Revealing the Invisible:

Systematic Investigation of Prostate Cancer Undetected by Multiparametric Magnetic Resonance Imaging

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DECLARATION

I, Joseph Michael Norris, confirm that the work presented in this thesis is my own. Where information has been derived from other sources, I confirm that this has been indicated in the thesis. I hereby give consent for my thesis to be available for photocopying and for inter-library loan, and for the title and summary to be made available to outside organisations.

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ABSTRACT

Multiparametric magnetic resonance imaging (mpMRI) has improved risk stratification for patients with suspected prostate cancer. However, as with other diagnostic instruments, there remains a disease spectrum undetected by mpMRI. Through systematic analysis, the aim of this doctoral research was to enhance current understanding of mpMRI-undetected prostate cancer and thus potentially refine the modern diagnostic prostate cancer pathway.

The PROMIS (Prostate Magnetic Resonance Imaging Study; $n = 576$) and PICTURE (Prostate Imaging Compared to Transrectal Ultrasound [TRUS]-Guided Biopsy for Significant Prostate Cancer Risk Evaluation Study; $n = 249$) trials assessed diagnostic performance of prostate mpMRI against a stringent reference standard (5mm transperineal template mapping biopsy) and, as such, enabled analysis of the histopathological characteristics of mpMRI-undetected prostate cancer in this doctoral research. In both studies, all patients underwent 5mm mapping biopsy, regardless of their mpMRI result, thus providing a unique opportunity to study prostate cancer that is not detected by pre-biopsy mpMRI (i.e. a biopsy was done for both visible and non-visible cancer, thus allowing comparative analysis). To delineate the molecular landscape of mpMRI-undetected prostate cancer, a combination of systematic literature synthesis and bioinformatic analysis of publicly-available MRI-correlated genetic data was undertaken. Finally, patient perspectives on prostate mpMRI, and mpMRI-undetected cancer, were elicited and analysed using mixed methodology in the PACT (Patient Acceptance of Magnetic Resonance Imaging) study.

In both PROMIS (biopsy-naïve patients) and PICTURE (non-biopsy-naïve patients) cohorts, mpMRI-undetected cancer appeared to be significantly lower in pathological grade ($p = 0.0007$, and $p = 0.02$) and tumour size ($p < 0.0001$, and $p < 0.02$) compared to mpMRI-detected disease. Furthermore, none of the most aggressive cancers (Gleason Grade Groups 4–5) were overlooked by mpMRI, in either cohort. Next, through systematic literature review, mpMRI-undetected prostate cancer appeared to have significantly reduced enrichment of the genetic hallmarks of aggressivity, compared to mpMRI-detected disease. Bioinformatic analysis of large public genetic databases demonstrated 42 genes (including, alanyl aminopeptidase [*ANPEP*] and, cholinergic receptor nicotinic alpha 2 subunit [*CHRNA2*]) that appeared to be significantly associated with prostate cancer detection on mpMRI. These genes appear to be linked to biological processes (e.g. cell proliferation) and clinical events (e.g. biochemical recurrence post-radical prostatectomy) that may help provide a link between the mpMRI visible prostate cancer phenotype and prognostic implications.

In the PACT study, views from 117 patients undergoing mpMRI for suspected cancer (predominantly, due to raised levels of serum prostate-specific antigen [PSA]) were surveyed. The majority (96%) appeared to express favourable opinion towards mpMRI, and lower levels of concern regarding mpMRI-undetected prostate cancer, provided follow-up

measures were instigated (e.g. PSA surveillance). During selected in-depth, semi-structured interviews (n = 20), thematic analysis suggested that avoidance of invasive procedures, and improved diagnostic accuracy, were key themes. Most patients seemed to favour the non-invasive nature of pre-biopsy mpMRI, and the possibility of avoiding biopsy. Fear of invasion may have been informed by prior individual experience or negative second-hand reports regarding unpleasant biopsy side-effects. When biopsy was required, most patients seemed to value increased accuracy of MRI-guidance, however, mixed views were expressed regarding biopsy strategy, with some preferring MRI-targeted biopsy alone, and others favouring concomitant systematic biopsy (approximately 50:50 split between the two approaches).

In conclusion, this doctoral research provides a degree of support to the primacy held by mpMRI in the current prostate cancer diagnostic paradigm, by suggesting, at several levels of analysis, the reassuring nature of prostate cancer undetected by mpMRI. Furthermore, mixed methods research in the PACT study appeared to demonstrate cohesive views held by patients that directly experience this novel technology. Upcoming future research will focus on correlating baseline mpMRI phenotypes to longitudinal clinical outcomes to further expound the long-term prognostication that may be afforded in this setting.

IMPACT STATEMENT

Diagnosis of suspected prostate cancer is increasingly informed by pre-biopsy imaging, including, multiparametric magnetic resonance imaging (mpMRI). National and international guidelines now advocate pre-biopsy mpMRI be used to direct biopsy deployment in cases of suspicious mpMRI (i.e. MRI-targeted biopsy), but also, to help inform whether a biopsy can be omitted, for instance, in cases of non-suspicious mpMRI. For this reason, it is important to understand the nature of prostate cancer that is detected and undetected by mpMRI, particularly given the incumbent risk that prostate cancer may be 'overlooked' if upfront biopsy is not performed for patients with normal pre-biopsy imaging.

Overall, the research presented in this thesis suggests that detection of prostate cancer on mpMRI appears to be associated with increased clinical significance, compared to cancer that is overlooked. At the molecular level, it appears that mpMRI-detected tumours are enriched with genetics of clinically aggressive disease; a finding that was ratified at both the histopathological (e.g. Gleason grading) and tumoural (e.g. cancer length) levels. Finally, through engaging patients with suspected prostate cancer, it appears that the majority of patients value this diagnostic characteristic (i.e. detection of the most significant disease) as this potentially enables evidence-based avoidance of immediate painful biopsy in the setting of non-suspicious mpMRI, and conversely, targeted biopsy of the most aggressive tumours, in suspicious cases.

This work helps reinforce the current trajectory of integrating imaging into the prostate cancer diagnostic and treatment pathway, which now requires validation at the long-term clinical outcome level. Furthermore, bioinformatic identification of mpMRI tumoural detection-associated genes has now potentially paved the way for targeted biomarker work in the future. Lastly, this doctoral research has suggested close cohesion between the imaging phenotype of prostate cancer on mpMRI and molecular/pathological aggressivity, and it seems possible that this may contribute to the eventual replacement of traditional approaches to grading of prostate malignancy.

During this doctoral degree, I have become involved with a range of research and supervised a number of students, and in doing so, have been fortunate to co-author over 70 peer-reviewed papers and abstracts, over three dedicated years. As a result of this body of work, I feel honoured to have gained a small degree of international recognition. In both 2020 and 2021, The American Urological Association (AUA) provided a platform for me to present my doctoral research, and in 2020, I was awarded First Prize for Best Poster in Section (Prostate Cancer Diagnostics). Next, the European Association of Urology (EAU) also granted me a similar platform, and additionally, invited me annually to join the prostate cancer abstract review panel (for the 2021-2024 congresses), and finally, I was honoured to have been invited to chair the EAU Prostate Cancer Diagnostics sections, in the 2021, 2023 and 2024 meetings.

To broaden the impact and scope of my research, I have collaborated with colleagues outside of the United Kingdom (UK), and during this doctoral degree, I have been lucky to form research relationships with experts in France, Australia, New Zealand, and the United States of America (USA). I have also worked with leaders from other disciplines, including the arts, and was privileged to be invited to contribute to the interdisciplinary *Picturing the Invisible* project (which included a conference, website, and book) led by the University of the Arts London (UAL). During my research, I have tried to continually involve patients and members of the public, and was fortunate to eventually receive a letter of commendation from the House of Lords for this work.

I hope that the work conducted in this project will help improve delivery of care for patients with suspected prostate cancer, as well as contributing to future diagnostic prostate cancer guidelines and recommendations. Furthermore, I hope that my research has begun to provide a framework from which myself and future researchers can build, integrating multi-modal prostate biomarker data with longitudinal clinical outcome research.

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PhD OUTPUTS

Peer-Reviewed Publications & Abstracts (Full bibliography available on ResearchGate: bit.ly/3taalf1)

During this period of doctoral research, I have co-authored over 70 peer-reviewed papers, abstracts and book chapters, of which I have been lead-author on 39. Highlights from each chapter include:

CHAPTER 1:

Norris JM, et al. Developments in MRI-targeted prostate biopsy. Curr Opin Urol. 2020 Jan;30(1):1-8.

Fiard G, **Norris JM**, et al. What to expect from a non-suspicious prostate MRI? A review. Prog Urol. 2020 Sep 29;S1166-7087(20)30588-1.

CHAPTER 2:

Norris JM, et al. What type of prostate cancer is systematically overlooked by multiparametric magnetic resonance imaging? An analysis from the PROMIS cohort. Eur Urol. 2020;S0302.

CHAPTER 3:

Norris JM, et al. Which prostate cancers are undetected by multiparametric magnetic resonance imaging in men with previous prostate biopsy? An analysis from the PICTURE study. Eur Urol Open Sci. 2021 Jun 15;30:16–24.

CHAPTER 4:

Norris JM, et al, Emberton M. Prostate cancer undetected by mpMRI: Tumour conspicuity is reliant upon optimal scan timing and quality. Urology. 2020 Dec 2;S0090-4295(20)31427-8.

CHAPTER 5:

Norris JM, et al. A modified Newcastle-Ottawa scale for assessment of study quality in genetic urological research. Eur Urol. 2020 Dec 26;S0302-2838(20)30965–9.

Norris JM, et al. Genetic landscape of prostate cancer conspicuity on multiparametric magnetic resonance imaging: A systematic review and bioinformatic analysis. Eur Urol Open Sci. 2020 Jul; 20; 37–47.

CHAPTER 6:

Norris JM, et al. Patient perspectives and understanding of MRI-directed prostate cancer diagnosis. Urology. 2021 Apr 3:S0090-4295(21)00301–0.

Norris JM, et al. Exploring patient views and acceptance of multiparametric magnetic resonance imaging for the investigation of prostate cancer (the PACT study): A mixed-methods study protocol. Methods Protoc. 2020 Mar 28;3(2).

CHAPTER 7:

Norris JM, et al. Conspicuity of prostate cancer on multiparametric magnetic resonance imaging: a cross-disciplinary translational hypothesis. FASEB J. 2020 Nov;34(11):14150–9.

Oral & Poster Presentations (Full bibliography available on ResearchGate: bit.ly/3taalf1)

During this period of doctoral research, I have presented (and co-presented) over 45 national and international oral and poster presentations, of which I have been lead-presenter on 37. Highlights include:

1. **Norris JM**, et al. Which prostate cancers are undetected by multiparametric magnetic resonance imaging in men with previous prostate biopsy? An analysis from the PICTURE study. *36th Annual European Association of Urology Congress 2021* (Milan).

2. **Norris JM**, et al. Patient perspectives of multiparametric magnetic resonance imaging-directed prostate cancer diagnosis: A prospective systematic mixed-methods study (the PACT study). *6th Meeting of the EAU Section of Urological Imaging 2021* (Athens).

3. **Norris JM**, et al. Exploration of patient trust on the use of multiparametric magnetic resonance imaging for the diagnosis of prostate cancer: Qualitative interim analysis of the PACT study. *2021 Qualitative Health Research Network Conference* (London).

4. **Norris JM**, et al. Which prostate cancers are overlooked by multiparametric magnetic resonance imaging? An analysis from PROMIS. *115th American Urological Association Annual Meeting 2020* (Washington).

5. **Norris JM**, et al. Histopathological basis of prostate cancer conspicuity on multiparametric magnetic resonance imaging: A systematic review and meta-analysis. *27th Annual Prostate Cancer Foundation Scientific Retreat 2020* (Virtual).

6. **Norris JM**, et al. Biparametric MRI detects the aggressive molecular features of prostate cancer. *55th International Congress of European Society for Surgical Research 2020* (Innsbruck).

7. **Norris JM**, et al. mpMRI-visible prostate cancer is enriched with genomic hallmarks of poor prognosis: A bioinformatic analysis. *35th Annual European Association of Urology Congress 2020* (Amsterdam).

8. Stavrinides V, **Norris JM**, et al. MRI-calculated PSAD and significant prostate cancer in the biopsy-naive prostate: Lessons from PROMIS. *115th American Urological Association Annual Meeting 2020* (Washington).

9. **Norris JM**. Revealing the invisible: investigating prostate cancer undetected by mpMRI. *Prostate Cancer UK Virtual Engagement Visit 2020* (London).

10. **Norris JM**. What does mpMRI miss? *UCL Prostate MRI Masterclass 2019* (London).

11. **Norris JM**, et al. Investigating men's perceptions on the use of multiparametric MRI for the diagnosis of prostate cancer. *BASO – Association for Cancer Surgery Conference 201*9 (London).

12. **Norris JM**, et al. Histopathological basis: Correlation of mpMRI with histology to define the margin. *Imperial Prostate: Prostate Imaging & Focal Therapy Masterclass 201*9 (London).

13. **Norris JM**, et al. Be prepared: A multidisciplinary, mpMRI-guided surgical planning meeting for localised prostate cancer. *54th International Congress of European Society for Surgical Research 2019* (Geneva).

14. **Norris JM**, et al. Looking to the horizon: are we on the brink of an artificial intelligence revolution in prostate cancer? *54th International Congress of European Society for Surgical Research* 2019 (Geneva).

15. **Norris JM**, et al. Inter-reader agreement in the reporting of multiparametric MRI for diagnosing prostate cancer. *53rd International Congress of European Society for Surgical Research 2018* (Madrid).

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-	*American Association of Urology 2020 Congress*	Best in Prostate Cancer Session	2020
-	*European Society for Surgical Research* (ESSR)	Fellowship (FESSR)	2020

CONTENTS

ABBREVIATIONS

4Kscore	Four kallikrein protein biomarker
95% CI	95% confidence interval
ACED	International Alliance for Cancer Early Detection
ADC	Apparent diffusion coefficient
AFMS	Anterior fibromuscular stroma
AI	Artificial intelligence
ANOVA	Analysis of variance
ANPEP	Alanyl aminopeptidase
AS	Active surveillance
ASAP	Atypical small acinar proliferation
ATM	Ataxia telangiectasia mutated
AUA	American Urological Association
AUC	Area under the curve
BAUS	British Association of Urological Surgeons
BCR	Biochemical recurrence
BMI	Body mass index
BPH	Benign prostatic hyperplasia
bpMRI	Biparametric magnetic resonance imaging
CAPRA	Cancer of the Prostate Risk Assessment
CD31	Cluster of differentiation 31
CHRNA2	Cholinergic receptor nicotinic alpha 2 subunit
CNA	Copy number alteration

COVID	Coronavirus disease
CRTF	Clinical Research Training Fellowship
csPCa	Clinically significant prostate cancer
CT	Computed tomography
CTU	Clinical Trials Unit
CZ	Central zone
DCE	Dynamic contrast enhancement
DNA	Deoxyribonucleic acid
DRE	Digital rectal examination
DWI	Diffusion-weighted imaging
EAU	European Association of Urology
EMBASE	Excerpta Medica Database
EPE	Extraprostatic extension
ERSPC	European Randomised Study of Screening for Prostate Cancer
ESSR	European Society for Surgical Research
ESUR	European Society of Urogenital Radiology
FESSR	Fellowship of the European Society for Surgical Research
FFPE	Formalin-fixed, paraffin-embedded
FN	False negative
FP	False positive
GC	Genomic classifier
GGG	Gleason Grade Group
GP	General Practitioner
H&E	Haematoxylin & eosin

HES	Hospital Episode Statistics
HGPIN	High-grade prostatic intraepithelial neoplasia
HR	Hazard ratio
IHC	Immunohistochemistry
IIEF	International Index of Erectile Function
IQR	Interquartile range
ISUP	International Society of Urological Pathology
LOO	Leave-one-out
LVI	Lymphovascular invasion
n	Sample size
MCCL	Maximum cancer core length
MDT	Multidisciplinary team meeting
MEDLINE	Medical Literature Analysis & Retrieval System Online
MeSH	Medical Subject Headings
mL	Millilitre
mm	Millimetre
mpMRI	Multiparametric magnetic resonance imaging
MRC	Medical Research Council
MRI	Magnetic resonance imaging
MRI-TB	MRI-targeted prostate biopsy
mRNA	Messenger ribonucleic acid
MYC	Myc proto-oncogene
NCCN	National Comprehensive Cancer Network
ng	Nanograms

NICE	National Institute for Health & Care Excellence
NIHR	National Institute for Health Research
NOS	Newcastle-Ottawa scale
NPV	Negative predictive value
ONS	Office for National Statistics
OR	Odds ratio
p	probability
PACT	Patient Acceptance of Magnetic Resonance Imaging Study
PCa	Prostate cancer
PCA3	Prostate cancer gene 3
PET	Positron emission tomography
PhD	Doctor of Philosophy
PHE	Public Health England
PHI	Prostate health index
PICTURE	Prostate Imaging Compared to TRUS-biopsy for Significant Prostate Cancer Risk Evaluation Study
PI-QUAL	Prostate Imaging Quality
PI-RADS	Prostate Imaging-Reporting and Data System
PNI	Perineural invasion
PPV	Positive predictive value
PRECISION	Prostate Evaluation for Clinically Important Disease: Sampling Using Image-guidance Or Not? Trial
PRISMA	Preferred Reporting Items for Systematic Reviews & Meta-Analyses
PRISMA-P	Preferred Reporting Items for Systematic Reviews & Meta-Analyses Protocol
PROMIS	Prostate Magnetic Resonance Imaging Study
ProtecT	Prostate Testing for Cancer and Treatment

PSA	Prostate-specific antigen
PSAD	Prostate-specific antigen density
PSMA	Prostate-specific membrane antigen
PTEN	Phosphatase & tensin homologue
PZ	Peripheral zone
REC	Research ethics committee
RNA	Ribonucleic acid
RNAseq	Ribonucleic acid sequencing
ROC	Receiver operator characteristic
RP	Radical prostatectomy
RTDS	National Radiotherapy Dataset
SACT	Systemic Anti-Cancer Therapy
SPCG	Scandinavian Prostate Cancer Group
SRE	Skeletal-related event
T2W	T2-weighted sequence
T	Tesla
tBCR	Time to biochemical recurrence
TN	True negative
TNM	Tumour, node, metastasis staging
TRUS	Transrectal ultrasound
TP	True positive
TTPM	Transperineal template-mapping
TZ	Transition zone
UAL	University Arts London

UCSF	University of California, San Francisco
UCL	University College London
UCLH	University College London University Hospitals NHS Foundation Trust
UK	United Kingdom
USA	United States of America
WHO	World Health Organisation

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NB: All tables were designed and created by me for this doctoral research, unless otherwise stated.

Table 22 Patient engagement workshop responses to PACT results

LIST OF FIGURES

NB: All figures were designed and created by me for this doctoral research, unless otherwise stated.

Fig. 22 Cellular density map examples of prostate biopsies from PROMIS

CHAPTER 1:

INTRODUCTION

1.1 BACKGROUND

Prostate cancer is a challenging disease in several ways. Firstly, prostate cancer generates a large healthcare burden (over 55,000 diagnoses per year in the UK) and secondly, accurate risk stratification, diagnosis and appropriate treatment delivery remain difficult problems inherent to this disease. There are a number of reasons that these issues have persisted, and a combination of disease misunderstanding, delayed clinical presentation, technological limitation, and anatomical positioning within the narrow male pelvis, stand out as predominant culprits.

The approach of using a combination of serum prostate-specific antigen (PSA) and systematic transrectal ultrasound (TRUS)-guided biopsy resulted in early detection (and thus, treatment) of a large proportion of patients with prostate cancer, before the disease manifested clinically. However, the poor diagnostic characteristics of systematic TRUS-guided biopsy (approximate sensitivity for detection of clinically significant disease, that is, in other words, likely to impact on survival, was 48% in the Prostate Magnetic Resonance Imaging Study [PROMIS] study)[1] has resulted in several drawbacks, particularly over-diagnosis of insignificant cancer, and under-diagnosis of significant cancer. Whilst the traditional TRUS technique provides a reasonable approximation of prostate volume and anatomy, the modality is largely blind to significant tumour presence or position within the prostate (resulting in the aforementioned stratification and diagnostic errors), due to poor disease visibility on traditional ultrasound.

Over the last decade, improvement in prostate cancer imaging has helped address this. Multiparametric magnetic resonance imaging (mpMRI) combines a number of distinct MRI sequences that exploit differences in tumoural (and normal) tissue (e.g. cellular density) to generate a three-dimensional assessment of the likelihood (and location) of significant disease.[1–4] This approach provides spatial information required for MRI-targeted biopsy, and also permits omission of biopsy in cases of non-suspicious pre-biopsy imaging, due to favourable diagnostic characteristics (approximate sensitivity for detection of significant disease: 93% in the PROMIS study).[1]

Despite considerable progress and integration of pre-biopsy mpMRI into international prostate cancer guidelines and risk models,[5–10] a number of challenges still surround this technology, and understandably, these are accompanied by academic and clinical scepticism. One of the most controversial debates in this field centres around disease conspicuity (i.e. visibility) on mpMRI.[11,12] Sustained research effort has helped elucidate the performance and clinical potential of prostate mpMRI, however, the nature and significance of prostate cancer that is detected or undetected by pre-biopsy mpMRI, has yet to be fully described.[13–17] The overarching aim of the doctoral research presented here was to systematically investigate prostate cancer that is undetected on mpMRI, using multiple levels of investigations (including, genetic, histopathological and radiological approaches).

1.2 PROSTATE CANCER

1.2.1 Prostate Anatomy

Positioned just superior to the bladder neck, the prostate comprises a mixture of glandular (70%) and fibromuscular tissue (30%). Prostatic stroma consists of contractile collagen and smooth muscle that assists with one of the key functions of the prostate – producing ejaculate (to aid transmission of spermatozoa, and enable conception). Anatomically, the gland is divided into three main zones. Firstly, the conical central zone (CZ), beneath the bladder around the ejaculatory ducts, harbours around a quarter of the prostatic glands. Secondly, encircling the urethra is the transition zone (TZ), which is the most commonly affected region by benign prostatic hyperplasia (BPH), with approximately 5–10% of the glandular tissue. Thirdly, the majority of glandular tissue (70%) is located in the peripheral zone (PZ), around the posterolateral prostate; classically, this is considered the commonest location for prostate cancer development.[18] Finally, the anterior fibromuscular stroma (AFMS) contributes approximately 33% of the prostate volume and spans from urethral sphincter to bladder neck.

1.2.2 Epidemiology of Prostate Cancer

Prostate cancer is the most prevalent male malignancy, and in 2017, the global incidence of prostate cancer was 1.3 million. For cancer-specific male mortality, prostate cancer remains the third most common cause despite introduction of diagnostic adjuncts, including PSA.[19,20] Whilst PSA screening appears to have reduced the proportion of patients with advanced disease, it has led to over-diagnosis and over-treatment of clinically insignificant cancer.[21] Older-aged patients are at a higher risk of developing prostate cancer (85% diagnosed are over 65-years-old) than younger patients.[22] Furthermore, patients with family history of prostate cancer have a higher risk of developing the disease.[23] Lastly, through a combination of socioeconomic, cultural and genetic factors, it appears that black patients are the highest-risk ethnic group, in terms of prostate cancer diagnosis incidence, and unfavourable outcome.[24,25] In addition to these factors, comorbidities, including hypertension and raised body mass index (BMI) appear to increase risk, particularly from a prognostic standpoint.[26–30]

1.2.3 Prostate Cancer Diagnosis

Before the introduction and widespread uptake of PSA (prostate-specific antigen; an enzyme produced by the prostate, noted to have increased serum values in prostate cancer) screening, patients with prostate cancer would often present with advanced disease, with symptoms including, metastatic boney-type pain and various obstructive lower urinary tract symptoms.[31] Association of PSA with prostate cancer stage was confirmed through measurement of serum PSA levels in patients with new diagnoses (with advanced disease presenting with the highest levels), and this was further ratified through observation of a fall in serum PSA following radical prostatectomy (RP).[31] When combined with digital rectal examination (DRE) and transrectal biopsy, PSA was shown to have decent utility in improving prostate cancer detection and treatment outcomes (e.g. time to biochemical recurrence after radical prostatectomy).[32,33] However, low sensitivity of PSA for significant disease has since resulted in overdiagnosis and overtreatment.[21]

Unlike other solid-organ cancers, once the suspicion of prostate cancer is raised (e.g. through raised serum PSA in primary care), the traditional diagnostic approach to prostate cancer is to undertake a systematic biopsy (i.e. non-image guided, in which 12 representative samples are taken across the gland, with a transrectal needle). This method does not account for cancer location, and relies on representative sampling of the peripheral zone to diagnose the disease. The technique carries several side-effects (including, sepsis, haemorrhage, and admission to hospital) and the diagnostic risk of overlooking significant tumours, especially anteriorly-located disease.[34–36] In the European Randomised Study of Screening for Prostate Cancer (ERSPC), 4.2% (392/9241) of patients undergoing systematic TRUS-guided biopsy reported fever, and 81% of hospital admissions were attributable to post-biopsy infection, with a background risk of sepsis from the procedure ranging from 0.5–3.1%.[36,37]

In the past decade, significant effort has been made to overcome drawbacks of traditional systematic TRUS-guided biopsy (with no targeting), including the move toward a transperineal approach (with a reduction in infection-related complications), and the addition of image-guidance (increasing diagnostic accuracy by providing an actual tumour target, identified on pre-biopsy mpMRI), with a range of targeting approaches, including cognitive-targeting and MRI-ultrasound fusion targeting.[38–45]

Once a prostate biopsy is acquired and prepared, it is graded histopathologically with the Gleason grading system.[46] This system uses assessment of cellular arrangement and glandular size to assign a Gleason pattern of 3, 4 or 5 (in ascending level of deviation from normal tissue morphology).[46,47] Gleason grades 1 and 2 were removed in 2005 due to their close resemblance to normal prostatic architecture. Once scored, the two most common Gleason patterns are assessed (primary and secondary patterns), and listed in order of overall prevalence (on that specimen). In addition to primary and secondary patterns, tertiary scores are occasionally listed, as these may affect clinical outcome.[48] Whilst the Gleason system provides an estimation of clinical risk, it does suffer moderate interobserver variability, with the

presence of fused and poorly fused glands in Gleason pattern 4 reducing inter-pathologist agreement further.[49–54] As with other diagnostic elements of the prostate cancer pathway, this has resulted in an effort to automate histopathological grading, with an increasing emphasis being placed on artificial intelligence (AI) integration.[55–57]

In a move to improve the Gleason grading system, the International Society of Urological Pathology (ISUP) designed a novel categorisation approach, referred to as Gleason Grade Grouping (GGG).[58,59] The purpose of Grade Grouping was to simplify Gleason scoring and acknowledge the different prognostic implications of each group. This was felt particularly important for Gleason score 7 (i.e. Gleason 3 + 4 or Gleason 4 + 3) as patients with higher proportions of Gleason pattern 4 (Gleason 4 + 3) are now known to have demonstrably poorer clinical outcomes, likely due to the unfavourable genetic landscape exhibited by Gleason pattern 4 compared to Gleason pattern 3.[60–63] When comparing outcomes of Gleason 3 + 4 to Gleason 4 + 3, primary pattern 4 were more likely to have seminal vesicle involvement, higher disease stage, extraprostatic extension (EPE), risk of progression at five years, earlier time to progression and time to biochemical recurrence (tBCR).[64,65]

1.2.4 Staging & Risk Prediction for Prostate Cancer

After diagnosis is established, prostate cancer is staged with the Tumour, Node, Metastasis (TNM) approach, and adjunctive risk models are often used to further aid treatment planning and prognostication. Contemporary imaging techniques, including mpMRI and prostate-specific membrane antigen positron emission tomography (PSMA-PET), now allow assessment of local and distant metastases, and facilitate precision treatment planning.[66–68]

Several risk models now exist for prostate cancer, however, the most well-known is the D'Amico model in which patients are stratified into three groups, using TNM stage, preoperative serum PSA and Gleason score. The primary purpose of these risk groups is to serve as a predictor for the risk of biochemical recurrence after radical surgery.[69] The D'Amico risk groups are: intermediate risk (T2b, PSA 10.1–20ng/mL, Gleason 7) and high risk (T2c, PSA > 20ng/mL, Gleason 8–10). The University of California, San Francisco (UCSF) Cancer of the Prostate Risk Assessment (CAPRA) tool also allows multivariate prediction of risk of recurrence post-treatment, with moderate-good concordance.[70] It acknowledges serum PSA, TNM staging, Gleason score, percentage of positive biopsies and patient age. Three risk groups are then generated: low risk, intermediate risk and high risk. Lastly, the National Comprehensive Cancer Network (NCCN) produced a risk estimation system that acknowledges serum PSA, GGG (with Gleason 3 + 4 and Gleason 4 + 3 given different scores), pathological stage, and the number of positive biopsy cores. Once these have been assessed, a patient is given a risk of either: very low, low, intermediate, high or very high. Previously, this risk classification approach

suggested active surveillance for patients with low risk disease, though this has controversially been removed in their latest guidelines.[71]

1.3 MULTIPARAMETRIC MRI

1.3.1 Development

Until the latter half of the 20th century, the predominant method of studying anatomy and disease of the prostate was either to expose it with major surgery (e.g. during radical prostatectomy) or with cadaveric dissection in the deceased. The considerable limitations of both of these invasive approaches increased the need to develop imaging approaches for the prostate. In 1957, John Wild and John Reid first posited the concept of transrectal ultrasound imaging, however, at this time, the technology was at an early developmental stage with only rectal wall contours being visualised.[72] In 1967, the first clinically applicable ultrasound device was released for imaging the oesophagus.[72] This device was then adapted to finally reveal what had been largely invisible until that point, the human prostate. Ultrasonic images of the prostate delivered useful information such as gland volume and approximate anatomy (Fig. 1). However, ultrasound images did not adequately identify cancer within the prostate. Even with advanced ultrasound techniques (e.g. microultrasound, contrast ultrasound, elastography or HistoScanning) the utility of this approach in locating prostate cancer appears to be limited.[73]

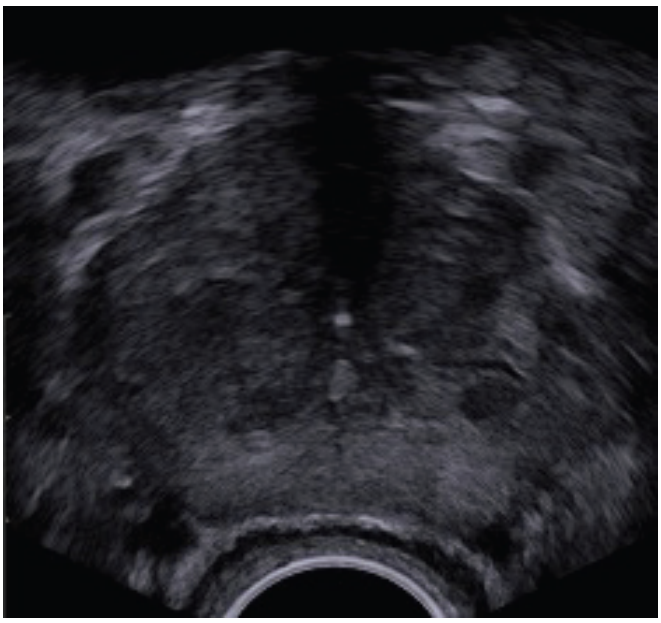


Fig. 1 – Transrectal ultrasound image of the prostate (axial view). (*Image courtesy of Clement Orczyk).*

The use of MRI for cancer diagnosis began in 1971 with rodent experimentation,[74] however, it was in 1982 that John Steyn and Francis Smith performed the first MRI study of the human prostate.[75] The image quality at this stage was low

with the prostate poorly discernible from surrounding organs. Since then, several further developments have occurred (Fig. 2). The introduction of higher strength MRI magnets, phased-array coils, newer sequences (including, the assessment of gadolinium contrast agent uptake by the prostatic tissue with the dynamic contrast-enhanced [DCE] sequence; and the diffusion of water in prostatic tissue with the diffusion-weighted imaging [DWI] sequence) have now greatly improved the accuracy of mpMRI for the detection of prostate cancer.

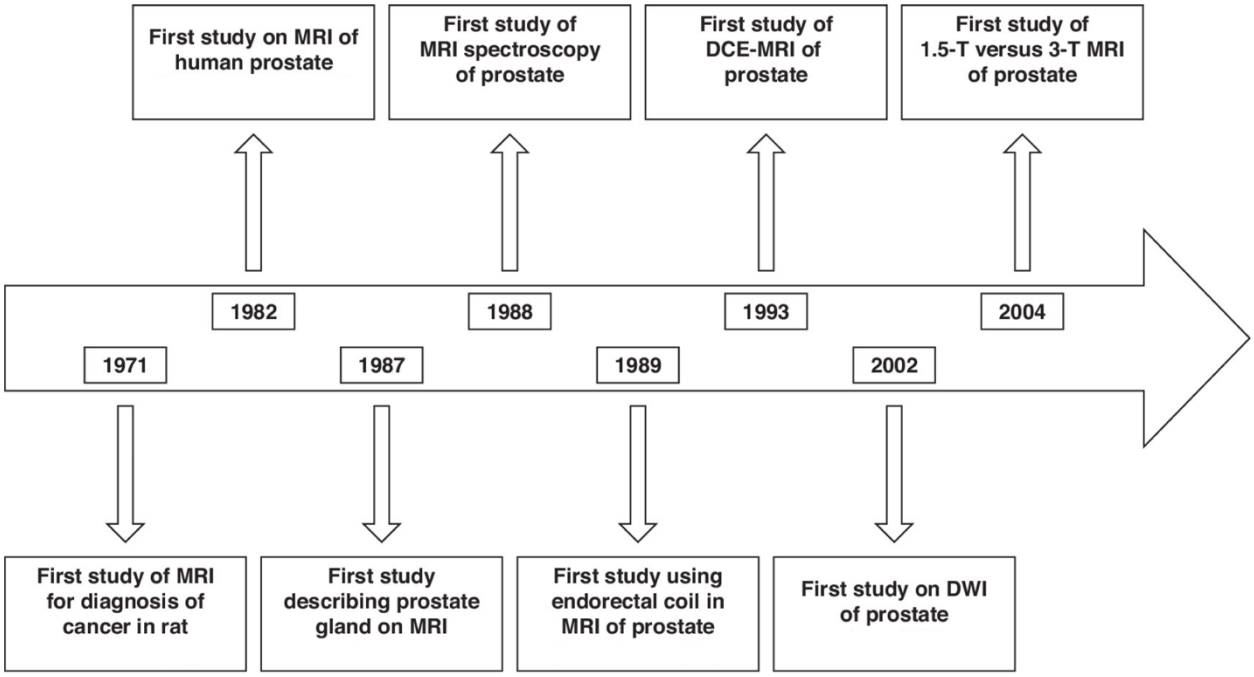


Fig. 2 – Timeline of key stages in the development of prostate mpMRI. (*Image courtesy of Francesco Giganti, as featured in: doi.org/10.2214/AJR.18.20796).*

To test the accuracy of mpMRI for the diagnosis of prostate cancer, several high-impact clinical studies have been conducted (two of which have been used for post hoc analyses in the doctoral research presented in this thesis). PROMIS was an important clinical study in which mpMRI and traditional systematic TRUS-guided biopsy were both compared against a strict reference standard (transperineal template mapping [TTPM] biopsy, in which prostates were sampled at every 5mm) to establish the diagnostic accuracy for both modalities.[1] For detection of the most significant prostate cancer (as defined as Gleason ≥ 4 + 3, or over 6mm length of any cancer, on biopsy), mpMRI was able to detect over 90% of this disease, whereas systematic TRUS-guided biopsy detected approximately 50%.[1] Furthermore, with mpMRI employed as a pre-biopsy triage tool, PROMIS demonstrated that around 27% of patients could safely omit immediate biopsy, whilst reducing the proportion of patients diagnosed with insignificant cancer. The findings of the

PROMIS study were then tested in the PRECISION (Prostate Evaluation for Clinically Important Disease: Sampling Using Image-guidance Or Not?) trial.[20] PRECISION was a randomised controlled trial in which patients with suspected prostate cancer either underwent traditional systematic TRUS-guided biopsy or an MRI-targeted biopsy, in which biopsies were only taken from tumours that were detected on pre-biopsy mpMRI. The results of this trial demonstrated the utility of mpMRI as a diagnostic tool for prostate cancer. Firstly, fewer patients required upfront biopsy (only patients who had suspicious findings on mpMRI were biopsied), and then secondly, patients who underwent MRI-targeted biopsy only had higher rates (38% vs. 26%) of detection of significant cancer and lower rates (9% vs. 22%) of detection of insignificant disease, compared to patients that had standard systematic (non-mpMRI guided) biopsy.

The accuracy of prostate mpMRI for the detection of significant prostate cancer may partly be attributed to the multiparametric approach that is used. With a multiparametric approach, the prostate is visualised with multiple sequences (Fig. 3) before a radiologist conducts an assessment of each sequence in tandem to generate an overall impression for the suspicion level for the presence of prostate cancer. Each MRI sequence examines the prostate tumour in a different, complementary way, and if a lesion appears to be suspicious in the same location on multiple sequences, then this raises the possibility of malignancy.

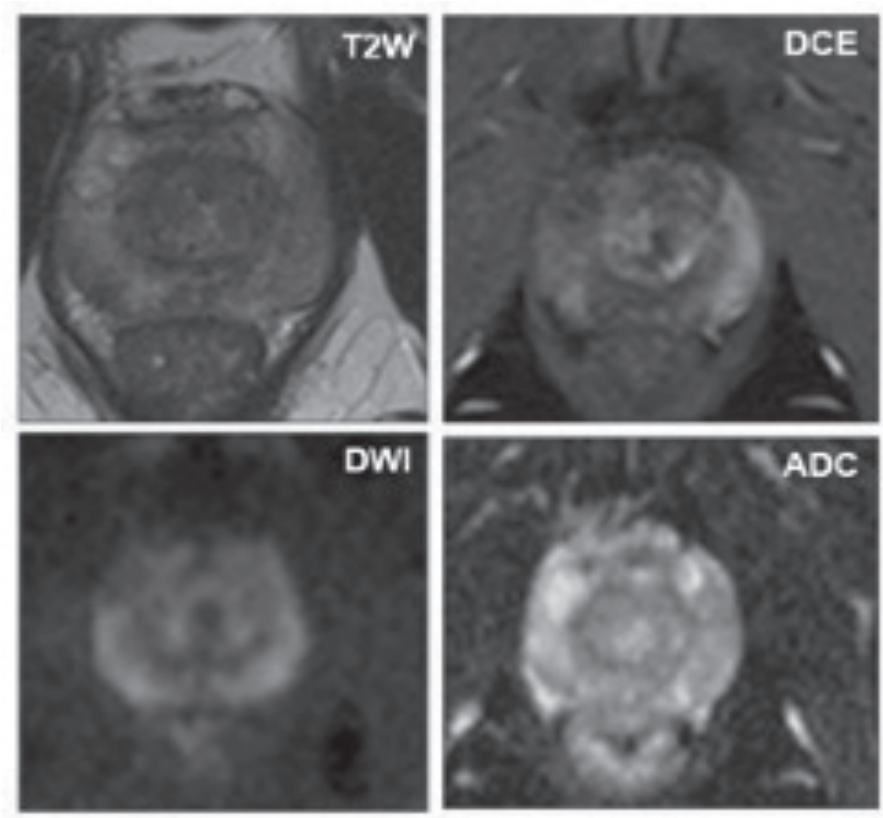


Fig. 3 – mpMRI images of the prostate. (*Clinically significant right PZ tumour. T2-weighted sequence [T2W] demonstrating the general anatomy of the gland and tumour; top left panel. DCE sequence demonstrating the increased tumour vasculature; top right panel. DWI and apparent diffusion coefficient [ADC] sequences demonstrating increased tumour tissue density; bottom*).

1.3.2 Scoring Systems

There are two predominant scoring systems used to assess prostate mpMRI (Table 1). Firstly, the Prostate Imaging-Reporting and Data System (PI-RADS) v2.1, which was originally produced by the European Society of Urogenital Radiology (ESUR) to standardise mpMRI reporting, and is widely used across Europe and the United States.[76–79] Updated versions now place stronger emphasis on using the T2W sequence for TZ tumours (to help discern from benign BPH nodules).[80–82] The PI-RADS scale ranges from 1–5, with increasing levels of clinical suspicion, based upon defined mpMRI features. Secondly, the Likert score, used predominantly in the UK, is an alternative to PI-RADS to again rate the level of clinical suspicion on an mpMRI scan on a scale of 1 to 5. In contrast to PI-RADS, the Likert scale includes clinical information (e.g. patient age, PSA level and family history) and does not rely on appearances from a dominant sequence.[83]

Table 1 – Interpretation of PI-RADSv2.1 & Likert mpMRI suspicion scores.

Suspicion score	PI-RADSv2.1	Likert
1	Very low (clinically significant cancer is highly unlikely to be present)	Presence of cancer is very unlikely
2	Low (clinically significant cancer is unlikely to be present)	Presence of cancer is unlikely
3	Intermediate (presence of clinically significant cancer is equivocal)	Presence of cancer is indeterminate
4	High (clinically significant cancer is likely to be present)	Presence of cancer is likely
5	Very high (clinically significant cancer is highly likely to be present)	Presence of cancer is highly likely

1.4 MRI-INVISIBLE PROSTATE CANCER

1.4.1 Historical & Cultural Context

Throughout history, humans have worked to reveal what is perceived to be invisible, predominantly due to curiosity or fear. There appears to be a continuous desire to find what is known to exist but is not visible, and also to find what is believed to exist, but is not presently perceptible. Often, technological innovation has been central to this endeavour, and there are several key examples, including, the use of mpMRI to detect prostate cancer.

In 1610, the Italian astronomer, Galileo Galilei, looked into the sky and considered the hidden details in the stars and planets that were faintly visible above.[84] To picture previously invisible features, Galileo created a simple prototypic refractor telescope (Fig. 4). His telescope consisted of a basic arrangement of lenses that began as simple optician glasses fixed to either end of a hollow cylinder. By a process of trial and error, he determined the correct lens shape, size and position needed to picture the invisible. Prior to his invention, the moon was thought to be featureless like a smooth gemstone (although a few basic features are visible to the naked eye), but with Galileo's telescope, he revealed it be 'uneven, rough, full of cavities and prominences'.[85] The details that he revealed about space and the solar system have since advanced the field of astronomy, and our appreciation and understanding of our position in the universe.

Fig. 4 – Galileo constructed a simple telescope to reveal the stars and planets. (*Image courtesy of the European Southern Observatory).*

In 1895, Professor of Physics in Worzburg, Wilhelm Roentgen, discovered that electromagnetic radiation could be used to see inside the human body – without the need for surgery or autopsy.[86] In a dark room, Roentgen explored the path of electrical rays from an induction coil, through a partially evacuated glass tube covered in black paper. He noted that across the room, a screen coated in fluorescent material was being illuminated by the rays, despite the tube being covered. He extrapolated from this finding and discovered that these rays could penetrate other objects before they reached the screen and, eventually, he showed that the rays could penetrate his own wife's hand, revealing the contrast between her bones and soft tissues. When he replaced the screen with a photographic plate, he realised that this contrasting image could be captured and in doing so created the first ever x-ray. This important serendipitous discovery plus subsequent thorough investigation enabled him to picture previously invisible details and catalysed the creation of medical imaging.

In both world wars of the twentieth century, incoming aircraft posed a significant threat and as such, considerable effort was placed into developing early methods of detection. Despite being large and loud, enemy planes often remained invisible for too long; for instance, when a bombing aircraft was visible by eye, it was likely too late to institute sufficient counter-measures or evacuations (interestingly, there is a close analogy here with cancer in the human body). Some of the earliest methods of detection were referred to as acoustic mirrors. Passive acoustic detection was done with horns or cones that would detect the vibrations as they were transmitted from the engines of distant planes. The location and distance of the incoming enemy threat was then estimated by the intensity and laterality of the incoming sound, but this was a crude test and many of the inbound aircraft still remained invisible for too long. This challenge was eventually addressed by the advent of a new piece of detection technology – radar.

During World War II, rapid innovations in engineering, science and technology were made in an attempt to gain advantage over enemy forces. This 'war effort' saw developments in several different scientific fields, and in many ways could be credited with the creation of the science of detection.[87] Early identification of incoming (invisible) enemy vehicles was important, as the sooner these invisible threats could be identified, the better the outcome. Existing technology, whether binoculars or acoustic mirrors, were inadequate and hence a new technological solution was created in the form of radar (Radio Detection And Ranging). In 1864, the British physicist James Clerk Maxwell described equations regarding electromagnetic wave behaviour that incorporated laws of radiowave reflection.[88] Taking this theory further, the German engineer Christian Hülsmeyer later proposed that radioechoes could be used to avoid ship collisions.[89] In 1935, Sir Robert Watson-Watt built upon these concepts and created the first working radar machine, which could emit radiowaves and detect them as they returned, having reflected off solid objects in the distance.[90] The intention of this device was to monitor reflected waves to identify the presence, location and size of seemingly invisible incoming aggressors. As a result of Watson-Watt's work, a series (or chain) of radar stations were established all along

the South and East coast of England in 1939 (Fig. 5). Amongst several other pertinent factors, the development of radar is considered one of the possible factors that may have helped in turning the tide of World War II.

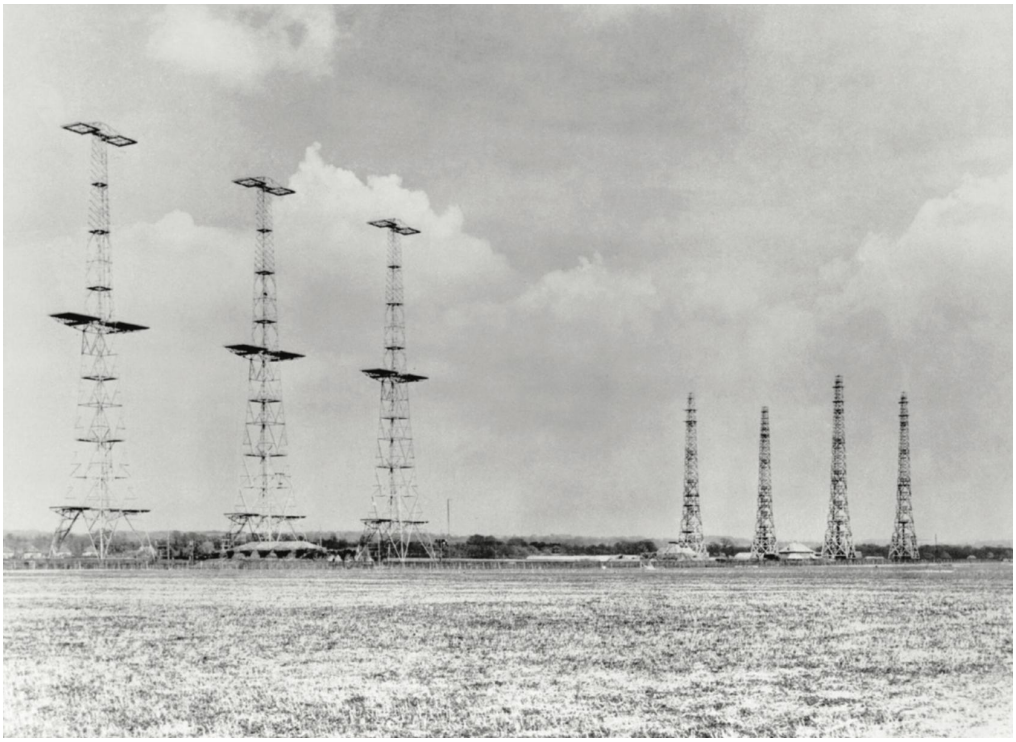


Fig. 5 – Chain Home radar stations. (*Image courtesy of the Imperial War Museum).*

In parallel with the development of radar, the science of detection and methods of assessing detection accuracy were also developed during the Second World War. The concept of the ROC curve (Receiver Operator Characteristic curve) was developed as a method of assessing the ability of radio operators to detect true incoming threats (e.g. aircraft) and distinguish these from false ones (e.g. flocks of geese). The ROC curve is plotted in a binary way, where all the 'hits' are plotted individually and a curve formed by connecting these. The higher the proportion of 'true hits' that the operator or test can identify, then the closer the curve will be to the vertical axis. The greater the amount of true positive results, then the more sensitive the test (Fig. 6).

This approach to assessing the ability of a test to distinguish true signal from noise is directly applicable to diagnostic medical imaging, including mpMRI and the detection of prostate cancer, which incidentally appears to perform well in this regard.[1].

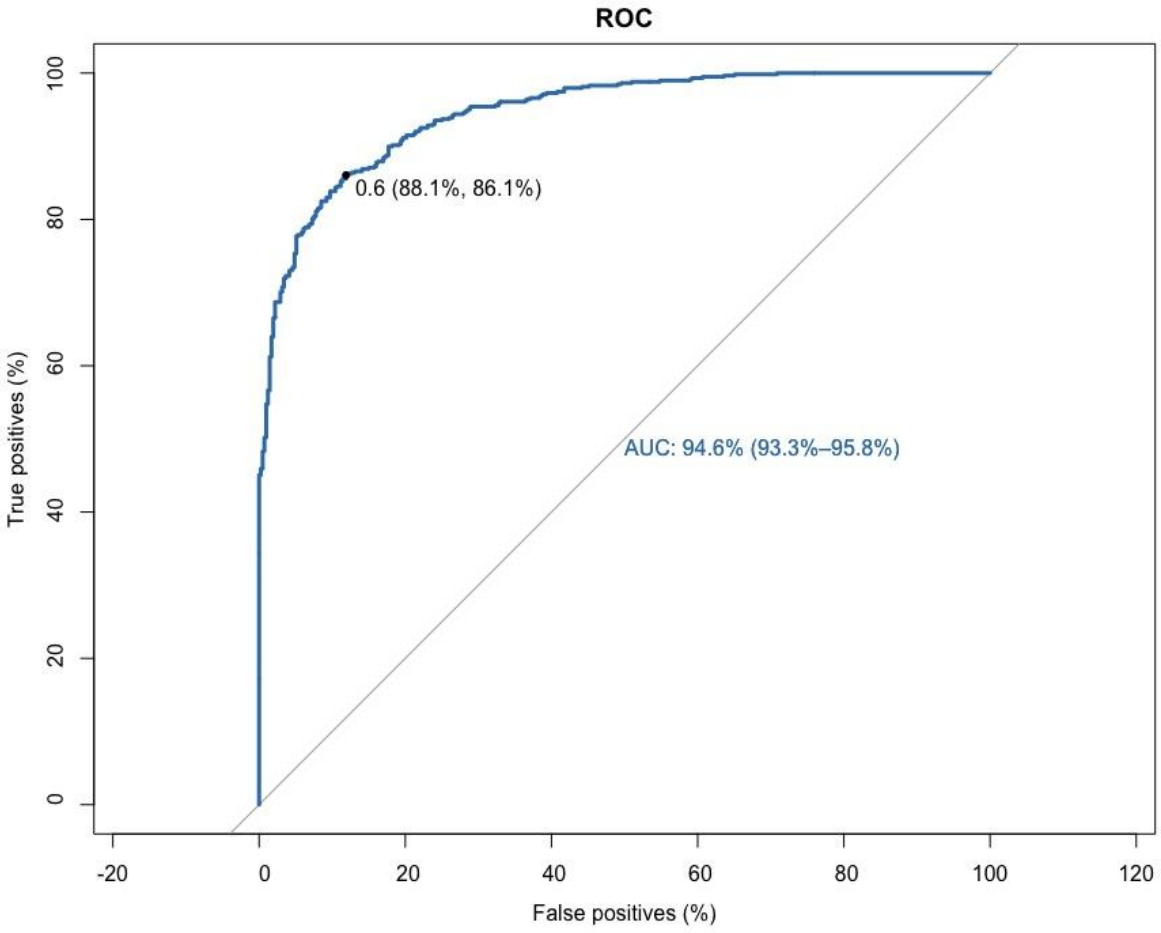


Fig. 6 – Example of a generic ROC curve. (*Image courtesy of Vasilis Stavrinides).*

1.4.2 Detection of Cancer by MRI in Other Organs

Pre-biopsy cross-sectional imaging has been adopted as an important part of the modern diagnostic approach for several solid organ cancers, and MRI now plays a key role in this process, particularly for the diagnosis of breast and hepatic malignancy. As with prostate cancer, the detection of breast and liver tumours with MRI is imperfect, and there remains a spectrum of undetected disease in both of these organs that may provide insight into the biology and factors that underpin cancer conspicuity on MRI. It is important to remember that non-detection of cancer by MRI may be a beneficial characteristic, particularly with regards to clinically insignificant disease, and the reduction of overdiagnosis; which is an aim common to all cancer management.

1.4.2.1 MRI-Undetected Breast Cancer

For several decades, x-ray mammography has been used as the classical way to screen and image for breast malignancy. However, increasingly, alternative imaging modalities, including ultrasound and MRI have been used as

imaging adjuncts for the diagnosis of breast cancer. Evidence from the Dutch National Cancer Registry suggests that the breast MRI has a high degree of accuracy for the detection of breast cancer, with an approximate sensitivity of 90%,[91] which is comparable to the sensitivity of mpMRI and the detection of significant prostate cancer. Several existing breast cancer studies have examined a number of important potential reasons that underpin the non-detection of breast cancer on MRI. In parallel with certain prostate cancer subtypes, it appears that there are particular forms of breast cancer (including, ductal carcinoma in situ, invasive lobular carcinoma, and certain well-differentiated invasive cancers) that have reduced visibility of MRI, potentially due to reduced angiogenesis and neovascularity, thus highlighting the importance of contrast enhancement for breast cancer detection.[92] This is an interesting factor, particularly given the current ongoing debate regarding the questionable necessity of the contrast-enhanced sequence for the detection of prostate cancer on mpMRI. The relationship between imaging phenotype and cancer genetic landscape has become increasingly relevant in recent years, and it appears that this is the case with both breast and prostate cancer. Interestingly, Vreeman and colleagues found that the presence of a *BRCA* mutation appeared to be associated with an increased likelihood of truly MRI-invisible breast cancer (as opposed to radiologist error).[91] The biology for this association is unclear, however, the authors theorised that this may be attributable to increased recall rate, and increased radiologist suspicion levels for patients known to have high-risk *BRCA* mutations (and thus more likely to receive a diagnosis, for example through mastectomy, and thus discovery that their disease is not visible to MRI).[91]

In a manner somewhat analogous to prostate active surveillance with MRI, the breast cancer literature describes certain features of breast cancers that are overlooked in initial MRI, but then detected on subsequent MRI – in particular, some authors (by reappraising previous MRI scans that were initially labelled as 'negative') have suggested that lesions that appear to increase in size over time, have rapid uptake kinetics or a change in kinetic pattern over time, or have an isolated focus or focus showing more enhancement than other foci, should all be treated with a high degree of suspicion.[93,94] These features may be important to consider when assessing serial mpMRI in patients with suspected prostate cancer. Finally, it appears that certain undetected breast cancers are likely to be attributable to reader-error on initial MRI (i.e. they were missed by mistake),[92,95] and this is also likely to be true for prostate mpMRI, however, the optimal use of 'double-reading' has yet to be fully described in uroradiology, particularly as this is a potentially resource and time-consuming solution.

1.4.2.2 MRI-Undetected Hepatocellular Carcinoma

Prevalence of MRI-undetected hepatocellular carcinoma (HCC) varies widely by definition and clinical setting (approximate range: 1.4–13%; often discovered on hepatic explants),[96,97] however, certain common features appear to

exist for disease that is undetected by MRI. A retrospective study from Choi and colleagues found a number of reassuring features of MRI-undetected HCC, in particular, these tumours tended to have a smaller diameter (mean: 1.1cm), especially in comparison to the overall organ volume, and furthermore, none of the overlooked tumours in their series were considered to be untreatable at the time of eventual detection. These reassuring features again appear to be reflected by prostate cancer that is not detected by mpMRI. In an attempt to reduce the rates of non-detection of HCC on MRI, several studies have identified potential opportunities for these initially false negative tumours. In these studies, a substantial number of initially overlooked tumours were actually classified as being of 'intermediate' suspicion, which potentially suggests that there may be a subset of these intermediate tumours that should have potentially been radiologically upgraded, and this may also be true for some intermediate-scoring (e.g. PI-RADS/Likert 3) prostate cancers. Interestingly, a number of MRI-overlooked HCC tumours were retrospectively visible on the arterial phase of contrast liver MRI,[96,97] however, the applicability of this characteristic to prostate mpMRI is not clear, particularly given current debates around the potential removal of the DCE sequence.

1.4.3 Contemporary Evidence

Over the past five years, research has been conducted to elucidate the nature of mpMRI-undetected prostate cancer, given the potential accompanying risk of biopsy omission in such cases. All imaging technology has limits of spatial resolution, which features-of-interest will fall below, if small enough. In keeping with this, evidence so far suggests that mpMRI-undetected tumours tend to be of smaller size, than those that are detected.[98] Furthermore, it appears that mpMRI-undetected tumours appear to be of lower pathological grade, and again, this may relate to underlying physics of mpMRI (lower grade tumours may have reduced tissue density, and thus be less conspicuous upon mpMRI).[13] However, as yet, the evidence supporting these tumoural characteristics of mpMRI-undetected disease is limited by intrinsic methodological drawbacks, particularly due to reliance on the use of imperfect histopathological reference standards (e.g. high selection bias of radical prostatectomy, or poor diagnostic accuracy and reliability of systematic TRUS-guided biopsy).

Beyond the tumoural-level, it seems that mpMRI-invisible disease is also differentiated from mpMRI-visible disease at a cellular level (Fig. 7). Miyai and colleagues recently compared mpMRI-visible and mpMRI-invisible tumours on whole-mount radical prostatectomy; they found that visible tumours had higher architectural density with increased proportions of cancer cells (60.9% vs. 42.7%, $p < 0.0001$), decreased stromal proportions (33.8% vs. 45.1%, $p = 0.00089$) and decreased luminal proportions (5.2% vs. 12.2%, $p < 0.0001$).[14] These results appear to confirm previous findings demonstrating that restricted diffusion was more strongly linked to the distribution of epithelial, luminal and stromal

components than to glandular differentiation.[88,89] Association of increased tissue density and tumour visibility on mpMRI has biological plausibility – diffusion of water on mpMRI is likely to be further restricted in tissue with higher density, thus increasing tumour conspicuity on the DWI sequence. In a similar study, Borren and colleagues found that mpMRI-visible tumours had higher cellular and microvessel density compared to mpMRI-invisible tumours (cell density: 3560 cells/mm^2 vs. 2910 cells/mm^2; microvessel density: 115 vessels/mm^2 vs. 90 vessels/mm^2).[15] In this case, tumour visibility could be potentially explained by higher microvessel density, which might generate higher DCE signal through higher tissue concentrations of gadolinium within microvessels.

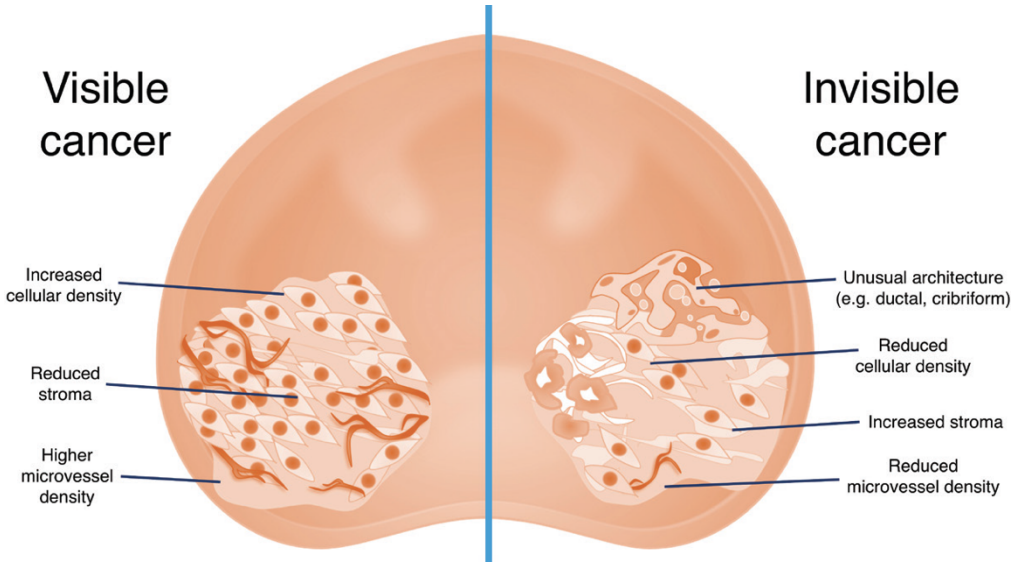


Fig. 7 – Features of mpMRI-visible (left) mpMRI-invisible & mpMRI-invisible prostate cancer (right) at the histopathological level.

Interestingly, there is a claim that there are two (potentially aggressive) prostate cancer subtypes that have reduced detection on mpMRI, namely ductal and cribriform, due to their potentially reduced tissue density (from increased luminal fraction; Fig 8). However, this claim is contested; Tonttila and colleagues recently examined a cohort of patients undergoing radical prostatectomy and found that preoperative mpMRI identified 90.5% (86/95) of tumours containing any cribriform or ductal pattern (95% CI 82.5–95.6), and as such, it appears that the link between histopathology and tumoural visibility on mpMRI warrants further research.[101]

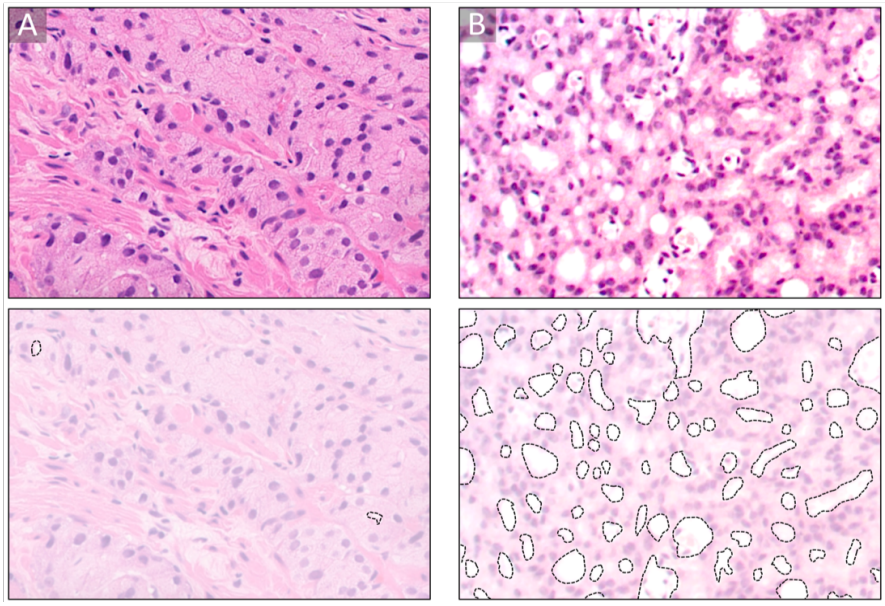


Fig. 8 – Typical prostate cancer (A) & cribriform pattern cancer (B) with numerous punched out lumina. (*Slide courtesy of Alex Freeman*).

1.4.4 Ongoing Challenges

There are a number of ongoing challenges surrounding the use of mpMRI (Table 2). The research conducted here aims to address these (or help to provide a framework for future research), through exploration of the nature of mpMRI-invisible prostate cancer.

Table 2 – Contemporary issues surrounding the use of prostate mpMRI

Challenge	Commentary
Imperfect diagnostic accuracy	As described, pre-biopsy mpMRI has good diagnostic accuracy for detection of clinically significant prostate cancer, however, some clinicians remain unsatisfied with the MRI-directed diagnostic approach, citing unacceptable levels of undetected cancer (false negatives; approximately 10–20%) and excessive proportions of non-malignant positive mpMRI (false positives; approximately 50%).
Biopsy strategy uncertainty	MRI-targeted biopsy is now more widely accepted as a diagnostic approach, however, debates continue regarding specific biopsy strategy, including: need for concomitant systematic biopsy (i.e. concern regarding mpMRI-invisible cancer in the non-suspicious areas of the prostate); the actual biopsy procedure (e.g. transrectal vs. transperineal; local vs. general anaesthetic; cognitive vs. fusion guidance); and the requirement for peri-lesional samples (to sample mpMRI-invisible disease at the tumour edge and to define extent of required treatment margin.
Increasing workload	Global integration of mpMRI into prostate cancer diagnostic pathways has increased radiology (and, urology and pathology) workloads. This has created a challenge in which various solutions have been proposed, including, potential introduction of AI adjuncts to aid reporting, use of additional risk stratifiers (including, genetic biomarkers) to refine pathway entry, and the potential (selective) removal of the DCE sequence, to create shorter “biparametric” MRI (bpMRI).
Paucity of patient engagement	Since the inception of prostate mpMRI, there has been continued clinical and academic involvement and debate surrounding the use of this technology, however, there has been a paucity of patient-centric research in this field. By not engaging patients directly, and not eliciting their views on the major changes catalysed by mpMRI, or explaining possible benefit effectively, we risk introducing novel technologies and diagnostic uncertainties that may be unacceptable to the patients that directly undergo this process.

1.5 AIMS & OBJECTIVES

1.5.1 Aims

The aim of this Medical Research Council (MRC)-funded doctoral research was to produce a cohesive first body of work examining the nature of prostate cancer undetected by mpMRI, at several analytical levels.

1.5.2 Objectives

1. Describe key histopathological characteristics of mpMRI-undetected disease in biopsy-naïve patients using post-hoc analysis of the PROMIS study
2. Describe key histopathological characteristics of mpMRI-undetected disease in non-biopsy-naïve patients using post-hoc analysis of the PICTURE (The Prostate Imaging Compared to Transperineal Ultrasound-guided biopsy for significant prostate cancer Risk Evaluation) study
3. Determine radiological factors associated with non-detection of clinically significant prostate cancer on pre-biopsy mpMRI using radiological re-analysis of a sub-population from the PROMIS study
4. Explore molecular landscape of mpMRI-detected and mpMRI-undetected disease using a bioinformatic and systematic review methodology
5. Explore perceptions of prostate mpMRI and mpMRI-undetected prostate cancer from patients that directly experience this technology using the PACT (Patient Views and Acceptance of Multiparametric MRI) study

1.5.3 Hypothesis:

The visibility of a prostate cancer on mpMRI provides guidance on when a biopsy should be performed, and where the needles should be deployed. The hypothesis tested in this thesis however is that tumour visibility on mpMRI has additional utility – due to inherent biological properties, mpMRI provides additive clinical information to guide future decision making. Due to intrinsic links between radiology and biology (at multiple levels: molecular, cellular, tissue, tumoural, prostatic, patient and population), mpMRI-detected prostate tumours should be monitored more closely, and treated more definitively, due to their enrichment with unfavourable biological features. Conversely, prostate cancers that are not detected by mpMRI lack the hallmarks of clinically aggressive disease, and therefore, can be dealt with a more conservative strategy.

The biological features that render prostate cancers visible or non-visible on mpMRI (e.g. cellular density) are likely to be the same features that convey overall oncological prognosis. In other words, larger and denser tumours are more likely to be visible on mpMRI, but are also more likely to have potential to grow, spread and limit life. Therefore, mpMRI may then be able to play a key role in prognostication, as well as diagnosis.

The PROMIS and PICTURE studies were specifically chosen as datasets to test this hypothesis, as they essentially provide globally-unique opportunities to do so, due to their study designs, in which patients underwent pre-biopsy mpMRI, followed by 5mm template mapping biopsy, regardless of mpMRI result. This then creates ideal rich datasets to examine the nature of mpMRI-detected and mpMRI-undetected cancer.

CHAPTER 2:

POST-HOC ANALYSIS OF THE PROMIS STUDY: MRI-UNDETECTED PROSTATE CANCER IN BIOPSY-NAIVE PATIENTS

2.1 INTRODUCTION

Introduction of mpMRI has help to enhance the risk stratification for patients at risk of prostate cancer, beyond the traditional standard of serum PSA and systematic TRUS-guided prostate biopsy.[1–4] It is now generally accepted that mpMRI has the greatest validity and reliability among all our diagnostic methods. Its role in the diagnostic process is now considered a central one.[5–9]

However, it is also acknowledged that mpMRI does not detect all prostate cancers. Some have argued that this is one of the most valuable attributes, due to the indolent nature of certain cancers.[9] For example, microfocal Gleason 3+3 (generally perceived as indolent disease), is often invisible on MRI, which may be beneficial in reducing overdiagnosis.[10] Indeed, mpMRI detection is positively associated with grade, volume, and stage.[11–13] The larger and more aggressive the cancer, the greater the probability of visibility on MRI.[14–17] However, there are concerns that a number of potentially clinically significant tumours can remain invisible on mpMRI. The literature demonstrates a wide variation in proportions of invisible prostate cancer, ranging between 7% and 55%[1,11] depending on study methodology and definitions of significant disease.

The PROMIS study was a multicentre, paired-cohort, confirmatory study that compared the diagnostic performance of mpMRI versus traditional systematic TRUS-guided biopsy against a strict reference standard. Each of the 576 patients included in the final PROMIS analysis underwent pre-biopsy mpMRI, followed by systematic TRUS-guided biopsy and concurrent TTPM biopsy (the reference test) in which biopsies were taken at 5mm intervals across the entire prostate. The analyses presented in this chapter report in detail the attributes of cancers (defined by a priori definitions 1 and 2) that were detected by mpMRI at 1.5 Tesla (T), compared with cancers that were overlooked.

2.2 MATERIALS & METHODS

The novel purpose of the analysis presented in this thesis is the specific comparison between patients with mpMRI-detected prostate cancer, against patients with mpMRI-undetected prostate cancer. This form of analysis was not presented in the original PROMIS study reports.

2.2.1 Study Population

PROMIS was a multicentre study in which biopsy-naïve patients with PSA ≤ 15 ng/mL underwent pre-biopsy 1.5 T mpMRI followed by a combined biopsy procedure under general anaesthesia. A PSA cut off of ≤ 15 ng/mL was chosen because, at the time of the PROMIS study, it was presumed that patients with PSA > 15 ng/mL would automatically be offered a biopsy, and that mpMRI would not have been used as a triage test at this stage (this approach has since changed). Patient enrolment began in 2012, through to 2015. Patients with PSA > 15ng/mL were excluded from PROMIS. All patients excluded from PROMIS went on to receive standard care at their respective centres.

The mpMRI parameters used are reported in full in the main PROMIS report.[1] mpMRI scans were scored on a 1-to-5 Likert clinical suspicion scale, in which a Likert scores 1–2 indicate a low level of suspicion for clinically significant prostate cancer (i.e. 'normal' mpMRI scans with no clearly visible tumour), and Likert scores 3–5 indicated higher levels of suspicion for clinically significant prostate cancer (i.e. visible tumour is seen on the mpMRI scan). In PROMIS, mpMRI-targeted biopsy was not performed, and as such, in this post hoc analysis, the status of 'mpMRI-visible' prostate cancer was given when the overall mpMRI score was high (Likert score 3–5) creating a per-patient analysis, rather than a per-lesion analysis.

Combined biopsy consisted of standard systematic TRUS-guided biopsy along with simultaneous 5mm TTPM biopsy (i.e. transperineal approach to prostate biopsy, with mapping of the entire prostate using a grid system, with 5mm spaces between each biopsy, to provide the most accurate histopathological representation as possible). Systematic TRUS-guided biopsy was carried out after TTPM. Each test was performed and reported blinded to results. PROMIS was registered on ClinicalTrials.gov (NCT01292291). The study protocol for PROMIS has been described in depth elsewhere.[1,102] For this chapter, all patients who met the definition of clinically significant disease (by either definition; given in the following section) were identified for analysis (Fig. 9). Patients without cancer were not included in the analysis presented here. Ethical approval for PROMIS was granted by the National Research Ethics Service Committee London (Ref: 11/LO/0185; applied for by the original PROMIS research team).

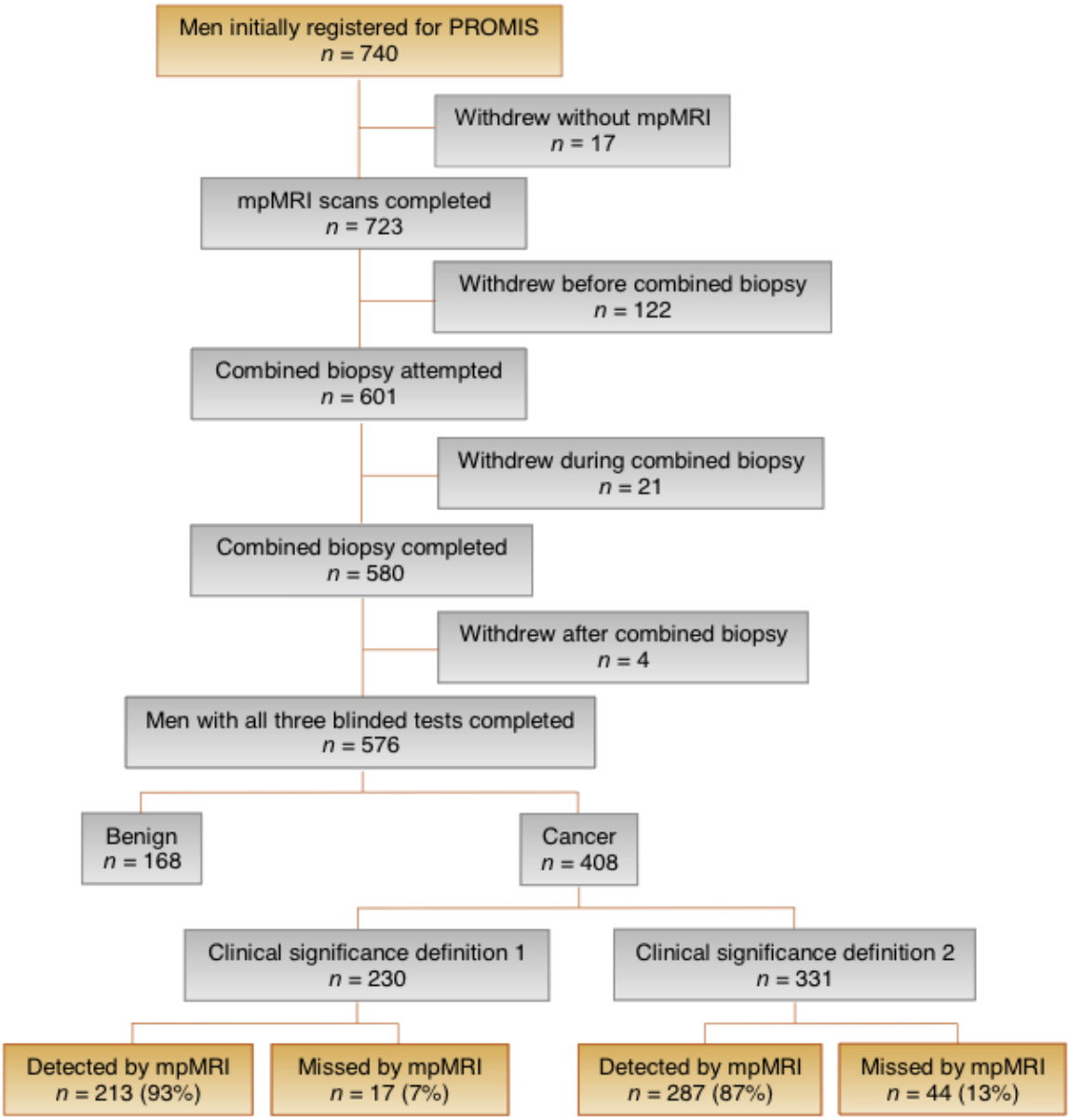


Fig. 9 – Flow chart for study inclusion in the analysis of the PROMIS cohort.

2.2.2 Definitions of Clinical Significance

Clinically significant prostate cancer was defined using the two definitions outlined in PROMIS.[1] Definition 1 for clinically significant disease was overall Gleason score ≥ 4 + 3 of any length or maximum cancer core length (MCCL) ≥ 6mm of any Gleason grade. Definition 2 for clinically significant disease was overall Gleason score ≥3 + 4 of any length or MCCL ≥ 4mm of any grade. These criteria were developed and validated for TTPM biopsy for the detection of Gleason score ≥ 4 and cancer core lengths representative of lesions ≥0.5 mL.[103–107] Detailed description of the Gleason scoring system is given in Chapter 1 (Section 1.2.3).

2.2.3 Post Hoc Analysis (Primary Analysis for this Thesis)

The secondary statistical analysis plan (SAP) for this post hoc analysis was designed by me and the PROMIS study team, and was conducted by me, and then later checked by the same research team. Once stratified by each definition of clinical significance, patients were divided into mpMRI-detected (Likert score 3–5) and mpMRI-undetected (Likert score 1–2) groups (Appendix 1). An additional threshold of tumour visibility was also evaluated (mpMRI-detected group: Likert score 4–5; mpMRI-undetected group: Likert score 1–3). Outcome measures for this post hoc analysis were based upon data gathered during PROMIS, including overall Gleason score per patient, maximum Gleason score per needle, MCCL per patient, and PSA density (PSAD). PSAD was calculated by dividing serum PSA by mpMRI-derived prostate volume (using the prolate ellipsoid method) (Appendix 2). Overall Gleason score was defined as the predominant Gleason pattern across the entire prostate and constituted the final pathological score. The maximum Gleason score was defined as the highest Gleason pattern found in any biopsy core.

2.2.4 Statistical Analysis

Characteristics were described for each patient with mpMRI-detected and mpMRI-undetected cancer, and then stratified analysis according to two definitions of clinical significance. Mean values with standard deviations and median values with interquartile ranges (IQR) were calculated with descriptive statistical techniques to characterise the measures of central tendency for demographic patient data, MCCL (maximum cancer core length) measurements, and PSAD values. All outcome data were unpaired and had non-normal distribution, and as such, two-sided nonparametric statistical tests were used. Overall and maximum Gleason scores were compared with the chi-square test, and MCCL and PSAD values were compared with the Mann–Whitney U test. Alpha level was 0.05 for all statistical tests. All analyses were conducted using GraphPad Prism 8 (Graph-Pad Software, Inc., La Jolla, CA, USA) and the R statistical environment.

2.3 RESULTS

2.3.1 Overall Detection

Demographic data for all 576 patients included in PROMIS are shown in Table 3. Overall, 7% (17/230; 95% confidence interval [CI] 4.4–12%) of patients according to definition 1, had significant prostate cancer not detected by mpMRI, whilst 13% (44/331; 95% CI 9.8–17%) of patients had mpMRI-undetected disease according to definition 2. The addition of systematic TRUS-guided biopsy would have failed to detect 59% (10/17; 95% CI 33–82%) of definition 1 cancers undetected by mpMRI and 70% (31/44; 95% CI 55–83%) of definition 2 cancers undetected by mpMRI (Appendix 4).

Table 3 – Summary of demographic data for all patients within PROMIS.

Characteristic	Result		Characteristic	Result
Sample size, *n*	576		Overall Gleason score, *n*	
Mean age, yr (SD)	63.4 (7.6)		3 + 3	100
Mean PSA, ng/mL (SD)	7.1 (2.1)		3 + 4	252
Mean BMI (kg/m^2) (SD)	27.8 (4.4)		3 + 5	1
Family history of prostate cancer, *n* (%)	127 (22)		4 + 3	44
Ethnicity, *n* (%)			4 + 5	7
White	502 (87)		5 + 4	4
Black	39 (7)		MCCL on TTPM, *n*	
Asian	16 (7)		1–5mm	186
Mixed	6 (1)		6–10mm	160
Other	12 (2)		11–15mm	59
			16–20mm	3

2.3.2 Cancer Grade

Table 4 compares key pathological outcomes between mpMRI-detected and mpMRI-undetected prostate cancer. Significant prostate cancer undetected by mpMRI was significantly lower in overall and maximum Gleason grades than significant cancer that was detected by mpMRI ($p = 0.0007$ and $p < 0.0001$, respectively). On a per-patient basis, no overall Gleason score >3 + 4 (Gleason Grade Groups 3–5) on TTPM biopsy was undetected by mpMRI throughout the entire cohort (95% CI 0–6.4%; Table 5). On a per-needle basis, no maximum Gleason score > 4 + 3 (Gleason Groups

4–5) on TTPM biopsy was undetected by mpMRI throughout the entire cohort (95% CI 0–8.0%). No overall Gleason pattern 5 (either primary or secondary) was undetected by mpMRI (95% CI 0–27%) (Appendix 3).

Table 4 – Key histopathological outcomes of MRI-detected and MRI-undetected prostate cancer in PROMIS.

Characteristic	Detected def 1	Undetected def 1	Difference, *p* value	Detected def 2	Undetected def 2	Difference, *p* value
Sample size, *n* (%)	213 (93) (95% CI 88–96%)	17 (7) (95% CI 4.4–12%)	-	287 (86) (95% CI 83–90%)	44 (13) (95% CI 9.8–17%)	-
Overall Gleason, % (*n*/N)			$p = 0.002$			$p = 0.0007$
3 + 3	4.2 (9/213)	5.9 (1/17)	1.7 (95% CI -8.4 to 12%)	5.9 (17/287)	14 (6/44)	8.1 (95% CI 0.02–16%)
3 + 4	69 (148/213)	94 (16/17)	25 (95% CI 2.6–47%)	75 (214/287)	86 (38/44)	11 (95% 2.5–24%)
3 + 5	0.47 (1/213)	0 (0/17)	-	0.35 (1/287)	0 (0/44)	-
4 + 3	2.1 (44/213)	0 (0/17)	-	15 (44/287)	0 (0/44)	-
4 + 5	1.9 (4/213)	0 (0/17)	-	2.4 (7/287)	0 (0/44)	-
5 + 4	3.3 (7/213)	0 (0/17)	-	1.4 (4/287)	0 (0/44)	-
Overall MCCL (mm), % (*n*/N)			$p = 0.14$			$p < 0.0001$
1-5	3.8 (8/213)	0 (0/17)	-	29 (82/287)	61 (27/44)	32 (95% CI 17–47%)
6-10	69 (147/213)	76 (13/17)	7 (95% CI -16 to 30%)	51 (147/287)	30 (13/44)	21 (95% CI 5.1–37%)
11-15	26 (55/213)	24 (4/17)	2 (95% CI -24 to 20%)	19 (55/287)	9.1 (4/44)	9.9 (95% CI 2.2–22%)
16-20	1.4 (3/213)	0 (0/17)	-	1 (3/287)	0 (0/44)	-
Median (IQR)	9 (7–11)	8 (6-11)	1 (95% 0–2)	8 (5–10)	5 (4–6)	3 (95% CI 1–3)

Table 5 – Proportions of cancer detected and undetected by mpMRI in PROMIS.

Gleason grade group	mpMRI-detected cancer, % (*n*/N)	mpMRI-undetected cancer, % (*n*/N)	Difference (95% CI)
GGG 1	5.9 (17/287)	14 (6/44)	8.1 (0.02–16)
GGG 2	75 (214/287)	86 (38/44)	11 (-2.5 to 24)
GGG 3	15 (44/287)	0 (0/44)	-
GGG 4	0.35 (1/287)	0 (0/44)	-
GGG 5	3.8 (11/287)	0 (0/44)	-

2.3.3 Cancer Core Length

Clinically significant prostate cancer undetected by mpMRI had significantly shorter MCCL than significant cancer that was detected by mpMRI (median difference: 3mm [5 vs. 8mm], $p < 0.0001$; 95% CI 1–3).

2.3.4 PSA Density

PSAD was significantly lower for patients with mpMRI-invisible disease than for patients with mpMRI-visible disease (median difference: 0.08 [0.12 vs. 0.20], $p < 0.0001$; 95% CI 0.05–0.11). Application of a theoretical PSAD threshold (above which a biopsy would be indicated) altered the rates of undetected significant prostate cancer. Using a PSAD threshold of 0.15ng/mL/mL in the context of negative mpMRI (Likert score 1–2) lowered the proportion of patients with undetected disease to 5% (12/230; 95% CI 2.7–8.9%) for definition 1 cancer and to 9% (30/331; 95% CI 6.2–13%) for definition 2 cancer. Application of a PSAD threshold of 0.10ng/mL/mL to negative mpMRI lowered the proportion of patients with undetected disease to 3% (6/230; 95% CI 1.0–5.6%) for definition 1 cancer and to 3% (11/331; 95% CI 1.7–5.9%) for definition 2 cancer.

2.3.5 Alternative Tumour Visibility Threshold

When the definition of mpMRI-undetected disease was raised to Likert 1–3, the proportion of clinically significant prostate cancers that were overlooked by mpMRI was 22% (51/230; 95% CI 17–28%) according to definition 1 and 34% (113/331; 95% CI 29–40%) according to definition 2. Overall and maximum Gleason grades were still significantly lower ($p < 0.0001$ and $p < 0.0001$, respectively), and MCCL was still significantly smaller (median difference: 4mm [8 vs. 9mm], $p < 0.0001$; 95% CI 2–4), even with a wider definition for non-detection.

2.4 DISCUSSION

In summary, this post hoc analysis of the PROMIS dataset has shown that the proportion of important cancers that systematically remain invisible to by 1.5 T mpMRI is low (7%). In the least stringent setting (i.e. upper limit of 95% CI for definition 2 disease detection), the estimate for clinically significant prostate cancer overlooked by mpMRI could be as high as 17%. However, in this same situation, the upper estimate for significant cancer overlooked by systematic TRUS-guided biopsy would be 45%.[1] In contrast, in the most stringent setting (i.e. lower limit of 95% CI for definition 1 disease detection), the estimate for clinically significant prostate cancer overlooked by mpMRI could be as low as 4.4%, thus highlighting the key importance of both statistical estimates and definitions of clinical significance. Overall, these findings support the observations made by others that cancers that are overlooked by mpMRI appear to be significantly smaller and less aggressive than those that are detected.[11-13,108]

Through evaluation of PROMIS, this analysis provides a detailed characterisation of significant prostate cancers that mpMRI does not detect, by using 5mm TTPM biopsy as the reference standard. This methodological strength avoids, to some extent, the inherent biases of radical prostatectomy–correlated studies, including the following: population and selection biases; registration challenges; ex vivo tissue with 10% shrinkage, distortion, and inconsistent 5–10mm sampling frame; and tissue loss from the trim of material to achieve full face. Aside from PROMIS, there are a small number of other trials that have used saturation TTPM biopsy to evaluate mpMRI accuracy.[109–111]

Whilst they offer advantage over radical prostatectomy–based interrogation, they remain limited by common drawbacks that PROMIS did not suffer, including retrospective single-centre design, heterogeneous uncontrolled patient populations, variable and simplistic definitions for clinical significance, and lack of evaluation of the performance of systematic TRUS-guided biopsy.[109–111]

One potential limitation of the study in this chapter is the reliance upon a per-patient approach, in which a single overall score was assigned to each mpMRI scan (Likert scores 1–5). The use of per-patient analysis has the benefit of mirroring a real-life diagnostic setting; however, it potentially limits detailed analysis of tumour conspicuity, as there is a possibility that patients with concurrent visible and invisible tumours may have their mpMRI-invisible cancer overlooked due to an overall positive mpMRI score generated by the visible lesion. Furthermore, the addition of targeted biopsy to the PROMIS protocol would have enabled increased confidence in radiological-pathological alignment.

An additional limitation of the PROMIS dataset is that radiologists were aware of PSAD at the time of reporting, and as such, may have attributed positive mpMRI scores in cases of high PSAD, again limiting analyses of mpMRI-invisible lesions. This is potentially important, as a recent systematic review with meta-analysis demonstrated that PSAD was

the strongest predictor for clinically significant prostate cancer in the context of negative pre-biopsy mpMRI.[112] An associated limitation of using PSAD thresholds to stratify patients with negative mpMRI is that, in a real-world setting, patients with high PSAD and negative mpMRI would be unlikely to be offered a TTPM biopsy, but rather a systematic TRUS-guided biopsy, which may still overlook significant cancer in this setting.

Where these findings differ from other estimates may be explained by issues of population characteristics, mpMRI quality, study design, and definitions of risk thresholds. There are methodological issues associated with all these types of studies. Within PROMIS, many of them were avoided (work-up, incorporation, and spectrum biases) as this was the rationale for the chosen study design. The fact that all components of the study (mpMRI, systematic TRUS-guided biopsy, and TTPM biopsy) were independent and blinded to each other would suggest that these estimates are likely to be as valid as they can be. The multicentre design means that different levels of expertise and competence in all three components of the study are represented. The choice of using 1.5 T was due to the fact that many studies prior to PROMIS had reported high-accuracy metrics with this magnetic field strength, and this was the norm in the UK at the time of the study; this of course may mean that the performance of mpMRI might be, if anything, underestimated compared with 3 T scanners.

The issue of disease threshold is perhaps the most contentious of issues within studies of this type. In order to calculate sensitivities and specificities, the disease entity that one is trying to rule-in or rule-out needs to be defined carefully. The chosen thresholds of risk in this chapter (definitions 1 and 2) incorporated both volume and grade – the two most important determinants of risk in all cancers. Moreover, they were constructed around the two prevailing thresholds at the time: Stamey's 0.5cc and Epstein's 0.2cc, both volume-based definitions of risk.[106,113] However, other studies have used different definitions, and there is no absolute consensus on which definition is the correct one. Indeed, different definitions of risk over a person's lifetime may be required, that are contingent on a person's life expectancy.

Given that mpMRI detects nearly all high-grade prostate cancers and that these cancers are most strongly associated with prostate cancer–related death,[114] it is possible that tumour visibility on mpMRI may confer useful prognostic information. However, this requires evaluation with long-term, mpMRI-correlated clinical trials. One potential trial design to evaluate the long-term clinical significance of mpMRI-undetected disease would be to enrol a cohort of patients with both mpMRI-visible and mpMRI-invisible disease, and then ensure that they are exposed to the same treatment (e.g. radical prostatectomy), and then compare the clinical outcomes (e.g. biochemical recurrence) over time. The suggestion that cancer not detected by mpMRI may be prognostically favourable compared with mpMRI-detected disease is also reinforced by enrichment of aggressive molecular and microenvironmental features in mpMRI-visible tumours.[16,17]

Disease volume and grade are strongly correlated with mpMRI visibility, but it is likely that there are other independent predictors of cancer conspicuity. In this analysis, it was shown that many of the tumours in PROMIS were of similar pathological grade. The majority of prostate cancers in PROMIS had an overall Gleason score of 3 + 4 (76% of mpMRI-detected tumours and 86% of mpMRI-undetected tumours), which suggests that Gleason grading alone may be inadequate to account for tumour conspicuity. Histopathologically, mpMRI inconspicuity may be related to a loose cellular and vascular arrangement of the tumour,[13–15] thus more closely resembling background stromal tissue. This feature is shared with some histological prostate cancer subtypes (ductal and cribriform) that are also associated with reduced detection rates by mpMRI.[115,116]

2.5 CONCLUSION

On a per-patient basis, it appears that few significant prostate cancers remain undetected by mpMRI in biopsy-naive patients. The proportion of significant mpMRI-undetected cancers seems to be low, even at the upper limit of statistical estimates. This post hoc analysis of the PROMIS cohort helps to support previous studies suggesting that prostate cancer undetected by mpMRI in biopsy-naive patients is lower in grade and size than the detected disease. These findings provide some reinforcement for the key role that mpMRI plays in risk stratification of biopsy-naive patients with suspected prostate cancer.

2.6 OVERALL CHAPTER SUMMARY & CANDIDATE CONTRIBUTION

1. Overall, it appears that a small proportion of cancers are overlooked by mpMRI, in biopsy-naive patients
2. Lower estimate of mpMR-undetected disease: 4.4% (lower boundary of 95% CI for definition 1)
3. Upper estimate of mpMRI-undetected disease: 17% (upper boundary of 95% CI for definition 2)
4. Prostate cancers undetected by mpMRI seem to be lower grade and shorter length than cancers that are detected
5. PSAD thresholds may provide a simple, effective way of reducing undetected disease in biopsy-naive patients

In this chapter, I devised the concept of utilising the PROMIS study dataset to compare key histopathological outcomes between mpMRI-detected and mpMRI-undetected prostate cancer, in biopsy-naïve patients. The statistical analysis plan was designed by me and the wider PROMIS team. All data analyses, syntheses and presentation were performed by me. All figures and tables presented in this chapter were conceived and newly created by me, unless specifically stated in parentheses. NB: I was not involved in the delivery of the original PROMIS study; my main contribution is the unique post hoc analysis presented here.

CHAPTER 3:

POST-HOC ANALYSIS OF THE PICTURE STUDY: MRI-UNDETECTED PROSTATE CANCER IN PATIENTS WITH PRIOR BIOPSY

3.1 INTRODUCTION

Pre-biopsy mpMRI has good test accuracy, validity, and reliability for detection of clinically significant prostate cancer resulting in its incorporation into national and international guidelines.[1,5,117–121] However, as with all cancer risk-stratification strategies, not every clinically significant prostate cancer is detected by mpMRI.[1] Understanding the nature of disease that is undetected by mpMRI is important, particularly given the increasing preference for omission of prostate biopsy in cases of non-suspicious pre-biopsy imaging.[120] In the previous chapter, it was shown that in biopsy-naïve patients, so-called mpMRI-invisible cancer appeared to be significantly smaller in tumour size and likely has lower maximum and overall Gleason scores compared to mpMRI-visible disease.[122]

Recent investigation into mpMRI performance in patients with prior biopsy has shown favourable features of undetected disease, consistent with a body of evidence identifying apparently reassuring genetic, molecular, histopathological, and clinical characteristics for mpMRI-undetected cancer in biopsy-naïve patients.[122–126] Nonetheless, concern remains regarding the potential for significant prostate cancer going undetected on mpMRI.[127] Existing evidence for patients with prior biopsy is limited by imperfect reference standards, retrospective study designs, lower mpMRI magnetic strength, or poor image quality due to close timing between prior biopsy and imaging.[128–131]

The PICTURE study was a prospective paired-cohort confirmatory study that compared the diagnostic performance of mpMRI against a strict reference standard (of TTPM biopsies, taken 5mm apart, up 26 per patient) in 249 patients with prior prostate biopsy who required repeat biopsy for further risk stratification.[117,132–134] Patients underwent pre-biopsy mpMRI at 3T, followed by transperineal template prostate mapping (TTPM) biopsy (the reference test) in which biopsies were taken at 5mm intervals throughout the prostate. In this chapter, cancer attributes (at the patient-level) between patients with mpMRI-detected and mpMRI-undetected disease are compared within the PICTURE study.

3.2 MATERIALS & METHODS

The novel purpose of the analysis presented in this thesis is the specific comparison between patients with mpMRI-detected prostate cancer, against patients with mpMRI-undetected prostate cancer. This form of analysis was not presented in the original PICUTRE study reports.

3.2.1 Study Population

PICTURE was a prospective single-centre study in which patients with prior systematic TRUS-guided biopsy and ongoing clinical suspicion (e.g. due to ongoing raised, or rising, PSA) underwent pre-biopsy 3T mpMRI, followed by TTPM biopsy under general anaesthesia.

The mpMRI parameters used are reported in full in the main PICTURE report.[117] mpMRI scans were scored on a 1-to-5 Likert clinical suspicion scale, in which a Likert scores 1–2 indicate a low level of suspicion for clinically significant prostate cancer (i.e. 'normal' mpMRI scans with no clearly visible tumour), and Likert scores 3–5 indicated higher levels of suspicion for clinically significant prostate cancer (i.e. visible tumour is seen on the mpMRI scan). In this post hoc analysis, the status of 'mpMRI-visible' prostate cancer was given when the overall mpMRI score was high (Likert score 3–5) creating a per-patient analysis, rather than a per-lesion analysis.

Each test was performed and reported blinded to results. Patients remained blinded to mpMRI results. PICTURE was registered on ClinicalTrials.gov (NCT01492270).[117,132] Ethics committee approval for PICTURE was granted by London City Road and Hampstead National Research Ethics Committee (11/LO/1657 applied for by the original PICTURE research team). For this chapter, all patients with prostate cancer were included (Fig. 10). Patients without cancer were not included in the analysis presented here.

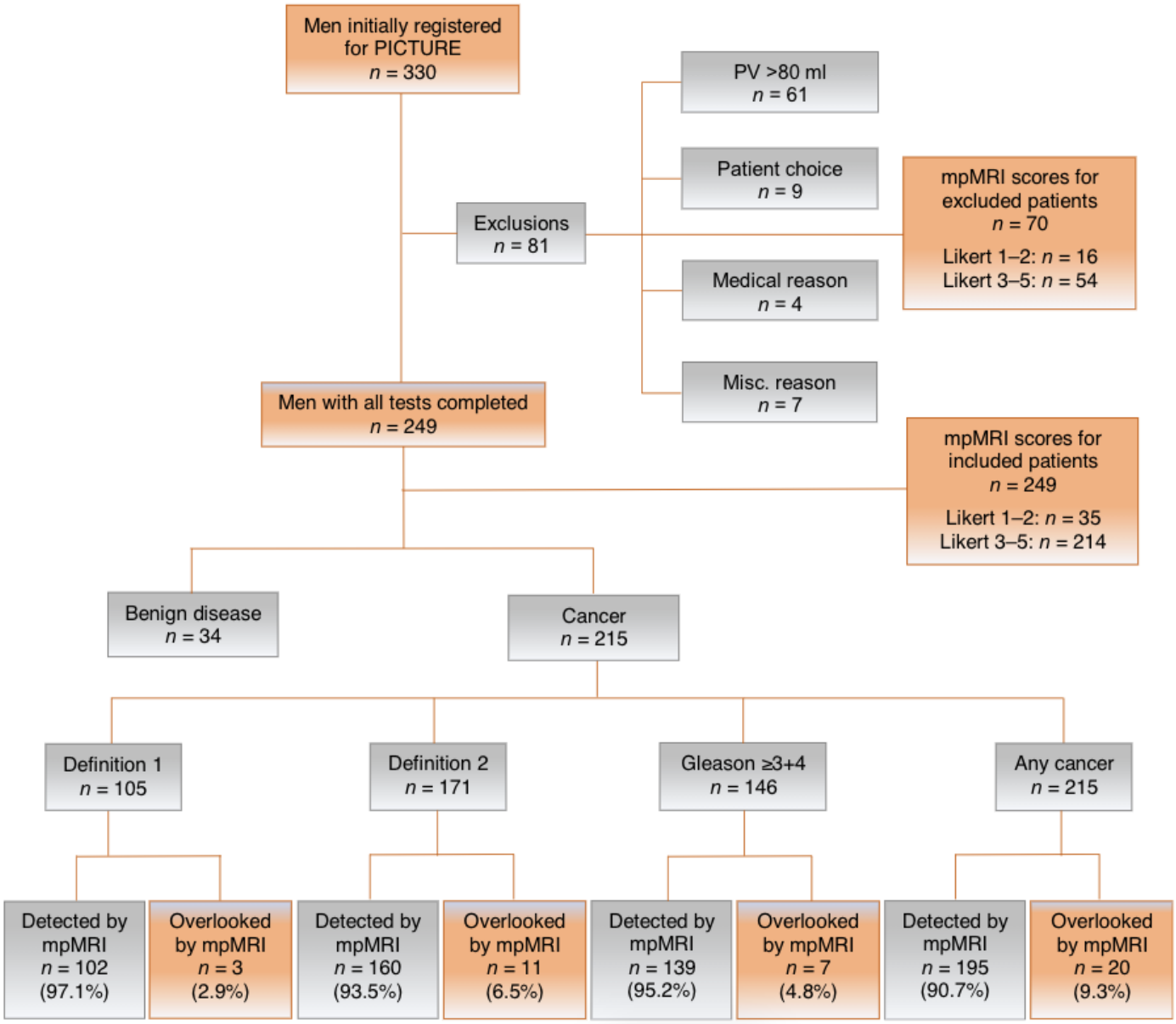


Fig. 10 – Flow chart for study inclusion in the analysis of the PICTURE cohort.

3.2.2 Definitions of Clinical Significance

Three thresholds for prostate cancer on TTPM biopsy were defined as the target conditions of interest to incorporate and reflect the uncertainty about what constitutes clinically significant prostate cancer. PROMIS study definition 1 was overall Gleason score ≥ 4 + 3 of any length or a MCCL ≥ 6mm of any grade. PROMIS definition 2 was overall Gleason score ≥ 3 + 4 of any length or MCCL ≥ 4mm of any grade. These two criteria were developed and validated for TTPM biopsy for the detection of Gleason score 4 and cancer core lengths representative of lesions of 0.5mL and 0.2mL[103–107] and were used in the main PICTURE and PROMIS trials.[1,117] The third threshold for clinically significant disease was any amount of overall Gleason score ≥ 3 + 4 cancer. The presence of any cancer was also used for completion.

3.2.3 Post Hoc Analysis (Primary Analysis for this Thesis)

Once stratified by cancer threshold, patients were divided into mpMRI-detected (Likert score 3–5) and mpMRI-undetected (Likert score 1–2) groups. An additional threshold for tumour visibility was also evaluated (mpMRI-detected group, Likert score 4–5; mpMRI-undetected group, Likert score 1–3). Prostate-specific antigen density (PSAD) was calculated by dividing serum PSA by mpMRI-derived prostate volume (using the prolate ellipsoid method). Overall Gleason score was defined as the predominant Gleason pattern across the entire prostate and constituted the final pathological score. Maximum Gleason score was defined as the highest Gleason pattern found per patient.

3.2.4 Statistical Analysis

The secondary statistical analysis plan (SAP) for this post hoc analysis was designed by me and the PICTURE study team, and was conducted by me, and then later checked by the same research team. Characteristics were described for the mpMRI-detected and mpMRI-undetected cancer groups and then stratified analysis according to the four cancer thresholds. Mean values with standard deviation and median values with interquartile range (IQR) were calculated with descriptive statistical techniques to characterise the measures of central tendency for demographic patient data, MCCL measurements, and PSAD values.

Data distribution was evaluated using D'Agostino-Pearson or Shapiro-Wilk normality tests. All outcome data were unpaired and had a non-normal distribution, so two-sided nonparametric statistical tests were used. At the patient-level, overall and maximum Gleason scores were compared using the χ^2 test, whilst MCCL and PSAD values were compared using the Mann-Whitney U test. Alpha level was 0.05 for all statistical tests. Binomial 95% confidence intervals (CIs) for proportions were calculated via approximation with the Poisson distribution method. Multiple testing was assessed via the false discovery rate using the Benjamini-Hochberg method. All analyses were conducted using GraphPad Prism 9.0.0 (GraphPad Software, La Jolla, CA, USA) and the R statistical environment (v3.6.3; R Foundation for Statistical Computing, Vienna, Austria).

3.3 RESULTS

3.3.1 Overall Detection

Demographic data for all 249 patients included in PICTURE are shown in Table 6. When non-suspicious mpMRI was defined as Likert score 1–2, 2.9% (3/103; 95% CI 0.6–8.3%) of patients with definition 1 disease had their cancer undetected by mpMRI. This proportion was 6.5% (11/168; 95% CI 3.3–11%) for definition 2 disease, 4.8% (7/146;95% CI 2.0–9.6%) for any amount of Gleason ≥ 3 + 4 cancer, and 9.3% (20/215; 95% CI 5.8–14%) for any cancer. When non-suspicious mpMRI was defined as Likert score 1–3, 19% (20/103; 95% CI 12–28%) with definition 1 disease, 32% (54/168; 95% CI 25–40%) with definition 2 disease, 30% (44/146; 95% CI 23–38%) with any Gleason ≥ 3 + 4, and 41% (89/215;95% CI 35–48%) with any cancer had cancer undetected by mpMRI.

Table 4 – Summary of demographic data for all patients within PICTURE.

Characteristic	Result	Characteristic	Result
Sample size (*n*)	249	Histopathology on prev biopsy, *n* (%)	
Mean age, yr (SD)	62.0 (7.2)	No cancer	74 (30)
Median PSA, ng/mL (IQR)	6.8 (4.8–9.8)	Gleason 2 + 3	2 (0.8)
Median prostat volume, mL (IQR)	37.0 (26.8–50.0)	Gleason 3 + 3	121 (49)
Family history of prostate cancer, *n*	78 (31)	Gleason 3 + 4	48 (19)
Ethnicity, *n* (%)		Gleason 4 + 3	4 (1.6)
White	208 (84)	Likert score on mpMRI, *n* (%)	
Black	25 (10)	1	1 (0.4)
Asian	8 (3)	2	34 (14)
Hispanic	1 (0.4)	3	85 (34)
Other	5 (2)	4	55 (22)
Median time since prev biopsy, days (IQR)	386 (269–607)	5	74 (30)
Median no. of prev biopsies per patient, *n* (IQR)	12 (11–13)	Overall Gleason on TTPM, *n* (%)	
Median no. of cores take per previous biopsy, *n* (IQR)	1 (1–2)	Gleason 3 + 3	69 (32)
Previous biopsy description, *n* (%)		Gleason 3 + 4	112 (52)
Transrectal ultrasound biopsy	342 (98)	Gleason 3 + 5	1 (0.47)
Transperineal template mapping biopsy	6 (1.7)	Gleason 4 + 3	29 (13)
Positive pathology result	217 (62)	Gleason 4 + 4	3 (1.4)
Negative pathology result	127 (36)	Gleason 5 + 4	1 (0.47)
Pathology report unavailable	4 (1.1)	MCCL on TTPM, *n* (%)	
Median PSAD, ng/mL/mL (IQR)	0.18 (012–0.28)	1–5mm	119 (55)
Median MCCL on TTPM, mm (IQR)	5 (3–8)	6–10mm	79 (37)
		11–15mm	17 (7.9)

3.3.1 Cancer Grade

Table 7 compares key pathological outcomes between mpMRI-detected and mpMRI-undetected prostate cancer. Definition 1 cancers undetected by mpMRI had lower overall Gleason scores ($p = 0.02$) and maximum Gleason scores ($p = 0.01$) compared to cancers detected by mpMRI; this was also the case when evaluating any cancer ($p = 0.01$ and $p = 0.02$, respectively).

Table 7 – Key histopathological outcomes of MRI-detected and MRI-undetected prostate cancer in PICTURE.

Property	Cancer definition 1			Cancer definition 2			Gleason ≥ 3 + 4			Any cancer		
	Visible	Invisib	Diff (95% CI)	Visible	Invisib	Diff (95% CI)	Visible	Invisib	Diff (95% CI)	Visible	Invisib	Diff (95% CI)
Sample size, % (*n*/N)	97 (102/105)	2.9 (3/105)	94.1 (90–99)	94 (160/171)	6.4 (11/171)	87.6 (82–92)	95 (139/146)	4.8 (7/146)	90.2 (86–95)	91 (195/215)	9.3 (20/215)	81.7 (76–87)
Overall Gleason, % (*n*/N)			*p* = 0.02			*p* = 0.09			*p* = 0.1			*p* = 0.01
3 + 3	8.8 (9/102)	33 (1/3)	24.2 (-29 to 78)	13 (21/160)	36 (4/11)	23 (-5.7 to 52)	0 (0/139)	0 (0/7)	-	29 (56/195)	65 (13/20)	36 (14–58)
3 + 4	59 (60/102)	33 (1/3)	26 (-29 to 80)	66 (106/160)	55 (6/11)	11 (-19 to 42)	76 (106/139)	86 (6/7)	10 (-17 to 36)	54 (106/195)	30 (6/20)	24 (3.1–56)
3 + 5	0.98 (1/102)	0 (0/5)	-	0.63 (1/160)	0 (0/11)	-	0.72 (1/139)	0 (0/7)	-	14 (28/195)	0 (0/20)	-
4 + 3	27 (28/102)	33 (1/3)	6 (-48 to 60)	18 (28/160)	9.1 (1/11)	8.9 (-9.6 to 26)	20 (28/139)	14 (1/7)	6 (-21 to 33)	0.51 (1/195)	5 (1/20)	4.5 (-5.1 to 14)
4 + 4	2.9 (3/102)	0 (0/3)	-	1.9 (3/160)	0 (0/11)	-	2.2 (3/139)	0 (0/7)	-	1.5 (3/195)	0 (0/20)	-
5 + 4	0.98 (1/102)	0 (0/3)	-	0.63 (1/160)	0 (0/11)	-	0.72 (1/139)	0 (0/7)	-	0.51 (1/195)	0 (0/20)	-
Overall MCCL, % (*n*/N)			*p* =0.02			*p* = 0.04			*p* = 0.03			*p* = 0.0009
1-5mm	7.8 (8/102)	33 (1/3)	25.2 (-28 to 80)	41 (66/160)	82 (9/11)	41 (17–65)	39 (54/139)	86 (6/7)	47 (20–74)	52 (101/195)	90 (18/20)	38 (23–53)
6-10mm	75 (77/102)	66 (2/3)	9 (-45 to 63)	48 (77/160)	18 (2/11)	30 (5.9–54)	49 (68/139)	14 (1/7)	35 (7.4–62)	39 (77/195)	10 (2/20)	29 (15–44)
11-15mm	17 (17/102)	0 (0/3)	-	11 (17/160)	0 (0/11)	-	12 (17/139)	0 (0/7)	-	8.7 (17/195)	0 (0/20)	-
Median MCCL, mm (IQR)	8 (6–10)	6 (2–6)	2 (0–6)	6 (4–8)	5 (4–5)	1 (0–3)	6 (4–9)	5 (3–5)	1 (0–4)	5 (3–8)	3 (2–5)	2 (1–3)

On a per-patient basis, no cancers with overall Gleason score > 4 + 3 (Gleason grade groups 4–5) on TTPM biopsy were undetected by mpMRI (95% CI 0–52%; Table 8). Furthermore, no cancer with maximum Gleason score > 4 + 3 (Gleason grade groups 4–5) on TTPM biopsy were undetected by mpMRI (95% CI 0–52%). No primary, secondary, or tertiary Gleason pattern 5 was undetected by mpMRI (95% CI 0–84%).

Table 8 – Proportions of cancer detected and undetected by mpMRI in PICTURE.

Gleason grade group	mpMRI-detected cancer, % (*n*/N)	mpMRI-undetected cancer, % (*n*/N)	Difference, % (95% CI)
GGG1	29 (56/195)	65 (13/20)	-36 (-58 to -14)
GGG2	54 (106/195)	30 (6/20)	2.4 (3.1–46)
GGG3	14 (28/195)	5.0 (1/20)	9.0 (1.4–46)
GGG4	2.0 (4/195)	0 (0/20)	-
GGG5	0.5 (1/195)	0 (0/20))	-

3.3.3 Cancer Core Length

Prostate cancers undetected by mpMRI had shorter MCCL than those detected by mpMRI for every cancer threshold: definition 1, 6mm vs. 8mm (difference: 2mm, 95% CI 0–6; $p = 0.02$); definition 2, 5mm vs. 6mm (difference: 1mm, 95% CI 0–3; $p = 0.04$); any Gleason ≥ 3 + 4 cancer, 5mm vs. 6mm (difference: 1mm, 95% CI 0–4; $p = 0.03$); and any cancer, 3mm vs. 5mm (difference: 2mm, 95% CI 1–3; $p = 0.0009$).

When non-suspicious mpMRI was defined as Likert score 1–3, prostate cancers undetected by mpMRI had significantly shorter MCCL than prostate cancers detected by mpMRI for all cancer definitions: definition 1, 6mm vs. 8mm (difference: 2mm, 95% CI 1–3; $p = 0.0008$); definition 2, 4.5mm vs. 7mm (difference: 2.5mm, 95% CI 1–3; $p < 0.0001$); any Gleason ≥ 3 + 4 cancer, 4mm vs. 7mm (difference: 3mm, 95% CI 2–4; $p < 0.0001$); and any cancer, 3mm vs. 6mm (difference: 3 mm, 95% CI 2–4; $p < 0.0001$).

3.3.4 PSA Density

Overall, median PSAD was 0.18ng/mL/mL (IQR 0.12–0.28) across the entire cohort. For patients with prostate cancer, PSAD did not significantly differ between those with mpMRI-detected disease (Likert score 3–5) and those with mpMRI-undetected disease (Likert score 1–2). However, application of theoretical PSAD thresholds, above which a biopsy would be indicated altered the rates of undetected significant prostate cancer. Multiple hypothetical PSAD thresholds were evaluated for all cancer definitions and mpMRI detection thresholds (Table 9).

When non-suspicious mpMRI was defined as Likert score 1–2, a PSAD threshold of 0.15ng/mL/mL reduced the proportion of patients with undetected disease to 0% (0/ 105; 95% CI 0–3.5%) for definition 1, 0.58% (1/171; 95% CI 0.01–3.2%) for definition 2, and 0% (0/146; 95%CI 0–2.5%) for any Gleason ≥ 3 + 4. A PSAD threshold of 0.10ng/mL/mL also reduced the proportion of patients with undetected disease to 0% (0/105; 95% CI 0–3.5%), 0% (0/171; 95% CI 0–

2.1%), and 0% (0/146; 95%CI 0–2.5%), respectively. However, when considering the entire cohort (including those with benign disease), the number of biopsies that could potentially be avoided decreased from 14% (35/249) when no PSAD threshold was applied to non-suspicious mpMRI (Likert scores 1–2) to 5.6% (14/249) when a PSAD threshold of 0.15ng/mL/mL was applied, and to 2.0% (5/249) for a PSAD threshold of 0.10ng/mL/mL.

When non-suspicious mpMRI was defined as Likert score 1–3, a PSAD threshold of 0.15ng/mL/mL reduced the proportion of patients with undetected disease to 1.9% (2/105; 95% CI 0.23–6.7%) for definition 1, 7.0% (12/171; 95% CI 3.7–12%) for definition 2, and 6.8% (10/146; 95% CI 3.3–12%) for any Gleason ≥ 3 + 4. A PSAD threshold of 0.10ng/mL/mL also lowered the proportion of patients with undetected disease to 0.95% (1/105; 95% CI 0.02–5.2%), 2.3% (4/171; 95%CI 0.64–5.9%), and 2.1% (3/146; 95% CI 0.43–5.9%), respectively. Again, the number of biopsies that could potentially be avoided across the entire cohort decreased from 48% (120/249) when no PSAD threshold was applied to non-suspicious mpMRI (Likert score 1–3) to 22% (55/249) when a PSAD threshold of 0.15ng/mL/mL was applied, and to 9.6% (24/249) for a PSAD threshold of 0.10ng/mL/mL.

Table 9 – Theoretical PSAD thresholds on cancer detection in patients with negative mpMRI in PICTURE.

	PSAD threshold (above which a biopsy would be performed)							
	0.08	**0.10**	**0.12**	**0.15**	**0.18**	**0.20**	**0.22**	**0.25**
Non-suspicious MRI: Likert 1–2								
mpMRI-detected disease, *n* (%)								
Definition 1 cancer	105 (100)	105 (100)	105 (100)	105 (100)	105 (100)	105 (100)	105 (100)	105 (100)
Definition 2 cancer	171 (100)	171 (100)	171 (100)	170 (99)	169 (99)	168 (98)	168 (98)	166 (97)
Gleason ≥ 3 + 4	146 (100)	146 (100)	146 (100)	146 (100)	145 (99)	144 (99)	144 (99)	143 (98)
mpMRI-undetected disease, *n* (%)								
Definition 1 cancer	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Definition 2 cancer	0 (0)	0 (0)	0 (0)	1 (0.58)	2 (1.2)	3 (1.8)	3 (1.8)	5 (2.9)
Gleason ≥ 3 + 4	0 (0)	0 (0)	0 (0)	0 (0)	1 (0.68)	2 (1.4)	2 (1.4)	3 (2.0)
Biopsies avoided, *n* (%)	2 (0.80)	5 (2.0)	10 (4.0)	14 (5.6)	23 (9.2)	24 (9.6)	28 (11)	29 (12)
Non-suspicious MRI: Likert 1–3								
mpMRI-detected disease, *n* (%)								
Definition 1 cancer	105 (100)	104 (99)	103 (98)	103 (98)	103 (98)	102 (97)	101 (96)	98 (93)
Definition 2 cancer	169 (99)	167 98)	164 (96)	159 (93)	155 (91)	151 (88)	148 (87)	141 (82)
Gleason ≥ 3 + 4	145 (99)	143 (98)	140 (96)	136 (93)	133 (91)	129 (88)	127 (87)	121 (83)
mpMRI-undetected disease, *n* (%)								
Definition 1 cancer	0 (0)	1 (0.95)	2 (1.9)	2 (1.9)	2 (1.9)	3 (2.9)	4 (3.8)	7 (6.7)
Definition 2 cancer	2 (1.2)	4 (2.3)	7 (4.1)	12 (7.0)	16 (9.4)	20 (12)	23 (13)	30 (18)
Gleason ≥ 3 + 4	1 (0.68)	3 (2.1)	6 (4.1)	10 (6.8)	13 (8.9)	17 (12)	19 (13)	25 (17)
Biopsies avoided, *n* (%)	15 (6.0)	24 (9.6)	38 (15)	55 (22)	73 (29)	81 (33)	88 (35)	92 (37)

3.4 DISCUSSION

In summary, this post hoc analysis of the PICTURE cohort showed that for patients with previous systematic TRUS-guided biopsy, the proportion of the most aggressive prostate tumours undetected by 3T mpMRI appears to be low (2.9%). Overall, the findings in this patient sub-group support results from other investigators who found that prostate cancers undetected by mpMRI appear to be significantly smaller and have lower pathological grade than those that are detected.[123,135] The results presented here also closely mirror the interrogation of the PROMIS dataset in the previous chapter in which undetected cancer seemed to have favourable characteristics at histopathology,[122] highlighting parallels in mpMRI performance between patients with and without prior biopsy.

Collectively, these findings help support avoidance of biopsy in patients requiring repeat risk stratification with non-suspicious mpMRI, especially when PSAD is low (e.g. < 0.15ng/mL/mL). Furthermore, while not the primary focus of this analysis, the re-stratification performed in PICTURE also suggests the potential utility of mpMRI in predicting pathological upgrading, with 92% (120/131) of patients with upgraded disease (compared to their pre-enrolment status) appearing to have positive or suspicious mpMRI findings (Appendices 5–6).

Using PICTURE, this analysis helps provide a description of prostate cancers that mpMRI does not detect by using 5mm TTPM biopsy as the reference standard. While this exhaustive approach may not represent the modern clinical approach (and thus may detect cancers with inherently different risk profiles) and is associated with higher risk of urinary retention and impairment of genitourinary function,[136] it does help overcome several methodological challenges intrinsic to whole-mount radical prostatectomy, especially selection bias.

In addition to providing a unique insight into patients requiring further risk stratification, the PICTURE dataset also offers a potential advantage over PROMIS by providing histopathological-radiological correlation at a higher MRI magnet strength (PROMIS exclusively examined 1.5T mpMRI, while PICTURE exclusively examined 3T mpMRI).[1,117] Indeed, the proportion of mpMRI-undetected disease was lower in PICTURE than in PROMIS, and this may be related to magnet strength, or to the higher risk cohort (i.e. the repeat stratification cohort, in which rates of cancer are higher, and for which radiologists are likely to have higher clinical suspicion). Nonetheless, both cohorts, regardless of population, had low rates of mpMRI-undetected disease, which perhaps is indicative of the poor prior risk stratification for patients in PICTURE (i.e. 12-core systematic transrectal TRUS-guided biopsy). Lastly, it is also interesting to note that application of numerous different PSAD thresholds resulted in a more pronounced reduction in non-detected cancer than was noted in the previous chapter, and this is potentially attributable to higher overall PSAD in PICTURE.

This analysis has limitations. PICTURE was a single-centre study conducted at an experienced academic centre and thus importantly lacks the generalisability provided by multi-centre studies such as PROMIS.[1,117] Another limitation of this analysis is the per-patient strategy, in which single overall mpMRI scores were assigned (Likert scores 1–5). This approach somewhat mirrors real-life diagnostic settings; however, it may limit detailed tumour conspicuity investigation because of the inherent possibility of concurrent visible and invisible tumours, risking the possibility of ignoring invisible tumours owing to the overall positive mpMRI scores generated by visible lesions. However, the original PICTURE report, which included targeted biopsy (not included here), demonstrated that such scenarios are uncommon;[134] nevertheless, there are still situations, particularly as MRI-target-only biopsy becomes more common, in which non-visible significant tumours may be overlooked in real-life clinical settings, when only visible lesions are targeted. Furthermore, the benefits demonstrated with the use of PSAD cut-offs for patients with non-suspicious mpMRI may be limited in reality, as they require full 5 mm TTPM in order to detect the same levels of significant disease that are shown here (in reality, a simple 12-core systematic TRUS-guided biopsy is more likely to be offered, which would have much lower detection rates). Lastly, whilst the cancer yield was high in this cohort (probably because of the chosen population, i.e. patients with prior risk stratification), the most aggressive cancers (e.g. Gleason Grade Groups 4–5) appeared to be uncommon, and thus analyses regarding detection and non-detection of this disease generated wide CIs, suggesting limited study power for this particular question.

As with the previous chapter, this analysis has shown that mpMRI seems to detect nearly all high-grade prostate cancers.[1,117,122] This is particularly important following the recent 29-year update of the Swedish Prostate Cancer Group (SPCG)-4 trial, which demonstrated that these cancers are most strongly associated with prostate cancer–related death.[114] Taken together, it appears that mpMRI might deliver useful prognostic information and requires prospective evaluation.

First, it appears that the genomic features (including, activation of proliferative signalling, DNA damage, and inflammatory processes) of disease progression are enriched in mpMRI-detected tumours. Furthermore, this phenomenon goes beyond tumour volume and grade, which are (as demonstrated here) likely to be more favourable in undetected cancers. Indeed, mpMRI-detected tumours ostensibly, as discussed in greater detail in Chapter 5, harbour a greater proportion of molecular features of progression, including phosphatase and tensin homolog (*PTEN*) loss, BCR-associated genes (e.g. *CENPF*), and elevated genomic scores (e.g. OncotypeDX, Decipher, and Prolaris) compared to undetected disease, thus helping to reinforce the potential prognostic utility of mpMRI conspicuity.[124,137] To validate this, future research should focus on exploring the molecular basis of cancer conspicuity on mpMRI in larger patient cohorts, and this, in part, is the focus of the multi-arm multi-centre ReIMAGINE trial (NCT04063566) investigating the role of genetic biomarkers in conjunction with mpMRI for diagnosis of prostate cancer.

Second, additional histopathological features of mpMRI-undetected disease beyond tumour grade and size also appear to be reassuring. For example, contrary to early accounts, aggressive prostate cancer subtypes (e.g. cribriform pattern disease) now in fact appear to be predominantly detected by mpMRI, according to pooling of data from multiple studies.[138–140] This is likely to be important, as these pathological entities are more strongly associated with BCR after radical prostatectomy.

Finally, it appears that undetected tumours on mpMRI behave favourably in the long-term setting, as demonstrated by retrospective clinical data and through prediction of biochemical failure following radical prostatectomy.[141,142] Likewise, in the active surveillance context, tumour detection status on mpMRI may potentially provide greater utility than pathological grade alone. Recent findings from a contemporary mpMRI-directed active surveillance cohort suggest that mpMRI-undetected moderate-risk prostate cancer behaves like low-risk prostate cancer, and conversely that mpMRI-detected low-risk cancer behaves more like moderate-risk prostate cancer.[143]

3.5 CONCLUSION

In patients with prior prostate biopsy, mpMRI appears to be highly unlikely to overlook clinically significant prostate cancer. Tumours undetected by mpMRI are likely to have significantly lower overall and maximum Gleason grade and are smaller in size. These results help further support the utility of mpMRI, not only for biopsy-naïve patients, but also for those who have been advised to undergo further biopsies for accurate risk stratification.

3.6 OVERALL CHAPTER SUMMARY & CANDIDATE CONTRIBUTION

1. Overall, it appears that a very small proportion of significant cancers are overlooked by mpMRI, in patients with prior biopsy
2. Prostate cancers undetected by mpMRI in patients with prior biopsy seem to be lower grade and shorter length than cancers that are detected
3. PSAD thresholds may provide a simple, effective way of reducing undetected disease in patients with prior biopsy
4. However, overly stringent PSAD thresholds (i.e. lower) may result in reduced numbers of avoided biopsies

In this chapter, I devised the concept of utilising the PICTURE study dataset to compare key histopathological outcomes between mpMRI-detected and mpMRI-undetected prostate cancer, in patients with prior biopsy. The statistical analysis plan was designed by me and the wider PICTURE team. All data analyses, syntheses and presentation were performed by me. All figures and tables presented in this chapter were conceived and newly created by me, unless specifically stated in parentheses. NB: I was not involved in the delivery of the original PICTURE study; my main contribution is the unique post hoc analysis presented here.

CHAPTER 4:

RADIOLOGICAL FACTORS ASSOCIATED WITH PROSTATE CANCER NON-DETECTION ON mpMRI

4.1 INTRODUCTION

Pre-biopsy mpMRI is now arguably central to the risk stratification process for suspected prostate cancer, identifying patients at potentially highest risk.[1,5,117–119] Good diagnostic test accuracy of prostate mpMRI for the detection of clinically significant disease[1,117] has resulted in progressive and widespread incorporation of mpMRI in national and international guidelines[120,121] and increasingly, risk stratification modelling.[144]

Given the important role now played by mpMRI in the diagnostic pathway for suspected prostate cancer, considerable effort has been invested in elucidating the nature of disease that is detected and undetected by this technology.[145] This research effort is motivated, in part, by a need to understand the risks associated with cancer not detected by mpMRI, given the increasing trend to omit biopsy in cases of non-suspicious pre-biopsy mpMRI.[120] Furthermore, characterisation of the factors that influence non-detection of significant cancer may enable improvement in the delivery of mpMRI, across multiple domains.

Intrinsically, prostate cancer undetected by mpMRI consistently appears to exhibit multiple potentially reassuring genetic, molecular, histopathological, and clinical features.[17,122,124] Furthermore, from a patient-centric viewpoint, patients at risk of prostate cancer appear encouraged by these features and as such, accepting of the incumbent risk of undetected cancer on mpMRI.[126] Extrinsically, several other factors seem to affect detection of prostate cancer on mpMRI. From a technological standpoint, it appears that magnet strength, presence of endorectal coil, and mpMRI sequence choice all have a potential impact on disease detection. From a radiologist perspective, first-reader error (or, second-reader benefit), mpMRI scoring systems, reader training, and experience[146–150] all seem to play a role in cancer detection; indeed, a combination of all of these factors likely contributes to the moderate inter-reader variation that is widely reported for mpMRI.[151] Finally, the relevance of mpMRI scan quality is increasingly cited as a potential contributor to cancer detection,[131] and the Prostate Imaging Quality (PI-QUAL) scale has recently been developed as a tool to help quantify and standardise the quality of mpMRI scanning.[152]

The Prostate MR Imaging Study (PROMIS) was a prospective multicentre study that compared diagnostic accuracy of mpMRI and systematic TRUS-guided biopsy, against a comprehensive reference of transperineal template mapping (TTPM) biopsy in which biopsies were taken at 5mm intervals across the whole prostate.[1] In this chapter, the radiological factors associated with non-detection of significant prostate cancer by mpMRI in PROMIS are systematically investigated, including the effects of scan quality, mpMRI scoring system, and first-read error.

4.2 MATERIALS & METHODS

4.2.1 Study Population

The PROMIS study was prospectively registered on ClinicalTrials.gov (NCT01292291) and the full protocol has been described previously.[1,102] In short, biopsy-naïve patients with suspected prostate cancer were referred with serum PSA ≥ 15ng/mL and underwent pre-biopsy mpMRI at 1.5T. The full mpMRI details are described in the original PROMIS report.[1,102] After mpMRI, participants underwent a combined biopsy under general anaesthetic, consisting of 5 mm TTPM biopsy, and then systematic TRUS-guided biopsy. Each procedure was performed and reported blind to other tests. Ethical approval for PROMIS was granted by the National Research Ethics Service Committee London (11/LO/0185).

4.2.2 Radiological Reporting

Original mpMRI reporting in PROMIS was performed with the Likert 1–5 suspicion scale. In the present study, mpMRI scans (both false negative and matched true positive) were re-reported using both the Likert and the Prostate Imaging-Reporting and Data System (PI-RADS) version 2.1 scoring schemes, with radiologists blinded to original radiology and histopathology results. Scan quality was assessed using the PI-QUAL score; a 1-to-5 Likert scale derived from evaluation of each sequence, against objective quality criteria in line with the PI-RADSv2 recommendations.[152] PSA density (PSAD) was defined as serum PSA divided by mpMRI-derived prostate volume (using the prolate ellipsoid method). Detection of cancer on pre-biopsy mpMRI was defined as Likert scores 3–5. Non-detection of significant prostate cancer on pre-biopsy mpMRI was defined as Likert scores 1–2.

4.2.3 Histopathological Definitions

Clinically significant prostate cancer was defined using the two definitions of clinical significance outlined in PROMIS.[1,102,122] In definition 1, clinically significant cancer was classified as overall Gleason score ≥ 4 + 3 of any length or MCCL ≥ 6mm of any grade. In definition 2, clinically significant cancer was classified as overall Gleason score ≥ 3 + 4 of any length or MCCL ≥ 4mm of any grade. Therefore, by virtue, all patients with definition 1 disease also fulfilled the requirements for definition 2. Criteria for clinical significance were developed and validated for TTPM-biopsy for the detection of Gleason score ≥ 4 and cancer core lengths representative of lesions 0.5mL.[103–107] Overall Gleason score

was defined as the predominant Gleason pattern across the entire prostate and constituted the final pathological score. Maximum Gleason score was defined as the highest Gleason pattern found in any biopsy core.

4.2.4 Sub-Population Analysis

All patients with both definitions of clinically significant cancer were considered for this analysis (Fig. 11). Next, patients with significant disease undetected by mpMRI were matched to patients with mpMRI-detected disease, for overall Gleason grade and MCCL (maximum cancer core length). Quality assessment, repeat Likert scoring, and PI-RADSv2.1 scoring was performed by experienced prostate uroradiologists (FG, LD) on the matched cohort, to assess impact of these factors beyond the confounders of tumour grade and size.

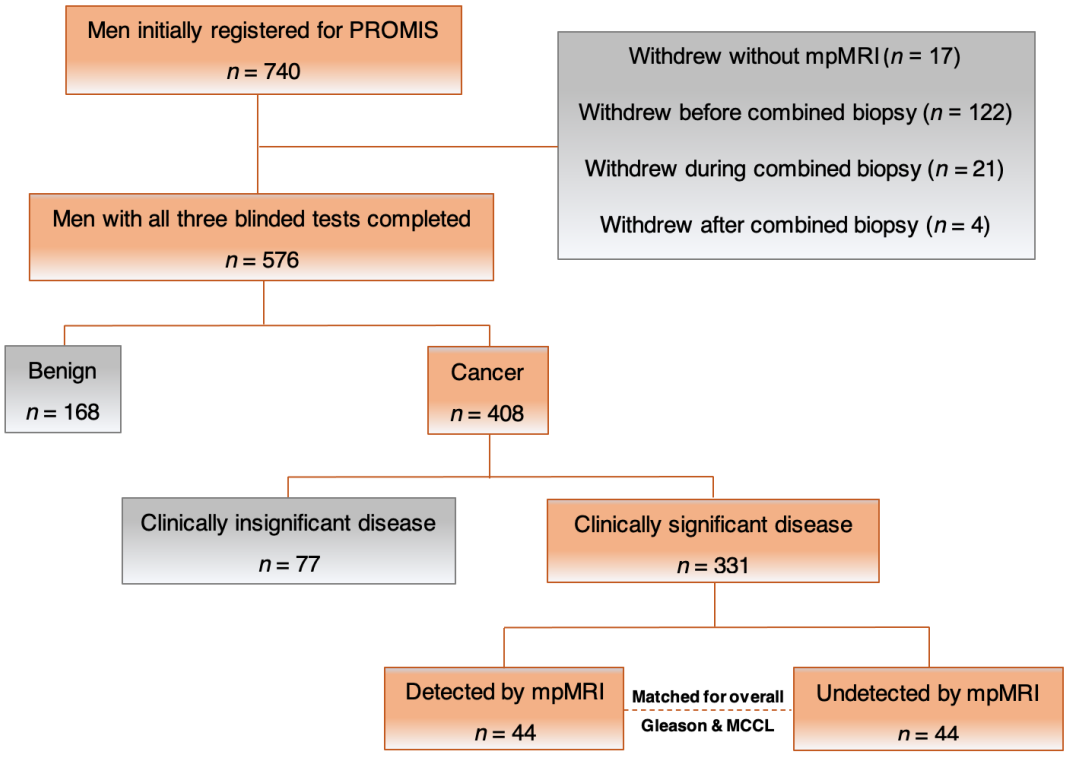


Fig. 11 – Flow chart for study inclusion in the sub-population analysis of PROMIS.

4.2.5 Statistical Analysis

Data distribution was evaluated using D'Agostino-Pearson or Shapiro-Wilk normality tests. All data had non-normal distribution, so two-sided nonparametric statistical tests were used. Correlation of mpMRI scores between readers and

scoring schemes were assessed using the Pearson correlation coefficient. The alpha level was 0.05 for all statistical tests. Binomial 95% confidence intervals (CIs) for proportions were calculated via approximation with the Poisson distribution method. Multiple testing was assessed via the false discovery rate using the Benjamini-Hochberg method. All analyses were conducted using GraphPad Prism 9.0.0 (GraphPad Software, La Jolla, CA, USA) and the R statistical environment (v3.6.3; R Foundation for Statistical Computing, Vienna, Austria).

4.3 RESULTS

4.3.1 Scan Quality

Summary demographic and radiological data are given in Table 10. Overall, 7% (17/230; 95% CI 4.4–12%) of patients with definition 1 prostate cancer and 13% (44/331; 95% CI 9.8–17%) of patients with definition 2 prostate cancer, had significant disease undetected by mpMRI. Of patients with mpMRI-undetected cancer, 45% (20/44; 95% CI 30–61%) had high quality mpMRI scans as defined by PI-QUAL scores 4–5. Whilst 55% (24/44; 95% CI 39–70%) had low quality mpMRI scans as defined by PI-QUAL scores 1–3. Qualitatively, several reasons were specified for reduced scan quality (Table 11), including, rectal air artefacts, partial motion artefacts, and diffusion-weighted imaging (DWI) artefacts (Fig. 12).

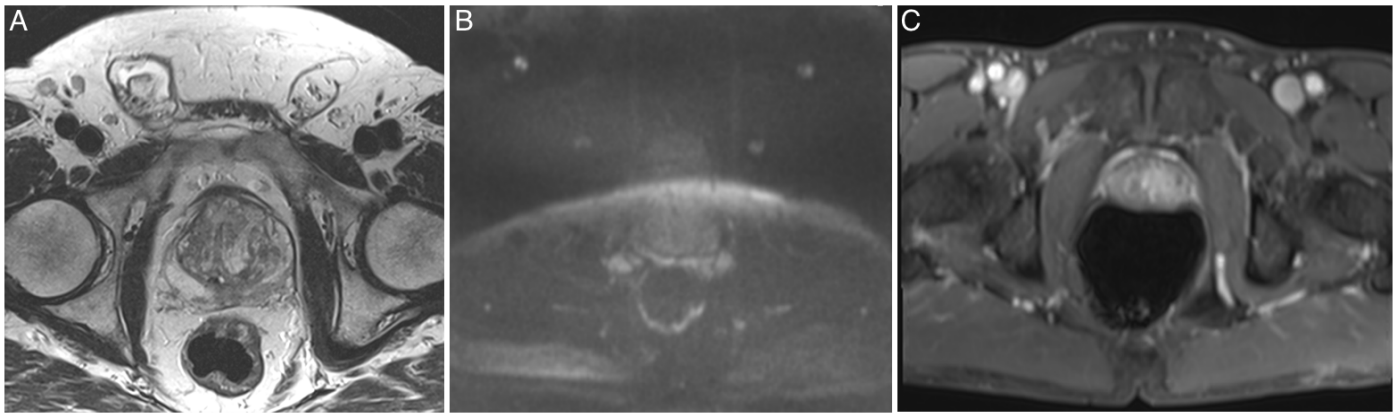


Fig. 12 – Example artefacts from low quality mpMRI (PI-QUAL 1–3) in patients with mpMRI-undetected cancer in PROMIS. (*A = T2W partial motion artefacts; B = DWI artefacts; C = low in-plane resolution and distended rectum on the DCE sequence*).

Table 11 – Characteristics of low quality mpMRI (PI-QUAL 1–3) in patients with significant prostate cancer in PROMIS.

Pt	PI-QUAL	Radiologist commentary	PSA, ng/mL	Pros vol, mL	PSAD, ng/mL/mL	Overall GI	Max. GI	MCCL, mm
1	2	Rectal air artefacts seen	5.7	23	0.25	3 + 4	3 + 4	6
2	2	DWI and T2 non-diagnostic	10	60	0.17	3 + 4	3 + 4	2
3	3	Artefacts seen on DWI	7.1	34	0.21	3 + 4	4 + 3	5
4	3	Artefacts seen on DWI	4.1	70	0.06	3 + 4	3 + 4	4
5	3	Not 4 on DCE sequence	8.3	53	0.16	3 + 4	3 + 4	6
6	3	Not 4 for artefacts on T2-WI	7.1	83	0.09	3 + 3	3 + 3	4
7	3	Artefacts seen on DWI	6.8	114	0.06	3 + 4	3 + 4	10
8	3	Artefacts seen on DWI	11.4	59	0.19	3 + 4	3 + 4	3
9	3	Artefacts seen on DWI	6.8	65	0.10	3 + 4	3 + 4	6

4.3.2 Scoring System

Rescoring with Likert and PI-RADSv2.1 schemes resulted in equivalent levels of disease detection on mpMRI (Fig. 13). In the original PROMIS study, 7% (17/230) of patients with definition 1 prostate cancer had disease overlooked by mpMRI (Reader 1); when rescored with Likert and PI-RADSv2.1 systems, this resulted in only 2.6% (6/230) cases of non-detection of definition 1 disease, for both scoring schemes (Reader 2).

For definition 2 disease, the Likert scoring system resulted in fewer patients with overlooked disease on mpMRI. In the original PROMIS study, 13% (44/331) of patients with definition 2 prostate cancer had disease overlooked by mpMRI (Reader 1); when rescored with Likert and PI-RADSv2.1, this resulted in 6.3% (21/331) and 9.6% (23/331) cases of non-detection of definition 1 disease (Reader 2).

4.3.3 Second Radiologist Reading

Here, rescoring of the original false negative mpMRI scans in PROMIS, resulted in a higher level of detection, on mpMRI, of clinically significant prostate cancer than was seen in the original PROMIS study. For definition 1 disease, 7% (17/230) of patients had cancer undetected by mpMRI in the original PROMIS study (Reader 1). When rescored with the Likert system, this resulted in non-detection of definition 1 disease in 2.6% (6/230), representing a 3.9% (9/230) reduction of undetected significant cancer (Reader 2). For definition 2 disease, 13% (44/331) of patients had cancer undetected by mpMRI in the original PROMIS study (Reader 1). When rescored with the Likert system, this resulted in non-detection

of definition 2 disease in 6.3% (21/331), representing a 6.9% (23/331) reduction of undetected significant cancer (Reader 2).

4.3.4 Inter-Reader & Inter-System Variation

Moderate inter-reader variation was observed between radiologists and between scoring schemes when both Likert and PI-RADSv2.1 systems were applied to the PROMIS subpopulation (Fig. 13). When rescored with the Likert system (Reader 2), moderate agreement was found with the original PROMIS scoring (Reader 1) ($R = 0.68$; $p < 0.0001$) (original Likert score vs. Likert rescore: Likert 1: 5.7% vs. 0%; Likert 2: 44% vs. 27%; Likert 3: 16% vs. 31%; Likert 4: 20% vs. 25%; Likert 5: 14% vs. 17%).

When rescored with the PI-RADSv2.1 system (Reader 2), again, moderate agreement was found with the original PROMIS scoring (Reader 1) ($R = 0.54$; $p < 0.0001$) (original Likert score vs. new PI-RADSv2.1 scores: Likert 1: 5.7% vs. 0%; Likert 2: 44% vs. 36%; Likert 3: 16% vs. 9%; Likert 4: 20% vs. 39%; Likert 5: 14% vs. 16%). Strong agreement was found when comparing rescored Likert scores with new PI-RADSv2.1 score (both Reader 2) ($R = 0.77$; $p < 0.0001$) (Likert rescore vs. new PI-RADSv2.1 score: Likert 1: 0% vs. 0%; Likert 2: 27% vs. 36%; Likert 3: 31% vs. 9%; Likert 4: 25% vs. 39%; Likert 5: 17% vs. 16%).

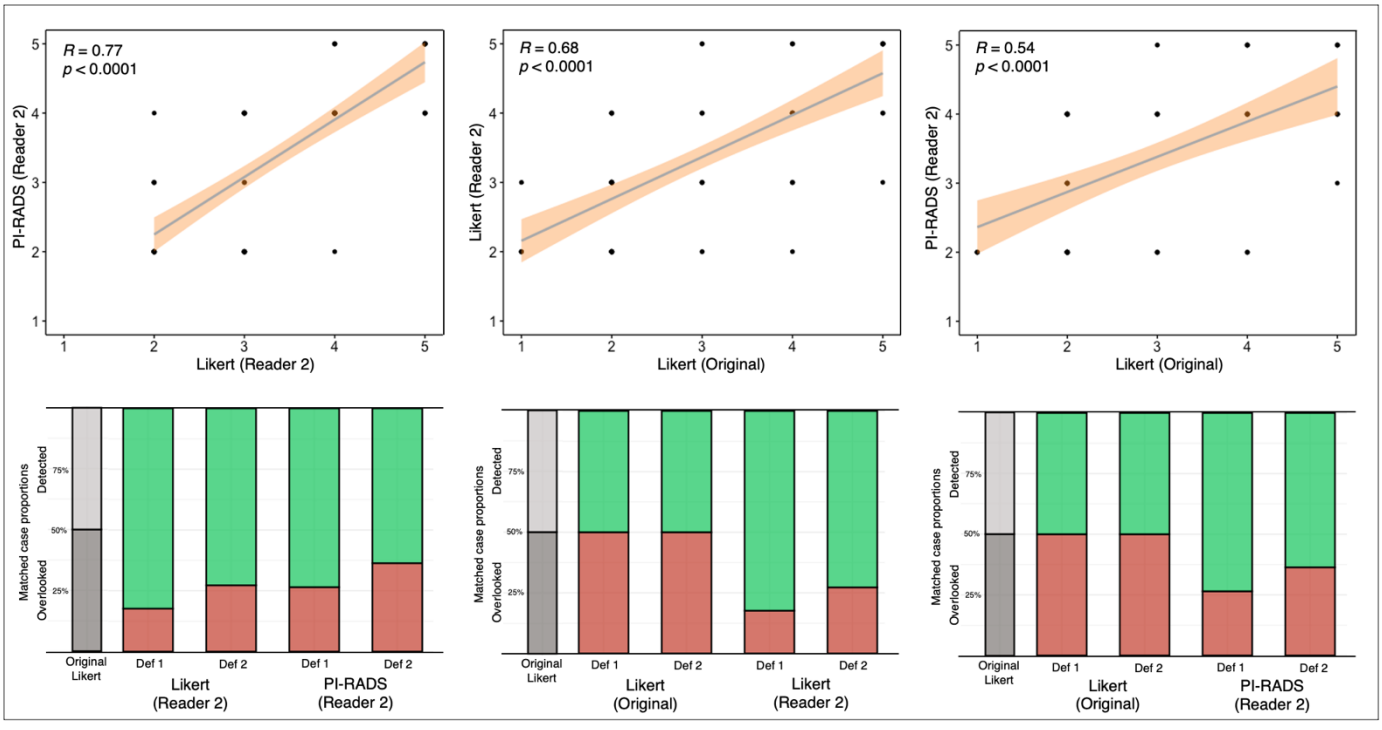


Fig. 13 – Impact of scoring system & second radiologist reading on mpMRI-undetected cancer in PROMIS. (*Green bars = prostate cancer detected by mpMRI; red bars = prostate cancer undetected by mpMRI*).

4.4 DISCUSSION

In summary, this re-appraisal of the mpMRI results from the PROMIS study has helped highlight the importance of high quality mpMRI acquisition and reporting for the detection of clinically significant prostate cancer. It appears that over half (55%) of patients with mpMRI-undetected disease had low quality mpMRI, as defined by PI-QUAL scores 1–3. The commonest specified reason for reduced mpMRI quality was artefact on the DWI sequence, however, rectal air artefacts and partial motion artefacts were also cited as potential causes of difficult interpretation. Both the Likert and PI-RADSv2.1 scoring systems seemed to perform well in detecting clinically significant prostate cancer, with the Likert system performing slightly better for the more lenient definition of significant disease (definition 2). In this analysis, it appears that a small proportion of significant cancers that were initially overlooked in the original PROMIS analysis (3.9% for definition 1 disease, and 6.9% for definition 2 disease) were visible to the second reader; however, the unknown effect of research bias should be acknowledged.

The major limitation of this analysis is the sub-population study design. Whilst this design was chosen for feasibility (i.e. manageable case-load) and to enable matching of the two strongest conspicuity influences (tumour size and Gleason grade), it does introduce the potential for selection bias, as the entire PROMIS cohort is not represented.[1,122] Another potential limitation is the use of the PI-QUAL scale to assess mpMRI quality, as this system is still in relative infancy.[152–155] Lastly, the possibility of researcher bias must be considered. Especially given that the second reader was aware of the purpose of this new analysis (to assess the impact of mpMRI quality), and that all cases in this sub-population had clinically significant prostate cancer present. This bias should be borne in mind, particularly when interpreting low PI-QUAL scores for mpMRI-undetected cancer, and the high levels of detection seen with the second reader mpMRI scoring, despite their blinding to original mpMRI and histopathology reports. Furthermore, this sub-analysis did not compare PI-QUAL scores for mpMRI-detected cancer against mpMRI-undetected cancer, which would have been an additional useful comparison, to assess whether patients with mpMRI-detected disease had, on balance, higher quality scans.

As yet, research surrounding the impact of mpMRI quality on detection of significant prostate cancer is limited, despite the clear plausibility of this factor. Here, diffusion-related artefacts appeared to be the most prominent reasons for reduced mpMRI quality (and thus, contributed to potential non-detection of significant disease). In a recent study examining the impact of hip arthroplasty-related artefacts (using the PI-QUAL scale), Boschheidgen and colleagues found that in around 30% of cases hip arthroplasty rendered mpMRI images non-diagnostic, thus creating the potential for non-detection of underlying cancer.[156] Interestingly, the authors found no significant differences in the level of artefact

generated between 1.5T or 3T mpMRI.[156] Clinically, implications of improved mpMRI quality are understandable, as was illustrated recently in a study by Alanee and colleagues, in which potentially lethal prostate cancer (Gleason 5+5) was overlooked by mpMRI due to the deleterious imaging results of recent transrectal biopsy.[130,131]

Inter-observer variation in prostate mpMRI reporting is now well acknowledged, and the introduction of continuous training and audit are now common-place in an attempt to address this.[150,151] In contrast, impact of second-reader detection of significant cancer is less well studied. In a study by Serrao and colleagues,[148] they explored mpMRI-invisible prostate cancer, and the factors affecting this phenomenon. As part of their analysis, they reported that 24.1% of patients with mpMRI-undetected prostate cancer (7/29, $p = 0.016$) had their disease detected on a second-read of their mpMRI, however, it is not clear from their methodology as to whether the second reader was blinded to the original mpMRI result.[148] Nonetheless, the findings reported in this chapter appear to be in keeping with findings from Serrao and colleagues, and so an important area for future research may be to expand upon this concept, particularly examining if and where second-read may be built into the routine prostate mpMRI pathway.

4.5 CONCLUSION

In summary, through re-analysis of the PROMIS cohort, it appears that mpMRI successfully detects the majority of clinically significant prostate cancers, however, this is likely reliant upon high standards of scan acquisition and reporting. Low quality mpMRI is potentially associated with non-detection of significant cancer, particularly through the impact of artefact on the DWI sequence. Individual radiologist performance varies, and multiple reads of mpMRI may result in an increased proportion of detected significant cancer, however, this should be balanced against a potential increase in false positive reports, with resultant excess biopsy numbers. Both the Likert and PI-RADSv2.1 reporting schemes appear to yield a similarly high diagnostic accuracy level for detection of significant disease.

4.6 OVERALL CHAPTER SUMMARY & CANDIDATE CONTRIBUTION

1. Multiple radiological factors appear to affect detection of significant prostate cancer on mpMRI
2. Low quality mpMRI seems to be associated with non-detection of significant cancer
3. Artefacts on the DWI mpMRI sequence appear to be the commonest quality-related cause for non-detection
4. Multiple reads of prostate mpMRI may result in an increased proportion of detected significant cancer
5. Likert and PI-RADSv2.1 reporting systems both appear to perform well for detection of significant prostate cancer
6. For more lenient definitions of disease significance, it appears that the Likert scale may outperform PI-RADS

In this chapter, the sub-project study was designed by me, in conjunction with members of the wider PROMIS team. Generation of the bespoke sup-population from PROMIS was conducted and curated by me. Re-scoring of mpMRI (with PI-QUAL, PI-RADS, and Likert) was conducted by expert UCLH uroradiologists, Dr Francesco Giganti and Dr Louise Dickinson. Analysis and presentation of all results was conducted by me. All figures and tables presented in this chapter were conceived and newly created by me, unless specifically stated in parentheses.

CHAPTER 5:

MOLECULAR LANDSCAPE OF MRI-UNDETECTED PROSTATE CANCER

5.1 INTRODUCTION

Introduction of mpMRI has helped improve risk stratification for patients at a risk of prostate cancer, through accurate pre-biopsy detection of clinically significant disease.[1] However, approximately 10–20% of clinically significant prostate cancers are not detected by mpMRI and the nature of mpMRI-invisible disease remains a potential source of concern.

The biology underlying mpMRI conspicuity of prostate cancer is poorly understood; however, tumour visibility on mpMRI appears to be associated with disease significance and aggressivity.[17] Disease aggressivity in prostate cancer can be defined clinically in several ways, including reduced time to recurrence following treatment, time to metastasis, and prostate cancer–specific mortality. Pathologically, the Gleason grading system appears to correlate with clinical outcome, with higher-grade disease exhibiting increased features of disease aggressivity.[114] Furthermore, aggressive cancer appears to harbour particular genomic hallmarks, including *MYC* amplification, *ATM* mutation, hypermethylation of *TCERG1L* (5' upstream), and loss of *PTEN*.[157] The potential mechanistic association of these molecular features with mpMRI phenotypes and their prognostic significance has been an area of recent research focus,[137] now warranting collation.

The aim of the work in this chapter is to systematically collate the evidence surrounding the genomic characteristics underlying the mpMRI conspicuity of prostate cancer. Furthermore, publicly available mpMRI-correlated genetic databases will be used in an attempt to identify genes associated with mpMRI conspicuity, and their associated enriched pathways and functions.

5.2 MATERIALS & METHODS

5.2.1 Study Design

The protocol for this systematic review and bioinformatic analysis has been published in detail,[158] and was based on the Preferred Reporting Items for Systematic Review and Meta-analysis Protocols (PRISMA-P) statement. This review was also prospectively registered in the PROSPERO International Registry (Ref: CRD42019147423).

5.2.2 Literature Search

A systematic search of the literature was conducted from 1990 to 2020 in four databases: MEDLINE, PubMed, EMBASE, and Cochrane. Controlled vocabulary was selected in the search engines to reduce the number of unrelated studies. The search strategy contained 11 components linked by the AND/OR operator terms: (Prostate AND cancer) AND (gene OR genetic OR genome OR genomic OR transcriptome OR transcriptomic OR epigenetic) AND (magnetic resonance imaging OR MRI).

5.2.3 Study Selection

Figure 14 shows an overview of the evidence acquisition process. Eligible studies were screened, assessing titles and abstracts for relevance (by JMN and BSS). Full texts were retrieved and reviewed further for eligibility. For inclusion in the analysis, studies had to demonstrate investigation of the genomic aspects of localised prostate cancer conspicuity on mpMRI. Genomic investigation was at the DNA level, including larger-scale alterations (copy-number changes or methylation). Transcriptomic data analysing RNA expression (coding or noncoding) or microRNA were also included. All proteomic methodologies were accepted, including immunohistochemistry (IHC). Conference abstracts, correspondence articles, expert opinions, non-English language studies and case reports were excluded. Studies with inappropriate study designs for this topic (e.g. that did not correlate tumour visibility on mpMRI with genomic data) were excluded. Articles focusing solely on clinical or histopathological features of mpMRI conspicuity were removed. Studies that focused on advanced or metastatic prostate cancer were excluded.

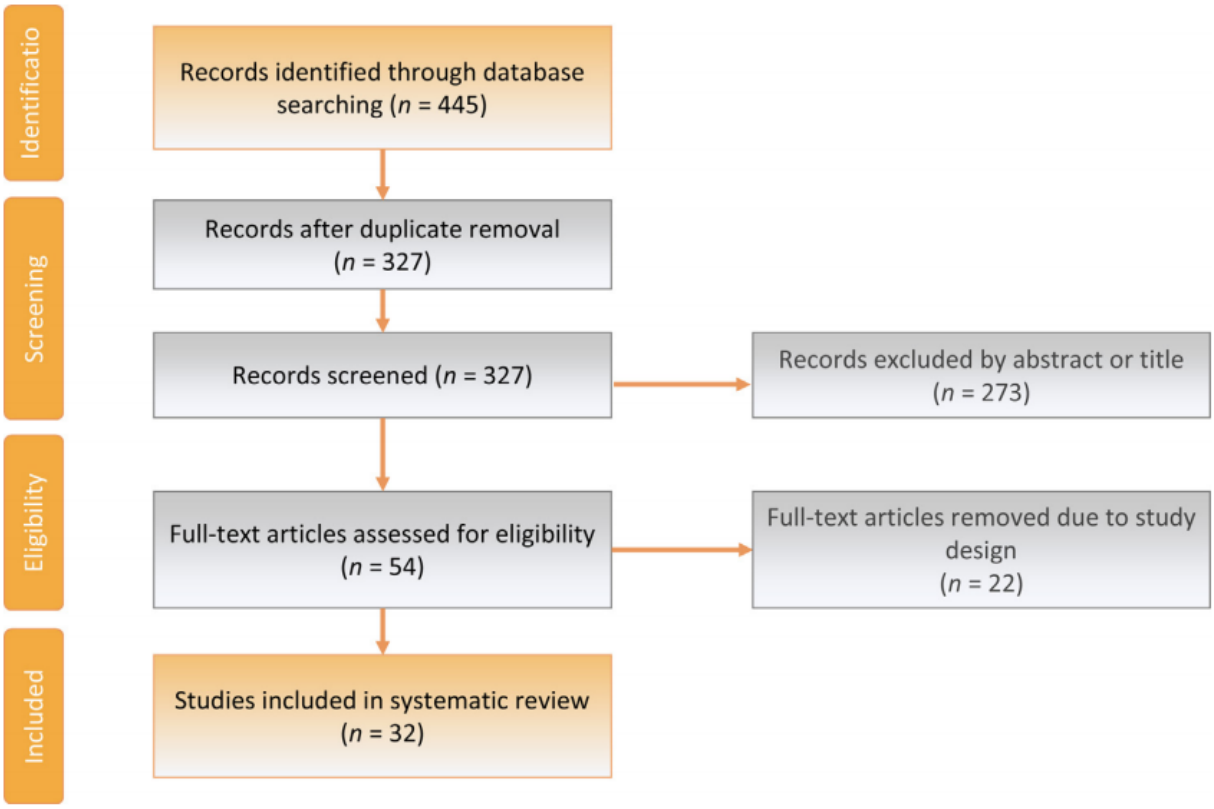


Fig. 14 – PRISMA flow diagram of systematic evidence acquisition on the genetic basis of prostate mpMRI.

5.2.4 Data Collection

Identified articles were uploaded to Rayyan (a web and mobile application for systematic reviews) to expedite initial screening and allow reviewers to filter studies. Reference sections of included articles were searched manually to identify missed studies and additional data. All extracted data were collected using a standardised form.

5.2.5 Quality Assessment

Risk of bias assessment was conducted using a modified Newcastle-Ottawa scale. Studies were assessed on grounds of patient selection, comparability, and outcome. Large biopsy cohorts were considered most representative, encompassing an accurate cross section of disease upon diagnosis, followed by smaller biopsy cohorts (< 50 patients) and then radical prostatectomy cohorts, and finally non-representative sampling from another route. The Newcastle-Ottawa scale is intended for traditional clinical outcome–focused meta-analyses, so in this analysis, outcome measures were simplified to a single parameter, whereby the quality of genetic outcome was assessed. Unbiased whole genome, methylome, transcriptome, or proteome-based approaches were considered gold standard (two stars), followed by

large-scale but limited methods based on arrays or very large gene panels (one star) and then selected gene panels (such as those used in commercial assays), and lastly, approaches that investigated single genes. The Newcastle-Ottawa scale allowed for a maximum of eight stars: four for selection, two for comparability, and two for outcome (Appendix 7).

5.2.6 Data Synthesis

The primary point of interest was differential gene expression between mpMRI-visible and mpMRI-invisible tumours. Secondary endpoints were explanatory links between gene function and mpMRI conspicuity, and potential prognostic value of differential gene enrichment. Key themes were derived from the included the literature with a focus on mpMRI scoring systems used (e.g. PI-RADS, Likert, and radiogenomic features), criteria used to define tumour visibility (usually a PI-RADS or Likert score cut-off), and the type of cohort used in the study (e.g. radical prostatectomy or biopsy cohort).

5.2.7 Bioinformatic Analysis

In the identified articles, there were an insufficient number of studies with single endpoints and comparable methodologies to conduct a typical meta-analysis. Therefore, an additional search was conducted to identify available genetic datasets for bioinformatic analysis in the NCBI GEO and European genome-phenome archives. For retrieved transcriptomic data, Log2-fold changes and associated false discovery rate (FDR)-adjusted values were compared between mpMRI-visible and mpMRI-invisible tumours. Differential gene expression was compared between studies; if unavailable, highlighted genomic features and the direction of change (e.g. correlation coefficients) were compared between groups. Genes highlighted in multiple studies were used (via over-representation analysis) to identify enriched pathways, components, and functions. Analyses were performed using the WebGestalt, a gene set analysis toolkit. This method enables a standardised and robust analysis, as it does not rely on significance or effect size weighting (measures of effect size differed between studies) and uses a modified Fisher's exact test to identify enriched biological processes.

5.3 RESULTS

5.3.1 Study Characteristics

Overall, 445 articles were retrieved: 262 from EMBASE, 129 from Medline, 42 from Cochrane, eight from PubMed, and four from reference searching or from expert suggestions. Of these, 32 articles were eligible for further analysis (Table 12).

Of the 32 studies, 14 used prostate biopsy as the source of prostate tissue for genetic analysis, 16 used radical prostatectomy specimens, and two used a combination of these two approaches. Median study size was 51 (range 2–532). The PI-RADS reporting scheme was the most commonly used mpMRI reporting approach, with 21 of the included studies using this system or a modified version. Of those using PI-RADS, 14 used PI-RADSv2. Assessment by an expert radiologist was the second most common mpMRI scoring approach, employed in six studies, followed by scores based on radiomic-derived features, used in three of the studies. Two studies used a modified or different reporting measure. For the purpose of comparison, 12 studies chose to discretise scoring systems into “mpMRI-visible” and “mpMRI-invisible” tumours, with the exception of two studies that included an “indeterminate” category.

Definitions of tumour conspicuity on mpMRI were heterogeneous between studies, with one study defining visibility (or high clinical suspicion) as PI-RADS scores 2–5, five as PI-RADS scores 3–5, three as PI-RADS scores 4–5, and two as PI-RADS score 5. Regarding MRI magnet strength, 3T systems were most common, used in 21/32 studies, with 5/32 using 1.5T systems (two studies used both magnet strengths). Four did not report the magnet strength, and 24 did not report echo times. The majority of studies (26/32) assessed mRNA to derive transcriptomic data in relation to mpMRI signal and used most commonly microarray or ribonucleic acid sequencing (RNAseq) methods (18 studies). Protein-based studies were the second most common approach (8/32) with all studies using IHC, followed by studies using DNA sequencing (seven studies). Two studies looked at DNA methylation. In studies using mRNA, 22 used samples processed with formalin-fixed paraffin-embedding (FFPE), three used fresh frozen tissue, and six used fluid biomarkers. One study did not state the preparation method. Seven studies used macrodissection prior to genomic analysis, two used microdissection, and eight used neither (often, tissue punches), and in 15 studies, this was not applicable given the study methodology.

Table 12 – Descriptive characteristics of included studies analysing the genetics of mpMRI conspicuity.

Author	Year	Cohort	*n*	MRI score	Def of MRI vis	DNA	DNA meth	RNA	Protein	Genes	Platform	Prep	MRI Tesla
Lenkinski	2008	Radical	2	Qualitative	-	No	No	Yes	Yes	Multiple	Micro/IHC	Fresh	3.0
Leyton	2013	Biopsy	115	Qualitative	-	No	No	Yes	No	*PCA3*	Commercial	FFPE	3.0
Busetto	2013	Biopsy	171	Qualitative	-	No	No	Yes	No	*PCA3*	*PCA3* assay	-	3.0
Renard-Penna	2015	Radical	106	PI-RADSv1	-	No	No	Yes	No	CCP	RT-PCR	FFPE	3.0
Kaufmann	2016	Biopsy	49	PI-RADSv1	≥7	No	No	Yes	No	*PCA3*	*PCA3* assay	-	1.5
Stoyanova	2016	Biopsy	6	Radiomic	-	No	No	Yes	No	Multiple	Microarray	FFPE	3.0
McCann	2016	Radical	30	Radiomic	-	No	No	No	Yes	*PTEN*	IHC	FFPE	3.0
De Luca	2016	Biopsy	282	PI-RADSv1	-	No	No	Yes	No	*PCA3*	*PCA3* assay	-	1.5
Dulaney	2017	Biopsy	11	PI-RADSv2	5	No	No	Yes	No	Multiple	Microarray	FFPE	-
Lee	2017	Radical	48	PI-RADSv2	2–5	Yes	No	No	Yes	Multiple	FISH/IHC	FFPE	1.5/3.0
Leapman	2017	Biopsy	100	PI-RADSv1	4–5	No	No	Yes	No	Oncotype	RT-PCR	FFPE	3.0
Jamshidi	2017	Radical	6	Qualitative	-	Yes	No	No	No	Multiple	Whole ex	FFPE	3.0
Palapattu	2017	Biopsy	31	Qualitative	-	Yes	No	Yes	Yes	Multiple	RNAseq	FFPE	3.0
Fenstermaker	2017	Biopsy	187	mSS	-	No	No	Yes	No	*PCA3*	*PCA3* assay	-	3.0
Gronberg	2018	Biopsy	532	PI-RADSv2	3–5	No	No	No	Yes	*STHLM3*	Ptn assay	-	1.5
Radtke	2018	Combo	11	PI-RADSv2	4–5	No	No	Yes	No	Multiple	Microarray	FFPE	3.0
Li	2018	Radical	16	PI-RADSv2	4–5	No	No	Yes	Yes	Multiple	RNAseq	FFPE	3.0
Kesch	2018	Biopsy	5	PI-RADSv1	-	Yes	Yes	No	No	Multiple	Meth array	-	3.0
Salmasi	2018	Combo	134	PI-RADSv2	-	No	No	Yes	No	Oncotype	Microarray	FFPE	3.0
Beksac	2018	Radical	206	PI-RADSv1	-	No	No	Yes	No	Multiple	Microarray	FFPE	3.0
Houlahan	2019	Radical	40	PI-RADSv2	5	Yes	No	Yes	No	Multiple	RNAseq	FFPE	-
Parry	2019	Radical	6	PI-RADSv2	3–5	Yes	Yes	Yes	No	Multiple	Multiple	Fresh	1.5
Baumgartner	2019	Biopsy	53	PI-RADSv2	3–5	No	No	No	Yes	*ERG*	IHC	FFPE	-
Purysko	2019	Radical	72	PI-RADSv2	3–5	No	No	Yes	No	Decipher	Microarray	FFPE	3.0
Hectors	2019	Radical	64	PI-RADSv1	-	No	No	Yes	No	Multiple	Microarray	FFPE	3.0
Martin	2019	Biopsy	102	PI-RADSv2	-	No	No	Yes	No	Decipher	Microarray	FFPE	3.0
Wibmer	2019	Biopsy	118	PI-RADSv2	-	No	No	Yes	No	CCP	Microarray	FFPE	3.0
Kornberg	2019	Biopsy	131	PI-RADSv2	-	No	No	Yes	No	Oncotype	Microarray	FFPE	3.0
Falagario	2019	Radical	520	Qualitative	-	No	No	Yes	No	Decipher	Microarray	-	1.5/3.0
Switlyk	2019	Combo	43	ADC	-	No	No	Yes	No	*PTEN*	RT-PCR	Fresh	1.5
Sun	2019	Radical	6	Radiomic	-	No	No	Yes	Yes	Multiple	RNAseq	FFPE	3.0
Salami	2019	Radical	10	PI-RADSv2	3–5	Yes	No	Yes	No	Multiple	Multiple	FFPE	-

5.3.2 Thematic Synthesis

5.3.2.1 Clinically-Validated Genetic Biomarker Panels

Validated commercial assays for the detection of prostate cancer or assessment of aggressive disease were investigated in 16 studies. Additionally, several larger-scale investigations used panels derived from these assays as part of their analysis.

Progensa prostate cancer antigen 3 (PCA3) is a prognostic marker that measures the ratio of PCA3 to PSA (KLK3) mRNA and appeared to be significantly higher in patients with mpMRI-visible tumours.[159,160] In contrast, another study found no probable correlation between PCA3 level and tumour conspicuity; however, this study had a relatively small sample size ($n = 49$).[161] Two other studies supported the use of PCA3 in conjunction with mpMRI to improve diagnostic accuracy significantly; however, they did not compare mpMRI-visible and mpMRI-invisible cancers,[162,163] and this was also true of the STKHLM3 assay.[164]

Oncotype DX genomic prostate score (GPS) is another prognostic marker, based on an RNA expression assay of 17 genes that is associated with pathological stage, grade, disease recurrence, and prostate cancer-specific mortality. Leapman and colleagues[165] found a likely significant association between GPS and prostate cancer visibility on mpMRI. This association persisted only for patients with significant disease (defined as Gleason score ≥ 3 + 4 cancer).[165] These findings were reiterated in other studies describing an association between GPS and mpMRI visibility of clinically significant prostate cancer.[166,167]

Decipher, a genomic classifier (GC), is a 22-gene prognostic signature associated with early metastasis of prostate cancer.[168] Overall, mpMRI-visible tumours appear to have increased Decipher scores compared with mpMRI-invisible tumours, in both biopsy cohorts and radical prostatectomy cohorts.[169–172] In contrast, two recent studies found no major association of a GC-based gene signature and tumour conspicuity on mpMRI; however, this may be attributed to a small sample size ($n = 6$)[173] and a low- to intermediate-risk cohort, mirroring similar results to studies using Oncotype DX in this patient population.[165,167,174] Additionally, another study found that GC appeared to add significant value to mpMRI in predicting adverse pathology upon radical prostatectomy, but did not correlate GC with mpMRI features directly.[159] In terms of radiogenomics, GC score was apparently highly correlated with grey-level co-occurrence matrix (GLCM) texture, a measure of regularity and local spatial variation of intensity or colour brightness in an image to determine its texture.[165,175] Thus, GC-related genes tend to correlate with mpMRI features, but, as with other candidate genes, only

correlative studies have been performed without controlling for additional pathological factors that exist between mpMRI-visible and mpMRI-invisible tumours.

Finally, Prolaris cell cycle progression (CCP) is a prognostic gene signature comprising CCP-associated genes wherein each 1-unit increase in CCP score represents doubling of the risk of prostate cancer–specific mortality. PI-RADS was seemed to weakly correlate with CCP ($r = 0.26$, $p = 0.007$), but was able to predict a CCP score of > 0 with sensitivity and specificity of 80.0% and 40.9%, respectively.[176] However, a small number of tumours with high CCP were overlooked by mpMRI.[176] Conversely, Wibmer et al. compared the CCP gene signature between mpMRI-visible and mpMRI-invisible cancers and found no significant difference.[177] Significant differences in CCP scores were, however, observed between patients with and without extracapsular disease extension on mpMRI.[177]

5.3.2.2 Biological Pathways & Functions

Transcriptomic analysis was used in 18 studies to identify key pathways differing between mpMRI-visible and mpMRI-invisible tumours. Several studies used gene set enrichment analysis or over-representation analysis to identify enriched processes, pathways, or functions.

Pathways that regulate cell cycle and growth appear to be related to mpMRI conspicuity. Li and colleagues[178] reported apparently enriched processes of mitotic cell cycle, protein folding, cell cycle, mitotic cell cycle process, and cell division in mpMRI-visible cancers. Furthermore, Dulaney and colleagues[179] reported that tumours with a PI-RADS score of 5 seemed to have significantly more deregulation of pathways involved in apoptosis and cell cycle (in particular, *TGFb*, *STAT*, and *RAS* pathways) compared with mpMRI-invisible tumours; however, this was unadjusted for multiple testing and this study scored relatively low using the modified Newcastle-Ottawa scale (3/8), indicating a potential a risk of bias. Finally, Beksac et al.[169] reported that pathways associated with CCP (*PI3K-AKT-mTOR* and *E2F*) and castration resistance (*WNT-b*) were found to be likely active in mpMRI-visible cancer (PI-RADSv2 score of 5) than in mpMRI-invisible cancer.

Another major hallmark of aggressive cancer is evasion of immune destruction, and this was highlighted across several articles.[180] Stoyanova et al.[181] reported seemingly increased immune/inflammatory and cell-stress responses in mpMRI-visible tumours in both the PZ and the TZ, as derived through radiomic feature analysis. Another radiogenomic study reported significant enrichment of genes involved in immune responses in mpMRI-visible tumours, as defined by ADC GLCM energy-derived features.[182] As further indicative evidence of the immunological component of mpMRI conspicuity,

Houlahan et al.[17] reported apparent 200-fold increase in *ANKRD30A* (NY-BR-1; a tumour-specific antigen that selectively activates CD8+ T cells) in mpMRI-visible cancers.

DNA damage repair pathway defects play an important role in prostate cancer carcinogenesis and progression, and mutations are present in around 19% of prostate tumours of Gleason grade ≥ 8;[183] these also appear to play a role in tumour conspicuity on mpMRI. Dulaney et al.[179] noted significantly higher deregulation of DNA repair–related genes in mpMRI-visible targeted tumours with higher dynamic contrast enhancement values, as also noted in other studies.[178] Another case study found lower ADC values in tumour regions with a greater number of copy-number alterations and higher mutational burden.[184] Houlahan et al.[17] also quantified genomic instability using the percentage of the genome altered (PGA) via copy-number alterations, finding elevated PGA in visible tumours ($p = 0.03$) with increased average length of individual amplifications and deletions. Tumour hypoxia is believed to be a characteristic driving cancer instability[185] and has been shown to correlate with mpMRI-derived radiomic features.[186] Contrasting this, a different study found no apparent significant difference in mutation load in cancer-associated genes between regions that were histopathologically benign and had low clinical suspicion on mpMRI, intermediate clinical suspicion on mpMRI, and high-grade cancer histopathologically; however, this study was limited by its small sample size ($n = 6$).[187]

Lastly, gene sets involved in cell structure (e.g. actin filament-based process and cytoskeleton organisation) were downregulated in mpMRI-invisible tumours, which may explain the physical properties (such as lower tissue density) associated with mpMRI-invisible cancer.[178] Salami et al.[188] also seemed to identify an MRI-visibility signature comprising predominantly cell organisation/structure genes from 10 patients, which was able to distinguish MRI-visible tumours in an independent cohort with an area under the curve (AUC) of 0.88. This is further supported by the apparent association of stromal-associated genes in the Oncotype DX assay being significantly associated with PI-RADS score, with little association seen in other gene groups.[165]

5.3.2.3 Gene Markers for Aggressivity & Prognosis

The association of *PTEN* loss (a known driver of prostate cancer) and mpMRI conspicuity was assessed in three included studies. *PTEN* loss was shown to likely be higher in mpMRI-targeted biopsies (i.e. of mpMRI-visible tumours) than in non–image-guided systematic biopsies (i.e. not of mpMRI-visible tumours).[189] This result seems to concordant with the fact that *PTEN* loss is highly correlated with Gleason grade and stage[190–192] and that mpMRI-targeted biopsies detect more clinically significant tumours compared with systematic biopsies.[1,193,194] However, even when Gleason grade was controlled for, *PTEN* loss seemed to remain higher in the targeted biopsy group. A similar association between *PTEN* loss and ADC values was demonstrated in a radical prostatectomy population; however, no apparent correlation

between *PTEN* expression and Gleason grade was shown.[195] Other studies found an association with Gleason score (r = 0.30, p = 0.04) and Kep (r = 0.35, p = 0.02) but not with ADC.[196] In contrast, a separate radical prostatectomy study found no probable association between *PTEN* and mpMRI characteristics; however, this study included PI-RADS score 2 tumours as visible, which may skew the study findings.[197]

Li et al. performed a full-scale transcriptomic analysis of mpMRI-visible tumours compared with mpMRI-invisible tumours.[178] They found 1,654 differentially expressed genes between these two visibility phenotypes. Expression of *CENPF*, *AGR2*, and *GDF15* was found to be enriched in mpMRI-visible tumours and was associated with reduced time to biochemical recurrence in an independent dataset, suggesting a potential link between mpMRI visibility and prognostic outcome.[178] *CENPF* (part of the Prolaris panel) was also suppressed using an inducible miRNA system in vivo, showing a reduction in mpMRI visibility when expression was reduced, suggesting a possible causal relationship between an identified gene and mpMRI conspicuity of prostate cancer.[178] Transcriptomic analysis also identified genes associated with tumour aggression in mpMRI-visible tumours, such as non-coding RNA *SCHLAP1* (linked to prostate cancer progression), several small nuclear RNAs,[17] and angiogenesis factor *VEGF*.[198] Indeed, mutations in tumourigenic drivers such as *SPOP* and *IDH1* have been found even in lower-grade mpMRI-visible tumours.[199]

One study derived an mRNA signature that could accurately predict visibility in both a training and a validation cohort (AUC = 0.89 and 0.88, respectively) but, when applied to The Cancer Genome Atlas (TCGA) cohort, found no apparent significant differences in biochemical recurrence, distant metastasis, or cancer-specific mortality. However, this signature was derived and tested on a total of 26 patients, and the mpMRI visibility groups that were predicted did not significantly differ by Gleason grade, positive lymph nodes, or positive surgical margins, which somewhat contradicts other histopathological evidence.[188,200]

5.3.3 Bioinformatic Synthesis

Four studies with available data were identified for bioinformatic analysis, three of which were large enough to compare the performance of gene panels.[17,178,181] All three studies used macrodissection of tumour tissue prior to nucleic acid extraction. For each study, a non-overlapping list of significantly altered or significantly correlated genes was included (Appendices 8–11). For example, in one study,[181] a selection of genes were correlated with multiple radiological features; in this case, every gene that was significantly correlated with at least one radiological feature was included in the analysis (196 total).

Overall, 42 genes appeared to demonstrate differential expression between mpMRI-visible and mpMRI-invisible tumours (in two or more of the included studies; Fig. 15A). Of note were *GDF15* and *AGR2*, which are thought to be involved in tumour progression.[201–204] Interestingly, 14 of the identified MRI conspicuity–related genes were reported in studies that used a matched cohort methodology, suggesting that the influence of these genes may be independent of Gleason grade. Shared cellular components were over-represented in two studies,[178,181] namely, anchoring junction ($p < 1.00E^{15}$ and $p = 0.0051$), adherens junction ($p = 1.34E^{12}$ and $p = 0.0041$), focal adhesion ($p = 1.34E^{12}$ and $p = 0.0041$), cell-substrate adherens junction ($p = 1.57E^{12}$ and $p = 0.0041$), and cell-substrate junction ($p = 2.11E^{-12}$ and $p = 0.0041$; Fig. 15). These cellular components are all involved in anchoring of cells to the extracellular matrix (ECM) or other cells, primarily through actin filaments or other components of the cytoskeleton. No significant over-representation of any components were identified in one study[17] after FDR correction; the closest enriched component was actin-based cell projection (raw $p = 0.0027$, after FDR $p = 0.67$), further implicating cell-ECM interaction as a determinant of conspicuity.

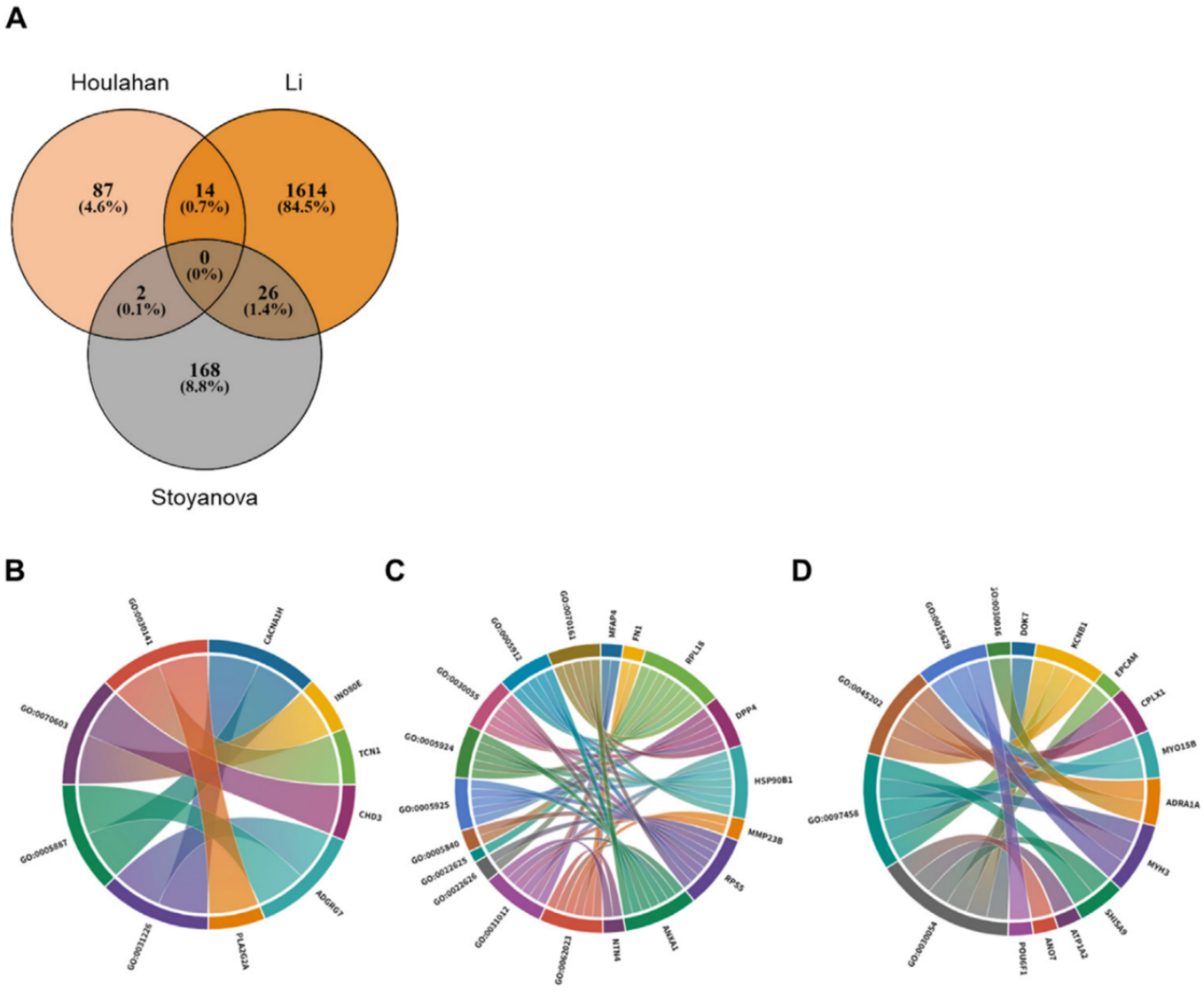


Fig. 15 – Bioinformatic synthesis of included studies analysing genetic landscape of prostate mpMRI. (*A = Venn diagram of genetic overlap for mpMRI conspicuity–associated genes; B–D = chord diagrams for each study (studies by Houlahan et al.,[17] Li et al.,[178] and Stoyanova et al.,[181] respectively, illustrating over-representation analysis of significant differentially expressed genes identified in each study and over-represented cellular component gene ontology terms associated with these genes; image courtesy of Benjamin Simpson*).

From the derived themes, several panels of genes were suggested to be altered between mpMRI-visible and mpMRI-invisible tumours. In order to compare how matching for size and grade may alter this result, the Log2-fold change of each gene was assessed within the panels and RNAseq data from two studies: one that matched for Gleason grade and tumour volume[17] and one that did not match for these factors.[178] Overall, gene signatures seemed to be more significantly altered between mpMRI-visible and mpMRI-invisible tumours in the unmatched study[178] compared with the matched study[17] which suggests that their discriminant ability may derive from the association with Gleason grade and tumour size, rather than purely conspicuity. The effect sizes seen in unmatched study also tended to be of greater magnitude.[178]

5.3.4 Risk of Bias

Overall, all included studies appeared to score highly in the Newcastle-Ottawa scale, indicating a likely acceptably low risk of bias, with 24 studies scoring above five stars out of eight. All studies scored highly on patient selection; however, a potential bias was the prevalence of studies based on radical prostatectomy specimens, which reduced generalisability of findings. The second major risk of bias identified was the use of smaller-scale genetic investigations, with 17 studies using either small targeted panels or single gene investigations. Some of the included studies scored low (or zero) on outcome due to single-gene investigation methodology.

5.4 DISCUSSION

In this chapter, a large contemporary systematic review and bioinformatic analysis of the molecular evidence of prostate cancer conspicuity on mpMRI has been presented (Table 13). Visible mpMRI tumours appear to be generally associated with genomic markers of disease aggressivity, including increased Decipher and Oncotype DX scores, and greater frequency of *PTEN* loss. This association is strengthened by increased enrichment of pro-proliferative signalling pathways, increased genome instability, DNA damage repair defects, and hypoxia in mpMRI-visible tumours. On balance, no overall, or comparable, genetic evidence of increased clinical aggression in mpMRI-invisible tumours compared with that in mpMRI-visible tumours was found; however, there were infrequent, isolated reports of mpMRI-invisible prostate cancer bearing genomic hallmarks of clinical aggressivity, which warrants future investigation.

It is important to note however that association demonstrated in this chapter (between tumour detection on mpMRI and adverse genetic features) is likely to be somewhat confounded by other key determinants of mpMRI-visibility, including tumour size, Gleason grade and cellular density, that are also likely themselves likely to be associated with worse clinical outcomes and genetic features of disease aggression. A small number of included studies here attempted to address this, by using a matched-cohort approach, but nonetheless the challenge of confounding factors remains.

Table 13 – Summary of genetic features associated with tumour visibility on mpMRI.

Feature type	Feature		Feature type	Feature
Commercial assays	Progensa PCA3		Cell structure components	Actin filament-based process
	Oncotype DX			Cytoskeleton organisation
	Decipher (GC)			Stromal components
	Prolaris (CCP)			Anchoring junction
DNA-related features	DNA repair defects			Adherens junction
	Copy-number alterations			Focal adhesion
	Mutational burden			Cell-substrate adherens junction
	Genomic instability (PGA)			Cell-substrate junction
	PTEN loss			Actin-based cell projection
Transcriptomic features	BCR-associated genes (*CENPF, AGR2*, *GDF15*)		Biological pathways	Mitotic cell cycle
	Progression-associated genes (*SCHLAP1*)			Protein folding
	Small nuclear RNAs			Cell cycle
	Angiogenesis factor (*VEGF*)			Mitotic cell cycle process
	Tumorigenic drivers (*SPOP*, *IDH1*)			Cell division
Biological hallmarks of cancer	Castration resistance (*WNT*)			Apoptosis
	Immunological response			Cell cycle progression (*PI3K-AKT-mTOR* and *E2F*)
	Tumour hypoxia			
	Tumour progression (*GD15*, *AGR2*)			

Transcriptomic data suggest that there is likely no single underlying biological process or pathway driving mpMRI visibility. However, cell-cell and cell-ECM–associated genes seem to exhibit differential expression between mpMRI-visible and mpMRI-invisible tumours, suggesting a possible explanation for the histopathological characteristics of prostate cancer conspicuity on mpMRI (including, cellular density).

Future research effort should aim to focus on exploring the molecular basis of tumour visibility in larger patient cohorts. Indeed, the ReIMAGINE trial (NCT04063566) is currently investigating the role of genetic biomarkers in conjunction with mpMRI for the diagnosis of prostate cancer and will provide important investigation into the clinical aspects of this research field. Furthermore, the current literature appears to be skewed towards transcriptomic analysis, and may benefit from further DNA and epigenetic investigation.

The studies included in this chapter used numeric radiological scoring systems (predominantly, Likert and PI-RADS) to define “visibility” and “invisibility”, and then compared genetic features between these two groups. As discussed, this methodology is fruitful to inform which features have higher enrichment in mpMRI-visible tumours than in mpMRI-invisible tumours. However, this approach does not necessarily provide a detailed description of the unique genetic features of what mpMRI-invisible disease may harbour, and dedicated research focussed primarily on disease invisibility is still warranted in the future. It was also noted that many studies did not include detailed methodology around mpMRI scan acquisition, which could potentially affect results; therefore, future studies may benefit from improved transparency to increase replicability.

It is increasingly apparent that tumour grade and size are not the only important histopathological determinants of tumour visibility and invisibility, with evidence that patterns such as intraductal carcinoma and cribriform pattern may have reduced visibility on mpMRI.[138] Unfortunately, a very small minority of the included studies in this review (4/32) used a matched cohort methodology, meaning that, in the majority of studies (28/32), the genetic influences on tumour conspicuity cannot be separated from the important influence that both tumour grade and volume have. Future studies may benefit from more rigorous histopathological matching[205] to help reveal the genetic aspects of disease conspicuity, beyond those associated with increased Gleason grade and tumour volume. However, this may increase the difficulty in obtaining large sample numbers, particularly with continuous features such as tumour volume. Alternatively, following the advent of spatial transcriptomics, future research could use an internal matched control methodology, to potentially illuminate distinct genetic signatures in visible and invisible regions of the same prostate.

Lastly, mpMRI-visible tumours seem to be more likely to have genetic variations that drive proliferation and therapeutic resistance. Therefore, if validated, mpMRI may have clinical utility in risk stratification and treatment selection, as tumour conspicuity may confer useful additional information, beyond tumour grade and size.[157,186] Additionally, almost all current studies are correlative, and only a single instance was found whereby visibility-associated genes were verified in a model; as such, there is still extensive scope for future work to establish causative links.[178]

5.5 CONCLUSION

Prostate cancer that is visible on mpMRI is generally enriched with molecular features of disease aggressivity and tumour development, including activation of proliferative signalling, DNA damage, and inflammatory processes. Bioinformatic analysis demonstrates seemingly concordant cellular components and biological processes associated with mpMRI conspicuity, which may in part account for the histopathological features of MRI-visible prostate cancer, such as higher Gleason grade disease and increased cellular density. Future radiogenomic studies in this field should endeavour to use matched cohort-based methodology to elucidate genetic aspects of tumour conspicuity more clearly when tumour size and grade are accounted for.

5.6 OVERALL CHAPTER SUMMARY & CANDIDATE CONTRIBUTION

1. Prostate cancer visible on mpMRI appears to be enriched with molecular features of tumour development & aggressivity
2. These features seem to include: activation of proliferative signalling, DNA damage, and inflammatory processes
3. Also, concordant cellular components & biological processes apparently associate with mpMRI conspicuity
4. These features, arising from bioinformatic analysis, may explain some of the observed tissue and histopathological features of mpMRI-visible and invisible tumours

In this chapter, I devised the concept of systematically reviewing the genetic literature surrounding prostate mpMRI (for the first time). I designed and led the systematic review process, which, in accordance to PRISMA guidelines, was conducted with a wider systematic review team. The members of the review team, and their roles are detailed in the full article (doi.org/10.1016/j.euros.2020.06.006), however, in summary, I conducted all syntheses. I collaborated with Dr Benjamin Simpson in this chapter, who kindly assisted with the bioinformatic elements. All figures and tables presented in this chapter were conceived and newly created by me, unless specifically stated in parentheses.

CHAPTER 6:

THE PACT STUDY: PATIENT PERCEPTIONS ON THE USE OF PROSTATE MRI

6.1 INTRODUCTION

The introduction of mpMRI has helped to enhance the risk stratification for patients at risk of prostate cancer.[1] Precision imaging, delivered through mpMRI, has partly addressed long-standing drawbacks of the traditional approach to prostate cancer diagnosis and is now integrated into the 2019 National Institute for Health and Care Excellence (NICE) Guidelines for patients with suspected prostate cancer.[5,9] Classically, patients with suspected prostate cancer would undergo serum PSA testing in the community, followed by systematic TRUS-guided biopsies. This approach carries risks, including the over-detection of insignificant cancer, over-treatment of insignificant cancer and under-detection of significant cancer,[206] likely because traditional TRUS-guided biopsy is not based upon knowledge of cancer location.[207] Moreover, combining PSA testing with systematic TRUS-guided biopsy has been shown to be poor at identifying patients at risk of premature prostate cancer-related death.[208] In contrast, mpMRI has good diagnostic accuracy in the detection of clinically significant prostate cancer and the use of mpMRI before prostate biopsy helps enable more accurate pre-biopsy risk-stratification and lesion identification.[1] Pre-biopsy triage with mpMRI has now demonstrated that a proportion of patients could potentially safely avoid systematic TRUS-guided biopsy and its associated side-effects, including pain, bleeding, infection, sepsis and anxiety (which is distinct from the general distress of a cancer diagnosis).[209,210]

The views of clinicians (primarily urologists, radiologists and oncologists) have generally been favourable toward mpMRI.[211–213] However, the views of the patients who experience this novel pathway remain unexplored, certainly in any depth. In one study, Ullrich and colleagues surveyed a mixed group of patients (with and without prostate cancer) on their views on prostate mpMRI in Germany.[214] They found that the majority (68%) seemed to consider mpMRI to be a useful method to obtain a prostate cancer diagnosis. However, they also found that only a minority (29%) had personally experienced mpMRI and that few had any knowledge of the role that mpMRI might play in any new risk-stratification process. Whilst this work helps somewhat in understanding the views that patients may have about mpMRI, it likely does not give enough detail to shape the way that this technology is both explained and delivered in practice.[215,216] A rigorous exploration of the perceptions that patients have about the accuracy and utility of mpMRI would potentially help to provide further impetus to resolve many of the uncertainties and questions that still surround its use.

A small proportion (10–20%) of significant prostate cancers go undetected by mpMRI;[1] however, the true sensitivity and specificity appears to vary due to moderate intra-reader and inter-reader variability. To date, it is unknown whether patients with suspected prostate cancer are willing to balance the benefits and drawbacks of the new mpMRI-directed diagnostic pathway (in which patients with non-suspicious mpMRI may forgo biopsy) as compared to the traditional

systematic TRUS-guided biopsy approach. The nature and acceptability (to clinicians and patients) of prostate cancer that is undetectable by mpMRI is important due to the ramifications it may have on how negative pre-biopsy mpMRI is managed, in which no significant cancer is visible (mpMRI scores 1–2). This also affects prostate biopsy strategies in which decisions are made whether to only biopsy visible mpMRI lesions, or whether the rest of the non-suspicious prostate should be sampled simultaneously. Eliciting and understanding the opinions that patients have on these important issues may help influence future clinical decision making (Table 14).

Exploration of the issues that matter to patients would help provide a dedicated evidence-base, demonstrating views held by patients who experience prostate mpMRI, and would help inform further development of the current clinical pathway and future research in this field – and this would also help to put patients at the centre of the diagnostic process. The purpose of the PACT study presented in this chapter, was to explore patient views on the role played by mpMRI and its level of diagnostic acceptability, with a systematic two-stage, mixed quantitative and qualitative approach.

Table 14 – Key outstanding uncertainties surrounding prostate mpMRI.

Uncertainty	Comment
Degree of diagnostic accuracy expected by patients	Pre-biopsy mpMRI appears to detect the majority of significant prostate cancers, however, a small number (approximately 10–20%) are overlooked by this technique.[122] As yet, the only reliable way of increasing detection rates seems to be 5mm transperineal template sampling.[1] In the PROMIS study, the difference in detection rates of significant disease between mpMRI and 5mm template sampling was 7% (17/230; 95% CI 4.4%–12%).[122] However, template sampling at this density is associated with known risks, principally, prolonged urinary retention (24%), detrimental impact on erectile function (decrease of International Index of Erectile Function [IIEF]-15 scores by 23%),[136] and infection-related complications, however, these appear to be lower than those of systematic TRUS-guided biopsy (0% vs 5%).[217] Currently, the values and utilities that patients express when choosing between the two, or the degree of error that they are willing to tolerate, are unknown. Nor are the drivers in their decision-making, assuming they have access to valid information, presented in a manner that is easily understood.
Patient willingness to forgo biopsy in cases of non-suspicious mpMRI	Increasingly, patients with 'non–suspicious' or 'negative' prostate mpMRI (i.e. Likert/PI-RADS scores 1–2) are offered omission or delay of immediate biopsy, on the basis of good sensitivity for significant disease.[1] In previous chapters, it was demonstrated that this strategy seems to be supported by favourable histopathological,[122] molecular and genetic[124] characteristics of mpMRI-invisible disease. However, as yet, it is not clear whether patients are willing to tolerate the incumbent risk of overlooking invisible significant cancer despite reassuring features,[1] or whether adjunctive strategies (e.g. use of PSA density thresholds, multidisciplinary team [MDT] discussion, or longitudinal PSA follow-up) would provide further security for them.
Patient preference toward mpMRI-targeted or combined biopsy strategy	Recent evidence has suggested that mpMRI-targeted biopsy detects more clinically significant prostate cancer than classical systematic TRUS-guided biopsy alone. However, many clinicians still perform simultaneous systematic biopsies in addition to mpMRI-targeted biopsies, due to ongoing concern regarding mpMRI-invisible disease. Exploration of patient perceptions regarding biopsy strategy would elucidate whether patients are supportive of MRI lesion-only targeting (with inherent risk of overlooking mpMRI-invisible cancer), or whether they would desire to have their entire prostate sampled, despite higher risks of detection of insignificant disease and biopsy-related side-effects.
Definitions of cancer significance from the patient perspective	There is no current, universally agreed definition of clinically significant prostate cancer (by urologists and patients alike). Ideally, such a definition would be calibrated on prognostic significance. In other words, prostate cancer that was deemed to be clinically significant might be associated with a 5% greater chance of resulting in a prostate cancer-related death, if left untreated. Instead, the community has landed on the presence of any Gleason pattern 4 (on prostate biopsy) as constituting clinical significance. The most common manifestation of 'any' Gleason pattern 4 is secondary pattern 4, with the proportion of pattern 4 constituting 10% or less of all the cancer present. It is worth noting, that cancer of this-type was not associated with prostate cancer related-death in the 29-year update of the SPCG-4 study.[114] As such, it would be interesting to speculate where patients, if asked, would place the bar on risk that they might deem to be clinically important or significant. Indeed, the definition of 'significance' is likely to vary from patient-to-patient, with some placing emphasis on quality-of-life, above longevity. It is now likely prudent to explore and recognise this, as the chosen diagnostic strategy is probably inherently linked to the definitions chosen for disease significance. It is also worth reflecting that definitions of clinical significance are likely to differ between urologists and their patients, with surgeons potentially favouring 'objective' metrics of significance (e.g. statistical likelihood of metastasis) and patients favouring 'subjective' values (e.g. careful balance of quantity- and quality-of-life).
Willingness for patients to undergo bpMRI without Level 1 evidence	Multiparametric MRI has traditionally involved delivery of gadolinium as part of the DCE MRI sequence, however, recent evidence has suggested that the DCE component of mpMRI may be unnecessary for accurate pre-biopsy tumour detection. Furthermore, contrast administration is associated with potential challenges, including, gadolinium-allergy, cerebral deposition, systemic fibrosis, and technical difficulties in-image acquisition and reporting. At present, Level 1 evidence to support removal of the DCE sequence (to create so-called 'biparametric' MRI) for prostate cancer diagnosis is lacking, however, at this early stage, ascertaining patient perceptions of biparametric MRI may be informative, particularly for delivery of clinical trials in this field.

6.2 MATERIALS & METHODS

6.2.1 Study Design

PACT was a prospective, observational, dual-stage mixed methods cohort study, designed to survey views of patients with suspected prostate cancer referred to secondary care (Fig. 16). In stage I, patients completed detailed surveys containing both quantitative and qualitative questions on the accuracy and use of mpMRI. In stage II, a subset of patients were recalled to undergo in-depth, semi-structured interviews to explore these topics in more detail. In an attempt to ensure that the study was reported to a high quality, the Standards for Reporting Qualitative Research (SRQR) were used to design the qualitative component of this study.[218] The SRQR consists of 21 items to improve the transparency of all aspects of qualitative research by providing clear standards for reporting qualitative research. Ethical permission for the PACT study was granted by the local governance committee (Ref: 2018/19–252).

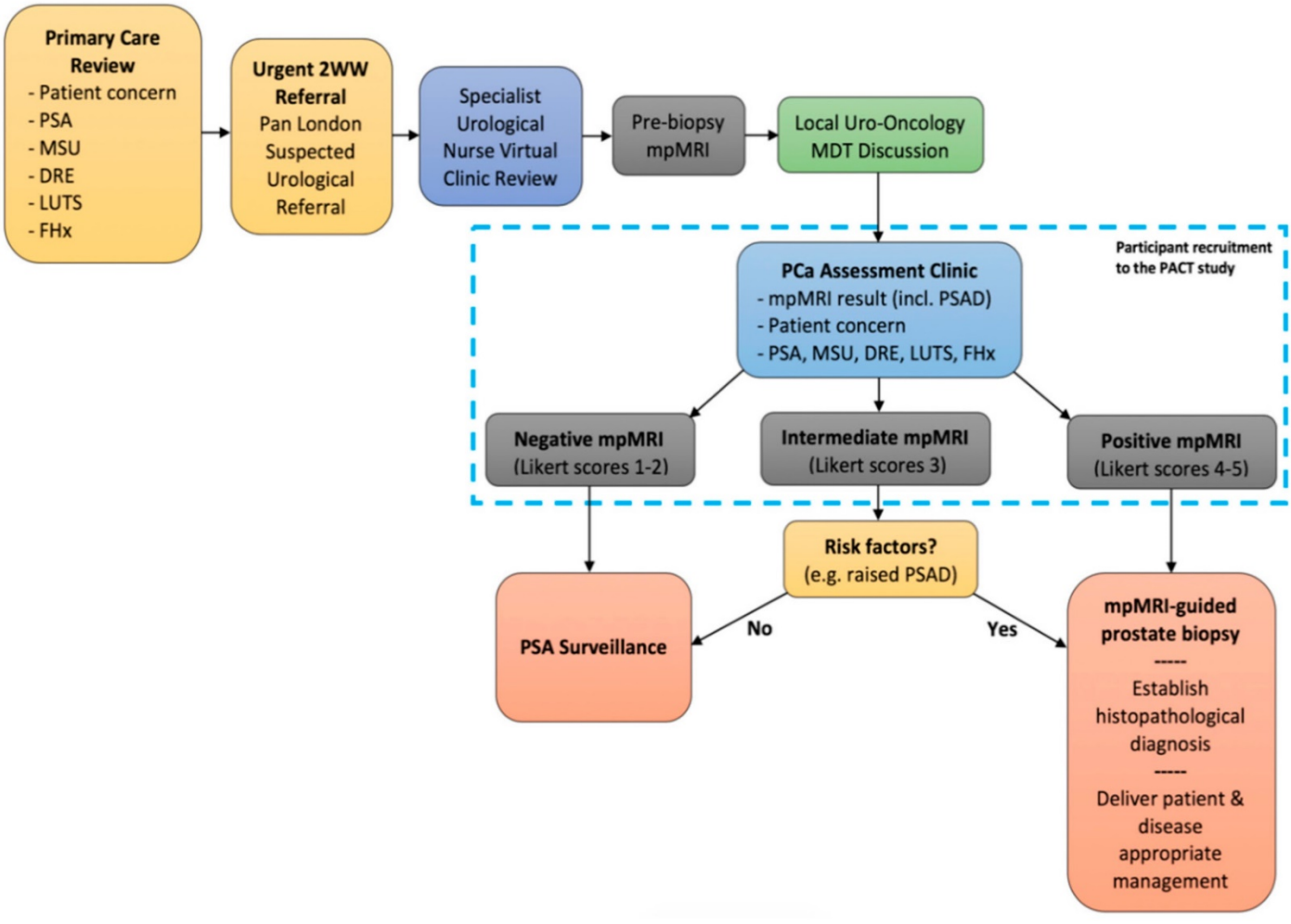


Fig. 16 – Recruitment of patients with suspected prostate cancer to the PACT study. ***(Blue dotted box = recruitment to study).***

6.2.2 Study Recruitment

All eligible patients who were referred to the prostate cancer assessment clinic were invited to be included in stage I of the study, provided that they did not have a prior diagnosis of prostate cancer and had sufficient English language skills. Patients who have had previous investigation (for example, a previous systematic TRUS-guided biopsy) were not excluded from the study, as this enabled these patients to compare their experience of the new diagnostic pathway with their experiences of the traditional approach. Target sample size for stage I (n = 117) was based upon similar patient engagement research in prostate cancer.[219,220]

All patients included in stage I were offered the opportunity to return to stage II to undergo semi-structured interviews to explore issues of relevance, in greater depth. A target of sample size of 20 patients was set for stage II based upon standard practice in qualitative research, providing a balance of gaining a sufficient breadth and depth of responses. In an attempt to obtain a rich and diverse qualitative dataset, patients recruited to the interview stage were drawn from varied ethnic, educational, socioeconomic and occupational backgrounds, and had undergone a range of diagnostic experiences (for example, a mixture of biopsy-naïve and biopsy-experienced patients) with the aim of enabling a more meaningful comparison of viewpoints.

6.2.3 Data Collection

In stage I, patients were given a specific patient information sheet (Appendices 12–14) that was designed by the PACT study research team, based upon contemporary evidence on the diagnostic performance of mpMRI, compared to systematic TRUS-guided prostate biopsy. In amongst other Level 1 evidence trials, the PROMIS study was used to inform this patient information sheet. Once the information sheet had been read by the patients, they then completed and returned their questionnaires, before leaving the prostate cancer assessment clinic. The study questionnaire (Appendix 15) consisted of a modified version of a validated questionnaire previously designed to elicit patient perceptions of cardiac MRI (permission from the original questionnaire authors was sought and approved).[221]

In stage II, interviews were conducted in a semi-structured approach using predetermined topic guides, covering five main thematic domains (Appendix 16). Interview questions aimed to explore patient perceptions of prostate mpMRI, prostate biopsy techniques and definitions of clinically significant disease. Questions were open-ended in nature, encouraging a conversational interview style, in which responses were expanded upon whenever possible. Before each

sub-section of the interview, a short paragraph was read to describe the contemporary evidence in the field (e.g. regarding prostate biopsy techniques). The patient information paragraphs were designed by the PACT study research team, and were included in the interview script, prior to the questions for each sub-section.

6.2.4 Quantitative Analysis

Questionnaire responses were converted to ordinal (Likert) values (e.g. 1–5) and responses were catalogued in an anonymised master database. When possible, analyses were stratified by demographic characteristics of interest (for example, age, ethnicity, medical history and diagnostic experience) to assess for differences in sub-groups. Descriptive statistical techniques were used to describe the data. GraphPad Prism 8 (Graph-Pad Software, Inc., La Jolla, CA, USA) was used for all statistical analyses of quantitative data.

6.2.5 Qualitative Analysis

Audio recordings of the semi-structured interviews were transcribed verbatim by an independent scribe and NVivo 12 (QSR International Pty Ltd., Doncaster, South Yorkshire, UK) was used for all analyses. To identify themes, and areas of consensus or difference, qualitative data were analysed using thematic analysis (Table 15) which is "a method for systematically identifying, organising and offering insights into patterns of meaning (themes) across a dataset".[222]

Table 15 – Methodological steps for qualitative analysis in the PACT study.

Thematic analysis step	Description
1	Transcripts were read whilst re-listening to audio recordings to check accuracy and build dataset familiarity.
2	Transcripts were coded manually to identify aspects of the data relevant to research objectives.
3	Codes were collated into themes.
4	Themes were reviewed by the broader research team to ensure code consistency within themes and to avoid overlap between themes.
5	A thematic map was developed by refining themes and analysing their relationships.
6	Qualitative results were collated and published using words of participants to illustrate areas of agreement, as well as divergences of views.

6.2.6 Further Patient & Public Involvement

To increase the level of patient involvement in the study, an expert patient workshop was held after collection of all results (survey and interviews). Patients with suspected prostate cancer, and those with various stages of the disease, were invited to attend the workshop, as were members of the study team, and well-known patient advocates who were active on prostate cancer social media. The group were presented with results from this study and were asked for their views on the validity of the results (and the study group interpretation of these) and to contribute their various lived experiences, citing perceived implementation challenges and areas for future development.

6.3 RESULTS

6.3.1 Study Population

In stage I, 117 patients with suspected prostate cancer were recruited between February 2019 and March 2020, and completed study questionnaires (Table 16). The majority of patients were white (86/117; 74%) and over the age of 60-years-old (81/117; 69%), however, the range of ages was wide (38–82). Most patients recruited to stage I were willing to return for in-depth interviews in stage II (87/117; 74%).

Table 16 – Summary patient demographics for stage I of the PACT study.

Characteristic	**Result**
Sample size, *n*	117
Age (yr), mean (SD)	64 (9.2)
Ethnicity, *n* (%)	
White	86 (74)
Black	19 (16)
Middle Eastern	6 (5.1)
Asian	4 (3.4)
Hispanic	2 (1.7)

In stage II, 20 patients with suspected prostate cancer from stage I returned to undergo semi-structured interviews between July 2019 and August 2018 (Table 17). These patients were chosen for maximal diversity, including diverse education, ethnicity, employment, family status and diagnostic experience. Again, the majority of patients were white (15/20; 75%) and over the age of 60-years-old (12/20; 60%), however, ethnic and age diversity was represented, with black (3/20; 15%), Asian (1/20; 5%) and younger patients (under 50-years old, 2/20; 10%) all being interviewed. The split between married patients and single patients was similar (11 vs. 9; 55% vs. 45%, respectively) and, of those that were not-married, there was a nearly equal divide between those that were, and were not, in long-term relationships (5 vs. 4; 56% vs. 44%, respectively). A large proportion of the patients interviewed in stage II had children (14/20; 70%),

but few had more than two (3/20; 15%). Almost all patients had pursued higher education (17/20; 85%), with the commonest degree level being bachelors (13/26; 50%), with only one doctorate degree being undertaken (1/26; 3.8%). A broad range of occupations, across numerous job sectors were represented in the interview group, whilst only four patients (4/20; 20%) considered themselves fully retired.

Table 17 – Summary patient demographics for stage II of the PACT study.

Characteristic	Result		Characteristic	Result
Sample size, *n*	20		Education status, *n* (%)	
Age (yr), mean (SD)	61 (7.6)		No higher degree	3 (15)
Ethnicity, *n* (%)			Bachelor degree	13 (65)
White	15 (75)		Masters degree	7 (35)
Black	3 (15)		Postgraduate Cert/Dip	4 (20)
Middle Eastern	0 (0)		Doctoral	1 (5)
Asian	1 (5)		Professional membership	1 (5)
Hispanic	1 (5)		Occupation, *n* (%)	
Marital status, *n* (%)			Unemployed	2 (10)
Single	9 (45)		Retired	4 (20)
Married	11 (55)		Leisure, sport & tourism	1 (5)
No. of children, *n* (%)			Property & construction	2 (10)
0	6 (30)		Business, consulting & management	3 (15)
1	3 (15)		Media & internet	3 (15)
2	7 (35)		Creative arts & design	1 (5)
3	1 (5)		Law enforcement & security	1 (5)
4	2 (10)		Information technology	2 (10)
			Teacher training & education	1 (5)

6.3.2 Questionnaire Study

6.3.2.1 Comparison of TRUS & mpMRI

When asked to quantify their levels of satisfaction regarding diagnostic accuracy of the predominant diagnostic approaches for suspected prostate cancer, patients appeared to report higher overall levels of satisfaction for mpMRI (Table 18). Patient satisfaction for the accuracy of systematic TRUS-guided biopsy alone seemed to be low with 60%

(71/117) of patients considering the ability of systematic biopsy alone to detect the most important prostate cancers to be “very poor” or “barely acceptable.” Patient satisfaction for the accuracy of pre-biopsy mpMRI appeared to be high with 96% (112/117) of patients considering the ability of mpMRI to detect the most important prostate cancers to be “good” to “very good.”

Table 18 – Questionnaire responses in stage I of the PACT study.

Thematic element	Response				
Satisfaction of TRUS-guided pathway *n* (%)	Very poor 30 (26) (95% CI 18–35)	Poor 16 (14) (95% CI 8.0–21)	Barely acceptable 25 (21) (95% CI 14–30)	Good 29 (25) (95% CI 17–33)	Very good 17 (15) (95% CI 8.7–22)
Satisfaction of MRI-directed pathway *n* (%)	Very poor 0 (0) (95% CI 0–3.1)	Poor 0 (0) (95% CI 0–3.1)	Barely acceptable 2 (1.7) (95% CI 0.21–6.0)	Good 41 (35) (95% CI 26–44)	Very good 71 (61) (95% CI 51–70)
Concern for MRI-invisible cancer *n* (%)	None 37 (32) (95% CI 23–41)	Little 46 (39) (95% CI 30–49)	Moderate 26 (22) (95% CI 15–31)	Intense 3 (2.6) (95% CI 0.53–7.3)	Very intense 5 (4.3) (95% CI 0.14–9.7)
Opt to forgo biopsy with negative mpMRI *n* (%)	Yes 91 (78) (95% CI 69–85)	No 12 (10) (95% 5.4–17)	Unsure 14 (12) (95% CI 6.7–19)		

6.3.2.2 Perception of Undetected Disease

When asked to consider the level of concern regarding prostate cancer that may be overlooked by mpMRI, a range of responses were returned. However, most patients (705; 83/117) appeared to report “no” to “little” levels of concern regarding prostate cancer overlooked by mpMRI. Despite this, concern was seemingly expressed from a small proportion of patients regarding mpMRI-undetected disease, with 22% (26/117) reporting moderate concern, and 6.8% (8/117) reporting “intense” to “very intense” concern. When asked to elaborate on reasons for concern regarding undetected cancer, patients seemed to give a number of different reasons, including the perception that a 10–20% false negative rate may be too high (Table 19). When presented with the hypothetical situation of a non-suspicious pre-biopsy mpMRI, the overall majority (78%; 91/117) of patients seemed to favour omission of immediate biopsy. A minority of patients (10%; 12/117) appeared to express that they would prefer biopsy regardless of mpMRI results, in keeping with those expressing concern for cancer that may be undetected by mpMRI.

Table 19 – Free-text responses in stage I of the PACT study.

Topic	Free-text quotation
Reasons for patient concern regarding cancer not detected by mpMRI	"*... [it may] reduce your treatment time*" "*Because it is not totally reliable*" "*I am a little concerned with 10 to 20%*" "*... [there is a] possibility that an infection might mask a tumour*" "*Because of danger of its fatality*" "*10–20% is a significant number of cases to miss*" "*What would the follow-up procedure be?*"
Important factors to define "significance" of prostate cancer to patients	"*... [the most important thing is] quality of life, followed by life expectancy, as I have a young family*" "*It would largely depend on how aggressive the cancer was*" "*The spread of cancer around the body, given my recent history of lymphoma, would be a concern*" "*Whilst it can be a slow acting cancer, it would be likely to prey on my mind, even whilst my health was good*" "*Physical wellbeing - ability to get out and enjoy life*" "*Don't know at this stage*" "*Too difficult to answer*"
Additional commentary (incl. issues with the physical process of undergoing an MRI scan)	**Commentary in favour of mpMRI use** "*I strongly support use of MRI in routine / mass checks for prostate cancer*" "*The best way of diagnosis of prostate [cancer] is to have MRI first*" "*MRI is a great system. Accurate & no pain!*" "*Delighted to have no further [invasive] tests*" "*I would prefer to have the MRI any time rather than biopsy alone (I'm also willing to try alternative drug treatments if required)*" **Concerns expressed towards use of mpMRI** "*Should consider enzyme 4K testing as a pre-MRI filter - cheaper and more reliable*" "*If alternatives to invasive biopsy are available then it would be good to use these to remove the 10% margin of missing prostate cancer*" "*When you go through the machine it would be better when they play music you can hear due to the machine [noise] - it would be better if music could be played through the headset on your ears*" "*I was given no warning of how alarming and very noisy the MRI scan was*" "*Not enough information was given on MRI in advance i.e. that it would involve needle in arm and liquid put in at end of MRI*" "*The MRI scanner is tight for my size*" "*MRI scan took too long and I had a sore back*"

6.3.2.3 Opinions on Cancer Significance

When asked to describe the factors that were most significant to patients (related to prostate cancer), it seemed that impact upon life expectancy was cited most commonly, with almost half of patients (43%; 50/117) describing this factor as having the largest impact on cancer significance. Patients that expanded upon their answers suggested that a potential reason to value life expectancy was the impact that this may have upon friends and family, particularly if they were younger (Table 19).

Life expectancy appeared to be closely followed by the likelihood that cancer might metastasise (36%; 42/117) or impact generally on quality of life (33%; 39/117), as factors influencing patient perception of cancer significance. When asked to expand on this, patients that valued metastatic cancer propensity as the most significant factor did this as they seemed to associate it with loss of curative window, or with their own personal experience of cancer.

Specific negative symptoms associated with prostate cancer and treatment were referenced least commonly as significant factors (urine symptoms: 18%; 21/117, and sexual symptoms: 14%; 16/117), however, it is possible that a proportion of patients may have already included the impact of symptomatology when citing quality of life as their most significant factor.

6.3.3 Interview Study

6.3.3.1 Patient Views of Key Topics

When asked to compare the traditional approach (serum PSA followed by systematic biopsy) to the modern approach (upfront mpMRI), each of the interviewed patients appeared to express a preference for an imaging-directed diagnostic pathway. Motivations for favouring mpMRI-directed care seem to interlink with many of the dominant themes of the PACT study, including, increased level of diagnostic accuracy for the detection of significant disease, and the opportunity to avoid immediate invasive biopsy. A small number of patients appeared to express negative/mixed views regarding mpMRI, including concerns regarding venous cannulation, scanner-related claustrophobia and noise, and risks of disease non-detection, however, when asked to compare pathways like-for-like, the majority of interviewed patients still seemed to prefer imaging-led diagnosis (Table 20).

When asked to consider the varied biopsy strategies available (e.g. targeted biopsy alone, or combined targeted with systematic biopsy), a range of views were elicited. The split between those favouring targeted or combined biopsy was approximately equal, however a slightly greater proportion of patients did favour (if given the choice) a more extensive

combination biopsy. Those that suggested superiority of MRI-targeted biopsy did so for a range of reasons, including the aforementioned accuracy of pre-biopsy mpMRI (and therefore an increased risk of indolent cancer detection through biopsy of non-suspicious prostate regions), as well as fear of further invasion, procedure length, and toxicity (predominantly, pain and bleeding). In some cases, patients that had previously undergone traumatic prior prostate biopsy expressed that the shorter procedure length and lower side-effect profile of targeted biopsy would be preferential. In contrast, patients that had major surgery in other areas (e.g. facial surgery), or had previous tolerable prostate biopsy experience did not hold such negative views toward the extended nature of combined prostate biopsy. Indeed, many patients expressed the opinion that sampling of non-suspicious prostate regions would be worthwhile due to the potential risk of mpMRI-invisible prostate cancer, and the capitalising on the opportunities of that particular diagnostic episode (i.e. “just do it – you are already there”).

When asked to consider what factors influenced the perception of prostate cancer significance, each of the patients that were interviewed expressed that knowing, in detail, the aggressivity of their prostate cancer, and the potential impact that this would have on their life expectancy would be important to them. A smaller proportion of the interviewed patients then also went on to describe that knowing the risks of metastasis and threat to their life quality or functioning ability would also be key factors. When asked to compare the relative importance of quality vs. quantity of life (i.e. life expectancy), the interviewed patients produced a number of varied, and in some cases, contradictory responses. In general, younger interviewed patients (e.g. < 60-years-old) tended to favour longevity as their highest rank factor, in the first instance. These patients cited ongoing responsibility (for example, children) and time left to plan and make arrangements/adjustments, as key reasons that prostate cancer impact upon life expectancy was the main factor of significance. However, this same sub-cohort of patients also discussed how these views may alter as their age and priorities change, and many suggested that their answer would be different later in life, in which impact on quality of life would likely be more important that impact on quantity. Two of the more elderly interviewed patients did still cite life expectancy as the main factor of significance, and highlighted that very high-quality life is not required continually, provided that certain goals can be achieved (e.g. completing personal projects, or watching grandchildren grow). Of the remaining patients (approximately 50%), impact on quality of life was cited as the predominant factor of prostate cancer significance, and many gave personal examples of family members (often, parents) that spent the latter years of their lives with low overall quality, due to comorbidities, including cancer. These same patients also expressed that they did not consider life prolongation to be the highest of importance due to other reasons, including not wanting to add additional burden to surviving family members, but also due to the personal and religious beliefs in the afterlife, in which a shortened life is therefore not to be feared.

When asked about the upcoming possibility of biparametric mpMRI (without the DCE sequence), each of the patients interviewed said that, in theory, they would be happy to undergo this as part of their prostate cancer risk stratification. However, a range of other responses were also received on this topic. Most patients perceived that removing the contrast sequence was potentially beneficial, by shortening the length of the scan, removing need for cannulation, reducing theoretical risks of gadolinium accumulation (within the brain, spleen, liver kidney and bone, with an unknown long-term effect) and enabling a higher throughput of patients with prostate MRI. However, the discussion around increased risks of overlooked prostate cancer (i.e. those requiring DCE for detection) was ubiquitous, and in some patients, was felt to be too high risk. For these patients, they expressed that diagnostic accuracy was of critical importance (citing their earlier responses when mpMRI was compared to systematic TRUS-guided biopsy) and that if given the choice, they would prefer that the DCE sequence would not be removed. Other patients were willing to tolerate the risk of increasing the proportion of MRI-invisible cancers, provided that additional security measures were taken, for example tight PSA surveillance, or the inclusion of machine learning or artificial intelligence assistance for scan reading.

Table 20 – Interview responses on key topics in stage II of the PACT study.

Topic	Interview quotation
Comparison of traditional (systematic TRUS-guided biopsy) to modern (MRI-directed) diagnostic approach	**Views in favour of mpMRI-direct pathway** *"Well I think, surely you're starting from a much better place… if you haven't got the MRI to start with, you're in an even worse starting place, which is why your chances are going to be even less of finding it if there was something to start with*" "*Oh one hundred times better, I'm glad I got the new way! Because I would have been fairly freaked out with the old way*" "*Well, the fact that [in the case of negative imaging] I didn't have to have a biopsy, which I assume would be painful*"
Consideration of different prostate biopsy strategies	**In favour of combined biopsy** "*Actually, I think I would prefer a more complete thing, and I don't think I would mind the label [of insignificant cancer] if it was explained – "we're not worried about it." I mean I realise cancer isn't necessarily a killer.*" "*I would prefer it to be as extensive as possible rather than, you know, have the possibility of having to go back to have it done again. But yeah, I mean I can understand potentially that's a problem clinically if you find something and then you've got to tell somebody that it is perhaps a cancer, that isn't necessarily an issue for them because that then becomes something that suddenly somebody is going to perhaps be concerned about, where they wouldn't necessarily need to be concerned*"
In-depth patient views of cancer significance	**Quality of life** "*Well, I'm old enough not to think my life would be cut short. I mean, If I was to die in a year, I've still done my three score and ten, you know! But as I said before, I'm a single person. It wouldn't cause huge problems, you know, whereas if you're married or whatever, if you're in a relationship and you're leaving a widow or widower, I think it must be much worse to feel you're going to die. But for me, I think I wouldn't be phased if you told me, look, it's serious and you probably haven't got more than a year to live. I don't think that would terrify me at all*" **Metastasis** "*Well, if it was aggressive and like going to spread. As I understand now, somebody, I was talking to a neighbour and she about this and she told me of someone she knew who has prostate cancer but no treatment. And now I understand why*" **Balanced** "*I mean it is completely a balance at the end of the day. And yes, I wouldn't want personally to have a longer life and have really low quality. I mean it's difficult to say until you're in that situation because you know, you adapt don't you, and you will kick into survival mode to do whatever's necessary to keep going. So, yeah, it's easy to perhaps say when you're, you know, healthy-ish that you'd have a certain approach, but it does come down to that balance between the quality and what's involved in sustaining that quality of life, against sort of longevity*" "*An aggressive one. I'd like to live as long as I can, as healthfully as I can*" "*Because I think that's the most important thing above longevity. I think living a long time being either miserable or despondent isn't a good life*"
Early perceptions of bpMRI	**In favour of bpMRI** "*I'm interested, I think, you know, if we had to trade affordability of doing a program which covered a larger section of the male population, because the contrast method was slightly more expensive, than I would trade it, because I think coverage is important. Of course, the risk of the contrast, to me, it sounds like it's speculative.*" **Uncertain / against bpMRI** "*I would rather do the more complete thing [like mpMRI]. Although, when you talk about the risk to the brain, that certainly is very serious*" **Regarding further bpMRI research** "*Well, [further bpMRI research] would be very important, because you said that as a moment you can miss 10 or 20%. So, if that increased slightly – makes no difference. If it increased massively – obviously it would be crazy.*"

6.3.3.2 Predominant Themes

A number of overarching themes emerged during the patient interview stage of the PACT study (Table 21). These were at times distinct from the intended objectives described in the PACT study protocol.

Maximising diagnostic accuracy (and by virtue, reducing uncertainty) is clearly the goal of clinicians that care for patients with suspected prostate cancer, however, during the patient interviews, it appeared that patients also strongly value this characteristic. This theme emerged at various stages of each interview. Initially, when asked to compare upfront systematic biopsy to mpMRI-directed biopsy triage, almost every patient described the increased diagnostic accuracy afforded by mpMRI was of very high importance to them. The value placed diagnostic accuracy was then also apparent when patients were asked about the differing biopsy strategies (i.e. target only vs. combined), and in fact patients that favoured either of the strategies reported increased accuracy was an important driver behind their individual decision making. Lastly, when considering the theoretical introduction of biparametric MRI, patients also referenced the potential loss of diagnostic accuracy (upon removal of the DCE sequence) as one of their major concerns with the proposed novel technique.

Another important theme that emerged during the patient interviews was the fear of invasion. In the PACT study, bodily invasion was attached predominantly to the process of prostate biopsy; a procedure that requires the dual bodily intrusion of transrectal ultrasound probe, and a transperineal (or transrectal) biopsy needle. Avoidance of this invasive procedure was expressed in almost all interviews, and informed decision making in several areas, including discussions surrounding imaging-directed pathways (e.g. avoidance of invasive biopsy in cases of non-suspicious pre-biopsy mpMRI), and around the predominant biopsy strategies (e.g. avoiding further invasion by taking prostate biopsies from suspicious MRI lesions alone). In several cases, patients described that they would tolerate ‘external’ invasion (or discomfort), for example with intravenous cannulation, over the pain and embarrassment of internal invasion, and in many cases, this was informed by negative prior biopsy experience, particularly when done under local anaesthetic (e.g. “it sounded like, and at times, felt like, a staple gun”).

Many, but not all, patients that were interviewed described that one of the most important drivers in their decision making was the influence, and impact upon, third parties (e.g. partners, children, parents, and friends). This theme (vicarious impact) emerged in different forms across each of the interview sections. At the superficial level, influence of third parties was apparent when patients described the negative experiences that their friends and family had (often regarding systematic TRUS-guided biopsy) that appeared to increase the perceived favourability of mpMRI. At another, similar level, some of the interviewed patients explained how they would now encourage their friends (of similar age) to engage with prostate cancer investigations (particularly when upfront biopsy was no longer a guaranteed endpoint). Next, other

third-party influences emerged when patients were asked to consider the factors that define prostate cancer significance; in this section, this theme was apparent in two ways. Firstly, patients (particularly younger) expressed the paramount importance of life expectancy to continue to support their ongoing commitments (especially children). Secondly, other patients suggested that quality of life was the most significant impact characteristic of prostate cancer, as they previously observed their elderly relatives suffering later in life, and as such the extension of life (at the expense of quality) was de-prioritised.

Throughout each interview, it became apparent that clinician (and researcher) trust was another key thematic element. A small number of patients (particularly those with strong educational background) undertook independent content research themselves prior to being interviewed; they read articles and abstracts regarding prostate MRI and as such, were well versed in the current literature. However, the majority of patients took clinician and research information (including, that provided on the PACT patient information sheets) at face value, and without question. Furthermore, many of the debates and uncertainties (e.g. decision on biopsy strategy, or validity of biparametric MRI) were often accompanied by a comment from each patient expressing how they believed that their decision making on such topics would be heavily influenced by clinician choice, implying a high level of trust in clinician decision making, and this of course, also then implies a heightened level of responsibility and integrity of the clinical team.

Table 21 – Predominant themes derived from stage II of the PACT study.

Theme	Interview quotation
Diagnostic accuracy	"*The implications and potentially the knock-on effects of the old way, you know, with potential infections and the chances of finding it are a lot lower in any case. Then that's definitely not looking so good*" "*Well, MRI, because it's more accurate. And secondly, because it's less painful though, I don't think I would really place a lot of stress on that because if you need the biopsy, you put up with whatever pain it is*" "*No, I would say the other factor is that I've got more confidence that it would make the right diagnosis*" "*Well, it's more or less overwhelming, in fact it gives me a lot of confidence, frankly*" "*Well, I can only talk about my opinion. In my case, I was given a sort of one-out-of-five, and I chose not to go to a biopsy, because I thought it was an acceptable risk [of mpMRI-invisible cancer]*" "*It's not a high risk [of mpMRI-invisible disease] and it doesn't worry me unduly. In fact, it gives me a bit more confidence that we have better techniques*"
Fear of invasion	"*So, I've had MRIs before where your head was completely inside. Kind of just doesn't bother me, you know, I'm quite happy with the fact that it's going on around me rather than going on in-me*" "*As we touched on – that it's non-invasive. Other than the needle in the arm, which is like a small price to pay*" "*Okay. It's two things [in favour of mpMRI]. One is that it's non-invasive, and it's reasonably quick*" "*Well, the fact that I didn't have to have a biopsy, which I assume would be painful*"
Reducing uncertainty	"*I take a deep interest in it and I obviously read as much as I could, and understand as much as I could. I think it's important. Knowledge is powerful. I think I'd like to know as much as I can. So, if I've a non-aggressive cancerous growth, then that's of interest to me. I mean, I know people who have died not of it, but with it. I think It's good to know your condition*" "*But, if you told me "well, you'll have another MRI scan, in, whenever, and then we can see." As long as I feel in control of my life, you know, that I have got time to get ready to die*" "*I know doctors are sometimes a bit reserved about saying things like that, aren't they? Well, I mean it's my impression, but they feel it might be misleading, but I would rather be completely open, even though you're not at all certain*" "*I would have thought then, you know, the follow-up should be a regular PSA test to see if there's any change in the level of the PSA, and if there is, then that would trigger another MRI*"
Third party influence	"*This might sound bad, but I suppose that's partly a reflection of me, in the sense that if you'd told me that you think I had prostate cancer – I wouldn't have been devastated. As long as you told me I probably have at least a year to live, to sort myself out. I don't mind if a hospital tells me I'm coming towards the end of my life – that's going to happen one day. It's probably because I'm single*" "[My friend] *is 10-12 years younger than me. I said, by the way, you also lose your sex drive. He said – anyway my wife will be pleased! I'm now able to tell him a bit more – god knows what – about this process. I want him to know*"
Clinician trust	"*I personally wouldn't want to know, because I value your professionalism and your knowledge…. as a professional myself, you know, I would expect somebody that wants some building work done, to come to me to help them through that process, and exactly the same way, if there's a significant issue with my health, I'm going to go and seek that professional advice rather than try and work it out for myself - how to build a house off the internet!*" "*I was brought up to trust doctors very much, but also brought up not to trouble them. So, you know, you don't go to the GP just because you've got pain for six months. You leave it, and hope it'll go away, sort of thing*"

6.4 DISCUSSION

In summary, the PACT study explored, in depth, the views held by patients on prostate mpMRI, and the associated controversies and uncertainties. Patients undergoing risk stratification for suspected prostate cancer appear to value the increased diagnostic accuracy afforded by pre-biopsy mpMRI, particularly the improved detection of aggressive cancer, and reduced detection of indolent cancer, as compared to traditional systematic TRUS-guided biopsy. Fear of bodily invasion (and the possibility of biopsy avoidance) appeared to be a driving factor in influencing patient opinion regarding pre-biopsy imaging. The vicarious impact on third parties (e.g. partners, children and parents) had a strong influence on patient perception on the most 'significant' aspects of suspected prostate cancer and its treatment. Lastly, the PACT study revealed differing patient perceptions of optimal biopsy strategy, with some patients preferring MRI-targeted biopsy only (due to reduced invasiveness) whereas others opted for a combined biopsy approach, due to ongoing concern regarding mpMRI-invisible disease.

To contextualise the findings, outcomes of the PACT study were presented to a group of expert patients that provided additional insights (Table 22). The expert patient group was diverse, containing prominent social media personalities, in addition to local patients that had never vocalised previously; it also contained patients with organ-confined cancer (post-surgery), patients with metastatic disease, and patients with no prostate cancer. Overall, the expert workshop agreed with the outcomes of the PACT study, in particular, the importance of delivering mpMRI prior to biopsy. Indeed, the group felt that from a patient perspective, that no patient in the modern diagnostic era should receive a non-image-guided prostate biopsy, and that transperineal biopsy should be the only technique offered (a topic not expanded upon in the PACT study). In parallel with the main results from PACT, the expert patient group was divided in their opinion regarding MRI-targeted biopsy compared to combined biopsy, and agreed that the PACT results reflected this ongoing debate. The theme of clinician trust drew contention; and the group agreed that whilst the PACT study has highlighted that trust in clinicians is very high and influential, it is not in fact universal, and depends upon interpersonal interactions, the clinician and the situation (the nuance of which was perhaps not conveyed in the thematic results from the PACT study). Furthermore, the expert patient group expressed dismay at their experience with primary care physicians, and a common theme was that of frustration towards doctors in primary care that convey distrust or dismissive attitudes toward PSA, based on perceived lack of reliability and accuracy. Lastly, the theme of patient education was developed further in this expert meeting than was done during PACT study. The expert group believed that they had largely been educated only after they had been through the diagnostic (and in some cases, therapeutic) pathway; and they felt that this should be the other way around (education prior to entry to the pathway). Other related themes raised (initially overlooked in PACT), included: discussion regarding the challenge to delivery of an effective mpMRI-led service (e.g.

reluctance of male patients to seek healthcare generally), and indeed that stigma (from both patients and doctors) remains a significant barrier, to be overcome and addressed with future research endeavours.

Table 22 – Patient engagement workshop responses to PACT results.

Theme	Workshop quotation
Validation & discussion of the PACT study results	Views on avoiding invasive biopsy (outcome: agreement with overall PACT results) *"I wasn't even concerned that I was having an MRI at all"* *"The old random scatter gun has got to be ancient history"* *"The more targeted approach with MRI has got to be the way forward"* *"MRI before a biopsy is a complete no brainer"* Biopsy choice (outcome: agreement that patients have divided views over biopsy strategy) *"I had an MRI then a targeted biopsy and I think that was the right thing"* *"I would be in favour of: PSA, then MRI, then biopsy of the target, then a couple of biopsies elsewhere"* *"Yes, I would go for a combined biopsy anyway, whilst you're there. Even if there are more complications later"* Clinician trust (outcome: agreement that trust is high, but in contrast to PACT, it is not felt to be universal) *"My doctors were fantastic. I got a PGDip [in prostate imaging] in an hour and half spent with this doctor!"* *"If you feel uncomfortable, or not getting the right answers, don't be afraid to go to someone else [another doctor]"* *"You can tell which doctor you can trust, and which you can't. It's not just a blanket thing"* Use of biparametric MRI (outcome: agreement that there are divided views of necessity of contrast/DCE) *"If the benefit of adding-in contrast is only around 5%, then it be should be ok to remove it"* *"I think this is a leap of faith. We just don't know"*
Additional considerations	Reflections on transrectal vs. transperineal biopsy *"There should be no more TRUS. It should be an act of Parliament"* *"Transperineal biopsy should be the* de facto *norm"* Ideas on MRI-based screening *"[Pre-biopsy mpMRI] makes PSA a much more reliable tool, until we get robust screening test"* *"We need to be able to diagnose prostate cancer with imaging alone [no biopsy]"* Remaining delivery challenges *"It remains very challenging to get prostate MRI in Northern Ireland!"* *"It seems that the 'postcode lottery' remains. It is a big issue'* *"It is a disgrace that [pre-biopsy MRI] is not yet the* de facto *norm across the UK"* *"I believe that there is more competition for MRI scanners within hospitals themselves, as MRI has become the best method to diagnose lots of different conditions"*
Areas for future development	Patient education aids *"I did all my prostate cancer education… post-operation"* *"I always joke [when talking to friends]... your biggest fear [of DRE] is that you're going to enjoy it!"* *"I didn't even know what a 'PSA' was"* *"If this was a mammogram or cervical smear, would you even have these challenges? Those born with a womb are far more outspoken with their health. Men are much better at servicing their car than their own body"* Clinical education *"Doctors are sometimes not good at managing expectations. I was told that once I start I ADT, I won't get erections, but that this won't be a problem, because I won't have libido. And this became a self-fulfilling prophecy"* *"Sometimes there is too much bluntness [from doctors]"* *"GP views [on PSA reliability] can colour patient views easily"* *"PSA should be done at 40. It should not be determined by the GP"* *"GP bias should be removed so patients can make informed decisions themselves"* Patient support *"Some men cannot live with the side-effects of the RALP and have ended their lives. They were saved from their cancer, but not their mind"* *"Sometimes we concentrate on the body and not the head"* *"There should be some sort of follow-up and mental health check [after prostate cancer investigation/intervention"* *"I have transgender friends who have not received support regarding prostate cancer"* *"1 in 4 men in Ireland have experienced child sex abuse and this creates serious issues when offering biopsy"*

The extant literature has shown that clinicians are largely in favour of the use of prostate mpMRI, and the increased use and uptake of technology over the last 5–10 years reflects this.[211–213] However, evidence supporting patient viewpoints

around prostate mpMRI remains limited. Focusing primarily on the procedure of MRI-guided biopsy, Pizzoli and colleagues compared psychological patient outcomes between traditional systematic TRUS-guided biopsy and in-bore MRI-guided biopsy. They showed that patients found MRI-guided biopsy to be a less worrisome procedure, with high levels of perceived necessity and tolerability. Their results are cohesive with those of the PACT study, and help provide insight into some of the patient emotions surrounding MRI-guided procedures; however, they did not explore the perceptions of patients that were able to avoid immediate biopsy, due to non-suspicious mpMRI.[223] In an earlier study, Ullrich and colleagues examined the views around prostate mpMRI held by cohort of patients in Germany.[214] In contrast to Pizzoli and colleagues, they did not examine patient opinions of MRI-guided biopsy, but instead demonstrated that 70% of included patients perceived the concept of 'diagnostic accuracy' to be of high importance for prostate cancer (as reiterated in the PACT study). They also showed that 68% of patients considered mpMRI to be a useful diagnostic adjunct (however, not all of them had direct experience of this technology).[214] In more recent years, Merriel and colleagues have further explored patient viewpoints in this field. They initially conducted a systematic review examining patient-centred outcomes from mpMRI and MRI-guided biopsy, focussing primarily on biomedical side-effects (e.g. post-procedural haemorrhage and infection) as opposed to psychological implications.[224] This review highlighted that mpMRI testing overall resulted in favourable patient-centred outcomes, but also concluded that there was a paucity of evidence for the effect of mpMRI and MRI-guided biopsy on emotional or cognitive outcomes, thus further illustrating the evidence deficit, that, in part has been fulfilled by the PACT study. This work was then followed by a qualitative study from the same group, in which patients (n = 22) and general practitioners (GPs; n = 10) were interviewed to explore their views on mpMRI-driven diagnostic pathways (including a novel 'one stop' pathway).[225] In this study, they showed that patients appeared to prefer one stop mpMRI pathways (as opposed to the traditional staged approach), so that consultations and decision making are delivered within shorter time-frames. They did not explore patient views regarding non-MRI-directed diagnosis, but in parallel to the PACT study, they did demonstrate that both family and personal experiences were key in shaping patients' viewpoints.

The PACT study had several potential limitations. Firstly, the study focused solely on patients at the beginning of the diagnostic pathway. Some of the included cohort had experienced prostate biopsy previously, and so were able to compare experiences, however, none of the included patients were interviewed at the 'conclusion' of the pathway, i.e. after their MRI-guided biopsy and diagnosis. Future work should aim to address this, as this would provide a more accurate picture of patient acceptance of mpMRI, as patients would be given the opportunity to reflect on the whole process, including the times when mpMRI is inaccurate. Secondly, the opinions of healthcare practitioners, and those who commission cancer services, were overlooked in the PACT study, and as such, the views of key stakeholders for the ongoing use of prostate mpMRI were overlooked. Thirdly, it should be acknowledged that patient viewpoints were

informed, in part, by the information that they were provided with (either in the form of a patient information sheet prior to their questionnaire completion, or by a scripted information paragraph, prior to sub-section questions within the interviews). This is an important potential source of bias to consider, as patient trust in clinicians was already noted to be high, and as such, the potential to guide/lead patients by providing them with incorrect or biased information is inherent to this approach. Lastly, the coronavirus disease (COVID) pandemic altered the data collection process midway through the study, and face-to-face interviews were changed to digital interviews (using the Microsoft Teams and Zoom interfaces), and as such, this may have created subtle differences in the nature of the interview responses, creating a potentially unknown source of data heterogeneity.

The findings of the PACT study may influence current clinical practice in several possible ways. By surveying the views held by patients undergoing prostate mpMRI, we are now able to appreciate the values and concerns that they hold, and in particular, the benefits that they perceive of undertaking imaging before biopsy. It is reassuring that the predominant patient views regarding mpMRI are positive, particularly as this technology has now become an integral part of the prostate cancer diagnostic pathway in the UK, as part of NICE guidance. In particular, it is useful to now understand that, overall, patients are accepting of the incumbent risk of mpMRI-invisible prostate cancer, especially given the increasing trend to forego immediate biopsy when pre-biopsy mpMRI reveals non-suspicious findings only. The PACT study did however reveal that patients at risk of prostate cancer tend to hold a large amount of trust in the clinicians who make diagnostic and therapeutic decisions regarding their care, even when genuine uncertainties and controversies remain. As clinicians and researchers, we should be aware that responses from patients may be inadvertently influenced by this trust, and as such, may be vulnerable to external biases.

Future research in this field should expand upon findings established in the PACT study. In particular, it will be important to further explore patient opinions regarding the benefits and drawbacks that prostate MRI may afford in the context of prostate cancer screening (e.g. with fast biparametric MRI), as this becomes an increasingly important research area, given growing healthcare demands. Furthermore, the study model outlined here in the PACT study protocol could be adapted and employed to evaluate patient perceptions of incoming diagnostic technologies, including PSMA-PET and various prostate cancer biomarkers, bringing the end user voice into these studies. It seems feasible that these technologies will enter the diagnostic pathway in the near future, and therefore it is crucial to ensure that patient viewpoints continue to be placed at the centre of this process.

6.5 CONCLUSION

In the PACT study, patients with suspected prostate cancer appeared to favour imaging-directed diagnosis over traditional up-front systematic biopsy. The diagnostic accuracy afforded by pre-biopsy mpMRI, and the potential to avoid immediate biopsy appeared to be key motivators of this perception. With regards to biopsy strategy, mixed views were expressed regarding the necessity of concomitant systematic biopsy, in addition to MRI-targeted biopsy. Throughout the study, patients appeared to express strong trust in clinician's views generally, including their perceptions on novel technology (e.g. mpMRI) and it may be important to consider this when interpreting findings from this study, and others. A degree of concern was raised regarding the various challenges to implementation and access to mpMRI, and these various factors should ideally be considered in future work.

6.6 OVERALL CHAPTER SUMMARY & CANDIDATE CONTRIBUTION

1. Patients with suspected prostate cancer appear to favour imaging-directed diagnosis compared to traditional up-front systematic biopsy
2. Diagnostic accuracy of mpMRI and potential biopsy avoidance were apparently cited as key motivators
3. Biopsy reluctance appeared to stem from personal experience of negative second-hand side-effect reports
4. Mixed patient views were expressed regarding necessity of concomitant systematic biopsy
5. Patient perspectives of disease significance appeared to be mixed, with some citing quantity over quality of life metrics
6. Consideration of impact on family and friends was appeared to be a driver of citing life expectancy for disease significance
7. Positive views were apparently expressed towards the concept of bpMRI, however, many patients appeared to prefer to maintain DCE sequence, due to the possibility of higher diagnostic sensitivity
8. Strong trust in clinicians was exhibited throughout the study, and ideally this should be considered when interpreting findings, as this may influence patient views

In this chapter, all work was primarily conducted by me. The novel PACT study design was conceived by me, in conjunction with the supervisory team, to explore in depth the views that patients have surrounding prostate mpMRI (for the first time). Following this, approval for the study, and delivery of the two-stages of the research, was performed by me. Processing and analysis of the PACT study results was conducted by me, with guidance from Professor Daniel Kelly. All figures and tables presented in this chapter were conceived and newly created by me, unless specifically stated in parentheses.

CHAPTER 7:

DISCUSSION

7.1 SUMMARY OF WORK

7.1.1 Overall Summary

In this thesis, I have systematically explored the nature of mpMRI-invisible prostate cancer, at different analytical levels.

Addressing the hypothesis

Overall, work presented in this thesis is supportive of the proposed hypothesis. Combination of pathological outcomes from PROMIS and PICTURE (albeit at the per-patient level), with synthesis of data from existing molecular studies, provide biological support for the hypothesis that mpMRI-detection of prostate cancer helps convey additional oncological detail, and as such, should be considered when making treatment and monitoring decisions. The missing component, to fully establish the hypothesis, is lack of long-term outcomes. Data presented here is cross-sectional, and it remains to be seen whether implied biological and clinical aggression will impact on eventual patient outcomes. The additional element provided by this doctoral work of the first prostate mpMRI patient engagement research helps support the hypothesis further; particularly with regards to avoidance of biopsy when no tumour has been detected by mpMRI, as this appears to be strongly supported by patients, even when risks of mpMRI-undetected disease are acknowledged.

Reliance upon a per-patient approach

Whilst the 'per-patient' approach used in the post hoc analyses of the PROMIS and PICTURE studies has been highlighted as a potential limitation, it is also possible to perceive this approach as a strength. Firstly, the per-patient approach mirrors real-life clinical practice more closely, in which often the urologist is presented with an overall mpMRI score for the patient, from which to make a clinical decision. The data produced in this doctoral research demonstrates, using the highest quality mpMRI dataset, for the first time, that a per-patient mpMRI score is likely to be safe method to guide investigative and treatment decisions (for example, avoidance of biopsy in reassuring mpMRI results). Secondly, the per-patient approach permitted the research to be conducted feasibly, as re-scoring every lesion within the PROMIS dataset for example (*n=576*) would arguably have had a detrimental effect on other elements of the research due to time consumption. Thirdly, and finally, the per-patient approach has the strength of avoiding inherent challenges of lesion alignment and incumbent bias that are likely to occur when attempting to take a per-lesion approach, in which mpMRI lesions may be inappropriately be assigned to benign or malignant tissue, as registration error.

CHAPTER 2

In Chapter 2, the dataset generated from the previously published PROMIS study (n = 576) was interrogated.[122] In this new analysis, I compared histopathological results between mpMRI-detected and mpMRI-undetected cancer. This analysis suggested that mpMRI-undetected disease tends to be smaller (as measured by maximum cancer core length) and lower grade (both, in overall and maximum pathological grades) for various definitions of detection and pathological significance (Fig. 17) for biopsy-naive patients. Furthermore, none of the most aggressive patterns (e.g. Gleason 5) were overlooked by mpMRI in this analysis. However, it should be noted, that there is a degree of uncertainty regarding these features of detection and non-detection, as this post hoc analysis was conducted using a per-patient analysis (as opposed to per-lesion analysis).

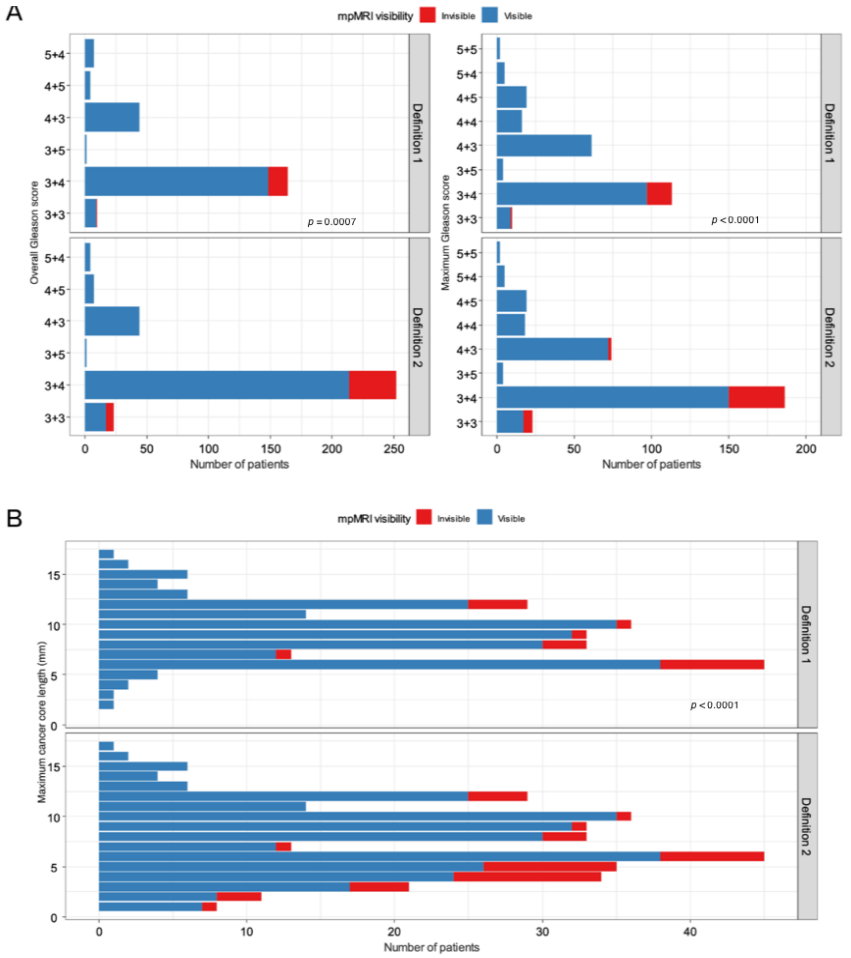


Fig. 5 – Tumour grade (A) & size comparison (B) for mpMRI-detected & mpMRI-undetected disease in PROMIS. (*Red bars = mpMRI-undetected cancer; blue bars = mpMRI-detected cancer*).

Utility of theoretical PSAD thresholds was also explored, and these were shown to potentially reduce proportions of overlooked significant cancer in cases of non-suspicious mpMRI, however, the trade-off of increasing overall biopsy numbers (when PSAD thresholds are applied), and proportion of clinically insignificant cancer, should be considered.

Work arising from Chapter 2:

- Norris JM. Uncovering the nature of MRI-invisible prostate cancer. *American Urological Association News*. Dec 2020;25(12):31-2. [Paper]
- Norris JM, et al. What type of prostate cancer is systematically overlooked by multiparametric magnetic resonance imaging? An analysis from the PROMIS cohort. *European Urology*. 2020;S0302-2838(20)30261-X. [Paper]
- Norris JM, et al. WHICH PROSTATE CANCERS ARE OVERLOOKED BY MULTIPARAMETRIC MAGNETIC RESONANCE IMAGING? AN ANALYSIS FROM PROMIS. *The Journal of Urology*. 2020;203(supp 4):e1243-4. [Abstract]
- Norris JM, et al. Which prostate cancers are overlooked by mpMRI? An analysis from PROMIS. *European Surgical Research*. Accepted: In Press. [Abstract]
- Norris JM, et al. Which prostate cancers are overlooked by mpMRI? An analysis from PROMIS. *European Urology Open Science*. 2020;19(Suppl 2);e465-6. [Abstract]

CHAPTER 3

In Chapter 3, the dataset generated from the previously published PICTURE study (n = 249) was interrogated.[226] In this new analysis, I compared histopathological results between mpMRI-detected and mpMRI-undetected cancer, and the results of this analysis recapitulated results from the PROMIS analysis in Chapter 2. However, in this analysis the focus was patients who had previously undergone prior risk stratification and prostate biopsy. Again, this analysis, on a balance, demonstrated that mpMRI-undetected disease tended to be smaller and lower grade for various definitions of mpMRI detection and pathological significance. As with the analysis of PROMIS study in Chapter 2, theoretical PSAD thresholds (above which a biopsy would be indicated) were applied to patients with non-suspicious mpMRI in the PICTURE study, and again demonstrated a potential opportunity to reduce the proportion of overlooked significant prostate cancer.

Interestingly, the proportion of the most clinically significant mpMRI-undetected prostate cancer was even less in PICTURE than it was in PROMIS (2.9% vs. 7%). This may be attributable to differences in the populations; specifically, the patients in PICTURE had already undergone previous prostate biopsy for suspected prostate cancer, and as such this population may have had a genuinely higher proportion of clinically significant disease. Another explanation is that the radiologists in the PICTURE study were aware of this higher risk population, and as such ascribed higher mpMRI scores than they may have already done. However, despite this, it should be noted that, in truth, the actual proportions of mpMRI-undetected prostate cancer is similar between the studies, and this may be indicative of the poor risk stratification tool that the patients in the PICTURE study had previously undergone (i.e. systematic TRUS-guided biopsy).

Work arising from Chapter 3:

- Norris JM, et al. Which prostate cancers are undetected by multiparametric magnetic resonance imaging in men with previous prostate biopsy? An analysis from the PICTURE study. *European Urology Open Science*. 2021 Jun 15;30:16-24. [Paper]
- Norris JM, et al. Which prostate cancers are undetected by multiparametric magnetic resonance imaging in men with previous prostate biopsy? An analysis from the PICTURE study. *The Journal of Urology*. Accepted: In Press. [Abstract]
- Norris JM, et al. Which prostate cancers are undetected by multiparametric magnetic resonance imaging in men with previous prostate biopsy? An analysis from the PICTURE study. *European Urology Open Science*. Accepted: In Press. [Abstract]

CHAPTER 4

In Chapter 4, a sub-population from the PROMIS cohort ($n = 88$) was re-analysed in an attempt to elucidate radiological factors affecting tumour detection, including the impact of mpMRI quality.[131] Quality of mpMRI (as assessed using the PI-QUAL scale) was tended to be low in approximately half of patients with mpMRI-undetected disease in the PROMIS study. On the whole, the commonest artefact in this group appeared to be DWI-related reduction of quality. Both Likert and PI-RADSv2.1 reporting schemes appeared to perform well in detecting clinically significant prostate cancer on mpMRI (for the same reader), with little difference seemingly reported between the two approaches.

Work arising from Chapter 4:

- Norris JM, et al. Prostate cancer undetected by mpMRI: tumour conspicuity is reliant upon optimal scan timing and quality. *Urology*. 2020 Dec 2;S0090-4295(20)31427-8. [Paper]
- Liebert C, et al. Diagnostic potential of radiological apical tumor involvement. *Journal of Robotic Surgery*. 2023 Apr;17(2):705-6. [Paper]

CHAPTER 5

In Chapter 5, the molecular landscape of mpMRI tumour detection was explored, using a combination of systematic literature review and bioinformatic techniques.[124] Here, collation of existing articles (*n* = 32) appeared to demonstrate a cohesive picture in which mpMRI-undetected cancer tended to have favourable molecular characteristics (as compared to mpMRI-detected disease), as illustrated by favourable scores on commercial genetic panels (including, Oncotype DX, Decipher, Prolaris and Progensa) and reduced genetic markers of progression, such as *PTEN* loss, copy number variation, DNA damage and repair, and angiogenesis. Bioinformatic analysis of publicly available data revealed a set of 42 genes (across three radiogenomic studies) that appeared to be directly associated with tumour detection on mpMRI (Fig. 18).[124] When biological functions of these genes was further explored, a variety of cellular components and processes were retrieved (including, anchoring junction, adherens junction, cell-substrate junction and actin filament-based process) which may all contribute to tumour visibility on mpMRI (via cellular density), and potentially, prognosis.

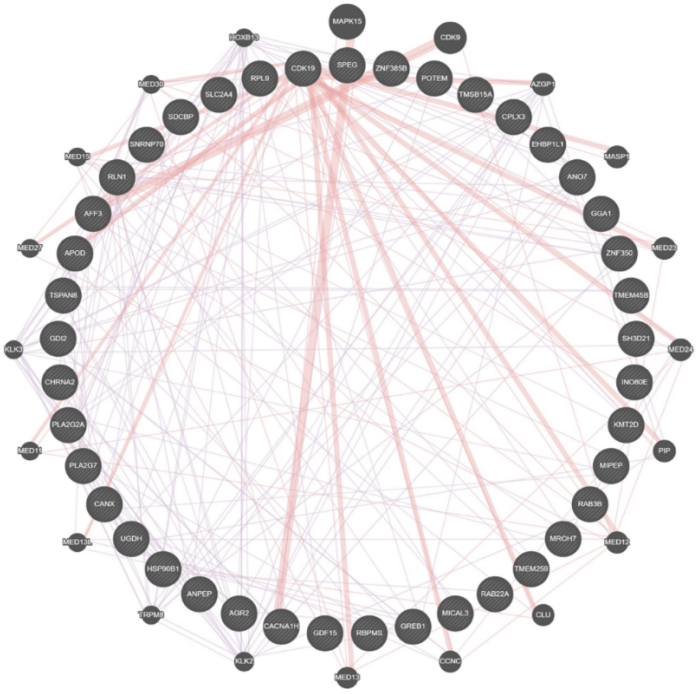


Fig. 18 – Bioinformatic analysis derived 42 genes associated with tumour detection on mpMRI. (*Image courtesy of Benjamin Simpson*).

Work arising from Chapter 5:

- Norris JM, et al. Genetic landscape of prostate cancer conspicuity on multiparametric magnetic resonance imaging: a systematic review and bioinformatic analysis. *European Urology Open Science*. 2020 Jul; 20; 37-47. [Paper]
- Norris JM, et al. The genetic landscape of prostate cancer conspicuity on multiparametric MRI: a protocol for a systematic review and bioinformatic analysis. *British Medical Journal Open*. 2020 Jan 27;10(1):e034611. [Paper]

- Norris JM, et al. Genetic correlates of prostate cancer visibility (and invisibility) on mpMRI: It's time to take stock. *British Journal of Urology International*. 2020 Mar;125(3):340-2. [Paper]

CHAPTER 6

In Chapter 6, patients (*n* = 117) undergoing mpMRI for suspected prostate cancer were recruited as part of the PACT study.[126] In the PACT study, patients seemed to express a wide-range of responses, elicited with a mixed methods dual-stage methodology (including, questionnaires and semi-structured interviews). Overall, patients that directly experience this technology appeared to favour the diagnostic accuracy provided, and the potential to avoid embarrassing and painful prostate biopsy. Mixed views seemed to be expressed regarding the factors that contribute to the 'significance' of prostate cancer, with some patients citing longevity over quality of life, and vice versa. The work produced in PACT represents early research in this field and may help to provide a framework on which further research can be conducted into patient engagement in imaging-directed prostate cancer diagnosis and risk stratification.

Work arising from Chapter 6:

- Norris JM, et al. Patient perspectives and understanding of MRI-directed prostate cancer diagnosis. *Urology*. 2021 Apr 3:S0090-4295(21)00301-0. [Paper]
- Norris JM, et al. Exploring patient views and acceptance of multiparametric magnetic resonance imaging for the investigation of prostate cancer (the PACT study): a mixed-methods study protocol. *MDPI Methods & Protocols*. 2020 Mar 28;3(2). [Paper]
- Norris JM, et al The PACT study: a prospective mixed-methods study of patient attitudes towards multiparametric magnetic resonance imaging-directed prostate cancer diagnosis. *European Surgical Research*. Accepted: In Press. [Abstract]
- Norris JM, et al. Patient perspectives of multiparametric magnetic resonance imaging-directed prostate cancer diagnosis: a prospective systematic mixed-methods study (the PACT study). *European Urology Open Science*. Accepted: In Press. [Absract]
- Norris JM, et al. Exploration of patient trust on the use of multiparametric magnetic resonance imaging for the diagnosis of prostate cancer: qualitative interim analysis of the PACT study. *British Medical Journal Open*. Accepted: In Press. [Abstract]
- Norris JM, et al. Exploration of patient trust on the use of multiparametric magnetic resonance imaging for the diagnosis of prostate cancer: qualitative interim analysis of the PACT study. *European Journal of Surgical Oncology*. 2021;47(1):23. [Abstract]
- Norris JM, et al. Investigating men's perceptions on the use of multiparametric MRI for the diagnosis of prostate cancer. *European Journal of Surgical Oncology*. 2020;45(11):2203. [Abstract]

7.1.2 The Conspicuity Hypothesis

When taken as a whole, the collective results of this doctoral research (and the work of others) potentially help to suggest a novel hypothesis that interlinks evidence from the molecular level, through to prostate mpMRI phenotype, and eventual clinical outcome.[145]

My hypothesis is that the positive mpMRI signal generated by visible prostate tumours may be associated with multiple layers of hallmarks of aggressive cancer, on a genetic, histopathological, and clinical level (Fig. 19).[145] To phrase this in alternative way – it seems probable that mpMRI-undetected prostate cancer is unlikely to harbour characteristics of unfavourable disease, at numerous possible levels of assessment.

Molecular evidence suggests that over-expression of proliferation-regulating genes and loss of tumour suppressor genes may lead to increased tumour growth, which is noted in aggressive prostate cancer, including cribriform pattern disease.[124] I believe that histopathologically, these genetic features may result in larger volume tumours (at the point of detection)[122] with increased tumour epithelial cell density, and thus, a reduced stromal-to-epithelial ratio. Rapid tumour growth stemming from these genetic influences may then result in areas of hypoxia, triggering vascularisation-signalling cascades, further increasing microvessel density, tissue density, and tumour size.[145,227]

Radiologically, it seems plausible that these features may contribute to tumour visibility in each of the constituent MRI sequences that form part of the mpMRI assessment. First, increased tumour size may directly result in increased lesion detection, as the larger the tumour volume, the more likely it is to be above the spatial resolution limits of mpMRI.[228] This may be true for all of the mpMRI sequences, especially the anatomical T2W sequence. Second, increased tumour tissue density may manifest in restriction of movement of water molecules within malignant tissue, resulting in a stronger (more restricted) signal on the DWI sequence and ADC map. Finally, increased vascular density may render tumours more apparent on mpMRI due to higher concentrations of gadolinium accumulating in additional vascular spaces, thus potentially generating stronger signal on the DCE sequence.

Given these factors, it seems plausible that larger, higher-grade tumours, enriched with unfavourable genetic features, may be associated with poor clinical prognosis. This then may support the notion that mpMRI-visible cancer may confer a worse prognosis over mpMRI-invisible counterparts. This integrated theory appears to be consistent with the natural pathogenesis of cancer and with a number of studies which have investigated the clinical, histopathological, and genetic features of disease detection on mpMRI.

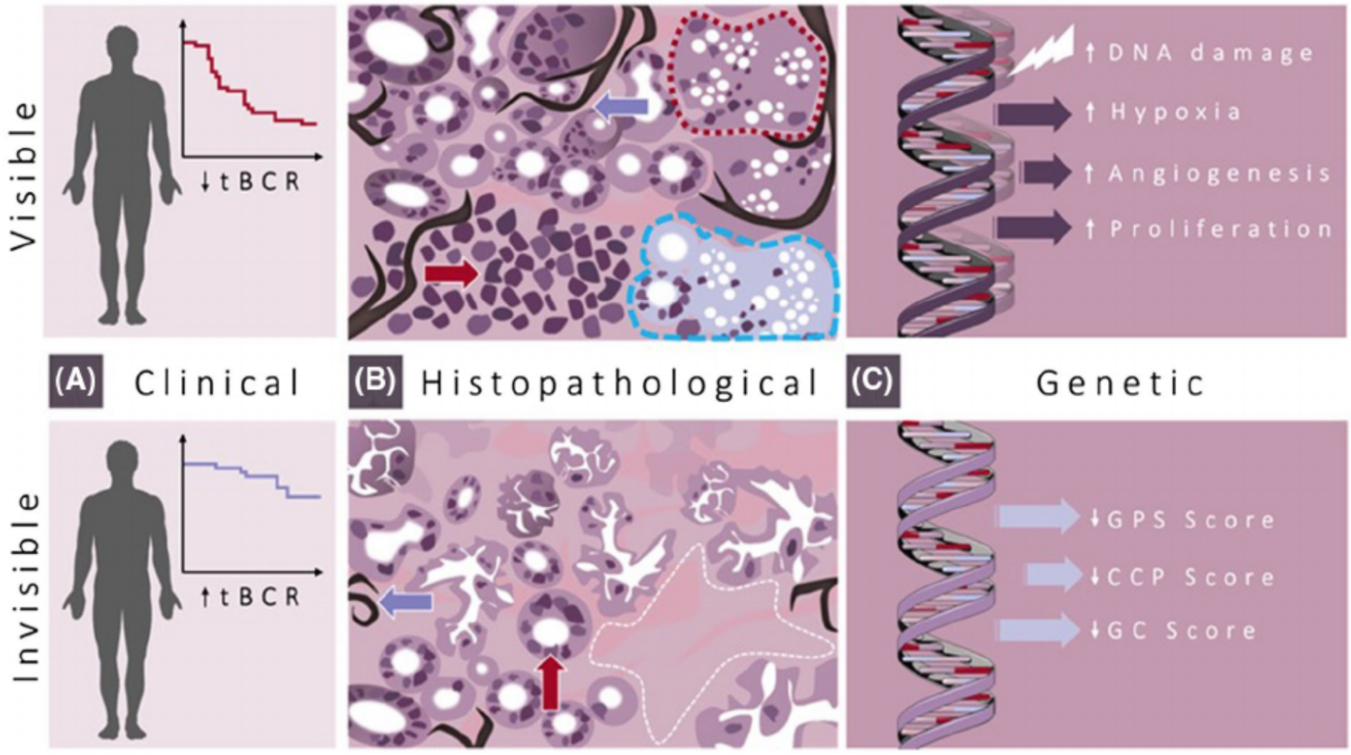


Fig. 19 – Integrated clinical, histopathological & genetic aspects of mpMRI-visible & mpMRI-invisible prostate cancer. (*Example Kaplan–Meier curves = hypothetical time-to-biochemical BCR [tBCR]; red arrow = cellular density; blue arrow = microvessel density; blue dashed line = hypoxia; stroma = white dashed line; red dotted line = cribriform disease*).

In addition to an integrated conspicuity hypothesis, it is likely important to consider thresholds (for both mpMRI detection and clinical significance), which are intrinsic to the diagnosis and treatment of cancer (Fig. 20). Firstly, the threshold for disease significance, in which there may be a point on a theoretical spectrum (largely calibrated by tumour grade, size, and stage) in which a cancer, having begun as a small number of malignant cells, grows, and might obtain oncological potential to spread and impact both quality and quantity of life (i.e. becomes clinically significant).

Secondly, a threshold for disease visibility on mpMRI, in which there may be a point on a theoretical spectrum where a cancer acquires sufficient characteristics (such as, size, vascularity, or density) to potentially become visible on mpMRI. It seems possible that tumour visibility on mpMRI may occur before onset of clinical significance, which carries the potential risk of disease over-treatment. My hypothesis, and the extant evidence, suggest this is may be unlikely, and in fact, mpMRI appears to enable avoidance of detection of insignificant disease, overall.[1,5]

Alternatively, tumour visibility may occur at the point of development of clinical significance, which might represent the best-case scenario, providing diagnosis at the point at which treatment would be beneficial. This scenario potentially supports my hypothesis, on multiple levels, however, the evidence used to construct this hypothesis is built on patients with timely referral from primary care (e.g. with PSA < 15ng/mL), which may skew the mpMRI literature towards early

detection.[1] Longer term data from large prostate cancer trials (e.g. ProtecT) suggest low levels of overall lethality from monitoring (as opposed to actively treating) for the majority of prostate cancers, which suggest the possible window for detecting treatable disease by mpMRI is probably quite large.[208]

Finally, tumour visibility may occur after the point of clinical significance has passed, in which the window for disease curability may be lost. Overall, this seems less likely, especially given the typically lower PSA thresholds used in primary care to trigger referral for assessment. However, there are a small number of research groups that have suggested that mpMRI may overlook a significant number of high-grade prostate cancers,[11] which might contradict the hypothesis that I have described. However, these studies appear to be outliers, and key considerations of study methodology, population bias, definitions of significance, and quality of mpMRI acquisition and interpretation may play a role in their conclusions.

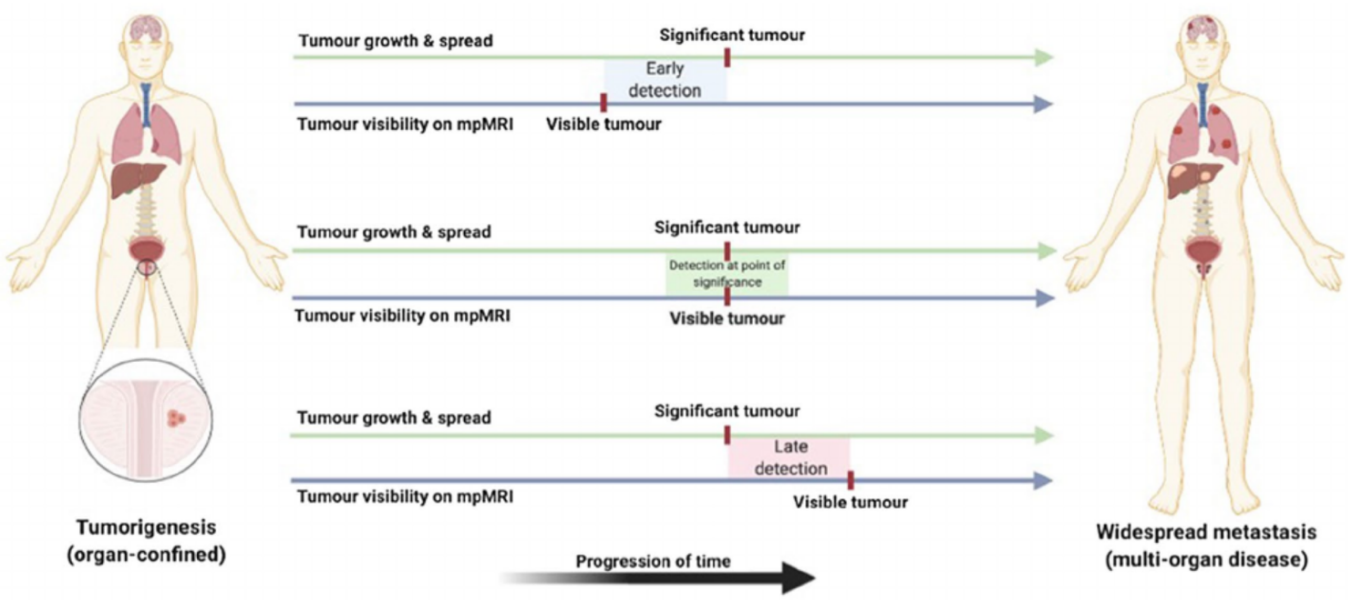


Fig. 20 – Scenarios for threshold alignment between development of clinical significance & mpMRI visibility. (*Green line = from organ-confinement to metastasis; blue line = from a small number of invisible cells to large visible tumours*).

7.1.3 Living with Uncertainty & Undetected Disease

The work in this doctoral thesis has aimed to delineate the nature of prostate cancer that is not detected by mpMRI – and the conclusions are, on the whole, reassuring. However, in the modern cost-conscious clinical environment, there is an increasing trend to avoid biopsy in cases of non-suspicious mpMRI, and as such, this creates a degree of

uncertainty, as we then lack histopathological characterisation for these patients. In turn, this then results in a situation in which patients and their clinicians must live with (and tolerate) a degree of uncertainty, especially regarding the ongoing possibility of undetected prostate cancer.

Each investigative modality (including cancer imaging) has an accompanying false negative rate, in which ongoing uncertainty must be tolerated. The field of prostate cancer diagnostics has a longstanding association with the philosophy of uncertainty, as exemplified by the dilemma created by an elevated serum PSA level. A recent Norwegian study took a quantitative and qualitative approach to comparing the distress of diagnostic uncertainty between two prostate cancer tests – PSA and Stockholm3 (an algorithm-based biomarker, based on protein and genetic markers, in conjunction with clinical variables).[229] They found that the information they received regarding the Stockholm3 test was of higher quality, and that this may have an impact on the degree of distress felt over test uncertainty; unfortunately, mpMRI was not evaluated.

Conceptually, the fear of the unknown (overlooking significant prostate cancer) has to be balanced against the clear risks of over-investigation (overdiagnosis, biopsy toxicity), and the point at which acquiescence is reached will differ from patient-to-patient, depending on personal circumstances, including age, co-morbidity and previous experiences. The work conducted in this doctoral research, when paired with (and integrated into) consistent high quality patient information, may help improve the process of living with the uncertainty of mpMRI-guided prostate cancer risk stratification.

7.1.4 Tumour Detection in Novel & Upcoming Imaging Techniques

In addition to mpMRI, other novel prostate cancer imaging modalities are now under evaluation to improve cancer diagnosis. Two of the most prominent techniques are microultrasound and PSMA-PET.[73] As with mpMRI, both microultrasound and PSMA-PET carry the risk of disease non-detection, and given the distinct radiological methods of detection between each modality, it seems plausible that the spectrum of invisible disease will differ depending on which technology is used. This then poses an interesting potential area for future development, in which novel modalities could potentially be combined to narrow the scope for undetected clinically significant disease.

Microultrasound employs high frequency (up to 29MHz), high resolution (down to 75μm) ultrasonography to generate detailed imaging of prostate anatomy that is reported to have good utility in the detection of clinically significant disease. However, this technique is highly operator-dependent, which at present limits clinician uptake of the technique. Recent comparison of transrectal microultrasound against quartermount radical prostatectomy specimens demonstrated

excellent detection of clinically significant disease (defined as GGG ≥ 2) by microultrasound.[230] Indeed, the authors concluded that microultrasound was able to detect all significant disease in the peripheral zone, and that the small number ($n = 3$) of significant microultrasound-invisible prostate cancers were confined to the transitional zone. In another similar recent study, microultrasound was found to have comparable levels of disease detection to mpMRI (sensitivity: 76.5% vs. 65.1%),[231] suggesting the technique may play a complementary role in the future, if issues surrounding technique accessibility can be overcome. Detailed molecular and histopathological comparison between mpMRI-invisible and microultrasound-invisible prostate cancer has not yet been undertaken, and this would be an interesting area for future research.

PSMA-PET is a technique that measures uptake of PSMA (an antigen selectively overexpressed in prostate cancer cells) along with radiolabelled peptide ligands (e.g. ^{68}Ga) by cross-section imaging (PET), and has, in recent years, shown good utility for restaging of recurrent and metastatic prostate cancer. However, interest is now growing to examine the use of PSMA-PET in the primary, diagnostic setting. Perhaps given the tissue-specificity of the PSMA antigen, the diagnostic potential of PSMA-PET appears impressive, with a recent radical prostatectomy cohort demonstrating comparable detection of index prostate cancer lesions, compared to mpMRI (sensitivity: 93% vs. 90%).[232] This has yet to be evaluated in a real-world clinical setting, and potential barriers include cost, scanner availability, and possible inability to discern high-grade lesions from low-grade lesions (an advantage demonstrated by mpMRI). Again, systematic in-depth comparison of mpMRI-invisible and PSMA-invisible prostate cancer would represent an important future project, to help plan future integration of imaging modalities.

7.2 METHODOLOGICAL LIMITATIONS

7.2.1 Summary of Intrinsic Methodological Limitations

Intrinsic limitations for each sub-study undertaken in this research have been outlined in detail in each respective chapter. For analysis of the PROMIS and PICTURE studies, the analyses were limited by a per-patient design in which individual mpMRI-undetected lesions may have been overlooked by an overall positive mpMRI score generated by a co-occurring mpMRI-visible tumour. Furthermore, these two analyses were limited through their retrospective and post hoc study design, and by the unknown clinical significance associated with detection or non-detection of tumours. In radiological re-analysis of the PROMIS sub-cohort, the major limitations were potential selection bias and reduced sample size, both of which arose from the analysis of a matched sub-cohort. For the genetic bioinformatic analysis, the predominant limitation was the drawback that few mpMRI-correlated genetic databases exist (n = 3) with appropriate data, from which the analysis could be based. Finally, for the PACT study, only patients with suspected prostate cancer were recruited to the study, whereas there is still a paucity of research examining clinician perception of prostate mpMRI. This may become particularly relevant if prostate mpMRI may move to become a primary care tool in the future, to address workload capacity issues.

7.2.2 Summary of Extrinsic Methodological Limitations

The overarching extrinsic limitation with all of the research presented here is with applicability and generalisability, particularly with work undertaken with the PROMIS, PICTURE and PACT studies. Trial data from each of these studies was gathered at centres with a background of mpMRI experience, and as such, it may be argued that favourability of outcomes (e.g. lower pathological grading in mpMRI-undetected disease) may not be reproducible at smaller, less-experienced centres. This argument is particularly valid for the PICTURE study, in which all data was gathered at a single tertiary referral academic centre. In some regards, the results from the PROMIS study have a higher level of generalisability, as they were gathered from 11 different sites across England and Wales, with a range of hospital size, population diversity, and experience with prostate mpMRI and biopsy.

7.2.3 Limitations of the COVID Pandemic

The COVID pandemic had a large impact on research in almost all areas, and the doctoral research presented here was similarly affected. Limitations from COVID impacted the research at almost all levels, from the basic (e.g. cessation of face-to-face meetings, and on-site university presence) to the more significant (e.g. removal of whole doctoral work packages due to lack of laboratory access). The original plan for the research presented here was to conduct wet-lab research on the biopsies collected during the PROMIS trial, however this research was postponed due to closure of the physical university premises. However, this work package will be resumed shortly, now that the laboratory has been reopened.

Database interrogation research (PROMIS, PICTURE) was arguably least affected by the COVID pandemic, as stay-at-home orders did not prevent database research on a remote workstation. However, COVID restrictions did prevent wide discussion of results (e.g. at laboratory meetings) in an engaged face-to-face manner, and did limit access to the PROMIS sample database (e.g. for further biological and histopathological research) as this was located within a closed site at UCL.

Engagement of expert collaborators and clinicians (radiologists, histopathologists) was limited by the COVID pandemic, for several reasons, but for the obvious reason that many healthcare workers were redeployed to frontline areas (including, intensive care). Furthermore, face-to-face meetings and discussion with these experts was no longer possible during the pandemic, due to the risk of spreading COVID in the pre-vaccine era of the pandemic.

The PACT study, as described elsewhere, was limited by the COVID pandemic in multiple ways. Firstly, the pandemic brought an end to the traditional prostate cancer diagnostic clinic (from which patients were recruited to the study) and in doing so, essentially ended the recruitment stage of this research. Secondly, the interview stage of this research was initially conducted as in-depth face-to-face interviews on the hospital site, however, these then had to then be converted to digital interviews once the pandemic began, and thus created a potential source of heterogeneity (NB: approximately half of the interviews were conducted pre-pandemic face-to-face, and the other were conducted digitally using Microsoft Teams and the Zoom interface).

7.2.4 Limitations of Analysis of the PROMIS & PICTURE Cohorts

The PROMIS and PICTURE cohorts are two of the most well standardised prostate mpMRI cohorts available, and as such, many of the limitations present in other studies (e.g. disease undersampling, population heterogeneity, radical prostatectomy population bias) are not present; however, some limitations of their analyses to still exist. A potential limitation of both the PROMIS and PICTURE analyses is the reliance upon the per-patient approach, in which a single

overall score was assigned to each mpMRI scan (Likert scores 1–5). This mirrors the real-life diagnostic setting but potentially prevents detailed analysis of tumour detection, as those patients with simultaneous visible and invisible tumours may have mpMRI-invisible cancer ignored due to an overall positive mpMRI score generated by the visible lesion. The analysis of PSAD (in both cohorts) showed the utility of this simple biomarker in patients with non-suspicious mpMRI, however this may not be representative of the situation in the real-world, as these patients would require full 5mm TTPM in order to detect the same levels of significant disease that are shown here (in reality, a simple 12-core systematic TRUS-guided biopsy is more likely to be offered, which would have much lower detection rates). This is likely important, as a recent systematic review demonstrated PSAD was the strongest predictor for clinically significant prostate cancer in the context of non-suspicious pre-biopsy mpMRI.[101] Lastly, the extrinsic validity of the PICTURE analysis may be limited, as PICTURE was a single-centre study conducted at an experienced academic centre and thus importantly lacks the generalisability provided by multi-centre studies such as PROMIS.[1,122]

The limitations of radiological sub-analysis of PROMIS (Chapter 4) predominantly stem from the sub-population study design. This project included patients from PROMIS that were matched (by tumour grade and size) to allow comparison of radiological factors that influence tumour detection. The process of creating these sub-cohorts could have theoretically created the potential for selection bias, as the entire study cohort is not represented (specifically, no benign cases were included, and no cases of mpMRI-detected prostate cancer were included).[1,122] An additional limitation of this project was the possibility of observer bias. Despite being blind to the original PROMIS mpMRI and histopathology reports, the radiologists that contributed to this subproject were aware of the purpose (i.e. evaluate radiological factors influencing tumour visibility). Therefore, it is possible that the conclusions of this project may have been affected by this bias, specifically, it is possible that they may have ascribed lower PI-QUAL scores for mpMRI-undetected prostate cancer, than they might have done in a normal clinical setting (not within a research project). The same applies for their Likert/PI-RADS scores; the researcher radiologists may have given higher Likert/PI-RADS scores than they would have done in a regular clinical context, as in this research project, they were aware that all included sub-cohort patients had clinically significant prostate cancer present.

7.2.5 Limitations of the Exploration of Molecular Landscape of Conspicuity

The limitations of the genetic systematic review and bioinformatic analysis are complex, and in many ways pertain to the relative immaturity of the literature. The included cohorts, on the whole, were cross-sectional, small in size, and generally used transcriptomic analysis. As such, as with all studies of small sample size, the results are likely to have reduced reliability, and furthermore, less likely to successfully demonstrate statistically significant differences between

groups. Lack of molecular analysis techniques used within included studies also creates another limitation, as certain molecular features are liable to be overlooked, if they are only measurable by other more advanced techniques. To address this, future research should aim to recruit larger (ideally longitudinal) cohorts, and should employ more advanced techniques, including further DNA and epigenetic investigation. Another limitation of the included studies arose from the lack of cohort matching – only a minority of the included studies in the review (4/32) used a matched analysis. This is important, as several tumoural features (e.g. size, grade) are likely to affect tumour visibility on mpMRI, and as such, it is difficult to draw firm conclusions regarding the molecular contribution to tumour visibility, if these features are not controlled for. The PROMIS cohort may provide an opportunity to address this, as it is a highly controlled population, but it should be acknowledged that this limitation does potentially undermine the conclusions of the genetic review, in part.

7.2.5 Limitations of the PACT Study

The limitations of the PACT study pertain primarily to the population. PACT centred on patients referred with suspected prostate cancer, and recruited them after having undergone mpMRI (and in some cases a historical biopsy), but did not survey them after the point of diagnosis (i.e. after their biopsy, MDT discussion, and diagnosis receipt). As such, it is possible that the recruited patients did not have a full and holistic view of the impact that mpMRI would have (both in a positive and negative way) on the diagnostic process. Furthermore, the PACT study only recruited patients, and did not engage the opinions of urologists (and other clinicians, or cancer service commissioners) and as such, the broader impact of prostate mpMRI was not evaluated. Another potential limitation is that the views obtained in this study may have been influenced by the information that was provided to the patients (i.e. patient information sheets, and descriptive paragraphs during the interviews). It is important to consider that the views expressed by patients could have been heavily influenced by the information they received from the start. To overcome this, the PACT research team attempted to provide a balanced summary of the contemporary literature for the patients, however, the true bias/impact on patient views from this information is unknown. However, the protocol and methodology generated by the PACT project can now be replicated and expanded in future research to address these limitations.

7.3 CLINICAL IMPLICATIONS

7.3.1 Ratification of Imaging-Directed Clinical Decision Making

Current national and international guidelines for patients with suspected prostate cancer suggest that mpMRI should be used prior to biopsy, to stratify patients requiring immediate biopsy, and to provide image-guidance for targeted biopsy when needed.[120,121] These guidelines are based on Level 1 evidence that demonstrates the diagnostic accuracy[1] and clinical utility[5] provided by upfront prostate mpMRI. However, a degree of scepticism still surrounds the reliability of mpMRI, particularly as the nature of mpMRI-undetected disease (that is likely to forgo biopsy) has remained relatively elusive.[127]

In this regard, the research presented in this thesis has important clinical implications. Through various approaches (and in various settings) the work conducted here appears to illustrate that mpMRI-invisible disease has reassuring features, including tumour volume, histopathological grade, and a variety of molecular characteristics.[122,24,226] Whilst some cases may not conform to these data, it appears that the majority of patients that undergo mpMRI and are then found to have non-suspicious mpMRI results would be unlikely to harbour significant disease, thus potentially bolstering current clinical guidelines that advocate omission of immediate biopsy in these cases.

Lastly, it is important to consider the question of whether mpMRI-invisible cancer must be detected at all. The combined results of the PROMIS study[1] and the SPCG-4 trial[114] offer interesting insights. In the recent long-term update of the Scandinavian SPCG-4 randomised controlled trial of watchful waiting compared to radical prostatectomy for prostate cancer, Bill-Axelson and colleagues found that after 29 years, intermediate risk prostate cancer (i.e. Gleason score 3 + 4) was not significantly associated with prostate-cancer-related death. In contrast, high risk prostate cancer (i.e. Gleason score 4 + 3 or worse) was significantly associated with prostate-cancer-related death. Given the results of the PROMIS study, in which no patients with overall Gleason 4 + 3 prostate cancer had mpMRI-invisible disease, this suggests that mpMRI may visualise all truly significant cancer (if SPCG-4 is used to guide the threshold for clinical significance).[1,114] This is interesting and raises the possibility that disease invisibility may in fact be useful, to help avoid unnecessary diagnoses and treatment – indeed, there may be utility in invisibility.

7.3.2 Refinement of Current mpMRI Application

Several simple, practical steps can be applied to improve the current use of mpMRI in the context of negative pre-biopsy investigation, including potential consideration of the use of PSAD thresholds. It is now reasonably well acknowledged that a raised PSAD may provide an indication of significant undetected prostate cancer (in cases of non-suspicious mpMRI),[112] and such, PSAD values are increasingly given by uroradiologists in mpMRI reports. However, evidence supporting PSAD threshold use in this context from high-quality trial data is lacking.

As part of the analyses of PROMIS and PICTURE presented here, the utility of various PSAD thresholds were evaluated, and the findings of this research may have clinical benefits. In this project, it was shown that if a PSAD threshold of 0.15ng/mL/mL was applied to biopsy-naive patients with non-suspicious mpMRI (above which a biopsy might be indicated), it was possible to reduce the proportion of overlooked clinically significant prostate cancer to just 5% (Fig. 21). This proportion was appeared to be lower in the same setting for non-biopsy-naive patients.[223] These data might then suggest refinement of the current pathway (i.e. reduced levels of non-detected disease), however, the decision to use PSAD thresholds to trigger biopsy must be carefully considered, as this is likely to increase the number of total biopsies performed and numbers of clinically insignificant cancers detected. Furthermore the data presented here may not be truly representative of a modern clinical context, as these findings are based upon saturation 5mm TTPM biopsy within a clinical trial, which in reality is unlikely to be offered today.

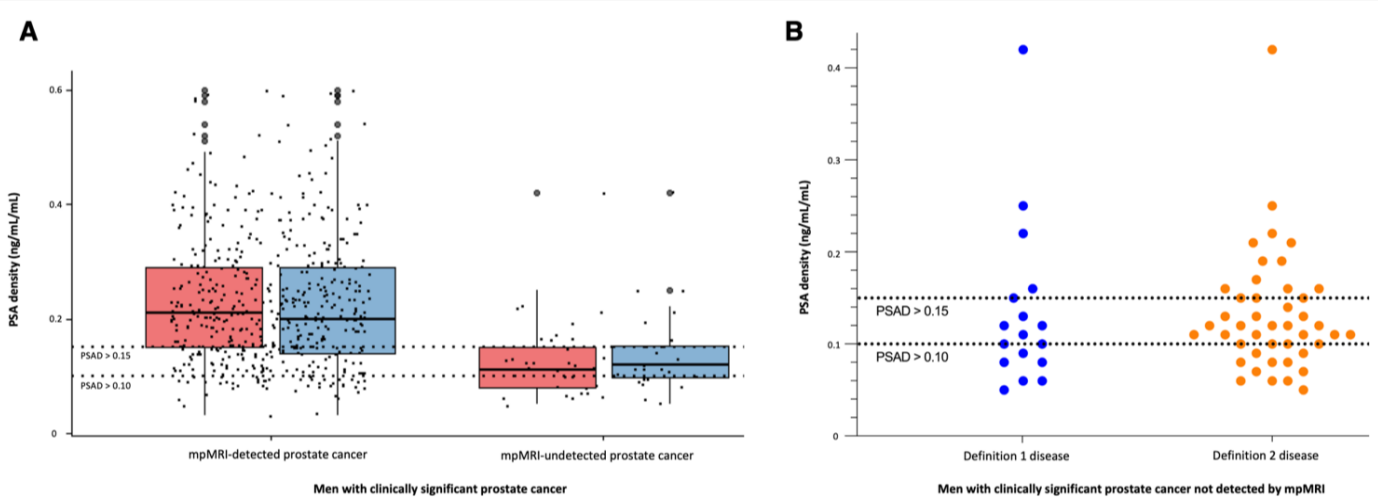


Fig. 21 – PSAD in mpMRI-detected & mpMRI-undetected disease (A), for various definitions of significance (B). (*Dotted lines = hypothetical PSAD thresholds, above which a biopsy is indicated; blue bars = definition 1 cancer; red bars = definition 2 cancer*).

7.3.3 Engagement & Involvement of Patients

Results presented here, as part of the PACT study, have helped provide some insight into the views held by patients that have experienced prostate mpMRI.[126,233] Clinically, the results of this study may have implications on future practice, as they have demonstrated a spectrum of values and beliefs held of patients at risk of prostate cancer, who are subjected to pre-biopsy mpMRI.

The findings presented here suggest that patients are, on the whole, supportive of an imaging-directed prostate cancer diagnostic pathway. Furthermore, it appears that patients that undergo this process may be willing to tolerate and accept risks of mpMRI-undetected cancer, provided that sufficient clinical follow-up (e.g. regular PSA surveillance) is provided, in at least a primary care setting. This view, in part, appears to be motivated by fear and reluctance surrounding prostate biopsy, which seemed to be motivated by either direct personal negative experience of such a biopsy, or negative second-hand reports from family or friends who had undergone the procedure.

A spectrum of opinions was expressed toward the significance of various cancer characteristics. Certain patients perceived the potential impact of malignancy (or treatment of this malignancy) on the quality of their life to be the most 'significant' feature of a threatened cancer, and this appeared to be an opinion expressed by more elderly patients, or those that had already experienced cancer treatment previously. In contrast, several patients appeared to reference potential negative effects on life expectancy from prostate cancer as their most important consideration, and often this appeared to be expressed by younger patients, or those with close friends, family or relatives. Furthermore, and in a similar manner, a variety of patient views were expressed toward the necessity of concomitant systematic biopsy at the time of MRI-targeted biopsy. Some patients favoured the diagnostic benefits of MRI-targeting alone, whilst other patients appeared to desire a 'belt and braces' approach, in they preferred the option of simultaneous systematic biopsy in conjunction with MRI-targeting. This early, but in depth, work therefore may help to highlight the need to actively engage patients in discussion around their diagnostic pathway, in an attempt to elucidate the values that matter most to them personally, as preferences and values do differ on a patient-by-patient basis.

7.4 FUTURE WORK

7.4.1 Longitudinal Clinical Outcome Analysis of Routine Hospital Data

Prostate cancer that is visible on mpMRI appears to have histopathological and genetically unfavourable characteristics (compared to undetected disease), as this body of doctoral research has helped to illustrate.[122,124] Given this growing biological evidence, it is plausible that in the long-term, patients with cancer that is not detected by mpMRI may have favourable clinical outcomes (e.g. with regards to disease progression) compared to patients with cancer that is detected by mpMRI. However, longitudinal ramifications of mpMRI appearances are not well characterised. In particular, it is unknown whether tumour conspicuity on baseline mpMRI confers long-term prognostic information. Extant evidence is this field is limited, and is largely short-term, based on note-review (with incumbent biases and limitations). During this doctoral research, two sub-projects were commenced in an attempt to address this challenge. Firstly, two dedicated medical students (N. Morka, C. Liebert) at University College London (UCL) were recruited to conduct an exhaustive systematic review and meta-analysis of MRI-correlated long-term clinical outcome studies (including, both multiparametric and biparametric MRI approaches)[234,235] to summarise the current evidence-base (results of this work are expected shortly). Next, collaboration was established with a French research team (led by J. Olivier, at the University of Lille) to examine medium-term outcomes of over 500 patients with negative prostate mpMRI. This retrospective project demonstrated that only 7–13% (36–66/503) of patients with non-suspicious mpMRI at baseline developed significant prostate cancer at follow-up (median: 4 years).[125]

An additional spin-off project is now underway to hopefully produce robust evidence to address this challenge. Well-characterised mpMRI and biopsy data from the PROMIS study[1] will be re-evaluated, and linked to eventual long-term clinical outcomes (e.g. at 8–10 years), including, disease progression (e.g. skeletal-related events [SRE])[236] and prostate cancer-related death. In an attempt to provide additional methodological rigour, this process will involve deterministic matching of pseudo-anonymised data (e.g. National Health Service [NHS] identification numbers) to outcome data accessed via Public Health England (PHE) from national databases (including, the National Radiotherapy Dataset [RTDS], the Office for National Statistics [ONS], the Hospital Episode Statistics [HES] database, the Systemic Anti-Cancer Therapy [SACT] dataset and the Cancer Registry). Application to PHE is underway (ODR2021_050). Eventually, this sub-project may reliably outline the prognostic potential of high-quality baseline mpMRI, which may in turn help to change clinical practice.

7.4.2 Delineation of Tissue Architecture with Digital Histopathology

In this project, study-reported histopathology outcomes in PROMIS and PICTURE were compared between mpMRI-detected and undetected disease.[122] However, there remains a wealth of additional histopathological research to be conducted with this study data, in particular, examining architectural features that were not originally reported, but may still impact on tumour conspicuity on mpMRI.[1,117] Beyond Gleason grading and tumour volume, it is plausible that additional features (e.g. cellular density, microvessel density) contribute to tumour detection,[138] and this seems particularly possible, given that there are a large number of tumours with similar pathological grade and size, but different mpMRI appearances. Unravelling this complexity will be key to understanding the mechanisms behind tumour conspicuity, and may have prognostic and treatment-delivery implications.

A digital histopathology sub-project (in collaboration with computer scientists at the University of Auckland and University of Melbourne, led by H. Reynolds) is now underway to address this research question. Patients in the PROMIS study with negative mpMRI and significant cancer on biopsy will be identified and compared to a group of patients with positive mpMRI (matched for Gleason grade and MCCL). Digitally scanned haematoxylin and eosin (H&E) biopsy slides will then be contoured by urological histopathologists to identify and compare regions of interest, including atrophy, inflammation, high-grade prostatic intraepithelial neoplasia (HGPIN), and prostate cancer variations. Finally, to compute histological attributes such as cellular density, and to generate density maps (Fig. 22) in MATLAB (The MathWorks Inc., Natick, MA, USA), contoured biopsy scans will be divided into tiles and H&E stain intensities are separated using colour deconvolution. Cell nuclei will then be identified (using a radial symmetry transform) and numbers of cell nuclei per tile will be automatically computed to produce density quantitation. Results of this project have the potential to transform our understanding of the relationship between radiology and pathology.

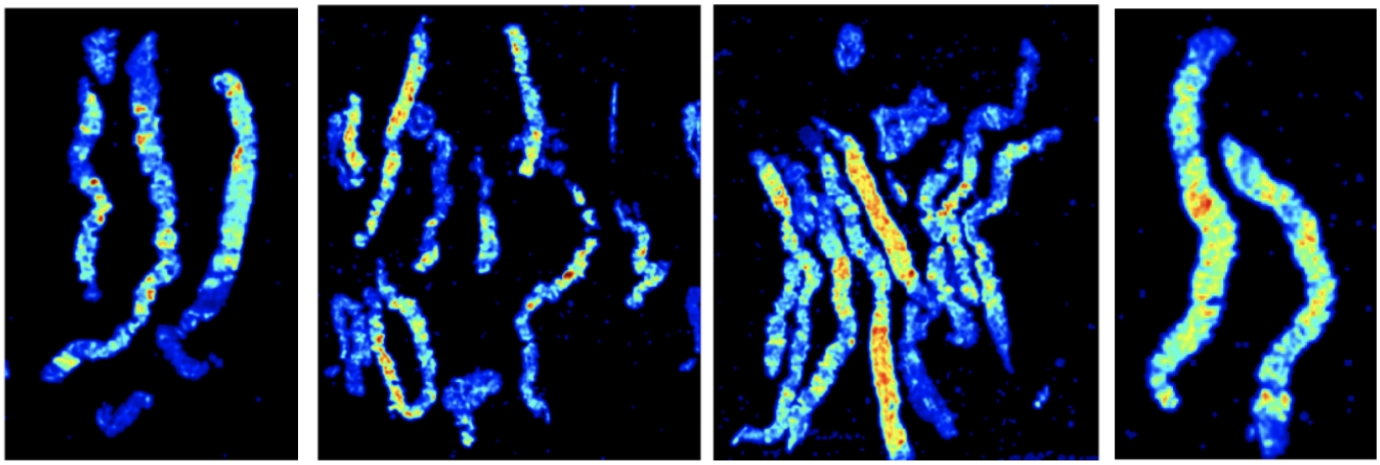


Fig. 22 – Cellular density map examples of prostate biopsies from PROMIS. (*Blue = low cellular density; red = high cellular density; image courtesy of Hayley Reynolds*).

7.4.3 Further Exploration of Biological Correlates of Conspicuity

In the research presented here, molecular features associated with tumour visibility on prostate mpMRI were collated, through a combination of bioinformatic and systematic review approaches.[124,137,145] This work contributes toward strengthening the biological rationale for imaging-directed practice in prostate cancer care, and also helps create foundations for a wide-scope of potential future research.

There are a number of ways in which this research can now be progressed. In this work, discordance in gene expression was observed between studies, despite many commonalities, and this was likely a result of methodological variations and limitations of each study.[124] However, one approach to overcome this drawback would be to use a highly-standardised TTPM-biopsy defined cohort (for example, as was used in the PROMIS and PICTURE studies).[1,117] Broad-spectrum RNAseq analysis of mpMRI-correlated prostate biopsies from PROMIS would allow generation of a robust RNA signature for mpMRI conspicuity, that could be compared to the molecular roster that was collated in this doctoral project.[117] Furthermore, mpMRI-correlated DNA and methylation analysis was lacking in the extant studies cited here,[117] and again this would be an important line of future enquiry. Indeed, with careful experimental planning, FFPE blocks from PROMIS could be subjected to both DNA and RNA interrogation, with shallow whole-exome analysis and methylation arrays. Ethical approval for this research has recently been granted (Research Ethics Committee [REC] Reference: 21/NE/0139 – J. Norris, V. Stavrinides, UCL).

Lastly, the research conducted here will have hopefully helped to create a springboard for further biomarker research, to enhance the current mpMRI-led paradigm. There are several valid potential biomarker projects arising from this research, however, pursuit of genetic-based biomarkers to aid identification of significant mpMRI-invisible prostate cancer would arguably have clinical utility. To identify such a candidate, samples from patients with clinically aggressive disease (e.g. those with biochemical recurrence post-radical prostatectomy) that was not detected on mpMRI should be analysed at the serum, urine, and tissue-levels, to potentially identify unique genetic signatures. However, one understandable challenge to this endeavour is the low likelihood of poor clinical outcome in this sub-population, as suggested at various analytical levels throughout this thesis.

CHAPTER 8:

CONCLUSIONS

CONCLUSIONS

In this doctoral research I interrogated clinical trial data and combined this with mixed methods and bioinformatic research techniques to further expound the nature of prostate cancer that is not detected by mpMRI. Overall, the multi-faceted evidence generated here appears to cohesively reiterate the same key message – detection of prostate cancer by mpMRI is associated with significant biological, pathological, and clinical disease characteristics. Furthermore, these features seem likely to align with views and expressed preferences held by patients at the centre of this diagnostic process.

The suggested radiogenomic mechanisms highlighted in this research that link each phenotypical level (e.g. molecular, architectural, tumoural, clinical) are plausible, and as such, have the potential to open up several research avenues – perhaps most importantly, the long-term clinical implications of baseline mpMRI phenotypes. Results of this next stage of research may play an important role in reshaping the diagnostic and risk stratification process for patients with prostate cancer, and eventually enable creation of bespoke risk profiling for each patient, and in so doing, hopefully allow delivery of higher levels of prostate cancer care, than were previously possible.

REFERENCES

1. Ahmed HU, El-Shater Bosaily A, Brown LC, et al. Diagnostic accuracy of multi-parametric MRI and TRUS biopsy in prostate cancer (PROMIS): a paired validating confirmatory study. Lancet 2017;389:815–22.

2. Radtke JP, Wiesenfarth M, Kesch C, et al. Combined clinical parameters and multiparametric magnetic resonance imaging for advanced risk modeling of prostate cancer-patient-tailored risk stratification can reduce unnecessary biopsies. Eur Urol 2017;72:888–96.

3. Mehralivand S, Shih JH, Rais-Bahrami S, et al. A magnetic resonance imaging-based prediction model for prostate biopsy risk stratification. JAMA Oncol 2018;4:678–85.

4. Moldovan PC, Van den Broeck T, Sylvester R, et al. What is the negative predictive value of multiparametric magnetic resonance imaging in excluding prostate cancer at biopsy? A systematic review and meta-analysis from the European Association of Urology prostate cancer guidelines panel. Eur Urol 2017;72:250–66.

5. Kasivisvanathan V, Rannikko AS, Borghi M, et al. MRI-targeted or standard biopsy for prostate-cancer diagnosis. N Engl J Med 2018;378:1767–77.

6. Sonn GA, Chang E, Natarajan S, et al. Value of targeted prostate biopsy using magnetic resonance-ultrasound fusion in men with prior negative biopsy and elevated prostate-specific antigen. Eur Urol 2014;65:809–15.

7. Valerio M, Donaldson I, Emberton M, et al. Detection of clinically significant prostate cancer using magnetic resonance imaging-ultrasound fusion targeted biopsy: a systematic review. Eur Urol 2015;68:8–19.

8. Tonttila PP, Lantto J, Pääkkö E, et al. Prebiopsy multiparametric magnetic resonance imaging for prostate cancer diagnosis in biopsy-naive men with suspected prostate cancer based on elevated prostate-specific antigen values: results from a randomized prospective blinded controlled trial. Eur Urol 2016;69:419–25.

9. Wise J. NICE recommends MRI for suspected prostate cancer to reduce biopsies. BMJ 2018;363:k5290.

10. Johnston MJ, Thorman H, Shah A, et al. Comparing significant prostate cancer detection rates after the introduction of pre-biopsy MRI: turning PROMIS into action. J Clin Urol 2019;12:341–6.

11. Johnson DC, Raman SS, Mirak SA, et al. Detection of individual prostate cancer foci via multiparametric magnetic resonance imaging. Eur Urol 2019;75:712–20.

12. Martorana E, Pirola GM, Scialpi M, et al. Lesion volume predicts prostate cancer risk and aggressiveness: validation of its value alone and matched with prostate imaging reporting and data system score. BJU Int 2017;120:92–103.

13. Tan N, Margolis DJ, Lu DY, et al. Characteristics of detected and undetected prostate cancer foci on 3-T multiparametric MRI using an endorectal coil correlated with whole-mount thin-section histopathology. JR Am J Roentgenol 2015;205:W87–92.

14. Miyai K, Mikoshi A, Hamabe F, et al. Histological differences in cancer cells, stroma, and luminal spaces strongly correlate with in vivo MRI-detectability of prostate cancer. Mod Pathol 2019;32:1536–43.

15. Borren A, Groenendaal G, Moman MR, et al. Accurate prostate tumour detection with multiparametric magnetic resonance imaging: dependence on histological properties. Acta Oncol 2014;53:88–95.

16. Panebianco V, Barchetti G, Simone G, et al. Negative multiparametric magnetic resonance imaging for prostate cancer: what's next? Eur Urol 2018;74:48–54.

17. Houlahan KE, Salmasi A, Sadun TY, et al. Molecular hallmarks of multiparametric magnetic resonance imaging visibility in prostate cancer. Eur Urol 2019;76:18–23.

18. McNeal JE, Redwine EA, Freiha FS, et al. Zonal distribution of prostatic adenocarcinoma. Correlation with histologic pattern and direction of spread. Am J Surg Pathol 1988;12:897–906.

19. Torre LA, Bray F, Siegel RL, et al. Global cancer statistics, 2012. CA Cancer J Clin 2015;65:87–108.

20. Fitzmaurice C, Abate D, Abbasi N, et al. Global, regional, and national cancer incidence, mortality, years of life lost, years lived with disability, and disability-adjusted life-years for 29 cancer groups, 1990 to 2017: a systematic analysis for the global burden of disease study. JAMA Oncol 2019;5:1749–68.

21. Barry MJ, Simmons LH. Prevention of prostate cancer morbidity and mortality: primary prevention and early detection. Med Clin North Am 2017;101:787–806.

22. Howlader N, Noone AM, Krapcho M, et al. SEER cancer statistics review, 1975-2014, National Cancer Institute. Bethesda, MD, https://seer.cancer.gov/csr/1975_2014/, based on November 2016 SEER data submission, posted to the SEER web site, April 2017.

23. Bratt O. Hereditary prostate cancer: clinical aspects. J Urol 2002;168:906–13.

24. Mcginley KF, Tay KJ, Moul JW. Prostate cancer in men of African origin. Nat Rev Urol 2016;13:99–107.

25. Rebbeck TR. Prostate cancer genetics: variation by race, ethnicity, and geography. Semin Radiat Oncol 2017;27:3–10.

26. Lebdai S, Mathieu R, Leger J, et al. Metabolic syndrome and low high-density lipoprotein cholesterol are associated with adverse pathological features in patients with prostate cancer treated by radical prostatectomy. Urol Oncol 2018;36:80.e17–24.

27. Alshaker H, Sacco K, Alfraidi A, et al. Leptin signalling, obesity and prostate cancer: molecular and clinical perspective on the old dilemma. Oncotarget 2015;6:35556–63.

28. Caliskan S, Kaba S, Özsoy E, et al. The effect of metabolic syndrome on prostate cancer final pathology. J Cancer Res Ther 2019;15:S47–50.

29. Esposito K, Chiodini P, Capuano A, et al. Effect of metabolic syndrome and its components on prostate cancer risk: meta-analysis. J Endocrinol Invest 2013;36:132–9.

30. Liang Z, Xie B, Li J, et al. Hypertension and risk of prostate cancer: a systematic review and meta-analysis. Sci Rep 2016;6:31358.

31. Stamey TA, Yang N, Hay AR, et al. Prostate-specific antigen as a serum marker for adenocarcinoma of the prostate. N Engl J Med 1987;317:909–16.

32. Catalona WJ, Smith DS, Ratliff TL, et al. Measurement of prostate-specific antigen in serum as a screening test for prostate cancer. N Engl J Med 1991;324:1156–61.

33. Etzioni R, Tsodikov A, Mariotto A, et al. Quantifying the role of PSA screening in the US prostate cancer mortality decline. Cancer Causes Control 2008;19(2):175–81.

34. Bittner N, Merrick G, Taira A, et al. Location and grade of prostate cancer diagnosed by transperineal template-guided mapping biopsy after negative transrectal ultrasound-guided biopsy. Am J Clin Oncol Cancer Clin Trials 2018;41:723–9.

35. Omer A, Lamb AD. Optimizing prostate biopsy techniques. Curr Opin Urol 2019;29:578–86.

36. Loeb S, Van Den Heuvel S, Zhu X, et al. Infectious complications and hospital admissions after prostate biopsy in a European randomized trial. Eur Urol 2012;61:1110–4.

37. Loeb S, Vellekoop A, Ahmed HU, et al. Systematic review of complications of prostate biopsy. Eur Urol 2013;64:876–92.

38. Gershman B, Zietman AL, Feldman AS, et al. Transperineal template-guided prostate biopsy for patients with persistently elevated PSA and multiple prior negative biopsies. Urol Oncol Semin Orig Investig 2013;31:1093–7.

39. Satoh T, Matsumoto K, Fujita T, et al. Cancer core distribution in patients diagnosed by extended transperineal prostate biopsy. Urology 2005;66:114–8.

40. Huang LH, Lin PH, Tsai KW, et al. The effects of storage temperature and duration of blood samples on DNA and RNA qualities. PLoS One 2017;12:e0184692.

41. Jones JS, Patel A, Schoenfield L, et al. Saturation technique does not improve cancer detection as an initial prostate biopsy strategy. J Urol 2006;175:485–8.

42. Pal RP, Elmussareh M, Chanawani M, et al. The role of a standardized 36 core template assisted transperineal prostate biopsy technique in patients with previously negative transrectal ultrasonography-guided prostate biopsies. BJU Int 2012;109:367–71.

43. Borghesi M, Ahmed H, Nam R, et al. Complications after systematic, random, and image-guided prostate biopsy. Eur Urol 2017;71:353–65.

44. Thurtle D, Starling L, Leonard K, et al. Improving the safety and tolerability of local anaesthetic outpatient transperineal prostate biopsies: a pilot study of the CAMbridge PROstate biopsy (CAMPROBE) method. J Clin Urol 2018;11:192–9.

45. Meyer AR, Joice GA, Schwen ZR, et al. Initial experience performing in-office ultrasound-guided transperineal prostate biopsy under local anesthesia using the PrecisionPoint transperineal access system. Urology 2018;115:8–13.

46. Latifoltojar A, Appayya MB, Barrett T, et al. Similarities and differences between Likert and PIRADS v2.1 scores of prostate multiparametric MRI: a pictorial review of histology validated cases. Clin Radiol 2019;74:895.e1-895.e15.

47. Chen N, Zhou Q. The evolving Gleason grading system. Chin J Cancer Res 2016;28:58–64.

48. Pan CC, Potter SR, Partin AW, et al. The prognostic significance of tertiary Gleason patterns of higher grade in radical prostatectomy specimens: a proposal to modify the Gleason grading system. Am J Surg Pathol 2000 Apr;24:563–9.

49. Singh RV, Agashe SR, Gosavi V, et al. Interobserver reproducibility of Gleason grading of prostatic adenocarcinoma among general pathologists. Indian J Cancer 2011;48:488–95.

50. Allsbrook WC, Mangold KA, Johnson MH, et al. Interobserver reproducibility of Gleason grading of prostatic carcinoma: urologic pathologists. Hum Pathol 2001;32:74–80.

51. Netto GJ, Eisenberger M, Epstein JI. Interobserver variability in histologic evaluation of radical prostatectomy between central and local pathologists: Findings of TAX 3501 multinational clinical trial. Urology 2011;77:1155–60.

52. Berney DM, Algaba F, Camparo P, et al. The reasons behind variation in Gleason grading of prostatic biopsies: areas of agreement and misconception among 266 European pathologists. Histopathology 2014;64:405–11.

53. Egevad L, Ahmad AS, Algaba F, et al. Standardization of Gleason grading among 337 European pathologists. Histopathology 2013;62:247–56.

54. Kweldam CF, Nieboer D, Algaba F, et al. Gleason grade 4 prostate adenocarcinoma patterns: an interobserver agreement study among genitourinary pathologists. Histopathology 2016;69:441–9.

55. Ryu HS, Jin MS, Park JH, et al. Automated Gleason scoring and tumor quantification in prostate core needle biopsy images using deep neural networks and its comparison with pathologist-based assessment. Cancers (Basel) 2019;11:1860.

56. Lucas M, Jansen I, Savci-Heijink CD, et al. Deep learning for automatic Gleason pattern classification for grade group determination of prostate biopsies. Virchows Arch. 2019;47:77–83.

57. Kott O, Linsley D, Amin A, et al. Development of a deep learning algorithm for the histopathologic diagnosis and Gleason grading of prostate cancer biopsies: a pilot study. Eur Urol Focus 2021;7:347–51.

58. Epstein JI, Zelefsky MJ, Sjoberg DD, et al. A contemporary prostate cancer grading system: a validated alternative to the Gleason score. Eur Urol 2016;69:428–35.

59. Epstein JI, Egevad L, Amin MB, et al. The 2014 international society of urological pathology (ISUP) consensus conference on Gleason grading of prostatic carcinoma definition of grading patterns and proposal for a new grading system. Am J Surg Pathol 2016;40:244–52.

60. Georgescu I, Gooding RJ, Doiron RC, et al. Molecular characterization of Gleason patterns 3 and 4 prostate cancer using reverse Warburg effect associated genes. Cancer Metab 2016;4:8.

61. Sowalsky AG, Kissick HT, Gerrin SJ, et al. Gleason score 7 prostate cancers emerge through branched evolution of clonal Gleason pattern 3 and 4. Clin Cancer Res 2017;23:3823–33.

62. Lavery HJ, Droller MJ. Do Gleason patterns 3 and 4 prostate cancer represent separate disease states? J Urol 2012;188:1667–75.

63. Sweat SD, Bergstralh EJ, Slezak J, et al. Competing risk analysis after radical prostatectomy for clinically nonmetastatic prostate adenocarcinoma according to clinical Gleason score and patient age. J Urol 2002;168:525–9.

64. Traxer O, Gettman MT, Napper CA, et al. Prognostic factors for survival of patients with pathological Gleason score 7 prostate cancer: differences in outcome between primary Gleason grades 3 and 4. J Urol 2001;166:1692–7.

65. Chan TY, Partin AW, Walsh PC, et al. Prognostic significance of Gleason score 3+4 versus Gleason score 4+3 tumor at radical prostatectomy. Urology 2000;56:823–7.

66. Tan N, Margolis DJA, McClure TD, et al. Radical prostatectomy: value of prostate MRI in surgical planning. Abdom Imaging 2012;37:664–74.

67. Marenco J, Orczyk C, Collins T, et al. Role of MRI in planning radical prostatectomy: what is the added value? World J Urol 2019;37:1289–92.

68. Kilcoyne A, Price MC, McDermott S, et al. Imaging on nodal staging of prostate cancer. Future Oncol 2017;13:551–65.

69. Hernandez DJ, Nielsen ME, Han M, et al. Contemporary evaluation of the D'Amico risk classification of prostate cancer. Urology 2007;70:931–5.

70. Brajtbord JS, Leapman MS, Cooperberg MR. The CAPRA score at 10 Years: contemporary perspectives and analysis of supporting studies. Eur Urol 2017;71:705–9.

71. Mohler J, Bahnson RR, Boston B, et al. NCCN clinical practice guidelines in oncology: prostate cancer. J Natl Compr Canc Netw 2010;8:162–200.

72. Watanabe H. History of transrectal ultrasound (TRUS). Ultrasound Med Biol 2017;43(supplement 1):S207.

73. Morozov A, Kozlov V, Rivas JG, et al. A systematic review and meta-analysis of Histoscanning™ in prostate cancer diagnostics. World J Urol 2021;39:3733–40.

74. Damadian R. Tumor detection by nuclear magnetic resonance. Science 1971;171:1151–3.

75. Steyn JH, Smith FW. Nuclear magnetic resonance imaging of the prostate. Br J Urol 1982;54:726–72.

76. Smith CP, Harmon SA, Barrett T, et al. Intra- and inter-reader reproducibility of PI-RADSv2: a multireader study. J Magn Reson Imaging 2019;49:1694–703.

77. Padhani AR, Barentsz J, Villeirs G, et al. PI-RADS steering committee: the PI-RADS multiparametric MRI and MRI-directed biopsy pathway. Radiology 2019;292:464–74.

78. Weinreb JC, Barentsz JO, Choyke PL, et al. PI-RADS Prostate imaging - reporting and data system: 2015, version 2. Eur Urol 2016;69:16–40.

79. Park KJ, Choi SH, Lee JS, et al. Inter-reader agreement in prostate imaging reporting and data system version 2 for prostate cancer: a systematic review and meta-analysis. J Urol 2020;204:661–70.

80. Muller BG, Shih JH, Sankineni S, et al. Prostate cancer: interobserver agreement and accuracy with the revised prostate imaging reporting and data system at multiparametric mr imaging. Radiology 2015;277:741–50.

81. Asvadi NH, Afshari Mirak S, Mohammadian Bajgiran A, et al. 3T multiparametric MR imaging, PIRADSv2-based detection of index prostate cancer lesions in the transition zone and the peripheral zone using whole mount histopathology as reference standard. Abdom Radiol 2018;43:3117–24.

82. Rosenkrantz AB, Ginocchio LA, Cornfeld D, et al. Interobserver reproducibility of the PI-RADS version 2 lexicon: a multicenter study of six experienced prostate radiologists. Radiology 2016;280:793–804.

83. Zawaideh JP, Sala E, Pantelidou M, et al. Comparison of Likert and PI-RADS version 2 MRI scoring systems for the detection of clinically significant prostate cancer. Br J Radiol 2020;93:20200298.

84. Zanatta A, Zampieri F, Basso C, et al. Galileo Galilei: science vs. faith. Glob Cardiol Sci 2017;2:10.

85. Hallyn F. Metaphor and analogy in the sciences. Volume 1 of origins: studies in the sources of scientific creativity. Dordrecht: Springer Science & Business Media; 2013, p.90.

86. Sternbach G, Varon J. Wilhelm Konrad Roentgen: a new kind of rays. Journal Emerg 1993;11:743–5.

87. Carter JV, Pan J, Rai SN, et al. ROC-ing along: Evaluation and interpretation of receiver operating characteristic curves. Surgery 2016;159:1638–45.

88. Reid JS, Wang CHT, Thompson JMT. James Clerk Maxwell 150 years on. Philos Trans R Soc A 2008;366:1651–9.

89. Blanchard Y. Une histoire du radar en lien avec les mutations du système technique. REE 2019;2:35–46.

90. Galati G. 100 years of radar. Cham: Springer; 2015, p.88.

91. Vreemann S, Gubern-Merida A, Lardenoije S, et al. The frequency of missed breast cancers in women participating in a high-risk MRI screening program. Breast Cancer Res Treat 2018;169:323–31.

92. Korhonen KE, Zuckerman SP, Weinstein SP, et al. Breast MRI: False-negative results and missed opportunities. Radiographics 2021;41:645–64.

93. Yamaguchi K, Schacht D, Newstead GM, et al. Breast cancer detected on an incident (second or subsequent) round of screening MRI: MRI features of false-negative cases. AJR Am J Roentgenol 2013;201:1155–63.

94. Kim YE, Cha JH, Kim HH, et al. Analysis of false-negative findings of breast cancer on previous magnetic resonance imaging. Acta Radiol 2021;62:722–34.

95. Maxwell AJ, Lim YY, Hurley E, et al. False-negative MRI breast screening in high-risk women. Clin Radiol 2017;72:207–16.

96. Choi D, Mitchell DG, Verma SK, et al. Hepatocellular carcinoma with indeterminate or false-negative findings at initial MR imaging: effect on eligibility for curative treatment initial observations. Radiology 2007;244:776–83.

97. Karadeniz-Bilgili MY, Braga L, Birchard KR, et al. Hepatocellular carcinoma missed on gadolinium enhanced MR imaging, discovered in liver explants: retrospective evaluation. J Magn Reson Imaging 2006;23:210–5.

98. Borofsky S, George AK, Gaur S, et al. What are we missing? False-negative cancers at multiparametric MR imaging of the prostate. Radiology 2018;286:186–95.

99. Chatterjee A, Watson G, Myint E, et al. Changes in epithelium, stroma, and lumen space correlate more strongly with Gleason pattern and are stronger predictors of prostate ADC changes than cellularity metrics. Radiology 2015;277:751–62.

100. Kwak JT, Sankineni S, Xu S, et al. Prostate cancer: a correlative study of multiparametric MR imaging and digital histopathology. Radiology 2017;285:147–56.

101. Tonttila PP, Ahtikoski A, Kuisma M, et al. Multiparametric MRI prior to radical prostatectomy identifies intraductal and cribriform growth patterns in prostate cancer. BJU Int 2019;124:992–8.

102. El-Shater Bosaily A, Parker C, Brown LC, et al. PROMIS—Prostate MR imaging study: a paired validating cohort study evaluating the role of multi-parametric MRI in men with clinical suspicion of prostate cancer. Contemp Clin Trials 2015;42:26–40.

103. Stark JR, Perner S, Stampfer MJ, et al. Gleason score and lethal prostate cancer: does 3 + 4 = 4 + 3? J Clin Oncol 2009;27:3459–64.

104. Kepner G, Kepner J. Transperineal biopsy: analysis of a uniform core sampling pattern that yields data on tumor volume limits in negative biopsies. Theor Biol Med Model 2010;7:23.

105. Wolters T, Roobol MJ, van Leeuwen PJ, et al. A critical analysis of the tumor volume threshold for clinically insignificant prostate cancer using a dataset of a randomized screening trial. J Urol 2011;185:121–5.

106. Stamey TA, Freiha FS, McNeal JE, et al. Localized prostate cancer. Relationship of tumor volume to clinical significance for treatment of prostate cancer. Cancer 1993;71(3 Suppl.):933–8.

107. Ahmed HU, Hu Y, Carter T, et al. Characterizing clinically significant prostate cancer using template prostate mapping biopsy. J Urol 2011;186:458–64.

108. Wysock JS, Mendhiratta N, Zattoni F, et al. Predictive value of negative 3T multiparametric magnetic resonance imaging of the prostate on 12-core biopsy results. BJU Int 2016;118:515–20.

109. Tsivian M, Gupta RT, Tsivian E, et al. Assessing clinically significant prostate cancer: diagnostic properties of multiparametric magnetic resonance imaging compared to three-dimensional transperineal template mapping histopathology. Int J Urol 2017;24:137–43.

110. Mortezavi A, Märzendorfer O, Donati OF, et al. Diagnostic accuracy of multiparametric magnetic resonance imaging and fusion guided targeted biopsy evaluated by transperineal template saturation prostate biopsy for the detection and characterization of prostate cancer. J Urol 2018;200:309–18.

111. Thompson JE, van Leeuwen PJ, Moses D, et al. The diagnostic performance of multiparametric magnetic resonance imaging to detect significant prostate cancer. J Urol 2016;195:1428–35.

112. Pagniez MA, Kasivisvanathan V, Puech P, et al. Predictive factors of missed clinically significant prostate cancers in men with negative MRI: a systematic review and meta-analysis. J Urol 2020;204:24–32.

113. Epstein JI, Walsh PC, Carmichael M, et al. Pathologic and clinical findings to predict tumor extent of nonpalpable (stage t1c) prostate cancer. JAMA 1994;271:368–74.

114. Bill-Axelson A, Holmberg L, Garmo H, et al. Radical prostatectomy or watchful waiting in prostate cancer - 29-year follow-up. N Engl J Med 2018;379:2319–29.

115. Truong M, Feng C, Hollenberg G, et al. A comprehensive analysis of cribriform morphology on magnetic resonance imaging/ultrasound fusion biopsy correlated with radical prostatectomy specimens. J Urol 2018;199:106–13.

116. Schieda N, Coffey N, Gulavita P, et al. Prostatic ductal adenocarcinoma: an aggressive tumour variant unrecognized on T2 weighted magnetic resonance imaging (MRI). Eur Radiol 2014;24:1349–56

117. Simmons LAM, Kanthabalan A, Arya M, et al. The PICTURE study: diagnostic accuracy of multiparametric MRI in men requiring a repeat prostate biopsy. Br J Cancer 2017;116:1159–65.

118. Rouvière O, Puech P, Renard-Penna R, 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 Oncol 2019;20:100–9.

119. van der Leest M, Cornel E, Israël B, et al. Head-to-head comparison of transrectal ultrasound-guided prostate biopsy versus multiparametric prostate resonance imaging with subsequent magnetic resonance-guided biopsy in biopsy-naïve men with elevated prostate-specific antigen: a large prospective multicenter clinical study. Eur Urol 2019;75:570–8.

120. Dasgupta P, Davis J, Hughes S. NICE guidelines on prostate cancer 2019. BJU Int 2019;124:1.

121. Mottet N, van den Bergh RCN, Briers E, et al. EAU-EANM-ESTRO-ESUR-SIOG guidelines on prostate cancer—2020 update. Part 1: screening, diagnosis, and local treatment with curative intent. Eur Urol 2021;79:243–62.

122. Norris JM, Carmona Echeverria LM, et al. What type of prostate cancer is systematically overlooked by multiparametric magnetic resonance imaging? An analysis from the PROMIS cohort. Eur Urol 2020;78:163–70.

123. Abd-Alazeez M, Ahmed HU, Arya M, et al. The accuracy of multiparametric MRI in men with negative biopsy and elevated PSA level—can it rule out clinically significant prostate cancer? Urol Oncol 2014;32:45.e17–22.

124. Norris JM, Simpson BS, Parry MA, et al. Genetic landscape of prostate cancer conspicuity on multiparametric magnetic resonance imaging: a systematic review and bioinformatic analysis. Eur Urol Open Sci 2020;20:37–47.

125. Buisset J, Norris JM, Puech P, et al. Negative pre-biopsy magnetic resonance imaging and risk of significant prostate cancer: baseline and long-term follow-up results. J Urol 2021;205:725–31.

126. Norris JM, Kasivisvanathan V, Whitaker HC, et al. Investigating men's perceptions on the use of multiparametric MRI for the diagnosis of prostate cancer. Eur J Surg Oncol 2020;45:2203.

127. Schoots IG. Omission of systematic transrectal ultrasound guided biopsy from the MRI targeted approach in men with previous negative prostate biopsy might still be premature. Ann Transl Med 2016;4:205.

128. Salami SS, Ben-Levi E, Yaskiv O, et al. In patients with a previous negative prostate biopsy and a suspicious lesion on magnetic resonance imaging, is a 12-core biopsy still necessary in addition to a targeted biopsy? BJU Int 2015;115:562–70.

129. Mendhiratta N, Meng X, Rosenkrantz AB, et al. Prebiopsy MRI and MRI-ultrasound fusion-targeted prostate biopsy in men with previous negative biopsies: impact on repeat biopsy strategies. Urology 2015;86:1192–8.

130. Alanee S, Deebajah M, Taneja K, et al. Post prostatectomy pathologic findings of patients with clinically significant prostate cancer and no significant PI-RADS lesions on preoperative magnetic resonance imaging. Urology 2020;146:183–8.

131. Norris JM, Allen C, Ball R, et al. Prostate cancer undetected by mpMRI: tumor conspicuity is reliant upon optimal scan timing and quality. Urology 2021;148:316–7.

132. Simmons LAM, Ahmed HU, Moore CM, et al. The PICTURE study—prostate imaging (multiparametric MRI and prostate HistoScanning) compared to transperineal ultrasound guided biopsy for significant prostate cancer risk evaluation. Contemp Clin Trials 2014;37:69–83.

133. Simmons LAM, Kanthabalan A, Arya M, et al. Accuracy of transperineal targeted prostate biopsies, visual estimation and image fusion in men needing repeat biopsy in the PICTURE trial. J Urol 2018;200:1227–34.

134. Simmons LAM, Kanthabalan A, Arya M, et al. Prostate imaging compared to transperineal ultrasound-guided biopsy for significant prostate cancer risk evaluation (PICTURE): a prospective cohort validating study assessing prostate HistoScanning. Prostate Cancer Prostat Dis 2019;22:261–7.

135. Arsov C, Quentin M, Rabenalt R, et al. Repeat transrectal ultrasound biopsies with additional targeted cores according to results of functional prostate MRI detects high-risk prostate cancer in patients with previous negative biopsy and increased PSA - a pilot study. Anticancer Res 2012;32:1087–92.

136. Miah S, Eldred-Evans D, Simmons LAM, et al. Patient reported outcome measures for transperineal template prostate mapping biopsies in the PICTURE study. J Urol 2018;200:1235–40.

137. Norris JM, Simpson BS, Parry MA, et al. Genetic correlates of prostate cancer visibility (and invisibility) on multiparametric magnetic resonance imaging: it's time to take stock. BJU Int 2020;125:340–2.

138. Norris JM, Carmona Echeverria LM, Simpson BS, et al. Prostate cancer visibility on multiparametric magnetic resonance imaging: high Gleason grade and increased tumour volume are not the only important histopathological features. BJU Int 2020;126:237–9.

139. Norris JM, Carmona Echeverria LM, Simpson BS, et al. Conspicuity of cribriform prostate cancer on multiparametric magnetic resonance imaging: the jury is still out. BJU Int 2021;127:169–70.

140. Norris JM, Carmona Echeverria LM, Simpson BS, et al. Histopathological basis of prostate cancer conspicuity on multiparametric magnetic resonance imaging: a systematic review and meta-analysis. Eur J Surg Oncol 2020;47:e25.

141. Buisset J, Norris JM, Puech P, et al. Negative pre-biopsy magnetic resonance imaging and risk of significant prostate cancer: baseline and long-term follow-up results. J Urol 2021;205:725–31.

142. Stabile A, Mazzone E, Cirulli GO, et al. Association between multiparametric magnetic resonance imaging of the prostate and oncological outcomes after primary treatment for prostate cancer: a systematic review and meta-analysis. Eur Urol Oncol 2020, 28:S2588-9311.

143. Stavrinides V, Giganti F, Trock B, et al. Five-year outcomes of magnetic resonance imaging-based active surveillance for prostate cancer: a large cohort study. Eur Urol 2020;78:443–51.

144. Callender T, Emberton M, Morris S, et al. Benefit, harm, and cost-effectiveness associated with magnetic resonance imaging before biopsy in age-based and risk-stratified screening for prostate cancer. JAMA Netw Open 2021;4:e2037657.

145. Norris JM, Simpson BS, Freeman A, et al. Conspicuity of prostate cancer on multiparametric magnetic resonance imaging: A cross-disciplinary translational hypothesis. FASEB J 2020;34:14150–9.

146. Barth BK, Cornelius A, Nanz D, et al. Comparison of image quality and patient discomfort in prostate MRI: pelvic phased array coil vs. endorectal coil. Abdom Radiol (NY) 2016;41:2218–26.

147. Sherrer RL, Glaser ZA, Gordetsky JB, et al. Comparison of biparametric MRI to full multiparametric MRI for detection of clinically significant prostate cancer. Prostate Cancer Prostatic Dis 2019;22:331–6.

148. Serrao EM, Barrett T, Wadhwa K, et al. Investigating the ability of multiparametric MRI to exclude significant prostate cancer prior to transperineal biopsy. Can Urol Assoc J 2015;9:E853–8.

149. De Visschere P, Pattyn E, Ost P, et al. Comparison of the prostate imaging reporting and data system (PI-RADS) version 1 and 2 in a cohort of 245 patients with histopathological reference and long-term follow-up. J Belg Soc Radiol 2016;100:108.

150. Akin O, Riedl CC, Ishill NM, et al. Interactive dedicated training curriculum improves accuracy in the interpretation of MR imaging of prostate cancer. Eur Radiol 2010;20:995–1002.

151. Purysko AS, Bittencourt LK, Bullen JA, et al. Accuracy and interobserver agreement for prostate imaging reporting and data System, version 2, for the characterization of lesions identified on multiparametric MRI of the prostate. AJR Am J Roentgenol 2017;209:339–49.

152. Giganti F, Allen C, Emberton M, et al. Prostate imaging quality (PI-QUAL): a new quality control scoring system for multiparametric magnetic resonance imaging of the prostate from the PRECISION trial. Eur Urol Oncol 2020;3:615–9.

153. Giganti F, Dinneen E, Kasivisvanathan V, et al. Inter-reader agreement of the PI-QUAL score for prostate MRI quality in the NeuroSAFE PROOF trial. Eur Radiol 2021 Jul 29.

154. Giganti F, Kasivisvanathan V, Kirkham A, et al. Prostate MRI quality: a critical review of the last 5 years and the role of the PI-QUAL score. Br J Radiol 2021:20210415.

155. Giganti F, Kirkham A, Kasivisvanathan V, et al. Understanding PI-QUAL for prostate MRI quality: a practical primer for radiologists. Insights Imaging 2021;12:59.

156. Boschheidgen M, Ullrich T, Blondin D, et al. Comparison and prediction of artefact severity due to total hip replacement in 1.5 T versus 3 T MRI of the prostate. Eur J Radiol 2021;144:109949.

157. Fraser M, Sabelnykova VY, Yamaguchi TN, et al. Genomic hallmarks of localized, non-indolent prostate cancer. Nature 2017;541:359–64.

158. Norris JM, Simpson BS, Parry MA, et al. Genetic landscape of prostate cancer conspicuity on multiparametric MRI: a protocol for a systematic review and bioinformatic analysis. BMJ Open 2020;10:e034611.

159. Leyten GH, Wierenga EA, Sedelaar JP, et al. Value of PCA3 to predict biopsy outcome and its potential role in selecting patients for multiparametric MRI. Int J Mol Sci 2013;14:11347–55.

160. De Luca S, Passera R, Cattaneo G, et al. High prostate cancer gene 3 (PCA3) scores are associated with elevated Prostate Imaging Reporting and Data System (PI-RADS) grade and biopsy Gleason score, at magnetic resonance imaging/ultrasonography fusion software-based targeted prostate biopsy after a previous negative standard biopsy. BJU Int 2016;118:723–30.

161. Kaufmann S, Bedke J, Gatidis S, et al. Prostate cancer gene 3 (PCA3) is of additional predictive value in patients with PI-RADS grade III (intermediate) lesions in the MR-guided re-biopsy setting for prostate cancer. World J Urol 2016;34:509–15.

162. Busetto GM, De Berardinis E, Sciarra A, et al. Prostate cancer gene 3 and multiparametric magnetic resonance can reduce unnecessary biopsies: decision curve analysis to evaluate predictive models. Urology 2013;82:1355–60.

163. Fenstermaker M, Mendhiratta N, Bjurlin MA, et al. Risk stratification by urinary prostate cancer gene 3 testing before magnetic resonance imaging-ultrasound fusion-targeted prostate biopsy among men with no history of biopsy. Urology 2017;99:174–9.

164. Gronberg H, Eklund M, Picker W, et al. Prostate cancer diagnostics using a combination of the Stockholm3 blood test and multiparametric magnetic resonance imaging. Eur Urol 2018;74:722–8.

165. Leapman MS, Westphalen AC, Ameli N, et al. Association between a 17-gene genomic prostate score and multiparametric prostate MRI in men with low and intermediate risk prostate cancer (PCa). PLoS One 2017;12:e0185535.

166. Salmasi A, Said J, Shindel AW, et al. A 17-gene genomic prostate score assay provides independent information on adverse pathology in the setting of combined multiparametric magnetic resonance imaging fusion targeted and systematic prostate biopsy. J Urol 2018;200:564–72.

167. Kornberg Z, Cowan JE, Westphalen AC, et al. Genomic prostate score, PI-RADS version 2 and progression in men with prostate cancer on active surveillance. J Urol 2019;201:300–7.

168. Dalela D, Loppenberg B, Sood A, et al. Contemporary role of the Decipher test in prostate cancer management: current practice and future perspectives. Rev Urol 2016;18:1–9.

169. Beksac AT, Cumarasamy S, Falagario U, et al. Multiparametric magnetic resonance imaging features identify aggressive prostate cancer at the phenotypic and transcriptomic level. J Urol 2018;200:1241–9.

170. Martin DT, Ghabili K, Levi A, et al. Prostate cancer genomic classifier relates more strongly to Gleason grade group than prostate imaging reporting and data system score in multiparametric prostate magnetic resonance imaging-ultrasound fusion targeted biopsies. Urology 2019;125:64–72.

171. Purysko AS, Magi-Galluzzi C, Mian OY, et al. Correlation between MRI phenotypes and a genomic classifier of prostate cancer: preliminary findings. Eur Radiol 2019;29:4861–70.

172. Radtke JP, Takhar M, Bonekamp D, et al. Transcriptome wide analysis of magnetic resonance imaging-targeted biopsy and matching surgical specimens from high-risk prostate cancer patients treated with radical prostatectomy: the target must be hit. Eur Urol Focus 2018;4:540–6.

173. Parry MA, Srivastava S, Ali A, et al. Genomic evaluation of multiparametric magnetic resonance imaging-visible and -nonvisible lesions in clinically localised prostate cancer. Eur Urol Oncol 2019;2:1–11.

174. Falagario UG, Beksac AT, Martini A, et al. Defining prostate cancer at favorable intermediate risk: the potential utility of magnetic resonance imaging and genomic tests. J Urol 2019;202:102–7.

175. Zhang X, Cui J, Wang W, et al. A study for texture feature extraction of high-resolution satellite images based on a direction measure and gray level co-occurrence matrix fusion algorithm. Sensors (Basel) 2017;17:1474.

176. Renard-Penna R, Cancel-Tassin G, Comperat E, et al. Multiparametric magnetic resonance imaging predicts postoperative pathology but misses aggressive prostate cancers as assessed by cell cycle progression score. J Urol 2015;194:1617–23.

177. Wibmer AG, Robertson NL, Hricak H, et al. Extracapsular extension on MRI indicates a more aggressive cell cycle progression genotype of prostate cancer. Abdom Radiol (NY) 2019;44:2864–73.

178. Li P, You S, Nguyen C, et al. Genes involved in prostate cancer progression determine MRI visibility. Theranostics 2018;8:1752–65.

179. Dulaney CR, Rais-Bahrami S, Manna DD, et al. DNA repair deregulation in discrete prostate cancer lesions identified on multi-parametric MRI and targeted by MRI/ultrasound fusion-guided biopsy. Oncotarget 2017;8:68038–46.

180. Hanahan D, Weinberg RA. Hallmarks of cancer: the next generation. Cell 2011;144:646–74.

181. Stoyanova R, Pollack A, Takhar M, et al. Association of multiparametric MRI quantitative imaging features with prostate cancer gene expression in MRI-targeted prostate biopsies. Oncotarget 2016;7:53362–76.

182. Hectors SJ, Cherny M, Yadav KK, et al. Radiomics features measured with multiparametric magnetic resonance imaging predict prostate cancer aggressiveness. J Urol 2019;202:498–505.

183. Mateo J, Boysen G, Barbieri CE, et al. DNA repair in prostate cancer: biology and clinical implications. Eur Urol 2017;71:417–25.

184. Kesch C, Radtke JP, Wintsche A, et al. Correlation between genomic index lesions and mpMRI and (68)Ga-PSMA-PET/CT imaging features in primary prostate cancer. Sci Rep 2018;8:16708.

185. Bristow RG, Hill RP. Hypoxia and metabolism. Hypoxia, DNA repair and genetic instability. Nat Rev Cancer 2008;8:180–92.

186. Sun Y, Williams S, Byrne D, et al. Association analysis between quantitative MRI features and hypoxia-related genetic profiles in prostate cancer: a pilot study. Br J Radiol 2019;92:20190373.

187. Jamshidi N, Margolis DJ, Raman S, et al. Multiregional radiogenomic assessment of prostate microenvironments with multiparametric MR imaging and DNA whole-exome sequencing of prostate glands with adenocarcinoma. Radiology 2017;284:109–19.

188. Salami SS, Kaplan JB, Nallandhighal S, et al. Biologic significance of magnetic resonance imaging invisibility in localized prostate cancer. JCO Precis Oncol 2019;3:1–12.

189. Baumgartner E, Del Carmen Rodriguez Pena M, Eich ML, et al. PTEN and ERG detection in multiparametric magnetic resonance imaging/ultrasound fusion targeted prostate biopsy compared to systematic biopsy. Hum Pathol 2019;90:20–6.

190. Krohn A, Diedler T, Burkhardt L, et al. Genomic deletion of PTEN is associated with tumor progression and early PSA recurrence in ERG fusion-positive and fusion-negative prostate cancer. Am J Pathol 2012;181:401–12.

191. Troyer DA, Jamaspishvili T, Wei W, et al. A multicenter study shows PTEN deletion is strongly associated with seminal vesicle involvement and extracapsular extension in localized prostate cancer. Prostate 2015;75:1206–15.

192. Feilotter HE, Nagai MA, Boag AH, et al. Analysis of PTEN and the 10q23 region in primary prostate carcinomas. Oncogene 1998;16:1743–8.

193. Gordetsky JB, Thomas JV, Nix JW, et al. Higher prostate cancer grade groups are detected in patients undergoing multiparametric MRI-targeted biopsy compared with standard biopsy. Am J Surg Pathol 2017;41:101–5.

194. Yarlagadda VK, Lai WS, Gordetsky JB, et al. MRI/US fusion-guided prostate biopsy allows for equivalent cancer detection with significantly fewer needle cores in biopsy-naive men. Diagn Interv Radiol 2018;24:115–20.

195. Switlyk MD, Salberg UB, Geier OM, et al. PTEN expression in prostate cancer: relationship with clinicopathologic features and multiparametric MRI findings. AJR Am J Roentgenol 2019;212:1206–14.

196. McCann SM, Jiang Y, Fan X, et al. Quantitative multiparametric MRI features and PTEN expression of peripheral zone prostate cancer: a pilot study. AJR Am J Roentgenol 2016;206:559–65.

197. Lee D, Fontugne J, Gumpeni N, et al. Molecular alterations in prostate cancer and association with MRI features. Prostate Cancer Prostatic Dis 2017;20:430–5.

198. Lenkinski RE, Bloch BN, Liu F, et al. An illustration of the potential for mapping MRI/MRS parameters with genetic over-expression profiles in human prostate cancer. MAGMA 2008;21:411–21.

199. Palapattu GS, Salami SS, Cani AK, et al. Molecular profiling to determine clonality of serial magnetic resonance imaging/ultrasound fusion biopsies from men on active surveillance for low-risk prostate cancer. Clin Cancer Res 2017;23:985–91.

200. De Visschere PJ, Naesens L, Libbrecht L, et al. What kind of prostate cancers do we miss on multiparametric magnetic resonance imaging? Eur Radiol 2016;26:1098–107.

201. Rodriguez-Blanco G, Zeneyedpour L, Duijvesz D, et al. Tissue proteomics outlines AGR2 AND LOX5 as markers for biochemical recurrence of prostate cancer. Oncotarget 2018;9:36444–56.

202. Kani K, Malihi PD, Jiang Y, et al. Anterior gradient 2 (AGR2): blood based biomarker elevated in metastatic prostate cancer associated with the neuroendocrine phenotype. Prostate 2013;73:306–15.

203. Husaini Y, Qiu MR, Lockwood GP, et al. Macrophage inhibitory cytokine1 (MIC-1/GDF15) slows cancer development but increases metastases in TRAMP prostate cancer prone mice. PLoS One 2012;7:e43833.

204. Wang W, Yang X, Dai J, et al. Prostate cancer promotes a vicious cycle of bone metastasis progression through inducing osteocytes to secrete GDF15 that stimulates prostate cancer growth and invasion. Oncogene 2019;38:4540–59.

205. Shoag JE, Tosoian JJ, Salami SS, et al. Unraveling prostate cancer genomics, pathology, and magnetic resonance imaging visibility. Eur Urol 2019;76:24–6.

206. Loeb S, Bjurlin MA, Nicholson J, et al. Overdiagnosis and overtreatment of prostate cancer. Eur Urol 2014;65:1046–55.

207. Ukimura O, Coleman JA, De la Taille A, et al. Contemporary role of systematic prostate biopsies: indications, techniques, and implications for patient care. Eur Urol 2013;63:214–30.

208. Hamdy FC, Donovan JL, Lane JA, et al. 10-year outcomes after monitoring, surgery, or radiotherapy for localized prostate cancer. N Engl J Med 2016;375:1415–24.

209. Skouteris VM, Crawford ED, Mouraviev V, et al. Transrectal ultrasound-guided versus transperineal mapping prostate biopsy: complication comparison. Rev Urol 2018;20:19–25.

210. Wade J, Rosario DJ, Macefield RC, et al. Psychological impact of prostate biopsy: physical symptoms, anxiety, and depression. J Clin Oncol 2013;3:4235–41.

211. Tooker GM, Truong H, Pinto PA, et al. National survey of patterns employing targeted MRI/US guided prostate biopsy in the diagnosis and staging of prostate cancer. Curr Urol 2018;12:97–103.

212. Bukavina L, Tilburt JC, Konety B, et al. Perceptions of prostate MRI and fusion biopsy of radiation oncologists and urologists for patients diagnosed with prostate cancer: results from a national survey. Eur Urol Focus 2020;6:273–9.

213. Manley BJ, Brockman JA, Raup VT, et al. Prostate MRI: a national survey of urologist's attitudes and perceptions. Int Braz J Urol 2016;42:464–71.

214. Ullrich T, Schimmöller L, Oymanns M, et al. Current utilization and acceptance of multiparametric MRI in the diagnosis of prostate cancer. A regional survey. Rofo 2018;190:419–26.

215. Tallon D, Chard J, Dieppe P. Relation between agendas of the research community and the research consumer. Lancet 2000;355:2037–40.

216. Rossi SH, Fielding A, Blick C, et al. Setting research priorities in partnership with patients to provide patient-centred urological cancer care. Eur Urol 2019;75:891–3.

217. Grummet JP, Weerakoon M, Huang S, et al. Sepsis and 'superbugs': should we favour the transperineal over the transrectal approach for prostate biopsy? BJU Int 2014;114:384–8.

218. O'Brien BC, Harris IB, Beckman TJ, et al. Standards for reporting qualitative research: a synthesis of recommendations. Acad Med 2014;89:1245–51.

219. Kazer MW, Bailey DE, Chipman J, et al. Uncertainty and perception of danger among patients undergoing treatment for prostate cancer. BJU Int 2013;111:E84–91.

220. Sakpal TV. Sample size estimation in clinical trial. Perspect Clin Res 2010;1:67–9.

221. Schönenberger E, Schnapau D, Teige F, et al. Patient acceptance of noninvasive and invasive coronary angiography. PLoS ONE 2007;2:e246.

222. Braun V, Clarke V. Using thematic analysis in psychology. Qual Res Psychol 2006;3:77–101.

223. Pizzoli SFM, Marton G, Pricolo P, et al. Patients' experience with MRI-guided in-bore biopsy versus TRUS-guided biopsy in prostate cancer: a pilot study. Ecancermedicalscience 2020;14:1127.

224. Merriel SWD, Hardy V, Thompson MJ, et al. Patient-centered outcomes from multiparametric MRI and MRI-guided biopsy for prostate cancer: a systematic review. J Am Coll Radiol 2020 Apr;17(4):486–95.

225. Merriel SWD, Archer S, Forster AS, et al. Experiences of 'traditional' and 'one-stop' MRI-based prostate cancer diagnostic pathways in England: a qualitative study with patients and GPs. BMJ Open 2022;12:e054045.

226. Norris JM, Simmons LAM, Kanthabalan A, et al. Which prostate cancers are undetected by multiparametric magnetic resonance imaging in men with previous prostate biopsy? an analysis from the PICTURE study. Eur Urol Open Sci 2021;30:16–24.

227. Melegh Z, Oltean S. Targeting angiogenesis in prostate cancer. Int J Mol Sci 2019;20:2676.

228. van Houdt PJ, Ghobadi G, Schoots IG, et al. Histopathological features of MRI-invisible regions of prostate cancer lesions. J Magn Reson Imaging 2020;51:1235–46.

229. Søndergaard MEJ, Lode K, Husebø SE, et al. Men's perception of information and psychological distress in the diagnostic phase of prostate cancer: a comparative mixed methods study. BMC Nurs 2022;211:266.

230. Callejas MF, Klein EA, Truong M, et al. Detection of clinically significant index prostate cancer using micro-ultrasound: correlation with radical prostatectomy. Urology 2022;169:150–55.

231. Lorusso V, Kabre B, Pignot G, et al. Comparison between micro-ultrasound and multiparametric MRI regarding the correct identification of prostate cancer lesions. Clin Genitourin Cancer 2022;20:e339–45.

232. Donato P, Roberts MJ, Morton A, et al. Improved specificity with 68Ga PSMA PET/CT to detect clinically significant lesions "invisible" on multiparametric MRI of the prostate: a single institution comparative analysis with radical prostatectomy histology. Eur J Nucl Med Mol Imaging 2019;46:20–30.

233. Norris JM, Kasivisvanathan V, Allen C, 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 Protoc 2020;3:26.

234. Morka N, Simpson BS, Emberton M, et al. Re: Giorgio Gandaglia, Guillaume Ploussard, Massimo Valerio, et al. Prognostic implications of multiparametric magnetic resonance imaging and concomitant systematic biopsy in predicting biochemical recurrence after radical prostatectomy in prostate cancer patients diagnosed with magnetic resonance imaging-targeted biopsy. Eur Urol Oncol 2020;7:739–47. Eur Urol Oncol 2021;4:127–8.

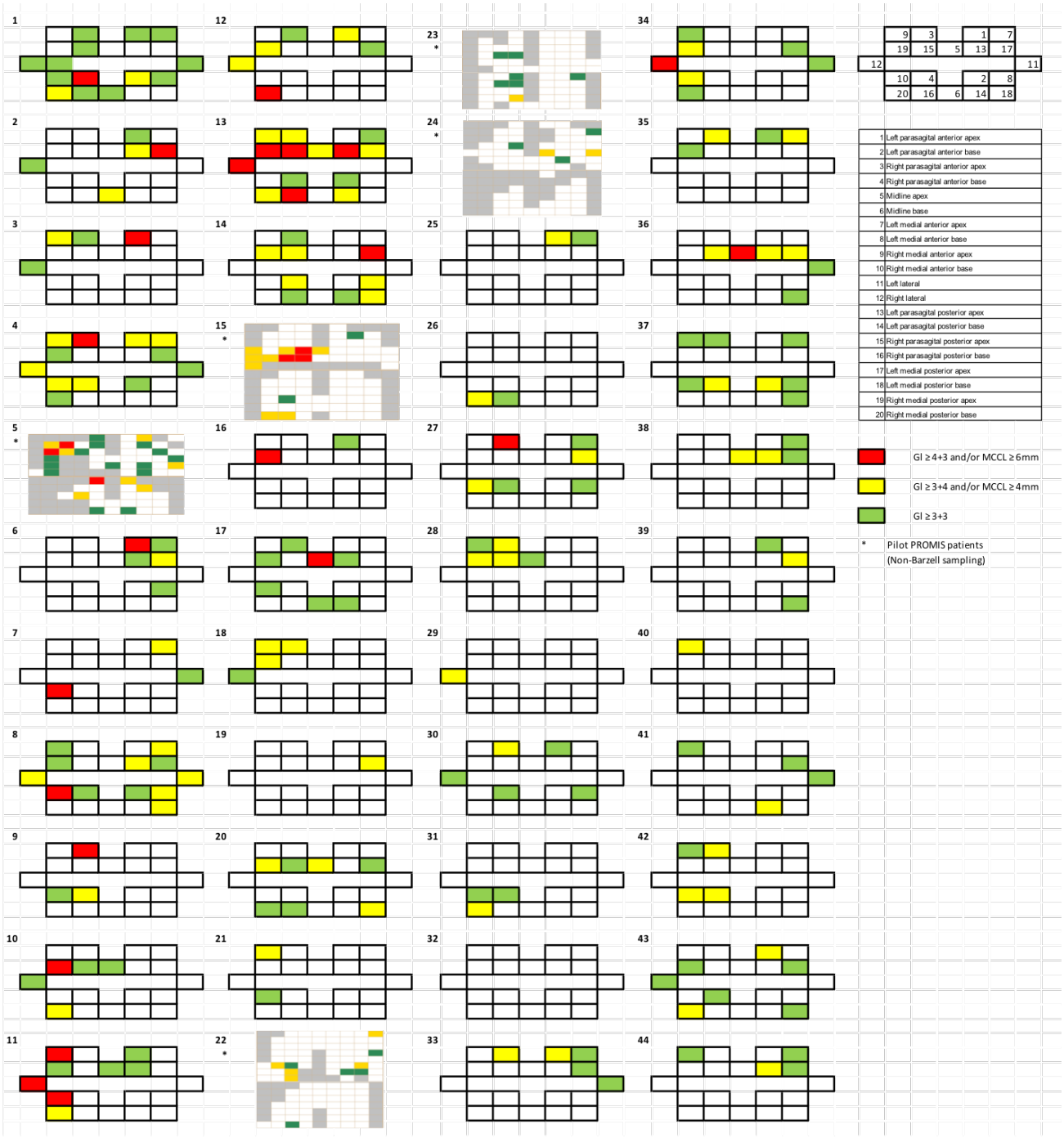
235. Morka N, Simpson BS, Ball R, et al. Clinical outcomes associated with prostate cancer conspicuity on biparametric and multiparametric MRI: a protocol for a systematic review and meta-analysis of biochemical recurrence following radical prostatectomy. BMJ Open 2021;11:e047664.

236. Parry MG, Cowling TE, Sujenthiran A, et al. Identifying skeletal-related events for prostate cancer patients in routinely collected hospital data. Cancer Epidemiol 2019;63:101628.

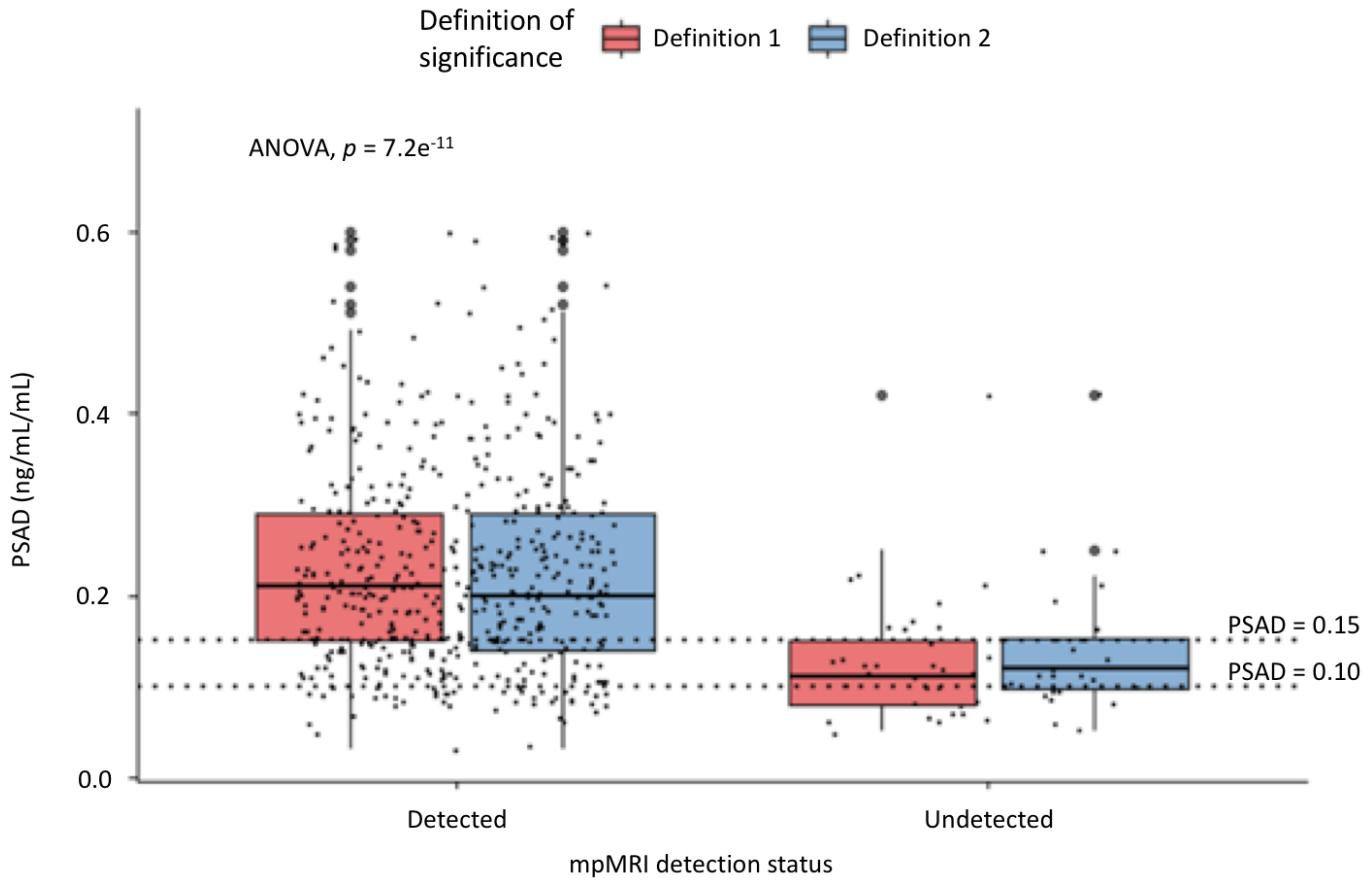
APPENDICES

APPENDICES

Appendix 1: Barzell Maps for Patients with mpMRI-Invisible Cancer in PROMIS



Appendix 2: PSAD for mpMRI-Visible & mpMRI-Invisible Disease in PROMIS



Appendix 3: Characteristics of mpMRI-Invisible Cancer in PROMIS

Patient	Age	PSA	PSAD	Likert	Prostate Vol, mL	Overall GI (TTPM)	Max GI (TTPM)	MCCL, mm (TTPM)	Overall GI (TRUS)	Max GI (TRUS)	MCCL, mm (TRUS)
1	66	4	0.12	1	33	3 + 4	3 + 4	12	3 + 3	3 + 3	2
2	63	5	0.08	2	66	3 + 4	3 + 4	6	3 + 3	3 + 3	7
3	68	5.5	0.12	2	46	3 + 4	3 + 4	6	4 + 3	4 + 3	4
4	68	4.8	0.05	2	89	3 + 4	3 + 4	7	3 + 3	3 + 3	2
5	63	12.7	0.42	2	30	3 + 4	3 + 4	12	3 + 4	3 + 4	11
6	66	4.8	0.15	2	33	3 + 3	3 + 3	8	-	-	-
7	57	3.6	0.1	2	35	3 + 4	3 + 4	12	3 + 3	3 + 3	1
8	73	4.7	0.11	2	41	3 + 4	3 + 4	8	-	-	-
9	59	1.3	0.06	2	21	3 + 4	3 + 4	6	-	-	-
10	64	7.3	0.13	2	55	3 + 4	3 + 4	6	3 + 3	3 + 3	2
11	73	6.8	0.06	2	114	3 + 4	3 + 4	10	3 + 3	3 + 3	3
12	67	8.3	0.16	2	53	3 + 4	3 + 4	6	3 + 3	3 + 3	2
13	54	4.2	0.08	2	50	3 + 4	3 + 4	12	3 + 4	3 + 4	12
14	67	5.7	0.25	2	23	3 + 4	3 + 4	6	3 + 4	3 + 4	10
15	75	6.3	0.09	2	70	3 + 4	3 + 4	9	3 + 4	3 + 4	10
16	72	5.1	0.22	2	23	3 + 4	3 + 4	8	3 + 4	3 + 4	4
17	64	6.8	0.1	2	65	3 + 4	3 + 4	6	3 + 3	3 + 3	3
18	57	7.6	0.11	2	69	3 + 4	3 + 4	3	3 + 4	3 + 4	6
19	61	6.3	0.11	2	58.5	3 + 3	3 + 3	4	3 + 3	3 + 3	2
20	53	2.8	0.12	2	24	3 + 4	3 + 4	4	3 + 3	3 + 3	5
21	74	5.1	0.12	1	43	3 + 4	3 + 4	3	3 + 3	3 + 3	1
22	59	9.5	0.16	2	59	3 + 4	3 + 4	5	3 + 3	3 + 3	2
23	68	4.9	0.13	2	39	3 + 3	3 + 3	4	3 + 3	3 + 3	1
24	63	5.5	0.1	2	54	3 + 4	3 + 4	4	-	-	-
25	66	7.1	0.09	2	83	3 + 3	3 + 3	4	-	-	-
26	67	4.1	0.06	2	70	3 + 4	3 + 4	4	-	-	-
27	51	7	0.21	2	34	3 + 4	4 + 3	5	3 + 3	3 + 3	4
28	52	6.5	0.12	2	53	3 + 4	3 + 4	4	3 + 3	3 + 3	5
29	58	4.4	0.11	2	41	3 + 4	3 + 4	1	-	-	-
30	53	3.9	0.14	2	27	3 + 4	3 + 4	5	-	-	-
31	56	10	0.17	2	60	3 + 4	3 + 4	2	-	-	-
32	57	5.4	0.07	2	75	3 + 4	3 + 4	2	3 + 3	3 + 3	8
33	67	10.6	0.15	2	71	3 + 4	3 + 4	5	3 + 4	3 + 4	1.5
34	51	4.4	0.11	2	40	3 + 4	4 + 3	2	-	-	-
35	63	6.3	0.19	2	33	3 + 3	3 + 3	4	-	-	-
36	65	5.4	0.07	2	79	3 + 4	3 + 4	5	-	-	-
37	60	4.9	0.11	2	44	3 + 4	3 + 4	5	-	-	-
38	62	6.7	0.13	2	51	3 + 4	3 + 4	3	-	-	-
39	72	11.4	0.19	2	59	3 + 4	3 + 4	3	3 + 3	3 + 3	2
40	67	6	0.1	1	63	3 + 4	3 + 4	5	-	-	-
41	66	9.4	0.15	1	63	3 + 3	3 + 3	5	-	-	-
42	64	5	0.16	1	32	3 + 4	3 + 4	5	3 + 3	3 + 3	3
43	65	7.5	0.21	2	35	3 + 4	3 + 4	4	3 + 3	3 + 3	3
44	70	7.1	0.08	2	90	3 + 4	3 + 4	4	3 + 3	3 + 3	3

Appendix 4: Detection of mpMRI-Invisible Cancer in PROMIS, per Modality

Patient	mpMRI	TTPM biopsy	Systematic TRUS-guided biopsy
1			
2			
3			
4			
5			
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44			

Detected significant prostate cancer (definition 2)

Undetected significant prostate cancer (definition 2)

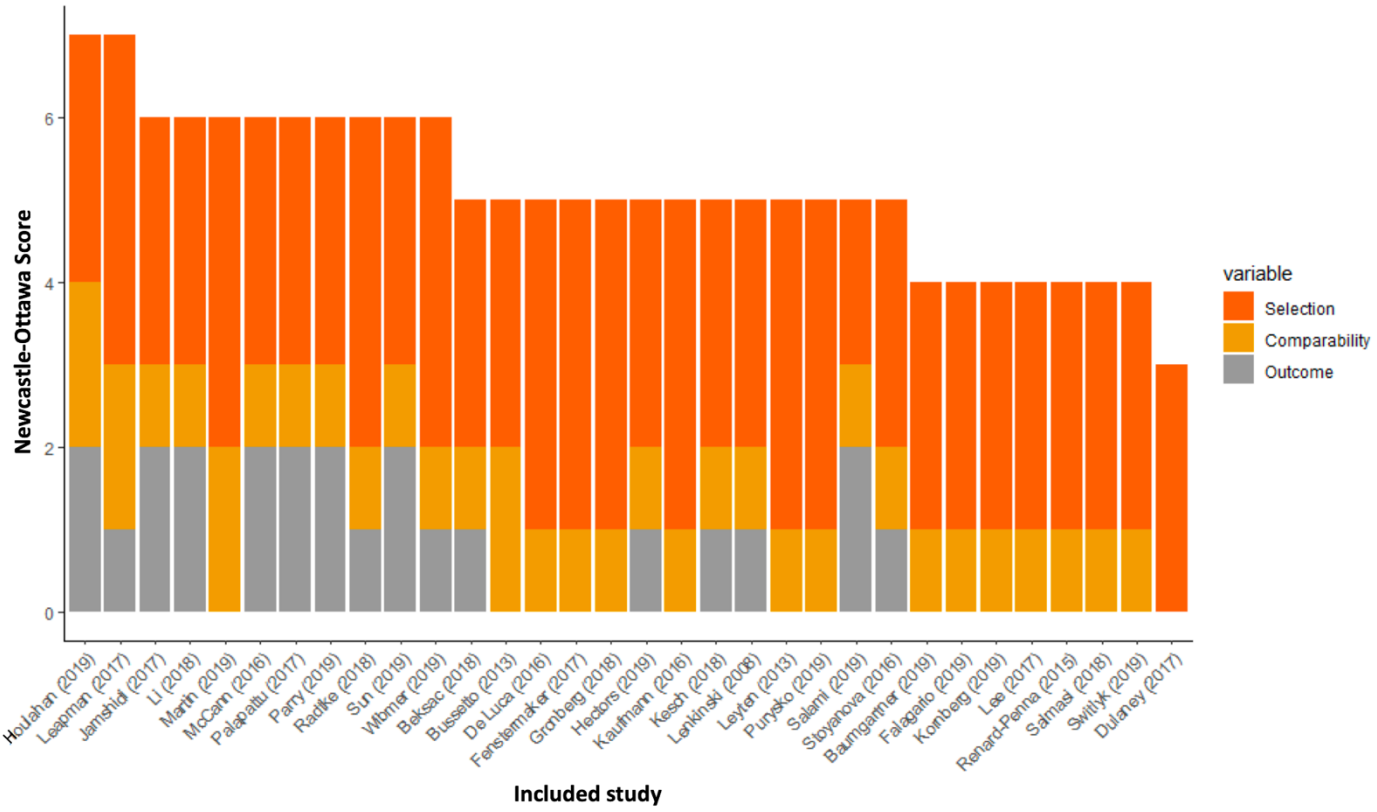
Appendix 5: Overall Cancer Status of Patients Before & During PICTURE

Overall Gleason score	Pre-enrolment (on TRUS), *n* (%)	PICTURE (on TTPM), *n* (%)
No cancer	74 (30)	34 (14)
2 + 3	2 (0.8)	0 (0)
3 + 3	121 (49)	69 (28)
3 + 4	48 (19)	112 (45)
3 + 5	0 (0)	1 (0.4)
4 + 3	4 (1.6)	29 (12)
4 + 4	0 (0)	3 (1.2)
5 + 4	0 (0)	1 (0.4)

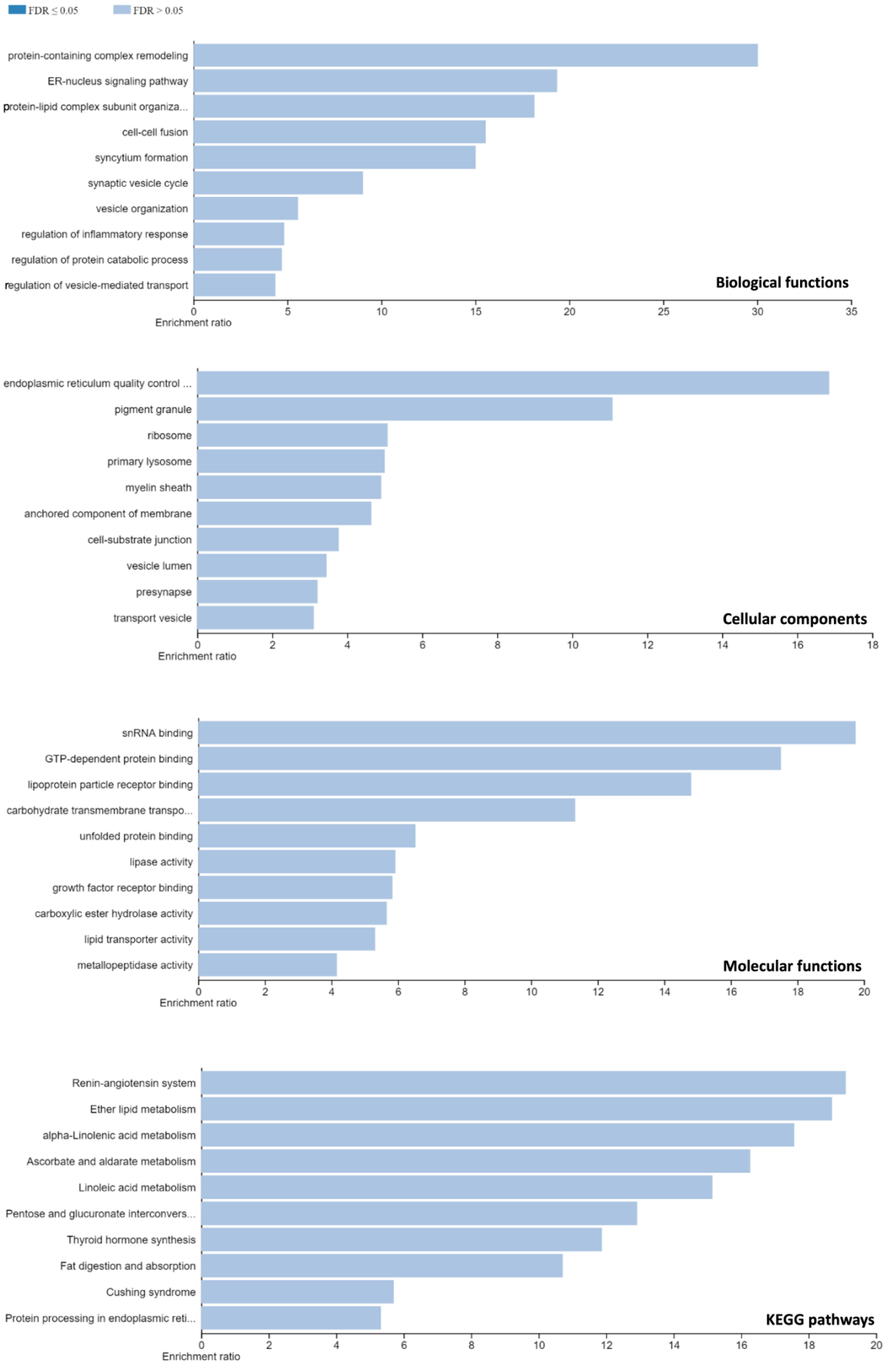
Appendix 6: Change in Cancer Status & Relationship to mpMRI in PICTURE

Re-classification characteristic	Result
Change in cancer status	
Overall upgrade	131 (53)
Overall downgrade	12 (4.8)
No change	106 (43)
Positive mpMRI result (Likert 3–5)	
Overall upgrade	120 (48)
Overall downgrade	11 (4.4)
No change	83 (33)
Negative mpMRI result (Likert 1–2)	
Overall upgrade	11 (4.4)
Overall downgrade	1 (0.4)
No change	23 (9.2)

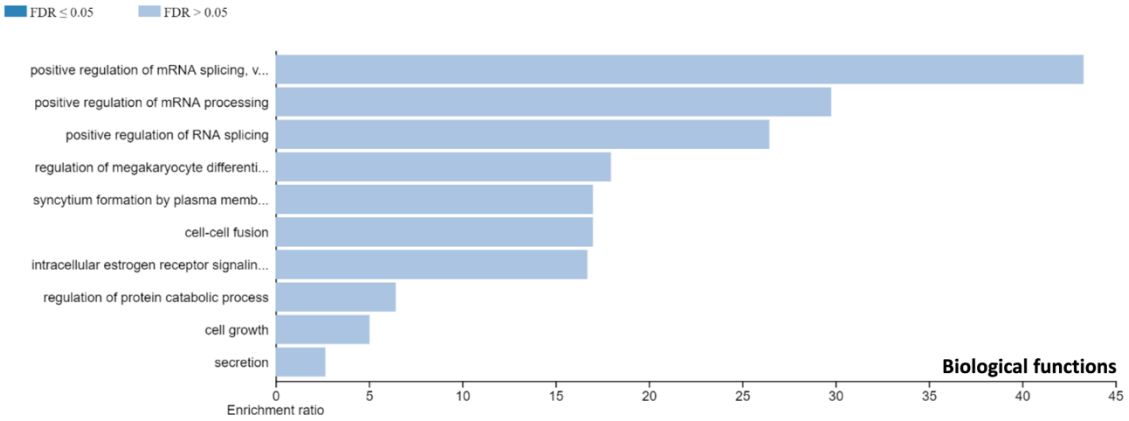
Appendix 7: Newcastle-Ottawa Bias Risk Assessment for Included Studies

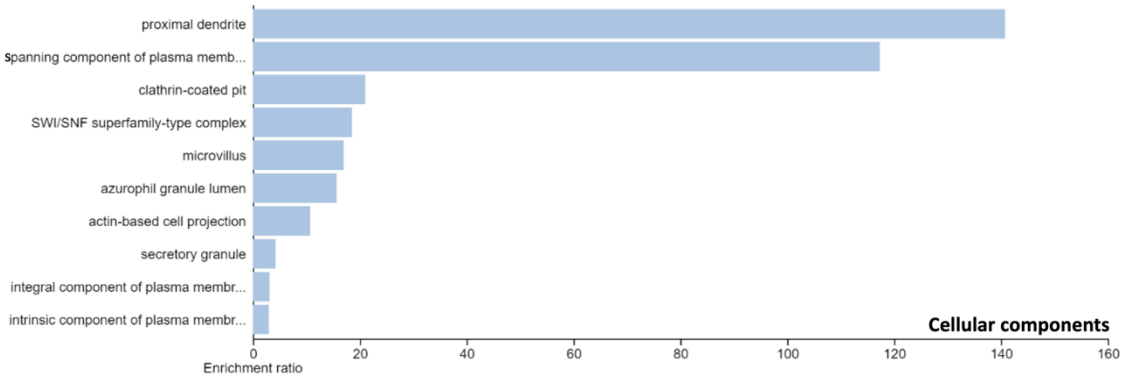


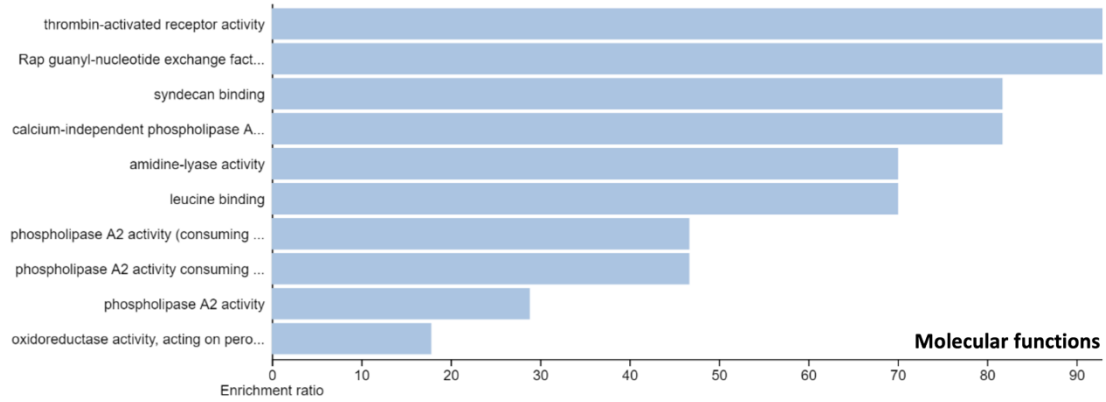
Appendix 8: Over-Representation Analysis of 42 Validated Detection-Associated Genes

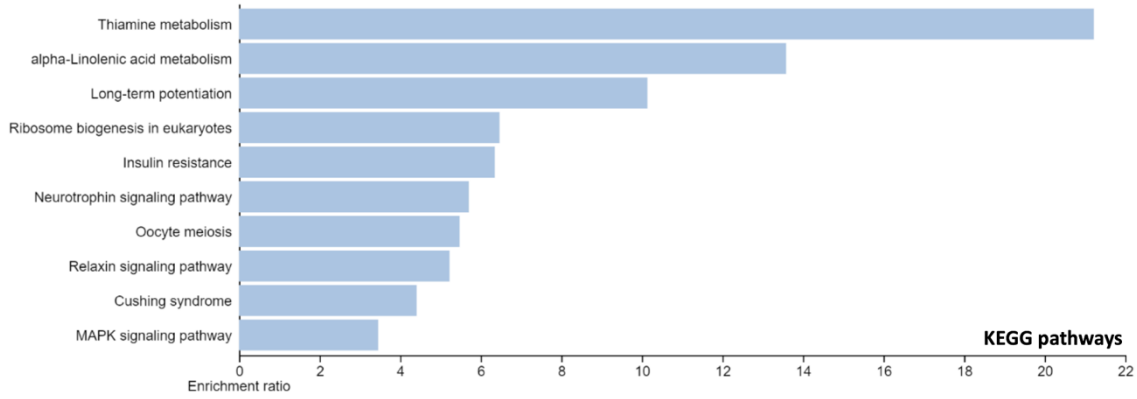


Appendix 9: Over-Representation Analysis of Detection-Associated Genes (as reported by Houlahan)

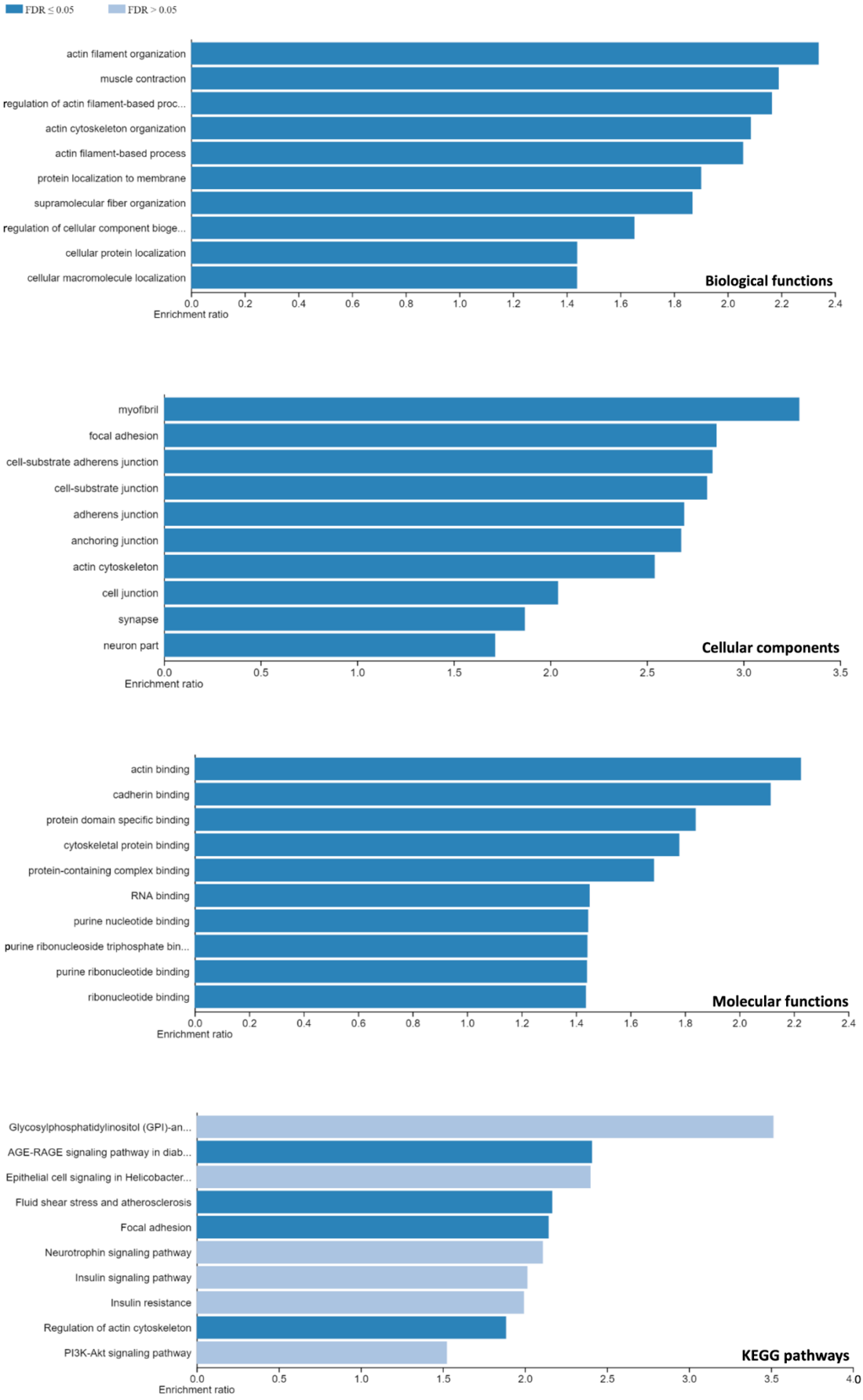




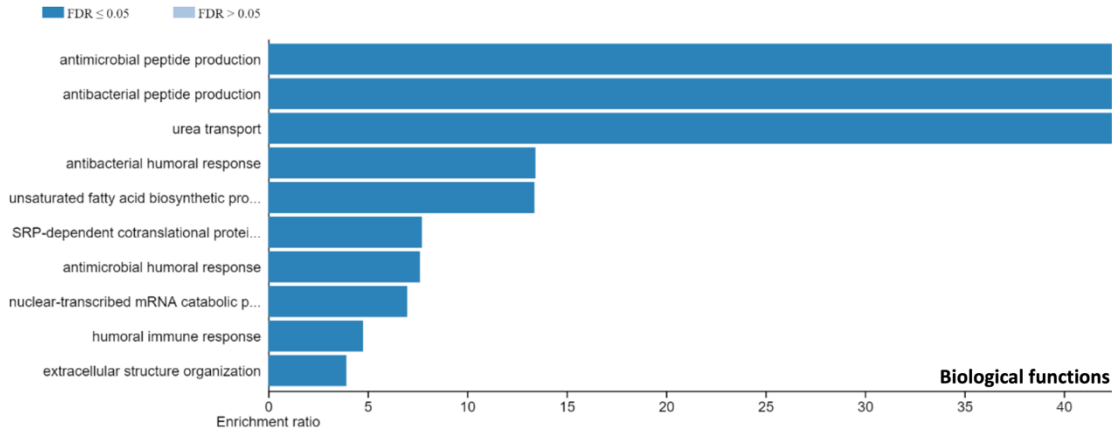


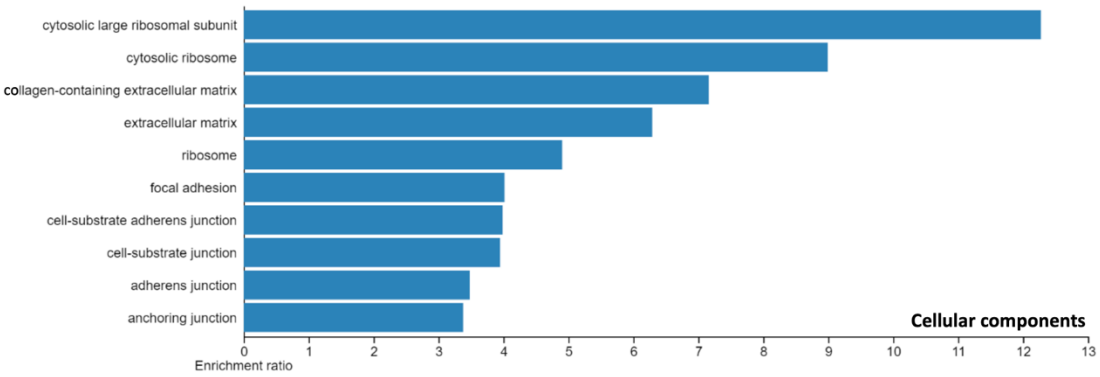


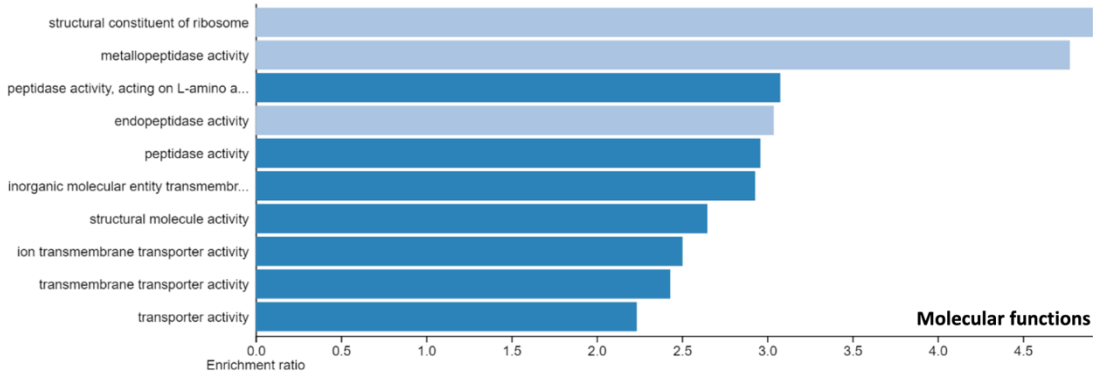
Appendix 10: Over-Representation Analysis of Detection-Associated Genes (as reported by Li)

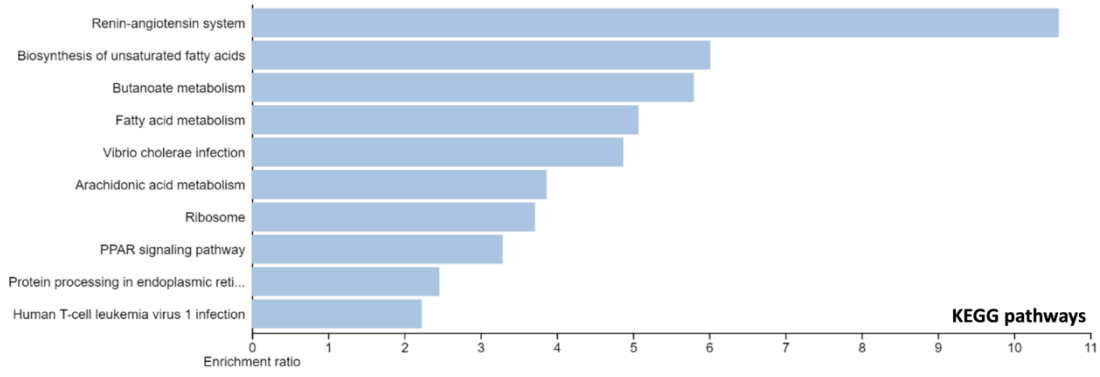


Appendix 11: Over-Representation Analysis of Detection-Associated Genes (as reported by Stoyanova)









Appendix 12: Patient Information Sheet for the PACT Study

Acceptability of Prostate MRI:

Patient Information Sheet

- In the past (1980s – 2000s) – MRI had very limited availability and was not commonly used:
  - Men suspected to have prostate cancer would not normally have an MRI scan
  - They would normally undergo a prostate biopsy (tissue sample) through the rectum (bottom)
  - This could cause side-effects, including: pain, infection (1-3%) and bleeding

  But, this technique did not detect every prostate cancer: approximately 50% could still be missed
    - Furthermore, many of these men did not need a prostate biopsy in the first place

- Today – MRI is now widely available in the UK:
  - We now use MRI scans to see if prostate cancer is likely to be present or not (before a biopsy is performed)
  - If the MRI scan shows:
    - Suspicious areas in the prostate – then you will likely be advised to still have a prostate biopsy
    - No suspicious areas in the prostate – then you will probably not need to have biopsy
  - MRI scans can now detect around 80-90% of important prostate cancers
  - So, by using MRI we can prevent many men from unnecessarily having a prostate biopsy

  But, MRI does not detect every prostate cancer: approximately 10-20% can still be missed by MRI
    - Therefore, by using MRI, we could miss approximately 10-20% of important prostate cancers

Appendix 13: Consent Form for Stage I of the PACT Study

Acceptability of Prostate MRI:

Patient Consent Form 1 (Questionnaire)

Please initial box

1. I confirm that I have read and understood the information sheet dated …… (version ……) for the above questionnaire study. I have had the opportunity to consider the information, ask questions and had these answered satisfactorily. ☐

2. I understand that my participation is voluntary and that I am free to withdraw at any time without giving any reason, without my medical care or legal rights being affected. ☐

3. I agree to my GP being informed of my participation in the study. ☐

4. I agree to take part in the above study. ☐

Name of participant:

Date:

Signature:

Name of person taking consent:

Date:

Signature:

Appendix 14: Consent Form for Stage II of the PACT Study

Acceptability of Prostate MRI:

Patient Consent Form 2 (Interview)

Please initial box

1. I confirm that I have read and understood the information sheet dated …… (version ……) for the above interview study. I have had the opportunity to consider the information, ask questions and had these answered satisfactorily. ☐

2. I understand that my participation is voluntary and that I am free to withdraw at any time without giving any reason, without my medical care or legal rights being affected. ☐

3. I agree to my GP being informed of my participation in the study. ☐

4. I agree to take part in the above study. ☐

Name of participant:

Date:

Signature:

Name of person taking consent:

Date:

Signature:

Appendix 15: Questionnaire for the PACT study

Acceptability of Prostate MRI:

Patient Questionnaire

(Adapted from: Schönenberger et al. 2007, with kind permission of Professor Marc Dewey)

Please give your answers based on your own knowledge and having read the patient information sheet.

---

1. How satisfied are you with the ability of prostate biopsy alone to help detect prostate cancer?

   Very poor ☐ Poor ☐ Barely Acceptable ☐ Good ☐ Very good ☐

2. How satisfied are you with the ability of MRI scans to help detect prostate cancer?

   Very poor ☐ Poor ☐ Barely Acceptable ☐ Good ☐ Very good ☐

---

3. Please rate your degree of concern that your MRI scan might miss important prostate cancer:

   No concern ☐ Little ☐ Moderate ☐ Intense ☐ Very intense ☐

   If you are concerned, why are you concerned? ……...

---

4. If your MRI scan showed low suspicion of prostate cancer, would you be happy to not have a prostate biopsy?

   No ☐ Yes ☐ Don't know ☐

5. If your MRI scan showed low suspicion of prostate cancer, would you want to have a biopsy anyway?

   No ☐ Yes ☐ Don't know ☐

---

6. If you were diagnosed with prostate cancer, which aspect of the disease do you think would be most important to you? (For example: life expectancy, quality of life, spread of cancer around the body, urine/sexual symptoms)
7. Are there any additional comments that you would like to make?

If you would be willing have a short interview on this topic, then please leave your contact details below:

Phone number: Email address: Postal address:

Appendix 16: Interview Schedule for the PACT Study

Acceptability of prostate MRI: Interview schedule

Interview schedule (v.2.1 – 24/09/2019)

Interview information

Thank you for attending today and for being willing to be interviewed as part of this research project. We are consulting patients to get their opinions on using MRI scans to detect prostate cancer. The interviews will expand on themes that were previously explored in our questionnaire, including the possible risk of missing prostate cancer on MRI scans, and also what is perceived to be the definition of clinically significant prostate cancer. The interview is comprised of sets of questions, and each set of questions is preceded by a sentence or two, to give some background information.

We wish to record the interviews to enable us to analyse full and accurate transcripts of what was said – the interview recordings will be anonymous and confidential. We will send you a transcript in case you might wish to comment or expand on the interview at a later stage.

RECORD:

Age	
Hospital number	
Trial number	
Site	

Date of interview	
Name of interviewer	
Recording no.	

QUESTIONS

Background

We have recently begun to use MRI scans to help us with detection of prostate cancer and would value your thoughts on this.

1. Can you tell me what experience you have had, if any, of MRI scans in relation to prostate cancer?
2. Can you tell me what you understand about the use of MRI scans to detect prostate cancer?
3. Are there particular aspects of MRI scanning that appeal to you?
4. Are there any aspects of MRI scanning that concerns you?

Comparison of new and traditional pathways

Previously, men with suspected prostate cancer would not have an MRI scan. They would normally simply have a tissue samples taken through a probe in the rectum. This could cause pain, infection and bleeding, and could miss about 50% of important prostate cancers. Also, many of these men did not need a sample taking in the first place. Today, MRI scans are widely available and can detect around 80-90% of important prostate cancers – so we now use them to guide us and see if cancer is likely to be present, even before we have taken any samples. For example, if the MRI scan shows a suspicious area, then we recommend that a sample is taken from this area. But, if the MRI scan shows no suspicious areas, then we recommend that a sample is usually not required.

5. Any new approach has drawbacks and benefits, and even the new MRI approach can miss 10-20% of prostate cancers – what do you think of this? How far does this risk worry you?
6. Can you tell me how you feel about this when compared to the traditional TRUS biopsy approach (that could miss up to 50% of cancers)?
7. When comparing these two approaches (using MRI or not), which do you think is more appealing? And, why?
8. From your point of view, are there any aspects of either of these approaches that would especially concern you?
9. If you were concerned, what kind of information would help you, and in what form would be easiest easy for you to access and use?
10. Given your own experience to date can you think of any changes, or improvements, to these two pathway options that you would like to see being made?

Biopsy strategies

We have different methods to choose from when we take a tissue sample from the prostate. We can choose to sample only the cancers that we can "see" on the MRI scan, however, this has a risk of missing cancer elsewhere in the prostate. Or, we can choose to sample the "whole prostate" but this has a risk of detecting of non-harmful cancer, which can lead to unnecessary treatment/anxiety.

11. Can you tell me, what experience you have had, if any, of having a prostate biopsy?
12. Do you have any thoughts on which of the two major types of biopsy do you think that you would now prefer? And, why?
13. Are any there aspects about the two different types of biopsy that might concern you?

Significance of prostate cancer

There are different types of prostate cancer. Some are "more aggressive" and can spread around the body and cause harm – these generally benefit most from treatment. Others are "less aggressive" and do not spread around the body or cause harm – these generally do not benefit from treatment, and in fact, treatment can sometimes cause more harm than the cancers themselves.

14. If you were diagnosed with prostate cancer, which aspect of your cancer would be most concerning to you?
15. Can you say whether you might be more concerned about the potential effect on your quality of life, or your life expectancy? And, can you say more about why you might feel this way?
16. From your point of view, if you had prostate cancer, would it be useful to know about the aggressiveness or danger posed by your cancer? And, in what way could we best provide such information to you?
17. How much detail would you would want to know about possible cancers in your prostate?
18. Thinking about this further, do you think you would want to know about every cancer that is present (even the "less aggressive" cancers), or do you think you would only want to know only about the "more aggressive" cancers? And, why would you feel this way?

Educational material

There are lots of different information sources available for patients (for example, books, websites, leaflets).

19. What format is normally best for you when it comes to information about your health?
20. Are there any aspects of this topic that you would like to have more information on?
21. Can you summarise any key lessons for us about your diagnostic experience to date?

Biparametric MRI

Traditionally, when we perform an MRI scan of the prostate it takes around 40 minutes, and involves three methods of viewing the prostate – one of which involves giving an injection of 'contrast' into a vein. The contrast injection may help to identify some suspicious areas in the prostate, but is generally not considered as important as the rest of the scan. Some people find the needle insertion for the injection painful, and rarely people can have an allergic reaction to the contrast. Also, this contrast is known to accumulate in the brain, but it is not known whether this causes long-term harm; and, this additional contrast-step takes up 20 minutes of the 40 minute scan. Avoiding this part of the scan may improve affordability of the scan to the NHS and could double the number of scans that can be done in a day. Interestingly, recent research has suggested that prostate MRI scans that do not use contrast appear to detect a very similar level of prostate cancers to MRI scans that do use contrast. However, there are a few prostate cancers that can be missed by not using contrast.

22. Given this information, can you tell me what you think about this new type of shortened MRI scan without a contrast injection?
23. Would any aspects of this new type of scan concern or worry you? And if so, why?
24. If this shortened scan became available, and you needed another prostate MRI scan, would you be prepared to have it?
25. If there was a robust study proposed to evaluate the true amount of prostate cancer missed by the new shortened version of the MRI without contrast, how important do you think this study would be?