 14 days, range 1-56). Consistent with most other PCOs, this was measured by self-report in the majority of studies. Sarkar *et al*(81) used PREMs (as outlined above), and Dowrick *et al* employed the Expanded Prostate cancer Index Composite (EPIC-26)(84). Kasivisvanthan et al featured MRI-GB via the transrectal or transperineal approach and found a slightly higher rate of retention in the patients undergoing MRI-GB (1.4%) versus TRUS-GB (1%)(54). 22.6% (56/249) of men suffered urinary retention in the study by Miah et al(85), which used MRI-guided transperineal template mapping biopsy. Retention was much less common in the other studies which used TRUS-GB (0.1% -11%) or MRI/TRUS fusion biopsy (1.9%).

Erectile dysfunction

Problems achieving and/or maintaining erection after prostate biopsy are recognised as a potential adverse effect. Eight studies used the International

Index of Erectile Function (IIEF)(83,86–92), with most studies showing a non-significant decrease post-biopsy (changes in IIEF -0.15 to -9.02) with the exception of Miah *et al* (IIEF pre-biopsy 47.7 vs post-biopsy 38.7 p<0.001). Dowrick *et al* used the EPIC-26 scale(85) and three used self-report methods(53,54,94) to measure this outcome. Follow-up time for this PCO was also longer than for other PCOs (median 30 days, range 20-90).

Lower Urinary Tract Symptoms

Symptoms such as waking frequently in the night to pass urine (nocturia), passing urine often (frequency), and having a poor stream are amongst a group of symptoms commonly referred to as lower urinary tract symptoms (LUTS). LUTS usually occur due to diseases of the prostate and can also occur after prostate biopsy. 8 of 14 studies measuring LUTS used the International Prostate Symptoms Score (IPSS)(84,85,88–90,93,95,96), which is an internationally recognised and validated score for symptoms resulting from prostatic disease. Miah *et al* was the only MRI-GB study measuring IPSS and showed a significant worsening of LUTS at 56 days post-biopsy (10.93 +/- 6.77 vs 11.76 +/- 6.56 p = 0.024)(97). In the TRUS-GB studies, having a high prostate volume(95), presence of renal calculi(96), and a periprostatic nerve block(87) were associated with worsening of LUTS.

Psychological effects

Five studies measured anxiety levels following prostate biopsy(85,98–101); four assessed for signs of possible depression(85,93,98,101); and two measured stress levels associated with the procedure(79,101). A range of validated questionnaires were used to measure these effects, including the Hospital Anxiety and Depression Scale (HADS)(98,101), the Generalised Anxiety Disorder Scale (GADS)(93), and the Patient Health Questionnaire-9 (PHQ-9)(93). Stanley *et al* was the only study to measure anxiety relating to undergoing an MRI scan and found that there was no difference whether patients received a sensory intervention aimed at reducing anxiety or not. 39% of participants in both the intervention and control groups reported pre-procedure anxiety(99). Awsare *et al*(101) and Dowrick *et al*(84) found lower levels of anxiety after undergoing TRUS-GB compared to baseline using the HADS and GAD-7 respectively. Linden-Castro *et al*(98) and Saracoglu *et*

al(100) found no change in anxiety. No studies found any change in depression scores. Qualitative interviews from Chapple *et al*(103) and Oliffe(104) suggested that psychological factors may have affected patient's perceptions of pain, and the minority experienced significant stress and anxiety from the biopsy.

Quality of life and patient satisfaction

Eight studies assessed for changes in quality of life (QoL) for patients undergoing prostate biopsy. All of these studies used different measures to assess this PCO, including the IPSS(95), EuroQoL version 5 (EQ-5D)(54), short form 36 of the Health Index(105), and an adapted ProBE PROM(83). Kasivisvanthan *et al* found a small, non-significant difference in change in QoL after MRI-GB (EQ-5D score -0.0004) compared to TRUS-GB (-0.27 $p > 0.05$). Miah *et al* found a significant reduction in QoL using the IPSS following transperineal template MRI-GB (1.57 +/- 1.28 vs 1.76 +/- 1.39 $p = 0.03$). High prostate volume(95), the presence of renal calculi(96), and periprostatic nerve block(87) were associated with reduced QoL, however three other TRUS-GB studies found no difference(84,89,105). Six studies measured patient satisfaction from undergoing the procedure, mostly using a Likert scale(106–108) or VAS(73) to assess for differences between analgesic techniques in TRUS-GB studies.

2.4 Discussion

Key findings

Pain and bleeding were the most commonly measured patient centred outcomes resulting from mpMRI, MRI-GB and TRUS-GB for investigation of possible prostate cancer. A number of other outcomes, such as infection, erectile dysfunction and urinary symptoms were assessed in some studies included in this systematic review. PCOs measured were mainly physical or psychological in nature. No studies that were included in this review assessed the behavioural or cognitive effects of prostate cancer diagnostic tests. There was wide variation in study quality, PCOs measured, tools to assess each PCO, follow-up of patients, and results across these studies. In the four studies which compared mpMRI and subsequent MRI-GB to TRUS-GB, most adverse PCOs were less frequently reported with MRI-based investigations. Qualitative studies of men's experiences of undergoing transrectal biopsy suggested most found it "uncomfortable". Meta-analysis of quantitative studies was not attempted due to significant study heterogeneity.

Comparison with existing literature

This is the first systematic review of PCOs associated with mpMRI/MRI-GB 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 following early reports in the field(109). The authors looked at TRUS-GB only and considered the relationship of these outcomes with factors such as analgesic approaches and type of approach to TRUS-GB. They found that there is evidence suggesting a transient increase in LUTS, and a relationship between TRUS-GB and erectile dysfunction in the short-term. The authors felt the impact on erectile dysfunction needed further research to determine the aetiology of this effect. There was limited justification for choosing to focus on these outcomes, or why others weren't included.

Efficace *et al* undertook a systematic review of health-related quality of life (HRQoL) measurements performed in RCTs relating to prostate carcinoma patients(110). The authors found a range of HRQoL assessments were used, and some studies had methodological limitations that could have affected the measurement of HRQoL. The same authors assessed the methodological

quality of PROs in RCTs with prostate cancer patients in 2014(111). PRO quality improved over time, and approximately 20% of PROs assessed were considered to gather sufficient detail to inform clinical practice and health policy. These two systematic reviews only focused on studies of conventional prostate cancer treatments, excluding any other intervention such as diagnostic testing or alternative therapies.

There is growing recognition of the importance of PCOs for diagnostic tests within radiology, especially in the USA with the establishment of PCORI(112). 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, which are not easily captured with existing measures used in research(113). The relationship between these short-term effects and the ultimate patient outcome may be tenuous as diagnostic testing makes up just one element in a patient's illness journey(114).

This review found very little evidence of patient involvement in identifying PCOs 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 what the important patient outcomes for radiology research are(115). A recent study of patient-centred outcomes in primary care for imaging tests interviewed patients who had undergone x-ray, Computerised Tomography (CT) scan, MRI, or ultrasound in the 12 months prior. The four key themes for PCOs 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(116). Studies in this systematic review appears to consider the latter two patient priorities, but don't consider the knowledge gained or the impact of MRI or TRUS-GB 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 was deliberately broad to include as many relevant studies as possible to obtain a clear picture of current research. Some recent studies comparing mpMRI/MRI-GB to TRUS-GB were identified, allowing some tentative conclusions to be drawn between the two diagnostic tests regarding their comparative effectiveness.

This systematic review has some important limitations that affect the generalisability of the results. There were a limited number of MRI studies relative to studies that assessed TRUS-GB, and no studies that measured PCOs from bpMRI. This was not unexpected and was one of the reasons behind my decision to include both the current gold standard diagnostic test (TRUS-GB) and the new tests (MRI and MRI-GB) in the review. Most included studies were considered to be at moderate-to-high risk of bias, and there was significant heterogeneity between studies in all aspects, which limits the comparability. However, the four studies that included mpMRI/MRI-GB and TRUS-GB were all at low risk of bias, meaning some comparisons could be drawn with confidence.

Implications for policy and practice

Within the limited evidence currently available, there is some indication that mpMRI and MRI-GB may perform better than TRUS-GB in terms of patient-centred outcomes. TRUS-GB is the current standard diagnostic test for prostate cancer, despite its known limitations(27). Following on from the PROMIS(53) and PRECISION(54) trials showing the diagnostic accuracy of mpMRI and MRI-GB for prostate cancer, the National Institute for Health and Care Excellence (NICE) in the UK has recently updated guidelines for prostate cancer to include a recommendation for pre-biopsy mpMRI in all patients with possible prostate cancer(12). 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-GB truly do outperform TRUS-GB in key domains outside of diagnostic accuracy.

2.5 Conclusions

The movement towards demonstrating comparative effectiveness between different healthcare interventions is driven by the need to help patients decide which test or intervention to undergo and to improve the value of healthcare services for patients. PCOs have been measured in studies of diagnostic tests for prostate cancer in terms of the physical and emotional effects for patients, but evidence is lacking for the social, cognitive, and behavioural impacts. mpMRI and MRI-GB appear to perform generally better compared to TRUS-GB in the PCOs which have been measured. However, patients need to be involved in the selection of PCOs to be measured in diagnostic test research, and PCOs need to be better integrated into study design and analysis. These steps will produce better evidence to inform clinicians and policy makers about the re-design of diagnostic pathways for prostate cancer, to improve the diagnosis of clinically significant prostate cancer and the diagnostic experience for patients.

The next chapter in this PhD focuses on another key element of the CanTest framework for patients; the acceptability of prostate MRI as a diagnostic test for prostate cancer.

Chapter 3 – Acceptability, understanding and experience of diagnostic tests for prostate cancer: a qualitative study with patients and GPs

Chapter two demonstrated that prostate MRI appears to have more favourable patient centred outcomes than the traditional diagnostic test for prostate cancer, an ultrasound guided biopsy. Another important feature of a new diagnostic test that should be understood prior to implementation is the acceptability of the test. This applies not only to patients undergoing the test, but also to clinicians ordering, performing and interpreting the test. This chapter seeks to understand the acceptability of prostate MRI for patients and GPs using a theoretically informed approach, and addresses objective two of the PhD.

3.1 Introduction

The traditional gold standard diagnostic test for prostate cancer has been a transrectal or transperineal ultrasound guided (TRUS) biopsy of the prostate. Magnetic Resonance Imaging (MRI) of the prostate, and reporting using the PiRADS version 2(117) reporting system, has been compared to TRUS biopsy in recent large, multicentre trials(53,54) in the UK and other high-income countries, with favourable results in terms of diagnostic accuracy. Few studies have been performed assessing other aspects of the implementation of MRI for prostate cancer diagnosis, including patient experience or understanding, and clinician acceptability, which is not uncommon in diagnostic research(118).

Implementation of new diagnostic tests into routine clinical practice, such as MRI for prostate cancer, should ideally follow a rigorous process of evaluation, from showing analytical validity and diagnostic accuracy, through to acceptability and cost effectiveness. A number of frameworks for assessing and evaluating tests for use in healthcare have been proposed(42,119–123). They suggest the test should be able to be performed by the operator(s); it should

demonstrate more patient benefit than harm; it should be cost effective relative to currently available tests; it should be able to be integrated into the diagnostic pathway; and it should be acceptable to patients and clinicians.

Acceptability of diagnostic tests has been measured in a number of ways, but no agreed definition for 'acceptability' exists(124). Sekhon *et al* have proposed a 'Theoretical Framework of Acceptability' (TFA) relating to healthcare interventions, not just diagnostic tests, which includes seven key constructs (See Figure 3.1): Affective attitude, Burden, Ethicality, Intervention coherence, Opportunity costs, Perceived effectiveness, Self-efficacy(125). The definition of acceptability and the TFA were developed by Sekhon *et al* by performing a review of systematic reviews of acceptability of healthcare interventions, then applying deductive and inductive reasoning to theorise the concept of acceptability and design a theoretical framework. This framework is intended to be applicable to both patients and clinicians involved in healthcare interventions and has a number of key constructs that are particularly relevant to the study aims. Eliciting how a patient feels about undergoing prostate MRI ('Affective attitude'), the extent to which patients and clinicians understand the test and its purpose ('Intervention coherence'), and how likely they perceive MRI will achieve the purpose of diagnosing prostate cancer ('Perceived effectiveness') will aid understanding in the acceptability of MRI as a diagnostic test.

Studies of patient acceptability of TRUS prostate biopsy for prostate cancer have focussed on the prevalence of side effects and patient anxiety relating to the test(126–128). Only two studies to date have assessed patient acceptability of MRI tests for prostate cancer, which also involved questionnaires assessing side effects and attitudes towards the test(79,128). There are no studies that examine acceptability of MRI as a diagnostic test for prostate cancer with any theoretical underpinning, and questions remain about men's experience of undergoing the test and receiving the results. There are also very few studies involving GPs, or other primary care clinicians, and exploring their understanding of diagnostic tests for prostate cancer outside of Prostate Specific Antigen (PSA).

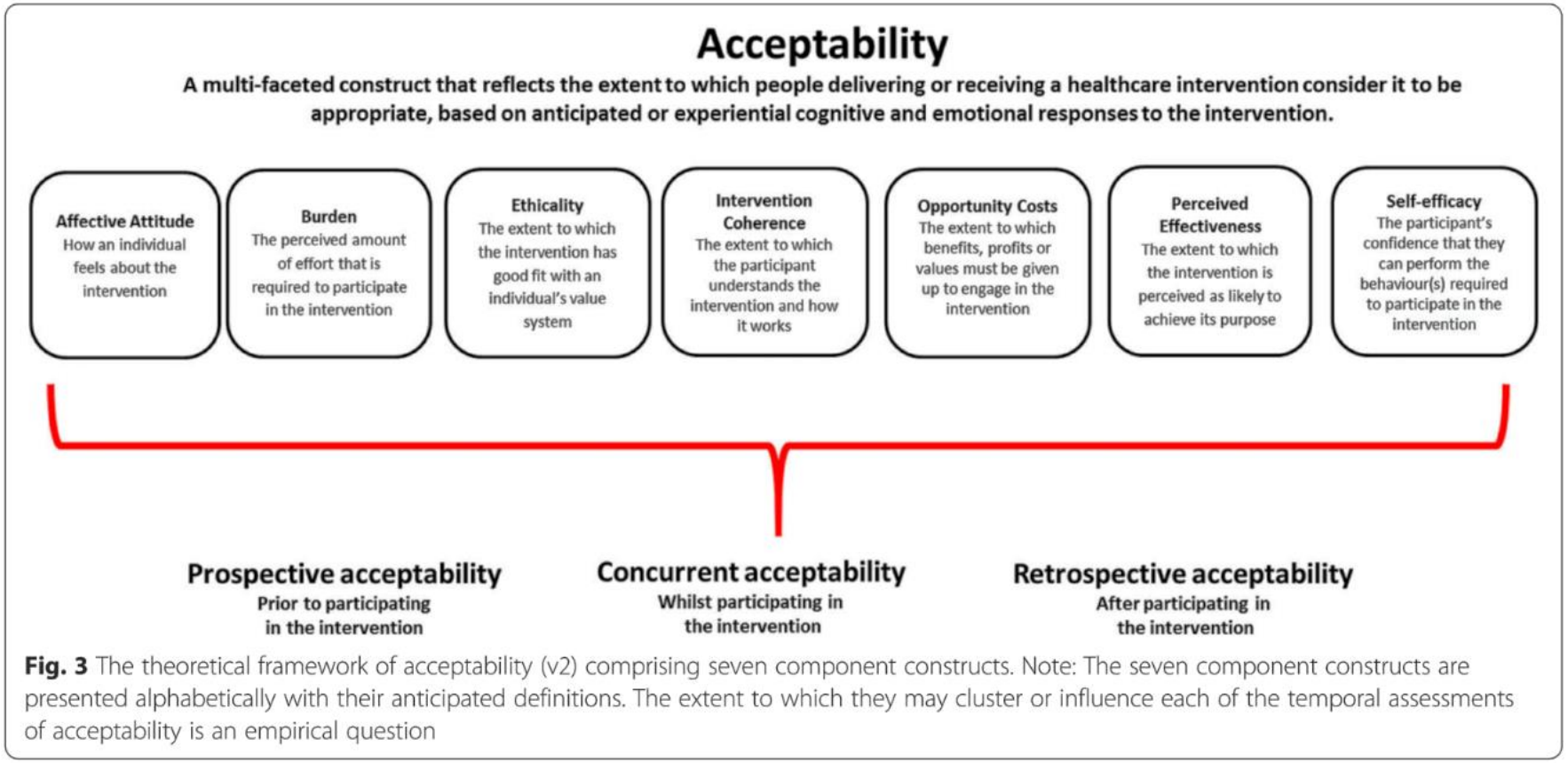


Fig. 3 The theoretical framework of acceptability (v2) comprising seven component constructs. Note: The seven component constructs are presented alphabetically with their anticipated definitions. The extent to which they may cluster or influence each of the temporal assessments of acceptability is an empirical question

Figure 3.1 – Sekhon's Theoretical Framework of Acceptability

The aim of this study was to understand, from the perspective of patients and GPs, the acceptability of mpMRI for men as a diagnostic test for prostate cancer. Given that mpMRI is one test within a diagnostic pathway, and it is not used in isolation, this study also sought to elicit the experiences of patients and GPs of the current prostate cancer diagnostic pathways and all tests involved.

3.2 Methods

This qualitative study employed semi-structured interviews with men referred from primary care with possible prostate cancer who had undergone prostate MRI, and GPs who have referred men with possible prostate cancer for further investigation. Qualitative research methods lend themselves to increasing the understanding of patient and clinician acceptability with regard to diagnostic tests. Such methods allow researchers to “uncover the nature of a person’s experience with a phenomenon” such as cancer and “understand what lies behind any phenomena”(130). Interview studies provide the opportunity to dig deeper and explore how and why patients and clinicians form their beliefs and understanding. Semi-structured interviews were the most appropriate method for data collection for this study. Focus groups could have been an alternative method to employ, however issues relating to the prostate can be a sensitive topic for some men to discuss, possibly limiting the engagement of some participants. Survey methods could also have been used, however there is no opportunity to ask follow-up questions and explore people’s experiences in detail with such an approach.

The aim of this study is to understand the experiences of the current prostate cancer diagnostic pathways in the eyes of patients and GPs. I assumed that the meanings of experiences applied by the participants would come from their interactions with the prostate cancer pathway and the MRI scanners. As such, constructivism was adopted at the epistemological approach and underlying theoretical perspective underpinning the conduct and analysis of this research(131). It was assumed that each participant will experience the prostate cancer diagnostic pathway and the diagnostic tests differently, influenced by both internal (e.g. fears/anxieties about a possible diagnosis of cancer) and external (e.g. experiences of family or friends being investigated for a possible cancer) factors, and therefore no one ‘truth’ exists when it comes to the experience of being investigated for suspected prostate cancer.

Participants

This study recruited participants from two populations;

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

Patients who already had a diagnosis of prostate cancer and were undergoing MRI for active surveillance or watchful waiting were not invited to participate, as the focus of this study was on the role of MRI in the diagnosis of prostate cancer rather than management. GPs and patients were recruited separately, and not in dyads.

A purposive sampling approach was be taken for participant recruitment to this study in order to attempt to obtain a diverse group of participants and experiences. This allowed recruitment of a sample of men with a range of PiRADS v2 scores (1-2 being low risk of prostate cancer; 3-5 being medium-high risk), ages (<70 years or 70+ years), geographical locations (urban or rural/countryside), and ethnic backgrounds (any white background / Black or Minority Ethnic [BME]). In terms of GPs, a purposive sampling approach allowed recruitment of clinicians with a range of ages, genders, practice locations (urban or rural) and levels of experience. See the *Recruitment* section below for more information about how purposive sampling was performed. Approximately 30 participants (10 GPs and 20 patients) were expected to be interviewed for this study, although the recruitment of participants was intended to cease when no new major themes emerged during interview coding.

Recruitment

Recruitment sites were selected to increase the diversity in the sample of patients and GPs in terms of geography, ethnicity, age, gender (GPs), and clinical experience (GPs). Recruiting a diverse sample was important to obtain a range of views and experiences of diagnostic testing for prostate cancer and of different prostate cancer pathway designs.

Patients were recruited from two NHS Trusts: the Imperial College Healthcare NHS Trust in London and the Royal Devon & Exeter NHS Foundation Trust in Exeter. Most men referred by their GP for possible prostate cancer undergo an MRI prior to clinical review by a Urologist and potentially a prostate biopsy, depending on the MRI report (see Appendix 3.1 & 3.2). Research nurses and/or fellows working within the clinic 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 – see Appendix 3.4), with instructions on how to contact the lead researcher (myself) to express interest in participating. Regularly communication with staff at the study sites about patient recruitment was undertaken to ensure a range of age, ethnicity and geographical backgrounds were present in the study sample. Follow-up contact was made by the research nurse/fellow once if the man did not contact the lead researcher to check whether they wish to participate in the study or not. Reasonable travel costs for patient participants to attend a face-to-face interview were reimbursed, and participants were offered a gift voucher in recognition of contributing their time to participate in the study.

GPs were recruited through two National Institute for Health Research (NIHR) Clinical Research Networks (CRNs): North West London CRN and the South-West Peninsula CRN (see Appendix 3.3). The CRNs identified local practices from which to recruit eligible GPs to participate in this study, favouring Research Site Initiative (RSI) practices as these practices have an ongoing commitment to research and may have allocated research clinician time. In practices that did not have funded research clinician time, the CRNs provided financial support for participation in the study. Eligible GPs were identified by the CRN and the practices, and regular communication was used regarding progress of recruitment. GPs chosen for invitation into the study were given a PIL (see Appendix 3.5) to consider participating in the study, and follow-up contact will be made by the CRN to confirm participation. GP practices were reimbursed for the GP's time to participate in an interview.

Consent procedures

Consent was taken at the start of the interview. The purpose of the study and the interview was explained in conjunction with the information presented in the PIL. Each participant's ability to consent was assessed, and then the participant was presented with a consent form (see Appendix 3.6) to complete if they were still willing to participate in the study.

Conducting patient interviews in their own home sometimes resulted in other parties being present during the interview, such as the patient's spouse. If another person was present, the patient participant was asked if they were happy to be initially interviewed in private. If the patient participant wished for another person to be present, the additional person was also consented for participation and asked to complete a consent form before they joined the interview.

Data collection

One-to-one interviews were conducted for all participants in this study between July and November 2019. Patient participants were mostly interviewed face-to-face in their own home. If this was not acceptable to a patient participant, the interviews were either conducted at an alternative location or via telephone. All GP participant interviews were conducted via telephone.

A semi-structured approach was followed, with separate interview topic guides for patient and GP interviews to support discussions (see Appendix 3.7 & 3.8). The topic guide was developed to incorporate all aspects of the current prostate cancer diagnostic pathway in the UK, with a particular focus on the participant's experience and understanding of MRI. This was iteratively refined through discussions with the PhD supervisors, and some minor amendments were made following recommendations from the research ethics committee that approved the study. The topic guide was used flexibly within the interviews, to try to ensure that no key aspects of the diagnostic pathway experience were missed.

An encrypted audio recording device was employed to record all interviews, which were downloaded onto a secure university network computer drive for

storage. Written notes were taken during and immediately following the interviews, which were stored in a secure university research office. Repeated or follow-up interviews were not performed. Interview times ranged between 15-45 minutes each.

Data management

All audio data collected in the interviews were transferred to a trusted transcription service through a secure online platform, and transcribed verbatim. The written transcripts were then checked, edited and anonymised against the audio data to confirm accuracy and completeness. Transcriptions were imported into NVivo v12 to manage the data for the analysis. All electronic audio and data files related to this study were stored on an encrypted university laptop and backed up to secure university networked servers.

Data analysis

There were two main potential analytical approaches considered. Framework analysis, developed by Jane Ritchie and Liz Spencer at the National Centre for Social Research in the 1980s(132), is a systematic, rigorous, and transparent approach to qualitative data analysis with a series of interconnected stages a researcher follows to develop an understanding of the data(133). Framework analysis is often seen as falling within the group of analytical approaches known as content analysis. Framework analysis provides a structure, based on *a priori* themes, that the researcher can use to categorise and code the data in a transparent manner(134). Framework analysis could be considered a somewhat simpler analytical approach to engage with for less experienced qualitative researchers, but it potentially loses rich and insightful themes that come from the data which do not fit into the *a priori* categories chosen for the framework. Given that prostate MRI is not used in isolation for the investigation of possible prostate cancer, and insights about the experience of the prostate cancer diagnostic pathway were also being sought in this study, it was decided not to follow a Framework analysis approach.

Thematic analysis is another commonly used qualitative analysis method, first described by Virginia Braun and Victoria Clarke as ‘a method for identifying, analysing and reporting patterns (themes) within data’. There are a range of

different approaches within thematic analysis that can be undertaken, and themes can be identified inductively (generated from the data collected) or deductively (driven by the researcher). Thematic analysis searches for common and shared patterns of meaning across the data gathered(135), and provides a more flexible approach for this study with a set of different key objectives and two participant groups (patients and GPs).

The intention was to utilise Sekhon's Theoretical Framework of Acceptability (TFA)(125) to aid in understanding the acceptability of prostate MRI from the perspective of patients and GPs in the analysis. Employing a theoretical framework to underpin data analysis was important to clearly define acceptability and the relevant constructs that can be used to assess the acceptability of prostate MRI(136). Similar existing studies in this area have no underlying theoretical underpinning or justification for the measures used to assess acceptability, which has repeatedly been highlighted as a weakness in the literature(124). Using an existing theory therefore necessitates an analytical approach that can help apply the chosen theory to the data to understand the participant's view of MRI for suspected prostate cancer. Sekhon's Theoretical Framework of Acceptability can be applied prospectively, concurrently, or retrospectively in relation to the timing of the intervention or test, so the analysis approach looking at the acceptability of MRI for the patients was performed using their retrospective reflections and thoughts.

A deductive thematic analysis approach was used to answer the question of acceptability of MRI as a diagnostic test for possible prostate cancer using the constructs of Sekhon's TFA, and an inductive thematic analysis approach was used to understand the experiences of participants of the prostate cancer diagnostic pathway. Immersion in the data was initially undertaken through reading and re-reading individual transcripts and listening back to the audio recordings of the interviews. General thoughts and initial ideas were recorded throughout this process. A selection of early interviews were coded, and this initial coding framework was reviewed with my PhD supervisors in the first analysis meeting. Refinements to the coding approach and framework were discussed and agreed, and then the remaining interview transcripts were reviewed and coded, both inductively from the entirety of the data, and

deductively applying Sekhon's TFA to any discussion about MRI. The code lists were reviewed and arranged into categories and themes through an iterative process, returning to the original data as needed. The categories and themes developed were discussed and refined in the subsequent analysis meetings, and summary thematic diagrams were crafted to communicate the main themes and sub-themes identified and the relationships between them.

Reflexivity

I had no prior relationship with any of the participants in the study before the interviews were conducted. I am a middle-aged, white, male GP currently practicing within the NHS in the South-West of England. I was funded by Cancer Research UK (CRUK) through the CanTest Collaborative, a CRUK Catalyst Award supporting research into cancer testing in primary care. All patient and GP participants were made aware that I was a practicing medical doctor, that the study was part of my PhD, and that it was funded by CRUK. I did not reveal I was a GP, and any medical questions from patient participants were directed back to the participant's GP and/or treating urology team.

Having a clinical background, it was challenging to keep my 'researcher hat' on, and not think about what the patient participants were sharing with me from a clinical perspective. Using an interview topic guide helped me keep to questions that were most relevant to the research, and I felt I got better as my interviews progressed. I also undertook training in qualitative research interviews and data analysis and received feedback on my qualitative interview technique from the members of the supervisory team with qualitative research expertise. The training, experience, and feedback I have had has left me feeling more confident I could undertake and deliver on further qualitative studies in the future.

Patient & Public Involvement

This study received significant input from the PhD Patient & Public Involvement (PPI) group to inform numerous aspects of the research. 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. At one of

the biannual PhD PPI group meetings one of the anonymised patient interview transcripts was shared with the group, which was read and discussed to explore themes emerging from the text. The group was presented with a draft thematic diagram based on the analysis performed to date, and their feedback was integrated into subsequent drafts.

A study summary report was sent to all study participants after all data had been collected and analysed. Participant feedback was sought on the major findings of the study prior to preparation of this thesis chapter.

Ethical approval

This study received NHS Health Research Authority (HRA) approval (IRAS project ID 259602) and NIHR CRN portfolio adoption for the recruitment of NHS patients and GPs to participate in the study. Ethical approval was received from the NHS HRA South-West Frenchay research ethics committee (REC reference 19/SW/0040) (See Appendix 3.9)

COREQ reporting guidelines

This chapter has been written in accordance with the consolidated criterion for reporting qualitative research (COREQ) (137).

3.3 Results

Participants

Twenty-two patients were interviewed, and two chose to have their wives present and involved in the interview. A further three expressed an interest in participating but were not able to be contacted subsequently to arrange an interview. The ages of patient participants ranged from 47 – 80 years, 12 of whom lived in a rural area. Further details about patient participant demographics can be found in Table 3.1.

	Interviewees (n = 22)	**Not interviewed (n = 3)**
Age		
<65	8	2
65+	14	1
Geography		
Urban	10	3
Rural	12	0
Ethnicity		
White	19	1
BME	3	2
PIRADS v2		
1-2	6	0
3-5	15	0
Unknown	1	3

Table 3.1 – Patient demographics for those who expressed an interest in participating in the study

Ten GPs were interviewed. Another two GPs expressed an interest, but an interview time could not be arranged, and they subsequently chose not to participate. Most GP participants were female (n = 6) in the 41-50 year age range. Further details about GP participant demographics can be found in table 3.2.

	Interviewees (n = 10)	Not interviewed (n = 2)
Age		
31-40	3	1
41-50	6	1
50+	1	0
Gender		
Male	4	1
Female	6	1
Geography		
Urban	4	1
Rural	6	1
Role		
Partner	8	1
Salaried	2	1

Table 3.2 – GP demographics for those who expressed an interest in participating in the study

Acceptability of MRI for possible prostate cancer

All patient participants in this study had undergone an MRI scan as part of their diagnostic work-up for possible prostate cancer. The timing of the interviews in relation to the scan varied; some men had had their MRI scan a matter of days prior to the interview whilst others had undergone the scan weeks before. This was mainly due to the timing of recruitment and the ability of the researcher and the patients to find a mutual time to meet for the interview.

GPs working in the NHS cannot currently order an MRI of the prostate; the request must come from a secondary or tertiary care clinician. Therefore, it was attempted to apply Sekhon's TFA in a prospective fashion for them. However, not all GPs would engage with discussions about MRI and its role in prostate cancer during the interviews as they felt it was outside their clinical area.

> *"No, I mean, it's… it's not something that I, sort of… it's not something that enters my orbit." GP02 (Male, Rural, 31-40)*
> *"Well, it's great, but it's not available to me. It's not something I decide on." GP05 (Female, Rural, 41-50)*

Affective attitude refers to how the individual receiving or delivering the intervention feels about it. The vast majority of patient interviewees were positive about the idea of having an MRI of the prostate. They were quite happy to undergo a scan and would do so again if required.

> *"I'd go for any scan, anything like that. Needles don't bother me, scans don't bother me." P21 (Rural, 65+)*
> *I: "Okay. And if you had to have an MRI in the future, would you do it again?"*
> *P20: "Yeah. Fine. That was no great shakes, to be honest." (Urban, <65)*

The concept of using MRI as a test to detect prostate cancer was welcomed by some GP interviewees, even if they felt they had a limited understanding of the test and its potential role. Other GPs were reticent to give an opinion.

> *"I think it will be a really useful idea" GP03 (Male, Urban, 31-40)*
> *"I'm not sure I have a view on that either way so as a GP I tend to kind of... if you like, kind of restrict my opinion and expertise to things that I have direct contact with. And that... that... that diagnostic process... diagnostic process that takes place after referral is something that I... I'm not directly involved in, you know?" GP10 (Male, Rural, 41-50)*

GPs also considered the potential of MRI from the patient's perspective. They identified the non-invasive nature of the test as an attractive attribute for their patients relative to biopsy procedures.

> *"I guess, I would welcome something that would be non-invasive for patients because that's always good" GP05 (Female, Rural, 41-50)*

Even when a patient had a misleading result from his scan, where the abnormal area identified on the scan was not actually cancer, but cancer was found in a

biopsy sample from another part of the prostate, his opinion of MRI of the prostate was not diminished.

> *"It was probably more lucky, the biopsy wasn't lucky, it was probably more lucky that the MRI picked up something even if it wasn't what they thought it picked up, because I wouldn't have had the biopsy without that." P04 (Rural, 65+)*

A partner of one of the patient interviewees, who was diagnosed with prostate cancer, was also very positive about MRI of the prostate.

> *"And so I think, if that can show up cancer and prostate and stuff like that, it's a brilliant piece of kit and I think it should be used as much as it can be." P03's partner (Rural, <65)*

Burden refers to how much effort is involved in participating in the intervention. Most, but not all, patients reported that undergoing an MRI of the prostate was not a significant undertaking.

> *"Whereas the scans just takes a bit of time, and it's no hassle at all" P05 (Urban, 65+)*
> *"It didn't bother me at all." P12 (Urban, 65+)*
> *"To be honest with you, when I had that done, it bloody vibrated... and when I had it done at XXXX it thumped and bumped and, you know... and it is a little bit traumatic, you know?" P18 (Rural, 65+)*

The noise emitted by the MRI scanner whilst they were inside surprised some patients.

> *"…it wasn't so loud that…it wasn't the sort of noise that made your body vibrate, I mean, it was very loud, but it wasn't really uncomfortable; it was surprising and unpleasant, and it didn't go on for that long." P11 (Urban, 65+)*

"And it's quite noisy in there, isn't it? Strange, like… well, I was thinking about these… these are the noises that they listen to coming from outer space." P14 (Urban, <65)

Patient interviewees reported a range of views towards the amount of time required to be inside the MRI scanner

"A bit boring lying there for twenty minutes but apart from that, that was it." P04 (Rural, 65+)
"… and they told me it would be 35 to 40 minutes, which is a long time, isn't it, to be in there?" P14 (Urban, <65)

Claustrophobia and being in a small, enclosed space for a period of time was a challenge for some patients.

"They put me in head first, yeah. So actually my feet I think was probably not inside; I don't… I'm not quite sure. But it's quite a sort of small tube and it's kind of roughly there [hand close to face] at the top of the tube so it didn't bother me too much but I could think it might bother some people." P05 (Urban, 65+)
"Mainly because I suffer from claustrophobia. And the first one, because it was lower back, I was pretty much inside the machine, which I did not enjoy." P23 (Rural, 65+)

Ethicality explores how the intervention fits with an individual's value system. This construct was more difficult to explore with the interviewees with any clarity. There did not seem to be any significant conflicts on a personal level with undergoing an MRI scan.

Intervention coherence covers the participant's understanding of the intervention and how it works. Patient interviewees reported varied understanding of the role of MRI in the prostate cancer diagnostic pathway. Some had no knowledge, whereas others were aware of the nuances of test interpretation, and that confirmation of a diagnosis of prostate cancer still

requires a tissue sample from a biopsy. This seemed to be affected in part by the communication from the clinicians about the tests they recommended.

> *"…but I think I knew pretty well what it was for, that they were basically looking for cancer." P02 (Rural, 65+)*
> *"The MRI scan basically found some areas that were, let's say, suspicious. I don't think they exactly found cancer but…" P02 (Rural, 65+)*
> *"Not really, so that part of it was a bit of a… as I say, a mystery because you don't… as you say, they didn't say, well, we're looking for so and so." P07 (Urban, 65+)*

The patients' understanding of how an MRI scanner works and what the technicians are doing when taking the scan was generally poor.

> *"I don't ask them how to drive a tractor, I don't ask them how to use a scanner." P18 (Rural, 65+)*
> *"To be honest with you, I don't think they really defined that. It may have been that they didn't do that because they realised in conversation that I had a reasonably good grasp of what it was anyway. It's another form virtually of x-ray." P19 (Rural, 65+)*

Similar to the patients, GPs reported a range of understanding about the role MRI plays in the diagnosis of prostate cancer, which was sometimes not up to date with current evidence.

> *"I don't know quite how an MRI of the prostate is done, how much you have to… MRI, how long it takes. I don't know all of that" GP08 (Female, Urban, 41-50)*
> *"Yeah, so, I think, the main role is staging, I would think. I mean, that's how I've always been taught." GP09 (Female, Urban, 41-50)*
> *"I think that the real... that is more relevant or perhaps most relevant if you're considering using MRI to avoid biopsy. So actually selecting patients out who've got the lowest risk disease just on the basis of MRI images without biopsy." GP10 (Male, Rural, 41-50)*

Opportunity costs explores what an individual must give up in order to engage with the intervention. As outlined for the *'burden'* construct, there were a range of views regarding the time required to complete the scan. For patients who had to travel to hospital by car for their MRI appointment, some reported that it took them a long time to find a car park.

> *"So you've seen where we live and what parking is like in bloody... the hospital, excuse my language, sorry, the hospital, I left here... I had a 9.30 appointment, yeah... no I had a 10.30 appointment was it something like that? No, 9... whatever it was... Anyway, I got there an hour early, at least an hour early, you know, to find a parking space." P18 (Rural, 65+)*

Perceived effectiveness relates to how the participant perceives the likelihood of the intervention achieving its purpose. Patients generally had confidence in MRI as a test for possible prostate cancer, and trusted the results they were given, but not all were convinced.

> *"…and it's 90 something percent accurate, so it would tell us, you know, if there's any further investigation needed, and it came back okay." P14 (Urban, <65)*
>
> *"So you know, the MRI gives me confidence in some respects that they will find the problem." P18 (Rural, 65+)*
>
> *"However, if it's the case, as I understand, that some thirty or forty per cent of biopsies turn out to be unnecessary it suggests to me that some readings of MRI scans are not correct. That's the logical conclusion." P23 (Rural, 65+)*

Self-efficacy refers to the confidence of the participant that they can complete the activities or behaviours required for the intervention. In this area, the patients generally felt they could do what was needed to obtain an MRI of the prostate.

> *"Oh, fine yes, just lie down and put the ears on. There's no problems with that." P03 (Rural, <65)*

"The scan itself was a sort of normal relaxed... so I wasn't panicky about it, I wasn't frightening, it wasn't daunting or anything like that, it was just one of those things that you sort of get your mind set about it, it's just the enclosure was a little bit sort of squashed in for a little while, but then it's just what it is isn't it, the machine? P07 (Urban, 65+)

Self-efficacy was also considered by GPs both from their own perspective and that of their patients. Access to MRI for other reasons varies by region, so some GPs felt unsure whether they would be able to order an MRI for their patients whilst others had more MRI availability.

"Certainly, I can't… I… I can't request MRI for anything else apart from I think we can request them for back… certain back pain and that's it. Actually, I think there's just such limited availability for us requesting a… an MRI ever. It's not something I feel that I have direct access to" GP05 (Female, Rural, 41-50)
"we can get most of our patients for most MRIs, generally, within about two to three weeks…" GP09 (Female, Urban, 41-50)

GPs identified groups of patients who they felt might struggle to complete an MRI examination, again considering the impact of prostate MRI from the patient's perspective.

"…but, yeah, I think the elderly and people who don't tolerate them well it might prove problematic." GP09 (Female, Urban, 41-50)
"You know, there's a lot… you know, surprisingly, you know, a lot of patients don't like MRIs. You know, they find them claustrophobic and really noisy and stuff." GP09 (Female, Urban, 41-50)

MRI is one test within an entire diagnostic pathway, and often patients need both an MRI and a biopsy of the prostate. For patients who had experienced both tests, it was very consistent which test they would prefer to have (even though it is often not a matter of one or the other).

"I have done a biopsy as well at the beginning of last year and I can tell you that the MRI scan is about 50 times better than doing a biopsy. You can quote me on that" P05 (Urban, 65+)

Concerns were also raised by some GPs about the potential for increased clinical responsibility and workload, as well as increased demand for MRI from patients if GPs were able to order the test. Others felt that health service commissioners may consider GP direct access to MRI beneficial.

"…but if I have to have another conversation with somebody about the pros and cons of whether they want to go see a urologist, have a biopsy, have a PSA or have an MRI scan, that's not so great really. That's just another conversation about a complex thing that I'm going to have to try and weigh up for the patient." GP05 (Female, Rural, 41-50)
"The only thing if MRI became more... if an MRI for prostate became more access... became accessible to GPs I think there probably is a risk that we would be under pressure to be referring people asymptomatically, who are educated people who want to just have an MRI to be sure. And I think that... that's not a great thing. I would be quite resistant to that." GP07 (Female, Urban, 31-40)
"So... so from a... so with... from a commissioning perspective it seems like a sensible thing to be doing." GP10 (Male, Rural, 41-50)

Experiences of the prostate cancer diagnostic pathway - patients

Inductive thematic analysis of interviews with patients uncovered three main themes for each participant group, with interlinking sub-themes. The first main theme (The 'C Word') relates to the language used by patient interviewees when talking about cancer and the tests involved in investigating for a possible prostate cancer, and how cancer was discussed (or not) within their interactions with members of the healthcare team (sub-themes = *Health language; Attitude to diagnosis; Outside influences*). The second main theme (Communication) explores the communication between patient interviewees and the health service through their diagnostic journeys, how MRI and other test results were conveyed, and what they were understood (sub-themes = *Personal contact; Conveying significance; Gaps in understanding; Reaction to findings*). The third

main theme for the patient interviewees (Pathway experience) focuses on the patient's diagnostic journey and how MRI fits in (sub-themes = *Mixed routes; Appointments burden; MRI acceptability*). The findings are summarised in figure 3.2, a thematic diagram presenting the themes and sub-themes identified with patients, and their relationships.

The 'C word' – Avoiding the word 'cancer'

The 'C word' describes one of the key themes that emerged from interviews with patients. The word cancer was often not used at all.

> *"And then this developed." P01 (Rural, 65+)*
> *"For me, my... my dad had it roughly about eight, nine years... eight to ten years ago, I suppose. He had it." P20 (Urban, <65)*

Some used the word 'cancer' hesitantly, and this was not restricted to the patient interviewees. Some also reported a reluctance from clinicians to raise cancer specifically as a possibility during a consultation, even if the patient was being referred for urgent tests to rule out a diagnosis of prostate cancer.

> *"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. But when you're being given leaflets and it's got cancer and all that written all over it, you think well, is it cancer? Isn't it cancer? You know? Possibly, you know, could have had a bit more explanation into you know… no one's actually said to me you have or you haven't. A straightforward answer, you have or you haven't. It's more that yeah, everything looks fine, you know there's no, but when you're being handed leaflets all the time it does become a bit of a worry for a while." P25 (Rural, <65)*

Language and humour (*Health language*) were key tools used by many patients to cope with discussing a private and sensitive health issue with other people,

especially friends and colleagues. This allowed them to identify with other men experiencing similar problems.

> *"And, I mean, there are jokes amongst friends, you know, of my own age about how many times we need to get up in the night…" P13 (Urban, 65+)*
> *"You know, when you discuss it with all your friends they're all, oh yeah, we've all got to do that, we've all got to get up and that… and so…" P17 (Rural, 65+)*

Prostate examination is a particularly intimate examination that some men will refuse to have (see GP data below). Patients also use humour to make light of having been through this experience when discussing it with their friends.

> *"You know, and then it's finger up the bum, you know, oh you know, it's... you know, and it's humour. But I think the boys are taking notice of getting it done." P18 (Rural, 65+)*

Sometimes using humour failed to achieve the desired result, leaving this patient feeling even more awkward about the subject and less inclined to discuss their experiences.

> *"We don't really talk about it. Actually, I... I went into the boys and spoke to them, I just said... I laughed and said, oh, I've just lost my virginity, and they were all looking at me very funny and stuff. I said, oh never mind." P12 (Urban, 65+)*

Descriptions of a prostate examination varied widely, and most reflected the discomfort with which patients feel discussing the subject.

> *"Another doctor did the old, feel," P01 (Rural, 65+)*
> *"gone to the doctor, it's always been the finger, enlarged prostate." P04 (Rural, 65+)*
> *"after seeing my GP and I did the usual prostate check, I sort of had an enlarged prostate" P07 (Urban, 65+)*

Most patient's attitudes towards a diagnosis of cancer (*Attitude to diagnosis*) were fairly relaxed. Many seemed philosophical about the possibility of being diagnosed.

> *"it is what it is" P03 (Rural, <65)*
> *"If I've got it, I've got it. No... no, doesn't particularly bother me, yeah. Fine." P12 (Urban, 65+)*

In contrast to these relaxed attitudes, a minority expressed anxiety about being told they might have prostate cancer.

> "so I'm panicking obviously, we have a young family, I'm thinking I'm going to have problems, but no-one was panicking which kind of made me feel a bit secure I must admit." P08 (Urban, <65)

Most patients held the belief that an earlier diagnosis of prostate cancer would increase their chances of a good outcome, and this drove the desire for some to have a quick answer as to whether they had prostate cancer or not.

> *"but I know it's... if it's caught early enough there's a good chance that I've got another five or ten years." P18 (Rural, 65+)*
> *"I said, no I'm not prepared to do that [repeat a blood test prior to referral], I want it now... done now." P19 (Rural, 65+)*

The decision for a patient to see their doctor about potential prostate problems was not undertaken in isolation (*Outside world*). The experiences of family members and friends shaped the patients' expectations for testing and treatment, and family members and partners were often key in encouraging men to be tested.

> *"I don't really know what to expect. I've met blokes who have had it done and they seem to be fine and so I'm just hoping I will be as well." P03 (Rural, <65)*

"For me, my... my dad had it roughly about eight, nine years... eight to ten years ago, I suppose. He had it. Obviously back then he 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 (Urban, <65)

Communication – helping patients understand their prostate MRI results

Communication was another key theme that significantly impacted on patients' experiences of the prostate cancer diagnostic pathway. Right from the first consultation with their GP, through to various appointments for testing and seeing a specialist to receiving their diagnosis, communication between the patient and their doctors influenced their understanding and feelings about their prostate-related problems.

The mode of communication to the patient (*personal contact*) appeared to directly affect their experiences of the pathway. Patients who sat down with their consultant and reviewed the MRI images together generally had a clearer understanding of the MRI findings and the next steps in their clinical assessment.

"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 (Urban, 65+)

Some patients received their MRI results via a letter, which was perceived as a more impersonal approach, particularly if the letter was addressed to their GP rather than to them.

P23: "Most of the letters go to the GP and I just get a copy."
I: "Okay."
P23: "There's something about the medical profession, where they always write I met a very nice, polite, 74 year old gentleman today

called… where they get that from I don't know. They all do it." (Rural, 65+)

Communicating the meaning (*conveying significance*) of the results of various tests along the prostate cancer diagnosis pathway was very important to help patients understand what the results mean for them as an individual, from whether prostate cancer was present or not to what treatments were recommended if they did have cancer.

"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 (Rural, <65)

Despite most of the patients having been through the diagnostic pathway by the time of their interview, there were still some areas where they reported a limited understanding or lack of knowledge (*Gaps in understanding*) with regards to the tests they underwent and the results. Many of these gaps appeared to be a result of communication breakdown between the patient and the doctor.

"They didn't talk to me about that, no. They didn't explain it" P04 (Rural, 65+)

"And he told me all that but it was... course I was... I... I got a rough idea of it I did. But he... he sent a letter to doctor and... and the nurse saying he's not sure Mr X took everything... was able to take everything in [inaudible]." P01 (Rural, 65+)

"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 (Rural, 65+)

Consistent with the attitudes towards a possible diagnosis of prostate cancer prior to undergoing MRI, the reactions of patients who were diagnosed with prostate cancer (*Reaction to findings*) were mixed. Some patients took the news

very hard, and it altered their perspective on life, whilst others seemed determined to continue living their life in spite of a diagnosis of cancer.

> *"Not fair. No, it's... it's not fair on... on anyone, not just me. It isn't fair on anyone." P01 (Rural, 65+)*
> *"Well, I don't know, it's just dark times. It's just a bit of a surprise to know I've got it." P03 (Rural, <65)*
> *"Well, obviously one's a bit disappointed but I'm quite realistic about these things. I'm not prone to depression or anything like that so I just take it as that's what's happened." P02 (Rural, 65+)*

Pathway experience – impact of pathway design on patients

The pathway experience varied significantly for patient interviewees. Even accounting for the deliberate recruitment of patients in two very different geographical regions with different local health services, there was a range of experiences for men at all stages of the diagnostic pathway (*Mixed routes*). Some patients presented to their GP asking for a blood test; some were investigated for symptoms that suggested a possible prostate cancer. Some patients had a single PSA blood test; some had multiple blood tests prior to being referred for possible prostate cancer. Most patients in London received the MRI results on the same day or soon after, whereas patients in Devon sometimes waited weeks to receive their MRI report.

> *"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 (Urban, 65+)*
> *"It took about... it took nearly a month to come through, but that's it [MRI results letter] there." P19 (Rural, 65+)*

In spite of the range of experiences reported, most urban men were satisfied with the speed with which the whole pathway was completed.

> *"Yeah, and, you know, it was, you know, a great result at the end of the day, and that's what… you know, and I'm… I'm really pleased how…*

how quickly it went from GP to the NHS at [Hospital], and, you know, it was all resolved within a week or two…" P14 (Urban, <65)
"I'm glad everything's been so fast, you know, it makes it easier." P16 (Urban, 65+)

Some rural patients were affected by administrative errors or last-minute changes in plans for diagnostic testing, which created delays and caused some frustration.

"Well, I wasn't too happy about it because they'd put me back two month. You know, they let that time go, the month that... you know, I think it was five weeks or something I waited for the appointment, which was five weeks wasted." P21 (Rural, 65+)

The prostate cancer pathway required a number of individual appointments for patients before a diagnosis of prostate cancer could be ruled in or out (*Appointments burden*). Patients mostly saw their GP first, they may have had one or more appointments for blood tests and /or prostate examination, and then there would be one or more appointments with the hospital consultant, as well as an MRI appointment and possibly a biopsy of the prostate.

"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 (Rural, 65+)

This proved especially challenging for patients in rural and regional areas, who had to travel for many of these appointments.

"No, not really, no. Like I say, I would have no complaints, obviously, apart from the distance thing of it. You know, obviously, you can't expect to have fantastic hospitals, wherever you are, about five minutes away. You've got to… you got to be prepared to travel a bit." P17 (Rural, 65+)

Any patient who had to drive to hospital, no matter the distance, felt that car parking challenges added to their burden of attending appointments.

"Because you can't park easily, you need to leave an extra hour, it's just a real disaster from that point of view." P23 (Rural, 65+)
"So we end up going a couple of hours before the appointment, either first thing in the morning or lunchtime, to make sure that we get a car parking space…" P24 (Rural, <65)

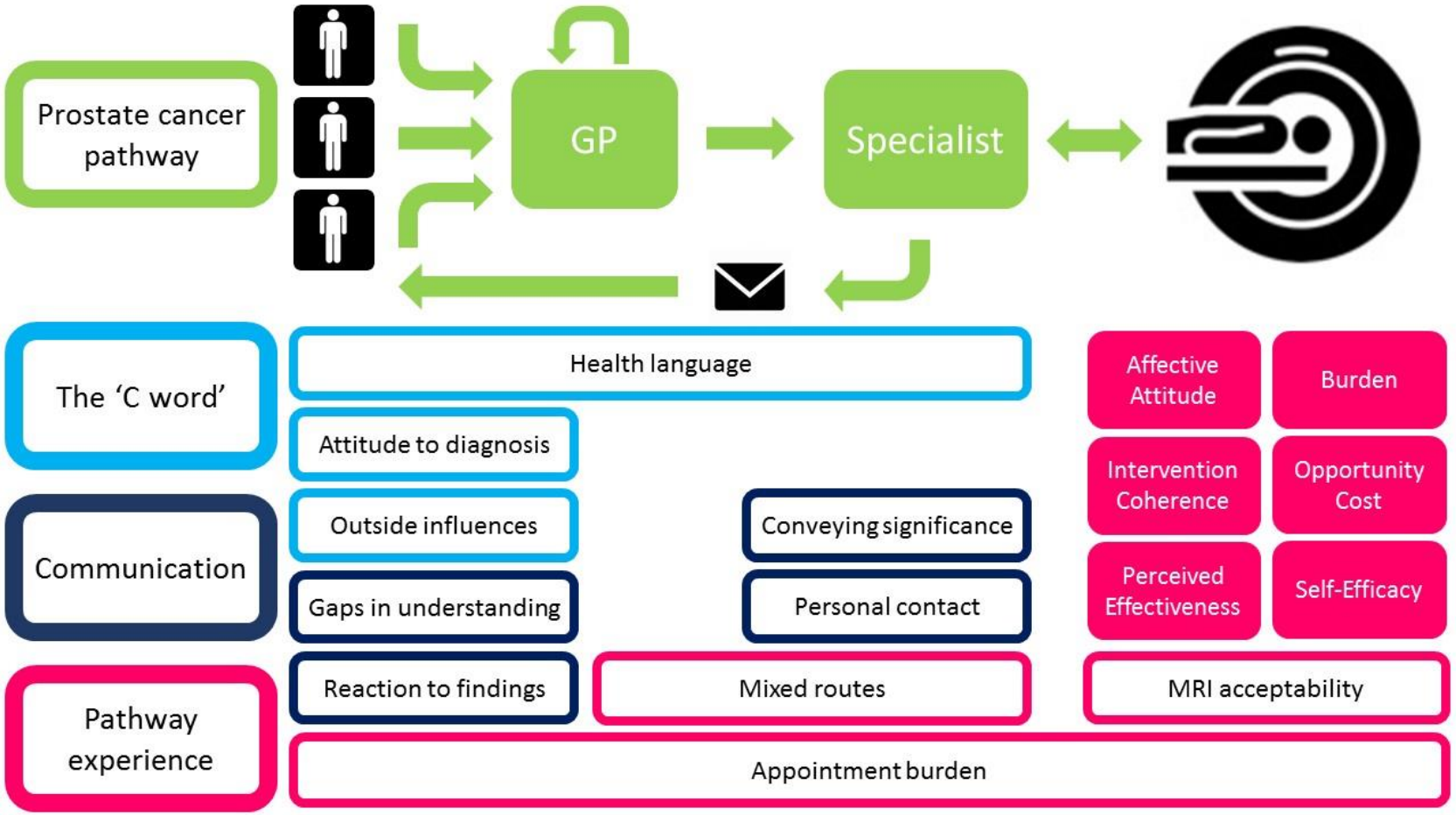


Figure 3.2 – Thematic diagram from patient participant interviews

Experiences of the prostate cancer diagnostic pathway - GPs

GP interviewees described a range of challenges in assessing patients for possible prostate cancer and deciding who and when to refer for further investigation. Three main themes were identified from the analysis of the interviews. There were a number of wider contextual influences which affected the consultation and the GP's decision-making process. Most GPs felt that they were dealing with imperfect information in their assessment for possible prostate cancer, and they involved patients and local specialists in managing uncertainty as they faced it (see figure 3.3).

Contextual influences – internal and external factors

A spectrum of broader influences had an effect on when men chose to present to their GP with concerns about or symptoms possibly relating to prostate cancer, and the consultation itself (*Gender, society & culture*). Female GPs reported that male patients are already more reluctant to see their GP about any health condition, let alone a condition as intimate as a prostate problem and as significant as a possible cancer. Male patients were often less comfortable seeing a female GP for prostate-related problems and a prostate examination.

> *"I think men don't... it's such a sweeping statement but men don't like coming to the doctor" GP07 (Female, Urban, 31-40)*
> *"I don't see that… men often don't come to women to discuss this" GP05 (Female, Rural, 41-50)*

Consistent with the patient interviews, 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, Urban, 31-40)*

Cultural and ethnic norms relating to the patient and their partners also influenced the consultation and acceptance of prostate examination. Awareness

of these norms affected how GPs communicated with their patients about the need to investigate for possible prostate cancer.

> *"And over here I notice there are some patients of south Indian descent where, it's [DRE] almost like a taboo really." GP03 (Male, Urban, 31-40)*
> *"Yeah, so… I have to be very careful with the Asian population. Often they're accompanied by their wife and there's often a lot of anxiety if I use the word cancer, so I have to be very careful how I phrase it." GP09 (Female, Urban, 41-50)*

GPs were also aware of the influence of news and media stories relating to prostate cancer that were encouraging men with symptoms or concerns to see their GP and get tested. Some GPs held misgivings about these messages conflicting with the evidence for prostate cancer testing in patients without symptoms.

> *"…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, Urban, 41-50)*
> *"…despite the evidence being very strongly against screening many individual... many prominent individuals and some organisations encourage men without symptoms to go and get their P... their PSA checked or get their prostate checked." GP10 (Male, Rural, 41-50)*

Some GPs felt that, as a result of stories about prostate cancer shared by the news, media, family and friends, most patients to be 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. The level of demand for testing appeared to be affected by a range of factors (*Patient expectations*).

> *"Lots of people are aware of the PSA" GP07 (Female, Urban, 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, Rural, 41-50)*

The decision-making of GPs was also affected by the own experiences in their personal and professional lives (*Personal & professional experience*). Some of them had had family or friends go through the investigations for prostate cancer or even had a diagnosis. Cases where there had been a complication from testing or a missed diagnosis for their patients also seemed to be prominent in GP's thinking. 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, Urban, 31-40)*
>
> *"…at our practice recently were actually one of my partners had that test with the patient... they'd had, sorry... they'd had that discussion with the patient and the patient had decided not to have the test and then two or three years later at most the patient presented with brain mets from prostate cancer, you know?" GP10 (Male, Rural, 41-50)*

The health service context in which GPs practise was another significant influence on their approach to patients with possible prostate cancer (*Health services & guidelines*). All GP interviewees practiced in the NHS, a publicly funded national health service that is free at the point of delivery and funded through general taxation. They often rely on guidance from a number of sources, including national guidelines and local diagnostic pathways. Most GPs had a good opinion of their local urology service, although inconsistencies in how some of their patients were treated left them a bit mystified at times.

> *"I think we've got some, you know, very good local colleagues who offer good pragmatic advice and are very approachable." GP02 (Male, Rural, 31-40)*
>
> *"Umm…I think… yeah, I mean, it's mainly those things you've mentioned, like, the inconsistency in… in advice and thresholds and*

things which leave me and my colleagues sometimes just quite confused." GP04 (Female, Rural, 41-50)

Imperfect information – uncertainties in detecting prostate cancer

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. Current guidance recommends a prostate examination and a blood test for men with symptoms, but GPs often saw men with no symptoms who were concerned about prostate cancer and wanted the PSA blood test.

"So we probably have two groups of patients. So the ones that come in who tell me they've got obstructive symptoms, of getting up at night to pee and poor flow, hesitancy, dribbling, all that sort of thing and they're the ones where I think of it…. And then we have another group of patients in [practice location] here, who would come in, who just know about prostate cancer, who want a check and they have no obstructive symptoms at all." GP08 (Female, Urban, 41-50)

A few GPs described a sense of inevitability about patients presenting with lower urinary tract symptoms, which could relate to an underlying prostate cancer or benign prostate problems, 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, Urban, 31-40)

As described earlier, GPs experienced men refusing to have a prostate examination when prostate cancer is suspected (*Examination acceptance*). GPs value the added clinical information examination can offer, but they perceive that patients may still be worried even if the prostate feels normal.

"I can feel a little bit of a lump in the prostate, I just want to check it out." GP03 (Male, Urban, 31-40)

"Lots of them aren't terribly keen on an examination. The ones who are real, sort of, accept it as far as we're trying to get them better. The ones who aren't ill, sort of, feel it's a bit intrusive sometimes, so they'll… they're the ones more likely to decline a rectal examination and… and even if I don't feel anything or it feels very smooth and things, I don't think it reassures them often enough." GP08 (Female, Urban, 41-50)

GPs 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, Rural 31-40)
"So it's [PSA] quite a pain in the neck actually, to be honest…" GP05 (Female, Rural, 41-50)
"Well, I don't like doing the PSA levels I suppose is one thing to say." GP07 (Female, Urban, 31-40)
"I think we do… we do the best we can with the tests available" GP02 (Male, Rural 31-40)

Managing uncertainty – GP decision-making with the patient

GPs made efforts to share their 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, Urban, 31-40)

In preparing patients for the necessary diagnostic tests to rule in or out a prostate cancer, GPs perceived that the thought of a biopsy of the prostate was unwelcome news for most patients.

"They certainly don't… [inaudible] the next step is saying to a man, right, well, it's... it's raised, I think your prostate's abnormal, I think you need to have a biopsy, that is something they really don't want and they think it's a pretty traumatic process." GP07 (Female, Urban, 31-40)

Whilst most GPs reported feeling satisfied with their local urology service (see *health service & guidance* above), many still experienced inconsistencies in the advice and management plans for their patients that came back from hospital specialists (*seeking advice*). This inconsistency added to the uncertainty GPs experienced in knowing what would happen to patients they referred with possible prostate cancer if they were also diagnosed.

"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, Rural, 41-50)
"…they might have seen urology and they'll often say, "This person has got a large prostate, and the PSA is elevated at 9, but I think that's normal for age. Please only refer them if it's gone to 15." So there's a lot of varied… it's, like, individual discussions that's not very clear." GP05 (Female, Rural, 41-50)

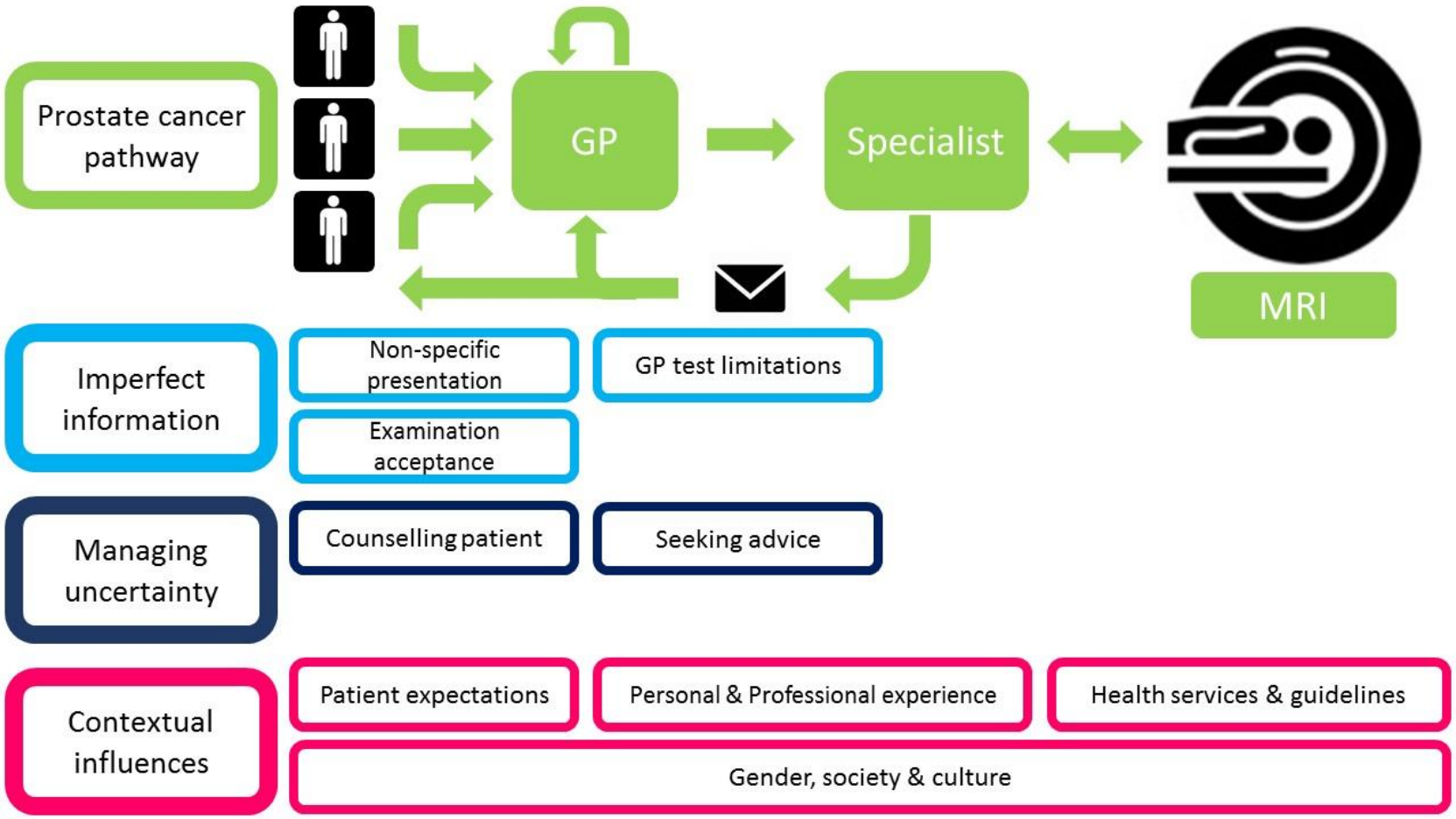


Figure 3.3 – Thematic diagram from GP participant interviews

3.4 Discussion

Key findings

The findings from this interview study suggest that MRI scanning for possible prostate cancer is acceptable to most patients. The patient interviewees felt generally positive towards having an MRI of the prostate, they felt confident they could do what was required of them to undergo an MRI, and they had confidence in the ability of MRI to detect prostate cancer. GP's views on acceptability were more varied and often limited owing to lack of access to MRI. Whilst some clinicians were supportive about the idea of an MRI of the prostate, others felt that MRI of the prostate was not within their scope of clinical practice or worried about patient demand and increased clinical responsibility if it were made available in primary care. These concerns were raised despite GP's reporting that the existing tests for prostate cancer available in primary care are of limited value.

Communication was a key element in the experience of the prostate cancer diagnostic pathway for both patients and GPs. Patients reported hesitancy at times to use the word 'cancer' in the consultation by clinicians and in the interviews for this study. Clinicians tried to share the diagnostic dilemma they faced with their patients, in the context of relying upon imperfect information to come to a shared decision about onward referral for further investigations. Patients appeared to value more personal contact with their doctors by receiving and discussing their test results in person rather than via a letter or telephone call. Patients and GPs still reported some gaps in their understanding at the latter stages of the pathway, particularly with regards to how tests for prostate cancer work.

Relation to published literature

To the author's knowledge this is the first qualitative study to evaluate the acceptability of MRI for prostate cancer. Ullrich *et al* distributed questionnaires to patients, urologists and GPs in Düsseldorf, Germany, to assess the acceptance, value and clinical role of mpMRI for prostate cancer diagnosis. 328 patients returned their questionnaires, including 251 who had undergone mpMRI, with 223 (68%) considering MRI to be useful and roughly one quarter of respondents reported MRI to be constricting, loud and too expensive(138).

These responses appear consistent with the experiences of patients in this study, although cost was not raised as a significant concern, which is perhaps unsurprising given healthcare is free at the point of care for UK citizens and residents. Ullrich *et al's* paper did not give a definition for how a test is considered to be 'useful'.

Egbers *et al* assessed the acceptance of MRI-guided biopsy (MRI-GB) in Germany and performed MRI-GB and TRUS biopsy on 54 patients with suspected prostate cancer and at least one negative TRUS biopsy. One week later they were contacted for a telephone questionnaire that included questions about a patient's preference for MRI-GB or TRUS biopsy, and whether they would undergo MRI-GB again. MRI-GB was the preferred biopsy mode for 35 patients (64%), and 44 patients (82%) would undergo MRI-GB again(79). Patients in this study reported a preference for MRI over biopsy if given the option, but it was not possible to establish whether the interview participants had had an MRI-GB or TRUS biopsy in order to compare these biopsy approaches.

There is more evidence for patient acceptance of TRUS biopsy and the associated adverse effects of the test, which is unsurprising given this test has been used in clinical practice for the last few decades. More recently published studies have often been embedded in larger trials of PSA-based prostate cancer screening. Makinen *et al* measured acceptability through willingness to undergo a repeat biopsy for patients in a Finnish prostate cancer screening trial and hospital patients referred for further investigation of symptoms. The majority of patients in both groups indicated a willingness to have a repeat biopsy (82% and 86% respectively)(127). Within the UK PROTECT study, a minority of men who underwent prostate biopsy would consider a repeat biopsy to be a major problem (213/1085 [19.6%])(82). A greater proportion of patients interviewed for this study expressed a reticence for further prostate biopsies in the future compared to these larger studies, although this may have been driven in part by the focus of the interview being on their experience of a different test that is non-invasive.

The PSA blood test for prostate cancer has also been used in clinical practice for a number of years now, and was discussed extensively in the study, particularly by the GPs. It is well established that UK GPs are less likely to recommend PSA testing to asymptomatic patients compared to GPs in other countries, but they will arrange the test after ensuring a patient who requests it is making an informed decisions about the benefits and risks of opportunistic screening(139,140). A range of factors from GP training to health policy and national guidance seem to influence these attitudes(141). In spite of the broadly negative attitude towards PSA from GPs in this study, nationally there is a trend towards more PSA testing in UK primary care and lower PSA thresholds for referral to secondary care(142,143).

Delivering test results occurs in the latter stages of the diagnostic pathway. Some patient interviewees felt that they preferred to receive and discuss their test results in person with their doctor rather than over the telephone or via a letter, which is consistent with other literature in the field(144). The language used in these consultations is key to avoid miscommunication or misinterpretation about the results and their significance(145). Doctors have a tendency to communicate in a less open manner when delivering bad news to patients(146); however, in this study it appeared both doctors and patients had a hesitancy to discuss openly the possibility of a prostate cancer diagnosis.

Patient interviewees demonstrated a seemingly relaxed attitude towards the possibility of being diagnosed with prostate cancer (“It is what it is”). These attitudes could have been driven by social norms relating to traditional male gender identity, with men demonstrating their masculinity by acting tough and not showing emotion in the face of a potentially serious illness(147,148). It may also relate to the patients’ understanding of the likely prognosis for prostate cancer and the benefits of screening and testing, which can sometimes be misinformative(145).

Strengths

This qualitative study of acceptability of MRI for possible prostate cancer employed a clear definition of acceptability and used a published theoretical framework to underpin data analysis. This approach is rare in studies of the

acceptability of healthcare interventions to date, as most studies of acceptability are ‘poorly defined, under theorised, and poorly assessed’(125). Acknowledging the influence of theory and choosing relevant concepts is important in the conduct of healthcare research as it ‘shapes the way practitioners and researchers collect and interpret evidence’(149).

A range of views and experiences of the prostate cancer diagnostic pathway and the various tests involved via purposively recruiting participants with a range of ages, genders and geographical locations across two English regions. The diversity in the sample of patients and GPs allowed key similarities and differences in the experiences of the two pathways to be identified from the data collected.

The influence of the researcher on data collection and analysis is important to consider in qualitative research. Participants were aware that the interviewer was a clinician, and that may have given some level of respectability and authority to the interviewer and the study. 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(150) and annual appraisal by a fellow GP(151). 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 also have helped patient participants be more comfortable and open in the interviews.

Limitations

Whilst employing a published theoretical framework to support this analysis can be argued to be a strength, applying it to the GP interviews proved challenging. Sekhon *et al* proposed that the framework could be applied prospectively, before the intervention had been delivered/received. MRI of the prostate is not currently available for GPs in the UK to order for their patients, so in the analysis of their interviews the subject of acceptability of MRI was prospective in nature. Some GP interviewees were not prepared, or able, to engage with a discussion about MRI for prostate cancer and were reticent to give their opinion on the acceptability of the test as it was seen as beyond their scope of practice. The GPs who did engage sometimes responded to questioning by giving their

opinion about how their patients may feel about MRI, rather than from their own perspective.

There is a wider question about whether Sekhon's framework is the most appropriate theory to apply to the analysis of these data. The framework has been developed for the assessment of acceptability of healthcare interventions more broadly, and it could be argued it is not specific enough to a single test. The TFA is also relatively new and has not yet been used in many studies. It may be that it requires some refinement on the basis of more primary data. However, as Sekhon *et al* highlight in their published work, there are no clearly defined alternatives in existence at this point in time(125). This potential limitation was also mitigated by undertaking a broader inductive thematic analysis approach to the entirety of the interviews, recognising that MRI is one test in an extensive diagnostic pathway that does not occur in isolation.

3.5 Conclusions

This study suggests that MRI for possible prostate cancer may be an acceptable test to patients. GPs were more reserved in their judgement of MRI, as it is not current within their scope of clinical practice but could see the potential benefits of its use for their patients. The current prostate cancer diagnostic pathway holds challenges for GPs, who have to manage uncertainty arising from limitations in all the tools they currently have available to identify patients with possible prostate cancer needing referral for further investigation. Patients experience a significant appointment burden in attending outpatient appointments to see a specialist, undergo imaging test, and often have a prostate biopsy; all before they are informed whether they have a diagnosis of prostate cancer or not. Communication between patients and doctors, and between GPs and specialists, was a key influence in the experience of the pathway for participants in this study.

Chapter 4 – Systematic review and narrative synthesis of economic evaluations of pre-biopsy magnetic resonance imaging (MRI) based prostate cancer diagnostic pathways

Chapters two and three have sought to establish new evidence in the understanding of the impact of prostate MRI and prostate cancer diagnostic pathways on patients, and the acceptability of prostate MRI as a diagnostic test for prostate cancer amongst patients and GPs. Another crucial area in diagnostic test development and implementation is generating evidence for the cost-effectiveness of the test in the setting that is intended for implementation. This chapter outlines a systematic review and narrative synthesis of economic evaluations that compare prostate cancer diagnostic pathways incorporating prostate MRI prior to biopsy with more traditional pathways that relied on ultrasound guided biopsy. Of particular relevance is to understand if direct access to prostate MRI in primary care for assessing patients with suspected prostate cancer has been modelled previously. The evidence generated from this review contributes towards objectives one, three and four of the PhD.

4.1 Introduction

Prostate cancer incidence globally has risen in recent decades and is expected to continue to rise in many countries, including the UK(152). Prostate cancer is the most common cancer in males in the UK, with 52,580 new cases diagnosed in 2017-18(2). Whilst prostate cancer causes a significant number of cancer-related deaths in the UK (12,032 in 2017)(153), an increasing proportion of men diagnosed with prostate cancer have low risk disease that is unlikely to cause significant morbidity or mortality (particularly in men diagnosed at an older age). This is suspected to have been driven in part by the increasing use of prostate specific antigen (PSA) in clinical practice for screening or early detection for

symptomatic men in primary care. PSA does not easily distinguish between clinically significant prostate cancer (that warrants treatment) and clinically non-significant prostate cancer (which could be monitored through active surveillance to avoid or delay treatment)(21).

Magnetic Resonance Imaging (MRI) has emerged in recent years as a new diagnostic test for prostate cancer that may have multiple benefits for more accurate diagnosis relative to the existing standard diagnostic test of an ultrasound-guided biopsy (TRUS). There are two main MRI approaches to assess for the presence of prostate cancer; multiparametric MRI (mpMRI), which requires intravenous contrast, and biparametric MRI (bpMRI), where no contrast agent is given. The recent PROMIS trial found that using multiparametric MRI scans prior to a prostate biopsy increased the number of men being diagnosed with clinically significant prostate cancer, without increasing the number of men being diagnosed with clinically insignificant prostate cancer and could potentially avoid the need for a biopsy altogether in up to 27% of men(53). The PRECISION trial demonstrated that performing pre-biopsy MRI and MRI-guided biopsies also increased diagnoses of clinically significant prostate cancers and resulted in greater diagnostic yield with fewer biopsy samples needed compared to an ultrasound-guided approach(54). A 2019 Cochrane review of all existing evidence suggests MRI-based prostate cancer diagnostic pathways can result in more accurate diagnoses of clinically significant tumours(29).

The costs associated with prostate cancer care are significant. The overall annual economic costs of prostate cancer, taking into account healthcare costs and lost earnings after premature death, for the UK has been estimated to be £666million(154). In addition to the survival benefits of diagnosing patients with prostate cancer at an earlier stage(155), there are also much lower costs associated with treating a patient with localised prostate cancer compared to metastatic disease(156). With the rising incidence of prostate cancer in UK men, the implementation of MRI to improve diagnostic accuracy for clinically significant prostate cancers, and earlier detection of disease, could help to reduce the number of men with a late-stage diagnosis. Reductions in the number of men undergoing prostate biopsies for suspected prostate cancer by

undergoing an MRI of the prostate first could also reduce the healthcare costs associated with the procedure and post-biopsy infection(157). However, concerns have been raised that the cost of MRI scanners, the training requirements for radiographers and radiologists to perform and interpret images, and the time taken per test could limit the benefits of MRI for prostate cancer-related healthcare expenditure(30).

The evidence for the cost effectiveness of new MRI-based prostate cancer diagnostic pathways is still evolving. A National Institute for Health Research (NIHR) Health Technology Assessment (HTA) report from the PROMIS trial concluded that 'incorporating mpMRI into the diagnostic pathway as an initial test prior to prostate biopsy may increase the cost effectiveness of the prostate cancer diagnostic and therapeutic pathway'(158). Willis *et al* undertook a limited review of economic evaluations of prostate cancer diagnostic pathways incorporating imaging and found a wide range of research questions and modelling assumptions among the five included studies published up until 2015(159). A rapid response report prepared for the Canadian Agency for Drugs and Technology in Health (CADTH) in 2018 found that 'including MRI before TRUS-guided biopsy was more cost effective than standard TRUS-guided biopsy alone, despite the testing costs associated with the former being higher'(160). There is no systematic review of economic evaluations published, or registered with PROSPERO, to date that identifies and critically appraises all existing evidence for this area. This systematic review aims to assess the evidence for the cost effectiveness of pre-biopsy magnetic resonance imaging (MRI) based prostate cancer diagnostic pathways.

4.2 Methods

Systematic reviews of economic evaluations (SR-EEs) aim to identify, evaluate and summarise the economic evidence for healthcare interventions. The purposes of SR-EEs include a summary of current evidence, informing new or updated clinical practice guidelines, and developing decision analytic models. There are two main types of EE that can be included: full and partial EEs. Full EEs are defined by Drummond *et al*(161) to: (1) compare two or more alternative interventions, and (2) compare the costs and effects of the alternative interventions. Within cancer, full EEs often involve a linked data approaches to extrapolate the end point of trials to a policy relevant outcome such as Quality Adjusted Life Years (QALY) or Survival(162). In comparison, partial EE focus upon one only aspect of the decision problem; for example, outcomes in effectiveness studies or costs in cost analysis, or provide a simple cost-outcome description rather than a comparison. Full EEs provide the most comprehensive framework to inform decision making and are the focus of this review.

A range of journal articles and guidelines regarding the recommended conduct of SR-EEs have been published(71,163–167). In part, this is due to the challenges of assessing the quality of economic evaluations and meaningfully synthesising data from studies that vary widely in their approaches. A recently published framework for SR-EEs developed by van Mastrigt *et al* (see figure 4.1 below) is the most up-to-date, practical overview in this area that was identified, and was utilised to guide this systematic review(168–170).

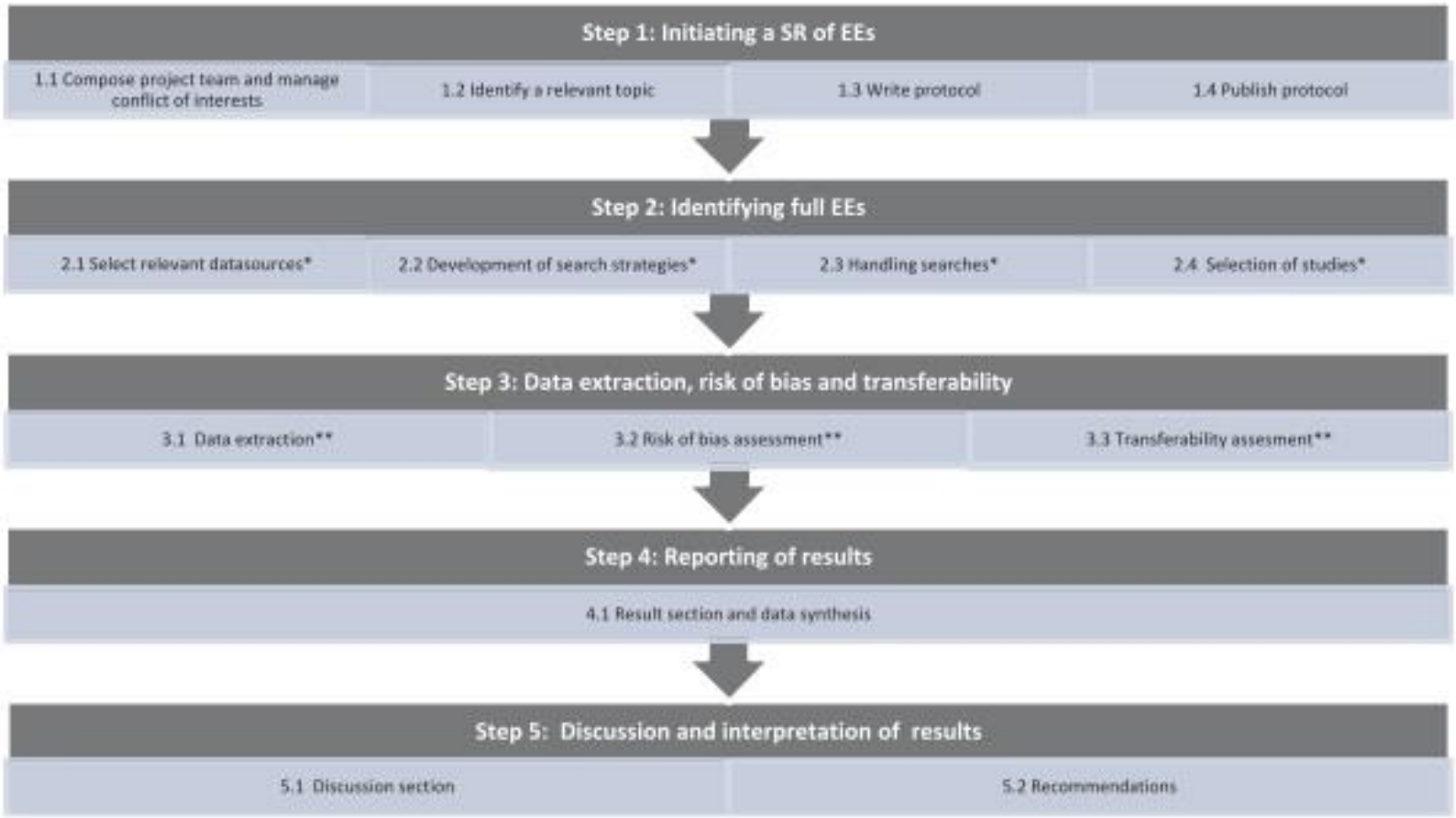


Figure 4.1 – Five-step approach to SR-EEs from van Mastrigt *et al* (2016)(168)

Data sources

Bibliographic databases and other sources of publications that were searched included MedLine, PubMed, the Cochrane Library, EMBASE, Psycinfo, Cumulative Index of Nursing and Allied Health Literature (CINAHL), Web of Science, EconLit, clinicaltrials.gov, University of York Centre for Reviews and Dissemination (CRD) database (including NHS Economic Evaluation Database [EED]), and the International Standard Randomised Controlled Trial Number (ISRCTN) registry. A wide range of databases and registries covering medicine, allied health, clinical trials, and health economics were searched in order to increase the likelihood of identifying all relevant studies.

Search strategy

Recommended search strategies for economic evaluations(171) from the INTERTASC Information Specialists Sub-Group (ISSG - https://sites.google.com/a/york.ac.uk/issg-search-filters-resource/home) for MedLine, EMBASE, PsycINFO and CINAHL were adapted and combined with subject specific search terms. Search terms and MeSH headings included 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 (See Appendix 4.1 for full search strategies). Technical reports relating to prostate cancer were also searched for on the National Institute for Health and Care Excellence (NICE) website. References were obtained by hand searching for relevant papers in the bibliographies of papers and reviews selected. Citation searching was performed via Web of Science (WoS) using a search strategy combining the terms prostate and MRI with a proven WoS filter for economic evaluations used in an NIHR HTA by Snowsill *et al*(172).

Inclusion criteria

Search hits were included in this review if they met the following criteria:

1. Full economic evaluations
2. Assessing prostate cancer diagnostic pathways for adult males that included MRI as a diagnostic test for prostate cancer prior to biopsy

Exclusion criteria

Search hits were excluded from the study if they met any of the following criteria:

1. Partial economic evaluations
2. Studies that only include diagnostic tests/pathways for prostate cancer that do not feature pre-biopsy MRI
3. Case studies
4. Unpublished/incomplete studies
5. Conference abstracts
6. Studies and papers published in languages other than English

No restrictions were placed on study setting, country or comparators used. Economic evaluations on the basis of modelling and/or randomised controlled trials were considered for inclusion.

Screening search hits

Search hits from each database were downloaded and combined into a review database managed in a shared folder in Mendeley Desktop (Version 1.19.4, Mendeley Ltd). An initial search of all identified databases using the proposed search terms was conducted to identify potentially relevant papers through titles and abstracts. Any duplicate search hits were removed. Title and abstract of potentially relevant papers were screened by me and a second reviewer (Rebekah Hall [RH], Health Economic PhD student, University of Exeter) independently using the inclusion/exclusion criteria. In the event of disagreement between reviewers of study eligibility on basis of title and abstract, a decision reached by consensus with a PhD supervisor (WH). Full paper review of all studies included on initial screening of title and abstract was performed by me and RH independently, with any disagreements resolved through discussion with a PhD supervisor (WH).

Data extraction

I extracted data from included papers selected using a standardised form. This form was piloted on two included papers, then adapted through an iterative process with input from a PhD supervisor (AS), before being used for extracting data on the remaining papers. A random selection of 10% of included full-text

papers was reviewed by the second reviewer (RH) to confirm accuracy of data extraction. Disagreements were resolved by consensus discussion, involving a PhD supervisor (WH or AS).

Basic study and methods data (first author, year of publication, country, study population, setting, EE type, analytic/modelling approach, time horizon, data sources, currency, discounting, and methods to address uncertainty) were extracted from each included paper. Modelled pathway characteristics were extracted including items such as patient selection criteria, tests done, MRI approach (multiparametric or biparametric), thresholds for diagnostic test, and non-MRI pathways used for comparison. Primary and secondary outcome measures, including cost effectiveness measures in terms of Incremental Cost Effectiveness Ratios (ICERs) or Quality Adjusted Life Years (QALYs), were also extracted from each study. The specified contact author of primary studies was contacted in the event that additional data was required for the analysis.

Risk of bias assessment

There are numerous tools available for the assessment of risk of bias in economic evaluations. Wijnen *et al* identified 13 different checklists and quality appraisal tools in the study series that informed the conduct of this systematic review. Some checklists were better for economic evaluations based on trials and other more appropriate for model-based studies. They identified the Philips framework(173) as the optimal choice for economic evaluations based on modelling, particularly in systematic reviews where the expected number of included studies is low(169). Thus, the Philips framework was used for model-based studies included in this review. A broader range of options for risk of bias assessment is available for trials-based economic evaluations, and there is limited evidence for greater validity or reliability of one checklist over another(174). In the absence of an optimal choice for these studies, the quality assessment of included economic evaluations associated with trials was performed using the Critical Appraisal Skills Programme (CASP) checklist for Economic Evaluation(175).

Narrative synthesis

A narrative synthesis of data extracted from included studies was undertaken. This included a summary of the modelled pathways to compare and contrast different pathways assessed within and between studies. The cost effectiveness measures were presented and summarised. Data were presented in tabular format and with a hierarchical decision matrix(176).

PRISMA reporting guidelines

The Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement(72) is one of the most widely cited reporting guidelines for systematic reviews and is followed by numerous peer-reviewed published systematic reviews. This chapter has been written with reference to the PRISMA statement.

Protocol publication

The protocol for this systematic review has been published on PROSPERO, an international prospective register of systematic reviews hosted by the University of York (See Appendix 4.2).

4.3 Results

Searches

Database searching yielded 6,875 total search hits, with one additional potentially relevant study identified from searching the NICE website for any relevant reports. No additional studies were identified through hand-searching reference lists of included papers. After removing duplicates, 6,550 studies were excluded on the basis of title and abstract. 43 full text papers were reviewed, and 8 studies met the inclusion criteria for this review (see figure 4.2).

Study quality

Two economic evaluations were based on the PROMIS trial(158,177). Both studies were assessed as having an overall low risk of bias, with the study by Faria *et al*(177) meeting all domains of the CASP checklist, with the exception of an incremental analysis (see Table 4.1). Six studies included in this review were model-based economic evaluations. All of these had some concerns about study quality in at least four of the 22 elements; most areas of concern fell into the 'Structure' domain of the framework from Philips *et al*. The paper by Pahwa *et al*(178) was adjudged to have a high risk of bias in two of the nine elements of this domain (See Table 4.2).

Study characteristics

The study characteristics can be found in Table 4.3. Seven studies were published in peer-reviewed journals, and one was an NIHR HTA report. All studies were performed as cost-effectiveness analyses. All were based in a single country, spread across a range of high-income countries with different healthcare service structures and policies (USA [n = 3], UK [n = 2], Canada [n = 1], The Netherlands [n = 1], and Australia [n = 1]). Five studies were conducted in a secondary care setting(158,177,179–181), two within a national prostate cancer screening programme(182,183), and one did not state the healthcare setting within which an MRI-based prostate cancer diagnostic pathway would be utilised(178).

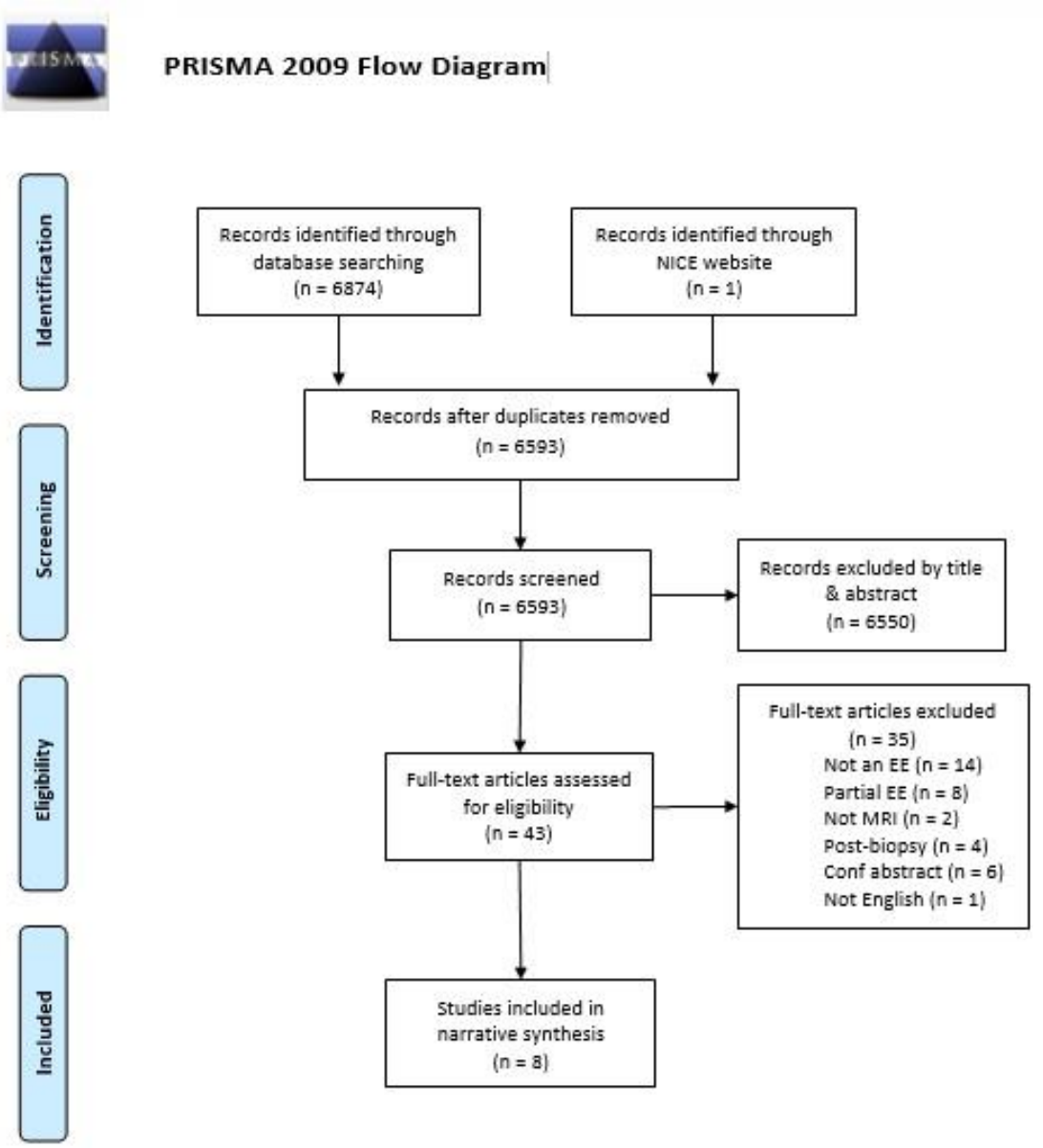


Figure 4.2 – 2009 PRISMA diagram outlining the number of studies identified, screened and included in this systematic review

The patient populations these studies were based on varied widely. Five studies specified age ranges for men, ranging from age 60(180) to 41-70(178). Three studies, all in secondary care settings, did not specify any age range for the patient population(158,177,184). Four studies specified males needed to have a clinical suspicion of prostate cancer(158,177,180,184), and only Cerantola *et al* included any criteria about life expectancy (at least 20 years)(180).

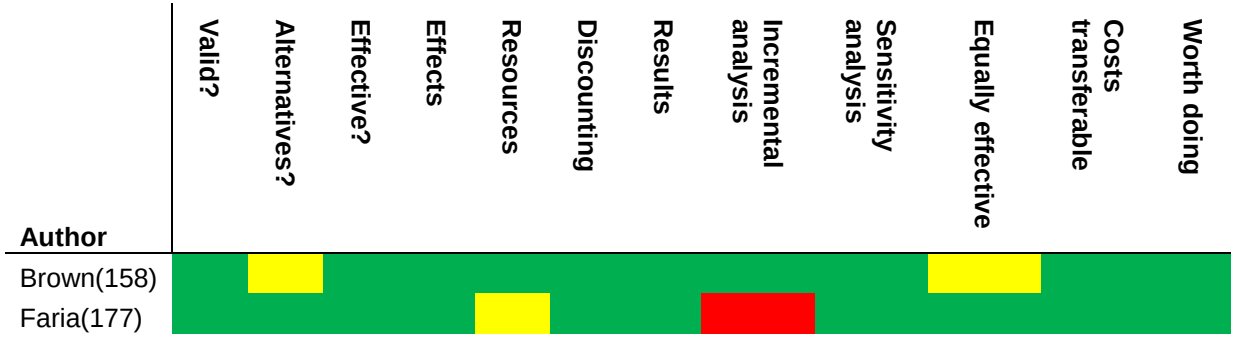


Table 4.1 – Quality assessment of trial-based economic evaluations using the CASP checklist(175)

Green – low risk of bias; Yellow – some risk of bias; Red – high risk of bias

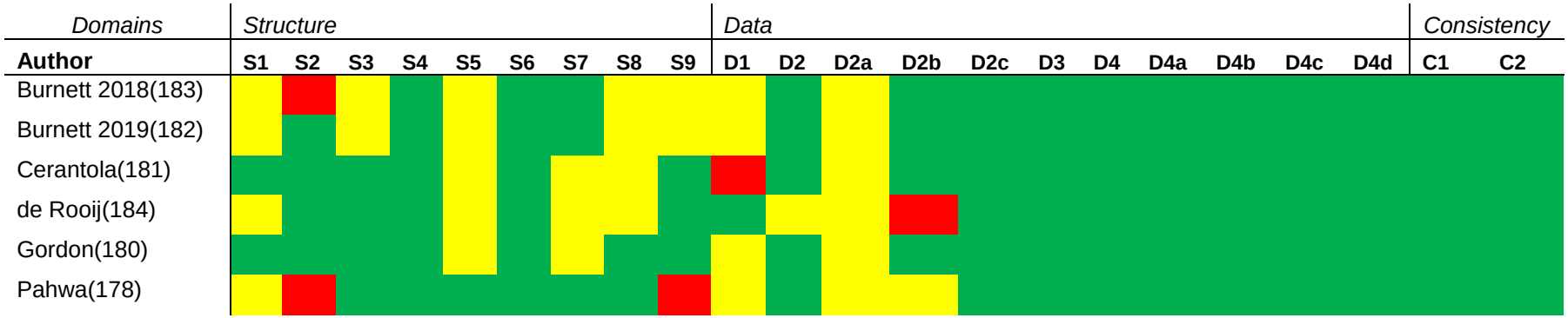


Table 4.2 – Quality assessment of model-based economic evaluations using the Philips framework(173)

Green – low risk of bias; Yellow – some risk of bias; Red – high risk of bias

Author	Year	Publication type	Study type	Country	Currency	Patient population	Setting
Barnett(183)	2018	Journal article	CEA	USA	USD	Biopsy naïve men aged 55-69 years undergoing PSA screening	National PSA Screening Programme
Barnett(182)	2019	Journal article	CEA	USA	USD	Biopsy naïve men aged 55-69 years undergoing PSA screening	National PSA Screening Programme
Brown(158)	2018	HTA	CEA	UK	GBP	Men with suspected prostate cancer referred to secondary care	Secondary care
Cerantola(181)	2016	Journal article	CEA	Canada	CAD	Caucasian males aged 60-65 with PSA 4-10ng/mL and life expectancy of 20 years	Secondary care
de Rooij(184)	2014	Journal article	CEA	The Netherlands	Euros	Average population of men with a suspicion of PCa	Secondary care
Faria(177)	2018	Journal article	CEA	UK	GBP	Men at risk of prostate cancer referred to secondary care	Secondary care
Gordon(180)	2017	Journal article	CEA	Australia	AUD	Australian men aged 60 with suspected PCa	Hospital in a public healthcare system
Pahwa(178)	2017	Journal article	CEA	USA	USD	Men aged 41-70	Not stated

Table 4.3 – Study characteristics

HTA – Health Technology Assessment; CEA – Cost Effectiveness Analysis; USA – United States of America; UK – United Kingdom; USD – US Dollars; GBP – British Pounds; CAD – Canadian Dollars; AUD – Australia Dollars; PSA – Prostate Specific Antigen; PCa – Prostate Cancer

Modelled pathways

Data extracted regarding the diagnostic pathways modelled in the studies is presented in Table 4.4. All studies, except Faria *et al*(177), specified the clinical criteria for pre-biopsy prostate MRI as either a raised PSA or abnormal digital rectal examination (DRE) of the prostate. PSA thresholds were mixed; three studies had a PSA threshold of >4ng/mL(182–184), one study limited PSA levels to 4-10ng/mL(181), one study used age-standardised reference ranges(158), and two studies only referred to 'abnormal' PSA(178,180). Only the 2018 study by Barnett *et al* considered symptoms of a possible prostate cancer, in combination with a PSA level > 3ng/mL, as MRI referral criteria(183).

Seven studies specified the use of mpMRI for the detection of prostate cancer. Pahwa *et al* incorporated bpMRI into the modelled diagnostic pathway and compared it to mpMRI as part of the sensitivity analysis to assess whether the addition of dynamic contract enhancement (DCE) affected the cost-effectiveness of the pathway(178). MRI reporting was mixed: two studies relied on Prostate Imaging-Reporting and Data Systems (PIRADS) version 1(181,183); one study used PIRADS version 2(182); two studies used Likert scales for the likelihood of a lesion being a prostate cancer(158,177); and two relied on radiologist reports(180,184). Pahwa *et al* did not specify how the MRI was judged to be suspicious for cancer or not. Six studies gave definitions for clinically significant prostate cancer, and they were all different.

All studies modelled at least one diagnostic pathway with pre-biopsy MRI. All studies compared MRI-based pathways to the more traditional route employing TRUS biopsy in men with possible prostate cancer, with the exception of Gordon *et al* in which all men had an mpMRI followed by either a TRUS biopsy, transperineal ultrasound guided biopsy, or MRI-guided biopsy to confirm the diagnosis and select the appropriate treatment(180). The 2019 Barnett *et al* study compared TRUS biopsy with mpMRI pathways and combined mpMRI/18 F-Choline Positron Emission Tomography (PET) scanning to assess whether the combined scan was more cost-effective for detecting clinically significant prostate cancer than mpMRI alone in the pre-biopsy setting(182). The number of different testing pathways compared within studies ranged from 2 to 383. For the MRI-based pathways, men with a negative MRI result were assumed not to

go on for biopsy and were either discharged at that point or had some further clinical follow-up. A range of different biopsy approaches for men with positive MRI results were modelled.

Author	Year	MRI criteria	MRI approach	MRI reporting	Clinically significant PCa definition	Testing strategies	Treatment strategies
Barnett(183)	2018	PSA > 4 ng/mL OR PSA > 3 ng/mL + symptoms	Multiparametric	PIRADs v1	Gleason score ≥ 7	1 TRUSGB 2a mpMRI PIRADS 3-5 → targeted biopsy PIRADs 1-2 → TRUSGB. 2b mpMRI PIRADS 4-5 → targeted biopsy PIRADs 1-3 → TRUSGB 3a mpMRI PIRADS 3-5 → targeted biopsy PIRADS 1-2 → no biopsy. 3b mpMRI PIRADS 4-5 → targeted biopsy PIRADS 1-3 → no biopsy 4a mpMRI PIRADS 3-5 → combined biopsy PIRADS 1-2 → TRUSGB 4b mpMRI PIRADS 4-5 → combined biopsy	Gleason 7 or higher → Radical prostatectomy Patients age 80+ → WW Gleason 3+3 → 48.5% had AS; 51.5% had prostatectomy AS = annual PSA + standard biopsy every 2 years. Any progression in Gleason score → prostatectomy

						PIRADs 1-3 → TRUSGB 5a mpMRI PIRADS 3-5 → combined biopsy PIRADs 1-2 → no biopsy. 5b mpMRI PIRADS 4-5 → combined biopsy PIRADs 1-3 → no biopsy	
Barnett(182)	2019	PSA > 4 ng/mL	Multiparametric ^{18}F-choline PET/mpMRI (without DCE)	PIRADS v2 Likert	Gleason score ≥ 3+4	1 TRUSGB 2 mpMRI Likert 4-5 → combined biopsy Likert 1-3 → TRUSGB 3 mpMRI PIRADS v2 3-5 → combined biopsy PIRADS v2 1-2 → TRUSGB 4 ^{18}F-choline PET/mpMRI, Likert 4-5 → combined biopsy Likert 1-3 → TRUSGB 5 ^{18}F-choline PET/mpMRI PIRADS v2 3-5 → combined biopsy PIRADS v2 1-2 →TRUSGB 6 mpMRI	Gleason 3+4 or higher → Radical prostatectomy Patients age 80+ → WW Gleason 3+3 → 48.5% had AS; 51.5% had prostatectomy AS = annual PSA + standard biopsy every 2 years. Any progression in Gleason score → prostatectomy

						Likert 4-5 → combined biopsy Likert 1-3 → no biopsy. 7 mpMRI PIRADS v2 3-5 → combined biopsy PIRADS v2 1-2 → no biopsy 8 ^{18}F-choline PET/mpMRI Likert 4-5 → combined biopsy Likert 1-2 → no biopsy 9 ^{18}F-choline PET/mpMRI PIRADS v2 3-5 → combined biopsy PIRADS v2 1-2 → no biopsy	
Brown(158)	2018	PSA elevated above age-reference standard OR Abnormal DRE	Multiparametric	Likert	Primary – Dominant Gleason pattern 4-5 and/or cancer core length >6mm Secondary – Any Gleason 4+ and/or	32 diagnostic strategies using mpMRI, TRUSGB and TPMB in different combinations, for each of the two diagnostic definitions for mpMRI, TRUSGB and TPMB and between two and five cut-off points on the mpMRI Likert scale for suspicion of	Low-risk cancer → AS Intermediate-risk cancer → AS or radical treatment High-risk → AS or radical treatment

					cancer core length >4mm	cancer, under the following principles: 1. The only tests considered are mpMRI, TRUSBG and TPMB. This follows from PROMIS, which compared mpMRI and TRUSGB with TPMB. 2. There can be up to three tests in one diagnostic strategy. Diagnostic episodes may be repeated over time, but this is not explicitly modelled in this analysis. 3. A diagnostic strategy can include up to two biopsies. 4. If included in the strategy, mpMRI can be used only once.	
Cerantola(181)	2016	Abnormal DRE OR PSA 4-10ng/mL	Multiparametric	PIRADS v1	Not stated	1 MRTB strategy Positive MRI → MRTB Positive MRTB → Treatment Negative MRTB → Follow-up as required Negative MRI → Follow-up as required 2 TRUSGB strategy	Distributed to AS or definitive treatment based on risk stratification at diagnosis. After AS or initial treatment, patients could die, relapse,

						Positive TRUSGB → Treatment Negative TRUSGB → Follow-up as required	or progress to CPRC
de Rooij(184)	2014	PSA > 4ng/mL and suspicion of PCa	Multiparametric	Radiologist report	Large Gleason Score 3+3 tumour OR Gleason Score ≥3+4	1 MRI strategy = mpMRI for all men, with MRGB for +ve mpMRI 2 TRUSGB strategy = TRUS for all men	Radical prostatectomy Radiation therapy Brachytherapy WW/AS (Probabilities of receiving treatment for patients diagnosed with clinically significant or insignificant tumours derived from the literature and expert opinion)
Faria(177)	2018	Not stated	Multiparametric	Likert	1 Gleason Score ≥ 4+3 or max core length ≥ 6mm 2 Gleason Score ≥ 3+4 or max core length ≥ 4mm	The diagnostic strategies consisted of clinically feasible combinations of MPMRI, TRUSGB, and TPMB, in addition to the use of TRUSGB and TPMB in isolation. A diagnosis of CS cancer requires a biopsy; hence strategies were defined to always end	Low-risk cancer → WW Intermediate-risk cancer → WW or radical prostatectomy High-risk → radical prostatectomy

						with a confirmatory biopsy. Each of the 32 test combinations were tested for the alternative classifications and cut-offs, returning a total of 383 strategies.	
Gordon(180)	2017	Abnormal PSA AND/OR Abnormal DRE	Multiparametric	Radiologist report	Not stated	Pre-biopsy mpMRI, followed by TRUSGB, TPUSGB, or MRTB	Population-based proportions of men with PCa receiving treatments = AS for under 75 years WW for 75 years and over Radical prostatectomy External beam radiotherapy Brachytherapy Androgen Deprivation Therapy
Pahwa(178)	2017	Elevated PSA OR Abnormal DRE	Biparametric	Not stated	Gleason Score ≤6 and tumour volume < 0.5mm^3	1 Standard TRUSGB 2 bpMRI + cognitive MR-guided biopsy if MRI +ve 3 bpMRI + fusion-guided biopsy if MRI +ve	Probabilities of patient choosing treatment in clinically significant and insignificant cancer derived from the literature. Options =

						4 bpMRI + in-bore MR-guided biopsy if MRI +ve 5 bpMRI + cognitive MR-guided biopsy if MRI +ve OR TRUSGB if MRI –ve 6 bpMRI + fusion-guided biopsy if MRI +ve OR TRUSGB if MRI –ve 7 bpMRI + in-bore MR-guided biopsy if MRI +ve OR TRUSGB if MRI –ve	AS WW Radiation therapy Brachytherapy Prostatectomy Androgen deprivation therapy

Table 4.4 – Modelled diagnostic pathways

MRI – Magnetic Resonance Imaging; PCa – Prostate Cancer; PSA – Prostate Specific Antigen; WW – Watchful Waiting; AS – Active Surveillance; PET – Positron Emission Tomography; DCE – Dynamic Contrast Enhancement; DRE – Digital Rectal Examination; TRUSGB – Transrectal Ultrasound guided biopsy; TPUSGB – Transperineal Ultrasound guided biopsy; TPMB – Template Prostate Mapping biopsy; MRTB – Magnetic Resonance imaging Targeted Biopsy; CRPC – Castration Resistant Prostate Cancer; CS – Clinically Significant; mpMRI – Multiparametric MRI; bpMRI – Biparametric MRI

All studies modelled treatment outcomes on the basis of the diagnoses made in the various modelled testing strategies. Most studies assumed biopsy results were perfectly accurate for the presence and grade of the prostate cancer. The modelling-based studies estimated the proportion of men opting for different treatment options based on a review of the literature, national prostate cancer registries, and/or expert opinion. The two trial-based economic evaluations based the options for treatment of different prostate cancer risk groups on national guidance but did not explain what proportion of men diagnosed with intermediate- or high-risk prostate cancer received radical treatment, or how this was measured(158,177).

Model characteristics

The characteristics of the models from the studies are presented in Table 4.5. Seven of the eight studies employed a Markov model. Three combined a decision tree model with a Markov model(158,177,184). Pahwa *et al* employed a decision-analytic model(178). Four studies employed lifetime horizon modelling(177,178,182,183), with the remaining time horizons ranging from 10 to 30 years. Studies outside the US took a health department or governmental perspective, with two US studies considering MRI-based pathways from a third-payer perspective(182,183). Pahwa *et al* did not state what perspective their study was conducted from(178). Annual discounting ranged from 1.5% - 5%. All studies performed sensitivity analyses.

Study outcomes

The key outcomes from the modelling studies of pre-biopsy MRI for prostate cancer are presented in Table 4.6. MRI-based pathways were less expensive than TRUS biopsy pathways in six of the studies. MRI-based pathways were found to be more effective in all eight studies. The most cost-effective testing strategies in each study varied in terms of type of pre-biopsy MRI test, threshold for a positive MRI result, and biopsy approach for men with a positive MRI. Cerantola *et al* and de Rooij *et al* featured the most similar MRI-based pathway, whereby patients with suspected prostate cancer undergo mpMRI, followed by MRI-guided biopsy for men with a positive mpMRI result; the approach currently in use in the UK. Both studies found the MRI-based pathway to be more effective compared to a TRUS-biopsy pathway but differed on whether it was

more or less expensive(181,184). Despite applying slightly different methods to data generated from the same trial, Brown *et al* and Faria *et al* both concluded the same testing strategy was the most cost-effective from various combinations of mpMRI, TRUS-biopsy, and template prostate mapping biopsy(158,177).

Author	Year	Approach	Time Horizon	Perspective	Discounting	Outcome measure	Sensitivity analysis
Barnett(183)	2018	Markov model	Lifetime from age 40	Third-party payer	3%	ICERs	Yes
Barnett(180)	2019	Markov model	Lifetime from age 40	Third-party payer	3%	ICERs	Yes
Brown(156)	2018	Decision tree + Markov model	20 years	UK NHS	3.5%	Cost per QALY gained at different thresholds	Yes
Cerantola(179)	2016	Markov model	20 years	Public healthcare system	5%	ICERs at 5-, 10-, 15- , and 20-year time horizon	Yes
de Rooij(182)	2014	Decision tree + Markov model	10 years	Healthcare system	QALYS by 1.5% Costs by 4%	ICERs	Yes
Faria(175)	2018	Decision tree + Markov model	Lifetime	UK NHS	3.5%	Cost-effectiveness of diagnosis Long-term cost-effectiveness	Yes
Gordon(180)	2017	Markov model	30 years from age 60	Australian government	5%	ICERs	Yes
Pahwa(178)	2017	Decision analytic model	Lifetime	Not stated	3%	ICERs Net Health Benefit	Yes

Table 4.5 – Model characteristics

UK – United Kingdom; NHS – National Health Service; ICERs – Incremental Cost Effectiveness Ratios; QALY – Quality Adjusted Life Year

Author	Year	MRI-based pathway more expensive	MRI-based pathway more effective	Optimal testing strategy	QALYs gained	ICER	Threshold
Barnett(183)	2018	Yes	Yes	mpMRI PIRADs 3-5 → combined biopsy. PIRADS 1-2 → no biopsy.	60.7 (95% CI 60.1 – 61.3) QALYs gained compared to no screening	$23, 483 USD (per 1,000 men)	WTP $100,000 USD per QALY
Barnett(182)	2019	No	No	^{18}F-choline PET/mpMRI Likert 4-5 → combined biopsy. Likert 1-3 → no biopsy	60.4 (95% CI 59.4 – 61.4) compared to no screening	£35,108 USD (per 1,000 men)	WTP $100,000 USD per QALY
Brown(158)	2018	No	Yes	Testing all men with mpMRI at definition 2, cut-off point 2 for CS cancer, using MRTB to detect CS cancer and rebiopsying men in whom CS cancer was not detected	8.72 (95% CI 8.4o – 9.04) discounted QAYs gained	Not presented	£13,000, £20,000, or £30,000 per QALY gained
Cerantola(181)	2016	No	Yes	MRTB strategy	0.168 (95% CI not stated) incremental QALYs at 20 years	Not presented	$50,000 CAD per QALY gained
de Rooij(184)	2014	Yes	Yes	MRI strategy	0.10 (95% CI -0.18, 0.34) incremental QALYs at 10 years	€323	Range of WTP thresholds from €1 - €100,000

Faria(177)	2018	No	Yes	Testing all men with mpMRI at definition 2, cut-off point 2 for CS cancer, using MRTB at definition 2 to detect CS cancer. Repeat biopsy for men in whom CS cancer was not detected	8.72 (95% CI 8.40, 9.04)	£7,076	£13,000, £20,000, or £30,000 per QALY gained
Gordon(180)	2017	Yes (if same rates of AS) No (if increased rates of AS)	No (if same rates of AS) Yes (if increased rates of AS)	All men receive mpMRI. Positive mpMRI → TRUSGB, TPUSGB, or MRTB. All men with very-low or low-risk cancer assumed to undergo AS.	7.83 (95% CIs not stated)	$3,980 AUD	WTP $50,000 AUD per QALY gained
Pahwa(178)	2017	No (except strategy 6)	Yes	bpMRI with cognitive MR-guided biopsy if MRI +ve	8.90 (95% CI 7.34, 10.21) NHB in QALYs	$8,946 USD	WTP $10,000, $25,000, $50,000, or $100,000 USD

Table 4.6 – Study outcomes

mpMRI – Multiparametric MRI; PET – Positron Emission Tomography; QALY – Quality Adjusted Life Year; ICER – Incremental Cost Effectiveness Ratio (Cost per QALY gained); WTP – Willingness To Pay; CS – Clinically Significant; MRTB – Magnetic Resonance Targeted Biopsy; AS – Active Surveillance; TRUSGB – Transrectal Ultrasound guided biopsy; TPUSGB – Transperineal Ultrasound guided biopsy; bpMRI – Biparametric MRI; NHB – Net Health Benefit

They were the only studies to suggest a repeat biopsy was needed for patients with a positive MRI and negative initial biopsy; an approach that was still found to be cost-effective.

Table 4.7 uses the visual presentation suggested by Nixon *et al* to qualitatively summarise the impacts of costs or health outcomes in the MRI-based pathways compared to TRUS biopsy pathways, and links this to the overall decision on whether to MRI pathway dominates or not (accept, neutral, reject)(176).

Cost	No. of studies	Health outcomes	Decision
More	0	Worse	Reject MRI pathway
Same	0	Worse	
More	0	Same	
Less	0	Worse	Neutral
Same	0	Same	
More	2	Better	Incremental analysis suggested accept
Less	6	Same	Accept MRI pathway
Same	0	Better	
Less	0	Better	

Table 4.7 – Hierarchical matrix of studies comparing MRI-based pathways to TRUS-biopsy pathways

4.4 Discussion

Key findings

This systematic review of economic evaluations found that prostate cancer diagnostic pathways incorporating pre-biopsy MRI can be cost-effective when compared with diagnostic pathways relying on TRUS-biopsy. All studies modelled pathways that started with a patient in secondary care referred for diagnostic testing for suspected prostate cancer. Despite significant variation in terms of their setting, modelled pathways, and key parameters for the included studies, all studies reported cost-effectiveness outcomes in favour of MRI-based prostate cancer diagnostic pathways. The evidence for the optimal use of pre-biopsy MRI for prostate cancer and reporting systems to identify suspicious lesions for biopsy is still evolving, and further economic evaluation will be needed to understand how healthcare systems can best integrate this new diagnostic test into clinical pathways.

The studies varied widely in a number of key parameters. The patient populations were either men aged 55-69 years participating in a prostate cancer screening programme, or men with suspected prostate cancer based on elevated PSA or abnormal DRE in different age ranges. A range of MRI reporting systems were modelled, including PIRADS v1, PIRADS v2, and Likert scales, which is an important consideration for diagnostic accuracy of pre-biopsy MRI as each system produces different results(186,187). The definition of clinically significant prostate cancer was also different in each study that reported them. A key purported benefit of MRI in prostate cancer detection is that more clinically significant prostate cancers are diagnosed – without an increase in the diagnosis of clinically insignificant prostate cancers. This should result in better outcomes for patients in terms of reducing over diagnosis and overtreatment of prostate cancers that are very unlikely to cause significant morbidity or mortality. Reductions in overtreatment and unnecessary prostate biopsies should also reduce healthcare costs. The variation in definition of clinically significant prostate cancer in studies from this review likely stems from the fact there is no clear consensus definition at this time(11). Prostate biopsy approach is another area where there is no clinical consensus for an optimal method(188), and this is reflected in the fact that a number of different biopsy approaches were modelled in the economic evaluations.

There were some areas of commonality for the studies in this systematic review. All studies undertook a cost-effectiveness analysis, with all but one utilising a Markov model. All studies performed sensitivity analyses to varying degrees. Seven of eight studies employed multiparametric MRI, with Pahwa *et al* using biparametric MRI. All studies included a TRUS biopsy only diagnostic pathway for comparison to their proposed MRI-based pathway(s), which was the standard of care before the prostate MRI era. Despite some of the significant differences highlighted above, all studies found that MRI-based pathways were more effective and cost-effective than TRUS biopsy pathways.

Comparison to published literature

The only other literature review addressing the question of the cost-effectiveness of pre-biopsy MRI for prostate cancer detection was undertaken by Chiu & Adcock in a 2018 report compiled for the Canadian Agency for Drugs and Technology in Health (CADTH)(160). Six studies were included in that review(158,181,184,189–191), and the authors concluded that MRI prior to TRUS biopsy was more cost effective that TRUS biopsy alone despite higher testing costs with the MRI-based pathways. The review by Chiu & Adcock did not cover as wide a range of databases as this review, was only single screened, and was trying to establish the evidence for effectiveness as well as cost-effectiveness of pre-biopsy MRI. Even so, the conclusions were similar to this review.

Willis *et al* undertook a literature review of economic evaluations of prostate cancer diagnostic strategies involving imaging, with a particular interest in the evidence for mpMRI(159). This review considered cost-effectiveness studies of pre-biopsy mpMRI and mpMRI performed after an initial negative biopsy where prostate cancer is still suspected. The methods were sparingly reported, although the authors did state they were available upon request, and the inclusion criteria were very broad. Five economic evaluations were included in the review by Willis *et al* (184,190,191),(192,193); two of which found diagnostic strategies incorporating mpMRI to be cost effective, two studies did not conclude them to be cost-effective, and one study did not find clear evidence either way. The authors judged that existing studies of the cost-effectiveness of

prostate cancer diagnostic pathways involving MRI lacked consistency in reporting and key modelling assumptions, and that future studies needed broader sensitivity analyses to gain a clearer understanding.

Strengths and limitations

This study has a number of key strengths to increase confidence in the findings. It is the first review addressing the cost-effectiveness of pre-biopsy MRI for prostate cancer detection conducted in a systematic manner. We adhered closely to the PRISMA guidelines for the conduct of systematic review, with two independent reviewers screening articles, extracting data and assessing study quality. A wide range of relevant databases were searched in order to capture a more complete number of studies for possible inclusion. The included studies were generally assessed as having a low risk of bias, improving the likelihood of contributing strong evidence to the review.

There are some limitations that need to be taken into consideration when interpreting the findings of this study. MRI is a relatively new test for prostate cancer detection, with new evidence around the optimal use of MRI being published all the time. Some key clinical controversies remain unanswered, such as a consensus definition of clinically significant prostate cancer and the optimal biopsy approach for men with suspected prostate cancer, which create variation in the assumptions of cost effectiveness analyses as demonstrated in the studies for this review. In spite of the differences in key assumptions for cost-effectiveness analyses, the direction of benefit was the same in all studies.

Implications for policy and practice

Pre-biopsy prostate MRI for the detection of clinically significant prostate cancer is already recommended in national guidelines in the UK(12), Europe(194) and Australia(195). The use of prostate MRI in other high-income countries with wider availability of MRI scanners is growing as the evidence for the use of this test evolves. All but one of the studies took the perspective of healthcare system decision-makers and third-party payers, increasing the relevance of the findings for those deciding whether to fund prostate MRI for their local or national service. This review found that whichever MRI-based pathway(s) was modelled, they were all cost-effective compared to the previous standard

diagnostic test of TRUS-biopsy. This implies that commissioning and recommending pre-biopsy prostate MRI will result in better outcomes for patients with suspected prostate cancer for the relevant costs involved. Relatively little consideration was given to the opportunity cost of MRI, and the potential for increasing prostate MRIs to reduce availability of MRI scanners and staff resources for other uses of MRI. Healthcare decision-makers will need to review their available MRI scanners and radiology department workforce to assess the implications of introducing MRI-based prostate cancer pathways on the wider health service.

Most studies in this review modelled mpMRI as the imaging modality of choice. There is growing evidence that bpMRI has equivalent diagnostic accuracy for clinically significant prostate cancer when compared to mpMRI and has the added benefit of shorter scan time and not requiring the administration of intravenous contracts(196–198). As the evidence for bpMRI evolves in years to come, the optimal MRI approach for use in clinical practice may change.

4.5 Conclusions

Prostate cancer diagnostic pathways in secondary care or screening programmes that incorporate pre-biopsy MRI are likely to be more cost-effective than pathways relying on TRUS biopsy as a diagnostic test alone. Owing to the lack of consensus in a number of areas related to prostate MRI and MRI-guided biopsy techniques, the currently available economic evaluations varied in a number of key parameters. Despite these differences, all studies found MRI-based pathways in secondary care or screening programmes to be more cost effective. It is unknown what impact the presentation, triage testing, risk stratification, and identification of patients with suspected prostate cancer in primary care for referral to secondary care has on the cost effectiveness of the prostate cancer diagnostic pathway. Further clinical and health economic research is needed to determine the optimal application of pre-biopsy prostate MRI to maximise benefits for patients and healthcare budgets.

The findings of this review will inform the decision-analytic modelling undertaken for this PhD in a number of ways. Firstly, it demonstrates the need for the modelling to be performed as no existing economic modelling studies incorporating direct access to prostate MRI in primary care were found. Secondly, the included full economic evaluations highlight key parameters and evidence sources that need to be considered in my own modelling work. Thirdly, they form a set of comparator studies to use to contextualise the findings of my own modelling study.

Chapter 5 – Early economic evaluation of magnetic resonance imaging as a diagnostic test for prostate cancer in primary care using decision analytic modelling

5.1 Introduction

Prostate cancer diagnostic pathway

Integration of prostate magnetic resonance imaging (MRI) into existing prostate cancer diagnostic pathways in the NHS has been a focus in recent years following publication of the PROMIS(53) and PRECISION(54) trials. A 2018 report prepared for NHS clinical commissioning groups (CCGs), cancer alliances and hospital trusts titled '*Implementing a timed prostate cancer diagnostic pathway'* outlined the case for pre-biopsy prostate MRI. It highlighted the benefits for patients in terms of avoiding unnecessary prostate biopsies and improving the detection of clinically significant cancers and presented a recommended 28-day pathway that integrates prostate MRI based on NHS vanguard pathways implemented in London and Manchester (see figure 5.1)(47).

The pathway starts with an urgent GP referral for suspected prostate cancer, and all patients who are able to undergo a pre-biopsy prostate mpMRI. The result of the mpMRI determines the need for prostate biopsy; some patients could avoid prostate biopsy following a discussion with a clinician if the MRI shows no suspicious-looking lesions. Patients with a suspicious area on MRI who have a negative biopsy would be reviewed at an imaging meeting with urologists and radiologists to decide if repeat biopsy is needed. Patients with cancer detected on biopsy would progress to a multidisciplinary team (MDT) discussion to decide on an appropriate management plan. Subsequently published guidance

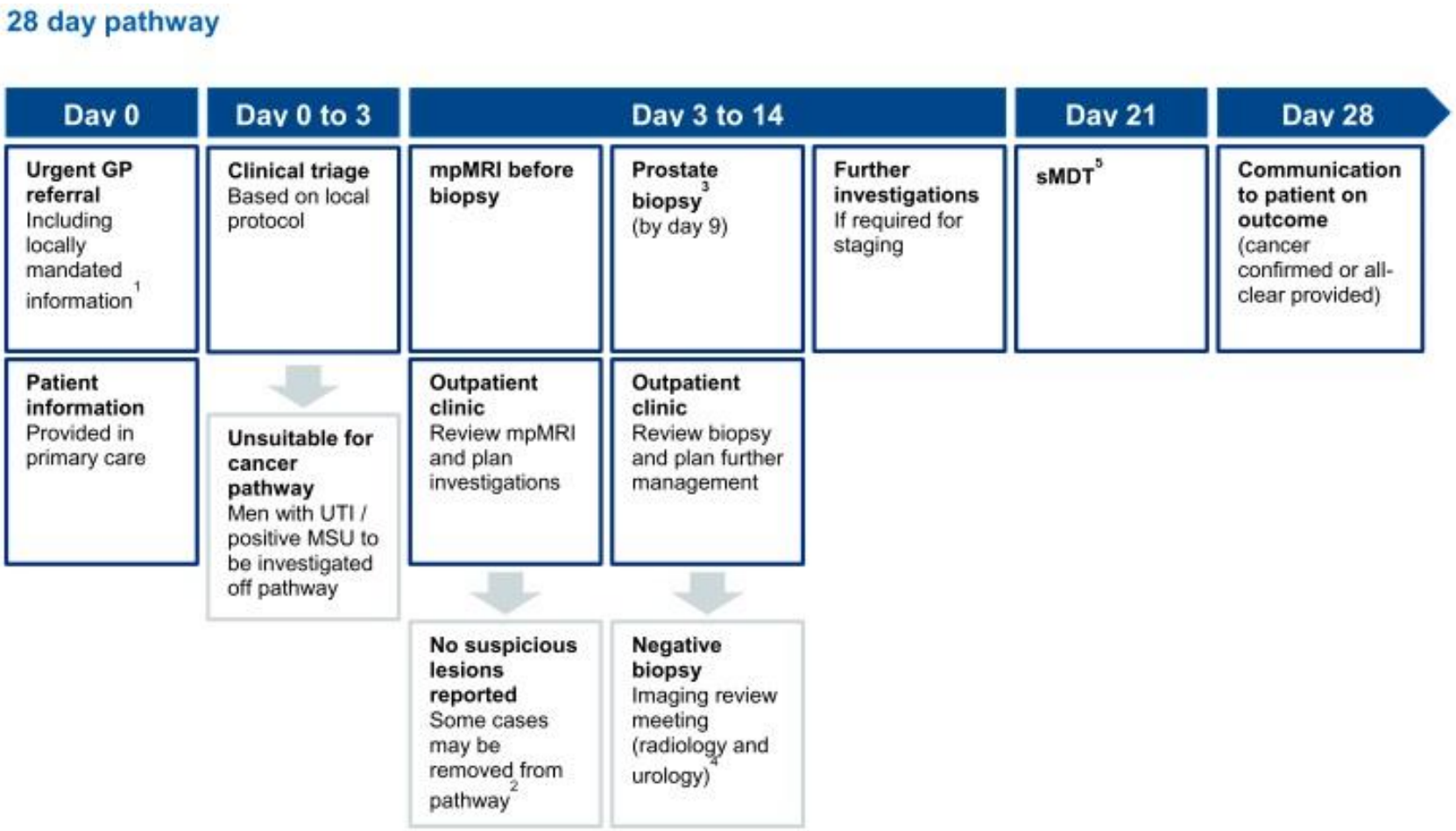


Figure 5.1 Recommended 28-day pathway from '*Implementing a timed prostate cancer diagnostic pathway'*(47)

GP – General Practitioner; UTI – Urinary Tract Infection; MSU – Mid Stream Urine; mpMRI – Multiparametric MRI; MDT – Multidisciplinary Team

from the National Institute for health and Care Excellence (NICE) in 2019 also recommended this approach for the diagnosis of prostate cancer(12).

The main proposed benefits for patients of integrating prostate MRI into the diagnostic pathway are: increasing the detection of clinically significant prostate cancer, without diagnosing more cases of clinically insignificant prostate cancer, and safely avoiding biopsies in patient without prostate cancer. A reduction in the number of prostate biopsies would be expected to reduce costs for the NHS, both from fewer biopsies being performed and a resulting reduction in complications such as urosepsis(27). The proposed pathway would require at least the same number of outpatient consultations before biopsy, or possibly more, and adds a further diagnostic test. Patients attending hospital outpatient appointments face several challenges, including transport and parking (see Chapter 3). Furthermore, NHS urological cancer services were already struggling to meet NHS targets for time to diagnosis and time to commencing treatment prior to the publication of recommendations for implementing prostate MRI from NHS England and NICE(199).

The current NHS prostate cancer diagnostic pathway employs prostate MRI as a secondary care test, as do other comparable healthcare systems (see Chapters One and Four). There are no known examples of primary care use of prostate MRI for the early detection of clinically significant prostate cancer. The only test for prostate cancer currently available to primary care clinicians is the Prostate Specific Antigen (PSA) blood test. The increasing use of PSA is thought to have been a key contributing factor to the rise in the incidence of prostate cancer (more often lower risk disease) in high-income countries in recent decades(21), and has not been clearly shown to reduce mortality as a screening test in asymptomatic patients(22). PSA has poor face validity with GPs owing to the perceived poor diagnostic accuracy (see Chapter Three), and the diagnostic accuracy of PSA for clinically significant prostate cancer and in symptomatic patients is unknown(200). Implementing a more accurate test for prostate cancer, such as prostate MRI, in primary care could have similar benefits to those found already in the published literature. It may have additional benefits for the NHS in terms of reducing waiting times in the prostate

cancer diagnostic pathway, given the MRI has already been performed to inform the referral decision, and reducing urology referrals from primary care.

Chapter Four showed that there are currently no published full economic evaluations of MRI-based prostate cancer diagnostic pathways that consider the primary care elements of the pathway, and no studies which have modelled the use of prostate MRI in a primary care setting. An approach to estimating the impact of a new diagnostic test on a clinical pathway where the optimal pathway design is uncertain is early economic evaluation(201). This approach can provide an initial assessment about the potential cost-effectiveness of a new technology, particularly when the optimal pathway using the technology is unknown and can identify key model parameters that will have a large influence on the final cost-effectiveness analysis(202).

Aim & objectives

The aim of this early economic evaluation is to explore the potential impacts of incorporating pre-biopsy magnetic resonance imaging into the primary care prostate cancer diagnostic pathway. The objectives were to explore the following questions:

1. What is the proportion of patients currently referred on the urgent suspected prostate cancer pathway following NICE guidance NG12 who are potentially referred unnecessarily, and what proportion of prostate cancer cases are missed by the current primary care diagnostic pathway?
2. What would be the expected differences in costs for the NHS and utility for patients between the existing primary care prostate cancer diagnostic pathway and a pathway employing pre-referral prostate MRI in primary care?
3. What would be the expected difference in costs and outcomes between using multiparametric magnetic resonance imaging (mpMRI) and biparametric magnetic resonance imaging (bpMRI) for pre-referral MRI in the proposed primary care prostate cancer diagnostic pathway?

4. What would be the expected difference in costs and outcomes in the proposed primary care prostate cancer diagnostic pathway between symptomatic patients being investigated for prostate cancer and asymptomatic patients undergoing opportunistic screening for prostate cancer?

5.2 Development of the model

The conceptualisation, construction and development of this decision analytic model has been undertaken following the process outlined by the International Society for Pharmacoeconomics and Outcomes Research – Society for Medical Decision Making (ISPOR-SMDM) modelling good research practices task force(203).

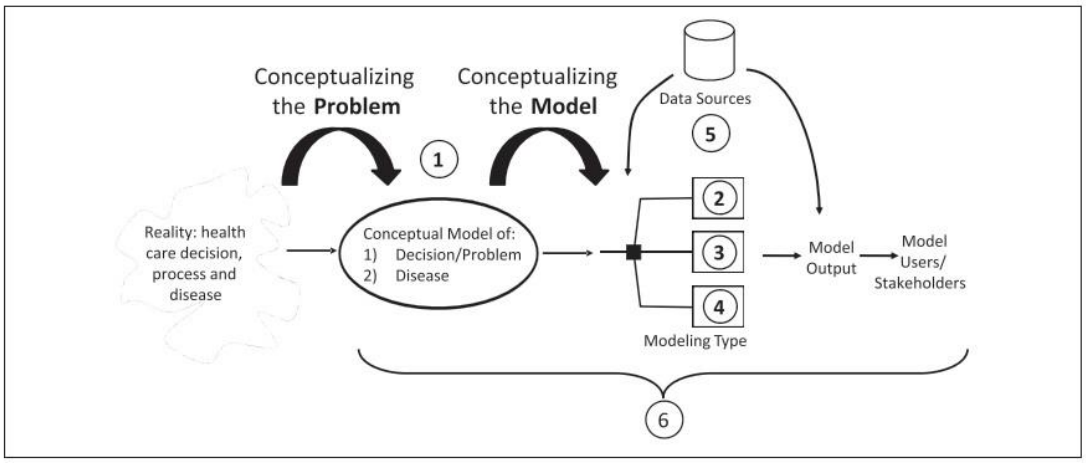


Figure 5.2 Process of model development and analysis from Roberts at al (ISPOR-SMDM paper 2) (2012)(204)

Conceptualising the model

There are two main routes through which most patients with prostate cancer will ultimately be diagnosed. The first relates to screening asymptomatic patients with a PSA blood test and referring patients who have a raised PSA above recommended thresholds. There are very few national, PSA-based prostate cancer screening programmes globally due to the lack of evidence for a mortality benefit and concerns about overdiagnosis and overtreatment(8,14). In the UK, patients can undergo opportunistic PSA screening for prostate cancer following an informed discussion with their GP about the potential benefits and harms involved(25). Estimates vary as to the level of PSA testing undertaken that is for screening purposes in primary care, but it appears to be a significant proportion(143,205).

The second common route through which patients are diagnosed with prostate cancer is following the development of lower urinary tract symptoms (LUTS). The association between prostate cancer and LUTS is controversial(14),

although the majority of patients with prostate cancer report having symptoms such as LUTS prior to their diagnosis(15). NICE guideline NG12 '*Suspected cancer: recognition and referral*' recommends GPs consider a Digital Rectal Examination (DRE) of the prostate and PSA test for any patients presenting with LUTS, visible haematuria or erectile dysfunction, and to refer urgently for further investigation if either the DRE or PSA is abnormal(24).

These two main routes to diagnosis are consistent with my own clinical experience as a practicing GP. This was supported through discussions with my two clinical supervisors (WH and FMW), and from feedback following the presentation of a conceptual model (see Figure 5.3 below) to a meeting of the CanTest International School in February 2021(206). This model also incorporates secondary care testing leading to diagnosis as outlined above. The other potential routes to diagnosis a patient with prostate cancer may follow to get their diagnosis – which are less common – include incidental abnormal findings on DRE for other purposes, discovery of a prostate cancer following a routine urology referral for non-cancer reasons, or late-stage diagnosis through emergency presentation(48).

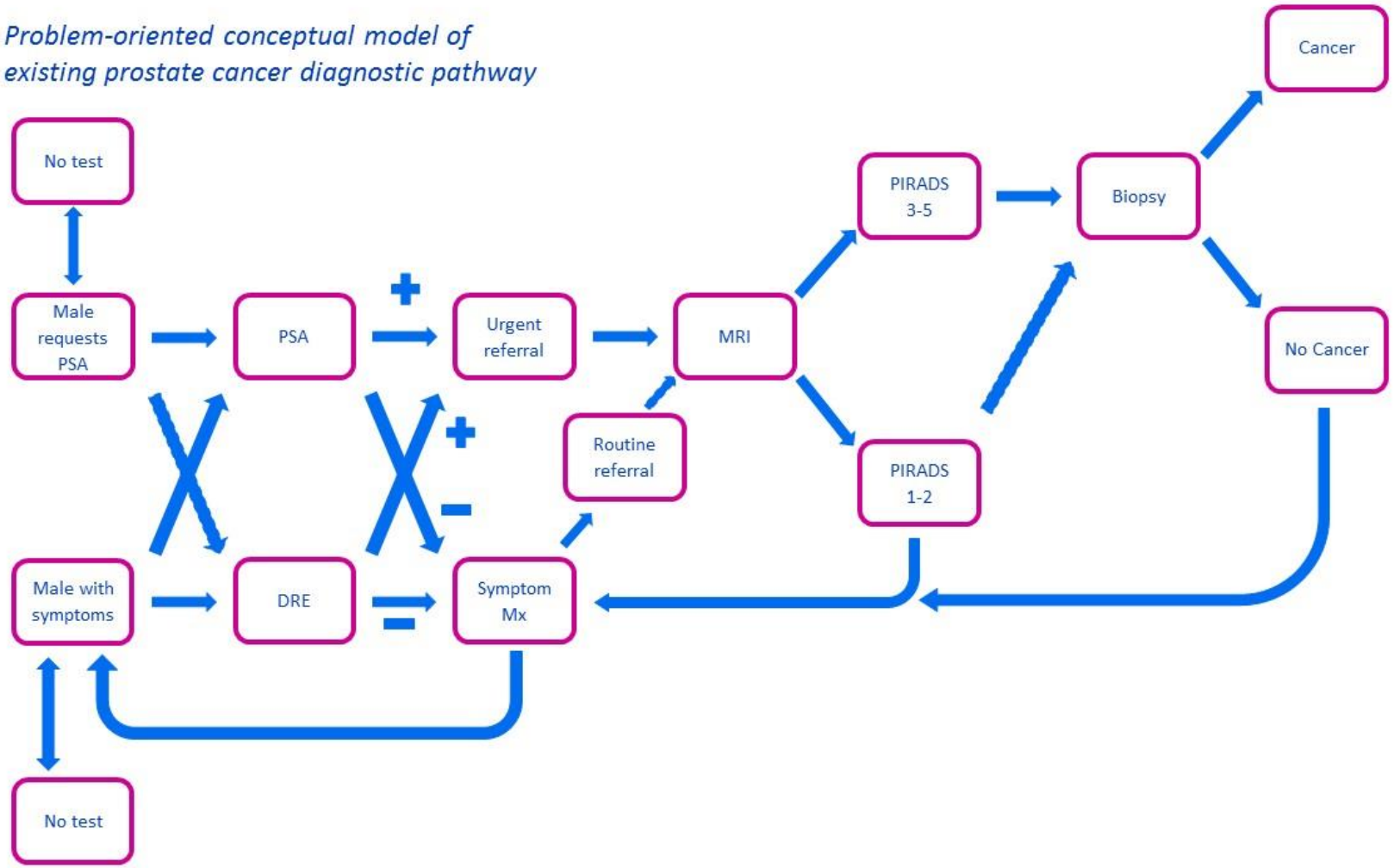


Figure 5.3 – Conceptual model of the existing prostate cancer diagnostic pathway

+ indicates an abnormal/positive result; **–** indicates a normal/negative result

PSA – Prostate Specific Antigen; DRE – Digital Rectal Examination; Mx – management; MRI – Magnetic Resonance Imaging; PIRADS – Prostate Imaging-Report and Data System

Modelling approach

A decision analytic modelling approach using decision trees was undertaken to address the research questions for several key reasons. Decision modelling allows the comparison of expected costs and outcomes for a range of options being considered for a particular problem, even when there is uncertainty around the decision(s)(207,208). Employing decision trees is a simple but effective method for decision problems with shorter time horizons that captures the potential consequences of following different clinical pathways.(209)

Disease

The primary disease of interest for this evaluation is clinically significant prostate cancer. As outlined earlier, clinically significant prostate cancer is defined based on the histology of the tumour using the Gleason scoring system (Gleason score ≥ 7 or Gleason Grade Group ≥ 2) and informs treatment and prognosis(11). Patients with localised clinically significant prostate cancer at diagnosis are recommended to have invasive treatments, including radical prostatectomy or radiotherapy, whilst patients with clinically insignificant tumours (Gleason score = 6 or Gleason Grade Group = 1) are recommended to undergo active surveillance as there is a very low risk of tumour progression, cancer-related morbidity or mortality(12). The diagnostic accuracy of mpMRI and bpMRI for clinically significant prostate cancer has been extensively researched(29,35). However, the ability of DRE and PSA to discriminate between clinically significant and clinically insignificant prostate cancer is less well understood and assumed to be poor(200). Therefore, a diagnosis of any prostate cancer was used as an outcome for the models.

Perspective

The perspective chosen for this model was a health system perspective. Specifically, this model sought to generate data on the potential impacts of prostate MRI on the existing prostate cancer diagnostic pathway in primary care to inform the design of clinical pathways by NHS commissioners and cancer alliances. This approach is similar to that used by the NICE HTA reference case(210).

Target population

The population of interest for this model includes patients in the UK with symptoms of possible prostate cancer presenting to NHS primary care, or patients without any symptoms requesting PSA screening in NHS primary care. As demonstrated in the conceptual model of the existing pathway, these are two common routes to diagnosis for prostate cancer that begin in primary care, and the exclusion of patients undergoing opportunistic PSA screening for this modelling study would potentially exclude many patients investigated for possible prostate cancer in primary care(205). Prostate cancer guidelines often focus on patients aged 50 years and over, as prostate cancer is uncommon in younger patients, so the population for this model was also limited to patients in this age group.

Strategies/comparators

The primary strategy assessed with this model is the addition of prostate MRI in primary care as a triage test for all patients meeting the NICE Guidance 12 (NG12) urgent suspected prostate cancer referral criteria (abnormal DRE or raised PSA). mpMRI and bpMRI are two approaches for using prostate MRI to detect prostate cancer, and both are considered in the analysis. Two decision trees were developed for testing the primary strategy; one for patients presenting with symptoms included in NG12 that warrant further assessment with DRE and PSA (figure 5.4), and one for patients with no symptoms undergoing opportunistic PSA screening for prostate cancer (figure 5.6). Separate models were needed as the performance of PSA is assumed to be different in a screening context as compared to assessing patients who have developed symptoms and the likelihood of representing to primary care differs depending on symptom status; an assumption which is supported by the data sources used to inform the model (see Section 5.3). The comparator for these proposed new pathways is the current standard practice of referral of symptomatic patients in primary care meeting NICE NG12 referral criteria (figure 5.5) or having a raised PSA screening test (figure 5.7).

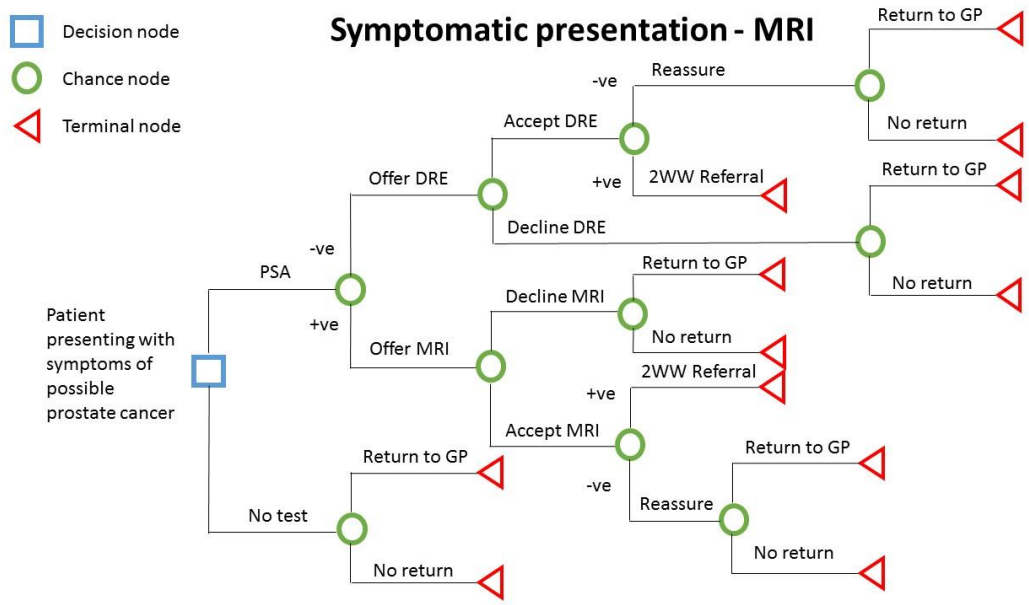


Figure 5.4 – Primary strategy integrating prostate MRI for symptomatic patients presenting in primary care

PSA – Prostate Specific Antigen; DRE – Digital Rectal Exam; MRI – Magnetic Resonance Imaging; 2WW – Two Week Wait referral

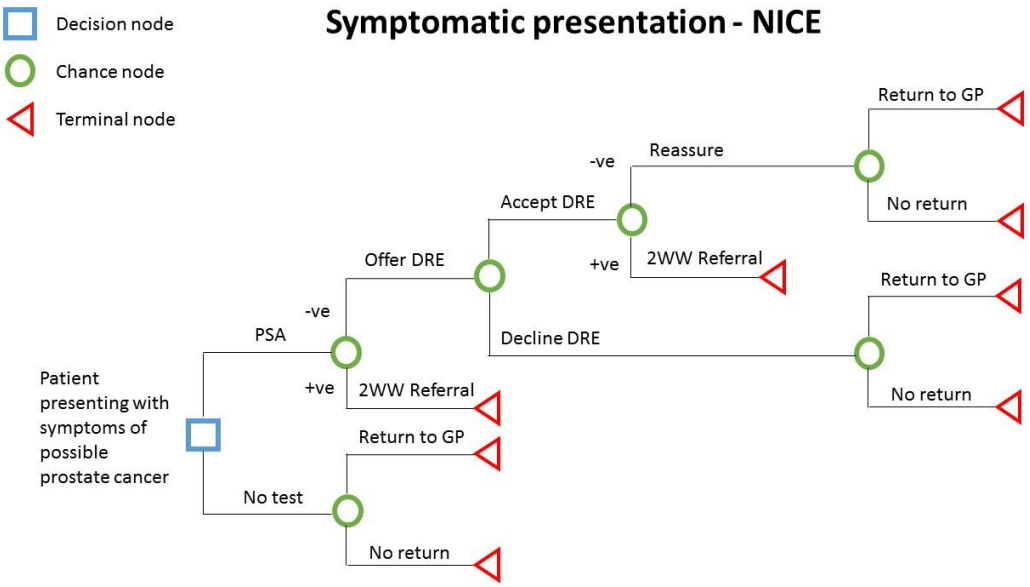


Figure 5.5 – Comparator strategy for symptomatic patients presenting in primary care following current NICE guidelines

PSA – Prostate Specific Antigen; DRE – Digital Rectal Exam; 2WW – Two Week Wait referral

Both symptomatic pathways have common trunks and early branches of the decision tree. A patient aged 50 years and above presents to primary care for the first time with symptoms that may relate to an undiagnosed prostate cancer that are highlighted in NICE NG12 (LUTS, visible haematuria, or erectile

dysfunction). All patients are offered a PSA test and DRE. In the current pathway (figure 5.5), patients with an abnormal result for either PSA or DRE receive a 2WW urgent suspected prostate cancer referral for outpatient prostate MRI and biopsy (if there is an abnormal finding on the MRI). The primary strategy assessed by this model would involve all patients with an abnormal PSA test result undergoing prostate MRI, and only referred on the 2WW pathway if the MRI is reported as abnormal (see figure 5.4). Patients with abnormal DRE would still be referred urgently without a subsequent MRI as a palpable abnormality of the prostate has a very high PPV for prostate cancer (42.3%)(27).

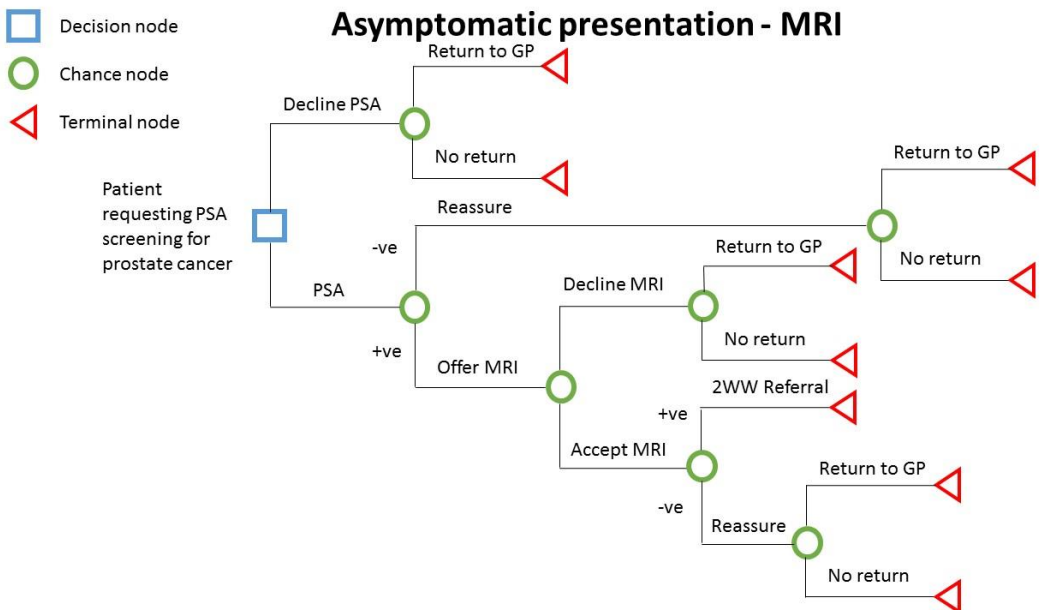


Figure 5.6 – Primary strategy integrating prostate MRI for patients presenting in primary care for opportunistic PSA screening

PSA – Prostate Specific Antigen; MRI – Magnetic Resonance Imaging; 2WW – Two Week Wait referral

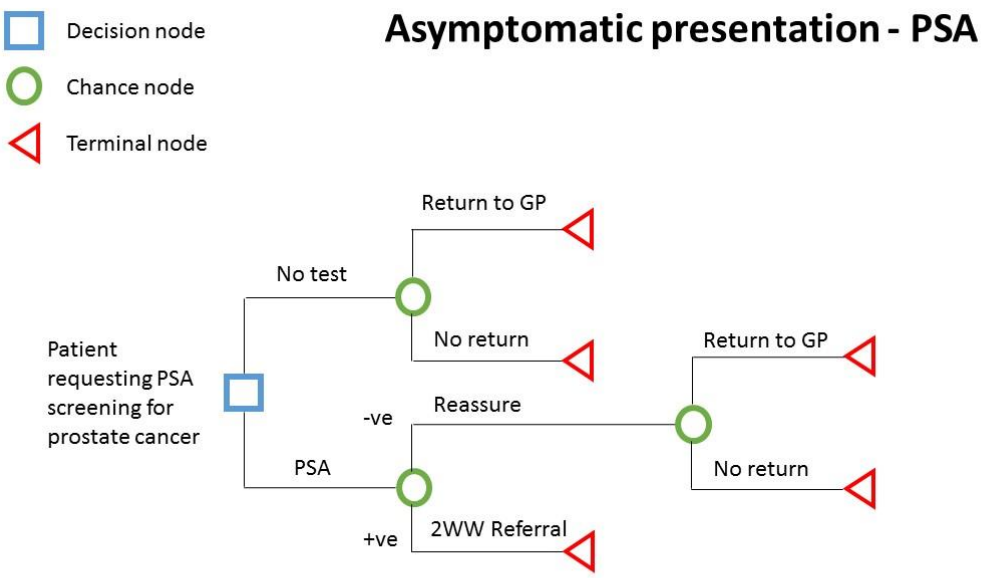


Figure 5.7 – Comparator strategy integrating prostate MRI for patients presenting in primary care for opportunistic PSA screening
PSA – Prostate Specific Antigen; 2WW – Two Week Wait referral

The opportunistic prostate cancer screening pathways being modelled also have similar origins. A patient aged 50 years and above presents to their GP requesting a PSA screening test for possible undiagnosed prostate cancer. Current practice dictates that any patient with a raised PSA level is referred on the 2WW pathway for further investigation (see figure 5.6). The primary strategy being assessed for this patient population involves a prostate MRI for any patient with an elevated PSA, and only referring on the 2WW pathway if the MRI is reported as abnormal (see figure 5.7)

The focus of this PhD is on prostate MRI and its potential for improving the primary care prostate cancer diagnostic pathway. There are other potential tests for detecting prostate cancer, including DECIPHER(211), the Prostate Health Index (PHI)(212) and Polygenic Hazard Scores(213) for prostate cancer. However, most of these tests have been assessed in a screening context, without considering their role in the assessment of patients with symptoms of prostate cancer. None of them are currently used in clinical practice in the UK and implementing these tests in the community is more difficult that PSA owing to logistical challenges around sample collection, processing and analysis.

Resources/costs

Resource costs used in the analyses of this model included staffing costs for clinicians in primary and secondary care involved with the pathways to the point of diagnosis(214). Outpatient appointments, including two week wait consultations, were also considered(215). Tests used in primary care, and diagnostic tests following referral were included as well(216).

Time horizon

The time horizon considered for this model was 12-months following first presentation to primary care. This time horizon was chosen to reflect the focus on understanding the role of prostate MRI in the diagnosis of prostate cancer in primary care in this PhD. It also fits with the chosen approach of employing decision trees, and the simple comparison between existing clinical practice following NICE NG12 guidelines and the addition of prostate MRI as a further triage test to inform referral decisions from primary care for diagnostic testing. A further reason for a relative short time horizon is the lack of evidence around the discriminative ability of symptoms, PSA and DRE for differentiating clinically significant from clinically insignificant prostate cancer, which is needed to confidently estimate likely treatments and long-term outcomes following diagnosis.

Health outcomes

The primary outcome for this model is a diagnosis of prostate cancer. Diagnosis of clinically significant prostate cancers is important, but not used as an outcome for reasons outlined above. Further relevant health outcomes captured by this model include the annual disutility experienced by patients from the various tests and stage at diagnosis, number of prostate MRI scans undertaken per year, proportion of patients referred for prostate biopsy unnecessarily due to false positive test results, and the proportion of patients with a delayed diagnosis of prostate cancer.

Assumptions

A number of assumptions have been made in the models developed for this PhD

1. Test performance characteristics for PSA and MRI are similar in primary care to secondary care, as there are no primary care studies to estimate test accuracy in this clinical setting.
2. All patients in the cohort for the models have the same average prostate cancer risk
3. All GPs refer patients in accordance with NG12 recommendations
4. All referred patients would undergo a transperineal prostate biopsy (which is the recommended approach)
5. Prostate cancer specific survival at 12 months is 100%

Linked-data approach

This model employed a linked data approach to combine a range of data sources, including observational studies, diagnostic test accuracy studies, cost-effectiveness analyses, systematic reviews, and analyses of existing datasets. This approach was necessary as there is no existing primary care trial of prostate MRI in primary care upon which to base an economic evaluation.

Sensitivity analysis

Analyses were performed within the MRI models using multiparametric MRI and biparametric MRI separately to assess for non-inferiority of bpMRI. One-way deterministic sensitivity analysis (DSA) was performed to estimate the effect of the uncertainty around baseline estimates for the parameters included in the models, using the 95% confidence intervals obtained from the included studies and additional analyses (see Section 5.3). A tornado diagram was produced to visually summarise the DSA results and demonstrate the impact of uncertainty for individual model parameters. Probabilistic sensitivity analysis (ProbSA) was also performed, using beta-distributions for probabilities and utilities and gamma distributions for costs. ProbSA was run for 1,000 cycles of the model, and results presented using cost-effectiveness scatter plots and cost-effectiveness acceptability curves.

5.3 Evidence sources

This decision analytic modelling study employed a link data approach to generate the baseline parameter estimates to populate the decision trees, and to perform the baseline and sensitivity analyses. Data were obtained from a range of sources to generate baseline parameter estimates, including primary and secondary analyses of existing relevant datasets, a systematic review with meta-analysis, and identifying published primary studies and systematic reviews. An outline of the evidence sources used for this study can be found in the sub-sections below.

5.3.1 Published studies

Bass EJ, Pantovic A, Connor M, *et al*. A systematic review and meta-analysis of the diagnostic accuracy of biparametric prostate MRI for prostate cancer in men at risk. Prostate Cancer Prostatic Dis. Published online 2020. doi:10.1038/s41391-020-00298-w

This systematic review and meta-analysis updated a recent review examining the diagnostic performance of biparametric magnetic resonance imaging (bpMRI) for the detection of any prostate cancer and clinically significant prostate cancer and compared the performance of bpMRI to multiparametric MRI (mpMRI). This review identified 11 new studies since the previous review on this subject was published and found a pooled sensitivity of 0.87 (95% CI 0.78, 0.93) and pooled specificity of 0.72 (95% CI 0.56, 0.84) for clinically significant prostate cancer. The AUC was 0.87. Meta-regression found no significant difference between the performance of bpMRI and mpMRI. The majority of studies were assessed as having a low risk of bias, although 16/45 studies had a high risk of bias for the ‘patient selection’ domain of the Quality Assessment of Diagnostic Accuracy Studies – 2 tool (QUADAS-2)(35).

Drost FJ, Osses DF, Nieboer D, Bangma CH, Steyerberg EW, Roobol MJ, *et al*. ‘Prostate MRI, with or without targeted biopsy and standard biopsy for detecting prostate cancer: A Cochrane systematic review and meta-analysis’. *Cochrane Database Syst Rev*. 2019;(4):CD012663.

This Cochrane systematic review and meta-analysis aimed to determine the diagnostic accuracy of prostate MRI, MRI-targeted biopsy, an MRI pathway

(prostate MRI with MRI-targeted biopsy for patients with a positive MRI), and systematic TRUS biopsy compared to template-guided biopsy (reference standard) for the detection of clinically significant prostate cancer. Pooled sensitivity of MRI was found to be higher than TRUS biopsy (0.91 95% CI 0.83, 0.95 vs 0.63 95% CI 0.19, 0.93) but with a lower specificity (0.37 95% CI 0.29, 0.46 vs 1.00 95% CI 0.91, 1.00). The MRI pathway had the most favourable diagnostic accuracy (pooled sens 0.72 95% CI 0.60, 0.82, pooled spec 0.96 95% CI 0.94, 0.98) of all methods assessed. The authors rated the quality of evidence as low and recommended further development of new prostate cancer diagnostic pathways incorporating MRI(29).

Ilic D, Djulbegovic M, Jung JH, Hwang EC, Zhou Q, Cleves A, *et al*. 'Prostate cancer screening with prostate-specific antigen (PSA) test: a systematic review and meta-analysis'. *BMJ*. 2018;362:k3519.
This systematic review and meta-analysis was written as an update of a Cochrane review following the publication of the findings of the Cluster Randomized Trial of PSA testing for Prostate cancer (CAP)(217). The review sought to assess the latest evidence on the potential benefits and harms of PSA screening for prostate cancer. The primary outcomes related to all-cause and prostate cancer specific mortality, for which there was no clear evidence of an effect of PSA screening. The study also reported estimates for the false positive screening rate (67%, high quality evidence) and false negative screening rate (15%, low quality evidence), from which estimates were generated for the model(22). A 2x2 table was imputed from estimated false-positive and false-negative rates reported in the paper, and exact confidence intervals calculated using the Clopper-Pearson method(218).

Jones D, Friend C, Dreher A, Allgar V, Macleod U. 'The diagnostic test accuracy of rectal examination for prostate cancer diagnosis in symptomatic patients: a systematic review'. *BMC Fam Pract.* 2018;19:79.
This systematic review and meta-analysis aimed to assess the evidence for the diagnostic accuracy of digital rectal examination (DRE) for the detection of prostate cancer in symptomatic patients presenting to primary care. Four studies with 3,225 patients were included; all were assessed to be of high methodological quality with significant heterogeneity. The pooled sensitivity of

DRE for prostate cancer was found to be 0.29 (95% CI 0.25, 0.32) and the pooled specificity was 0.91 (95% CI 0.89, 0.92)(18).

Young SM, Bansal P, Vella ET, Finelli A, Levitt C, Loblaw A. 'Systematic review of clinical features of suspected prostate cancer in primary care'. *Can Fam Physician*. 2015;61(1):e26–35.

This systematic review and narrative synthesis sought to provide an update to evidence included in national guidelines for prostate cancer diagnosis in primary care. The authors identified two UK studies reporting the proportion of referred hospital patients with suspected prostate cancer that had a recorded DRE performed in primary care varied from 32% (48/148) to 77% (221/287), and the proportion with a pre-referral PSA result varied from 74% (211/287) to 97% (144/148). These studies were small, single-centre, retrospective observational studies(219). These samples were combined to generate a single proportion estimate with standard error and 95% confidence intervals.

Ahmed HU, Bosaily AE-S, Brown LC, Gabe R, Kaplan R, Parmar MK, *et al*. 'Diagnostic accuracy of multi-parametric MRI and TRUS biopsy in prostate cancer (PROMIS): a paired validating confirmatory study'. *Lancet*. 2017 Jan 19;380:1–8.

The PROMIS trial was a prospective, multi-centre, paired-cohort, confirmatory study comparing the diagnostic accuracy of multiparametric magnetic resonance imaging (mpMRI) to Transrectal Ultrasound guided (TRUS) biopsy, using template prostate mapping biopsy (TPMB) as the reference standard. The PROMIS trial was included in the Cochrane review by Drost *et al*(29), and the sensitivity (0.93 95% CI 0.88, 0.96) and specificity (0.41 95% CI 0.36, 0.46) in the trial were not dissimilar to the pooled findings of the review. 97.8% (723/740) of potentially eligible participants underwent mpMRI in the PROMIS trial(53).

Clift AK, Coupland C, Hippisley-Cox J. 'Prostate-specific antigen testing and opportunistic prostate cancer screening: a cohort study in England'. *Br J Gen Pract*. 2021;71(703):e157–65.

This cohort study of 3,211,276 patients from 1,457 GP practices within the QResearch database aimed to estimate the cumulative incidence of PSA

testing and opportunistic PSA screening in UK GP practices between 1998 and 2017. Included patients had to have no previous PSA testing or history of prostatic disease, aged 40 years and above, and registered with an included GP practice for at least 12 months. The cumulative risk for a patient having at least one PSA test within 12 months of follow-up for any reason was 2.28% (95% CI 2.23, 2.32); and the cumulative risk of opportunistic PSA screening in the same time period was 1.67% (95% CI 1.66, 1.69)(205).

Young GJ, Harrison S, Turner EL, Walsh EI, Oliver SE, Ben-Shlomo Y, *et al*. 'Prostate-specific antigen (PSA) testing of men in UK general practice: A 10-year longitudinal cohort study'. *BMJ Open*. 2017;7(10).
This retrospective cohort study of 450,000 patients from within the Clinical Practice Research Datalink (CPRD) database was similar to Clift *et al*, in that the authors aimed to estimate the cumulative risk of PSA testing in UK primary care patients without a diagnosis of prostate cancer over a 10-year period. Unlike Clift *et al*(205), the study by Young *et al* assessed the risk of repeat testing and factors associated with repeat testing. They found that 20% (17,775 / 90,252) of patients with at least 12-months follow-up attended for a repeat test, which was more likely to occur for patients with a higher initial PSA test result(143).

Barnett CL, Davenport MS, Montgomery JS, Wei JT, Montie JE, Denton BT. 'Cost-effectiveness of magnetic resonance imaging and targeted fusion biopsy for early detection of prostate cancer'. *BJU Int*. 2018 Jul;122(1):50–8.
This cost-effectiveness analysis study employed a validated, partially observable Markov model to estimate outcomes for PSA screening programmes that include pre-biopsy prostate MRI. The model employed published estimates for annual disutility relating to diagnostic tests and health states within the five screening strategies that were compared. This study found using pre-biopsy prostate MRI was cost-effective assuming a willingness-to-pay threshold of $100,000(183).

Risk of bias for the selected systematic reviews was assessed using A Measurement Tool to Assess systematic Reviews-2 (AMSTAR-2) critical

appraisal tool(220). Four out of five reviews were graded as low confidence due to not reporting on the funding sources of included studies in the respective reviews. The review by Young *et al* was assessed as critically low confidence as the review team did not utilise two reviewers to independently identify included studies, in addition to not reporting individual study funding sources (see table 5.1). The three selected observational studies were assessed as high quality using the MINORS checklist(66) (see table 5.2), and the cost-effectiveness analysis by Burnett *et al* was found to have a low risk of bias on a majority of domains in the Philips framework(221) (see table 5.3).

Author	PCIO question	Protocol followed	Design selected	Search strategy	Two reviewers	Two data extractors	Exclusions justified	Describe studies	Risk of bias	Funding sources	Meta-analysis	RoB impact	RoB interpreted	Heterogeneity discussed	Publication bias	Conflict of interest	Overall confidence
Bass 2020(35)	Y	Y	N	Y	Y	Y	Y	Y	Y	N	Y	Y	Y	Y	N	Y	L
Drost 2019(29)	Y	Y	Y	Y	Y	Y	Y	Y	Y	N	Y	Y	Y	Y	N	N	L
Ilic 2018(22)	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	N	Y	L
Jones 2018(18)	Y	Y	N	Y	Y	Y	Y	Y	Y	N	Y	N	Y	Y	N	Y	L
Young 2015(219)	N	N	Y	Y	N	N	Y	Y	Y	N	NA	NA	NA	Y	N	Y	CL

Table 5.1 – quality appraisal of systematic reviews used for parameter estimates using AMSTAR-2 (Y – Yes; N – No; NA – Not Applicable; H – High; M – Moderate; L – Low; CL – Critically Low)(220)

PICO – Patient, Intervention, Comparison, Outcome; RoB – Risk of Bias

Author	Aim	Consecutive patients	Prospective data	Endpoints	Unbiased assess	Follow-up appropriate	Loss to follow-up	Size calculation	**Subtotal**	Adequate control	Contemporary	Equal groups	Analysis	**Total**
Ahmed 2017(53)	2	2	2	2	2	0	2	2	14					
Clift 2021(205)	2	2	1	2	1	2	2	2	14					
Young 2017(143)	2	2	1	2	1	2	2	2	14					

Table 5.2 **–** Study quality assessment of observational studies using MINORS (2 – reported and adequate; 1 – reported, not adequate; 0 – not reported; Red – low quality; yellow – medium quality; green – high quality)(66)

Domains	*Structure*									*Data*											*Consistency*	
Author	**S1**	**S2**	**S3**	**S4**	**S5**	**S6**	**S7**	**S8**	**S9**	**D1**	**D2**	**D2a**	**D2b**	**D2c**	**D3**	**D4**	**D4a**	**D4b**	**D4c**	**D4d**	**C1**	**C2**
Burnett 2018(183)																						

Table 5.3 – Quality assessment of model-based economic evaluations using the Philips framework(173) (Green – low risk of bias; Yellow – some risk of bias; Red – high risk of bias)

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

Introduction

Prostate specific antigen (PSA) testing for the detection of prostate cancer is usually performed in primary care for one of two reasons; assessing a patient presenting to their GP with lower urinary tract symptoms (LUTS), or opportunistic screening for a patient who is asymptomatic but concerned about their risk of prostate cancer. Some very large randomised controlled trials of PSA-based prostate cancer screening have been performed, as outlined in the systematic review by Ilic *et al*(8); however uncertainty remains about the diagnostic accuracy of PSA for prostate cancer in patients with lower urinary tract symptoms. The most recent systematic review of the diagnostic accuracy of PSA was published by Harvey *et al* in 2009(20). That review presented limited information on their methods. It was unclear whether the included studies were assessing PSA in symptomatic or asymptomatic patients, nor whether any were relevant to a primary care population. Just *et al* published a brief review of the literature in 2018, highlighting a paucity of research in this area that can be applied to primary care still remains(200).

PSA is the only test currently available in primary care for the detection of prostate cancer. In order to attempt to address the uncertainty of the diagnostic accuracy of PSA in symptomatic patients, a systematic review and meta-analysis was undertaken. Given the findings of Just *et al*(200), studies considered for inclusion in this review were not limited to primary care settings. This review will also generate parameter estimates for the accuracy of PSA that will be incorporated into the PhD modelling.

Aim

To determine the diagnostic accuracy of prostate specific antigen (PSA) for the detection of prostate cancer in patients with symptoms that might relate to prostate cancer.

Objectives

1. To identify studies that assess the diagnostic accuracy of prostate specific antigen for prostate cancer in symptomatic patients
2. To determine the diagnostic accuracy of prostate specific antigen for the detection of clinically significant prostate cancer in symptomatic patients
3. To determine the diagnostic accuracy of prostate specific antigen for the detection of prostate cancer in symptomatic patients at different test thresholds

Review question

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

Patients – Men with symptoms of possible prostate cancer and no history of prostate cancer
Intervention – Prostate specific antigen (PSA) test
Comparison – Prostate biopsy (as reference test)
Outcome – Diagnosis of prostate cancer within 12 months of symptom onset

Definitions

Symptoms relating to possible prostate cancer – lower urinary tract symptoms (at least one of nocturia, hesitancy, poor stream, incomplete voiding, double voiding, terminal dribbling, urgency, incontinence, frequency), haematuria, erectile dysfunction, lower back pain. These symptoms may be measured by a standardised tool, such as the International Prostate Symptom Score (IPSS), or through patient self-report.
Prostate cancer – biopsy proven prostate cancer
Prostate Specific Antigen (PSA) – total serum prostate specific antigen levels measured in nanograms per millilitre (ng/mL)

Methods

Search strategy

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. See Appendix 5.1 for the full search strategy.

Achieving a balance between sensitivity and specificity for the search strategy in this review was challenging. There is a view within the field of prostate cancer research held by many specialists and cancer screening researchers that lower urinary tract symptoms are not meaningfully associated with prostate cancer, in particular clinically significant prostate cancer(222,223). This assumption is largely untested in primary care populations, and contrasts with a number of studies showing that the majority of patients diagnosed with prostate cancer present to their GP with LUTS prior to diagnosis(14–16,224). However, this assumption also means that LUTS and other relevant symptoms may not be reported or be the focus of apparently relevant studies. This was demonstrated when search terms for LUTS were added to the search strategy and the number of search hits was significantly reduced (see Appendix 5.1). I decided to focus the search on those studies that did report symptoms, and early iterations of the searches included known key papers in the field, suggesting this approach was appropriate.

Inclusion criteria

Search hits were included in this systematic review if they met the following inclusion criteria:

1. Studies of the diagnostic accuracy of prostate specific antigen (PSA) testing for prostate cancer diagnosis.
2. Patients included (or a subset of included patients) had at least one symptom that could relate to an undiagnosed prostate cancer
3. Included patients have no history of prostate cancer

Exclusion criteria

Search hits were excluded if they featured any of the following exclusion criteria:

1. Prostate specific antigen (PSA) testing for prostate cancer in asymptomatic patients / screening studies
2. Studies of prostate specific antigen (PSA) for prostate cancer that do not measure/report sufficient data to calculate diagnostic accuracy
3. Case reports, conference abstracts, protocols, letters, editorials or commentaries
4. Studies with non-human subjects

There were no limits set on date of publication or study type for this review

Screening search hits

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 me and a 2nd reviewer (either Dr Lucy Pocock [LP], NIHR Doctoral Research Fellow, University of Bristol; Dr Sam Creavin [SC], NIHR Academic Clinical Lecturer in General Practice, University of Bristol; or Miss Emma Gilbert [EG], research associate, University of Bristol) 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 PhD supervisor (WH or AS).

Quality assessment

Risk of bias and applicability of all included studies were assessed using the QUADAS-2(225) tool.

Data extraction

A pre-prepared proforma for data extraction was used to collate relevant data from each included study in the following fields:

Study details	Symptom(s)	PSA	Prostate cancer
First author	Number of symptoms	Number of PSA tests performed	Number of cancers diagnosed
Year of publication	Duration	PSA result	Cancer type
Country(s)	Type	Threshold for prostate cancer detection	Gleason score / Grade Group
Patient population		Definitions of diagnosis	TNM stage
Patient demographics		Sens, Spec, PPV, NPV	

Table 5.4 – Data fields for extraction template used in this review

I extracted the data from all included studies. A 2nd reviewer (LP) extracted data from a random sample of 10% of included studies for verification of accuracy of data extraction. Any discrepancies were adjudicated by a PhD supervisor (WH or AS).

Meta-analysis

Raw data extracted from included papers on PSA result and prostate cancer diagnoses were extracted and combined into 2 x 2 tables to assess diagnostic accuracy. Measures of diagnostic accuracy were calculated for the following outcomes using a bi-variate mixed effects regression:

Any prostate cancer diagnosis

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

Protocol publication

The protocol for this systematic review and meta-analysis has been registered with PROSPERO (See Appendix 5.2).

PRISMA reporting guidelines

This systematic review was conducted following the PRISMA reporting guidelines for systematic reviews and meta-analyses(226).

Results

Database searching identified 631 potentially relevant studies, and a further 42 studies were identified through reference list checking and snowballing techniques. Following de-duplication, 563 search hits were assessed independently by myself and a 2nd reviewer, and 75 papers selected for full text assessment. 19 papers were ultimately included in this review. Details of full-text exclusions can be found in figure 5.8 below.

Risk of bias assessment using the QUADAS-2 tool demonstrated a number of potential areas of bias in the studies (see table 5.4 and figure 5.9). None of the studies was 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. The reference standard was performed with knowledge of the index test (PSA) in 16 of 19 studies. 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.

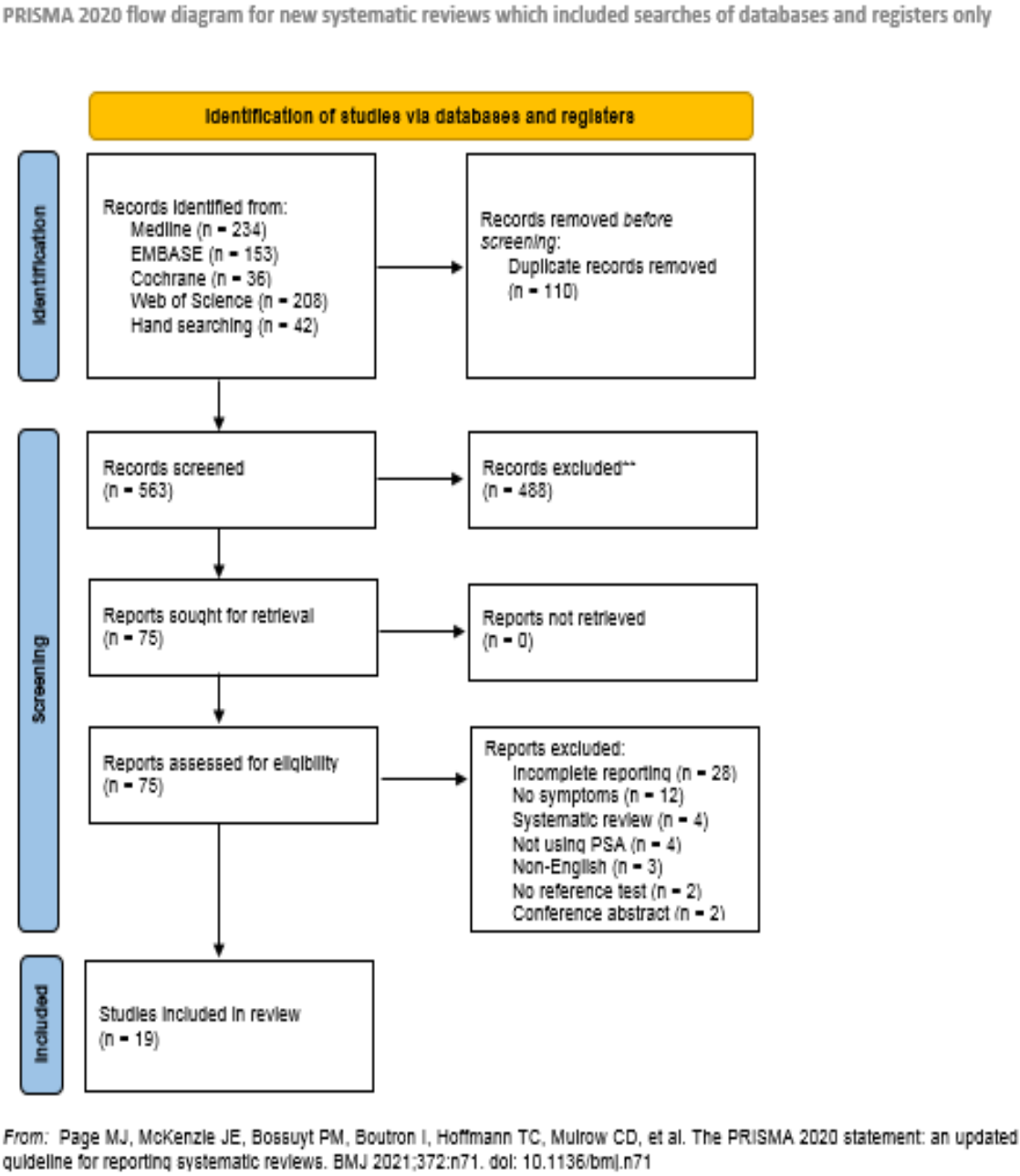


Figure 5.8 – 2020 PRISMA diagram outlining the number of studies identified, screened and included in this systematic review

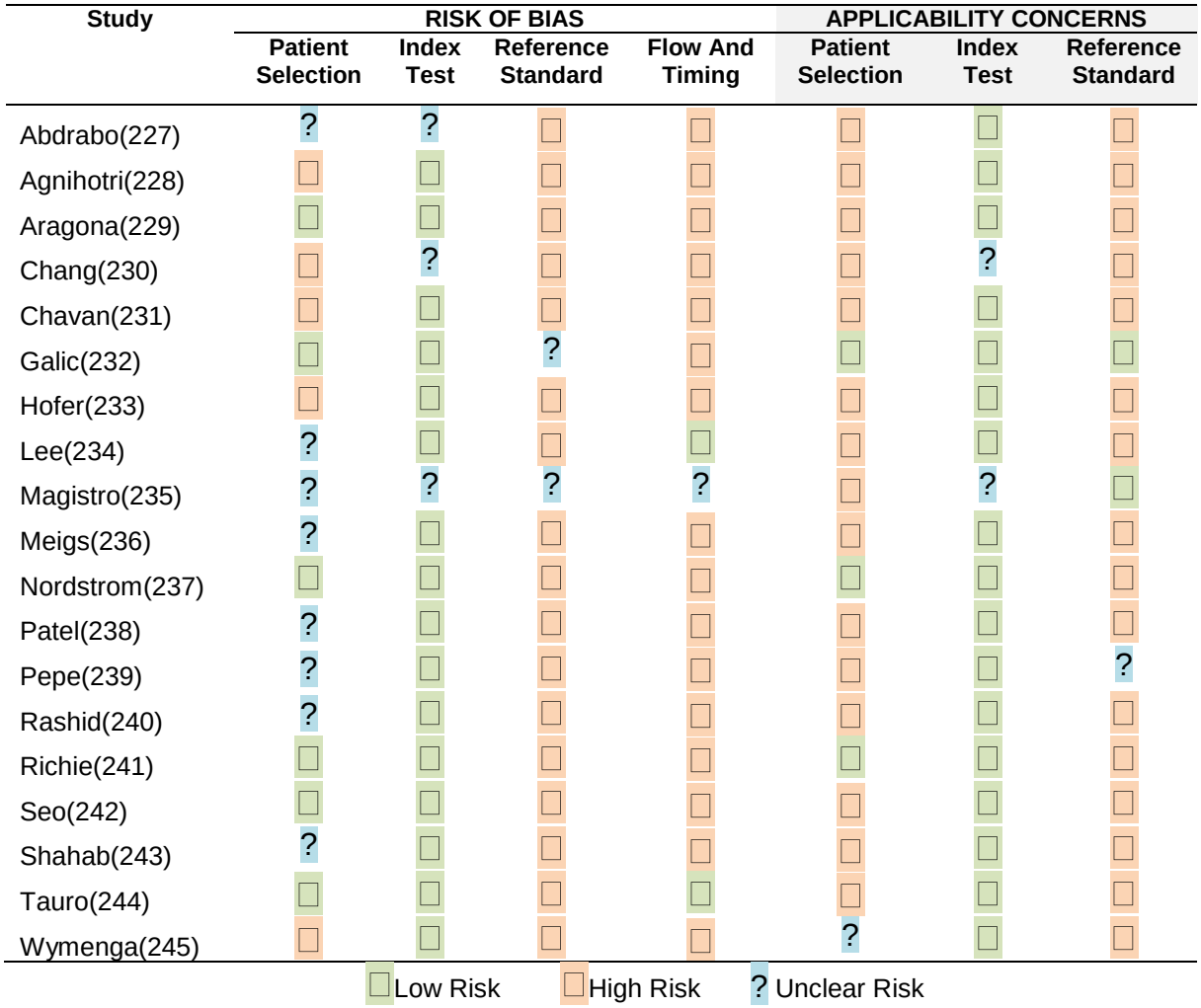


Table 5.5 – Risk of bias assessment of included studies using QUADAS-2 tool

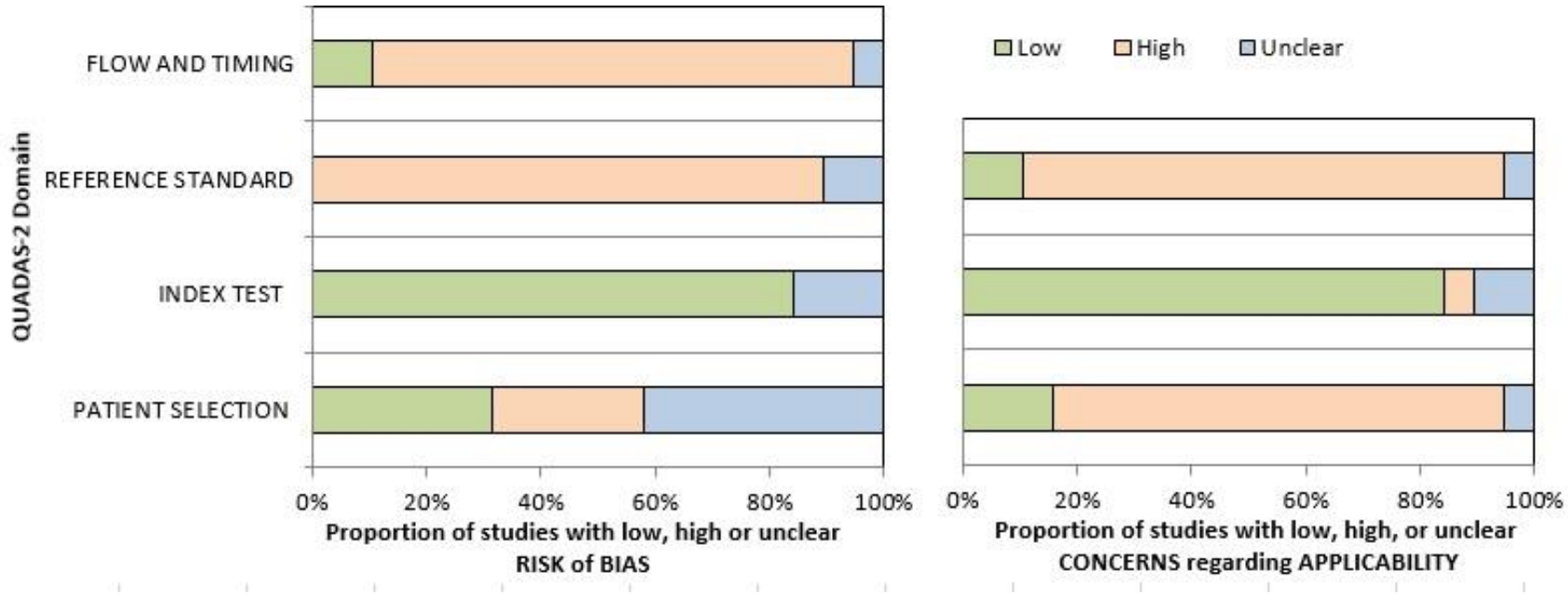


Figure 5.9 – Summary of QUADAS-2 risk of bias assessments

Author	Year	Country	Number of patients	Setting	PSA range	Stage/Grade data	Reference test
Abdrabo(227)	2011	Sudan	118	One hospital urology clinic	2.5-10ng/mL	No	TRUS biopsy
Agnihotri(228)	2014	India	875 biopsied (of 4,702)	One hospital urology clinic	Any	No	TRUS biopsy
Aragona(229)	2005	Italy	3,171 biopsied (of 16,298)	15 hospital urology clinics	Any	Clinical TNM staging	TRUS biopsy
Chang(230)	2015	Taiwan	225	One hospital urology clinic	Any	TNM stage and Gleason Score	TRUS biopsy
Chavan(231)	2009	India	440 biopsied (of 922)	One tertiary hospital urology clinic	Any	No	TRUS biopsy
Galic(232)	2003	Croatia	88 biopsied (of 944)	Recruited from two villages to attend hospital clinic	Not stated	No	TRUS biopsy
Hofer(233)	2000	Germany	188	One hospital urology clinic	Any	No	TRUS biopsy / TURP/ non-cancer surgery
Lee(234)	2006	Korea	201	One hospital urology clinic	< 4ng/mL	No	TRUS biopsy

Magistro(235)	2020	Germany	1,125	One hospital urology clinic	Any	TNM stage and Gleason Score	HoLEP (+ mpMRI with targeted and systemic biopsy for some patients)
Meigs(236)	1996	USA	1,524	One hospital urology clinic + two BPH study cohorts	Any	Clinical T stage	TRUS biopsy / TURP/ non-cancer surgery
Nordstrom(237)	2021	Sweden	1,554	Population-based screening study cohort	>3ng/mL	TNM stage and Gleason Score	TRUS biopsy
Patel(238)	2009	UK	647 biopsied (of 3,976)	One hospital urology clinic	Any	No	TRUS biopsy
Pepe(239)	2007	Italy	403 biopsied (of 13,294)	Two hospital urology clinics	<4ng/mL	Pathological T stage	TRUS biopsy
Rashid(240)	2012	Bangladesh	206	One hospital urology clinic and one nursing home	>2.5ng/mL	No	TRUS biopsy
Richie(241)	1993	USA	1,167 biopsied (of 6,630)	Six medical centres	Any	TNM stage and Gleason Score	TRUS biopsy

Seo(242)	2007	Korea	4,967	25 hospital urology clinics	Any	No	TRUS biopsy
Shahab(243)	2013	Indonesia	404	One hospital urology clinic	Any	TNM stage and Gleason Score	TRUS biopsy
Tauro(244)	2009	India	100	One hospital urology clinic	Any	No	TRUS biopsy
Wymenga(245)	2000	The Netherlands	716	Two hospital urology clinics	Any	Clinical T stage	TRUS biopsy / TURP/ prostatectomy

Table 5.6 – Details of included studies

USA – United States of America; PSA – Prostate Specific Antigen; TNM – Tumour-Node-Metastasis; TRUS – Transrectal Ultrasound guided; TURP – Transurethral Resection of Prostate; HoLEP – Holmium Laser Enucleation of the Prostate; mpMRI – Multiparametric Magnetic Resonance Imaging

Table 5.6 summarises the features of the studies. There was a wide range of countries and study sample sizes amongst the studies. One study focused on a cohort within a population screening study, and the remainder were set in hospital urology clinics. No studies were performed in a primary care population. Five studies gathered stage and grade data. All studies but one used TRUS biopsy as a reference test, with three studies also gathering diagnostic data from Transurethral Resection of the Prostate (TURP) or other surgical procedures involving the prostate.

Table 5.7 shows the measures of diagnostic accuracy calculated using reported data in 14 included studies that considered a PSA level of greater than or equal to 4ng/mL as abnormal. The remaining five studies only included patients with a PSA level to one side of a set threshold, and therefore could not be used in the meta-analysis. Meta-analyses showed an estimated combined sensitivity of a PSA threshold of 4ng/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 figure 5.10). Hierarchical Summary Receiver Operator Curve (HSROC) analysis showed an Area Under the Curve (AUC) of 0.72 (95% CI 0.68, 0.76) (See figure 5.11). Figure 5.12 shows a Fagan plot of the likelihood ratios generated.

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 threshold of ≥4ng/mL. Chang *et al*(230) did not report the accuracy of PSA *per se* but showed a statistically significant difference in free: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*(241) did not report the Gleason Score data they had collected but found higher PSA levels and increasing age were associated with a higher risk of metastatic prostate cancer. Shahab *et al*(243) identified a PSA threshold of 6.95ng/mL for differentiating ‘moderate’ versus ‘high’ Gleason Score (which was not defined).

Author	Year	Number of patients	Sensitivity	Specificity	Positive Predictive Value	Negative Predictive Value
Abdrabo(227)	2011	118	0.92	0.24	0.35	0.87
Agnihotri(228)	2014	875 biopsied (of 4,702 patients)	0.99	0.05	0.59	0.80
Aragona(229)	2005	3,171 biopsied (of 16,298 patients)	0.92	0.15	0.38	0.76
Chang(230)	2015	225	0.89	0.09	0.19	0.76
Chavan(231)	2009	440 biopsied (of 922 patients)	0.96	0.03	0.18	0.79
Galic(232)	2003	88 biopsied (of 944 patients)	0.91	0.32	0.47	0.85
Hofer(233)	2000	188	0.92	0.29	0.46	0.85
Meigs(236)	1996	1,524	0.61	0.74	0.34	0.89
Rashid(240)	2012	206	0.72	0.46	0.28	0.85
Richie(241)	1993	1,167 biopsied (of 6,630 patients)	0.82	0.48	0.31	0.90
Seo(242)	2007	4,967	0.98	0.04	0.33	0.87
Shahab(243)	2013	404	0.98	0.19	0.13	0.98
Tauro(244)	2009	100	1.00	0.38	0.40	1
Wymenga(245)	2000	716	0.95	0.16	0.44	0.82

Table 5.7 – Diagnostic accuracy of PSA ≥ 4ng/mL for prostate cancer detection in symptomatic patients

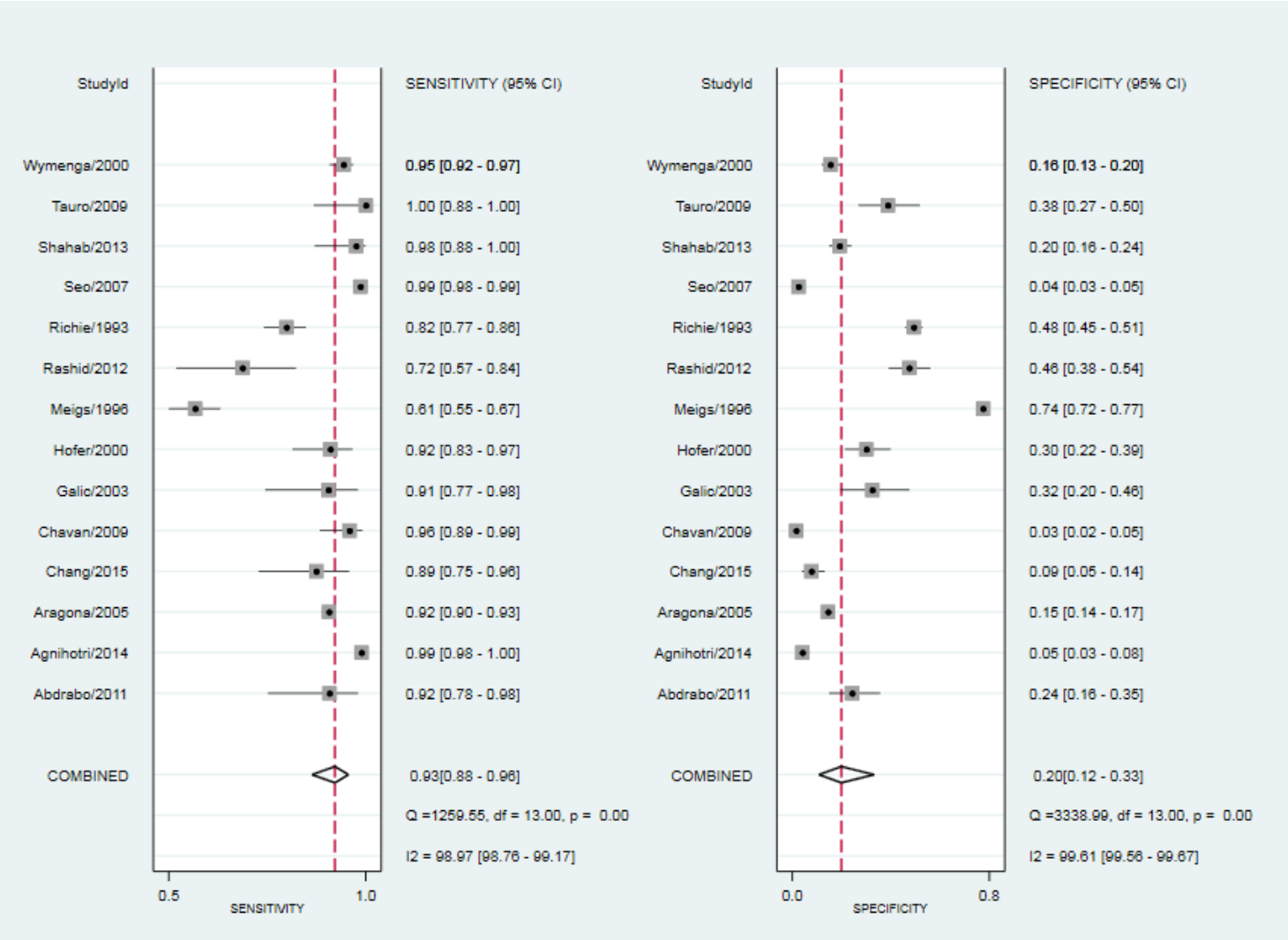


Figure 5.10 - Forest plot of included studies using PSA threshold of 4ng/mL

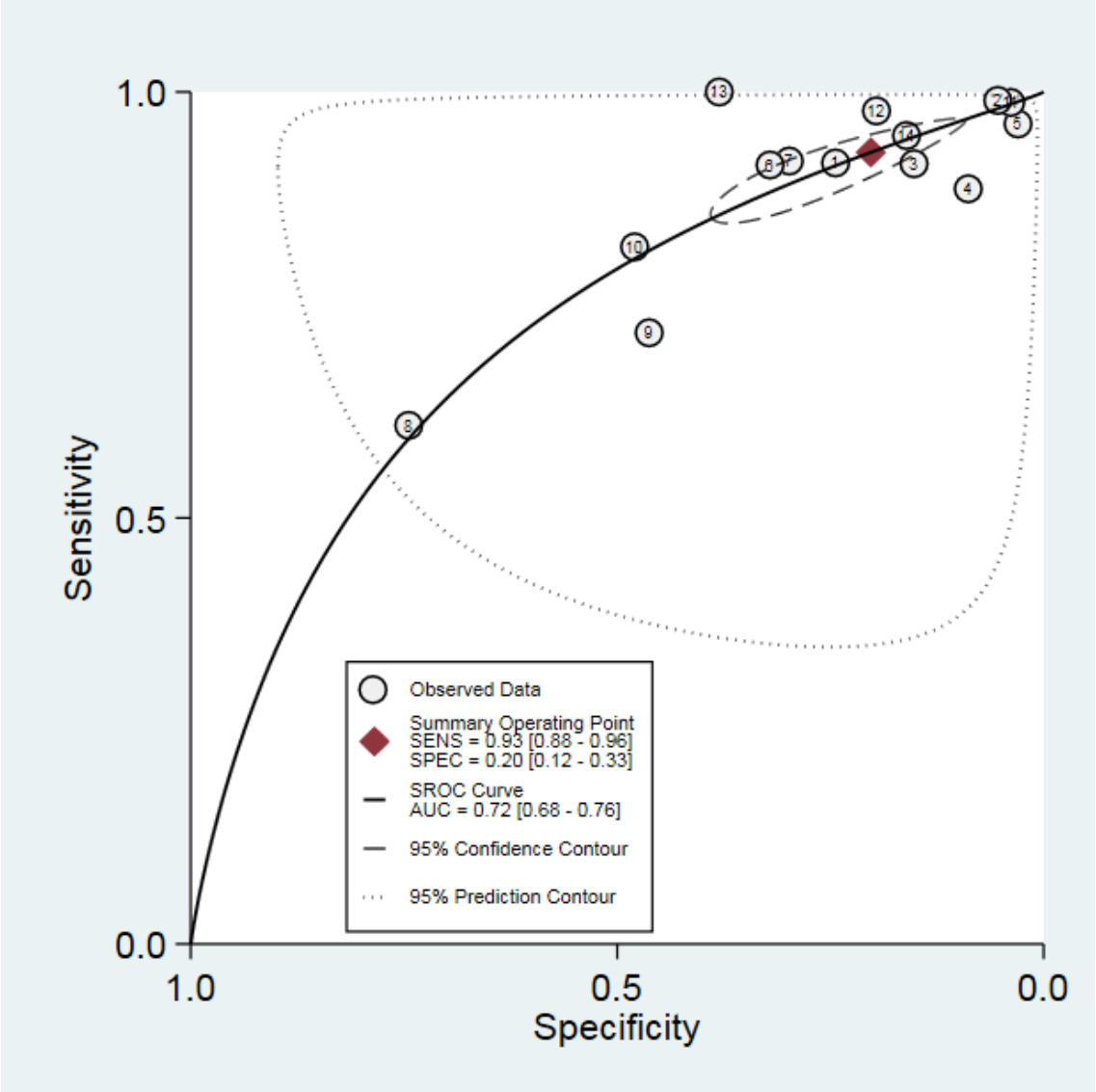


Figure 5.11 – Hierarchical Summary Receiver Operator Curve (HSROC) of included studies using PSA threshold of 4ng/mL

SENS – Sensitivity; SPEC - Specificity

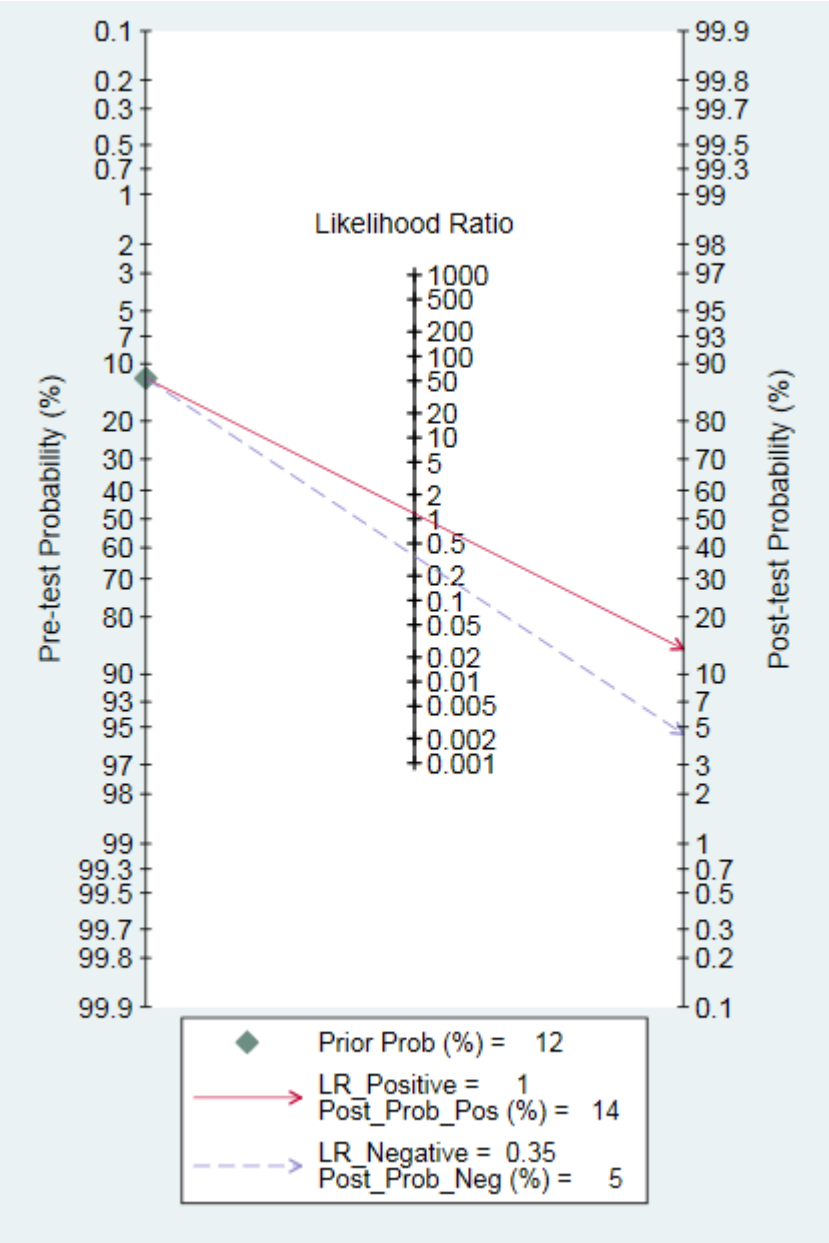


Figure 5.12 - Fagan plot of included studies using a PSA threshold of 4ng/mL

LR – Likelihood Ratio

Discussion

Summary of findings

Published studies assessing the diagnostic accuracy of PSA in symptomatic patients using a threshold of 4ng/mL reported high sensitivity but low specificity for the detection of prostate cancer. 18 of the 19 included studies were undertaken in hospital urology outpatient patient populations, with one study focused on a symptomatic cohort within a population screening study. There were no included studies assessing the performance of PSA in a primary care population. Insufficient data was available from included studies to assess the diagnostic accuracy of PSA for clinically significant prostate cancer, and all included studies were assessed as having high risk of bias in at least one key domain.

Comparison to existing literature

Harvey *et al*(20) published a systematic review of the diagnostic accuracy of PSA for prostate cancer, focused on studies published between 1998 and 2008 performed in European populations. Individual study level data from 10 included papers was presented, without estimating a combined level of accuracy. They considered the accuracy of PSA for all prostate cancer types and showed a range of accuracy estimates of a similar distribution to this study. Over half of the studies included in this review were published since Harvey *et al's* review. A review of clinical features of prostate cancer in primary care by *Young et al* (246) from 2015 identified one study from 1989 of 287 patients referred from primary 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 highlighted the true level of accuracy was likely to be lower given a minority of patients with a normal PSA level had the reference test of biopsy.

Strengths & limitations

This study benefited from a rigorous, focused, methodological approach. All clinical settings were considered to find relevant studies, and the included studies represent a diverse range of ethnic backgrounds amongst recruited patients. The majority of 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, in 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 (BPH)(42,43). LUTS most likely relates to BPH, which prompts a patient to see their GP and will undergo a PSA test that will detect most prostate cancers. This assumption is largely untested in primary care populations, although a number of studies showing that the majority of patients diagnosed with prostate cancer present to their GP with LUTS prior to diagnosis(14–16,224). This clinical uncertainty 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. This may have limited the sensitivity of the search strategy employed. However, key papers were picked up by the database searches. Furthermore, most PSA studies are 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 known to have poor sensitivity as a diagnostic test(53), owing to the inability to visualise lesions with the prostate resulting in a random sampling of the gland, resulting in misclassification bias. 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 & 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(24,194,247). The absence 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. High quality studies in primary care populations are needed to fill this gap and reduce biases and limitations of the existing evidence, such as the spectrum effect. With the advent of more

accurate diagnostic tests for prostate cancer, including multiparametric magnetic resonance imaging (mpMRI)(53), to use as a reference test, a better understanding of the role of PSA in the early detection of prostate cancer is possible.

Primary care clinicians are, by and large, already aware of the limitations of PSA testing(139), and clinical guidelines encourage a balanced discussion with patients of the potential benefits and harms of relying on PSA to detect prostate cancer(25,248). The findings of this review suggest this is a pragmatic approach in providing care to patients with LUTS. Alternative tests to PSA have been extensively researched(212,249), and some show promise of improving the level of confidence in detecting prostate cancer, though none have entered clinical practice as yet.

Conclusions

Published evidence from studies conducted in secondary care suggest that PSA has high sensitivity and low specificity for the diagnosis of prostate cancer in symptomatic patients. The studies included in this review suffered from a number of biases which are likely to result in overestimation of the accuracy of PSA, and there were no eligible studies identified assessing the accuracy of PSA in a primary care population. The utility of PSA for the diagnosis of clinically significant prostate cancer is unclear, and arguably of greatest importance to identify patients warranting radical treatments whilst avoiding exacerbating the issue of overdiagnosis of clinically insignificant prostate cancer.

5.3.3 Primary analysis of a regional NHS Cancer Alliance dataset

Aim

To analyse real-world, local, primary data on the performance of a prostate cancer diagnostic pathway incorporating pre-biopsy MRI

Objectives

1. To estimate the proportion of patients in the local region undergoing pre-biopsy prostate MRI after being referred on the urgent suspected prostate cancer pathway
2. To compare the diagnostic performance of prostate MRI in a real-world setting against published trials
3. To measure the time intervals from referral to specialist outpatient appointment, MRI, biopsy, and diagnosis in a regional dataset

Dataset outline

Since August 2018, NHS Trusts in the South-West of England have been extracting data on all patients referred on the 2WW prostate cancer pathway for a joint project between the NHS Cancer Alliances in the Peninsula and Somerset, Wiltshire, Avon and Gloucester (SWAG) regions. Staff at each Trust have collected data from clinical, radiological, and pathological health record systems for pre-specified variables (see table 5.8 below). These data are stored centrally by the Somerset NHS Foundation Trust on behalf of 19 Trusts participating in this project. The aim of the project is to understand how well prostate cancer diagnostics is performing in the region, in particular the implementation of multiparametric MRI (mpMRI) and biparametric MRI (bpMRI) into local prostate cancer diagnostic pathways.

Variable	Description	Measure
Referral year	Year in which 2WW prostate cancer referral was made	Year (XXXX)
Provider	NHS Trust submitting data to audit	Organisation code
RecordID	Unique ID number of each referral included in audit	Record ID
Age at referral	Age of patient at the time of 2WW prostate cancer referral	Years of age
PSA value at diagnosis	PSA result taken closest to time of diagnosis	PSA (ng/mL)
Family History	Recorded family history of prostate cancer for referred patient	Self-reported history (Yes/No)
Date of referral	Date of 2WW prostate cancer referral	Date (XX/YY/ZZZZ)
Other comments	Comments and notes made by data entrant	Free text
Date first seen	Date the patient was first seen in secondary care following referral	Date (XX/YY/ZZZZ)
Date diagnosis given to patient	Date when the patient was informed of their final diagnosis	Date (XX/YY/ZZZZ)
Type of biopsy	Biopsy approach taken to sample the prostate	TRUS – Transrectal Ultrasound guided biopsy TP GA – Transperineal under General Anaesthetic TP LA – Transperineal under Local Anaesthetic

Date of biopsy	Date that prostate biopsy was performed following 2WW prostate cancer referral	Date (XX/YY/ZZZZ)
Total no of systematic cores	Number of prostate cores taken at biopsy using a systematic approach	Number of cores
Total number of targeted cores	Number of cores taken at biopsy from the index lesion identified on pre-biopsy prostate MRI	Number of cores
For Targeted: Fusion or Cognitive?	In patients who underwent targeted biopsy, did the clinician use a fusion or cognitive technique?	Fusion / Targeted
For Template: Mapping or Targeted?	In patients who underwent template biopsy, was the approach targeted or systematic	Targeted / Systematic
For Template: Total number of zones?	In patients who underwent template biopsy, how many zones of the prostate were sampled?	Number of zones
Comments	Comments and notes made by data entrant regarding biopsy	Free text
Date of MRI	Date that prostate MRI was performed following 2WW prostate cancer referral	Date (XX/YY/ZZZZ)
MRI type	Type of approach used for prostate MRI	bpMRI / mpMRI / unknown
Prostate volume	Estimate of the volume of the prostate based on MRI data	Prostate volume (mL)
PSAD	Estimated PSA density based on PSA and MRI data	Total PSA / Prostate volume (ng/mL^2)

PIRAD score of the index lesion	Prostate Imaging-Reporting and Data System (PIRADS) score of the index prostate lesion from radiologist interpreting MRI scan	PIRADS score from 1-5
Confidence of PIRAD score	Subjective rating of confidence in PIRADS score by radiologist	Confident / Reduce confidence
Likert	Likert scale rating of likelihood of prostate cancer from radiologist interpreting MRI scan	Likert scale 1-5 1 – prostate cancer very unlikely 5 – prostate cancer very likely
Max diameter of index lesion	Maximum diameter of index prostate lesion from MRI	Diameter (mm)
Radiologist's t-stage	Assessment of T-stage of prostate lesion based on MRI by radiologist	Union of International Cancer Control (UICC) Tumour Node Metastases (TNM) tumour classification (T1 – T4)
Radiologist's n-stage	Assessment of N-stage of prostate lesion based on MRI by radiologist	Union of International Cancer Control (UICC) Tumour Node Metastases (TNM) node classification (N0 – N1)
Final pre-treatment staging T	Assessment of T-stage of prostate lesion by MDT after all investigations complete	Union of International Cancer Control (UICC) Tumour Node Metastases (TNM) tumour classification (T1 – T4)

Final pre-treatment staging N	Assessment of N-stage of prostate lesion by MDT after all investigations complete	Union of International Cancer Control (UICC) Tumour Node Metastases (TNM) node classification (T1 – T4)
Other MRI comments	Comments and notes made by data entrant regarding MRI	Free text
Date histology reported	Date that final histological report of prostate biopsy samples was confirmed	Date (XX/YY/ZZZZ)
Total number of cores taken	Number of prostate cores taken at biopsy	Number of cores
Right: number of cores positive	Number of prostate cores taken at biopsy from the right side of the prostate with prostate cancer cells seen	Number of cores
Right: maximum core length involvement	The maximum continual length of a prostate biopsy sample containing prostate cancer cells in the right side of the prostate	Length (mm)
Right: Gleason score	Gleason score of prostate cancer cells seen in biopsy samples from the right side of the prostate	Gleason score
Left: number of cores positive	Number of prostate cores taken at biopsy from the left side of the prostate with prostate cancer cells seen	Number of cores
Left: maximum core length involvement	The maximum continual length of a prostate biopsy sample containing prostate cancer cells in the left side of the prostate	Length (mm)

Left: Gleason score	Gleason score of prostate cancer cells seen in biopsy samples from the left side of the prostate	Gleason score
Targeted: number of cores positive	Number of prostate cores taken at biopsy from the index lesion in the prostate with prostate cancer cells seen	Number of cores
Targeted: maximum core length involvement	The maximum continual length of a prostate biopsy sample from the index lesion containing prostate cancer cells	Length (mm)
Targeted: Gleason score	Gleason score of prostate cancer cells seen in biopsy samples from the index lesion of the prostate	Gleason score
Overall: Number of cores positive	Number of prostate cores taken at biopsy with prostate cancer cells seen in total	Number of cores
Overall: maximum core length involvement	The maximum continual length of a prostate biopsy sample containing prostate cancer cells	Length (mm)
Overall: Worse Gleason Group	The highest Gleason Grade Group from all prostate tissue analysed histologically	Gleason Grade Group (1-5)
Other histology comments	Comments and notes made by data entrant regarding biopsy samples analysed	Free text
T-category (Pathological)	Assessment of T-stage of prostate lesion based on MRI by radiologist	Union of International Cancer Control (UICC) Tumour Node Metastases (TNM)

		tumour classification (T1 – T4)
N-category (Pathological)	Assessment of N-stage of prostate lesion based on MRI by radiologist	Union of International Cancer Control (UICC) Tumour Node Metastases (TNM) node classification (N0 – N1)
Other final comments	Comments and notes made by data entrant	Free text

Table 5.8 - Summaries of all available variables

2WW – Two Week Wait; PSA – Prostate Specific Antigen; MRI – Magnetic Resonance Imaging; bpMRI – Biparametric MRI; mpMRI – Multiparametric MRI; TP – Transperineal; GA – General anaesthetic; LA – Local anaesthetic; PSAD – Prostate Specific Antigen Density

Data access

A data sharing agreement was put in place between the participating NHS Trusts and the University of Exeter for me to access an anonymised subset of the data for the purposes of informing this model. As a current NHS employee, I was able to receive the data and store it on an NHS networked computer for the purposes of data cleaning, manipulation and analysis. Ethical approval for access to this data was not required, as the project is evaluating service delivery and routine clinical practice has not changed. The enabling legislation for this practice is the NHS Act 2006 section 13E(250).

Data quality measures

Levels of missing data for the audit dataset have been estimated based on a sub-sample of two randomly selected NHS Trusts' data collected from August 2018 to April 2020 (1967 records).

Variable	Missing data n (%)
Referral year	0 (0%)
Provider	0 (0%)
RecordID	0 (0%)
Age at referral	2 (0.1%)
PSA value at diagnosis	22 (1.1%)
Family History	1597 (81.2%)
Date of referral	0 (0%)
Other comments	N/A
Date first seen	0 (0%)
Date diagnosis given to patient	106 (5.4%)
Type of biopsy	2 of 883 biopsied (0.2%)
Date of biopsy	7 of 883 (0.8%)
Total no of systematic cores	58 of 883 (6.6%)
Total no of targeted cores	55 of 883 (6.2%)
For Targeted: Fusion or Cognitive?	883 (100%)
For Template: Mapping or Targeted?	433 (49%)
For Template: Total number of zones?	783 (88.7%)
Comments	N/A
Date of MRI	0 (0%)
MRI type	1 of 1084 undergoing MRI (0.1%)
Prostate volume	21 of 1084 (1.9%)
PSAd	660 (33.6% of all records)
PIRADS score of the index lesion	181 of 1084 (16.7%)
Confidence of PIRADS score	132 of 1084 (12.2%)
Likert	457 of 1084 (42.2%)
Max diameter of index lesion	266 of 1084 (24.5%)
Radiologist's t-stage	126 of 1084 (11.6%)
Radiologist's n-stage	161 of 1084 (14.9%)
Final pre-treatment staging T	143 of 624 diagnosed with prostate cancer (22.9%)
Final pre-treatment staging N	147 of 624 (23.6%)
Other MRI comments	N/A
Date histology reported	47 of 883 biopsied (5.3%)

Total number of cores taken	52 of 883 (5.9%)
Right: number of cores positive	49 of 883 (5.5%)
Right: maximum core length involvement	492 of 883 (55.7%)
Right: Gleason score	58 of 883 (6.6%)
Left: number of cores positive	51 of 883 (5.8%)
Left: maximum core length involvement	392 of 883 (44.4%)
Left: Gleason score	58 of 883 (6.6%)
Targeted: number of cores positive	200 of 883 (22.7%)
Targeted: maximum core length involvement	475 of 883 (53.8%)
Targeted: Gleason score	255 of 883 (28.9%)
Overall: Number of cores positive	47 of 883 (5.3%)
Overall: maximum core length involvement	375 of 883 (42.5%)
Overall: Worse Gleason Group	53 of 883 (6%)
Other histology comments	N/A
T-category (Pathological)	816 of 883 (92.4%)
N-category (Pathological)	816 of 883 (92.4%)
Other final comments	N/A

Table 5.9 – Estimates of data completeness from 1967 records

PSA – Prostate Specific Antigen; MRI – Magnetic Resonance Imaging; PSAd – PSA density; PIRADS – Prostate Imaging-Reporting And Data System

Data handling and analysis

The raw data were received in a Microsoft Excel spreadsheet. It was cleaned and prepared for transfer into Stata version 16. All variables were inspected for levels of missing data (see Table 5.9), and variables not relevant to the analysis were dropped. The proportion of patients in this subset undergoing a prostate MRI following referral was calculated. 2 x 2 tables were constructed to calculate the diagnostic accuracy (sensitivity, specificity, positive predictive value, and negative predictive value) of mpMRI and bpMRI for all patients with available MRI and pathology data. Mean time intervals and standard deviations,

measured in days, were calculated for the following parameters using date of referral as the index day:

Time to outpatient appointment

Time to prostate MRI

Time to prostate biopsy

Time to patient being informed of diagnosis

Results

Data were available for 1,967 patients referred on the 2WW prostate cancer pathway of two NHS Trusts participating in the audit. 624 patients were diagnosed with prostate cancer, 542 of whom were diagnosed with clinically significant prostate cancer. The mean number of days from the date of referral to the patient undergoing an MRI scan of the prostate was 16.2 (SD 25.1) days. Other time intervals measured in the audit are presented in Table 5.10 below.

Characteristic (n = 1967)	**Mean (years)**	**SD**
Age	69.9	9.7
	N	**%**
FHx of Prostate cancer	68	3.5%
New prostate cancer diagnosis	624	31.7%
Clinically significant	542	27.6%
Intervals	**Mean (days)**	**SD**
Referral to outpatients	8.8	13.0
Referral to MRI	16.2	25.1
Referral to biopsy	33.9	30.9
Referral to diagnosis	37.5	29.6

Table 5.10 – Audit participant characteristics

FHx – Family History; SD – standard deviation; MRI – Magnetic Resonance Imaging

The median PSA level for referred patients in the audit was 8.6ng/mL (Interquartile range 5.4, 15.0). 1,083 patients referred underwent an MRI of the prostate; 671 of whom had an mpMRI and 412 had bpMRI. A breakdown of PIRADS scores for patients with available data is shown below in Table 5.11.

Test	Median	IQR
PSA (ng/mL)	8.6	5.4, 15.0
Prostate volume (mL)	53	36, 77
PSA density (ng/mL^2)	0.1	0.04, 0.2
MRI approach	**N**	**%**
mpMRI		
Performed	671	34.1%
PIRADS 1-2	147	21.9%
PIRADS 3-5	373	55.6%
Missing	151	22.5%
bpMRI		
Performed	412	20.9%
PIRADS 1-2	146	35.4%
PIRADS 3-5	235	57.0%
Missing	31	7.5%

Table 5.11 – Diagnostic test results

PSA – Prostate Specific Antigen; ng/mL – nanograms per millilitre; mL – millilitre; MRI – Magnetic Resonance Imaging; mpMRI – Multiparametric MRI; PIRADS – Prostate Imaging-Reporting And Data System; bpMRI – Biparametric MRI; IQR – Interquartile Range

317 patients who had undergone pre-biopsy mpMRI had both a PIRADS score and final histopathological diagnosis available. 184 / 193 (95.3%) of patients with clinically significant prostate cancer on biopsy had a PIRADS score of three or greater. See Table 5.12 below for the two-by-two table and estimates of diagnostic accuracy of mpMRI in this cohort.

	Clinically significant prostate cancer	No cancer	
PIRADS ≥ 3	184	89	273
PIRADS < 3	9	35	44
	193	124	317

Table 5.12 – Diagnostic accuracy of elevated PIRADS score from mpMRI, with available biopsy data, for clinically significant prostate cancer

Sensitivity = 95.3% PPV = 67.4%

Specificity = 28.2% NPV = 79.5%

299 patients who had undergone pre-biopsy bpMRI had both a PIRADS score and final histopathological diagnosis available. 161 / 183 (87.9%) of patients with clinically significant prostate cancer on biopsy had a PIRADS score of three or greater. See Table 5.13 below for the two-by-two table and estimates of diagnostic accuracy of bpMRI in this cohort.

	Clinically significant prostate cancer	No cancer	
PIRADS ≥ 3	161	50	211
PIRADS < 3	22	66	88
	183	116	299

Table 5.13 – Diagnostic accuracy of elevated PIRADS score from bpMRI, with available biopsy data, for clinically significant prostate cancer

Sensitivity = 87.9% PPV = 76.3%

Specificity = 56.9% NPV = 75.0%

Discussion

Analysis of this dataset of almost 2,000 patients referred to two NHS Trusts in the South-West of England on the 2WW prostate cancer diagnostic pathway showed 55% of patients underwent a pre-biopsy MRI scan. More mpMRI scans were performed than bpMRI scans. The mean time to diagnosis from referral in days (37.5 days) was longer than the current NHS 28-day target. Sensitivity of a PIRADS score greater than or equal to three on prostate MRI for clinically

significant prostate cancer in this cohort was 95.3% for mpMRI and 87.9% for bpMRI.

The findings of this analysis are broadly consistent with the current literature on prostate cancer diagnostic pathways in the NHS and the performance of prostate MRI. Relative to other cancer types, the prostate cancer diagnostic pathway is known to be longer with more patients not receiving their cancer diagnosis within the time targets set by the Department for Health and Social Care(47). Diagnostic accuracy of mpMRI and bpMRI in this cohort is also comparable with published systematic reviews for prostate MRI(29,35).

The strengths of this dataset lie in the complete capture of all 2WW prostate cancer referrals in the time period, and the real-world data captured to assess the implementation of prostate MRI outside research settings. The diagnostic accuracy measures are likely to overstate the accuracy of mpMRI and bpMRI for clinically significant prostate cancer, as the cohort is a referred secondary care population and the majority of patients with a ‘normal’ MRI (PIRADS 1-2) were not biopsied, introducing partial verification bias. No data on the diagnostic journey prior to referral to secondary care was captured by this audit, so we are unable to determine what proportion of patients were symptomatic vs undergoing opportunistic PSA screening or what proportion of patients with an indication for 2WW prostate cancer referral were actually referred.

5.3.4 Secondary analysis of the CRUK IMPACT study Clinical Practice Research Datalink (CPRD) dataset

Aim

To estimate the probability of a patient presenting in primary care with lower urinary tract symptoms and an undiagnosed prostate cancer returning for repeat consultations when not referred for investigation at initial presentation

Methods

Data source

This analysis utilised a Clinical Practice Research Datalink (CPRD) dataset that has been used for the Cancer Research UK-funded IMPACT study. The CRUK IMPACT study aimed to estimate diagnostic intervals and patient outcomes for 22 cancer sites, including prostate cancer, and assess the impact of revisions made to National Institute for Health and Care Excellence (NICE) guidelines for GPs on suspected cancer referral. CPRD is a large, anonymised, primary care dataset consisting of coded data from primary healthcare records extracted by GP practices across the UK, including over 16 million currently registered patients. CPRD has been shown to be representative of the UK population(251).

Population

41,115 patients in CPRD with a diagnosis of prostate cancer between 01/01/2000 and 31/12/2017 were included in this dataset. The mean age at diagnosis for these patients was 72.11 years (+/- 9.42 years). See table 5.14 below for further information about geographical region and deprivation for the practice area from which the patients come from. Complete consultation data was available for 34,409 patients in this cohort (83.7%).

Socioeconomic status	
Townsend deprivation index	**N (%)**
1	7,111 (17.28%)
2	6,633 (16.12%)
3	5,083 (12.35%)
4	3,959 (9.62%)
5	1,985 (4.82%)
Missing	16,384 (39.81%)
Geography	
Region	**N (%)**
North East	549 (1.33%)
North West	4,217 (10.25%)
Yorkshire & Humber	1,141 (2.77%)
East Midlands	1,081 (2.63%)
West Midlands	4,000 (9.72%)
East of England	3,428 (8.33%)
South West	3,959 (9.62%)
South Central	4,643 (11.28%)
London	3,350 (8.14%)
South East Coast	4,835 (11.75%)
Northern Ireland	1,311 (3.19%)
Wales	3,406 (8.28%)
Scotland	5,235 (12.72%)

Table 5.14 – Included participant demographics

Consultation data, including date of consultation and coded reason for contact with primary care, and PSA testing data, including the date of test and result, was available from 01/01/1999 to 31/12/2017.

Data access

This CPRD dataset received regulatory and ethical approval from the Medicines and Healthcare products Regulatory Agency (MHRA) Independent Scientific Advisory Committee (ISAC) (ISAC protocol number 16_037A2). The analysis

performed was within the remit of the ISAC approval given, and therefore no amendment to the existing approval was necessary.

Data preparation

Analysis datasets from the CRUK IMPACT study covering baseline patient data, consultation data, and PSA testing data were combined using the CPRD *epatid* variable for the purposes of this analysis. Duplicate entries were removed. See Table 5.15 for a list of key variables that were prepared for the analysis.

Variable name	**Description**
epatid	Individual patient ID from CPRD
age_dx	Patient age at diagnosis (years)
region	Geographical region of patient's GP practice
townsend2001_5	Townsend Index of Deprivation for patient's GP practice
prostate_diagdate	Date of diagnosis of prostate cancer
eventdate_td	Date of consultation
pca_symptom	Symptom of possible prostate cancer coded in the consultation
psa_test	PSA test performed in the consultation

Table 5.15 – Variable descriptions

Statistical analysis

Summary descriptive statistics of patient demographics were performed. Number of consultations by individual patients for symptoms of possible prostate cancer and/or PSA testing in the 12-months prior to diagnosis were measured and summarised. The diagnostic interval was calculated from the date of first presentation with a symptom that might relate to a prostate cancer to the date of diagnosis in CPRD and summarised with median and interquartile range (IQR). Median diagnostic interval by number of pre-referral consultations was calculated and stratified by type of initial presentation (symptomatic vs opportunistic screening). Primary care interval (date of first presentation to date of first suspected cancer referral) could not be calculated owing to significant levels of missing data on the date of referral.

Estimation of the probability of returning to the GP having not been referred following the initial two consultations (one to present with symptoms and a follow-up consultation to discuss PSA results and possible referral) were estimated using the *proportion* command in Stata. Stratification by year of diagnosis was undertaken, as were analyses to compare outcomes in the time periods relating to publication of NICE guidelines on cancer diagnosis in primary care (pre-25/06/2005 vs 26/06/2005 – 22/06/2015 vs 23/06/2015 – 31/12/2017). Chi-squared testing was performed for changes between the NICE guideline time periods. Sub-group analyses were performed for different initial presentation types.

Results

78,812 consultations for 41,115 patients in this CPRD dataset were analysed. The mean number of pre-diagnostic consultations per patient as 1.9 (SD 0.8). Of the 34,410 initial consultations during the study period, 23,201 (67.4%) were for an initial PSA test without any recorded symptoms and classified as opportunistic screening. LUTS was the next most common initial presenting complaint (7,467 / 34,410 [21.7%]). See Table 5.16 for further details regarding the reasons for initial consultations.

Presenting problem	**n (%)**
LUTS	7,467 (21.7%)
Haematuria	1,352 (3.9%)
Erectile dysfunction	1,175 (3.4%)
Abnormal DRE	361 (1.0%)
Opportunistic PSA test	23,201 (67.4%)
Missing	854 (2.5%)

Table 5.16 – Proportions of index presentation types for patients with prostate cancer

n – number of patients; % - proportion; DRE – Digital Rectal Examination; PSA – Prostate Specific Antigen

49,619 PSA tests were performed on the patients in this cohort. From the initial PSA tests undertaken on patients who had at least one test taken (n = 34,410), the median PSA result was 10.8ng/mL (IQR 6.3, 27.1). Initial PSA results were

higher for patients with symptoms compared to those undergoing opportunistic screening (median PSA 14.6ng/mL [IQR 7, 43.6] vs 11.1ng/mL [IQR 6.4, 28.7]). Further details about PSA test results can be found in Table 5.17.

Overall (n = 34,410)	
	Median (IQR)
PSA level (ng/mL)	10.8 (6.3, 27.1)
	n (%)
PSA above lab reference range	13,446 (39.1%)
PSA above NICE threshold	21,544 (62.6%)
PSA > 3ng/mL	22,132 (64.3%)
Symptomatic	
	Median (IQR)
PSA level (ng/mL)	14.6 (7, 43.6)
	n (%)
PSA above lab reference range	4,326 (59.3%)
PSA above NICE threshold	6,678 (91.6%)
PSA > 3ng/mL	6,866 (94.1%)
Opportunistic screening	
	Median (IQR)
PSA level (ng/mL)	11.1 (6.4, 28.7)
	n (%)
PSA above lab reference range	13,446 (56.6%)
PSA above NICE threshold	21,544 (90.7%)
PSA > 3ng/mL	22,132 (93.2%)

Table 5.17 – Initial PSA results for patients with prostate cancer
n – number of patients; % - proportion; PSA – Prostate Specific Antigen; ng/mL – nanograms per millilitre; NICE – National Institute for health and Care Excellence; IQR – Interquartile Range

The median diagnostic interval for the cohort was 88 days (IQR 25, 197), with minimal differences between symptomatic patients (91 days IQR 45, 189) and patients undergoing opportunistic screening (87 days IQR 40,203). Median diagnostic interval was much longer before the introduction of NICE guidance compared to afterwards (107 days IQR 52,217 vs 83 IQR 44, 161). The median

diagnostic interval increased for each additional pre-referral consultation (See Table 5.18). 29.0% (9,994 / 34,410) of the cohort had three or more primary care consultations in the year prior to prostate cancer diagnosis, and this proportion was higher for symptomatic patients than patients initially presenting for opportunistic screening throughout the study period (See Table 5.19). Bootstrapping techniques using 1,000 repetitions estimated the proportion of patients with symptoms at initial presentation having three or more pre-referral consultations in primary care to be 13.82% (95% CI 13.53, 14.12).

	1 consult	**2 consults**	**3 consults**	**4 consults**	**5+ consults**
Overall					
n (%)	13,072	11,343	6,062	2,494	571
DI (Median, IQR)	54 (27, 107)	91 (45, 191)	139 (66, 255)	203 (101, 296)	274 (195, 337)
Symptomatic					
n (%)	1,932	3,665	2,734	1,248	320
DI (Median, IQR)	66 (30, 144)	73 (41, 144)	94 (49, 187)	140 (76, 238)	240 (162, 316)
Opportunistic screening					
n (%)	12,536	6,985	2,543	762	136
DI (Median, IQR)	55 (27, 109)	110 (51, 220)	209 (98, 293)	273 (184, 327)	314 (231, 347)

Table 5.18 – Diagnostic interval (DI) for patients by number of pre-referral consultations

n – number of patients; % - proportion; DI – Diagnostic interval; IQR – Interquartile range

	Whole cohort n = 34,410	Pre-CG27 n = 7,799	CG27 n = 23,644	NG12 n = 2,966
All patients*	9,994 (29.0%)	1,941 (24.9%)	7,190 (30.4%)	863 (29.1%)
Symptomatic patients*	4,757 (13.8%)	996 (12.8%)	3,362 (14.2%)	399 (13.5%)
Opportunistic screening*	5,184 (15.1%)	931 (11.9%)	3,793 (16.0%)	460 (15.5%)

Table 5.19 – Proportion of patients with 3+ pre-referral consultations overall, and within time periods relating to NICE suspected cancer guidelines.
* p<0.001 for difference between NICE time periods
CG27 – Clinical guideline 27; NG12 – NICE guideline 12

Discussion

This secondary analysis of a primary care dataset of men with prostate cancer showed that 29.0% of patients had three or more pre-referral primary care consultations overall, with patients having symptoms at initial presentation much more likely to have three or more pre-referral consultations. Median diagnostic interval increased with an increasing number of pre-referral consultations. Initial PSA levels were higher in patients presenting with symptoms compared to those undergoing initial opportunistic screening.

Estimates for the proportion of symptomatic patients with three or more consultations in this CPRD dataset were consistent with other studies. Lyratzopoulos *et al* found (2013) 15.2% of prostate cancer patients in the 2009-2010 National Cancer Diagnosis Audit (NCDA) had three or more pre-referral consultations(252). However, the median diagnostic interval for symptomatic prostate cancer patients in this analysis (91 days) was significantly higher than reported in the analysis of a more recent round of the NCDA in 2014 (55.5 days)(253). This appears to be at least in part due to the long time period covered by the IMPACT study data set (1999 – 2017), but even in recent years the diagnostic interval was much higher.

The strengths of this analysis lie in the large numbers of patients, covering a significant time period, with relatively complete primary care consultation data. Some patients may have been misclassified as undergoing opportunistic screening due to the 12-month pre-diagnosis window of the data and a possible lack of coding of symptoms in the GP record. PSA data is also skewed by only assessing patients with a diagnosis of prostate cancer.

5.3.5 Estimates for model parameters

Utilising the evidence outlined above, the following baseline estimates were generated for use in the modelling undertaken in this PhD (see Table 5.20)

Parameter	**Baseline estimate (95% CI)**	**Source**
Undergoing DRE	0.62 (0.57, 0.66)	Young *et al* 2015(219)
DRE sensitivity	0.29 (0.25, 0.32)	Jones *et al* 2018(18)
DRE specificity	0.91 (0.89, 0.92)	Jones *et al* 2018(18)
Undergoing PSA for symptoms	0.84 (0.80, 0.87)	Young *et al* 2015(219)
Undergoing PSA screening	0.017 (0.016, 0.017)	Clift *et al* 2021(205)
PSA sensitivity (symptomatic)	0.93 (0.88, 0.96)	Section 5.3.2
PSA specificity (symptomatic)	0.20 (0.12, 0.33)	Section 5.3.2
PSA sensitivity (screening)	0.69 (0.58, 0.78)	Ilic *et al* 2018(22)
PSA specificity (screening)	0.56 (0.50, 0.62)	Ilic *et al* 2018(22)
Undergoing MRI	0.98 (0.96, 0.99)	Ahmed *et al* 2017(53)
mpMRI sensitivity	0.91 (0.83, 0.95)	Drost *et al* 2019(29)
mpMRI specificity	0.37 (0.29, 0.46)	Drost *et al* 2019(29)
bpMRI sensitivity	0.87 (0.78, 0.93)	Bass *et al* 2020(35)
bpMRI specificity	0.72 (0.56, 0.84)	Bass *et al* 2020(35)
Returning with symptoms	0.14 (0.13, 0.14)	Section 5.3.4
Returning for repeat screening	0.20 (0.19, 0.20)	Young *et al* 2017(143)
Cost	**Amount (£)**	**Source**
GP appointment	£33.00	Curtis & Burns 2020(214)
Nurse appointment	£8.17	Curtis & Burns 2020(214)
PSA	£5.91	Ramsay *et al* 2012(216)
mpMRI (direct access)	£190.00	NHS reference costs 2019(215)

mpMRI (outpatient)	£217.00	NHS reference costs 2019(215)
bpMRI (direct access)	£121.00	NHS reference costs 2019(215)
bpMRI (outpatient)	£143.00	NHS reference costs 2019(215)
2WW appointment	£144.00	NHS reference costs 2019(215)
TRUS biopsy	£504.00	NHS reference costs 2019(215)
Transperineal template biopsy	£1,413.00	NHS reference costs 2019(215)
Health state	**Annual disutility (range)**	**Source**
DRE	0.00019 (0, 0.00019)	Assumption
PSA	0.00019 (0, 0.00019)	Barnett *et al* 2018(183)
MRI	0.00077 (0.00038, 0.00012)	Barnett *et al* 2018(183)
Biopsy	0.00577 (0.00346, 0.0075)	Barnett *et al* 2018(183)
Post biopsy infection	0.0161 (0.00969, 0.0291)	Barnett *et al* 2018(183)
Early diagnosis	0.0167 (0.0125, 0.0208)	Barnett *et al* 2018(183)
Delayed diagnosis	0.3 (0.3, 0.38)	Barnett *et al* 2018(183)
Late diagnosis	0.4 (0.14, 0.76)	Barnett *et al* 2018(183)

Table 5.20 – Probabilities, costs and utilities used in the model

DRE – Digital Rectal Examination; PSA – Prostate Specific Antigen; MRI – Magnetic Resonance Imaging; mpMRI – Multiparametric MRI; bpMRI – Biparametric MRI; 2WW – Two Week Wait; TRUS – Transrectal Ultrasound guided; CI – Confidence Interval

5.4 Results

Model outputs

Base case analysis

Table 5.21 shows the incremental costs and utilities of the mpMRI and bpMRI pathways compared to the PSA pathway. The PSA pathway was dominated by both MRI-based pathways for symptomatic patients and patients undergoing opportunistic screening. bpMRI pathways were more cost effective than mpMRI pathways in both patient groups. Figures 5.13 and 5.14 demonstrate these results graphically for each patient group.

Strategy	**Costs**	**Annual utility**	**Incremental costs (vs PSA)**	**Incremental utility**
Base case – Symptomatic patients				
PSA pathway	£1,294.22	0.9946824		
mpMRI pathway	£938.42	0.9962101	-£355.80	0.0015277
bpMRI pathway	£594.46	0.9975885	-£699.77	0.0029060
Base case – Screening patients				
PSA pathway	£739.90	0.9969314		
mpMRI pathway	£540.56	0.9976161	-£199.33	0.0006847
bpMRI pathway	£313.60	0.9983909	-£426.30	0.0014595

Table 5.21 – Costs and utilities of each strategy assessed in the base case analysis. Incremental costs and utilities for the mpMRI and bpMRI pathways were compared to the PSA pathway and were dominant compared to the PSA pathway for symptomatic and screening patients.

PSA – Prostate Specific Antigen; mpMRI – Multiparametric MRI; bpMRI – Biparametric MRI

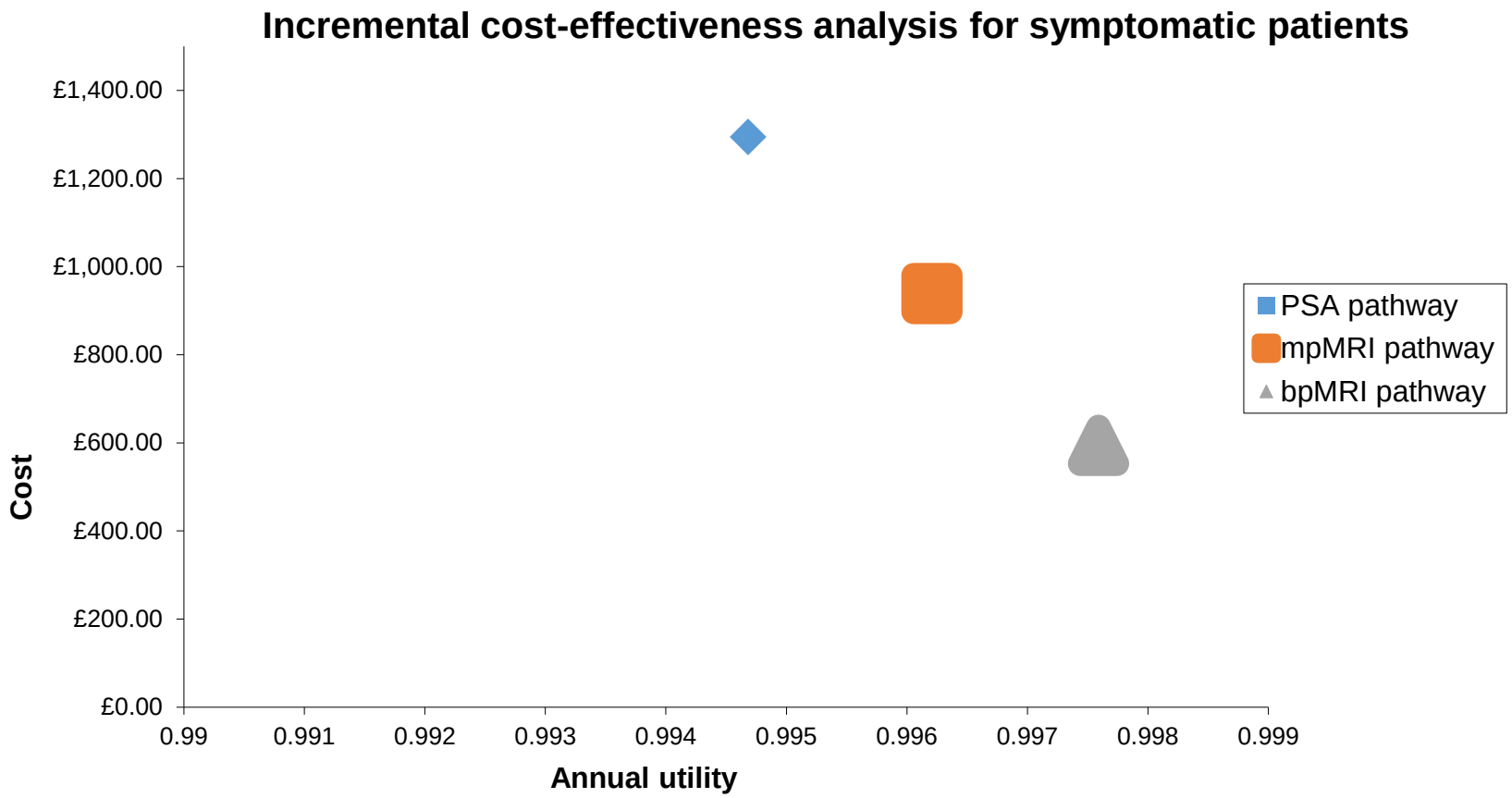


Figure 5.13 – Incremental cost-effectiveness of PSA, mpMRI and bpMRI pathways for symptomatic patients

PSA – Prostate Specific Antigen; mpMRI – Multiparametric MRI; bpMRI – Biparametric MRI

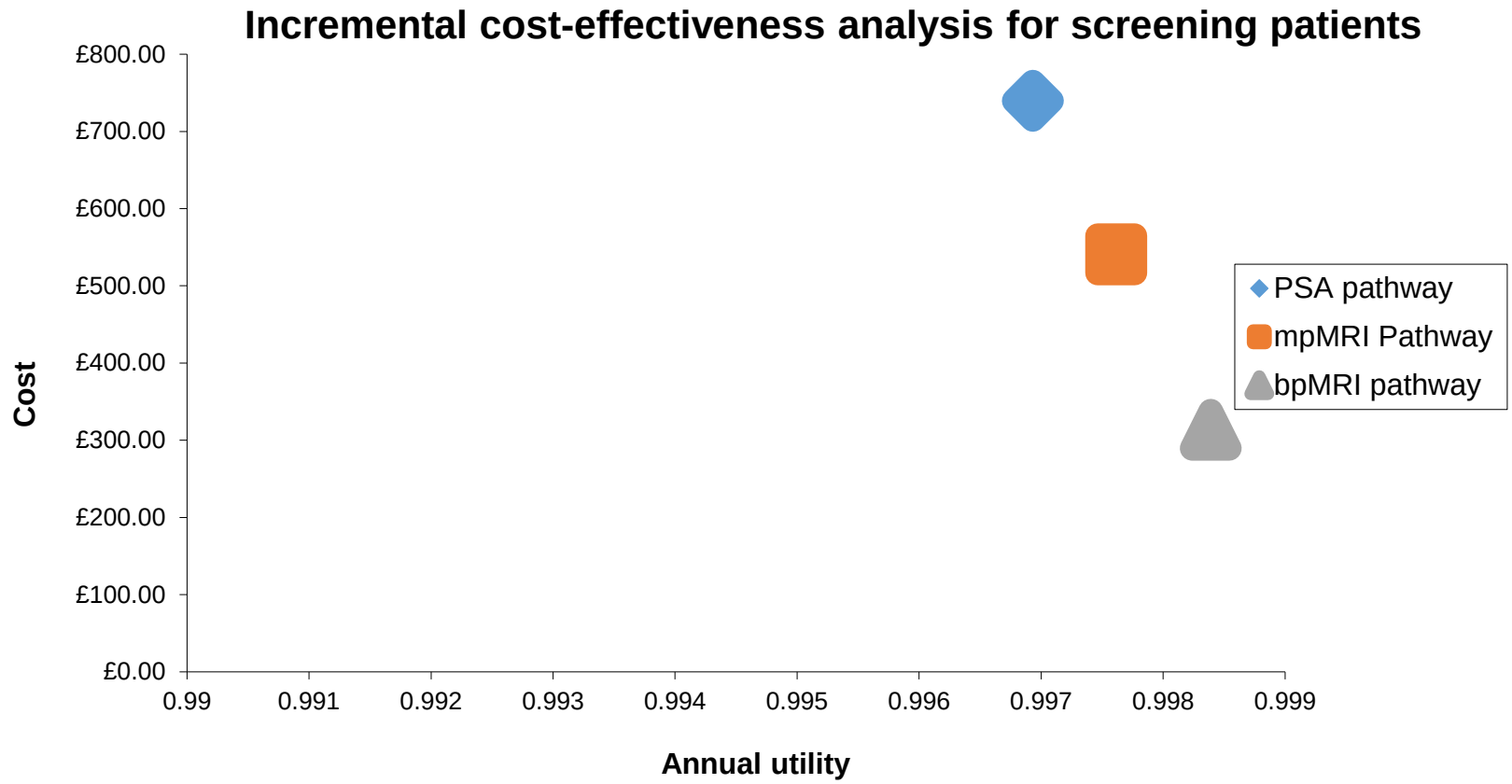


Figure 5.14 – Incremental cost-effectiveness of PSA, mpMRI and bpMRI pathways for screening patients

PSA – Prostate Specific Antigen; mpMRI – Multiparametric MRI; bpMRI – Biparametric MRI

Estimates of the potential impact of implementing prostate MRI into the primary care diagnostic pathway showed that significantly more MRI scans would be needed compared to the current PSA-based pathway for both symptomatic (66,626 scans per annum vs 37,456 scans per annum) and screening pathways (36,139 scans per annum vs 20,324 scans per annum) per 100,000 patients. 2WW referrals would reduce for both mpMRI (38% for symptomatic and screening patients) and bpMRI (71% for symptomatic and 72% for screening) pathways. Numbers of patients experiencing a missed diagnosis of prostate cancer would rise slightly for MRI-based pathways compared to a PSA pathway (see Table 5.22)

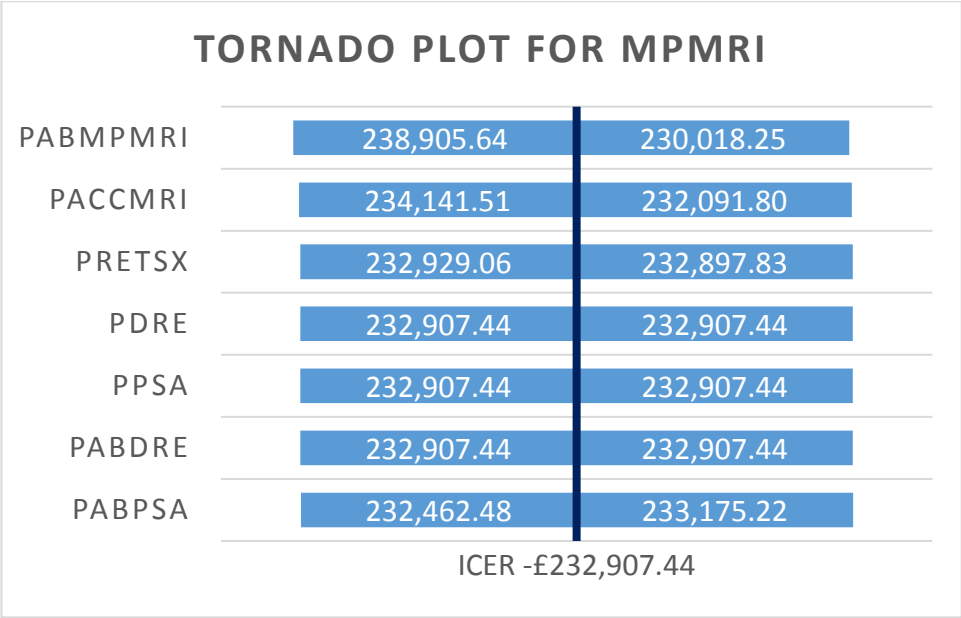
Strategy	**MRI scans done**	**2WW referrals**	**Missed diagnoses**
Base case – Symptomatic patients			
PSA pathway	37,456	68,103	36
mpMRI pathway	66,626	42,367	50
bpMRI pathway	66,626	19,426	56
Base case – Screening patients			
PSA pathway	20,324	36,952	50
mpMRI pathway	36,139	22,795	83
bpMRI pathway	36,139	10,176	87

Table 5.22 – Predicted effects of different prostate cancer diagnostic pathway strategies per 100,000 men

PSA – Prostate Specific Antigen; MRI – Magnetic Resonance Imaging; mpMRI – Multiparametric MRI; bpMRI – Biparametric MRI; 2WW – Two Week Wait

Sensitivity analyses

Deterministic sensitivity analyses varying each probability parameter by the upper and lower limits of the 95% CIs did not show any significant change in the dominance of the MRI-based prostate cancer diagnostic pathways in the models for symptomatic patients or patients undergoing opportunistic screening (see Tornado Plots in Figures 5.15 – 5.18)



Figures 5.15 Tornado plot for deterministic sensitivity analyses of mpMRI in symptomatic patients

PABMPMRI – Probability of abnormal mpMRI

PACCMRI – Probability of accepting MRI

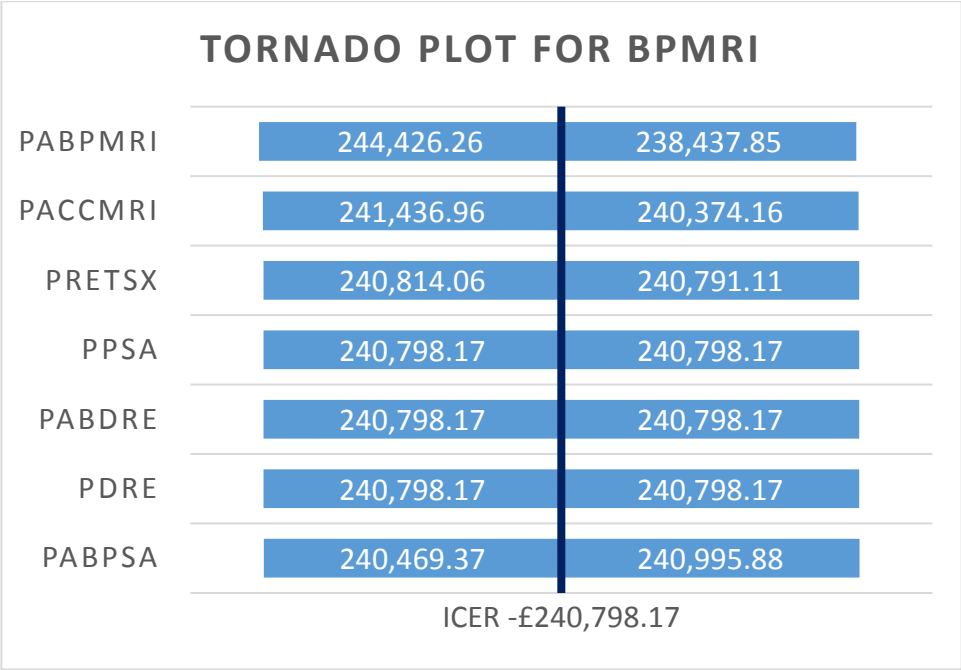
PRETSX – Probability of returning with symptoms

PDRE – Probability of accepting DRE

PPSA – Probability of accepting PSA

PABDRE – Probability of abnormal DRE

PABPSA – Probability of abnormal PSA



Figures 5.16 – Tornado plot for deterministic sensitivity analyses of bpMRI in symptomatic patients

PABBPMRI – Probability of abnormal bpMRI

PACCMRI – Probability of accepting MRI

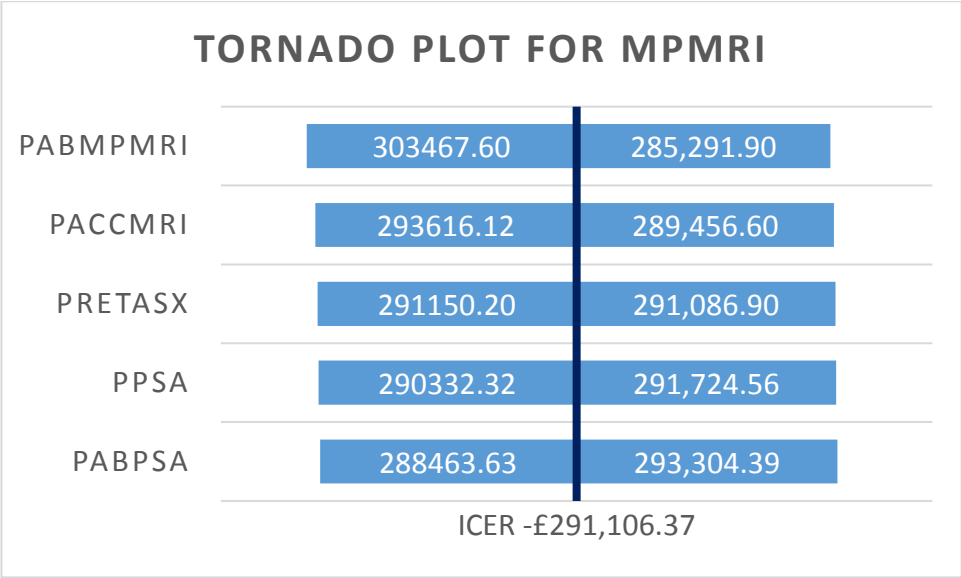
PRETSX – Probability of returning with symptoms

PDRE – Probability of accepting DRE

PPSA – Probability of accepting PSA

PABDRE – Probability of abnormal DRE

PABPSA – Probability of abnormal PSA



Figures 5.17 – Tornado plot for deterministic sensitivity analyses of mpMRI in screening patients

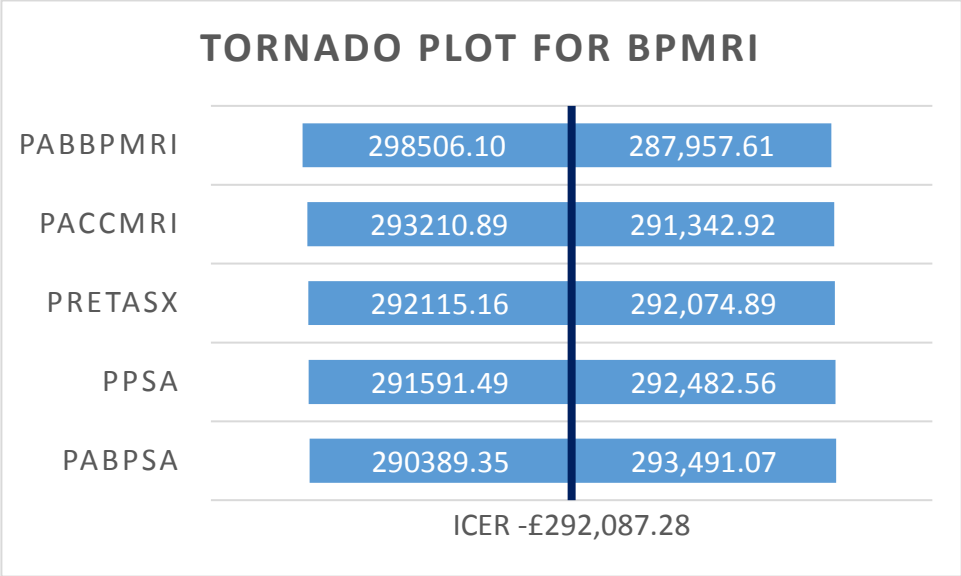
PABMPMRI – Probability of abnormal mpMRI

PACCMRI – Probability of accepting MRI

PRETSX – Probability of returning with symptoms

PPSA – Probability of accepting PSA

PABPSA – Probability of abnormal PSA



Figures 5.18 – Tornado plot for deterministic sensitivity analyses of bpMRI in screening patients

PABBPMRI – Probability of abnormal bpMRI

PACCMRI – Probability of accepting MRI

PRETSX – Probability of returning with symptoms

PPSA – Probability of accepting PSA

PABPSA – Probability of abnormal PSA

Probabilistic sensitivity analyses showed no significant change in estimated and incremental costs for the MRI pathways but suggested small incremental utility deficits relative to the PSA pathway (see Table 5.23). Cost-effectiveness planes show the bpMRI pathway is more often below the current NICE threshold of £30,000 compared to mpMRI for both symptomatic and screening patients (Figures 5.19 – 5.22).

Option	**Costs**	**Annual utility**	**Incremental costs (relative to PSA)**	**Incremental utility**	**ICER**
ProbSA (mean [95% credible interval)] – Symptomatic patients					
PSA pathway	£1,302.73 (£1,204.67, £1,400.78)	0.9894575 (0.9889880, 0.9899271)			
mpMRI pathway	£930.46 (£872.32, £988.60)	0.9894328 (0.9890866, 0.9897791)	-£372.26	-2.47031×10^{-5}	£15,069,451.36
bpMRI pathway	£610.66 (£582.74, £638.59)	0.9891136 (0.9887327, 0.9894946)	-£692.06	-0.0003439	£2,012,443.21
ProbSA (mean [95% credible interval)] – Screening patients					
PSA pathway	£735.27 (£683.77, £786.77)	0.9899513 (0.9895040, 0.9903987)			
mpMRI pathway	£531.53 (£499.01, £564.06)	0.9897120 (0.9893488, 0.9900753)	-£203.74	-0.0002392	£851,434.81
bpMRI pathway	£308.38 (£292.90, £323.86)	0.9894773 (0.9890787, 0.9898759)	-£426.89	-0.0004740	£900,600.60

Table 5.23 – Probabilistic sensitivity analyses of estimated costs and utilities associated with the three strategies in the model

ProbSA – Probabilistic Sensitivity Analysis; PSA – Prostate Specific Antigen; mpMRI – Multiparametric Magnetic Resonance Imaging; bpMRI – Biparametric Magnetic Resonance Imaging; ICER – Incremental Cost Effectiveness Ratio

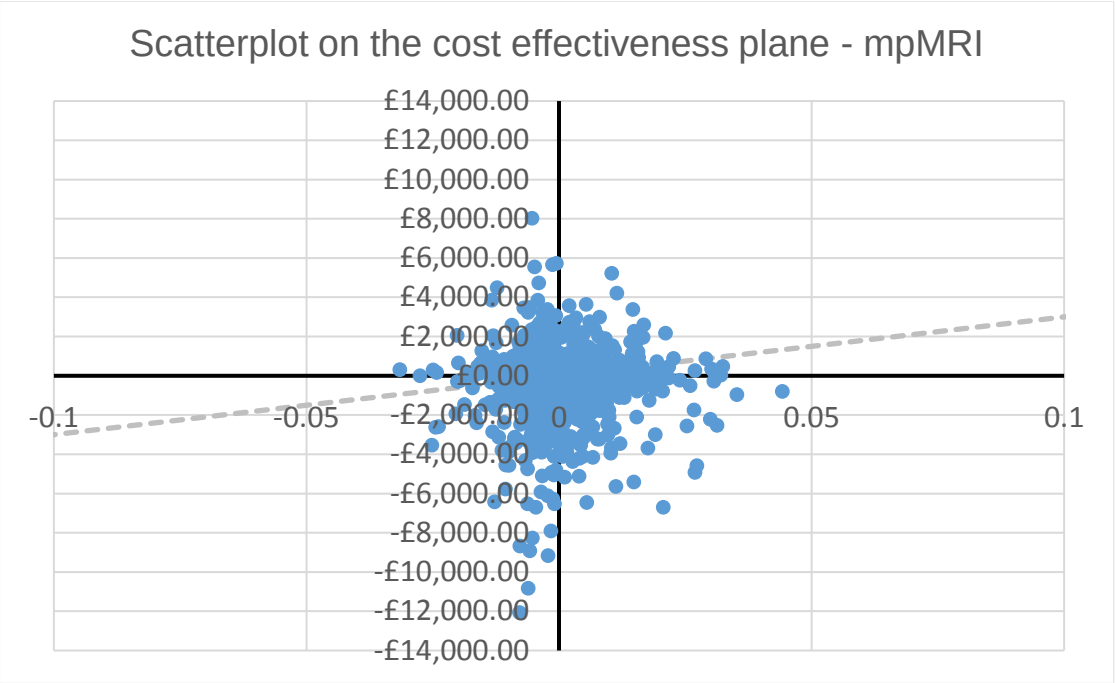


Figure 5.19 – Cost-effectiveness scatter plot of mpMRI for symptomatic patients

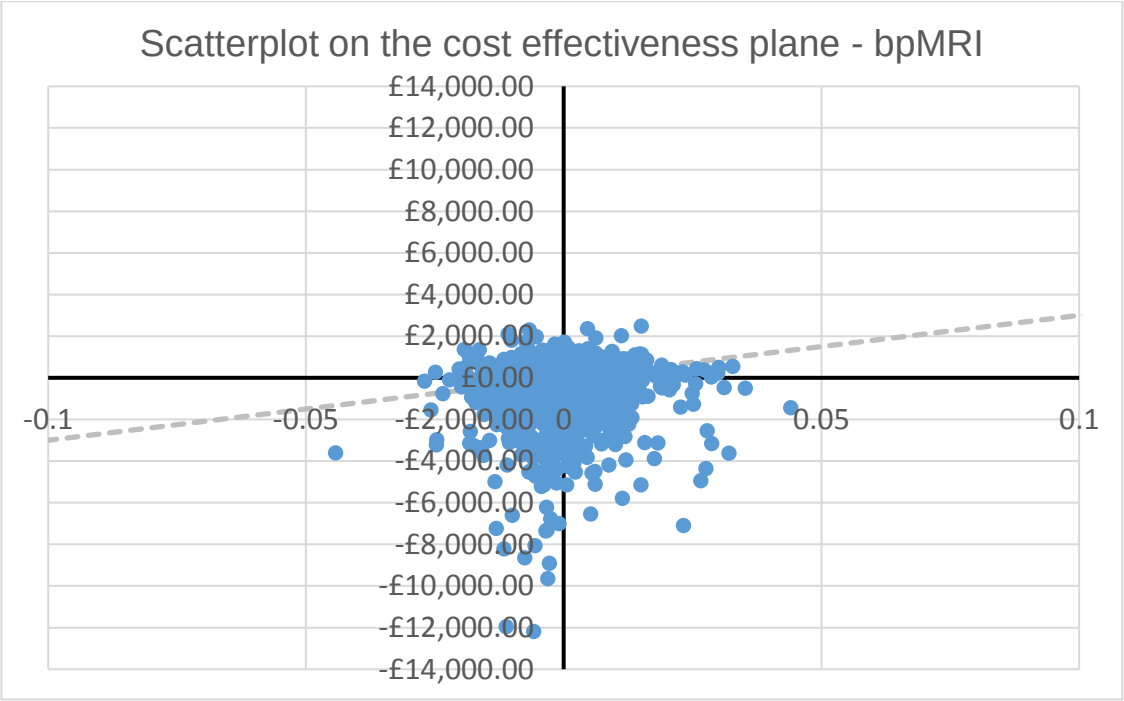


Figure 5.20 – Cost-effectiveness scatter plot of bpMRI for symptomatic patients

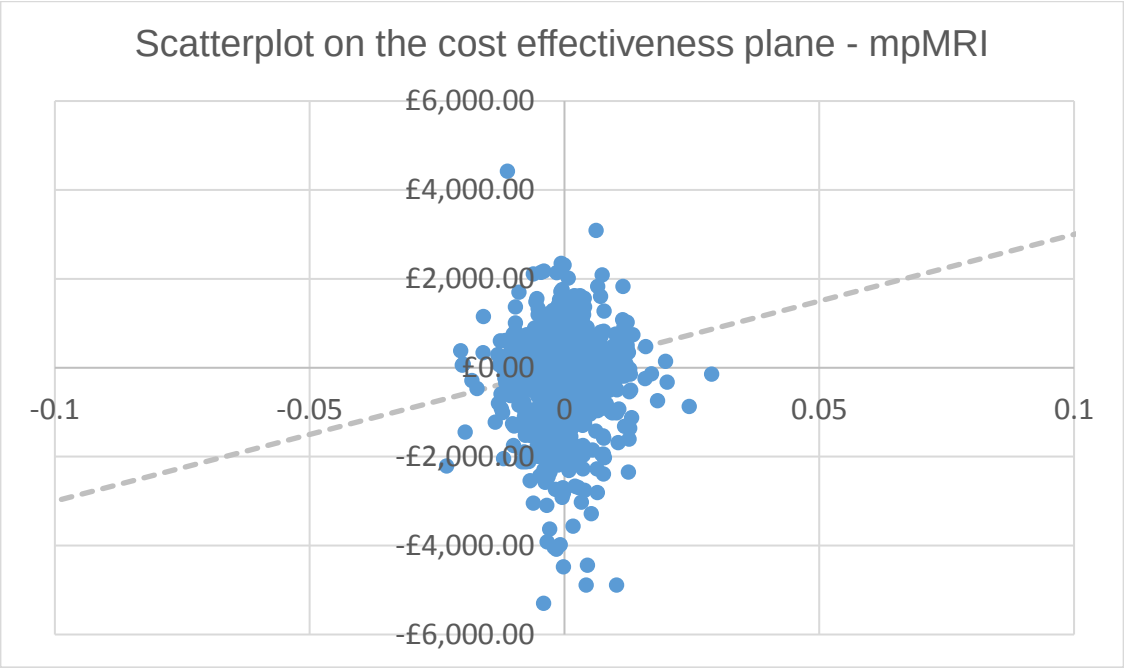


Figure 5.21 – Cost-effectiveness scatter plot of mpMRI for screening patients

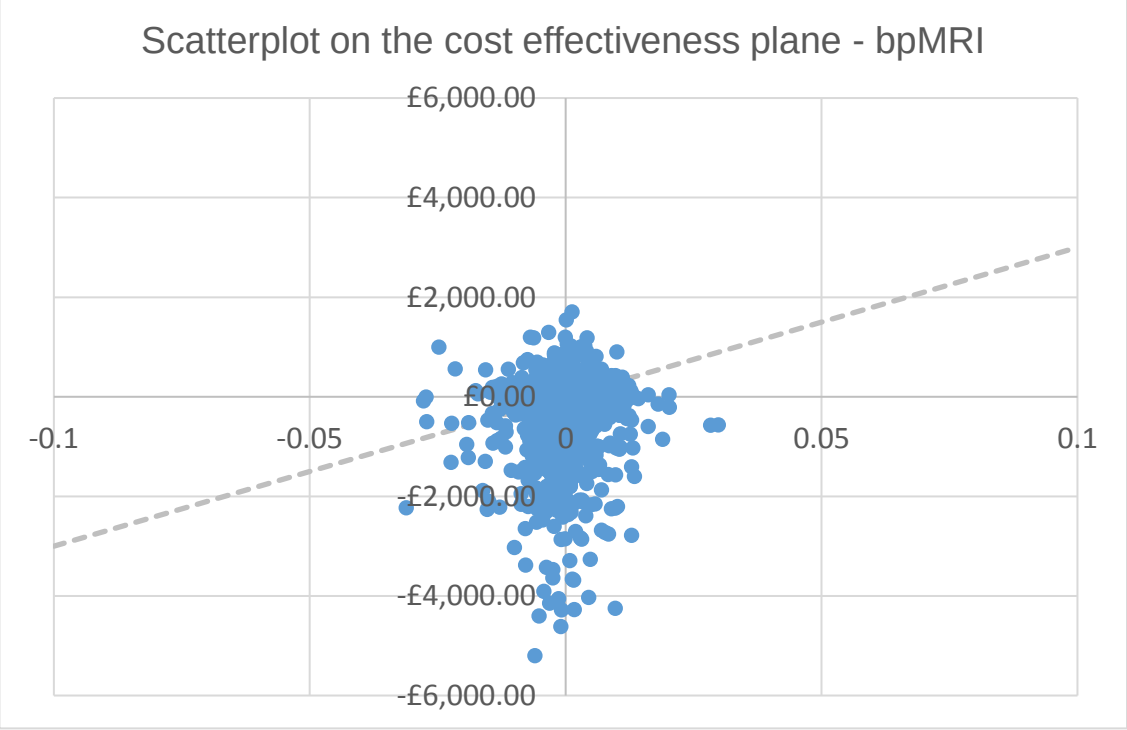


Figure 5.22 – Cost-effectiveness scatter plot of bpMRI for screening patients

Cost-effectiveness acceptability curves (CEACs) show MRI pathways were more likely to be cost-effective than PSA pathways regardless of the Willingness To Pay (WTP) threshold, with a much higher probability for bpMRI compared to mpMRI (see figures 5.23 – 5.26).

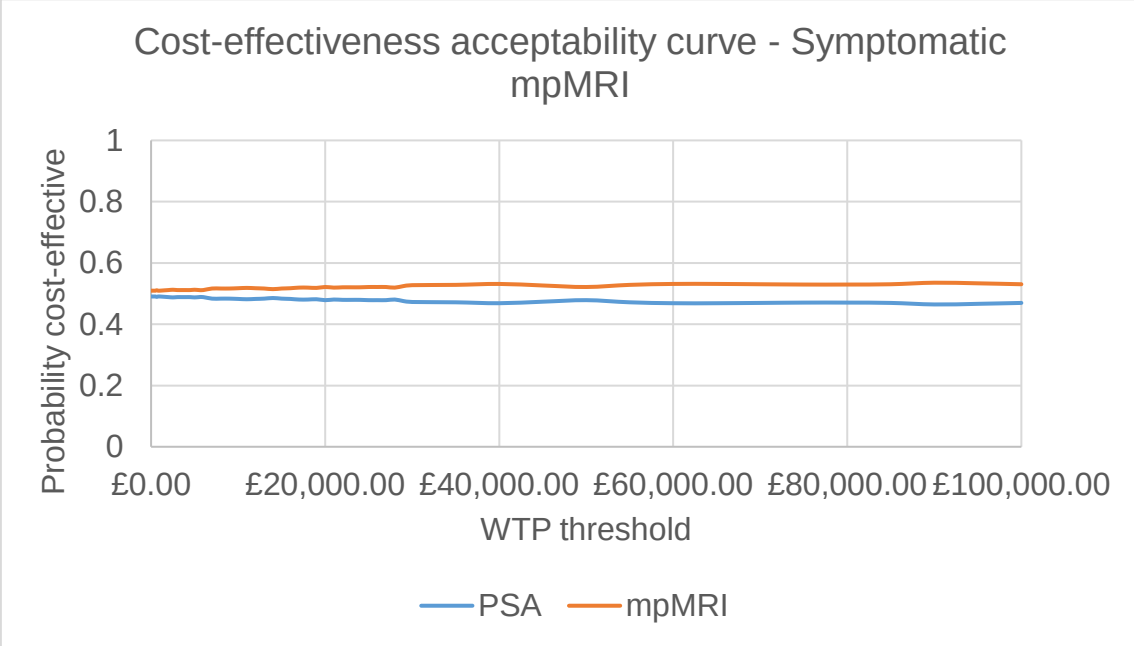


Figure 5.23 – Cost-effectiveness acceptability curve of mpMRI for symptomatic patients

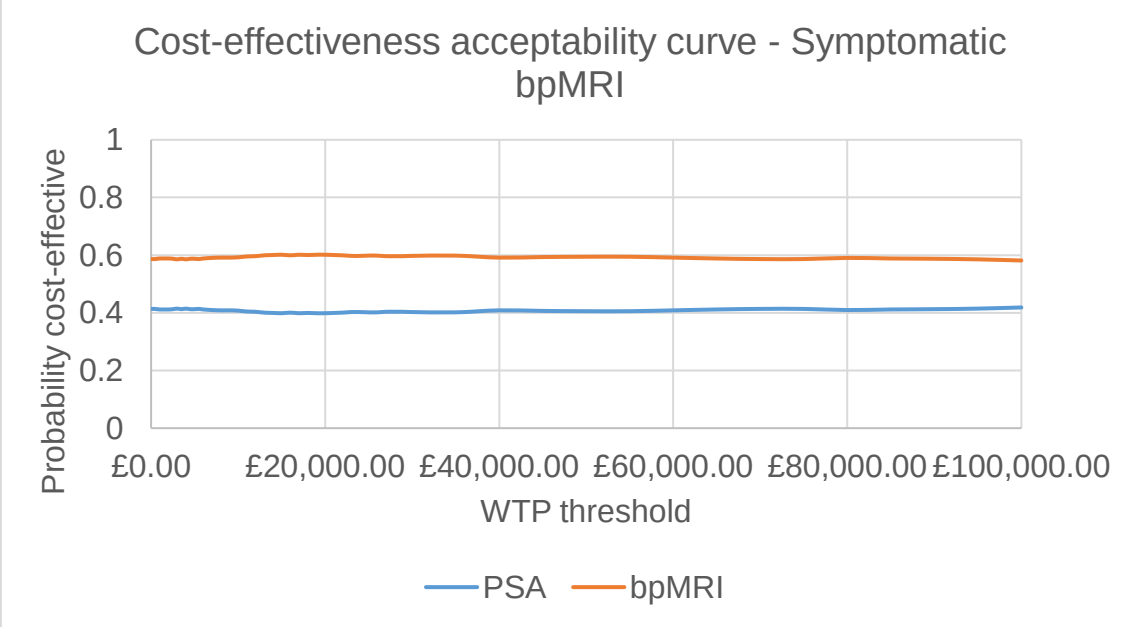


Figure 5.24 – Cost-effectiveness acceptability curve of bpMRI for symptomatic patients

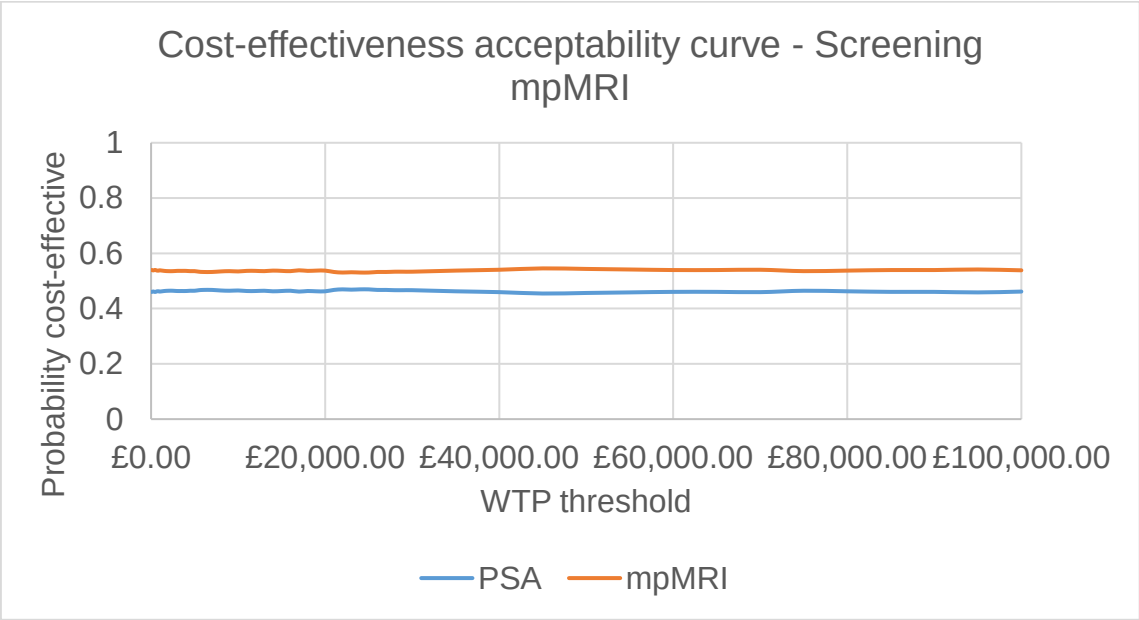


Figure 5.25 – Cost-effectiveness acceptability curve of mpMRI for screening patients

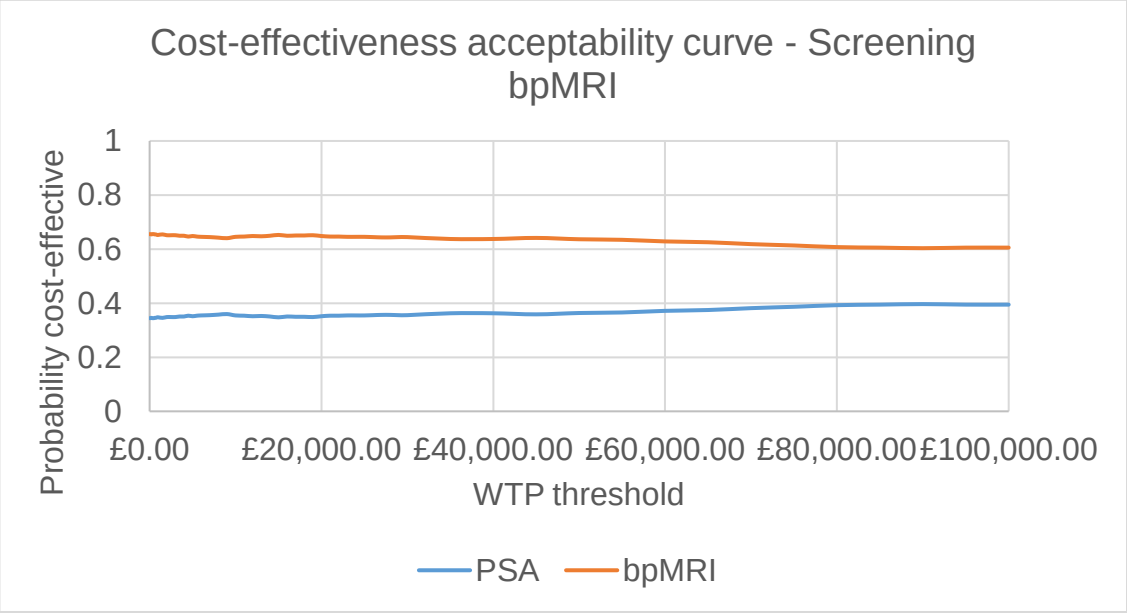


Figure 5.26 – Cost-effectiveness acceptability curve of bpMRI for screening patients

5.5 Discussion

Main findings

This early economic evaluation of integrating prostate MRI into the primary care prostate cancer pathway suggests it is may be more cost effective than the current practice of relying on PSA as a triage test, both for symptomatic patients and patients undergoing opportunistic screening. Using prostate MRI in primary care to determine which patients to refer urgently for diagnostic testing for suspected prostate cancer would result in fewer urgent cancer referrals, with the trade-off of needing to perform more prostate MRIs than currently being performed and a small increase in the number of men with a missed diagnosis. bpMRI was more likely to be cost effective than mpMRI when each was compared to the current standard of care. Sensitivity analysis was consistent with the base case analysis for costs of the different pathways compared, but found a small utility decrement with MRI pathways (as opposed to a small utility gain in the base case analysis).

The differences in cost-effectiveness found between the MRI pathways and the existing PSA-based pathway appear to be largely driven by costs, given the differences in the utilities between the pathways were very small. This small utility difference also likely impacted on the sensitivity analyses, generating a small utility decrement in the probabilistic sensitivity analysis compared to a small utility benefit in the base-case analysis resulting in significantly different ICERs. Costs were consistently lower in the sensitivity analyses. The small utility differences also likely drove the findings of the CEACs, where MRI pathways were more likely to be cost-effective regardless of the WTP threshold. These findings highlight the need for better data to be able to confidently estimate the long-term effects of the diagnostic tests used for prostate cancer detection in primary care.

Comparison to existing literature

No known study has modelled the estimated costs and utilities of the current primary care prostate cancer diagnostic pathway, nor considered the potential impact of prostate MRI on the pathway. All cost-effectiveness analyses included in the systematic review of economic evaluations of pre-biopsy MRI based prostate cancer diagnostic pathways in Chapter four started with a referred

population already in secondary care. This study models the current standard of practice in primary care of using PSA and DRE (for symptomatic patients) to identify which patients would be referred for further testing and estimates how the integration of mpMRI or bpMRI for prostate cancer detection into primary care might impact on this part of the diagnostic pathway.

Some published cost-effectiveness analyses focus on the use of prostate MRI as part of prostate cancer screening, using PSA to identify men at higher risk of prostate cancer(43,183,184), whilst others consider the effect of prostate MRI for patients referred on the basis of abnormal DRE and/or PSA(44,178,180,181). Consistent with the results of this study, in both scenarios the use of pre-biopsy MRI was found to be more cost-effective than the current pathway. In addition to attempting to locate suspicious-looking lesions within the prostate, a pre-biopsy MRI can provide additional information for the Urologist or Radiologist to perform an MRI-targeted biopsy. Biopsy-approach was not varied in this study, in contrast to other published economic evaluations where different biopsy approaches have been compared as part of the MRI-based diagnostic strategies.

Strengths & Limitations

This early economic evaluation has a number of strengths. A simple decision model was employed over a fixed time horizon to generate early estimates for the potential impact of an as-yet untested test in a primary care setting. Such an approach is appropriate to improve the interpretation of the findings and the reproducibility of the research. A linked data approach was undertaken to inform the model. This approach was in part due to necessity in the absence of a relevant trial of prostate MRI in primary care, but also allowed the integration of multiple data sources to generate a more robust analysis dataset. Sensitivity analyses broadly supported the base case findings, strengthening the confidence in the model outputs.

The findings of this modelling study need to be considered in the context of a number of limitations. Prostate MRI is not currently used in primary care in any country and there is no research evidence in this area, requiring assumptions to be made about the performance of the test in a primary care setting. Most of the

data from observational studies, trials and systematic reviews to inform study parameters was generated in secondary care settings, not primary care - where the focus of this study is. The majority of relevant studies on the performance of PSA for prostate cancer detection in patients with symptoms suffered from a high risk of bias and probably overestimated the accuracy of PSA. There is also no evidence for the accuracy of PSA in detecting clinically significant prostate cancer, nor for other clinical features used in primary care to identify patients with suspected prostate cancer such as a DRE. This limitation makes estimating the impacts of changes to the primary care prostate cancer diagnostic on treatments and outcomes in the long-term difficult.

Implications for practice

Evidence from clinical trials in the UK (54,254,255)(53) and other high-income countries shows that pre-biopsy prostate mpMRI is accurate in the detection of clinically significant prostate cancer. Prostate MRI also provides valuable information for guiding prostate biopsy. There is growing evidence that bpMRI is non-inferior to mpMRI in the detection of clinically significant prostate cancer, and benefits from being a quicker and cheaper test without the need for intravenous contrast(35). Prostate MRI is currently only used in secondary and tertiary care settings. By comparison, the limited evidence base for tests for prostate cancer detection in primary care such as PSA and DRE suggest they perform less well and it is not known whether these tests are able to accurately distinguish between clinically significant and clinically insignificant prostate cancer, which has important implications for treatment decisions and patient outcomes. This modelling study suggests integrating prostate MRI into the primary care diagnostic pathway could have significant benefits for patients and health services in the form of fewer urgent suspected cancer referrals and subsequent prostate biopsies. Direct access for primary care clinicians to cancer diagnostic tests is established for other cancer types, including upper and lower gastrointestinal cancers(256). Prostate MRI is potentially implementable for prostate cancer detection in primary care, but further research and more extensive modelling studies informed by stronger evidence (when available) is needed to confirm these earl findings.

5.6 Conclusions

Integration of prostate MRI into the primary care diagnostic pathway as a triage test to identify patients presenting in primary care who have a higher risk of prostate cancer and warrant urgent suspected prostate cancer referral for a prostate biopsy could potentially reduce costs for the health service. bpMRI is more likely than mpMRI to be cost effective in the proposed strategies. This early economic evaluation in primary care suggests prostate MRI could play a role in reducing avoidable referrals. Most evidence sources used to inform the models were not based in primary care settings, and the limitations of the evidence base impacted on the ability to accurately estimate longer-term treatment and survival outcomes.

Chapter 6 - Discussion

This chapter builds on the brief discussion sections at the conclusion of each research chapter to highlight the key findings of the research undertaken for this thesis, consider the findings in the context of the wider research, healthcare design and policy context, and identify further unanswered research questions that arise from this PhD.

6.1 Summary of findings

Chapter 2 outlined a systematic review and narrative synthesis of patient centred outcomes (PCOs) from diagnostic tests for prostate cancer. Evidence was available for physical and emotional outcomes related to transrectal ultrasound guided (TRUS) biopsy of the prostate, as well as mpMRI and MRI-guided biopsy. Included studies found that for most reported measures mpMRI and MRI guided biopsy had a lower risk of adverse physical and emotional outcomes for patients. These studies lacked consistency in the measures used for PCOs, did not demonstrate evidence of patient engagement with the identification of PCOs to measure, and did not report any PCOs relating to social, cognitive or behavioural impacts on patients.

Chapter 3 outlined a qualitative interview study with 22 patients who had undergone prostate MRI as part of the diagnostic work-up for suspected prostate cancer, and ten GPs who had recently referred at least one patient with suspected prostate cancer within the last 12 months. Key themes emerging from patient interviews centred on cancer beliefs, communication regarding testing strategies and results, and their pathway experience. GP interviews elicited themes on imperfect information with which they assess patients that might have undiagnosed prostate cancer, managing uncertainty with their patients, and the contextual influences on the consultation. Prostate MRI appeared to be an acceptable test for patients, meeting most key constructs of Sekhon's Theoretical Framework of Acceptability.

Chapter 4 outlined a systematic review and narrative synthesis of full economic evaluations of prostate cancer diagnostic pathways that incorporated pre-biopsy prostate MRI. Following title and abstract screening and full text assessment

against the inclusion criteria by myself and a second reviewer, eight papers were included in the narrative synthesis. Included studies were all based in high-income countries with long time horizons, featuring a wide range of clinical settings, patient populations, modelled pathways, and key parameters. Despite the heterogeneous nature of the included studies, they consistently demonstrated that prostate cancer diagnostic pathways that incorporate pre-biopsy prostate MRI were more cost-effective than pathways relying on ultrasound guided biopsy as the diagnostic test. All included studies started at the point of referral to secondary care, without any modelling of patient selection for referral in primary care.

Chapter 5 outlined the early economic evaluation of prostate MRI as a diagnostic test for prostate cancer in primary care. I undertook decision analytic modelling to compare the existing primary care elements of the prostate cancer diagnostic pathway with use of prostate MRI as a further triage test following an abnormal prostate specific antigen (PSA) test in primary care to determine which patients may need referral for biopsy in secondary care. I performed a cost-utility analysis using a linked data approach, with data from primary studies, systematic reviews, secondary data analysis and NHS reference costs feeding into the model. Base case analysis showed prostate MRI pathways using mpMRI or biparametric MRI (bpMRI) dominated existing pathways. Sensitivity analyses suggested integrating prostate MRI into primary care pathways would result in costs savings with a small decrement in utility. Utility differences between the modelled pathways were very small, leading to significant uncertainty in the sensitivity analyses. Outcomes were modelled on a 12-month time horizon, so it is unclear what the long-term impacts of implementing prostate MRI in primary care might be.

Overall, the evidence I have generated within this PhD adds to the understanding of the impact on clinical decision making and health outcomes for patients with the use of prostate MRI within the prostate cancer diagnostic pathway. This evidence mostly falls within phase 3 of the CanTest framework for evaluating and implementing diagnostic tests (see Chapter 1). There is some evidence for better patient centred outcomes from prostate MRI and MRI-guided biopsy relative to the existing standard diagnostic tests (TRUS biopsy).

Prostate MRI appears to be an acceptable test for patients, although GP understanding and acceptability of prostate MRI is less clear from the evidence gathered. Published studies suggest integrating pre-biopsy prostate MRI into clinical pathways in secondary care is cost-effective and modelling in this PhD estimated cost-savings for the health service with primary care use of pre-biopsy prostate MRI as a triage test for referral for biopsy.

6.2 Comparison with existing literature

Primary care use of prostate MRI for patients with suspected prostate cancer to identify patients needing biopsy and those who could safely avoid biopsy is not current clinical practice anywhere in the UK or internationally, as far as can be established. A consensus panel of specialists considering implementation of mpMRI for prostate cancer in the UK convened in 2018 recommended against primary care use of mpMRI, which is probably not surprising given there was no primary care representation within the panel and no previous experience in the NHS or internationally using prostate MRI in this clinical setting(257). It is relatively common for new diagnostic tests to be implemented in secondary and tertiary care settings initially for specialist use only, and with time their use becomes more liberalised. PSA testing followed a similar path after introduction into clinical practice for prostate cancer detection(258). Aside from the research I undertook in this PhD, there are no published studies of evaluations or modelling of direct access prostate MRI from primary care for prostate cancer detection.

Direct access to cancer diagnostic testing from primary care has precedent in the NHS and other health systems internationally. Regional variation in the UK does exist, but GPs in some areas can already access urgent imaging for suspected cancer, such as Computerised Tomography (CT) of the abdomen for suspected pancreatic cancer or CT or MRI of the head for suspected brain tumours(259). GPs can also refer directly for endoscopic procedures for suspected cases of upper or lower gastrointestinal (GI) cancers. Friedemenn Smith *et al* reviewed the evidence for direct access to cancer testing in primary care to establish the proportion of patients diagnosed with cancer and other diseases, the time to diagnosis, and patient and GP satisfaction. No studies included in the review assessed direct access for prostate cancer diagnostic

testing. Pooled conversion rates for cancer diagnosis were higher from primary care referral for lower GI endoscopy compared to specialist referral, but the reverse was found for upper GI endoscopy. There were insufficient studies to determine pooled conversion rates for other diagnostic tests, although measures of appropriateness of referrals used in individual included studies did not find any significant difference between diagnostic testing referrals originating from primary or secondary care. Overall, time to testing was faster with direct access to testing from primary care, but time to diagnosis was similar between primary care and specialist referrals. GP and patient satisfaction was consistently high across included studies. The quality of the included studies was assessed as low(49). Only three studies of direct access to MRI were found by the reviewers; two were focused on MRI of the brain(260,261) and the other on primary care MRI referrals for any indication, including non-cancer diagnoses(262). All three studies suggested direct access to MRI reduced hospital referrals, similar to the modelling results in this PhD, with high patient and GP satisfaction. Results for the detection of serious diseases with direct access MRI were mixed.

Despite recommendations against regular PSA screening for patients without any symptom of prostate cancer from the UK National Screening Committee(263), opportunistic PSA screening following a discussion about the risks and benefits in primary care still occurs in clinical practice(205). Given the reported benefits of increased detection of clinically significant prostate cancer and reduced detection of clinically insignificant prostate cancer with pre-biopsy prostate MRI, the role of MRI in prostate cancer screening has also been explored. Evidence from trials(254) and health economic modelling(43) of organised PSA-based prostate cancer screening programmes suggest that incorporating pre-biopsy prostate MRI for asymptomatic patients with raised PSA levels reduces overdiagnosis of clinically insignificant prostate cancer and could be cost-effective compared to using TRUS biopsy in this setting. These studies followed different approaches to screening compared to the modelling of my PhD, which focused on the current UK practice of opportunistic screening. However, pre-biopsy prostate MRI as part of asymptomatic screening was still shown to improve the detection of clinically significant prostate cancer and be cost-effective. Eldred-Evans *et al* undertook a pilot study comparing three

prostate cancer tests for screening in patients recruited from GP practices in London: serum PSA, a short prostate MRI protocol, and prostate ultrasound. The study found setting a higher threshold for further investigation (PIRADS 4-5) following a screening prostate MRI scan in a primary care asymptomatic population could increase detection of clinically significant prostate cancer without an increase in biopsy rates or over-detection of clinically insignificant prostate cancer compared to PSA alone(249). Further research in larger study populations is needed to confirm the utility of prostate MRI screening.

The current recommended primary care prostate cancer diagnostic pathway relies on PSA and Digital Rectal Examination (DRE) in patients presenting with symptoms to identify patients for onwards referral for diagnostic testing(24). Patients undergoing opportunistic PSA screening in the UK are also referred if they have an abnormal PSA. Modelling in this PhD added prostate MRI as a further triage test in these patient populations (see Chapter 5). The combination of prostate MRI with tests other than PSA has also been explored to determine the ability to improve the detection of prostate cancer compared to MRI and/or PSA alone. PSA density (PSAd) is one such measure. PSAd is calculated by dividing PSA (ng/mL) by the volume of the prostate gland (mL), giving a measure in ng/mL^2. Prostate volume can be estimated clinically via DRE, or with imaging using TRUS or MRI data(264). Studies comparing the performance of prostate MRI alone versus MRI in combination with PSAd found that a greater number of patients can safely avoid prostate biopsy with minimal increases in missed diagnoses of clinically significant prostate cancer. PIRADS and PSAd thresholds for the optimal balance of sensitivity and specificity varied between studies(265–269). Other biomarkers for prostate cancer not currently in clinical use in the UK that have been tested in combination with prostate MRI include the Prostate Health Index (PHI)(212,270), 4K score (271), and Prostate Cancer Antigen 3 (PCA3)(272). These studies also show potential improvements in identifying patients with clinically significant prostate cancer prior to biopsy. Combining mpMRI with a second imaging modality, Prostate-Specific Membrane Antigen Positron Emission Tomography Computerised Tomography (PSMA PET-CT), was evaluated in a recent prospective, multicentre phase 2 trial in high-risk men, showing improved sensitivity and negative predictive value for clinically significant prostate cancer(273). It is

currently not known which tests, or combination of tests, provides the optimal diagnostic pathway for accurately diagnosing clinically significant prostate cancer and reducing the risk of overdiagnosis of clinically non-significant prostate cancer. The economic models developed for my PhD could be extended to incorporate such tests, with sufficient data, to determine if they perform better than currently recommended clinical practice.

Risk adapted approaches to prostate cancer screening and symptomatic diagnosis in primary care are another potential avenue to improve outcomes for patients with prostate cancer. Risk prediction tools, incorporating a range of demographic, clinical, biomarker, imaging, and pathology data, allow relevant determinants of risk of disease to be combined to improve detection of undiagnosed disease or predict future diagnoses(274). Numerous examples of published prostate cancer risk prediction models exist, but very few have been validated in multiple study populations for the prediction of clinically significant prostate cancer(275) and the impact on clinical decision making and the cost-effectiveness of these models is largely unknown(274). With the advent of prostate MRI, data from mpMRI and bpMRI has been integrated into new and existing models; however only one has been externally validated(276). In a review of prostate cancer models that could potentially be applied at low-cost in a primary care setting, only five models met the criteria set by Aladwani *et al*. One had been externally validated and none incorporated prostate MRI(277). Prostate cancer risk prediction tools could be used to stratify patients prior to prostate MRI or models could incorporate MRI data to determine the risk of clinically significant prostate cancer and inform decisions for referral for prostate biopsy. Either approach could be explored by extending the models developed in my PhD to inform the integration of prostate MRI into clinical practice in primary care in future. Exploration of patient and clinician acceptability of risk stratified approaches to cancer diagnosis in primary care is also an under-explored area that is needed before these tools are implemented in clinical practice.

Prostate MRI, like all diagnostic tests, is not a perfect test, and has some limitations that need to be considered if it were to be used for prostate cancer detection in primary care. Sensitivity of mpMRI for clinically significant prostate

cancer has been estimated to be 91% (95% confidence interval 83%, 95%); meaning potentially up to 17% of patients with prostate cancers that would benefit from early detection could be missed (or at least have a delayed diagnosis) with pre-biopsy mpMRI(29). Additional analyses of the PROMIS trial data showed that tumours missed by mpMRI were significantly more likely to have lower Gleason scores and smaller size compared to those that were detected, and no tumours with Gleason Grade Group 3-5 were missed(278). The key factors that influence the performance of mpMRI in the detection of clinically significant prostate cancer are the experience of the radiologist in reporting and interpreting prostate MRI images and the experience of the urologist or radiologist undertaking the prostate biopsy following MRI(30). This is important, as it affects the confidence in generalising from the findings of studies such as the PROMIS trial that follow strict trial protocols to real world settings. Access to MRI scanners and workforce shortages in diagnostics in the NHS present additional potential barriers to the implementation of prostate MRI in primary care (see 'Implications for policy, practice & research' below). Additionally, interviews with GPs in this PhD (see Chapter 3) uncovered a very mixed understanding of prostate MRI and the role it plays in the diagnosis of prostate cancer. This needs further exploring as education and awareness initiatives regarding prostate MRI targeted at GPs will be needed prior to any implementation of prostate MRI for prostate cancer detection in primary care. Combining prostate MRI with other tests that can be implemented in primary care, such as PSAd, and artificial intelligence (AI) assisted image interpretation could also improve the performance of prostate MRI in this clinical setting.

6.3 Implications for policy, practice & research

Increasing the proportion of patients diagnosed with cancer at an early stage is a strategic priority for the NHS in England, with a target of 75% of new cancer diagnoses to be identified at stage 1 or 2 by 2028 set in the NHS Long Term Plan(46). The proportion of early-stage prostate cancer diagnoses in England and Wales stood at 54% in 2018, prior to the COVID-19 global pandemic which has reduced the numbers of patients in England being diagnosed with prostate cancer(4) and has potentially impacted on early diagnosis of the disease. Increasing access to diagnostics directly from primary care could reduce the time taken for patients with suspected cancer to undergo diagnostic testing and

speed up diagnosis, leading to increased early-stage diagnosis and improve outcomes for patients. Following publication of the NHS Long Term Plan in 2019, Professor Sir Mike Richards, the first national cancer director for NHS England, was commissioned to undertake an independent review of NHS diagnostic services. A key recommendation of the Richards report was the development of community diagnostic hubs outside acute hospitals. These centres would be able to separate emergency from elective and urgent diagnostics, deliver diagnostic testing closer to patient's homes, and mitigate the risk of the spread of COVID-19 from the community to acute hospitals and vice versa(279). An initial tranche of 40 community diagnostic centres was announced by NHS England in October 2021, with the aim of being operational by April 2022(280). Soon after this announcement, the funding allocated for community diagnostic centres was increased by the Chancellor in the UK Government's Autumn Budget and Spending Review to support the establishment of 100 centres(281). Direct access to prostate MRI within these community diagnostic centres in the future could be a potential vehicle for implementation if further research confirms the benefits for patients and the health service suggested from my PhD.

Increasing primary care access to diagnostics needs to be considered in the context of the current challenges faced by healthcare services to meet current demand for radiology investigations. The NHS has a number of significant infrastructure and workforce limitations that may hamper the roll out of the proposed community diagnostic centres and could affect direct access to prostate MRI if this was added into the prostate cancer diagnostic pathway in the future. The UK has amongst the lowest number of MRI scanners in the Organisation for Economic Cooperation and Development (OECD) countries (7.8 units per million population)(282). The NHS also has a serious diagnostic workforce shortage, including radiographers to organise and perform the diagnostic investigations and radiologists to interpret the results. The Royal College of Radiologists estimates that the NHS has a current shortage of 1,939 radiologists, equivalent to 33% of the workforce, and this shortfall is forecast to increase to 3,600 radiologists (44% of the workforce) by 2025(283). The *Diagnostic Radiography Workforce UK Census* undertaken by the College of Radiographers in 2020 showed an average vacancy rate of radiographers in the

UK of 10.5%(284). Modelling I undertook in this PhD demonstrated a significant increase in the number of patients requiring prostate MRI, assuming that GPs followed the new proposed diagnostic pathway for all patients with an elevated PSA, relative to current practice. This would potentially be difficult to implement without addressing the current problems in NHS diagnostics and could create significant waiting times for MRI scans for men with suspected prostate cancer and patients awaiting MRI for other clinical indications. The impact of the COVID-19 pandemic on diagnostic waiting times has meant hundreds of thousands of NHS patients are waiting longer for diagnostic tests(285), and the existing workforce shortages will likely mean this backlog takes a long time to clear. Alterations to testing in NHS diagnostic pathways in the short- to medium-term future will need to take this into account, and innovative solutions such as AI-assisted MRI interpretation may help address these challenges.

A key potential benefit for patients in the application of prostate MRI for suspected prostate cancer is the high negative predictive value of the test, allowing a significant proportion of patients to safely avoid an invasive prostate biopsy. This is estimated to be possible for up to 31% of patients currently undergoing pre-biopsy prostate MRI(29). However, as discussed earlier in this chapter, mpMRI and bpMRI are not 100% accurate, and the use of pre-biopsy prostate MRI to determine whether a patient should progress to a prostate biopsy or not will result in delayed diagnosis of prostate cancer for a small number of patients. Current NICE guidance for prostate cancer diagnosis and management has the following recommendation(12):

> 1.2.4 Consider omitting a prostate biopsy for people whose multiparametric MRI Likert score is 1 or 2, but only after discussing the risks and benefits with the person and reaching a shared decision

Integration of prostate MRI into the primary care prostate cancer diagnostic pathway would mean that GPs would be having this conversation with patients about referral to a Urologist for a prostate biopsy or not, rather than specialists. GPs have an awareness of the limitations of tests currently available in primary care for detecting cancer and making decisions about onwards referral, including PSA, so this clinical scenario would not be new. However, interviews

with GPs regarding prostate MRI in Chapter 3 of this PhD suggested there is a spectrum of knowledge, understanding and confidence with regards to the use of MRI for prostate cancer detection, and further education and support for GPs will be needed if prostate MRI was used in primary care in the future.

There are a number of pragmatic issues that could potentially affect the implementation of prostate MRI in primary care. Access to MRI from primary care already varies on a local and regional basis. GPs from Devon who were interviewed for Chapter 3 described only being able to order MRI scans for their patients in very specific circumstances, whereas GPs in London generally had wider access. Patients may also have to travel long distances for an MRI scan, particularly those living in more rural areas such as North Devon. Increased demand on MRI scanners from GPs ordering prostate MRIs as part of the modelled pathways in Chapter 5 would increase the pressure on an already stretched diagnostic workforce as outlined above, so accessing urgent prostate MRI scans in a timely manner may prove challenging. GPs would need to confidently interpret the prostate MRI report and know the features that necessitate urgent onward referral for further investigation, and insights gained from GP interviews suggest this would require significant education and support for GPs to ensure successful implementation.

The technology in prostate MRI for the detection of prostate cancer continues to evolve, even since publication of the PROMIS trial results in 2017. Biparametric MRI (bpMRI), omitting the use of contrast enhancement needed for mpMRI, is faster, cheaper, and does not expose the patient to risks associated with intravenous contrast injection(286), and appears to be non-inferior to mpMRI for the detection of clinically significant prostate cancer(35). Shorter prostate MRI protocols are currently under investigation to determine how simplified the process can be whilst retaining diagnostic accuracy(287). The application of AI in the processing and interpretation of prostate MRI imaging data could potentially improve the accuracy of prostate cancer diagnosis and address some of the medical workforce shortages in radiology through automation of reporting(288). Radiomics, the high-throughput extraction of medical imaging features converted to data that can be quantitatively analysed, can also be applied to MRI imaging data. Radiomics models have the potential to improve

the utility of prostate MRI for diagnosing clinically significant prostate cancer(289). Continuing rapid advances in MRI technology could make integration of prostate MRI into primary care more feasible and retain the level of diagnostic accuracy demonstrated in secondary and tertiary care settings.

Economic evaluation of diagnostic tests generate evidence regarding the cost-effectiveness of implementing new tests or changing the clinical use of existing tests in a diagnostic pathway and can be very informative for policymakers and healthcare decision-makers. The systematic review in Chapter 4 of full economic evaluations of prostate cancer diagnostic pathways that incorporate pre-biopsy MRI showed a complete lack of evidence with regards to the primary care element of the pathway. A rapid review of the literature on the cost effectiveness for primary care systems for diagnosing any cancer undertaken by the UK Department of Health Policy Research Unit in Economic Evaluation of Health and Care Interventions (EEPRU) in 2014 also did not discover any studies relating to prostate cancer diagnosis in primary care. The review did identify two US studies of imaging techniques for low back pain to identify undiagnosed cancers, which are potentially relevant as prostate cancer may present with new onset lower back pain. One study included the use of MRI of the lumbar spine and found this not to be cost-effective(290). Modelling in Chapter 5 of this PhD performed early economic evaluation of the current primary care prostate cancer diagnostic pathway and sought to estimate the potential impact of integrating pre-biopsy prostate MRI in primary care. Extension of the modelling undertaken I have undertaken and further economic evaluation of alternative prostate cancer diagnostic strategies in primary care could assist with improving the diagnosis of clinically significant prostate cancer at an early stage.

6.4 Future research directions

The research I have undertaken for this PhD has generated a number of new research questions in relation to prostate cancer diagnosis in primary care and the potential role of prostate MRI. GPs were clear that the currently available examinations and tests to detect prostate cancer in primary care have significant limitations and are not always acceptable to patients. Section 5.3.2 of Chapter 5 demonstrated the absence of primary care evidence for the currently

recommended use of PSA for assessing symptomatic patients presenting to their GP, which needs addressing to inform clinical practice. Alternative tests and risk stratification approaches to help GPs identify patients needing referral for prostate biopsy could improve care for patients. Prostate MRI presents a potential new diagnostic test for primary care; however, interviews I undertook with GPs in Chapter 3 of this PhD uncovered a range of levels of knowledge about prostate MRI and how it is used in the diagnostic pathway, and concerns about current access to MRI affecting confidence that GPs could one day be able to use prostate MRI for their patients. A large-scale questionnaire-based study of GP knowledge and awareness of prostate cancer diagnostic pathways and the role of prostate MRI may prove useful to further explore the understanding of GPs of these tests and their information needs prior to implementation. This study could also assess how GPs feel about using additional diagnostic tests in primary care for early prostate cancer detection in the context of very significant primary care workloads and a chronic shortage of GPs in the NHS. Determining acceptability of prostate MRI amongst GPs was hampered by a lack of data and engagement by some GPs on the subject for this PhD and would ideally be explored further in future research.

Modelling I have undertaken as part of this PhD, outlined in Chapter 5, goes some way to filling an existing evidence gap regarding the cost-effectiveness of the prostate cancer pathway incorporating the primary care interval. The models I developed compare current practice of investigating symptomatic patients presenting to primary care and opportunistic screening of asymptomatic patients against a primary care diagnostic pathway that incorporates pre-biopsy prostate MRI to inform clinical triage and decision-making for onward referral to secondary care. As discussed earlier in this chapter, there are other tests that could also be incorporated to improve the identification of patients with clinically significant prostate cancer alongside prostate MRI. Risk stratification models can be used to identify patients at high risk of prostate cancer in primary care, and these tools could also be incorporated into the diagnostic pathway. The models developed in this PhD could be extended to incorporate combinations of triage tests and/or risk stratification models in addition to PSA and MRI to determine optimal diagnostic strategies for prostate cancer detection in primary care.

Implementation of new diagnostic tests into clinical practice should ideally be informed by research covering a range of aspects of testing, including patient and clinician acceptability, patient reported outcomes(41,42). Interviews with patients reported on in Chapter 3 of this PhD suggest that prostate MRI is an acceptable test, meeting many of the key constructs in Sekhon's Theoretical Framework of Acceptability(124). A systematic review of patient-reported outcomes from diagnostic tests for prostate cancer in Chapter 2 demonstrated an absence of evidence for the social, behavioural and cognitive effects of these tests on patients. Future studies of prostate cancer diagnostic tests should incorporate these assessments and engage with patients on the choice of appropriate outcome measures that matter to them.

An overall view of the evidence generated in my PhD suggests that the concept of primary care direct access to prostate MRI for the investigation of patients with suspected prostate cancer merits further exploration. In the event that further research consistently demonstrates benefits for patients and the health service, and potential for engagement with GPs in using this new diagnostic test in a primary care setting, then piloting direct access of prostate MRI from primary care could be undertaken and evaluated prior to any larger diagnostic cohort studies being performed. Widening the use of prostate MRI for prostate cancer detection would be contingent on increasing MRI scanner capacity within the NHS and finding solutions to the current diagnostic workforce challenges.

6.5 Conclusions

Prostate MRI is a relatively new, non-invasive, more accurate test for prostate cancer compared to the existing tests used in clinical practice in the form of PSA and TRUS biopsy. It is rapidly being adopted within national guidelines in the UK and internationally and will likely be a key test for patients with suspected prostate cancer going through the diagnostic pathway in the future. The optimal MRI sequence(s) used and integration of prostate MRI with other tests and methods of risk stratification within the diagnostic pathway is still to be determined. Prostate MRI could have a role in the early detection of prostate cancer in primary care and would likely outperform currently available tests and

examinations for GPs. Prior to the realisation of this new application of prostate MRI, it must be demonstrated that the diagnostic performance in primary care is non-inferior compared to secondary care, patient outcomes are improved relative to the existing pathway, and it remains cost-effective for health services to implement in a primary care setting.

Bibliography

1. Zhai Z, Zheng Y, Li N, Deng Y, Zhou L, Tian T, et al. Incidence and disease burden of prostate cancer from 1990 to 2017: Results from the Global Burden of Disease Study 2017. Cancer. 2020;1969–78.
2. Royal College of Surgeons of England. Results of the NPCA Prospective Audit in England and Wales for men diagnosed from 1 April 2018 to 31 March. London; 2021.
3. Cancer Research UK. Prostate cancer statistics.
4. NCRAS. CancerData. 2021 [cited 2021 Sep 2]. Available from: https://www.cancerdata.nhs.uk/
5. Lloyd T, Hounsome L, Mehay A, Mee S, Verne J, Cooper A. Lifetime risk of being diagnosed with, or dying from, prostate cancer by major ethnic group in England 2008-2010. BMC Medicine. 2015;13(1):1–10.
6. Mucci LA, Hjelmborg JB, Harris JR, Czene K, Havelick DJ, Scheike T, et al. Familial risk and heritability of cancer among twins in Nordic countries. JAMA - Journal of the American Medical Association. 2016 Jan 5;315(1):68–76.
7. Sandhu S, Moore CM, Chiong E, Beltran H, Bristow RG, Williams SG. Prostate cancer. Lancet. 2021 Aug 6;
8. Royal College of Pathologists. TNM classification of prostatic carcinomas (UICC TNM 8). 2017 [cited 2021 Sep 2]. Available from: https://www.rcpath.org/profession/guidelines/cancer-datasets-and-tissue-pathways.html#
9. Gleason DF. Histologic Grading of Prostate Cancer: A Perspective. Human Pathology. 1992;23:273–9.
10. JLH van Leenders G, van der Kwast TH, Grignon DJ, Evans AJ, Kristiansen G, Kweldam CF, et al. The 2019 International Society of Urological Pathology (ISUP) Consensus Conference on Grading of Prostatic Carcinoma. American Journal of Surgical Pathology. 2020;44:e87–99.
11. Matoso A, Epstein JI. Defining clinically significant prostate cancer on the basis of pathological findings. Histopathology. 2019;74:135–45.
12. NICE. Prostate Cancer: Diagnosis and Management. ng131. London: National Institute for Health and Care Excellence; 2019.
13. Amico AVD, Whittington R, Malkowicz SB, Schultz D, Blank K, Broderick GA, et al. Biochemical Outcome After Radical Prostatectomy, External Beam Radiation Therapy, or Interstitial Radiation Therapy for Clinically Localized Prostate Cancer. JAMA. 1998 Jan 1;280(11):969–74.
14. Østerø i Jákupsstovu J, Brodersen J. Do men with lower urinary tract symptoms have an increased risk of advanced prostate cancer? BMJ. 2018;361(1202):1–6. Available from: https://www.bmj.com/content/bmj/361/bmj.k1202.full.pdf
15. Donnelly DW, Vis LC, Kearney T, Sharp L, Bennett D, Wilding S, et al. Quality of life among symptomatic compared to PSA-detected prostate cancer survivors-results from a UK wide patient-reported outcomes study. BMC Cancer. 2019;19(1).
16. Hamilton W, Sharp DJ, Peters TJ, Round AP. Clinical features of prostate cancer before diagnosis: a population-based, case-control study. Br J Gen Pract. 2006;56(531):756–62.

17. Hamilton W, Sharp D. Symptomatic diagnosis of prostate cancer in primary care: a structured review. Br J Gen Pract. 2004;54(505):617–21.
18. Jones D, Friend C, Dreher A, Allgar V, Macleod U. The diagnostic test accuracy of rectal examination for prostate cancer diagnosis in symptomatic patients : a systematic review. BMC Family Practice. 2018;19:79.
19. Milford Ward A, Catto JWF, Hamdy FC. Prostate specific antigen: biology, biochemistry and available commercial assays. Annals of Clinical Biochemistry. 2001;38(6):633–51.
20. Harvey P, Basuita A, Endersby D, Curtis B, Iacovidou A, Walker M. A systematic review of the diagnostic accuracy of prostate specific antigen. BMC Urology. 2009;9(1):1–9.
21. Welch HG, Albertsen PC. Reconsidering Prostate Cancer Mortality — The Future of PSA Screening. New England Journal of Medicine. 2020;382(16):1557–63.
22. Ilic D, Djulbegovic M, Jung JH, Hwang EC, Zhou Q, Cleves A, et al. Prostate cancer screening with prostate-specific antigen (PSA) test: a systematic review and meta-analysis. BMJ. 2018;362:k3519.
23. US Preventive Services Task Force. Screening for Prostate Cancer: US Preventive Services Task Force Recommendation Statement. JAMA. 2018;319(18):1901–13.
24. NICE. Suspected cancer: recognition and referral. 2015 [cited 2021 Oct 13]. p. 1–95. Available from: https://www.nice.org.uk/guidance/ng12
25. Public Health England. Prostate Cancer Risk Management Programme (PCRMP): benefits and risks of PSA testing. PCRMP. 2016 [cited 2018 Nov 6]. Available from: https://www.gov.uk/government/publications/prostate-cancer-risk-management-programme-psa-test-benefits-and-risks/prostate-cancer-risk-management-programme-pcrmp-benefits-and-risks-of-psa-testing
26. Prostate Cancer UK. Prostate biopsy. Prostate tests. 2021 [cited 2021 Sep 20]. Available from: https://prostatecanceruk.org/prostate-information/prostate-tests/prostate-biopsy
27. Loeb S, Vellekoop A, Ahmed HU, Catto J, Emberton M, Nam R, et al. Systematic review of complications of prostate biopsy. European Urology. 2013 Dec 1;64(6):876–92.
28. Bass EJ, Orczyk C, Grey A, Freeman A, Jameson C, Punwani S, et al. Targeted biopsy of the prostate: does this result in improvement in detection of high-grade cancer or the occurrence of the Will Rogers phenomenon? BJU International. 2019 Oct 1;124(4):643–8.
29. Drost FJ, Osses DF, Nieboer D, Bangma CH, Steyerberg EW, Roobol MJ, et al. Prostate MRI, with or without targeted biopsy and standard biopsy for detecting prostate cancer: A Cochrane systematic review and meta-analysis. Cochrane Database of Systematic Reviews. 2019;(4):CD012663.
30. Stabile A, Giganti F, Rosenkrantz AB, Taneja SS, Villeirs G, Gill IS, et al. Multiparametric MRI for prostate cancer diagnosis: current status and future directions. Nature Reviews Urology. 2020 Jan 17;17(1):41–61.
31. Turkbey B, Rosenkrantz AB, Haider MA, Padhani AR, Villeirs G, Macura KJ, et al. Prostate Imaging Reporting and Data System Version 2.1: 2019 Update of Prostate Imaging Reporting and Data System Version 2. European Urology. 2019;0232:1–12.
32. Milot L. Variation of PI-RADS Interpretations between Experts: A Significant Limitation. Radiology. 2020;00:1–2.

33. Mussi TC, Baroni RH, Zagoria RJ, Westphalen AC. Prostate magnetic resonance imaging technique. Abdominal Radiology. 2020 Jul 7;45(7):2109–19.
34. EAU, EANM, ESTRO, ESUR, ISUP, SIOG. EAU-EANM-ESTRO-ESUR-ISUP-SIOG Guidelines on Prostate Cancer. 2021.
35. Bass EJ, Pantovic A, Connor M, Gabe R, Padhani AR, Rockall A, et al. A systematic review and meta-analysis of the diagnostic accuracy of biparametric prostate MRI for prostate cancer in men at risk. Prostate Cancer and Prostatic Diseases. 2020; Available from: http://dx.doi.org/10.1038/s41391-020-00298-w
36. Haider MA, Brown J, Yao X, Chin J, Perlis N, Schieda N, et al. Multiparametric Magnetic Resonance Imaging in the Diagnosis of Clinically Significant Prostate Cancer: an Updated Systematic Review. Clinical Oncology. 2021 Aug;
37. van Luijtelaar A, Bomers J, Fütterer J. A comparison of magnetic resonance imaging techniques used to secure biopsies in prostate cancer patients. Expert Review of Anticancer Therapy. 2019;19(8):705–16.
38. Kasivisvanathan V, Stabile A, Neves JB, Giganti F, Valerio M, Shanmugabavan Y, et al. Magnetic Resonance Imaging-targeted Biopsy Versus Systematic Biopsy in the Detection of Prostate Cancer: A Systematic Review and Meta-analysis. European Urology. 2019;44.
39. Chuang RJ, Marks LS. Targeted and Systematic Biopsy for Diagnosis and Management of Prostate Cancer. Clinical Oncology. 2020 Mar;32(3, SI):144–8.
40. Usher-Smith JA, Sharp SJ, Griffin SJ. The spectrum effect in tests for risk prediction, screening, and diagnosis. BMJ. 2016;353.
41. Bossuyt PMM, McCaffery K. Additional patient outcomes and pathways in evaluations of testing. Medical Decision Making. 2009;29(5):30–8.
42. Walter FM, Thompson MJ, Wellwood I, Abel GA, Hamilton W, Johnson M, et al. Evaluating diagnostic strategies for early detection of cancer: the CanTest framework. BMC Cancer. 2019;19(1):586. Available from: https://bmccancer.biomedcentral.com/articles/10.1186/s12885-019-5746-6
43. Callender T, Emberton M, Morris S, Pharoah PDP, Pashayan N. Benefit, Harm, and Cost-effectiveness Associated with Magnetic Resonance Imaging before Biopsy in Age-based and Risk-stratified Screening for Prostate Cancer. JAMA Network Open. 2021;4(3):1–12.
44. Faria R, Soares MO, Spackman E, Ahmed HU, Brown LC, Kaplan R, et al. Optimising the Diagnosis of Prostate Cancer in the Era of Multiparametric Magnetic Resonance Imaging: A Cost-effectiveness Analysis Based on the Prostate MR Imaging Study (PROMIS). European Urology. 2017;73(1):23–30. Available from: http://dx.doi.org/10.1016/j.eururo.2017.08.018
45. Norris JM, Kasivisvanathan V, Allen C, Ball R, Freeman A, Ghei M, et al. Exploring patient views and acceptance of multiparametric magnetic resonance imaging for the investigation of suspected prostate cancer (The pact study): A mixed-methods study protocol. Methods and Protocols. 2020;3(2):1–11.
46. NHS. The NHS Long Term Plan. NHS Long Term Plan. London; 2019.
47. NHS England. Implementing a timed prostate cancer diagnostic pathway. NHS; 2018.
48. National Cancer Intelligence Network. Routes to Diagnosis workbook 2006-2017. 2020 [cited 2020 Nov 20]. Available from: http://www.ncin.org.uk/publications/routes_to_diagnosis

49. Friedemann Smith C, Tompson AC, Jones N, Brewin J, Spencer EA, Bankhead CR, et al. Direct access cancer testing in primary care: a systematic review of use and clinical outcomes. British Journal of General Practice. 2018;(August):1–10.
50. Vickers AJ, Sjoberg DD, Ulmert D, Vertosick E, Roobol MJ, Thompson I, et al. Empirical estimates of prostate cancer overdiagnosis by age and prostate-specific antigen. BMC Medicine. 2014;12(1):1–7.
51. Grossman DC, Curry SJ, Owens DK, Bibbins-Domingo K, Caughey AB, Davidson KW, et al. Screening for prostate cancer: US Preventive services task force recommendation statement. JAMA - Journal of the American Medical Association. 2018;319(18):1901–13.
52. Heijnsdijk EAM, Bangma CH, Borràs JM, de Carvalho TM, Castells X, Eklund M, et al. Summary statement on screening for prostate cancer in Europe. International Journal of Cancer. 2018;142(4):741–6.
53. Ahmed HU, Bosaily AE-S, Brown LC, Gabe R, Kaplan R, Parmar MK, et al. Diagnostic accuracy of multi-parametric MRI and TRUS biopsy in prostate cancer (PROMIS): a paired validating confirmatory study. The Lancet. 2017 Jan 19;380:1–8. Available from: http://dx.doi.org/10.1016/S0140-6736(16)32401-1
54. Kasivisvanathan V, Rannikko AS, Borghi M, Panebianco V, Mynderse LA, Vaarala MH, et al. MRI-Targeted or Standard Biopsy for Prostate-Cancer Diagnosis. New England Journal of Medicine. 2018; Available from: http://www.nejm.org/doi/10.1056/NEJMoa1801993
55. Rouvière O, Puech P, Renard-penna R, Claudon M, Roy C, Mège-lechevallier F, et al. Use of prostate systematic and targeted biopsy on the basis of multiparametric MRI in biopsy-naive patients (MRI-FIRST): a prospective , multicentre , paired diagnostic study. Lancet. 2019;20:100–9.
56. Bossuyt PMM, McCaffery K. Additional patient outcomes and pathways in evaluations of testing. Medical Decision Making. 2009;29(5):30–8.
57. PCORI. Patient-Centered Outcomes Research Definition Revision: Response to Public Input. Washington DC: Patient-Centred Outcomes Research Institute; 2012. p. 1–6.
58. PCORI. PCORI - About us. 2011 [cited 2018 Nov 7]. Available from: https://www.pcori.org/about-us
59. PCORI. Rationale: Working Definition of Patient-Centered Outcomes Research. Washington DC: Patient-Centred Outcomes Research Institute; 2011. p. 1–7.
60. Smith S, Weldring T. Patient-Reported Outcomes (PROs) and Patient-Reported Outcome Measures (PROMs). Health Services Insights. 2013;61.
61. FDA. Patient-Reported Outcome Measures: Use in Medical Product Development to Support Labeling Claims. Rockville: U.S. Department of Health and Human Services Food and Drug Administration; 2009.
62. Beynon R, Leeflang MMG, McDonald S, Eisinga A, Mitchel RL, Whiting PF, et al. Search strategies to identify diagnostic accuracy studies in MEDLINE and EMBASE (Review). Cochrane Database of Systematic Reviews. 2013;(9).
63. de Vet HC, Eisinga A, Riphagen II, Aertgeerts B, Pewsner D. Chapter 7: Searching for studies. In: Cochrane Handbook for Systematic Reviews of Diagnostic Test Accuracy. The Cochrane Collaboration; 2008.
64. Mayo-Wilson E, Golozar A, Cowley T, Fusco N, Gresham G, Haythornthwaite J, et al. Methods to identify and prioritize patient-centered outcomes for use in comparative effectiveness research. Pilot Feasibility Stud. 2018;4(1):95.

65. Higgins JP, Savović J, Page MJ, Sterne JA, A H, I B, et al. Revised Cochrane risk-of-bias tool for randomized trials (RoB 2). 9 October 2018. Cochrane Database of Systematic Reviews. London: Cochrane Collaboration; 2018.
66. Slim K, Nini E, Forestier D, Kwiatkowski F, Panis Y, Chipponi J. Methodological index for non-randomized studies (MINORS): Development and validation of a new instrument. ANZ Journal of Surgery. 2003;73(9):712–6.
67. Carroll C, Booth A. Quality assessment of qualitative evidence for systematic review and synthesis: Is it meaningful, and if so, how should it be performed? Research Synthesis Methods. 2015;6(2):149–54.
68. Dixon-Woods M, Shaw RL, Agarwal S, Smith JA. The problem of appraising qualitative research. Quality and Safety in Health Care. 2004;13(3):223–5.
69. Majid U, Vanstone M. Appraising Qualitative Research for Evidence Syntheses: A Compendium of Quality Appraisal Tools. Qualitative Health Research. 2018;28(13):2115–31.
70. Critical Appraisal Skills Programme. CASP Qualitative Checklist. Oxford: Critical Appraisal Skills Programme; 2018.
71. Mueller M, D'Addario M, Egger M, Cevallos M, Dekkers O, Mugglin C, et al. Methods to systematically review and meta-analyse observational studies: a systematic scoping review of recommendations. BMC Medical Research Methodology. 2018;18(44):1–18.
72. Centre for Reviews and Dissemination. Systematic Reviews: CRD's guidance for undertaking reviews in health care. Centre for Reviews and Dissemination; 2009. p. 1–294.
73. Moher D, Liberati A, Tetzlaff J, Altman DG. Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Medicine. 2009 Jul 21;6(7):e1000097.
74. Cazarim GDS, Verçosa N, Carneiro L, Pastor R, da Silva EF V, Barrucand L, et al. A 50-50% mixture of nitrous oxide-oxygen in transrectal ultrasound-guided prostate biopsy: a randomized and prospective clinical trial. PLoS one. 2018;13(4):e0195574.
75. Giannarini G, Autorino R, Valent F, Mogorovich A, Manassero F, De Maria M, et al. Combination of perianal-intrarectal lidocaine-prilocaine cream and periprostatic nerve block for pain control during transrectal ultrasound guided prostate biopsy: a randomized, controlled trial. Journal of urology. 2009;181(2):585-91; discussion 591-3.
76. Wu CL, Carter HB, Naqibuddin M, Fleisher LA. Effect of local anesthetics on patient recovery after transrectal biopsy. Urology. 2001;57(5):925-929.
77. Song PH, Ko YH. Lateral decubitus position vs. lithotomy position: which is the best way to minimize patient's pain perception during transrectal prostate biopsy? Int Braz J Urol. 2017;43(3):462–9.
78. Kim YU, Ji YS, Ko YH, Song PH. Effect of patient position on pain scales during transrectal ultrasound-guided prostate biopsy. Korean J Urol. 2015;56(6):449-454.
79. Oba A, Nakaya N, Hasumi M, Ono-Yanaba K, Saito-Nakaya K, Takechi H, et al. Psychosocial longitudinal study profile and distress of couples in relation to the conduct of prostate biopsy. Japanese Journal of Clinical Oncology. 2014;44(5):463–71.

80. Egbers N, Schwenke C, Maxeiner A, Teichgräber U, Franie T. MRI-guided core needle biopsy of the prostate: Acceptance and side effects. Diagnostic and Interventional Radiology. 2015;21(3):215–21.
81. Pokorny MR, de Rooij M, Duncan E, Schröder FH, Parkinson R, Barentsz JO, et al. Prospective study of diagnostic accuracy comparing prostate cancer detection by transrectal ultrasound-guided biopsy versus magnetic resonance (MR) imaging with subsequent mr-guided biopsy in men without previous prostate biopsies. European Urology. 2014;66(1):22–9.
82. Sarkar D, Ekwueme K, Parr N. Patient-Reported Experience of Modified Transperineal Template Guided Saturation Biopsy Under General Anaesthesia and without Prophylactic Catheterisation. Urol Int. 2016;96(4):479–83.
83. Rosario DJ, Lane JA, Metcalfe C, Donovan JL, Doble A, Goodwin L, et al. Short term outcomes of prostate biopsy in men tested for cancer by prostate specific antigen: Prospective evaluation within protect study. BMJ. 2012;344.
84. Wadhwa K, Carmona-Echeveria L, Kuru T, Gaziev G, Serrao E, Parashar D, et al. Transperineal prostate biopsies for diagnosis of prostate cancer are well tolerated: A prospective study using patient-reported outcome measures. Asian Journal of Andrology. 2017;19(1):62–6.
85. Dowrick AS, Wootten AC, Howard N, Peters JS, Murphy DG. A prospective study of the short-term quality-of-life outcomes of patients undergoing transperineal prostate biopsy. BJU International. 2016;118:60–7.
86. Eldred-Evans D, Brittain J, Servian P, Miah S, Tam H, Ahmed H. The role of multi-parametric MRI as a triage test: A propensity-matched comparison of a MRI-triage and a TRUS-biopsy pathway. European Urology, Supplements. 2018;17(2):e695–6.
87. Helfand BT, Glaser AP, Rimar K, Zargaroff S, Hedges J, McGuire BB, et al. Prostate cancer diagnosis is associated with an increased risk of erectile dysfunction after prostate biopsy. BJU Int. 2013;111(1):38–43.
88. Klein T, Palisaar RJ, Holz A, Brock M, Noldus J, Hinkel A. The impact of prostate biopsy and periprostatic nerve block on erectile and voiding function: a prospective study. J Urol. 2010;184(4):1447–52.
89. Losa A, Gadda GM, Lazzeri M, Lughezzani G, Cardone G, Freschi M, et al. Complications and quality of life after template-assisted transperineal prostate biopsy in patients eligible for focal therapy. Urology. 2013;81(6):1291–6.
90. Miah S, Eldred-Evans D, Simmons LAM, Shah TT, Kanthabalan A, Arya M, et al. Patient Reported Outcome Measures for Transperineal Template Prostate Mapping Biopsies in the PICTURE Study. Journal of Urology. 2018;200(6):1235–40.
91. Stravodimos KG, Haritopoulos KN, Alamanis C, Anastasiou I, Constantinides C. Local anesthesia during transrectal ultrasonography-guided prostate biopsy: Does it have any effect on sexual function? International Urology and Nephrology. 2007;39(3):893–6.
92. Aktoz T, Kaplan M, Turan U, Memis D, Atakan IH, Inci O. “Multimodal” approach to management of prostate biopsy pain and effects on sexual function: efficacy of levobupivacaine adjuvant to diclofenac sodium - a prospective randomized trial. Andrologia. 2010;42():35-40.
93. Merrick GS, Irvin S, Fiano R, Anderson R, Butler WM, Adamovich E. Pathology and Quality of Life Outcomes Following Office-based Transperineal Prostate Biopsy. Urology. 2016;94:24–8.

94. Kuru TH, Roethke M, Boxler S, Schlemmer H-P, Hohenfellner M. Critical evaluation of MRI-targeted TRUS-guided transperineal fusion biopsy for detection of prostate cancer. Urologe - Ausgabe A. 2013;52(1 SUPPL. 1):71.
95. Aktas BK, Bulut S, Gokkaya CS, Ozden C, Salar R, Aslan Y, et al. Association of prostate volume with voiding impairment and deterioration in quality of life after prostate biopsy. Urology. 2014;83(3):617–21.
96. Gu M, Li W, Chen Q, Chen Y, Xu M, Wang Z. Prostate calculi can higher urinary retention probability and worsen uncomfortable feeling after prostate biopsy but not predict cancer. Int J Clin Exp Med. 2015;8(4):6282–6.
97. Miah S, Eldred-Evans D, Simmons LAM, Shah TT, Kanthabalan A, Arya M, et al. Patient Reported Outcome Measures for Transperineal Template Prostate Mapping Biopsies in the PICTURE Study. J Urol. 2018;
98. Linden-Castro E, Pelayo-Nieto M, Alias-Melgar A, Ramirez-Galindo I, Espinosa-Perez-Grovas D, Ordaz-Macias D, et al. The Psychological Impact of Prostate Biopsy: Anxiety and Depression Associated with a Positive Biopsy Result. Urology Practice. 2016;3(1):32–5.
99. Stanley E, Cradock A, Bisset J, McEntee C, O'Connell MJ. Impact of sensory design interventions on image quality, patient anxiety and overall patient experience at MRI. British Journal of Radiology. 2016;89(1067):20160389.
100. Saraçoğlu T, Unsal A, Taşkın F, Sevinçok L, Karaman CZ. The impact of pre-procedural waiting period and anxiety level on pain perception in patients undergoing transrectal ultrasound-guided prostate biopsy. Diagnostic and interventional radiology (Ankara, turkey). 2012;18(2):195-199.
101. Awsare NS, Green JSA, Aldwinckle B, Hanbury DC, Boustead GB, McNicholas TA. The measurement of psychological distress in men being investigated for the presence of prostate cancer. Prostate Cancer Prostatic Dis. 2008;11(4):384–9.
102. Dowrick AS, Wootten AC, Howard N, Peters JS, Murphy DG. A prospective study of the short-term quality-of-life outcomes of patients undergoing transperineal prostate biopsy. BJU International. 2016;118:60–7.
103. Chapple A, Ziebland S, Herxheimer A, Mcpherson A, Shepperd S, Miller R. Is "watchful waiting" a real choice for men with prostate cancer? A qualitative study. BJU International. 2002;90(3):257–64.
104. Oliffe JL. Transrectal ultrasound prostate biopsy (TRUS-Bx): patient perspectives. Urologic nursing : official journal of the American Urological Association Allied. 2004;24(5):395–400.
105. Naughton CK, Miller DC, Yan Y. Impact of transrectal ultrasound guided prostate biopsy on quality of life: a prospective randomized trial comparing 6 versus 12 cores. J Urol. 2001;165(1):100–3.
106. Kucur M, Goktas S, Kaynar M, Apiliogullari S, Kilic O, Akand M, et al. Selective Low-Dose Spinal Anesthesia for Transrectal Prostate Biopsy: a Prospective and Randomized Study. Journal of endourology / Endourological Society. 2015;29(12):1412-1417.
107. Doganca T, Savsin A, Erdogan S, Altindas F, Ozdemir F, Ekici B, et al. Procedural sedation and analgesia as an adjunct to periprostatic nerve block for prostate biopsy: A prospective randomized trial. J Clin Ultrasound. 2015;43(5):288–94.
108. Kang HW, Yang JB, Kwon WA, Lee YS, Kim WT, Kim YJ, et al. Diagnostic role of prostate resection in the elderly patients who experience significant co-morbidity with a high clinical suspicion of prostate cancer. Journal of Korean Medical Science. 2013;28(12):1796–800.

109. Glaser AP, Novakovic K, Helfand BT. The impact of prostate biopsy on urinary symptoms, erectile function, and anxiety. Current Urology Reports. 2012;13(6):447–54.
110. Efficace F, Bottomley A, Van Andel G. Health related quality of life in prostate carcinoma patients: A systematic review of randomized controlled trials. Cancer. 2003;97(2):377–88.
111. Efficace F, Feuerstein M, Fayers P, Cafaro V, Eastham J, Pusic A, et al. Patient-reported outcomes in randomised controlled trials of prostate cancer: Methodological quality and impact on clinical decision making. European Urology. 2014;66(3):416–27.
112. Carlos RC, Buist DSM, Wernli KJ, Swan JS. Patient-centered outcomes in imaging: Quantifying value. Journal of the American College of Radiology. 2012;9(10):725–8.
113. Swan JS, Miksad RA. Measuring the Quality-of-Life Effects of Diagnostic and Screening Tests. Journal of the American College of Radiology. 2009;6(8):567–75.
114. Blackmore CC, Black WC, Jarvik JG, Langlotz CP, Mushlin AI, Bree RL. A critical synopsis of the diagnostic and screening radiology outcomes literature. Academic Radiology. 1999;6(SUPPL. 1):8–18.
115. Mathers SA, Chesson RA, Proctor JM, McKenzie GA, Robertson E. The Use of Patient-Centered Outcome Measures in Radiology:. A Systematic Review. Academic Radiology. 2006;13(11):1394–404.
116. Zigman Suchsland ML, Witwer E, Truitt AR, Lavallee DC, Zhang Y, Posner P, et al. Patient-Centered Outcomes Related to Imaging Testing in US Primary Care. Journal of the American College of Radiology. 2019;16(2):156–63.
117. Hassanzadeh E, Glazer DI, Dunne RM, Fennessy FM, Harisinghani MG, Tempany CM. Prostate imaging reporting and data system version 2 (PI-RADS v2): a pictorial review. Abdom Radiol (NY). 2017;42(1):278–89.
118. Forster AS, Rubin G, Emery JD, Thompson M, Sutton S, de Wit N, et al. Measuring patient experience of diagnostic care and acceptability of testing. Diagnosis. 2021;0(0).
119. Lijmer JG, Leeflang M, Bossuyt PMM. Proposals for a phased evaluation of medical tests. Medical Decision Making. 2009;29(5):13–21.
120. Fryback DG, Thornbury JR. The Efficacy of Diagnostic Imaging. Medical Decision Making. 1991;11:88–94.
121. Horvath AR, Lord SJ, St John A, Sandberg S, Cobbaert CM, Lorenz S, et al. From biomarkers to medical tests: The changing landscape of test evaluation. Clinica Chimica Acta. 2014;427:49–57.
122. Lin JS, Thompson M, Goddard KAB, Piper MA, Heneghan C, Whitlock EP. Evaluating genomic tests from bench to bedside: A practical framework. BMC Medical Informatics and Decision Making. 2012;12(1):1.
123. Thompson M, Weigl B, Fitzpatrick A, Ide N. More Than Just Accuracy: A Novel Method to Incorporate Multiple Test Attributes in Evaluating Diagnostic Tests Including Point of Care Tests. IEEE Journal of Translational Engineering in Health and Medicine. 2016;4(January).
124. Sekhon M, Cartwright M, Francis JJ. Acceptability of healthcare interventions: An overview of reviews and development of a theoretical framework. BMC Health Services Research. 2017;17(1):1–13. Available from: http://dx.doi.org/10.1186/s12913-017-2031-8

125. Sekhon M, Cartwright M, Francis JJ. Acceptability of health care interventions: A theoretical framework and proposed research agenda. British Journal of Health Psychology. 2018;1–13.
126. Peters JL, Thompson AC, McNicholas TA, Hines JEW, Hanbury DC, Boustead GB. Increased patient satisfaction from transrectal ultrasonography and biopsy under sedation. BJU International. 2001;87(9):827–30.
127. Makinen T, Auvinen A, Hakama M, Stenman UH, Tammela TLJ. Acceptability and complications of prostate biopsy in population-based PSA screening versus routine clinical practice: A prospective, controlled study. Urology. 2002;60(5):846–50.
128. Clements R, Aideyan OU, Griffiths GJ, Peeling WB. Side effects and patient acceptability of transrectal biopsy of the prostate. Clinical Radiology. 1993;47(2):125–6.
129. Ullrich T, Schimmöller L, Oymanns M, Blondin D, Dietzel F, Kirchner J, et al. Current Utilization and Acceptance of Multiparametric MRI in the Diagnosis of Prostate Cancer. A Regional Survey. RöFo - Fortschritte auf dem Gebiet der Röntgenstrahlen und der bildgebenden Verfahren. 2017;419–26.
130. Strauss A, Corbin J. Basics of qualitative research. Sage; 1990.
131. Silverman D. Doing qualitative research. Sage; 2013.
132. NatCen. What is Framework?. Leaders in Qualitative analysis. 2020 [cited 2020 Feb 28]. Available from: http://www.natcen.ac.uk/our-expertise/methods-expertise/qualitative/framework/
133. Smith J, Firth J. Qualitative data analysis: application of the framework approach. Nurse Researcher. 2011;2(18):52–62.
134. Gale NK, Heath G, Cameron E, Rashid S, Redwood S. Using the framework method for the analysis of qualitative data in multi-disciplinary health research. BMC Medical Research Methodology. 2013;13(1):1.
135. Braun V, Clarke V. Using thematic analysis in psychology. Qualitative Research in Psychology. 2006;3(2):77–101.
136. Grant C, Osanloo A. Understanding, Selecting, and Integrating a Theoretical Framework in Dissertation Research: Creating the Blueprint for Your “House.” Administrative Issues Journal Education Practice and Research. 2014;12–26.
137. Tong A, Sainsbury P, Craig J. Consolidated criterion for reporting qualitative research (COREQ): a 32- item checklist for interviews and focus group. International Journal of Qualitative in Health Care. 2007;19(6):349–57.
138. Ullrich T, Schimmöller L, Oymanns M, Blondin D, Dietzel F, Kirchner J, et al. Current Utilization and Acceptance of Multiparametric MRI in the Diagnosis of Prostate Cancer. A Regional Survey. RöFo - Fortschritte auf dem Gebiet der Röntgenstrahlen und der bildgebenden Verfahren. 2017;419–26.
139. Evans R, Edwards AGK, Elwyn G, Watson E, Grol R, Brett J, et al. It’s a maybe test’: men’s experiences of prostate specific antigen testing in primary care. British Journal of General Practice. 2007 Apr 1;57(537):303–10.
140. Clements A, Watson E, Rai T, Bukach C, Shine B, Austoker J. The PSA testing dilemma: GPs’ reports of consultations with asymptomatic men: a qualitative study. BMC Family Practice. 2007 Jun 25;8(1):35.
141. Pickles K, Carter SM, Rychetnik L, Entwistle VA. Doctors’ perspectives on PSA testing illuminate established differences in prostate cancer screening rates between Australia and the UK: A qualitative study. BMJ Open. 2016;6(12).

142. Thurtle DR, Gordon EM, Brierly RD, Conway CJ, McLoughlin J. General practitioner perception of prostate-specific antigen testing has improved, but more awareness of prostate cancer risk in younger patients is still awaited. Prostate International. 2018;6(2):61–5.
143. Young GJ, Harrison S, Turner EL, Walsh EI, Oliver SE, Ben-Shlomo Y, et al. Prostate-specific antigen (PSA) testing of men in UK general practice: A 10-year longitudinal cohort study. BMJ Open. 2017;7(10).
144. Brown VA, Parker PA, Furber L, Thomas AL. Patient preferences for the delivery of bad news - the experience of a UK Cancer Centre. European Journal of Cancer Care. 2011;20(1):56–61.
145. Partin MR, Lillie SE, White KM, Wilt TJ, Chrouser KL, Taylor BC, et al. Similar perspectives on prostate cancer screening value and new guidelines across patient demographic and PSA level subgroups: A qualitative study. Health Expectations. 2017;20(4):779–87.
146. Furber L, Cox K, Murphy R, Steward W. Investigating communication in cancer consultations: What can be learned from doctor and patient accounts of their experience? European Journal of Cancer Care. 2013;22(5):653–62.
147. Kiss A, Meryn S. Effect of sex and gender on psychosocial aspects of prostate and breast cancer. BMJ. 2001;323(November):1055–8.
148. Courtenay WH. Constructions of masculinity and their influence on men's well-being: a theory of gender and health. Social Science & Medicine. 2000;50:1385–401.
149. Alderson P. The importance of theories in health care. British Medical Journal. 1998;317(7164):1007–10.
150. Roberts M. Balint groups: A tool for personal and professional resilience. Canadian Family Physician. 2012;58(3):2012.
151. NHS England. Appraisal. 2020 [cited 2020 Apr 1]. Available from: https://www.england.nhs.uk/medical-revalidation/appraisers/
152. Teoh JYC, Hirai HW, Ho JMW, Chan FCH, Tsoi KKF, Ng CF. Global incidence of prostate cancer in developing and developed countries with changing age structures. PLoS ONE. 2019;14(10):1–9.
153. Cancer Research UK. Prostate cancer statistics. 2015. Available from: http://www.cancerresearchuk.org/health-professional/cancer-statistics/statistics-by-cancer-type/prostate-cancer#heading-Two
154. Luengo-Fernandez R, Leal J, Gray A, Sullivan R. Economic burden of cancer across the European Union: a population-based cost analysis. Lancet Oncology. 2013 Nov;14(12):1165–74.
155. CRUK. Cancer incidence statistics. 2020 [cited 2020 Apr 8]. Available from: https://www.cancerresearchuk.org/health-professional/cancer-statistics/incidence#heading-Zero
156. Sintonen H, Torvinen S, Färkkilä N, Roine RP, Saarto T, Taari K. Costs in different states of prostate cancer. Acta Oncologica. 2016 Jan;55(1):30–7.
157. Gross MD, Alshak MN, Shoag JE, Laviana AA, Gorin MA, Sedrakyan A, et al. Healthcare Costs of Post-Prostate Biopsy Sepsis. Urology. 2019 Nov;133:11–5.
158. Brown LC, Ahmed HU, Faria R, El-Shater Bosaily A, Gabe R, Kaplan RS, et al. Multiparametric MRI to improve detection of prostate cancer compared with transrectal ultrasound-guided prostate biopsy alone: the PROMIS study. Health Technology Assessment. 2018 Jul;22(39):1–176.

159. Willis SR, van der Meulen J, Valerio M, Miners A, Ahmed HU, Emberton M. A review of economic evaluations of diagnostic strategies using imaging in men at risk of prostate cancer. Vol. 25, Current Opinion in Urology. 2015. p. 483–9.
160. Chiu S, Adcock L. Magnetic Resonance Imaging for Prostate Assessment: A Review of Clinical and Cost-Effectiveness. Magnetic Resonance Imaging for Prostate Assessment: A Review of Clinical and Cost-Effectiveness. Ottawa; 2018.
161. Drummond MF, Sculpher MJ, Claxton K, Stoddart GL, Torrance GW. Methods for the economic evaluation of health care programmes. Oxford: Oxford University Press; 2015.
162. Bullement A, Cranmer HL, Shields GE. A Review of Recent Decision-Analytic Models Used to Evaluate the Economic Value of Cancer Treatments. Vol. 17, Applied Health Economics and Health Policy. Adis; 2019. p. 771–80.
163. Pignone M, Saha S, Hoerger T, Lohr KN, Teutsch S, Mandelblatt JS. Challenges in Systematic Reviews of Economic Analyses. Annals of Internal Medicine. 2005;142(12):1073–80.
164. Mathes T, Walgenbach M, Antoine S-L, Pieper D, Eikermann M. Methods for Systematic Reviews of Health Economic Evaluations. Medical Decision Making. 2014;34(7):826–40.
165. Carande-Kulis VG, Maciosek M V., Briss PA, Teutsch SM, Zaza S, Truman BI, et al. Methods for systematic reviews of economic evaluations for the Guide to Community Preventive services. American Journal of Preventive Medicine. 2000;18(1 SUPPL. 1):75–91.
166. Kaltenthaler E, Tappenden P, Paisley S. Reviewing the Evidence to Inform the Population of Cost-Effectiveness Models within Health Technology Assessments. Value in Health. 2013;16(5):830–6.
167. NICE. Developing NICE guidelines: the manual. London: National Institute for Health and Care Excellence; 2020.
168. van Mastrigt GAPG, Hiligsmann M, Arts JJC, Broos PH, Kleijnen J, Evers SMAA, et al. How to prepare a systematic review of economic evaluations for informing evidence-based healthcare decisions: a five-step approach (part 1/3). Expert Review of Pharmacoeconomics and Outcomes Research. 2016;16(6):689–704.
169. Wijnen B, Van Mastrigt G, Redekop W, Majoie H, De Kinderen R, Evers SMAA. How to prepare a systematic review of economic evaluations for informing evidence-based healthcare decisions: data extraction, risk of bias, and transferability (part 3/3). Expert Review of Pharmacoeconomics and Outcomes Research. 2016;16(6):723–32.
170. Thielen FW, Van Mastrigt GAPG, Burgers LT, Bramer WM, Majoie H, Evers S, et al. How to prepare a systematic review of economic evaluations for clinical practice guidelines: database selection and search strategy development (part 2/3). Expert Review of Pharmacoeconomics and Outcomes Research. 2016;16(6):705–21.
171. Glanville J, Kaunelis D, Mensinkai S. How well do search filters perform in identifying economic evaluations in MEDLINE and EMBASE. International Journal of Technology Assessment in Health Care. 2009;25(4):522–9.
172. Snowsill T, Huxley N, Hoyle M, Jones-Hughes T, Coelho H, Cooper C, et al. A systematic review and economic evaluation of diagnostic strategies for Lynch syndrome. Health Technology Assessment. 2014;18(58).

173. Philips Z, Bojke L, Sculpher M, Claxton K, Golder S. Good practice guidelines for decision-analytic modelling in health technology assessment: A review and consolidation of quality assessment. Pharmacoeconomics. 2006;24(4):355–71.
174. Walker DG, Wilson RF, Ritu Sharma M, John Bridges B, Niessen L, Bass EB, et al. Best Practices for Conducting Economic Evaluations in Health Care: A Systematic Review of Quality Assessment Tools. Vol. 12, Methods Research Report. Rockville, Maryland; 2012.
175. CASP. CASP checklist: 12 questions to help you make sense of an Economic Evaluation. 2018;
176. Nixon, John; Khan, Khalid S; Kleijnen J. Summarising economic evaluations in systematic reviews: a new approach. BMJ. 2001;322:1596–8.
177. Faria R, Soares MO, Spackman E, Ahmed HU, Brown LC, Kaplan R, et al. Optimising the Diagnosis of Prostate Cancer in the Era of Multiparametric Magnetic Resonance Imaging: A Cost-effectiveness Analysis Based on the Prostate MR Imaging Study (PROMIS). European Urology. 2018 Jan;73(1):23–30.
178. Pahwa S, Schiltz NK, Ponsky LE, Lu Z, Griswold MA, Gulani V. Cost-effectiveness of MR Imaging-guided Strategies for Detection of Prostate Cancer in Biopsy-Naive Men. Radiology. 2017;285(1):157–66.
179. de Rooij M, Crienen S, Witjes JA, Barentsz JO, Rovers MM, Grutters JPC. Cost-effectiveness of magnetic resonance (MR) imaging and MR-guided targeted biopsy versus systematic transrectal ultrasound-guided biopsy in diagnosing prostate cancer: a modelling study from a health care perspective. Eur Urol. 2014;66(3):430–6.
180. Gordon LG, James R, Tuffaha HW, Lowe A, Yaxley J. Cost-Effectiveness Analysis of Multiparametric MRI With Increased Active Surveillance for Low-Risk Prostate Cancer in Australia. Journal of magnetic resonance imaging. 2017;45:1304–15.
181. Cerantola Y, Dragomir A, Tanguay S, Bladou F, Aprikian A, Kassouf W. Cost-effectiveness of multiparametric magnetic resonance imaging and targeted biopsy in diagnosing prostate cancer. Urologic Oncology: Seminars and Original Investigations. 2016;34(3):119.e1-119.e9. Available from: http://dx.doi.org/10.1016/j.urolonc.2015.09.010
182. Barnett CL, Davenport MS, Montgomery JS, Kunju LP, Denton BT, Piert M. 18F-Choline PET/mpMRI for Detection of Clinically Significant Prostate Cancer: Part 2. Cost-Effectiveness Analysis. J Nucl Med. 2019;60(12):1705–12.
183. Barnett CL, Davenport MS, Montgomery JS, Wei JT, Montie JE, Denton BT. Cost-effectiveness of magnetic resonance imaging and targeted fusion biopsy for early detection of prostate cancer. BJU Int. 2018;122(1):50–8.
184. de Rooij M, Crienen S, Witjes JA, Barentsz JO, Rovers MM, Grutters JPC. Cost-effectiveness of magnetic resonance (MR) imaging and MR-guided targeted biopsy versus systematic transrectal ultrasound-guided biopsy in diagnosing prostate cancer: a modelling study from a health care perspective. Eur Urol. 2014;66(3):430–6.
185. Cerantola Y, Dragomir A, Tanguay S, Bladou F, Aprikian A, Kassouf W. Cost-effectiveness of multiparametric magnetic resonance imaging and targeted biopsy in diagnosing prostate cancer. Urologic Oncology: Seminars and Original Investigations. 2016 Mar;34(3):119.e1-119.e9.
186. Khoo CC, Eldred-Evans D, Peters M, Bertoncelli Tanaka M, Noureldin M, Miah S, et al. Likert vs PI-RADS v2: a comparison of two radiological scoring systems for

detection of clinically significant prostate cancer. BJU International. 2020 Jan;125(1):49–55.
187. Dutruel SP, Jeph S, Margolis DJA, Wehrli N. PI-RADS: what is new and how to use it. Abdominal Radiology. 2020 Mar 17;
188. Stabile A, Giganti F, Rosenkrantz AB, Taneja SS, Villeirs G, Gill IS, et al. Multiparametric MRI for prostate cancer diagnosis: current status and future directions. Nature Reviews Urology. 2020 Jan 17;17(1):41–61.
189. Venderink W, Govers TM, de Rooij M, Fütterer JJ, Sedelaar JPM. Cost-Effectiveness Comparison of Imaging-Guided Prostate Biopsy Techniques: Systematic Transrectal Ultrasound, Direct In-Bore MRI, and Image Fusion. American Journal of Roentgenology. 2017 May;208(5):1058–63.
190. Lotan Y, Haddad AQ, Costa DN, Pedrosa I, Rofsky NM, Roehrborn CG. Decision analysis model comparing cost of multiparametric magnetic resonance imaging vs. repeat biopsy for detection of prostate cancer in men with prior negative findings on biopsy. Urologic Oncology: Seminars and Original Investigations. 2015 Jun;33(6):266.e9-266.e16.
191. Mowatt G, Scotland G, Boachie C, Cruickshank M, Ford JA, Fraser C, et al. The diagnostic accuracy and cost effectiveness of magnetic resonance spectroscopy and enhanced magnetic resonance imaging techniques in aiding the localisation of prostate abnormalities for biopsy: A systematic review and economic evaluation. Health Technology Assessment. 2013;17(20).
192. Nicholson A, Mahon J, Boland A, Beale S, Dwan K, Fleeman N, et al. The clinical effectiveness and cost-effectiveness of the PROGENSA® prostate cancer antigen 3 assay and the Prostate Health Index in the diagnosis of prostate cancer: a systematic review and economic evaluation. Health Technology Assessment. 2015 Oct;19(87):1–192.
193. Cancer NCC for. Prostate Cancer: diagnosis and treatment. NICE; 2014 Nov.
194. Mottet N, Bellmunt J, Briers E, Bolla M, Bourke L, Cornford P, et al. EAU - ESTRO - ESUR - SIOG Guidelines on Prostate Cancer. European Association of Urology; 2017.
195. MSAC. Protocol to guide the assessment of mpMRI prostate diagnostic scans for diagnosis of prostate cancer. Canberra: Medical Services Advisory Committee; 2016.
196. Wang B, Gao J, Zhang Q, Zhang C, Liu G, Wei W, et al. Investigating the equivalent performance of biparametric compared to multiparametric MRI in detection of clinically significant prostate cancer. Abdominal Radiology. 2020 Feb 6;45(2):547–55.
197. Padhani AR, Schoots I, Villeirs G. Contrast Medium or No Contrast Medium for Prostate Cancer Diagnosis. That Is the Question. Journal of Magnetic Resonance Imaging. 2020 May 3;jmri.27180.
198. Jambor I, Verho J, Ettala O, Knaapila J, Taimen P, Syvänen KT, et al. Validation of IMPROD biparametric MRI in men with clinically suspected prostate cancer: A prospective multi-institutional trial. Johnstone RW, editor. PLOS Medicine. 2019 Jun 3;16(6):e1002813.
199. Richardson J, Ubaldo AR, Dai D, McDonnell P. Waiting Times for Suspected and Diagnosed Cancer Patients 2019-20 Annual Report. London; 2020.
200. Just J, Osgun F, Knight C. Lower urinary tract symptoms and prostate cancer: is PSA testing in men with symptoms wise? British Journal of General Practice.

2018 Nov;68(676):541–2. Available from: http://bjgp.org/lookup/doi/10.3399/bjgp18X699689
201. Abel L, Shinkins B, Smith A, Sutton AJ, Sagoo GS, Uchegbu I, et al. Early Economic Evaluation of Diagnostic Technologies: Experiences of the NIHR Diagnostic Evidence Co-operatives. Medical Decision Making. 2019;39(7):857–66.
202. Buisman LR, Rutten-van Molken MPMH, Postmus D, Luime JJ, Uyl-de Groot CA, Redekop WK. The early bird catches the worm: Early cost-effectiveness analysis of new medical tests. Int J Technol Assess Health Care. 2016;32(1/2):46–53.
203. Caro JJ, Briggs AH, Siebert U, Kuntz KM. Modelling Good Research Practices — Overview : A Report of the ISPOR-SMDM Modelling Good Research Practices Task Force-1. Value in Health. 2012;15(6):796–803.
204. Roberts M, Russell LB, Paltiel AD, Chambers M, McEwan P, Krahn M. Conceptualizing a model: A report of the ISPOR-SMDM modelling good research practices task force-2. Medical Decision Making. 2012;32(5):678–89.
205. Clift AK, Coupland C, Hippisley-Cox J. Prostate-specific antigen testing and opportunistic prostate cancer screening: a cohort study in England. British Journal of General Practice. 2021;71(703):e157–65.
206. CanTest. CanTest Spring School 2021. 2021 [cited 2021 Nov 26]. Available from: https://www.cantest.org/faculty/school-2021/
207. Gray A, Clarke PM, Wolstenholme JL, Wordsworth S. Applied Methods of Cost-Effectiveness Analysis in Health Care. Oxford: Oxford University Press; 2011.
208. Briggs A, Claxton K, Sculpher M. Decision Modelling for Health Economic Evaluation. Gray A, Briggs A, editors. Oxford: Oxford University Press; 2011.
209. Roberts M, Russell LB, Paltiel AD, Chambers M, McEwan P, Krahn M. Conceptualizing a model: A report of the ISPOR-SMDM modelling good research practices task force-2. Medical Decision Making. 2012;32(5):678–89.
210. NICE. Guide to the methods of technology appraisal 2013. Process and methods [PMG9]. 2013. Available from: https://www.nice.org.uk/process/pmg9/chapter/the-reference-case
211. Jairath NK, Dal Pra A, Vince R, Dess RT, Jackson WC, Tosoian JJ, et al. A Systematic Review of the Evidence for the Decipher Genomic Classifier in Prostate Cancer. European Urology. 2020;79(3):374–83. Available from: https://doi.org/10.1016/j.eururo.2020.11.021
212. Kim L, Boxall N, George A, Burling K, Acher P, Aning J, et al. Clinical utility and cost modelling of the phi test to triage referrals into image-based diagnostic services for suspected prostate cancer: the PRIM (Phi to RefIne Mri) study. BMC Medicine. 2020 Dec 17;18(1):95.
213. Seibert TM, Fan CC, Wang Y, Zuber V, Karunamuni R, Parsons JK, et al. Polygenic hazard score to guide screening for aggressive prostate cancer: development and validation in large scale cohorts. BMJ. 2018;j5757. Available from: http://www.bmj.com/lookup/doi/10.1136/bmj.j5757
214. Curtis LA, Burns A. Unit Costs of Health & Social Care 2020. 2020. Available from: https://doi.org/10.22024/UniKent%2F01.02.84818
215. NHS England and NHS Improvement. National Cost Collection 2019. 2020.
216. Ramsay C, Pickard R, Robertson C, Close A, Vale L. Systematic review and economic modelling of the relative clinical benefit and cost-effectiveness of laparoscopic surgery and robotic surgery for removal of the prostate in men with localised prostate cancer. Health Technology Assessment. 2012;16(41).

217. Martin RM, Donovan JL, Turner EL, Metcalfe C, Young GJ, Walsh EI, et al. Effect of a low-intensity PSA-based screening intervention on prostate cancer mortality: The CAP randomized clinical trial. JAMA - Journal of the American Medical Association. 2018;319(9):883–95.
218. Newcombe RG. Two-sided confidence intervals for the single proportion: Comparison of seven methods. Statistics in Medicine. 1998;17:857–72.
219. Young SM, Bansal P, Vella ET, Finelli A, Levitt C, Loblaw A. Systematic review of clinical features of suspected prostate cancer in primary care. Canadian Family Physician. 2015;61(1):e26–35.
220. Shea BJ, Reeves BC, Wells G, Thuku M, Hamel C, Moran J, et al. AMSTAR 2: A critical appraisal tool for systematic reviews that include randomised or non-randomised studies of healthcare interventions, or both. BMJ (Online). 2017;358:1–9.
221. Philips Z, Ginnelly L, Sculpher M, Claxton K, Golder S, Riemsma R, et al. Review of guidelines for good practice in decision-analytic modelling in health technology assessment. Health Technology Assessment. 2004;8(36).
222. Bhindi A, Bhindi B, Kulkarni GS, Hamilton RJ, Toi A, van der Kwast TH, et al. Modern-day prostate cancer is not meaningfully associated with lower urinary tract symptoms: Analysis of a propensity score-matched cohort. Journal of the Canadian Urological Association. 2017;11(1-2February):41–6.
223. Cicione A, Cormio L, Cantiello F, Palumbo IM, de Nunzio C, Lima E, et al. Presence and severity of lower urinary tract symptoms are inversely correlated with the risk of prostate cancer on prostate biopsy. Minerva Urologica e Nefrologica. 2017;69(5):486–92.
224. Barrett J, Hamilton W. Pathways to the diagnosis of prostate cancer in a British city. A population-based study. Scand J Urol Nephrol. 2005;39(4):267–70.
225. Whiting PF, Rutjes AWS, Westwood ME, Mallet S, Deeks JJ, Reitsma JB, et al. QUADAS-2: A Revised Tool for the Quality Assessment of Diagnostic Accuracy Studies. Annals of Internal Medicine. 2011;155(4):529–36.
226. Liberati A, Altman DG, Tetzlaff J, Mulrow C, Gøtzsche PC, Ioannidis JPA, et al. The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate health care interventions: explanation and elaboration. PLoS Medicine. 2009;6(7):e1000100.
227. Abdrabo AA, Fadlalla AI, Fadl-Elmula IM. Significance of serum total prostate specific antigen and digital rectal examination in the diagnosis of prostate cancer. Saudi Med J. 2011;32(11):1133–6.
228. Agnihotri S, Mittal RD, Kapoor R, Mandhani A. Raising cut-off value of prostate specific antigen (PSA) for biopsy in symptomatic men in India to reduce unnecessary biopsy. Indian J Med Res. 2014;139(6):851–6.
229. Aragona F, Pepe P, Motta M, Saita A, Raciti G, la Rosa P, et al. Incidence of prostate cancer in Sicily: Results of a multicenter case-findings protocol. European Urology. 2005;47(5):569–74.
230. Chang CC, Yi-Chen L, Huang-Wen T, Shyi-Chun Y, Tzung-Hai Y, Fang-Yen C. Diagnostic Role of Serum Free-to-Total Prostate Specific Antigen (PSA) Ratio in Prostate Cancer with Serum Total Concentration of PSA below 4 ng/mL. Asian Pac J Cancer Prev. 2015;16(13):5261–4.
231. Chavan PR, Chavan V S, Chavan NR, Trivedi VD. Detection rate of prostate cancer using prostate specific antigen in patients presenting with lower urinary

tract symptoms: A retrospective study. Journal Of Postgraduate Medicine. 2009;55(1):17–21.
232. Galic J, Karner I, Cenan L, Tucak A, Hegedus I, Pasini J, et al. Comparison of Digital Rectal Examination and Prostate Specific Antigen in Early Detection of Prostate Cancer. Collegium Antropologicum. 2003;27(S1):61–6.
233. Hofer C, Sauerstein P, Wolter C, Scholz M, Hartung R, Breul J. Value of free prostate-specific antigen (Hybritech Tandem-R) in symptomatic patients consulting the urologist. Urologia Internationalis. 2000;64(1):18–23.
234. Lee SW, Byun SS, Lee SE. The Diagnostic Significance of Abnormal Findings on Transrectal Ultrasonography in Patients with Serum Prostate-Specific Antigen Levels Equal or Less than 4.0ng/ml. Korean Journal of Urology. 2006;47(7):752.
235. Magistro G, Keller P, Westhofen T, Schott M, Tamalunas A, Weinhold P, et al. The significance of a high preoperative PSA level for the detection of incidental prostate cancer in LUTS patients with large prostates. World J Urol. 2020;
236. Meigs JB, Barry MJ, Oesterling JE, Jacobsen SJ. Interpreting results of prostate-specific antigen testing for early detection of prostate cancer. J Gen Intern Med. 1996;11(9):505–12.
237. Nordström T, Engel JC, Bergman M, Egevad L, Aly M, Eklund M, et al. Identifying Prostate Cancer Among Men with Lower Urinary Tract Symptoms. European Urology Open Science. 2021;24:11–6.
238. Patel NS, Blick C, Kumar PVS, Malone PR. The diagnostic value of abdominal ultrasound, urine cytology and prostate-specific antigen testing in the lower urinary tract symptoms clinic. Int J Clin Pract. 2009;63(12):1734–8.
239. Pepe P, Panella P, Savoca F, Cacciola A, D'Arrigo L, Dibenedetto G, et al. Prevalence and clinical significance of prostate cancer among 12,682 men with normal digital rectal examination, low PSA levels (<= 4 ng/ml) and percent free PSA cutoff values of 15 and 20%. Urologia Internationalis. 2007;78(4):308–12.
240. Rashid MM, Alam AKMK, Habib AKMK, Rahman H, Hossain AKMS, Salam MA, et al. Efficacy of lower cut off value of serum prostate specific antigen in diagnosis of prostate cancer. Bangladesh Med Res Counc Bull. 2012;38(3):90–3.
241. Richie JP, Catalona WJ, Ahmann FR, Hudson MA, Scardino PT, Flanigan RC, et al. Effect of patient age on early detection of prostate cancer with serum prostate-specific antigen and digital rectal examination. Urology. 1993;42(4):365–74.
242. Seo HK, Chung MK, Ryu SB, Lee KH, Oncologic U, Prostate S, et al. Detection Rate of Prostate Cancer According to Prostate-Specific Antigen and Digital Rectal Examination in Korean Men : A Nationwide Multicenter Study. Journal of Urology. 2007;70(6):1109–12.
243. Shahab AA, Soebadi DM, Djatisoesanto W, Hardjowijoto S, Soetojo S, Hakim L. Prostate-specific antigen and prostate-specific antigen density cutoff points among Indonesian population suspected for prostate cancer. Prostate International. 2013;1(1):23–30. Available from: http://dx.doi.org/10.12954/PI.12003
244. Tauro LF, Rao K, Shetty M, Rao BSS, Shenoy DH. Significance of prostate specific antigen and prostate volume in the diagnosis of prostatic diseases. Journal of Clinical and Diagnostic Research. 2009;3(1):1274–84. Available from: http://www.jcdr.net/articles/PDF/442/355.pdf
245. Wymenga LFA, Duisterwinkel FJ, Groenier K, Visser-van Brummen P, Marrink J, Mensink HJA. Clinical implications of free-to-total immunoreactive prostate-

specific antigen ratios. Scandinavian Journal of Urology and Nephrology. 2000;34(3):181–7.
246. Young S-M, Bansal P, Vella ET, Finelli A, Levitt C, Loblaw A. Systematic review of clinical features of suspected prostate cancer in primary care. Canadian family physician Medecin de famille canadien. 2015;61(1):e26-35.
247. Carter B, Albertsen P, Barry M, Etzioni R, Freedland S, Greene K, et al. Early Detection of Prostate Cancer: AUA Guideline. American Urological Association Education and Research. 2018. p. 1–28.
248. Roland M, Neal D, Buckley R. What should doctors say to men asking for a PSA test? BMJ. 2018;3702(September):k3702.
249. Eldred-Evans D, Burak P, Connor M, Day E, Evans M, Fiorentino F, et al. Population-based prostate cancer screening with Magnetic Resonance or Ultrasound Imaging: The IP1-PROSTAGRAM study. JAMA Oncology. 2021;1–7.
250. UK government. National Health Service Act 2006. London: UK government; 2006. Available from: https://www.legislation.gov.uk/ukpga/2006/41/contents
251. Wolf A, Dedman D, Campbell J, Booth H, Lunn D, Chapman J, et al. Data resource profile: Clinical Practice Research Datalink (CPRD) Aurum. International Journal of Epidemiology. 2019;48:1740–1740g.
252. Lyratzopoulos G, Abel GA, McPhail S, Neal RD, Rubin GP. Measures of promptness of cancer diagnosis in primary care: Secondary analysis of national audit data on patients with 18 common and rarer cancers. British Journal of Cancer. 2013;108(3):686–90.
253. Swann R, McPhail S, Shand B, Rashbass J, Witt J, Abel GA, et al. Diagnosing cancer in primary care: Results from the National Cancer Diagnosis Audit. British Journal of General Practice. 2018;68(666):e63–72.
254. Eklund M, Jäderling F, Discacciati A, Bergman M, Annerstedt M, Aly M, et al. MRI-Targeted or Standard Biopsy in Prostate Cancer Screening. New England Journal of Medicine. 2021 Jul 9;
255. Klotz L, Chin J, Black PC, Finelli A, Anidjar M, Bladou F, et al. Comparison of Multiparametric Magnetic Resonance Imaging–Targeted Biopsy With Systematic Transrectal Ultrasonography Biopsy for Biopsy-Naive Men at Risk for Prostate Cancer. JAMA Oncology. 2021;
256. Smith CF, Tompson AC, Jones N, Brewin J, Spencer EA, Bankhead CR, et al. Direct access cancer testing in primary care: a systematic review of use and clinical outcomes. British Journal of General Practice. 2018;(August):1–10.
257. Appayya MB, Adshead J, Ahmed HU, Allen C, Bainbridge A, Barrett T, et al. National implementation of multi-parametric magnetic resonance imaging for prostate cancer detection – recommendations from a UK consensus meeting. BJU International. 2018;122(1):13–25.
258. Alberts AR, Schoots IG, Roobol MJ. Prostate-specific antigen-based prostate cancer screening: Past and future. International Journal of Urology. 2015 Jun;22(6):524–32. Available from: http://doi.wiley.com/10.1111/iju.12750
259. Bristol North Somerset and South Gloucestershire CCG. REMEDY : BNSSG referral pathways & Joint Formulary. 2021 [cited 2021 Oct 20]. Available from: https://remedy.bnssgccg.nhs.uk/
260. White PM, Halliday-Pegg JC, Collie DA. Open access neuroimaging for general practitioners - diagnostic yield and influence on patient management. British Journal of General Practice. 2002;52:33–5.

261. Taylor TR, Evangelou N, Porter H, Lenthall R. Primary care direct access MRI for the investigation of chronic headache. Clinical Radiology. 2012;67(1):24–7.
262. Apthorp LA, Daly CA, Morrison ID, Field S. Direct Access MRI for General Practitioners-Influence on Patient Management. Clinical Radiology. 1998;53:58–60.
263. UK National Screening Committee. Adult screening programme: Prostate cancer. 2020 [cited 2021 Oct 20]. Available from: https://view-health-screening-recommendations.service.gov.uk/prostate-cancer/
264. Yusim I, Krenawi M, Mazor E, Novack V, Mabjeesh NJ. The use of prostate specific antigen density to predict clinically significant prostate cancer. Scientific Reports. 2020 Dec 1;10(1).
265. Deniffel D, Healy GM, Dong X, Ghai S, Salinas-Miranda E, Fleshner N, et al. Avoiding unnecessary biopsy: MRI-based risk models versus a PI-RADS and PSA density strategy for clinically significant prostate cancer. Radiology. 2021 Aug 1;300(2):369–79.
266. Pye H, Singh S, Norris JM, Echeverria LMC, Stavrinides V, Grey A, et al. Evaluation of psa and psa density in a multiparametric magnetic resonance imaging-directed diagnostic pathway for suspected prostate cancer: The innovate trial. Cancers (Basel). 2021 Apr 2;13(8).
267. Falagario UG, Jambor I, Lantz A, Ettala O, Stabile A, Taimen P, et al. Combined Use of Prostate-specific Antigen Density and Magnetic Resonance Imaging for Prostate Biopsy Decision Planning: A Retrospective Multi-institutional Study Using the Prostate Magnetic Resonance Imaging Outcome Database (PROMOD). European Urology Oncology. 2020 Sep;
268. Zalesky M, Stejskal J, Adamcova V, Hrbacek J, Minarik I, Pavlicko A, et al. Use of Prostate Specific Antigen Density Combined with Multiparametric Magnetic Resonance Imaging Improves Triage for Prostate Biopsy. Urol Int. 2019;103(1):33–40.
269. Görtz M, Radtke JP, Hatiboglu G, Schütz V, Tosev G, Güttlein M, et al. The Value of Prostate-specific Antigen Density for Prostate Imaging-Reporting and Data System 3 Lesions on Multiparametric Magnetic Resonance Imaging: A Strategy to Avoid Unnecessary Prostate Biopsies. European Urology Focus. 2019 Dec;
270. Hsieh P-F, Li W-J, Lin W-C, Chang H, Chang C-H, Huang C-P, et al. Combining prostate health index and multiparametric magnetic resonance imaging in the diagnosis of clinically significant prostate cancer in an Asian population. World Journal of Urology. 2020 May 22;38(5):1207–14. Available from: http://link.springer.com/10.1007/s00345-019-02889-2
271. Falagario UG, Martini A, Wajswol E, Treacy P-J, Ratnani P, Jambor I, et al. Avoiding Unnecessary Magnetic Resonance Imaging (MRI) and Biopsies: negative and Positive Predictive Value of MRI According to Prostate-specific Antigen Density, 4Kscore and Risk Calculators. Eur Urol Oncol. 2019;
272. Perlis N, Al-Kasab T, Ahmad A, Goldberg E, Fadak K, Sayid R, et al. Defining a Cohort that May Not Require Repeat Prostate Biopsy Based on PCA3 Score and Magnetic Resonance Imaging: The Dual Negative Effect. Journal of Urology. 2018 May;199(5):1182–7.
273. Emmett L, Buteau J, Papa N, Moon D, Thompson J, Roberts MJ, et al. The Additive Diagnostic Value of Prostate-specific Membrane Antigen Positron Emission Tomography Computed Tomography to Multiparametric Magnetic

Resonance Imaging Triage in the Diagnosis of Prostate Cancer (PRIMARY): A Prospective Multicentre Study. European Urology. 2021 Aug;
274. Usher-Smith J, Emery J, Hamilton W, Griffin SJ, Walter FM. Risk prediction tools for cancer in primary care. British Journal of Cancer. 2015 Dec 3;113(12):1645–50. Available from: http://dx.doi.org/10.1038/bjc.2015.409
275. Louie KS, Seigneurin A, Cathcart P, Sasieni P. Do prostate cancer risk models improve the predictive accuracy of PSA screening? A meta-analysis. Annals of Oncology. 2015;26(5):848–64. Available from: https://academic.oup.com/annonc/article-lookup/doi/10.1093/annonc/mdu525
276. Schoots IG, Roobol MJ. Multivariate risk prediction tools including MRI for individualized biopsy decision in prostate cancer diagnosis: current status and future directions. World Journal of Urology. 2020 Mar 13;38(3):517–29.
277. Aladwani M, Lophatananon A, Ollier W, Muir K. Prediction models for prostate cancer to be used in the primary care setting: A systematic review. BMJ Open. 2020 Jul 19;10(7).
278. Norris JM, Carmona LM, Bott SRJ, Brown LC, Burns-cox N, Dudderidge T, et al. What Type of Prostate Cancer Is Systematically Overlooked by Multiparametric Magnetic Resonance Imaging ? An Analysis from the PROMIS Cohort. European Urology. 2020;43–5. Available from: https://doi.org/10.1016/j.eururo.2020.04.029
279. Richards M. Diagnostics: Recovery And Renewal – Report of the Independent Review of Diagnostic Services for NHS England – October 2020. 2020.
280. NHS England, Department of Health and Social Care. 40 community diagnostic centres launching across England. gov.uk. 2021 [cited 2021 Oct 6]. Available from: https://www.gov.uk/government/news/40-community-diagnostic-centres-launching-across-england
281. HM Treasury. Budget and Spending Review - October 2021: What you need to know. 2021 [cited 2021 Nov 1]. Available from: https://www.gov.uk/government/news/budget-and-spending-review-october-2021-what-you-need-to-know
282. OECD. Health Equipment - Magnetic Resonance Imaging (MRI) units. 2021 [cited 2021 Nov 12]. Available from: https://data.oecd.org/healtheqt/magnetic-resonance-imaging-mri-units.htm
283. Royal College of Radiologists. Clinical radiology UK workforce census 2020 report. 2021.
284. College of Radiographers. Diagnostic Radiography Workforce UK Census 2020. 2020.
285. NHS England and NHS Improvement. NHS Diagnostic Waiting Times and Activity Data. 2021.
286. Pecoraro M, Messina E, Bicchetti M, Carnicelli G, del Monte M, Lorio B, et al. The future direction of imaging in prostate cancer: MRI with or without contrast injection. Andrology. 2021;(March):1–15.
287. Marsden T, Ahmed HU, Emberton M. An update from the ReIMAGINE Prostate Cancer Risk Study (NCT04060589): A prospective cohort study in men with a suspicion of prostate cancer who are referred onto a magnetic resonance imaging–based diagnostic pathway with donation of tissue, blood, and urine for biomarker analyses. European Urology. 2021 Oct 1;

288. Hötker AM, da Mutten R, Tiessen A, Konukoglu E, Donati OF. Improving workflow in prostate MRI: AI-based decision-making on biparametric or multiparametric MRI. Insights into Imaging. 2021 Dec 1;12(1).
289. Li M, Chen T, Zhao W, Wei C, Li X, Duan S, et al. Radiomics prediction model for the improved diagnosis of clinically significant prostate cancer on biparametric MRI. Quantitative Imaging in Medicine and Surgery. 2020 Feb;10(2):368–79. Available from: http://qims.amegroups.com/article/view/36608/28292
290. Barbieri M, Richardson G, Paisley S, Sculpher M. Rapid Review Of Existing Literature On The Cost Effectiveness Of Alternative Systems For Diagnosis And Referral Of Any Cancer In Primary Care. Sheffield; 2014.