PROSTATE SPECIFIC ANTIGEN (PSA) RETESTING INTERVALS FOR PROSTATE CANCER IN PRIMARY CARE

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Dedicated to those who think they can't do it.

Keep going - you might surprise yourself.

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STATEMENT OF CONTRIBUTIONS

All aspects of the research presented in this thesis are my own work, completed under the supervision of A/Prof Brian D. Nicholson, Prof Rafael Perera, Dr Jason L. Oke, and Dr Claire Friedemann Smith at the Nuffield Department of Primary Care Health Sciences, University of Oxford. This work has not been submitted for any other degree at the University of Oxford or elsewhere.

For each chapter, and the associated publications of Chapters 2, 3, and 5, I conceptualised and led the study design, data management, statistical analyses, and write-up. All contributions from collaborators are outlined below and were in line with standard research practice. Patient and Public contributors were Rashmi Kumar, Sue Duncombe, Ikenna Okapala, Lucia Jena, and Francesco Palma.

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ABSTRACT

Background: The utility of the prostate-specific antigen (PSA) test in primary care remains uncertain. It is unclear whether screening with PSA reduces prostate cancer mortality sufficiently to outweigh the harms of overdiagnosis and overtreatment. For this reason, PSA screening is not recommended in the UK. Instead, patients may request a PSA test following shared decision-making with their GP. However, once a PSA test has been performed, there is limited evidence to guide whether the patient should be retested and, if so, what the appropriate intervals should be.

Aim: To generate evidence to support the development of evidence-based recommendations on PSA retesting intervals in primary care.

Methods: This thesis includes two systematic reviews of clinical practice guidelines and three retrospective cohort studies. The first review summarised recommendations for PSA retesting intervals and evaluated the evidence cited by each guideline. The second review assessed the evidence supporting guideline recommendations monitoring patients diagnosed with a low-risk cancer.

The three analytical studies used a dataset of over ten million patients contributing to the Clinical Practice Research Datalink Aurum linked to the Cancer Registry, Hospital Episode Statistics database and the Office for National Statistics death registry between 2000 and 2018.

The first study described PSA retesting patterns in primary care, stratified by demographic characteristics, PSA values, symptoms, and family history. The second study estimated prostate cancer risk by age and baseline PSA to derive population-level, risk-stratified retesting intervals. The third study applied joint modelling to combine longitudinal PSA trajectories with time-to-cancer diagnosis to evaluate the feasibility of personalised, dynamic retesting intervals.

Results: Internationally, the recommended PSA retesting interval ranged from one to ten years. Most guidelines relied on indirect evidence derived from studies investigating a single PSA value, assessments of risk of prostate cancer progression, or data from randomised screening trials primarily aimed at mortality reduction rather than determining retesting intervals. Generally, for asymptomatic patients aged over 50 with PSA levels between 1 and 3 ng/mL, most guidelines recommend a retesting interval of two-to-four years, with the possibility of extending the interval to four to ten years for asymptomatic patients with a PSA value less than 1 ng/mL.

Variations in guideline recommendations may contribute to the varied rates of PSA testing rates observed in England. Among patients who had a PSA test between 2000 and 2018, 48% had multiple PSA tests and 73% of those patients never presented with a PSA value above the age-specific referral threshold. The median retesting interval for patients with multiple tests was 12.6 months (IQR 6.2 to 27.5). Testing rates varied by region, deprivation, ethnicity, family history, age, PSA value and symptoms. Despite considerable variation in testing rates by region and deprivation, the length of retesting intervals was similar across these groups.

Population-level risk estimates by baseline PSA and age were consistent with European evidence, confirming that patients under 60 with a PSA of less than 1 ng/mL can safely wait ten years before retesting. Joint modelling extended this analysis and demonstrated the feasibility of generating personalised PSA retesting intervals that update with patient age and evolving PSA measurements.

Conclusion: This thesis provides new evidence on how often PSA retesting occurs in primary care in England. It highlights that PSA retesting interval recommendations are both varied in guidelines and inconsistently applied in practice. As a result, some patients are overtested while others may be undertested. Both population-based and individualised approaches offer feasible strategies to support future evidence-based recommendations on PSA retesting intervals.

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LIST OF ABBREVIATIONS AND ACRONYMS

Abbreviation	Definition
ACR	American College of Radiology
ACS	American Cancer Society
AGREE	Appraisal of Guidelines for Research & Evaluation
AI	Artificial Intelligence
AIC	Akaike Information Criterion
AIM	Assessment and Improvement of Measurement
ASCO	American Society of Clinical Oncology
ASTRO	American Society for Radiation Oncology
AUA	American Urological Association
AUC	Area Under the Curve
BAUS	British Association of Urological Surgeons
BBC	British Broadcasting Corporation
BCR	Biochemical Recurrence
BIC	Bayesian Information Criterion
BLOTTED	Blood Test Trends for Early Cancer Detection
BMJ	British Medical Journal
BNF	British National Formulary
BPH	Benign Prostatic Hyperplasia
C61	ICD-10 Code for Prostate Cancer
CAP Trial	Cluster randomised trial of PSA testing for Prostate Cancer
CHAPS	Cancer Health Awareness in Prostate Study
CI	Confidence Interval
CIN3	Cervical Intraepithelial Neoplasia Grade 3
CLL	Chronic Lymphocytic Leukaemia
COVID	Coronavirus Disease
CPRD	Clinical Practice Research Datalink
CRUK	Cancer Research UK
CT	Computed tomography
CUA	Canadian Urological Association
CVD	Cardiovascular disease
DCE	Discrete choice experiment
DF	Degrees of freedom
DISSRM	Delayed Intervention and Surveillance for Small Renal Masses registry
DRE	Digital rectal examination
EANM	European Association of Nuclear Medicine
EAU	European Association of Urology
ED	Erectile dysfunction

EMIS	Egton Medical Information Systems (UK primary care software)
ERSPC	European Randomized Study of Screening for Prostate Cancer
ESMO	European Society for Medical Oncology
ESTRO	European Society for Radiotherapy and Oncology
ESUR	European Society of Urogenital Radiology
EU	European Union
FNA	Fine-needle aspiration
GP	General practitioner
GRADE	Grading of Recommendations Assessment, Development and Evaluation
HCL	Hairy Cell Leukaemia
HES	Hospital Episode Statistics
HPV	Human papillomavirus
HR	Hazard ratio
ICD	International Classification of Diseases
IMD	Index of Multiple Deprivation
IQR	Interquartile range
IRR	Incidence rate ratio
ISUP	International Society of Urological Pathology
JM	Joint model
LUTS	Lower urinary tract symptoms
MCMC	Markov chain Monte Carlo
MISCAN	Microsimulation Screening Analysis model
MRI	Magnetic resonance imaging
NCCN	National Comprehensive Cancer Network
NCRAS	National Cancer Registration and Analysis Service (England)
NDRS	National Disease Registration Service (England)
NG12	NICE guideline NG12 (Suspected cancer: recognition and referral)
NHS	National Health Service (UK)
NICE	National Institute for Health and Care Excellence (UK)
NPV	Negative predictive value
OCEBM	Oxford Centre for Evidence-Based Medicine
ONS	Office for National Statistics (UK)
OR	Odds ratio
ORCHID	ORCHID-E linked dataset (primary care–cancer linkage; your project)
PCRMP	Prostate Cancer Risk Management Programme (UK)
PCUK	Prostate Cancer UK
PIVOT	Prostate Cancer Intervention Versus Observation Trial
PLCO	Prostate, Lung, Colorectal and Ovarian Cancer Screening Trial
POMDP	Partially observable Markov decision process
PPGL	Paraganglioma–pheochromocytoma (contextual)
PPI	Patient and public involvement

PPV	Positive predictive value
PRAISE-U	Prostate cancer awareness and initiative for screening in the European Union
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
PROBASE	German prostate cancer screening trial
PRS	Polygenic risk score
PSA	Prostate-specific antigen
RCT	Randomised controlled trial
RECORD	REporting of studies Conducted using Observational Routinely-collected health Data
RR	Risk ratio / relative risk
SAIL	SAIL Databank (Wales)
SD	Standard deviation
SDM	Shared decision-making
SEER	Surveillance, Epidemiology, and End Results Program (US)
SEOM	Sociedad Española de Oncología Médica
SIOG	International Society of Geriatric Oncology
SNOMED CT	Systematized Nomenclature of Medicine
SPCG	Scandinavian Prostate Cancer Group
SQL	Structured Query Language
STROBE	Strengthening the Reporting of Observational Studies in Epidemiology
SUO	Society of Urologic Oncology
THIN	The Health Improvement Network (UK primary care database)
TNM	Tumour–Node–Metastasis (staging system)
TPP	TPP (SystmOne vendor; UK primary care IT)
TRIP	Turning Research into Practice
TRIPOD	Transparent Reporting of a multivariable prediction model for Individual Prognosis Or Diagnosis
TRUS	Transrectal ultrasound
UK	United Kingdom
USA	United States of America
USPSTF	U.S. Preventive Services Task Force
UWL	Unexpected weight loss

CHAPTER SUMMARIES

Chapter 1: Introduction

This chapter introduces the clinical and epidemiological background of prostate cancer and highlights the challenges associated with its diagnosis and management. It explores the conflicting evidence from PSA screening programmes and summarises current guidance for PSA testing. This chapter sets the rationale for investigating PSA retesting intervals in primary care.

Chapter 2: A Critical Appraisal of the Evidence for PSA Retesting Intervals: A Guideline Review

This chapter presents the findings of a systematic review of international clinical guidelines that provide recommendations for PSA retesting intervals in primary care. It summarises the recommendations and critically examines the studies cited as evidence for each interval recommendation.

Chapter 3: Adequacy of Guideline Recommendations for Monitoring Patients with Low-Risk Cancer: A Guideline Review

This chapter reports the results from a second systematic review focussed on guideline recommendations for monitoring patients diagnosed with low-risk cancer. It evaluates whether guidelines adequately identify patients suitable for monitoring, specify appropriate tests, define clear monitoring intervals, and outline triggers for further clinical intervention.

Chapter 4: Data Management

This chapter outlines the structure of UK primary care electronic health record databases, including linkages to The National Cancer Registry, Hospital Episode Statistics, and The Office for National Statistics. It describes the preparation and management of the dataset used throughout the following analytical chapters. The dataset included over ten million male patients over the age of 18 and 1.5 million patients who had at least one PSA test.

Chapter 5: PSA Retesting Intervals and Trends in England: A Population-based Cohort Study

This chapter reports findings from a population-based cohort study of PSA testing in England between 2000 and 2018. It describes trends in PSA testing frequency over time and explores variation by symptom presentation, family history, PSA level, age, ethnicity, region, and deprivation. It characterises the length of PSA retesting intervals in primary care and identifies demographic and clinical factors associated with shorter or longer intervals.

Chapter 6: Population-Based Static PSA Retesting Intervals

This chapter presents population-based estimates of PSA retesting intervals derived from baseline PSA values and age at first test. It describes the distribution of baseline PSA levels across age groups in a primary care setting and estimates the risk of prostate cancer controlling for age, region, ethnicity, deprivation, baseline PSA and family history. These findings provide population-level evidence to inform fixed, risk-based PSA retesting strategies in primary care.

Chapter 7: Estimation of Individualised Dynamic PSA Retesting Intervals

This chapter describes the development and internal validation of a joint model combining longitudinal PSA measurements and time-to-event outcomes to dynamically predict a patient's prostate cancer risk over time. It outlines the joint modelling framework and evaluates the feasibility of using personalised, dynamically updated risk predictions to inform PSA retesting intervals in primary care.

Chapter 8: Discussion

This chapter summarises the overall findings of the thesis. It compares the population-based and individualised retesting approaches and highlights how each can inform evidence-based PSA retesting strategies in primary care. It concludes with emphasising the importance of ensuring that the right patients are tested with PSA at the right intervals that are guided by the best available evidence.

Chapter 1: Introduction

1.1 Motivation

My motivation for undertaking a DPhil arose from my work in the Evidence team at Prostate Cancer UK (PCUK), where I became aware of major evidence gaps in the prostate cancer diagnostic pathway. I saw how uncertain general practitioners (GPs) were about the best way to use the PSA test and how they looked to PCUK for guidance. Within the Evidence team, we found it difficult to give GPs clear answers because the underlying evidence was limited and inconsistent. Existing evidence and clinical recommendations not only disagreed on whether PSA testing should be offered, but many questions remained about if, or how often, a PSA test should be repeated.

Another challenge I encountered at PCUK was the lack of insight into how frequently PSA testing was occurring in primary care. It was unknown how GPs were using the PSA test in practice. PSA testing data from English general practices is not publicly available, and purchasing data is expensive. As a result, national patterns of PSA testing were poorly understood. When the PCUK could not afford a primary care data cut in 2018, I moved to work as a data analyst for the primary care database called the Health Improvement Network (THIN). In this job I had access to the entirety of the THIN database. This is when I realised the potential of using routinely collected primary care data to answer the very questions that had remained unresolved at PCUK.

Opinions on PSA testing are divided, both nationally and internationally, due to persistent uncertainties in the evidence base, clinical practice, and guideline recommendations. Opinions differ particularly around how to balance the potential harms of overtesting and overdiagnosis against the small mortality benefit shown in PSA screening trials. Throughout this DPhil, I aimed to address three questions that affect clinicians, patients, and their families: What guidance currently exists for PSA retesting in primary care? How often are patients being retested in practice? And how often should patients be retested with PSA in primary care?

1.2 SUMMARY OF THE INTRODUCTION

In the first part of this chapter, I briefly summarise the biology, risk factors and staging for prostate cancer. I discuss the burden of prostate cancer within the UK and internationally. In the second part of the chapter, I explain what the prostate specific antigen (PSA) test is, including its history, challenges as a diagnostic tool and its use for monitoring prostate cancer progression. I then discuss how the diagnostic pathway for prostate cancer which begins with a PSA test and review evidence from key screening trials. I outline the lack of clear guidance on PSA testing and consider the perspectives of patients, clinicians, and policymakers. I discuss the controversies surrounding PSA when used for screening such as the overdiagnosis of prostate cancer and conclude with outlining the importance of retesting intervals.

1.3 WHAT IS PROSTATE CANCER

Prostate cancer is a malignant neoplasm that can grow in the gland-forming cells that make up the prostate. The prostate is a part of the male reproductive system and cancer may develop in people with a prostate. This includes men, trans-women and non-binary individuals who were assigned male at birth. Prostate cancer is a heterogeneous disease, ranging from indolent tumours that remain organ-confined to aggressive cancers that invade the prostatic capsule or seminal vesicles and metastasise. Most commonly to a patient's lymph nodes or bone. The natural history of prostate cancer is unknown, making it difficult to determine if each specific cancer will progress or not.

1.4 SURVIVAL OF PROSTATE CANCER

Diagnosing prostate cancer early improves survival. Almost 100% of patients survive for 5 years following a diagnosis of stage 1 or 2. This drops to 95% at stage 3 and 50% if diagnosed at stage 4 (1).

1.5 STAGES OF PROSTATE CANCER

Accurate staging of prostate cancer is a challenge. It is highly dependent on differences in clinical practices such as different biopsy and imaging techniques. There are multiple ways to describe prostate cancer stage and grade, all which have different meanings.

1.5.1 TUMOUR, NODE AND METASTASIS (TNM) STAGING

TNM staging is used to define how far the cancer has spread. There are four tumour T stages. T1 means the tumour is too small to see on a scan and T4 means the tumour has spread to other parts of the body. Middle T stages (2 and 3) correspond to the cancer spreading to different areas around the prostate. The N stands for nodes and this is a binary split into 0 or 1 to show if the cancer has spread to the patient's lymph nodes. M stands for metastasis which is also a binary measure to understand if the cancer has spread anywhere else in the body.

1.5.2 GLEASON SCORES

Gleason score is the grade of the prostate cancer (2). It is based on the pathologist's report of the cells extracted from the biopsies. A score is given to the most common and second most common cell patterns. Gleason scores range from 6 to 10 with 6 being the lowest score. Gleason 6 is made up of 3+3 where the first and second most common cells found from the biopsy are 3. The cells can be classified as any combination between 3 and 5. Where 5+5 is very aggressive cancer (2). Table 1.1 describes the combinations of Gleason scores. All reports of grade in this thesis are based on Gleason scores. This is what was available in the National Cancer Registry data between 2000 and 2018. Although Grade Groups have now replaced Gleason scores, these were not available in the data that was accessed for this work.

1.5.3 GRADE GROUPS

In 2014 the International Society of Urological Pathology (3) developed a new grading system called Grade Groups which have replaced Gleason scores. There are 5 Grade Groups ranging from 1 (least aggressive) to 5 (most aggressive). It is thought that Grade

Groups improve the stratification of patients into distinct grade groups, which have implications for treatment (4). The groups match to Gleason Scores as described in Table 1.1 (5).

Table 1.1 Prostate Cancer Grade Group mapped to Gleason Score

Grade Group	Gleason Score	Prostate Cancer Risk level
Grade Group 1	Gleason score 6 (or 3 + 3 = 6)	Low
Grade Group 2	Gleason score 7 (or 3 + 4 = 7)	Intermediate
Grade Group 3	Gleason score 7 (or 4 + 3 = 7)	Intermediate
Grade Group 4	Gleason score 8 (or 4 + 4 = 8, 3 + 5 or 5 + 3)	High
Grade Group 5	Gleason score 9 or 10 (or 4 + 5 = 9, 5 + 4 = 9 or 5 + 5 = 10)	High

Caption: Data in Table 1.1 is adapted from Cancer Research UK (2025) (5)

1.6 TREATMENT OF PROSTATE CANCER

There are many different treatment options for prostate cancer. Choosing a treatment depends on patient preferences for risk and side effects. Treatment choices depend on which stage of prostate cancer the patient is diagnosed with. Treatments range from active surveillance, which is preferred for patients with Gleason 6 disease (discussed in Chapter 3), to radical prostatectomy and radiotherapy which are common for patients with Gleason 7 and above. Details on specific prostate cancer treatments and their associated side effects are out of scope of this thesis.

1.7 NON-MODIFIABLE RISK FACTORS FOR PROSTATE CANCER

Age, race, family history, and germline mutations are well-established nonmodifiable risk factors for prostate cancer (6). The natural history of prostate cancer is unknown but understanding who is at risk of prostate cancer is essential for optimising early detection and reducing mortality. The following are risk factors for all types of prostate cancer. It is currently unknown which cancers will progress, and which will not.

1.7.1 AGE

Prostate cancer is strongly associated with increasing age (7, 8). An autopsy study of Japanese and Russian patients who died from other causes found that 40% of

unscreened patients older than 60 years and 60% of patients older than 80 years had prostate cancer when biopsied. A third of the cancers were Gleason 7 or higher (9). In the United States (US), it was found that the rate of latent prostate cancer was more than 75% in patients older than 85 (10).

1.7.2 Family history

Patients with a brother or father with a diagnosis of prostate cancer have a 2.5 times increased risk of being diagnosed with prostate cancer (11). In Sweden it was found that family history risk differs by the age of the family member when they were diagnosed. They found that having one first-degree relative diagnosed with prostate cancer before age 60 increased the risk of prostate cancer by 2.5 times, compared with 1.6 times if the relative was over 60. The risk increased to 5.7 times for people with two or more relatives diagnosed before 60 (12). A recent study using data from the UK found that family history of prostate cancer was inversely associated with prostate cancer mortality, possibly due to increased awareness of risk (13).

1.7.3 Genetics

Hereditary mutations in HOXB13 (14) and BRCA2 (15) have been identified as high risk alleles for prostate cancer. It was discovered that that MSH2 which causes Lynch syndrome was also associated with prostate cancer (16). Data from the UK Biobank show that 1.4% of patients carried a pathogenic mutation in BRCA2, HOXB13, or CHEK2. They found the performance of a genetic risk score was associated with prostate cancer incidence, diagnosis free survival time and prostate cancer mortality (17). Polygenetic risk scores for prostate cancer are becoming more mainstream as a potential diagnostic tool and include over 200 single nucleotide polymorphisms (18).

1.7.4 Ethnicity

Ethnicity as a risk factor for prostate cancer is well-documented, but the cause is uncertain. Genetics may be a potential contributor (19), but the relationship of ethnicity and prostate cancer is complex. Disparities in access to care, differences in healthcare systems, competing causes of mortality, systemic racism, and socioeconomic factors

(20) all likely play a confounding role and are not possible to fully control for in observational studies and audits. The 2024 National Prostate Cancer Audit (21) reported that patients of Black ethnicity have the highest number of new prostate cancer diagnoses, relative to their population size, across all stages of disease in England. Other studies found that younger patients of Black ethnicity aged 40 to 49 are more likely to be diagnosed at an advanced stage (22) and are twice as likely to die from prostate cancer compared to patients of White ethnicity (23). Similar associations are found in data from the US where patients of Black ethnicity have historically had higher rates of prostate cancer incidence and mortality. However, recently an American study adjusting for access to care, socioeconomic status, and treatment factors found that patients of Black ethnicity with nonmetastatic prostate cancer did not have a biologically higher risk of prostate cancer–specific mortality (20).

1.8 MODIFIABLE RISK FACTORS FOR PROSTATE CANCER

A wide range of modifiable risk factors for prostate cancer have been studied (24). The evidence is from observational studies with high potential for confounding and results are inconclusive. Dietary factors have received substantial attention. Several reviews have found a positive association between meat consumption and prostate cancer risk (25-28). Vegetarian diets were found to have a lower risk of prostate cancer than meat eaters hazard ratio (HR) 0.57 (95% CI 0.43 to 0.76) (28). In other studies, no association was found (29). A review on dairy consumption found an increase in prostate cancer risk for increased consumption of dairy milk risk ratio (RR) 1.11 (1.03 to 1.21) but a lower risk of cardiovascular disease, stroke, hypertension, colorectal cancer, metabolic syndrome, obesity and osteoporosis (30).

Some studies have shown that smoking may be associated with risk of prostate cancer mortality (31, 32), while others claim there is no significant association (33, 34). A meta-analysis of cohort studies found that current smokers have a RR of 1.42 (1.20 to 1.68) of prostate cancer mortality compared with-nonsmokers, but an inverse association with the incidence of prostate cancer (35). This is possibly due to an aspect of socioeconomic

status where people living in least deprived areas are more likely to be diagnosed with prostate cancer.

There are mixed results evaluating the association of inflammatory bowel disease with an increased risk of prostate cancer. Recent studies find an association (36-39) whereas a meta-analysis from 2010 does not (40). There are similar findings for fatty liver disease. One meta-analysis found no association (41), while another found a weak positive association with the overall risk of prostate cancer (42). One study found no association between obesity and prostate cancer or advanced prostate cancer (43). Although it reported that several other studies found a small increase in the risk of aggressive prostate cancer (44, 45). It is unclear if type 2 diabetes is associated with a lower risk of prostate cancer (46, 47). Results are mixed and it was found that diabetes was inversely associated with prostate cancer risk HR 0.81 (0.77 to 0.85) but only in overweight or obese patients (48). Other studies examining associations with prostate cancer have found mixed results and report the need for further research. For example in areas such as: sexual activity (49), HPV (50), vitamin D (51), baldness (52), aspirin use (53), finasteride and dutasteride (54), or occupational hazards such as firefighting (55, 56).

1.9 BURDEN OF PROSTATE CANCER

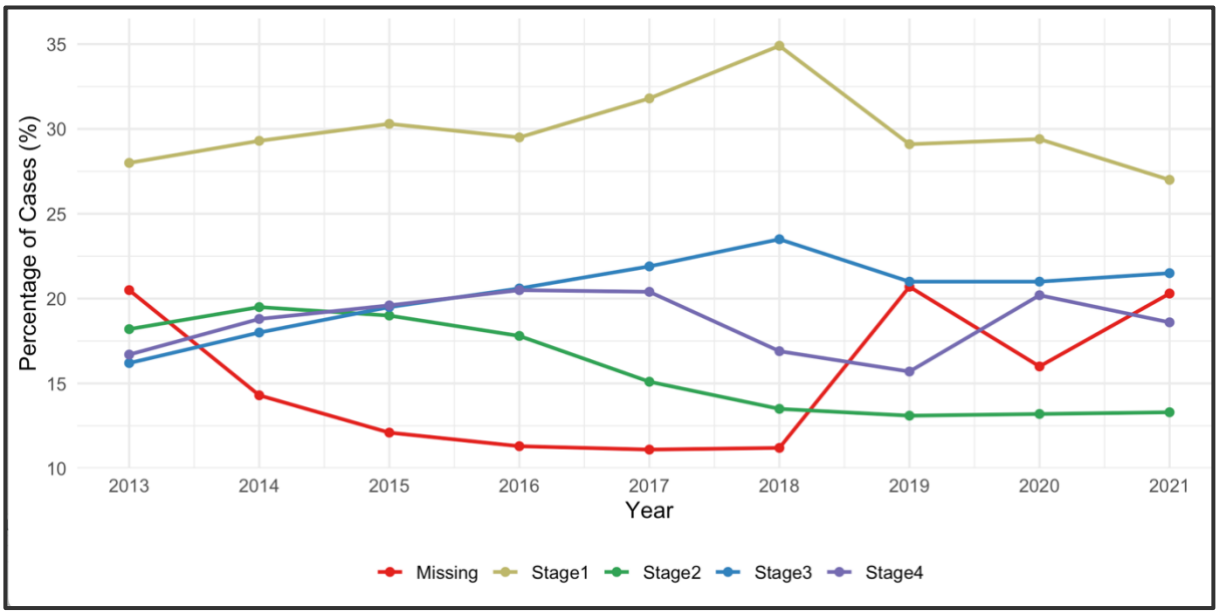
1.9.1 BURDEN OF PROSTATE CANCER INCIDENCE

Prostate cancer is the most common cancer diagnosed in the UK. It is estimated that one in eight people with a prostate will be diagnosed with prostate cancer in their lifetime (23). Incidence of prostate cancer in England surpassed breast cancer in 2018. In 2023, 55,241 patients were diagnosed. This was a 9% increase compared to 50,592 in 2022 (21). Forty-one percent of the patients diagnosed in 2023 were between the ages of 70 to 79 and 17% of patients were over the age of 80. While many prostate cancers are aggressive and eventually lead to death, at least an equal amount are indolent and never metastasise. To fully grasp the nuances of the burden of prostate cancer, it is important to consider the benefits of early detection alongside the harms of overdiagnosis.

1.9.2 BURDEN OF PROSTATE CANCER BY STAGE AT DIAGNOSIS

In England, the proportion of prostate cancers diagnosed at late stage has not declined over time. Detecting the cancers which progress to stage three and four is essential to improve patient outcomes. Trends in stage at diagnosis data from the National Disease Registration Service (NDRS) published in 2021 showed that between 2013 and 2021, the proportion of prostate cancers diagnosed at early stages (stages one and two) remained between 40% and 48%. Over the same period, stage three diagnoses increased and peaked at 24% in 2018, while stage four diagnoses stayed between 16% and 20%. In 2023, 17% of patients diagnosed in England presented with metastatic disease (21). The swap between stage two and stage three disease may be due to improved diagnostic methods such as multiparametric MRI (mpMRI) and targeted biopsies further described in Section 1.11.2.

Figure 1.1: Prostate Cancer Stage Distribution Over Time (NDRS)

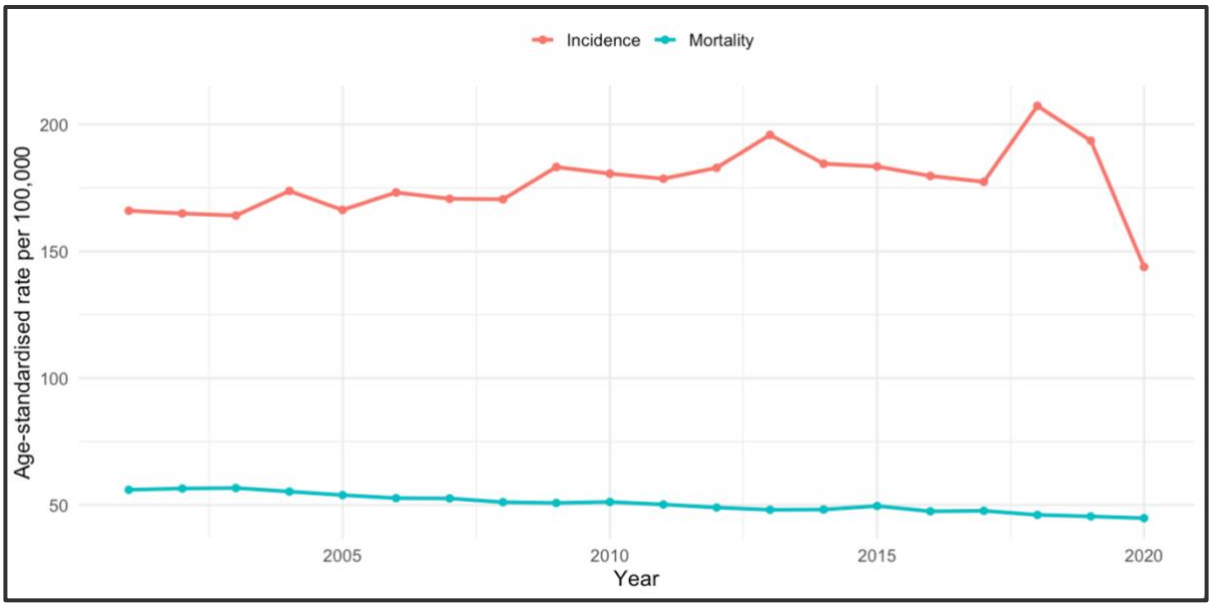


1.9.3 BUDEN OF PROSTATE CANCER MORTALITY

More than 12,000 patients a year die of prostate cancer. Based on data from the NDRS, in England, the age-standardised rate of mortality of prostate cancer fell from 56.0 (95%CI 54.7 to 57.3) per 100,000 in 2001 to 44.8 (43.9 to 45.7) in 2020 Figure 1.2. The

largest relative reduction in mortality were in age ranges 60 to 64 and 75 to 79 which both dropped over 31% and 32% respectively between 2001 and 2020 (57).

Figure 1.2: Prostate cancer incidence and mortality over time



1.9.4 INTERNATIONAL BURDEN OF PROSTATE CANCER

Internationally, prostate cancer remains the second most common cancer among people with a prostate and the fifth largest cause of cancer mortality. Approximately 335,000 new cases are reported annually in the European Union (EU). This results in over 100,000 deaths each year (58). Incidence and mortality rates significantly differ by geographical location (6). In 2022, rates of prostate cancer incidence across regions varied 13-fold and 9.5-fold for mortality (59). The highest incidence rates were in Australia/New Zealand, North America, Northern Europe, and Latin America/Caribbean. The highest mortality rates were in sub-Saharan Africa and Latin America/Caribbean (59). Differences in mortality are likely due to access and availability of treatments. In the United States (US), prostate cancer is the second leading cause of cancer death among people with a prostate (60). Many explanations for the differences exist, ranging from genetics (61), family history (11, 62), ethnicity (63), socioeconomic status (64), and different healthcare policies such as the widespread use of PSA testing (65, 66).

1.10 THE PROSTATE SPECIFIC ANTIGEN (PSA) TEST

The initial triage test in the diagnostic pathway is a blood test called the PSA test. PSA is a protein produced mainly by the epithelial cells of the prostate (67). Its normal role is to help liquefy semen after ejaculation and it is largely confined to the prostate. When the integrity of prostate tissue is disrupted, PSA can enter the bloodstream and appear elevated on a PSA test. This can occur when a patient has prostate cancer, but it can also occur due to several benign conditions as detailed in Section 1.10.2. The PSA test cannot distinguish cancer from non-cancer, nor can it differentiate aggressive tumours from indolent ones (60).

1.10.1 HISTORY OF THE PSA TEST

The PSA test is not new. It was partially described in the 1960s (68) and 70s by researchers investigating prostate and seminal fluid proteins (69, 70). Although various scientists identified related proteins, in 1979 T. Ming Chu and Ming C. Wang at the Roswell Park Memorial Institute (71) purified and characterised PSA to develop an immunoassay for blood testing. Initially, PSA was used only to monitor prostate cancer progression, as early clinical studies were in patients already diagnosed with prostate cancer. It was not considered reliable for early detection because of overlap in PSA levels between cancer and benign conditions. This changed in the early 1990s when studies demonstrated the effectiveness of PSA in detecting asymptomatic cancers missed by physical examination or ultrasound alone (72). The Food and Drug Administration subsequently approved PSA testing for early detection, sparking international widespread PSA testing and screening. Thirty-five years later, the utility of PSA for detecting prostate cancer remains uncertain as concerns of overdiagnosis and overtreatment persist.

1.10.2 ACCURACY OF THE PSA TEST AS A DIAGNOSTIC TOOL

The PSA test is sensitive, but it is not specific to prostate cancer. Consequently, its use as a diagnostic tool is limited. One systematic review of the diagnostic accuracy of PSA for all patients found that sensitivities ranged from 0.78 to 1.00 and specificities from 0.06 to 0.66. Positive likelihood ratios ranged from 0.83 to 2.90 and negative likelihood

ratios ranged from 0.00 to 3.75 (73). Another recent systematic review on the accuracy of PSA test for patients with symptoms of prostate cancer found that estimated sensitivity of PSA for prostate cancer was 0.93 (95%CI 0.88 to 0.96) and specificity was 0.20 (0.12 to 0.33). The area under the hierarchical summary receiver operator characteristic curve was 0.72 (0.68 to 0.76) (74).

The high false-positive rate represents a major limitation of PSA testing, with studies reporting false-positive rates between 46 and 48% in clinical practice (75). Data from the European Randomized study of Screening for Prostate Cancer (ERSPC) trial found that two thirds of patients with an elevated PSA level did not have prostate cancer (76). Raised PSA levels often reflect benign conditions, including benign prostatic hyperplasia (BPH), acute or chronic prostatitis, urinary tract infections, recent medical procedures such as biopsy or transrectal ultrasound, urinary catheterisation, and other factors such as ejaculation, prolonged cycling, constipation, or even warmer climates (77, 78). For patients with BPH, PSA levels correlate with prostate size and inflammation. For patients with acute prostatitis, PSA levels has been reported to be as high as 1,000 ng/mL (79). False negative results also pose a diagnostic challenge. A systematic review and meta-analysis (80) found that approximately 15% of patients with a PSA level less than 4 ng/mL had prostate cancer.

1.10.3 PSA FOR MONITORING PROSTATE CANCER PROGRESSION AND RECURRENCE

While the utility of PSA is debatable as a diagnostic tool, it is important for monitoring patient progression following treatment of localised prostate cancer (81). Between 20% and 50% of patients who have treatment for prostate cancer will develop biochemical recurrence (BCR) within 10 years after initial therapy (82, 83). This is characterised by rising serum PSA levels. PSA kinetics including PSA doubling time (length of time in months needed for the PSA level to double) are key predictors of metastasis and death in patients with BCR. The definition of what constitutes BCR is different depending on which prostate cancer treatment the patient received (84). For patients who undergo radical prostatectomy, the definition of BCR from the American Urology Association

(AUA) is a PSA ≥ 0.2 ng/mL. There is a lack of consensus among guideline associations regarding the most effective treatments for patients with BCR. Overtreating patients with BCR who may not benefit from further treatment remains an area of uncertainty and out of scope of this thesis. Ultra-sensitive PSA measurements five years post treatment may be a useful took to determine the need for follow-up beyond five years (85).

PSA is also used as a monitoring tool for patients diagnosed with low-risk prostate cancer who are being monitored under active surveillance protocols. If there is a sign of cancer progression the patient would then be treated appropriately. Most active surveillance protocols recommend to PSA test patients every three to twelve months in combination with other diagnostic tools (86). Rising PSA may prompt additional investigations, however, PSA alone is not sufficient to dictate change in management. The specific thresholds of PSA for monitoring prostate cancer progression and recurrence are under debate and out of scope of this thesis.

1.10.4 Challenges with interpreting the PSA test value

In addition to the limited specificity of the PSA test, there are further complications to consider when interpreting a patient's PSA test result. The use of finasteride, an alpha-5 reductase, as a hair loss medication is becoming more prevalent (87) and reduces a patient's PSA value by half. One study found that within 48 weeks of randomisation, patients aged 40 to 49 and 50 to 60 years who were assigned 1 mg/day finasteride had a median decrease in serum PSA concentration of 40% (95%CI 34 to 46) and 50% (44 to 57), respectively. Patients assigned to the placebo group, had a median changes of 0% (−14 to 14) and a median increase of 13% (2 to 24), respectively (88). If patients are on this medication, their PSA levels are likely less reliable and could miss cancers.

A further challenge with interpreting a patient's PSA result is that PSA results differ depending on the assay used in the pathology lab. Compared with the total PSA value from Roche, PSA values were significantly different for other companies ($p < 0.001$). On average PSA was 20.7% lower when the same blood samples were used with Beckman, 15.2% lower with Abbott, 6.1% lower with Diasorin, and 9.6% higher by Brahms (89). It

has been suggested to use assay-specific thresholds rather than a universal threshold for PSA levels and to ensure consistency in assay use to confirm that serial PSA measurements are interpreted appropriately, although it is uncertain if this is done in practice. A future challenge will then be how to compare these different assay results to at home PSA testing results when at home PSA testing becomes increasingly common. In addition to different PSA results from different assays, a patient's PSA can fluctuate overtime. Among men with a PSA above 4 ng/mL, it was found that 44% (68 of 154 participants) had a normal PSA finding at one or more subsequent visits during four-year follow-up (90).

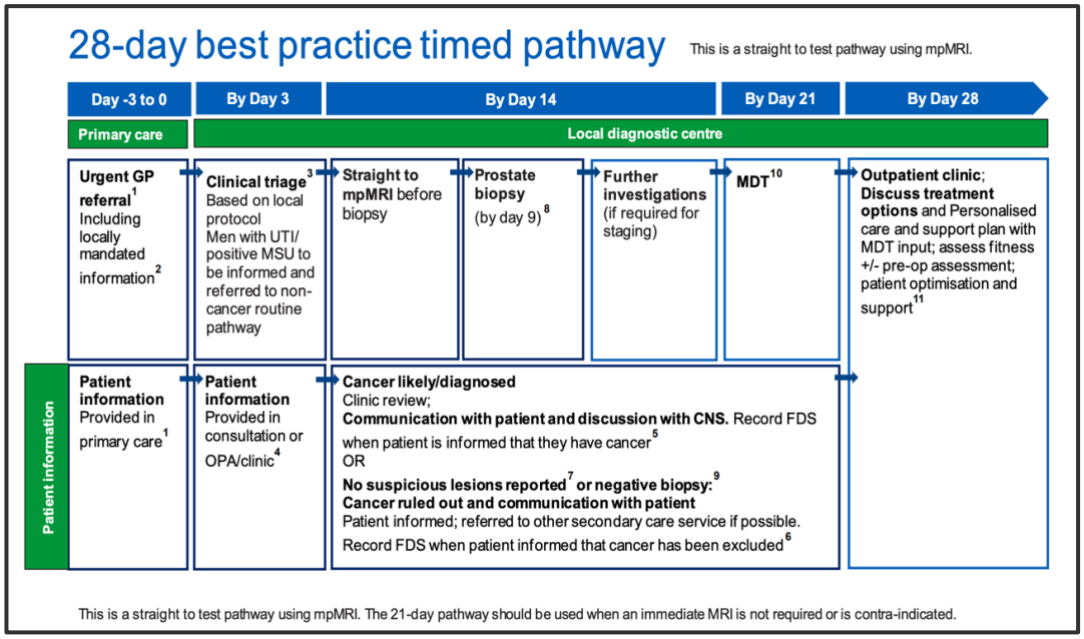
1.11 PROSTATE CANCER DIAGNOSTIC PATHWAY

The prostate cancer diagnostic pathway begins with the patient either presenting to their general practitioner (GP) or through emergency presentation in secondary care. The first step regardless is to perform a PSA test. From 2006 to 2020 in England, emergency presentation for prostate cancer was between 6% and 10% of cases. Over 80% of cases were diagnosed following an urgent or routine GP referral and less than 10% were categorised as "other outpatient." Of the patients diagnosed with stage four prostate cancer, 23% presented as an emergency presentation, 57% as an urgent referral and 13% as a routine referral (91).

1.11.1 THE 28-DAY PATHWAY

When a GP refers a patient for suspected prostate cancer, after having done a PSA test, the patient enters the 28-day pathway (Figure 1.3) from urgent referral to confirmed diagnosis. Regardless of whether the patient presented opportunistically or due to symptoms, the pathway begins with clinical triage, where patients with urinary tract infections are directed to for alternative non-cancer investigations. By day nine, patients attend an outpatient clinic for a mpMRI and, if indicated, a biopsy. Staging investigations are completed by day 14, and by day 28 patients should receive the outcome, either a confirmed cancer diagnosis or an all-clear result.

Figure 1.3: 28-day prostate cancer diagnostic pathway



Caption: This figure was developed by the NHS Cancer Programme and retrieved from Prostate Cancer UK (2025). https://prostatecanceruk.org/media/1qpnirjl/nhs-england-implementing-a-timed-prostate-cancer-diagnostic-pathway.pdf

1.11.2 Addition of mpMRI to the prostate cancer diagnostic pathway

Incorporating mpMRI into the pathway has led to a shift in the diagnostic pathway for prostate cancer. It helps reduce overdiagnosis, aids the identification of clinically significant cancers, and reduces unnecessary biopsies (92-95). The addition of mpMRI to the prostate cancer diagnostic pathway was confirmed in 2017 based on the results from the PROMIS trial (95) and was recommended by NICE NG 131 (96) in 2019 as first line investigation for patients with suspected localised prostate cancer. NICE further recommends to consider omitting prostate biopsies to patients who score 1 or 2 on the Likert score after a shared decision with the patient.

An example of an efficient use of mpMRI is the RAPID (Rapid Access to Prostate Imaging and Diagnosis) prostate cancer diagnostic pathway. It is an innovative one-stop diagnostic model designed to greatly speed up and improve the accuracy of prostate cancer diagnosis 28-day pathway. It has been successful in the United States (97) and is currently being piloted across several NHS Trusts in London. The model integrates

mpMRI, specialist clinical assessment, and if needed, a targeted biopsy, all on the same day. Those without prostate cancer or low-grade disease risk are often reassured and discharged back to primary care the same day, avoiding unnecessary invasive biopsies and lengthy waiting times. This pathway reduces the patient's diagnostic visits from four to one and provides quicker reassurance or a diagnosis within eight to ten days after biopsy. This pathway allows 43% of patients to avoid biopsy (98). Efficient changes to the diagnostic pathway similar to RAPID have the potential to mitigate the harms associated with increased PSA testing.

1.12 GUIDANCE FOR ASYMPTOMATIC/OPPORTUNISTIC PRESENTATION AND SHARED DECISION-MAKING

In England, asymptomatic PSA testing is controversial. It can lead to unintended consequences such as the increased detection of indolent disease and contributes to overdiagnosis of prostate cancer. The UK National Screening Committee (NSC) recommends against population-based PSA screening because while screening reduces prostate cancer specific mortality, its effect on overall mortality is small (80, 99) and it is unclear whether the benefits from screening patients with PSA outweigh the harms of overdiagnosis, overtreatment or uncertain findings (100). However, the Prostate Cancer Risk Management Programme (PCRMP) advises that patients over 50 can request a PSA test if they make an informed shared decision with their GP (101). If the patient's PSA result is greater or equal to 3ng/mL the PCRMP recommends referral to secondary care. The PCRMP has produced the only guidance in England that recommends PSA testing, after a shared decision-making process, but suggests that GPs should not proactively raise the issue with asymptomatic patients. PCRMP does not provide a recommended age to stop testing, nor does it recommend an interval to repeat the PSA test if the patients value is less than 3ng/mL.

Shared decision making (SDM) is currently considered best practice in the diagnostic pathway for prostate cancer. It represents clinical effort to navigate a challenging subject area in the primary care setting in a patient centred manner. It is recommended in the United States (102), Canada (103), Australia (104) and Europe (105) reflecting the

recognition that PSA testing is an area of medical uncertainty. When done properly, SDM ensures that patients understand their options alongside the potential benefits and harms of the PSA test. Therefore, their decisions are guided by their own preferences and risk profiles (106). In practice, this means the GP supports patients who are considering PSA testing to make a well-informed choice, while not being required to systematically raise the issue in every consultation with patient over the age of 50.

1.13 GUIDANCE FOR SYMPTOMATIC PRESENTATION

For patients presenting to primary care with possible symptoms of prostate disease, GP's in England are recommended to follow the NICE guideline NG12 for suspected cancer recognition and referral (107). A PSA test and rectal exam are recommended to assess prostate cancer risk for patients presenting with lower urinary tract symptoms, nocturia, frequency, hesitancy, urgency or retention, erectile dysfunction or visible haematuria. Referral to secondary care is based on the following age-specific PSA thresholds: greater than 2.5 ng/mL for patients aged 40 to 49, greater than 3.5 ng/mL for ages 50 to 59, greater than 4.5 ng/mL for ages 60 to 69, and greater than 6.5 ng/mL for ages 70 to 79. For patients aged below 40 or above 79, clinical judgement is advised. If the patient's PSA is above the age-specific threshold, NICE advises that before referral the GP should consider the patient's preferences and comorbidities to support shared decision-making before referring the patient for further investigations.

Guidance for patients presenting with symptoms varies slightly across the UK with differences in Northern Ireland (108) and Scotland (109). Northern Ireland follows the NICE NG12 age-specific thresholds but recommends for GPs to repeat the PSA test two to four weeks later, and then to consider referral. An urgent referral is advised immediately if a patient has a single PSA test greater than 20 ng/mL. In Scotland, the age-specific thresholds for referral are slightly different and referral is recommended if a patient is aged below 60 and has a PSA > 3 ng/mL, aged 60 to 69 with a PSA > 4 ng/mL or aged 70+ with a PSA > 5 ng/mL. PSA testing for patients who present with symptoms is debatable as it known that early stages of prostate cancer normally do not present with symptoms. Once symptoms appear patients have normally progressed to later stages of

cancer. However, even so, none of the guidelines in England, Scotland or Northern Ireland specify when to start, stop, or repeat a PSA test for symptomatic patients.

1.14 PROSTATE CANCER SCREENING INTERNATIONALLY

No international guidelines currently endorse routine population-wide PSA screening (110), but recommendations for PSA testing nationally (within the same country) and internationally (between different countries) vary.

Lithuania has implemented a variation of a PSA screening program. The program tests asymptomatic patients every two years, but only for those attending primary care for another reason (111). PSA tests are offered to all people with a prostate aged 50 to 74 and those aged 45 to 49 with a family history of prostate cancer. If a patient has a PSA greater than 3 ng/mL they are referred for further investigations. Those with a PSA less than 3 ng/mL were tested annually between 2006 and 2009 and every two years between 2010 and 2016. Since the program began in 2006, Lithuania has experienced a considerable increase in prostate cancer incidence with incidence rates over 125 per 100 000, making it the country with the highest incidence rate in the world (112). Analysis of stage distribution in Lithuania after implementation of PSA into clinical practice, revealed clear incidence reduction of advanced disease and stage with distant metastasis. It was also found that PSA screening substantially increased the overall incidence and incidence of localised cancer (113). The Czech Republic also recently began an early detection program for prostate cancer for patients (114). They are testing patients between the ages of 50 to 69. If the PSA value is less than 1 ng/mL, retesting happens in four years. For patients with a PSA value 1 to 2.99 retesting occurs in two years and patients will be referred if their PSA value is 3 ng/mL or greater. To date, no results have been published.

Sweden rolled out an Organised Prostate Cancer Testing (OPT) program in 2018. Although the Swedish National Board of Health and Welfare recommended against population-based prostate cancer screening (115), the board acknowledged that individual patients may balance the potential benefits and harms of PSA testing

differently. Due to the ineffective and increased use of opportunistic PSA testing in Sweden, the Swedish Ministry of Health and Social Affairs commissioned the Confederation of Regional Cancer Centres to develop OPT sites aiming at improving pre-testing information, reducing socioeconomic inequality, making the testing and subsequent diagnostics more effective, and gaining knowledge and experience to prepare for a future national screening programme (116).

Different recommendations for and against PSA testing exist within the same country. In the UK the NSC recommends against PSA screening but other organisations, within the UK, such as the PCRMP vaguely recommend for PSA testing. This also occurs in Germany and France, where there is clear a recommendation against population-based PSA screening by The German Institute for Quality and Efficiency in Health Care and the French Haute Autorité de Santé (117-119). However, the German Urological Society guidelines recommend urologists to proactively inform men of PSA testing as an individual screening method. In the same guideline, primary care physicians are advised not to proactively raise this issue with their patients unless they inquire about screening (120). Similarly, The French Committee of Urologic Oncology revised its recommendations and advocates that PSA testing should be considered after providing individuals with detailed information about the potential benefits and harms of the test.

The United States and Ireland leave the decision up to the patient. The US Preventive Services Task Force (USPSTF) changed its guidance in 2012 to recommend that “the decision about whether to be screened for prostate cancer should be an individual one,” without clearly suggesting for or against screening. The Irish Cancer Society suggests informed decision making and an active discussion on an individual level with men from the age of 40 to 50 depending on risk factors. However, routine testing is not advised for men older than 70 to 75 years (121). Other guideline agencies such as the Canadian Task Force on Preventative Health Care (122), the European Society for Medical Oncology(123), and the Dutch Urological Association guidelines (124, 125) recommend against population-wide asymptomatic screening with PSA.

1.15 EVIDENCE FROM PROSTATE CANCER SCREENING TRIALS

PSA testing for prostate is still one of the most controversial topics in the urological literature. Different perspectives on PSA testing occur as the evidence for the benefits and harms of PSA screening from five randomised controlled trials(126) are conflicting. Specifically, the evidence remains inconsistent on the effects of PSA-based screening on prostate cancer mortality (127-131). Five randomised trials with a total of 721,718 men, were included in a Cochrane review (80) which found no effect that PSA screening reduced all-cause mortality incident rate ratio (IRR) 0.99 (95%CI 0.98 to 1.01) and may have no effect on prostate-specific mortality IRR 0.96 (0.85 to 1.08). The three most influential trials are detailed below. (132)

1.15.1 PROSTATE LUNG COLORECTAL OVARIAN (PLCO) TRIAL

The PLCO Trial (133) did not find that annual PSA screening led to a reduction prostate cancer mortality. The trial randomised 76,693 American patients between 1993 and 2001 to annual PSA and DRE screening or usual care. After 17 years of follow-up, prostate cancer incidence was higher in the screening arm, but there was no significant reduction in mortality RR 0.93 (95%CI 0.81 to 1.08). Several factors may explain why PLCO showed no mortality benefit. The PSA threshold of 4 ng/mL may have been insufficient for effective detection, low biopsy uptake after abnormal PSA and approximately 44% of all participants had prior PSA tests at baseline with 52% in the control arm. As a result, this trial unintentionally compared organised PSA testing with opportunistic PSA testing.

In the PLCO trial, the rate of complications among 3,706 negative biopsies was 20.2 per 1000 biopsies for any complication, 7.8 for infectious complications, and 13.0 for non-infectious complications. The rate of overall complications (infectious and non-infectious) rose to 28.2 per 1000 for patients over the age of 70 (132).

1.15.2 European Randomised Study of Screening for Prostate Cancer (ERSPC) trial

The European Randomized study of Screening for Prostate Cancer (ERSPC) (131) reported the PSA screening significantly reduced prostate cancer mortality. After 16 years the rate ratio (RR) of prostate cancer mortality was 0.80 (95%CI 0.72 to 0.89). The difference in absolute prostate cancer mortality increased from 0.14% to 0.18% from the results published after 13 years of follow-up (134) to 16 years (131) respectively. After 13 years when adjusting for control arm contamination and non-attendance, it was found the screening arm showed a 51% decrease in prostate cancer mortality (134). The 23-year follow-up data was published in October 2025 and reported that prostate cancer mortality was 13% lower in the screening group RR 0.87 (0.80 to 0.95), and the absolute risk reduction was 0.22% (0.10 to 0.34) (135) .

A microsimulation model with data from the ERSPC trial was used to evaluate the effect of PSA based screening on quality-adjusted life years (QALYs) (136). It was found that PSA screening and subsequent treatment were associated with significant harms with only moderate benefits. One study reported that PSA screening, up to age 90, with a 9.2% active surveillance rate led to only 19 QALYS gained. This translated into more than a 75% relative loss in potential QALYS gained (136) due to aggressive treatment in patients with low risk disease and due to PSA testing in older patients.

1.15.3 Cluster Randomised Trial of PSA Testing for Prostate Cancer (CAP)

The CAP trial (99), based in the UK, invited patients aged 50 to 69 for a single PSA test found a small mortality benefit RR 0.92(0.085 to 0.99, p = 0.03) after 15 years of follow-up. Compared with the control arm, the PSA screening intervention increased detection of low-grade Gleason ≤6: (2.2% vs 1.6%, p < 0.001) and localised (T1/T2: 3.6% vs 3.1%, p <0.001) disease but not intermediate Gleason 7, high-grade Gleason ≥8, locally advanced (T3), or distally advanced (T4/N1/M1) tumours (99). There was low uptake of program with only 40% of the population accepted the PSA test invitation.

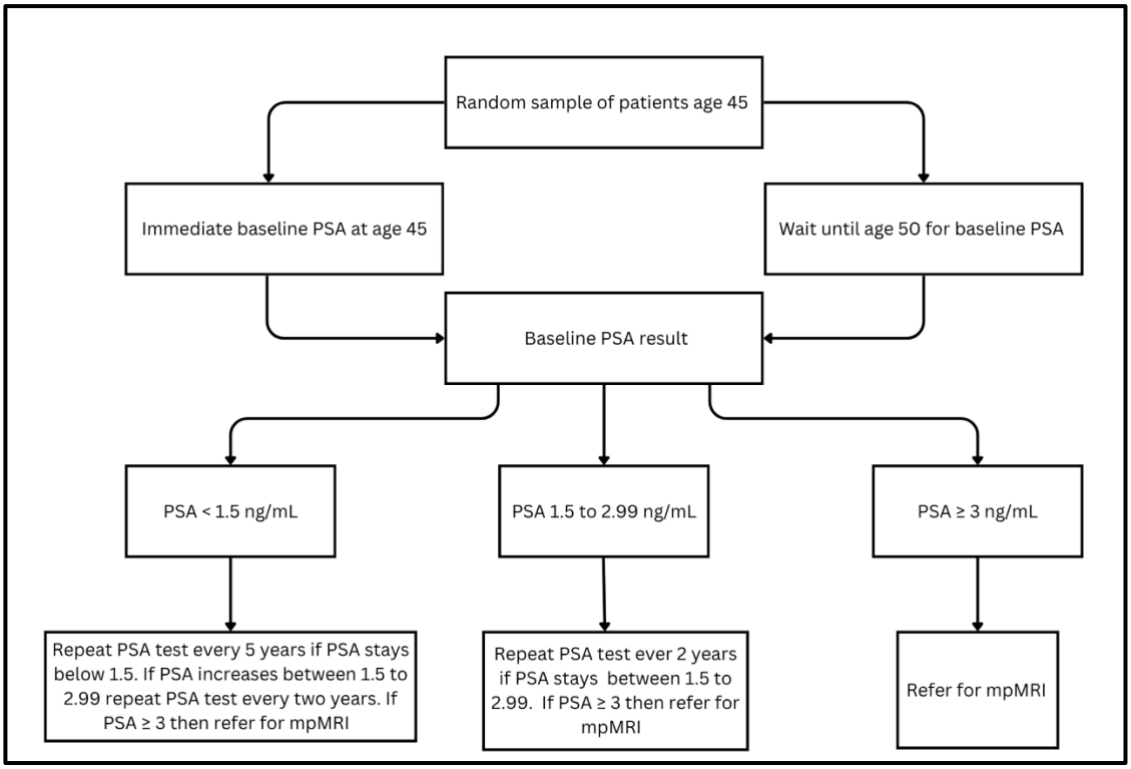
In a post hoc analysis of the CAP trial it was found that the mean probability of overdiagnosis was 9.2% (95%CI 8.9 to 9.4) for the age group 50 to 54 compared to 20.8% (20.6 to 21.0) those aged 65 to 69 (99). The future of prostate cancer detection (Recent screening trials)

1.15.4 PROBASE

The PROBASE trial in Germany recruited 46,642 patients aged 45 between 2014 and 2019 to evaluate risk-adapted PSA screening. It compares initiating screening at ages 45 versus age 50. After 5.9 years the first results were reported (137). At baseline, participants were stratified by PSA level into low risk (< 1.5 ng/mL), intermediate risk (1.5 to 2.99 ng/mL), and high risk (≥3 ng/mL). The majority (89%) of patients were classified as low risk. In the first screening round, prostate cancer prevalence among 45-year-olds was very low at 0.2%, with only 0.02% having aggressive disease. A total of 1.5% of patients had an initial PSA ≥ 3 ng/mL; among them, 52% were confirmed on repeat testing two weeks later. Patient risk categories and retesting intervals are described in

Figure 1.4. The trial is not stratifying patients in the same PSA risk category to different retesting intervals. This will make it challenging to determine the optimal retesting intervals by PSA value and age.

Figure 1.4: PROBASE trial PSA retesting strategy

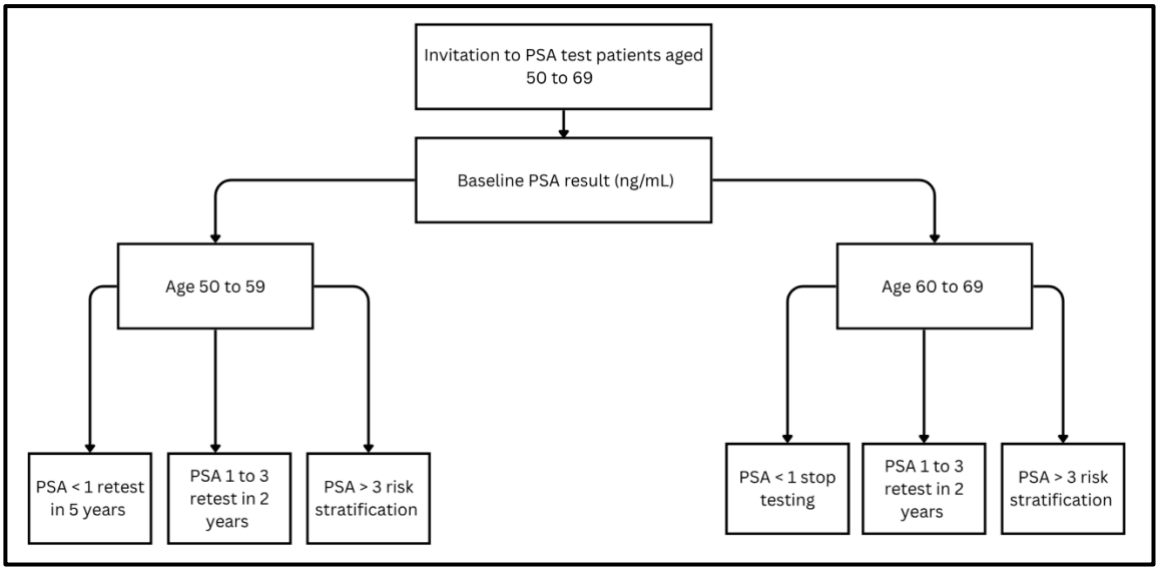


Caption: This figure is adapted from the PROBASE study. Available from: https://www.dkfz.de/en/personalized-early-detection-of-prostate-cancer

1.15.5 PRAISE-U

In 2023, the "PRostate cancer Awareness and Initiative in the EU" (PRAISE-U) consortium was formed. The PRAISE-U Project (138), which is led by the EAU, aims to provide concrete evidence on a risk-stratified approach to the early detection of prostate cancer outside a trial setting. In 2022, the EU Commission proposed introducing PSA testing for patients in an organised setting, in combination with mpMRI as a follow-up test to minimise these risks. PRAISE-U is a pilot study evaluating the implementation of a risk-stratified population-based approach to PSA screening in Ireland, Lithuania, Poland, and two areas in Spain (Galicia and Manresa) for feasibility, efficacy, and cost effectiveness. Patients aged 50 to 69 will be invited to participate. Those consenting undergo PSA testing, and men with a PSA greater than 3 ng/ml will undergo risk stratification before mpMRI and, if necessary, after mpMRI before undergoing biopsy (138). The retesting intervals will follow the EU -risk stratified guidance(138) depicted in Figure 1.5.

Figure 1.5: PRAISE-U PSA retesting algorithm



Caption: This figure was adapted from PRAISE-U. Available from: https://uroweb.org/news/praise-u-initiative-an-update-on-the-rapidly-evolving-landscape-of-pca-screening-in-europe

1.15.6 TRANSFORM TRIAL

The TRANSFORM trial is set to run recruitment between 2025 and 2027. It is a large UK study designed to evaluate new approaches to prostate cancer screening. Patients aged 50 to 74 are eligible, with the age threshold lowered to 45 for patients of Black ethnicity. Follow-up will be at least ten years. To improve ethnic representation, at least 10% of invited participants will have a Black ethnic background. In Stage 1, approximately 12,500 patients will be recruited over the three years. Four screening strategies will be compared:

1) If PSA is > 3 ng/mL, then mpMRI.
2) If PSA > 1ng/mL, then short mpMRI (10-12 minutes).
3) Short mpMRI regardless of PSA.
4) If polygenic risk score (PRS) is greater than 3.5% then short mpMRI

There are currently no details about retesting intervals, although this will be made available in the future.

1.16 STAKEHOLDER VIEWS OF THE PSA TEST

1.16.1 GP VIEWS OF THE PSA TEST

PSA testing patterns vary among GPs based on differing guidelines, patient pressure, time constraints and personal views or preferences (139). In Norway GPs have a general ambivalence to the use of PSA. One study that explored 17 GP participants' attitudes to national guidelines found there was uncertainty regarding the PSA test, specifically, when to use it, how to interpret the results and when to refer to specialist health services (140). In New Zealand it was found that all GPs in the study tested asymptomatic patients with PSA and believed in the benefits of PSA testing but had difficulty in providing patients with information about the pros and cons of PSA testing (141).

There is a general lack of understanding in the literature on GP perspectives of PSA testing in primary care in the UK post 2016. I found one study reporting GP perspectives on PSA testing from 2005 which surveyed 400 GPs across the UK (142). Seventy-six percent of GPs reported requesting a PSA test for an asymptomatic patient at least once in the previous three months, with 13% reported having tested more than five patients in this period. A majority agreed with SDM as a good policy and reported they would do a PSA test both for patients with a family history of prostate cancer who requested a test and for patients who presented with lower urinary tract symptoms. A study in 2007 with 21 GPs from 18 practices found that GPs' presentation of information to patients appeared to be affected by their personal views of the PSA test. For those more against PSA testing, GPs focussed the discussion on the false-positive and false-negative rates of the test, and the risks associated with a prostate biopsy (143).

In the UK a study published in 2016 assessed GPs' understanding of the PCRMP guidance (144) .There were 699 GPs who completed the survey, and of those 23% were aware of the latest PSA screening evidence and 94% said that they would like an update. Another study published in 2016 on 40 Australian and 29 UK-based GPs found that Australian GPs reported that they frequently spoke with asymptomatic men about being screened for

prostate cancer, while UK GPs reported that they did this rarely (145) and reported the long-standing consistency of a central position discouraging prostate cancer screening.

No recent studies have specifically examined GP perspectives on repeat PSA testing or on the uncertainty created by guidance that recommends offering a single PSA test but provides no advice on follow-up. This gap is particularly important given recent policy changes, advances in technologies, and increased public attention driven by celebrities and charities advocating for PSA testing.

1.16.2 PATIENT VIEWS OF THE PSA TEST

Patients judge the benefits and harms of PSA testing and its consequences differently. The decision to undergo PSA testing is highly preference sensitive (146). For instance how negative it would be if the patient were to suffer from permanent erectile dysfunction due to prostate cancer screening. Two studies suggested that patients were willing to forego screening with a small benefit in prostate cancer mortality if it would decrease the likelihood of unnecessary treatment or biopsies. In contrast, one study reported that men were willing to accept a substantial overdiagnosis to reduce their risk of prostate cancer mortality.

In a discrete choice experiment (DCE) of 459 individuals, it was found that people were willing to trade-off 2.0% (95%CI 1.6% to 2.4%) or 1.8% (1.3% to 2.3%) risk reduction of prostate-specific mortality to decrease their risk of unnecessary treatment or biopsy by 10%, respectively. Patient preferences in this study were substantial. Individuals with higher educational backgrounds were less likely to choose PSA screening once provided with the statistics compared to those from lower educational levels. It also found that people prefer a shorter screening interval compared to a longer one (147). A DCE study with over 650 Australian patients found that patients were willing to accept between 65 and 233 of 10 000 extra patients with unnecessary biopsies, and between 31 and 72 of 10 000 extra men with incontinence or bowel problems to avoid one prostate cancer death.

When considering the impact of patient perceptions on SDM as part of current PSA testing policies, patients may overestimate the accuracy and benefit of prostate cancer screening due to numeracy misinterpretations, impacting the outcome of SDM. A recent study (148) reported the importance of pre-screening counselling for patients. They found that patients were surprised to hear about the inaccuracy of the PSA test. Participants were surprised that screening was only expected to prevent one death per thousand people screened every ten years. Based on this information they still came to varying conclusions. Some perceived the benefit as disillusioning while others felt that testing was worth it to save this life (148).

No studies were found that specifically investigated whether values and preferences differed among men with family history of prostate cancer, of African descent, from lower socioeconomic levels or the impact of increased media attention. No studies were found with a focus on patient preferences of repeat PSA testing or preferences for a second PSA test following a first PSA test in a "grey zone" (1 to 4 ng/mL).

1.16.3 POLICY STAKEHOLDER VIEWS OF THE PSA TEST

Consistent messaging for PSA testing across the UK currently does not exist. As mentioned above between England and Wales, Scotland and Northern Ireland, there are three different PSA test referral thresholds for patients presenting to their GP with symptoms of prostate cancer. Within England the NSC clearly recommends against PSA testing while the PCRMP recommends for SDM for patients over 50. Unclear government policies on PSA testing leave many open questions such as what should be done for men at higher risk of prostate cancer, how often men who choose to have the PSA blood test should have one, and when it would be in a man's best interest to stop testing.

Charities and the media have further influence over the messaging around PSA testing, and it is important that trusted charities have consistent messaging. Cancer Research UK does not mention anything about the best use of the PSA test or retesting due to the lack of consistent evidence. Prostate Cancer UK recently published a consensus statement on optimising the use of the PSA blood test in asymptomatic men for early

prostate cancer detection in primary care (149) highlighting the need to raise awareness of prostate cancer among people aged over 50 and that all informed patients should have the ability to access a PSA test. They also recommend that primary care professionals should proactively discuss PSA testing with men of Black ethnicity, those with a family history of prostate cancer and those with genetic risk factors such as BRCA2. Additionally, Prostate Cancer UK released a "risk checker" which told every man over the age of 50 to ask their GP for a PSA test. Subsequently, some GP practices in London sent out text messages to all of their male patients in this age range with the link to the risk checker. While this is not a government led PSA testing program this initiative was very similar to PSA based screening and unwarranted (150). The Tackle Prostate Cancer charity advocates for screening with PSA for all patients starting no later than age 50 until age 70. They further recommend one-to-two-year intervals for patients at high risk. This charity also supports the Man Van run by the Royal Marsden which is a community-based PSA testing van (further discussed in Section 5.6.4). Additional charities in the UK supporting prostate cancer research are: Prostate Cancer Research, Orchid Male Cancer, and Movember.

1.17 OVERDIAGNOSIS AND OVERTREATMENT OF PROSTATE CANCER

Overdiagnosis is a serious challenge driven by opportunistic use of the PSA test. The increase in the incidence of prostate cancer illustrated above is likely a result of increased PSA testing practices as age-specific prostate cancer incidence rates largely mirrors PSA testing rates in Australia (151, 152), the US (153), and the UK(154). Many patients with cancers detected opportunistically undergo radical prostatectomy or radiotherapy, despite deriving no benefit if their cancers would have remained undiagnosed in the absence of PSA testing. These treatments often result in lasting urinary, sexual, and bowel complications (155), and are particularly unnecessary when patients are more likely to die from old age or other causes. From a health system perspective, overdiagnosis contributes to considerable resource use, driving increased diagnostic consultations, biopsies, treatments, and long-term follow-up.

Several approaches have been proposed to reduce overdiagnosis. For instance, limiting PSA testing to patients under 70 years. There is limited benefit and considerable harm for patients over the age of 70. Approximately 40% of overdiagnoses are in this age group (155). Restricting screening in patients over 60 to those with PSA above 1 ng/mL and screening patients over 70 only in selected circumstances.

Advancements in the diagnostic and treatment pathways may swing the balance of benefits of PSA testing with the harms of overdiagnosis. mpMRI (95), as detailed above, may reduce the number of biopsies and increase the proportion of clinically significant cancer diagnoses. Active surveillance offers another strategy, monitoring low-risk prostate cancer instead of treating it immediately, though it can still cause psychological distress and anxiety from living with a cancer diagnosis if patients feel like they are not being monitored appropriately. Other advancements include targeted biopsies, transperineal biopsies, focal therapy and improvements in survival of metastatic prostate cancer. Together with improved identification of patients at higher genetic risk and stronger evidence on optimal PSA retesting intervals, these innovations may help tip the balance of PSA testing towards a net benefit for patients and the healthcare system.

1.18 IMPORTANCE OF THE RIGHT PSA RETESTING INTERVALS

Evidence-based retesting intervals targeted at the right patient population provide a possible solution to overdiagnosis and overtreatment that occur from unregulated PSA testing. However, increasing the amount of PSA testing also poses a threat to overdiagnosis and overtreatment. The purpose of retesting patients in any disease area, including prostate cancer, is to detect disease early enough that treatment remains effective and the adverse consequences of delayed diagnosis can be avoided. Deciding when to retest a patient is fundamentally a balance. Short retesting intervals reduce the risk of delayed diagnosis and improve the chance of detecting disease at a treatable stage. At the same time, overly frequent testing provides little marginal benefit and can increase harms to the patient through the test itself, false-positive results, unnecessary follow-up investigations, or overdiagnosis (156). Longer intervals in the short term reduce the burden on the healthcare system by limiting unnecessary interventions. Longer

intervals increase a patient's risk of a late diagnosis, which is strongly associated with worse outcomes and potentially increased healthcare usage in the long term (e.g. more expensive treatments). Determining the appropriate retesting interval requires accounting for uncertainty around the natural history of the progression of disease, the accuracy of available tests, the effectiveness of treatments alongside associated side effects, and downstream clinical decision making.

Difficulty understanding when to retest a patient is partly due to lack of clinical trials in this area. For example, prostate cancer trials compare screening versus no screening (135, 157), rather than systematically evaluating different retesting intervals for either screening purposes or for monitoring low risk prostate cancer. No trials in the past have or are currently designed to address this question of retesting (86). Trials are costly, require large numbers of participants, and require long follow-up, which is especially challenging in chronic or slow-progressing disease areas such as prostate cancer. This uncertainty around optimal retesting intervals is not unique to prostate cancer. In population-based screening programmes for breast, cervical, colorectal, and lung cancers, debates persist over interval length, balancing the detection of interval cancers against the burden of over-testing.

Data driven models based on observational electronic health records could provide a solution to the impracticality of randomised control trials in this setting (156). Policy recommendations have previously shifted based on observational evidence. For example, in 2025 the NHS extended cervical screening from three to five years for women aged 25 to 49 who tested negative for HPV. This change was based on an observational study from English HPV pilot screening programme showing very low 3-year risks a diagnosis of CIN3+ after a negative HPV test compared with negative cytology (158).

1.19 Thesis Aims and Objectives

Different policies nationally and internationally in combination with varied results from clinical trials make it difficult to come to a consensus around the utility of PSA testing in general, let alone how often a PSA should be repeated. This thesis focusses on how to

subsequently manage patients who present to their GP (asymptomatically or symptomatically) and decide to have a PSA test.

The three objectives of this thesis are as follows:

1) Summarise recommendations and the evidence referenced in clinical practice guidelines for retesting intervals.
2) Characterise how PSA tests are currently used in English primary care for patients without a prostate cancer diagnosis.
3) Generate new evidence to inform optimal repeat testing intervals patients who have a PSA test in primary care.

Chapter 2: A Critical Appraisal of the Evidence for PSA Retesting Intervals: A Guideline Review

2.1 Dissemination

The work presented in this chapter was published in the British Journal of Urology International 2025 (159).

***Collins KK**, Virdee PS, Roberts N, Oke JL, Nicholson BD. Guideline of guidelines: a critical appraisal of the evidence for PSA retesting intervals. BJU International. 2025;136(3):372-84.*

Findings from this chapter were awarded Best Poster Presentation at the Cancer Primary Care Conference in Melbourne 2024.

2.2 Background

Clinical practice guidelines are essential tools for clinicians. They provide evidence-based frameworks to support clinical decisions with the aim of optimising patient outcomes (86). Guidance on testing and retesting with PSA is not clear. Due to updates from large, randomised PSA screening trials (Section 1.15), recommendations both advise for and against PSA screening change frequently. For example, in 2018 the US Preventive Services Task Force (USPSTF) published a guideline (102) that reversed its 2012 guidance which had advised PSA testing and instead recommended against PSA screening. Such changes pose challenges by increasing uncertainty about PSA testing for both GPs (160) and patients (161).

Almost all national healthcare authorities around the world recommend against population-wide PSA screening for prostate cancer (162). This is because evidence from five randomised controlled trials of PSA screening (126) are inconsistent, particularly concerning the impact on prostate cancer mortality (127-130, 134). Major concerns also

persist about the risks of overdiagnosis and overtreatment. The results of the 23-year follow-up for the ERSPC trial, described in Section 1.15.2, were recently published. The study reported a 13% relative risk reduction in prostate cancer mortality in the screening arm compared to the control arm (135). History may repeat itself, as the results of this trial indicate that targeted approaches to PSA testing may provide benefits to patients. It is possible that these results may trigger guideline developers to reassess the evidence on PSA testing and revise up their recommendations once again. It is unknown if this will cause more uncertainty with PSA testing guidance or provide the clarity that is needed. The bottom line is that recommendations for PSA testing and retesting continue to be uncertain.

Whilst healthcare authorities do not recommend population-based PSA testing, they acknowledge that individual patients weigh the potential benefits and harms of PSA testing differently and therefore advocate for shared decision-making. Some guidelines also recommend specific PSA retesting intervals for the patients who choose to be tested. In this chapter, I summarise guideline recommendations for repeat PSA testing intervals. I explore what evidence guideline developers consider sufficient to support their recommendations for PSA retesting intervals, and how consistently this evidence is interpreted across guidelines. While several reviews of PSA testing guidelines have been published (163-167), none have critically evaluated the evidence base that specifically underpins the retesting interval recommendations. Given how frequently PSA testing guidance changes, both internationally and within countries, it is important for policymakers to understand current recommendations and the extent to which the same evidence is interpreted and applied. The findings from this chapter directly inform Chapters 6 and 7, which focus on generating evidence for PSA retesting intervals in primary care.

2.3 OBJECTIVES

The objectives of this chapter were to:

1) Summarise recommendations for PSA retesting intervals in guidelines for symptomatic or asymptomatic patients in primary care.

2) Examine the methods and outcomes of each study cited as evidence for the recommendations.
3) Determine if the conclusion of the referenced study was adequately interpreted in the guideline recommendation.
4) Summarise the quality of guidelines using the AGREE II tool.

2.4 METHODS

I conducted a systematic review to identify guidelines with recommendations for PSA retesting intervals in primary care for symptomatic or asymptomatic patients without a prior diagnosis of prostate cancer. Ethical approval was not required because only data available to the public were included. All results in this chapter are reported according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines (168). The study protocol was registered on the Open Science Framework (https://osf.io/k6whd).

2.4.1 SEARCH STRATEGY

I searched PubMed, the Turning Research into Practice (TRIP) (169) database and any relevant grey literature. The first search was for the most up to date guidelines between 2013 and 2024. After receiving peer review comments from the British Journal of Urology International, I conducted an updated search in January 2025. The search strategy included terms and synonyms for: “detection”, “diagnosis”, “PSA” and “screening.” Examples of grey literature searches include guidance found on government websites or from urological associations. The full strategy is provided in Table 2.1.

Table 2.1 Search Strategy

	Number of Guidelines	Updated Search Date*
PubMed		
(("prostate neoplasms"[Text Word] OR "prostatic neoplasms"[Text Word] OR "prostate cancer"[Text Word] OR "prostatic cancer"[Text Word] OR "prostate carcinoma"[Text Word] OR "prostatic carcinoma"[Text Word]) AND ("screening"[Text Word] OR "psa"[Text Word] OR "diagnosis"[Text Word] OR "detection"[Text Word])) AND (guideline[Filter] OR practice guideline[Filter])	107	05/01/2025
TRIP database		
("prostate neoplasms" OR "prostatic neoplasms" OR "prostate cancer" OR "prostatic cancer" OR "prostate carcinoma" OR "prostatic carcinoma") AND ("screening" OR "psa" OR diagnosis OR detection) - limited to Guidelines within Secondary Evidence	923	05/01/2025
Grey literature		
Individual organisational websites: NICE, UPSTF, UK Screening Committee, Canadian Preventative Task Force, New Zealand Ministry, Danish ministry, Canadian Urological Association, American Urological Association, ESMO.	11	05/01/2025

2.4.2 SELECTION PROCESS

Title and abstract screening, in addition to full text screening, were conducted independently by myself and Pradeep S. Virdee (PSV). The Rayyan software was used (170) and any discrepancies were discussed until consensus was reached. If consensus was not reached a third reviewer (BDN) would make the final call. However, throughout the process of screening this was not required. Guidelines were defined as systematically developed statements written to assist practitioner and patient decisions about appropriate PSA retesting intervals (171).

Guidelines were eligible for inclusion if they met all of the following criteria:

1) Provided recommendations on PSA retesting intervals for asymptomatic or symptomatic patients in primary care, for patients without a prior diagnosis of prostate cancer.
2) Published between 2013 and 2024.
3) Written in English.

4) Developed or endorsed by a government agency or health professional association.

Guidelines were excluded if they met any of the following criteria:

1) Addressed cancer sites other than prostate.
2) Addressed PSA retesting in the context of prostate cancer recurrence or active surveillance.
3) Did not provide a specific retesting interval (e.g., only recommended shared decision-making or personalised intervals without defining a time frame for retesting).
4) Were position statements, consensus papers, or recommendations not formally endorsed by a guideline committee.

Older versions of guidelines were excluded as PSA testing guidelines change frequently. For example, the 2018 version of the AUA guideline (172) was not included as there was an updated 2023 guideline available. Guidelines were only included if they were written in English to ensure they were all available for practicing GPs in England. The French guideline was published in French and English.

2.4.3 DATA EXTRACTION

PSV and I independently extracted data from the eligible guidelines into Excel. Any disagreements were discussed until consensus was reached. The following data were extracted from each guideline: guideline developer, year, country, recommended PSA retesting interval, references for interval recommendation, if symptoms were mentioned, if retesting interval recommendations were stratified by risk (age, PSA, ethnicity, family history, germline mutations) and when to stop retesting. The following data were extracted from the referenced studies within each guideline: author, year of publication, type of study, methods, if single or multiple PSA tests were analysed, study outcomes, if the study specifically aimed to calculate intervals and the PSA retesting interval suggestion.

2.4.4 Data synthesis and analysis

I conducted a narrative summary of guidelines that recommended PSA retesting intervals. To categorise the evidence cited for each recommendation, I applied the Oxford Centre for Evidence-Based Medicine (OCEBM): Level of Evidence (173). Study design categories included systematic review, randomised trial, model, prospective, retrospective, and guidelines. I examined the research methods used in each study as well as the outcomes presented. PSV and I independently reviewed each cited study. We cross referenced the findings with the corresponding recommendation in the guideline to determine whether the findings from studies cited as evidence for PSA retesting intervals were appropriately reflected in the guideline recommendations. Alignment was categorised as "Yes" if the guideline recommendation matched the referenced study. "Partial" if the recommended intervals were similar to the study findings and "No" if the referenced studies recommended different intervals than the study recommended or cited studies that provided no explicit interval recommendation. If consensus was not reached on the alignment of the guideline recommendation with the cited evidence a third reviewer (BDN) reviewed the study and the guideline.

2.4.5 Quality appraisal of guidelines

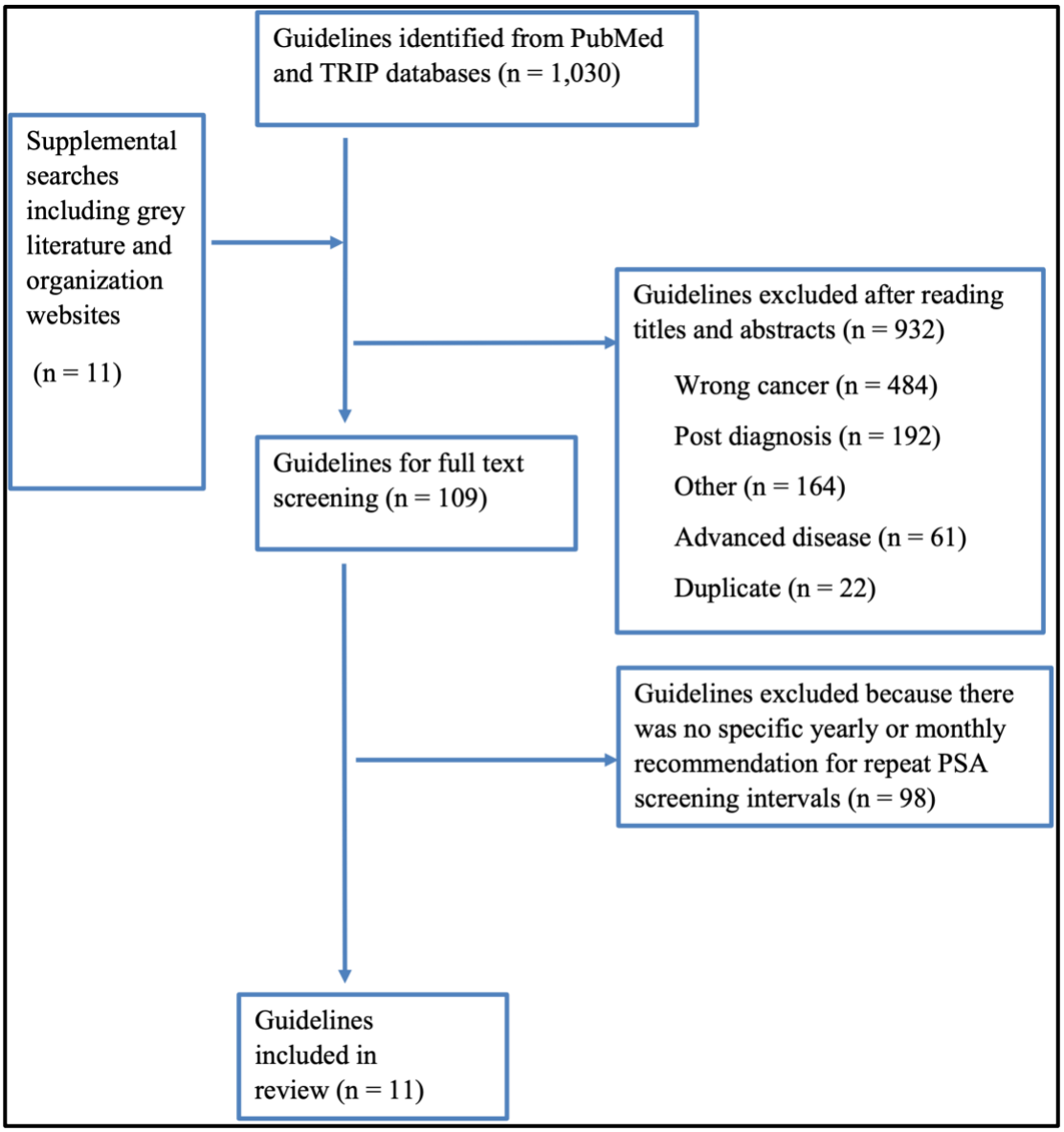
The quality of each guideline was assessed using the AGREE II tool (174). AGREE II comprises 23 items across six domains: 1. Scope and purpose, 2. Stakeholder involvement, 3. Rigor of development, 4. Clarity and presentation, 5. Applicability, and 6. Editorial independence. PSV and I independently scored each item using a 7-point scale (1-strongly disagree to 7-strongly agree). A standardised mean score for each of the 7 domains was calculated using the formula: ((actual score—minimum score)/(maximum score—minimum score)) × 100% (174).

2.5 Results

The initial search yielded 1,030 guidelines. Eleven were eligible for data extraction (Figure 2.1). Across the eleven included guidelines, 37 individual studies were referenced as evidence for the recommended PSA retesting intervals (Table 2.3). The most commonly

cited paper (175) was by Andrew Vickers looking at baseline PSA and risk of prostate cancer. It was cited in six (55%) of the guidelines (103, 105, 176-179).

Figure 2.1 PRISMA Diagram



2.5.1 Summary of Guideline Recommendations for Repeat PSA Testing Intervals

Recommendations for PSA retesting intervals ranged from one to ten years (Table 2.2). Nine (82%) guidelines recommended an interval of approximately two-to-four years (103-105, 176-181). Ten (91%) of the interval recommendations were stratified by risk, but not the same type of risk (103, 105, 176-183). Five (45%) adjusted by both

age and PSA value (105, 176-178, 183). Three (27%) were adjusted by PSA value only (103, 180, 182). Four (36%) recommended more frequent intervals by risk factors such as family history, germline mutations (BRCA1 or BRCA2) and African ethnicity (178, 179, 181, 183). Five (45%) recommended to start testing earlier (age 45 instead of age 50) for high-risk patients but did not recommend shorter subsequent retesting intervals (103-105, 176, 180). Five (45%) recommended to discontinue PSA testing at age 70 (103, 104, 181-183) and six (55%) recommended to stop testing based on life expectancy and health status (103, 105, 176, 179, 180, 183). PSA retesting intervals based on symptoms was not incorporated into any guidance.

Table 2.2 Clinical practice guideline findings

Guideline	Country	Recommended PSA testing interval	References	Are the conclusions of the referenced studies aligned to the interval recommendation*	Symptoms considered	Testing intervals stratified by patient risk	Recommendation on age to stop screening
American Cancer Society (2023) (180)	United States	2 years if PSA < 2.5 ng/ml, 1 year if PSA ≥2.5 ng/ml	Wolf(2010) (168), Smith(2018) (184)	Yes	No	PSA < 2.5 ng/ml and PSA ≥ 2.5 ng/ml.	Stop testing patients with no symptoms and have less than 10 years life expectancy
American Urological Association (2023) (176)	United States	2-4 years	Vickers (2013)(175), Carlsson (2014)(185), Robool (2005)(186), Preston (2016) (187), Vickers (2010)(188), Heijnsdijk (2020)(189), Gulati (2013)(190), Heijnsdiik (2012)(191), Ross(2000)(192)	Partial	No	Re-screening interval can be 1 to 4 years for patients with PSA levels of 1 to 3 ng/mL between the ages of 45 to 70 years. The re-screening interval can be prolonged for patients aged 45 to 70 years with a PSA < 1 ng/mL or those with a PSA below the age-specific median. Possible to lengthen interval for patients PSA < 1 age 60.	Individual decision for when to stop based on life expectancy for patients between the ages of 70 to 80. Can stop testing or substantially lengthen the re-screening interval for patients 75 years of age or older if PSA is < 3 ng/mL

Guideline	Country	Recommended PSA testing interval	References	Are the conclusions of the referenced studies aligned to the interval recommendation*	Symptoms considered	Testing intervals stratified by patient risk	Recommendation on age to stop screening
Canadian Urological Association (2022) (103)	Canada	4 years if PSA <1 ng/ml, 2 years if PSA 1-3 ng/ml, more frequent if PSA >3 ng/ml	Vickers (2013) (175), Gelfond (2015) (193), Preston (2016) (187)	No	No	PSA <1 ng/ml, PSA 1-3 ng/ml, and PSA >3 ng/ml	For men aged 60 with a PSA <1 ng/ml, consider discontinuing PSA screening For all other men, discontinue PSA screening at age 70 For men with a life expectancy less than 10 years, discontinue PSA screening
Cancer Council Australia (2016)(104)**	Australia	2 years	Andriole (2012)(127), Kipelainen (2013)(194), Kjellman (2009)(195), Bokhorst (2014)(196), Hugosson (2010)(197), Labrie (2004)(129), Roobol (2013)(198), Sandblom (2004)(199), Andriole (2009)(157), Sandblom (2011)(200)	No	Mentions asymptomatic patients	No	Recommends to test men between ages of 50 to 69

Guideline	Country	Recommended PSA testing interval	References	Are the conclusions of the referenced studies aligned to the interval recommendation*	Symptoms considered	Testing intervals stratified by patient risk	Recommendation on age to stop screening
EAU - EANM - ESTRO - ESUR - ISUP – SIOG (2024) (105)	Europe	Every 2 years for those initially at risk, or postponed up to 8 years in those not at risk	Vickers (2013)(175), Carlsson(2014)(185), Gelfond (2015)(193), Robool (2005)(186)	Partial	Mentions both symptomatic and asymptomatic patients but does not recommend different retesting intervals based on symptom presentation	Follow-up intervals of two years may be offered to those initially at risk (PSA > 1 ng/mL at 40 years; PSA > 2 ng/mL at 60 years)	Stop testing based on life expectancy and performance status. Patients with a life expectancy <15 years are unlikely to benefit from testing
French Urology Association Cancer Committee (2022) (179)	France	2 to 4 years but adapted to the patients risk profile Annually patients with BRCA2 or HOXB13 germline mutations.	Vickers (2013)(175), Hugosson (2019) (131), Preston (2016) (187), Heijnsdijk (2020)(189), Schroder (2014)(134), Lilja (2007)(201)	Partial	Mentions asymptomatic patients	Testing 2 to 4 years for patients over 50, age 45 for patients of Black ethnicity or family history Start at age 40 and test annually for those with BRCA2 or HOXB13	Stop testing patients with a life expectancy less than 10 years

Guideline	Country	Recommended PSA testing interval	References	Are the conclusions of the referenced studies aligned to the interval recommendation*	Symptoms considered	Testing intervals stratified by patient risk	Recommendation on age to stop screening
Memorial Sloan Kettering (2016) (177)	United States	PSA ≥ 1 but < 3 ng/mL: PSA testing every 2 to 4 years, PSA < 1 ng / mL: PSA testing at 6 to10 years	Vickers (2013)(175), Carlsson (2014)(185), Andriole (2012)(127), Schroder (2014)(134), Thompson (2006)(202), Lilja (2007)(201), Loeb (2012)(203), Eastham (2003)(204), Ven Leeuwen (2010)(205)	Partial	Mentions asymptomatic patients	Reported by age group (45-49, 50-59, 60-70) but generally the repeat testing interval was the same for each age group (2-4 years or 6-10 years depending on PSA)	Stop testing at age 76+ for all patients. Test patients if in good health 71-75. Stop testing if PSA ≤ 1 at age 60-70.
NCCN (2023) (178)	United States	2 - 4 years for those with a PSA level ≤1 ng/mL, 1- 2 years for high risk patients with PSA is ≤3 ng/mL and average risk patients with PSA 1-3ng/mL, and 1-2 years for those aged >75 years with PSA <4ng/mL.	Vickers (2013)(175), Carlsson (2014)(185), Robool (2005)(186), Preston (2016) (187), Vickers (2010)(188), Heijnsdijk (2020)(189), Vertosick (2020)(206), Preston (2019)(207), Kovac (2020)(208), Ulmert (2008)(209)	Partial	No	High risk is Black/African American individuals, germline mutations that increase the risk for prostate cancer, and those with suspicious family history), repeat testing is recommended at 1-2 year intervals if PSA is ≤3 ng/mL.	Stop testing at age 75 unless patient is exceptionally healthy
Prostate Cancer Working Group and	New Zealand	2-4 years if PSA is in normal range and no family history.	Basch (2012)(210), Catalona (2011)(211)	No	No	If patient has family history test every year if not 2-4 years. Same	Patients aged over 70 years can be reassured further prostate cancer

Guideline	Country	Recommended PSA testing interval	References	Are the conclusions of the referenced studies aligned to the interval recommendation*	Symptoms considered	Testing intervals stratified by patient risk	Recommendation on age to stop screening
Ministry of Health (2015) (181)		Annually if patient has family history				interval for all ages and PSA values.	testing is not likely to be of any benefit
SEOM (2014) (182)	Spain	1–2 years if PSA < 3 ng/mL, individualised risk assessment PSA 3-4, 6-12 months if PSA is > 4 ng/mL	Andriole (2012)(127), Schroder (2012)(212)	No	No	PSA <3 ng/mL and PSA >4 ng/mL For PSA levels between 3 and 4 ng/mL, consider an individualised risk assessment that incorporates other risk factors. These factors include age, family history, ethnicity, DRE or PSA kinetics – no interval provided	Recommends to test men between ages of 50 – 70
South African Urology Association and the Prostate Cancer Foundation of South Africa	South Africa	Age 45-49 PSA <1 retest in 2 years for patients PSA 1-2.5 retest in 1 year. Age 50 -59 PSA <1 retest in 2 years for PSA 1-	DeSantis (2019) (213)	No	Mentions asymptomatic patients	Retesting intervals for patients of Black ethnicity.	Stop testing men aged >70 years or with a life expectancy <10 years

Guideline	Country	Recommended PSA testing interval	References	Are the conclusions of the referenced studies aligned to the interval recommendation*	Symptoms considered	Testing intervals stratified by patient risk	Recommendation on age to stop screening
(2024) (183)		3.5 retest in 1 year. Age 60-70 PSA < 1 retest in 2 years for PSA 1-4.5 retest in 1 year.					

The Urological Society of Australia and New Zealand (2022) (214) published a position statement to serve as an interim document for the optimised use of PSA testing in Australia and New Zealand until the Prostate Cancer Foundation of Australia and Royal Australian College of General Practitioners guidelines are updated. It recommends clinicians should follow the EAU position statement (215) risk stratified PSA retesting intervals

2.5.2 SUMMARY OF STUDIES REFERENCED IN GUIDELINES AS EVIDENCE FOR PSA RETESTING INTERVALS

Across the 11 included guidelines, a total of 37 studies were cited as evidence supporting PSA retesting interval recommendations (Table 2.3). The most common study designs were randomised trials (41%) and retrospective studies (22%). The methods used in the randomised trial studies were more similar to retrospective cohort analyses, as no randomised trial directly compared different retesting intervals. Only American and French guidelines (176-179) referenced simulation or modelling studies Figure 2.2.

Five (14%) of the studies, cited in two (18%) of guidelines (176, 178), specifically aimed to determine PSA retesting intervals (189-192, 216) (Table 2.3). The remaining nine (82%) guidelines did not reference this type of applicable evidence (103-105, 177, 179-183). There were 14 (37%) cited studies that used a single baseline PSA test value to estimate the patients risk of prostate cancer diagnosis or mortality (175, 185, 187, 188, 193, 195, 201, 203, 205-209, 217) (Table 2.3). Seven (64%) of the guidelines cited at least one of these studies as evidence for intervals (103-105, 176-179).

The evidence cited by five (45%) of the guidelines did not align with the recommended PSA retesting interval reported in studies cited as evidence (103, 104, 181-183) and five (45%) partially aligned with the studies they referenced as evidence (105, 176-179) (Table 2.2). Recommendations did not align with the referenced studies for two main reasons: 1) the guidelines recommended different intervals than the study recommended (103), or; 2) they cited studies that provided no explicit interval recommendation (104, 181-183).

Table 2.3 Studies cited by guidelines as evidence for their recommended repeat PSA testing intervals

Paper	Referenced in Guidelines	Type of Study	Methods	Single or multiple test	Outcomes	Does the study specifically aim to calculate intervals and quantify risk for screening intervals	Interval recommendation
Vickers (2013)(175)	EAU, AUA, Memorial Sloan, NCCN, CUA, France	Retrospective Case-control study	Single baseline PSA test can predict risk of prostate cancer	Single PSA test	Metastases, prostate specific mortality	No	PSA <1 testing more than every 5 years is unnecessary
Carlsson (2014)(185)	EAU, AUA, Memorial Sloan, NCCN	Retrospective cohort study	Baseline PSA to stratify prostate cancer risk based on cumulative hazard	Single PSA test	Prostate cancer diagnosis, metastasis, and death	No	PSA <1 at age 60 don't need to test again based on 15-year risk
Gelfond (2015)(193)	EUA, CUA	Prospective cohort study	Kaplan-Meier and cox regressions predicting risk from baseline PSA test to prostate cancer diagnosis	Single PSA test	Prostate cancer diagnosis	No	PSA <1 10 years
Roobol (2005)(186)	EAU, AUA, NCCN	Retrospective cohort study based on ERSPC	Assessed PSA values and number of cancers detected	Single PSA test – but patient had multiple tests where they were <1	Prostate cancer diagnosis	No	PSA <1 8 years

Paper	Referenced in Guidelines	Type of Study	Methods	Single or multiple test	Outcomes	Does the study specifically aim to calculate intervals and quantify risk for screening intervals	Interval recommendation
Preston (2016)(187)	AUA, NCCN, CUA, France	Prospective case control	Baseline PSA and risk of prostate cancer by age	Single PSA test	Lethal prostate cancer	No	PSA level below the median at age 45 years followed by repeat measurements at 5-year intervals. People with PSA <1.0 ng/mL age 60 years are unlikely to develop lethal disease
Andriole (2012)(127)	Memorial Sloan, SEOM, Cancer Australia	Randomised trial PLCO	Relative risk of prostate cancer diagnosis and mortality	NA	Diagnosis and prostate cancer specific mortality	No	No interval recommendation. The study was an RCT with annual screening
Vickers (2010)(188)	AUA, NCCN	Retrospective case control	Multiple regression to find predict risk from PSA test at age 60	Single PSA test	Diagnosis, metastasis or prostate cancer specific mortality	No	PSA<1 at age 60 it is safe to never test again
Heijnsdijk (2020)(189)	AUA, NCCN, France	Model	Microsimulation model assessing screening policies. Evaluated the following strategies: lengthening the screening interval when PSA was below 1.0 ng/mL at	Multiple PSA tests over time using trajectories	Number of tests, overdiagnosis and lives saved	Yes. Compared with biennial screening for ages 45–69 years, lengthening screening intervals for men with PSA less than 1.0 ng/mL at	Can lengthen screening instead of test every 2 years.

Paper	Referenced in Guidelines	Type of Study	Methods	Single or multiple test	Outcomes	Does the study specifically aim to calculate intervals and quantify risk for screening intervals	Interval recommendation
			age 45 or 50 years, discontinuing screening when PSA was below 1.0 ng/mL at age 60 years, and biennial screening for all men			age 45 years led to 46.8–47.0% fewer tests 0.9–2.1% fewer overdiagnoses, and 3.1–3.8% fewer lives saved. Stopping screening when PSA was less than 1.0 ng/mL at age 60 years and older led to 12.8–16.0% fewer tests, 5.0–24.0% fewer overdiagnoses, and 5.0–13.1% fewer lives saved	
Schroder (2014)(134)	Memorial Sloan, France	Randomised trial ERSPC	Rate ratio prostate cancer incidence and mortality	NA	Diagnosis and prostate cancer specific mortality	No	No interval recommendation - Different intervals ranging from 2-7 years
Schroder (2012)(212)	SEOM	Randomised trial ERSPC	Rate ratio prostate cancer incidence and mortality	NA	Diagnosis and prostate cancer specific mortality	No	No interval recommendation - Different intervals ranging 2-7 years

Paper	Referenced in Guidelines	Type of Study	Methods	Single or multiple test	Outcomes	Does the study specifically aim to calculate intervals and quantify risk for screening intervals	Interval recommendation
Gulati (2013)(190)	AUA	Model	Microsimulation model of 35 screening strategies that varied by start/stop ages, inter-screening intervals, and thresholds for biopsy referral.	Multiple PSA tests over time	Prostate cancer incidence and mortality	Yes. A reference strategy that screened men aged 50 to 74 years annually with a PSA threshold for biopsy referral of 4 µg/L reduced the risk for prostate cancer death to 2.15%, with risk for overdiagnosis of 3.3%. A strategy that used higher PSA thresholds for biopsy referral in older men achieved similar risk for prostate cancer death (2.23%) but reduced the risk for overdiagnosis to 2.3%	PSA screening strategies that use higher thresholds for biopsy referral for older men and that screen men with low PSA levels less frequently, can reduce harms while preserving lives saved compared to standard screening.
Heijnsdiik (2012) (191)	AUA	Model	Microsimulation Screening Analysis	Multiple PSA tests	Prostate cancer,	Yes. Per 1,000 men of all ages	Annual screening of all men between the

Paper	Referenced in Guidelines	Type of Study	Methods	Single or multiple test	Outcomes	Does the study specifically aim to calculate intervals and quantify risk for screening intervals	Interval recommendation
			(MISCAN) to predict the number of prostate cancers, treatments, deaths and QALYs gained after the introduction of PSA screening	over time. Screening strategies simulated included: annual screening in the age groups 55–69 years and 55–74 years, screening at 4-year intervals between 55–69, and single screens performed either at age 55, 60 or 65 years	treatments, deaths and QALYs	followed for their entire lifespan they predicted for annual screening from age 55–69 years: 9 fewer deaths due to prostate cancer (28% reduction), 14 fewer men receiving palliative therapy (35% reduction), and 73 life-years gained (average 8.4 years per prostate cancer death avoided). QALYs gained were 56 (range: −21, 97), a reduction of 23% from unadjusted life-years gained. The number needed to screen was 98 and	ages of 55 and 74 resulted in more life-years gained but the same number of QALYs.

Paper	Referenced in Guidelines	Type of Study	Methods	Single or multiple test	Outcomes	Does the study specifically aim to calculate intervals and quantify risk for screening intervals	Interval recommendation
						number needed to detect 5.	
Ross (2000) (192)	AUA	Model	Monte-Carlo simulation based on a Markov model was used to simulate the natural history of prostate cancer using different starting ages, testing intervals, and PSA thresholds for prostate biopsy	Multiple PSA tests over time. Tested biennial and annual testing	Numbers of prevented prostate cancer deaths, PSA tests, and prostate biopsies per 1000 men aged 40 through 80 years, compared among 7 different strategies vs no screening.	Yes. Annual screening strategy at age 50 prevented 3.2 deaths, with an additional 10,500 PSA tests and 600 prostate biopsies, while the less frequent strategy (2-year interval) prevented 3.3 deaths, with an additional 7500 PSA tests and 450 prostate biopsies.	Screening strategy at age 40 and 45 years with a 2-year testing interval after age 50 years may be both more effective and require less testing than the standard strategy of annual PSA testing beginning at age 50 years.
Thompson (2006) (202)	Memorial Sloan	Model	Logistic regression was used to model the risk of prostate cancer and high-grade disease associated with age at biopsy, race, family history of prostate cancer, PSA level, PSA	Multiple PSA tests over time to compute PSA velocity	Prostate cancer diagnosis	No	Predictive model allows an individualised assessment of prostate cancer risk and risk of high-grade disease for men who undergo a prostate biopsy

Paper	Referenced in Guidelines	Type of Study	Methods	Single or multiple test	Outcomes	Does the study specifically aim to calculate intervals and quantify risk for screening intervals	Interval recommendation
			velocity, DRE result, and previous prostate biopsy				
Lilja (2007) (201)	Memorial Sloan, France	Retrospective case control	Logistic regression to estimate the risk of prostate cancer	Single test	Prostate cancer diagnosis	No	A single PSA test at age 44 to 50 years predicted prostate cancer. This raises the possibility of risk stratification for screening programs
Loeb (2012) (203)	Memorial Sloan	Review of literature	Review of baseline PSA testing at age ≤60 to predict prostate cancer risk and prognosis	Single test	Prostate cancer diagnosis	No	Baseline PSA measurements at a young age were significant predictors of later prostate cancer diagnosis and disease-specific outcomes. Baseline PSA testing may be used for risk stratification and to guide screening protocols.
Eastham (2003) (204)	Memorial Sloan	Retrospective cohort study	Analysis of an unscreened population of 972 men (median age, 62 years). Five	Multiple tests	How often a participant's PSA level would return to normal the year after	No	Among men with an abnormal PSA, a high proportion had a normal PSA finding at 1 or more subsequent

Paper	Referenced in Guidelines	Type of Study	Methods	Single or multiple test	Outcomes	Does the study specifically aim to calculate intervals and quantify risk for screening intervals	Interval recommendation
			consecutive blood samples were obtained during a 4-year period and were assessed for total and free PSA levels.		the level had been elevated		visits during 4-year follow-up: 68 (44%) of 154 participants with a PSA level higher than 4 ng/mL; 116 (40%) of 291 had a level higher than 2.5 ng/mL; 64 (55%) of 117 had an elevated level above the age-specific cutoff; and 76 (53%) of 143 had a level between 4 and 10 ng/mL and a free-to-total ratio of less than 0.25 ng/mL.
Ven Leeuwen (2010) (205)	Memorial Sloan	Retrospective cohort study – ERSPC Secondary analysis of ERSPC	Age adjusted cumulative hazards	Single test	Prostate cancer incidence and mortality	No	Adjusted absolute difference in prostate cancer specific mortality between the intervention population and the clinical population increased with increasing PSA level at study entry

Paper	Referenced in Guidelines	Type of Study	Methods	Single or multiple test	Outcomes	Does the study specifically aim to calculate intervals and quantify risk for screening intervals	Interval recommendation
Vertosick (2020) (206)	NCCN	Retrospective cohort	Absolute risks of prostate cancer metastasis or death at 10, 15 and 20 years were calculated using Kaplan-Meier methods	Single test	Prostate cancer metastasis or mortality	No	Patients 60 years old with PSA below median (less than 1.2 ng/ml) had 0.4% risk of prostate cancer death at 20 years. Screening should focus on men in top PSA-quartile at age 60. Men with elevated PSA but a low 4Kscore can safely be monitored with repeated blood markers in place of immediate biopsy
Preston (2019) (207)	NCCN	Prospective case control	Logistic regression estimated odds ratios for prostate cancer by category of baseline PSA.	Single test	Prostate cancer incidence and aggressiveness	No	PSA levels in midlife strongly predicted total and aggressive prostate cancer in Black men. Targeted screening based on a midlife PSA might identify men at high risk while minimizing screening in those men at low-risk.

Paper	Referenced in Guidelines	Type of Study	Methods	Single or multiple test	Outcomes	Does the study specifically aim to calculate intervals and quantify risk for screening intervals	Interval recommendation
Kovac (2020) (208)	NCCN	Secondary analysis of randomised trial (PLCO)	Competing risk regression to model risk of prostate cancer	Single test	Prostate cancer incidence, clinically significant prostate cancer	No	findings suggest that repeated screening can be less frequent among men aged 55 to 60 years with a low baseline PSA level (<2 ng/mL) and possibly discontinued among those with baseline PSA levels of less than 1 ng/mL.
Ulmert (2008) (209)	NCCN	Retrospective case control	Logistic regression to determine association between PSA at age 50 and risk of prostate cancer	Single test	Advanced prostate cancer diagnosis	No	Suggested the possibility of using an early PSA test to risk-stratify patients so that patients at highest risk receive intensive screening efforts.
Smith (2018) (218)	American Cancer Society	Review of guidelines	Summarises the current ACS cancer screening guidelines, including current recommendations, updates, and guidance related to early cancer	NA	NA	No	For PSA levels less than 2.5 ng/mL, screening intervals can be extended to every 2 years, and screening should be conducted annually for patients with PSA

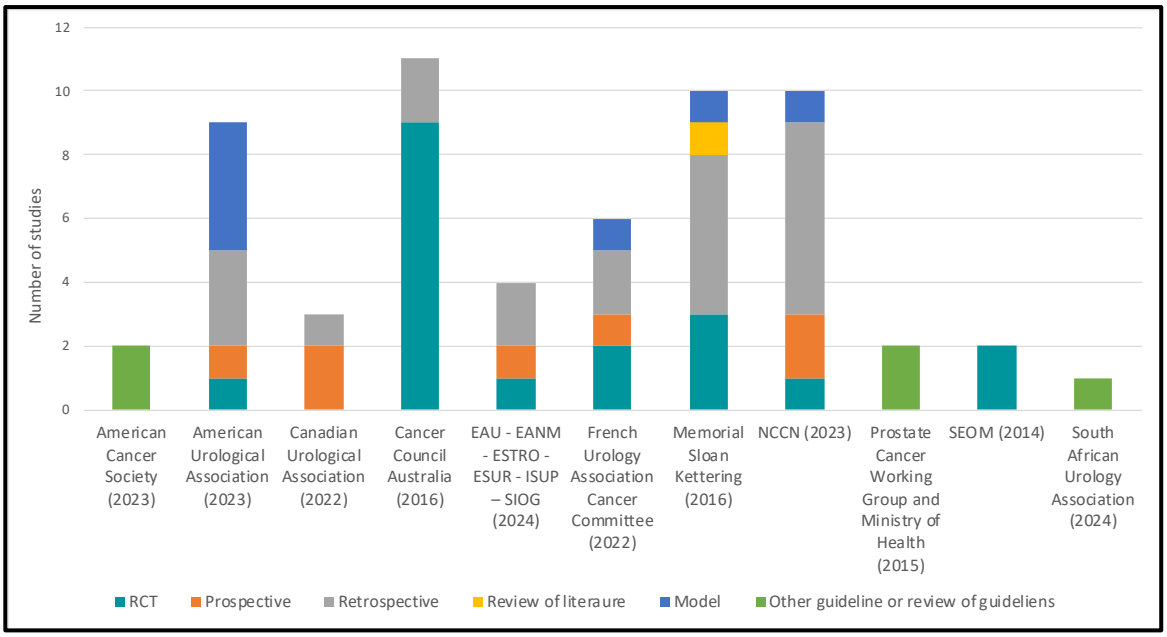
Paper	Referenced in Guidelines	Type of Study	Methods	Single or multiple test	Outcomes	Does the study specifically aim to calculate intervals and quantify risk for screening intervals	Interval recommendation
			detection when a direct recommendation for screening cannot be made				levels of 2.5 ng/mL or higher
Wolf (2010) (168)	American Cancer Society	Guideline	NA	NA	NA	No	For men whose PSA is less than 2.5 ng/mL, screening intervals can be extended to every 2 years. Men with higher PSA values should be tested annually.
Kipelainen (2013) (194)	Cancer Australia	Secondary analysis of randomised trial (ERSPC)	HR Cox model	Multiple tests	Incidence, mortality prostate cancer	No	No interval recommendation. Conservative screening protocol at 12 years of follow-up, resulted in a small, non-statistically significant, mortality reduction
Kjellman (2009) (195)	Cancer Australia	Randomised trial	Estimated the prostate specific mortality rates as well as all-cause mortality and	Single test	Prostate specific mortality	No	No interval recommendation. Found no effect of the screening procedure on the risk of death from prostate cancer

Paper	Referenced in Guidelines	Type of Study	Methods	Single or multiple test	Outcomes	Does the study specifically aim to calculate intervals and quantify risk for screening intervals	Interval recommendation
			calculated IRR using Poisson regression				and other causes of death
Bokhorst (2014) (196)	Cancer Australia	Secondary analysis randomised trial (ERSPC)	Prostate cancer mortality	Multiple	Mortality prostate cancer	No	No interval recommendation.4-year interval screening reduced the risk of dying from prostate cancer up to 51%
Hugosson (2010) (197)	Cancer Australia	Secondary analysis randomised trial (ERSPC)	Risk of dying prostate cancer	Multiple	Prostate cancer specific mortality	No	No interval recommendation
Labrie (2004) (129)	Cancer Australia	Randomised trial (Quebec study)	Cox regression	Multiple	Prostate cancer specific mortality	No	Recommend annual testing
Roobol (2013) (198)	Cancer Australia	Randomised trial (ERSPC)	Prostate cancer specific mortality analyses using Poisson regression	Multiple	Prostate cancer specific mortality	No	4-year interval. Systematic PSA-based screening reduced prostate cancer specific mortality by 32% in the age range of 55-69 yr.
Sandblom (2004)(199)	Cancer Australia	Randomised trial		Multiple	Prostate cancer incidence	No	3-year interval
Andriole (2009) (157)	Cancer Australia	Randomised trial (PLCO)	(123)	Multiple	Prostate-cancer mortality	No	No recommended interval. Annual

Paper	Referenced in Guidelines	Type of Study	Methods	Single or multiple test	Outcomes	Does the study specifically aim to calculate intervals and quantify risk for screening intervals	Interval recommendation
							screening found no difference in mortality
Sandblom (2011) (200)	Cancer Australia	Randomised trial	Cox risk of death	Multiple	Prostate cancer specific mortality	No	No recommended interval. 3-year screening found no difference in mortality
Basch (2012) (210)	New Zealand	Guideline	Clinical opinion	NA	NA	No	No recommended interval. Recommended for shared decision making
Catalona (2011) (211)	New Zealand	Prospective study	Diagnostic accuracy of the prostate health index (phi)	Single	Prostate cancer diagnosis (Gleason ≥7)	No	No recommended interval. Phi may be useful to reduce biopsies in men age ≥50 years with PSA 2–10 ng/mL and negative DRE
DeSantis (2019) (213)	South Africa	Review of reports	Review of Cancer Audit and SEER data	NA	Prostate cancer diagnosis	No	No recommended interval
Hugosson (2019) (131)	France	Secondary analysis randomised trial (ERSPC)	Rate ratio, number needed to diagnose, and the number needed to be invited for screening to prevent one death	NA	Prostate cancer specific mortality	No	No recommended interval. PSA screening reduces prostate specific mortality. Repeated screening may be important to reduce prostate cancer

Paper	Referenced in Guidelines	Type of Study	Methods	Single or multiple test	Outcomes	Does the study specifically aim to calculate intervals and quantify risk for screening intervals	Interval recommendation
							mortality on a population level.

Figure 2.2 Referenced Study Evidence Categorisation



2.5.3 QUALITY OF GUIDELINES

The AGREE II tool was used to appraise the overall quality of each guideline (Table 2.4). The scope and purpose (median score: 72% (IQR: 69% to 78%) and clarity of presentation (median score: 69% (IQR 58% to 90%) domains scored the highest overall. The range of scores in the editorial independence domain varied substantially with two (18%) scoring below 10% (180, 183) and four (36%) scoring over 92% (104, 105, 176, 177). The applicability domain had second lowest overall score with a median of 42% with the least variability (IQR: 34% to 49%). The rigour of development had the lowest overall median score of 40% (IQR 34% to 73%) but four guidelines (36%) (103-105, 176) scored over 70% in this domain.

Table 2.4 Overall AGREE II scores

Guideline	Domain 1: Scope and Purpose	Domain 2: Stakeholder Involvement	Domain 3: Rigour of Development	Domain 4: Clarity of Presentation	Domain 5: Applicability	Domain 6: Editorial Independence	Overall Scores
American Cancer Society (180)	69%	72%	31%	72%	46%	0%	48%
American Urological Association (176)	92%	86%	83%	64%	50%	92%	78%
Canadian Urological Association (103)	92%	56%	75%	81%	54%	50%	68%
Cancer Council Australia (104)	92%	89%	83%	83%	85%	96%	88%
EAU - EANM - ESTRO - ESUR - ISUP – SIOG (105)	56%	78%	69%	78%	42%	100%	71%
French Urological Association (179)	47%	28%	40%	75%	38%	63%	49%
Memorial Sloan Kettering (177)	89%	39%	40%	69%	31%	100%	61%
National Comprehensive Cancer Network (NCCN)(178)	75%	67%	38%	72%	38%	79%	62%
Prostate Cancer Working Group and Ministry of Health (181)	61%	42%	38%	78%	48%	17%	47%
Sociedad Espanola de Oncologia Medica (SEOM) SEOM (182)	53%	28%	28%	69%	31%	50%	43%
South African Urology Association (2024) [80]	61%	33%	31%	58%	19%	8%	35%

2.6 DISCUSSION

2.6.1 SUMMARY OF FINDINGS

In this chapter, I summarised international guideline recommendations for PSA retesting intervals. Retesting intervals ranged from one to ten years. Nine guidelines (82%) recommended an interval of approximately two-to-four years (103-105, 176-181). There were 37 studies referenced as evidence for the recommended intervals across the 11 guidelines. Five of the studies (14%) had the objective of determining PSA retesting intervals and fourteen studies (38%) were an analysis based on single PSA test results. I then assessed if the guideline recommendation aligned with the evidence it cited as support for the retesting intervals. I found that five guideline recommendations partially aligned with the evidence referenced and five guideline recommendations did not align.

2.6.1.1 Summary of the evidence underpinning guideline recommendations

In the absence of direct evidence for PSA retesting intervals (219), guideline developers rely on the best available evidence such as modelling, cohort studies and retrospective analyses of data from PSA screening trials. Cohort studies often focus on prostate cancer risk or mortality based on a single PSA measurement at a specific point in time (175, 185, 187, 188, 193, 195, 201, 203, 205-209, 217), rather than calculating retesting intervals. For instance, Preston (2016) concluded that risk of prostate cancer specific mortality in 30 years for patients with a baseline PSA below the median (0.68, 0.88, and 0.96 ng/mL for men aged 40 to 49, 50 to 54, and 55 to 59 respectively) was less than 2%. They argued for repeat testing at five-year intervals for patients aged 45 with a baseline PSA level below the median. Studies reporting low PSA values as an indicator to defer or stop testing (185) are relevant to advocate for the extension of PSA retesting intervals, but do not give evidence for the exact timing of the retesting intervals.

Vickers (2013) suggested that one possible cut-off point to determine more versus less frequent screening would be a PSA less than 1 ng/ml. They found that the risk of

metastasis within 15 years was less than 0.4%, suggesting that a retesting interval of less than five years was unnecessary for those patients. This type of research is crucial to understand the relationship between PSA values and the progression of prostate cancer but may not be suitable evidence to underpin recommendations for PSA retesting intervals. These studies however provide population-based evidence to lengthen retesting intervals in patients with low risk of cancer. No similar studies have been done using English data. It is unknown whether these patterns also present in England. In Chapter 6 I fill this gap in the literature.

2.6.2 COMPARISON TO THE LITERATURE

Other studies have summarised some PSA testing policies. Bratt (2023) (162) summarised PSA testing policies in the United States, European Union, Sweden and Lithuania. Denjis (2024) (165) summarised guidelines in the UK, Australia, the EU and the Netherlands. Both studies, similar to this chapter, found inconsistencies between guidance and there is strong agreement across the literature that guidelines for PSA testing in primary care are varied.

The variation in retesting intervals likely reflects the different intervals used in the randomised screening trials (126), ranging from annual screening in PLCO (127) to once every seven years in the Belgian ERSPC cohort (212). As a result, comparing the effect of different PSA retesting intervals on prostate cancer incidence and mortality remains unclear. Although these randomised trials have been instrumental in the domain of PSA screening, their primary objective was to ascertain whether screening conferred a mortality benefit, rather than to delineate the most suitable PSA retesting interval. The indirect evidence for retesting intervals found in this chapter is similar to guidance on retesting or monitoring in other disease areas. For example, in cervical cancer screening, the major trial evaluating HPV testing with cytology used a fixed three-year screening interval rather than comparing alternative retesting frequencies (220). Similarly, to the observational studies for extending prostate cancer retesting intervals, the evidence for extending cervical cancer retesting intervals is also from cohort studies based on future risk of cancer (221).

2.6.3 Strengths and Limitations

The systematic review presented in this chapter, is the first to synthesise guideline recommendations for PSA retesting intervals and compare the studies cited as evidence with the guideline recommendations. Another strength is that the AGREE II tool was used to appraise overall guideline quality and I additionally examined each study cited for the recommended PSA retesting interval. I evaluated which studies were designed with the aim of determining retesting intervals and whether these studies used single PSA test results or multiple PSA results to define intervals.

A limitation is that I did not conduct a wider search of the literature to determine what could or should have been included in the guideline recommendation as each guideline committee had its own internal processes to select supporting evidence. The focus of this chapter was therefore limited to guidelines recommending PSA retesting intervals to assess whether the evidence appropriately aligned with recommendations. As a result, guidelines that only recommended shared-decision making were not included. For example, the USPSTF (102) recommended shared decision-making when considering an initial PSA test but did not recommend any subsequent PSA retesting intervals. Other organisations such as Prostate Cancer UK (149), the Prostate Cancer Risk Management Programme(222), Japanese Urological Association (223) and ESMO (224, 225) recommend for PSA testing but provide no specific guidance on retesting intervals.

A second limitation is the interpretability of what constitutes a guideline. A guideline was defined as systematically developed statements written to assist practitioner and patient decisions to improve patient outcomes (171). The Memorial Sloan Kettering Cancer Centre guideline was included because it provided explicit, recommendations on PSA retesting intervals relevant to the review question. However, its development by a single institution highlights the challenges in applying a uniform guideline appraisal tool (AGREE II) across heterogeneous forms of guidance.

A third limitation is the subjectivity of the AGREE II tool. Although the AGREE II tool is widely used as a validated instrument for assessing the quality of guideline development

and reporting, the scoring used in the tool is dependent on interpretation. For example, Domain 6, (Editorial Independence) focusses on whether funding sources and conflicts of interests are reported in the guideline, rather than evaluating the appropriateness of each guideline's validity as an independent recommendation. An important example of this is highlighted by the Memorial Sloan Kettering Cancer Centre guideline. This was developed by a single institution and was rated highly in Domain 6 as all conflicts of interests were disclosed. This reflects the presence of the AGREE tools reporting statements instead of the degree to which editorial independence is assured.

A fourth limitation is that I did not use the GRADE tool to assess the evidence because I was not appraising the bias or strength of the evidence. Instead, I aimed to assess the methods used in papers cited by guidelines to support their interval recommendations. However, deciding if the evidence aligned with the guideline recommendation was a subjective judgement done by two independent reviewers. If there were any disagreements with the alignment of the evidence with the recommendation a third reviewer (BDN) was available to make a final call. When, categorising the evidence into aligned, partially aligned, or not aligned there were no major discrepancies between reviewers.

A final limitation is that Lithuanian guidance was not included in this chapter. As of 2025, Lithuania was the only country to offer a PSA-based screening programme (138). However, I was not able to locate a formal guideline or the evidence used to underpin Lithaunia's biennial retesting strategy. Therefore it was not included it in the analysis of this chapter. From published papers using Lithuania's national data, it was noted that the program began in 2006. Men aged 50 to 74, and those aged 45 to 49 with a family history of prostate cancer, were offered a PSA test annually through their GP between 2006 and 2008. This changed to every two years in 2009. However, currently the programme works on an invitation by opportunity basis and PSA tests are offered when men visit their general practitioner for another reason (226).

2.6.4 POLICY IMPLICATIONS

Policymakers should consider the impacts of shared decision making in combination with vague guideline recommendations. Many guidelines recommended "personalised" PSA retesting intervals (102, 105, 179). While this flexibility aligns with the shared decision-making approach, it provides no clear guidance on determining appropriate intervals based on risk. This leaves room for varying interpretations from no testing to regular testing. Shared-decision making may have been the best solution to provide flexibility and account for the lack of consensus and direct evidence for PSA retesting intervals, but it may be becoming less effective. For example, it remains unclear who should initiate the PSA discussion. If responsibility lies with the patient, education level and health literacy may lead to healthcare inequalities (227). Recently, it has become more clear that current PSA screening policies that encourage patients to make their own decisions about PSA testing exacerbate harms of overdiagnosis and reduce benefits of early detection (228). This is likely due to low rates of PSA testing in the patients most likely to benefit and high rates of testing in older patients who are the least likely to benefit. I provide a formal analysis of PSA testing rates in Chapter 5.

Policymakers should also be aware that guideline recommendations may not align with the underlying evidence. When assessing the alignment of guideline recommendations with conclusions of cited studies, the American Cancer Society (ACS) (180) was the only guideline where the recommendation fully matched the evidence cited. However, the ACS (180) exclusively referenced reviews and guidelines from its own organisation (168, 184). These are highly biased and not appropriate sources for evidence-based recommendations designed for the general population. Furthermore, ten (91%) guidelines cited evidence without accurately reflecting study conclusions (103-105, 176-179, 181-183). This inconsistency held true for various study types, including those focusing on interval calculations and those focused on risk of cancer mortality. For example, in a modelling study by Heijnsdijk (2020) (189), it was deemed safe to extend screening intervals beyond two years, but Heijnsdijk (2020) did not explicitly recommend two-to-four year intervals (Table 2.3), contrary to the recommendations provided by the AUA (176) and NCCN (178). This type of misalignment underscores challenges in

evidence-based guideline development. I found no examples where the guideline recommendation aligned with the findings of primary research. The determination of PSA retesting intervals involves multiple complexities, including the type of screening (population-based versus opportunistic), variations in prostate cancer prevalence, different PSA referral thresholds, the impact of accessibility and costs, and the role of additional tests such as pre-biopsy MRI.

Finally, policymakers should be prepared and consider advancements in multi-parametric MRI (mpMRI). These will radically impact the diagnostic pathway. I found that no guidelines that considered mpMRI results when determining PSA retesting intervals. Advances in mpMRI technology reduce clinically insignificant prostate cancer diagnoses by half (229), improve detection of significant cancers (230), and decrease unnecessary biopsies by 28% (231) to 48% (232). With reduced overdiagnosis, more frequent PSA retesting intervals may become feasible. Future guideline updates should incorporate these advancements to improve PSA testing recommendations. Additionally, it is important to consider that the UK National Screening Committee, Canadian Task Force on Preventative Health Care and the Danish Urological (Prostate) Cancer Group recommended against population-wide PSA testing. As well as consensus on retesting intervals, international consensus should also be reached on whether to use the PSA test for asymptomatic patients.

2.6.5 Research implications

In this chapter, there were six modelling studies cited in guidelines with the aim of calculating retesting intervals. They quantified the potential harms and benefits of reducing mortality with differing retesting intervals (189-192, 216, 219). The AUA (176) cited Gulati (2013) (190), a microsimulation study of 35 different screening strategies. They found that a strategy that screens patients aged 50 to 74 years annually with a PSA threshold of 4 ng/mL reduced the risk for prostate cancer death to 2.2%, with risk for overdiagnosis of 3.3%. Compared to a strategy that used higher PSA thresholds in older patients that achieved a similar risk for prostate cancer death (2.2%) but reduced the risk for overdiagnosis to 2.3%. The study did not make a specific interval recommendation

but asserted that extending PSA retesting intervals might be acceptable for certain patients with low PSA levels. Simulation studies based on individualised prostate cancer risk warrant further research. To strengthen the evidence base for interval recommendations, further research using longitudinal cohort studies, electronic health record analyses, and modelling or machine learning approaches is required. Such work could focus on individualised, dynamically updated retesting intervals that adapt to each patient's evolving risk rather than relying on fixed retesting intervals and population-level risk estimates. In Chapter 7, I test the feasibility of an individualised approach by applying a joint modelling framework to estimate dynamic, patient-specific retesting intervals. Outputs would then need to be modelled using a simulation study or tested in a randomised trial.

2.6.6 Clinical implications

Clinicians should be aware that the optimal PSA retesting interval is unknown and there is no direct evidence or consensus for guideline developers to base recommendations. Despite this, many guidelines included in this review recommended a retesting interval of two-to-four years. However, for a hypothetical patient of Black ethnicity, aged 55, with PSA of 2 ng/mL a test could be repeated annually based on the NCCN or South African guidelines (178, 183), as long as four years based on the AUA (176) or eight years following the recommendation from the EAU (105). Clinicians following these recommendations should take caution until direct evidence for PSA retesting intervals has been established.

Secondly, most guidelines recommended PSA retesting intervals adjusted by risk, but stratification methods varied between age, PSA, and other risk factors. No guidelines recommended PSA retesting intervals for patients presenting with symptoms of prostate cancer. Risk stratification could be done for patients presenting with symptoms. A provincial Canadian guideline from British Columbia (233) recommended shorter intervals for patients presenting with symptoms but this was not supported by evidence on PSA retesting intervals for symptomatic patients. Clinicians should be aware that NICE NG12 (234) guidance recommends to "consider PSA testing" for patients

presenting with lower urinary tract symptoms, weight loss or erectile dysfunction, but there are no recommendations for retesting with PSA if the patient does not qualify for referral.

Finally, current guidance on PSA retesting is primarily focused on the outcome of prostate cancer mortality but this may not align with patient priorities. Patients weigh mortality benefits against risks such as unnecessary biopsies or urinary and bowel incontinence, valuing these trade-offs differently (235). This suggests a one size fits all repeat PSA retesting approach may not reflect the preferences of patients (235). More individualised risk-based approaches to assist with shared decision making may help clinicians and patients to be less uncertain about retesting with PSA.

2.7 Conclusion

In this chapter, I found that recommendations for PSA retesting intervals for asymptomatic patients before a prostate cancer diagnosis varied between guidelines. There was no consensus on the optimal PSA retesting approach. To support PSA retesting interval recommendations, most guidelines relied on indirect evidence derived from studies investigating a single PSA value, assessments of risk of prostate cancer progression, or data from randomised screening trials primarily aimed at mortality reduction rather than determining retesting intervals. Generally, for asymptomatic patients aged over 50 with PSA levels between 1 and 3 ng/ml, most guidelines recommended a retesting interval of two-to-four years with the possibility to extend the interval to four to ten years for asymptomatic patients with a PSA value less than 1 ng/mL. Until research generates direct evidence for PSA retesting intervals for both asymptomatic and symptomatic patients, clinicians and patients engaging in shared decision-making should be aware that current guidelines lack direct evidence for recommended PSA retesting intervals.

Chapter 3: Adequacy of Guideline Recommendations for Monitoring Patients with Low-Risk Cancer: A Guideline Review

3.1 Dissemination

The work presented in this chapter was published in the Journal of Clinical Epidemiology (2024) (86).

***Collins KK**, Smith CF, Roberts N, Nicholson BD, Oke J. Adequacy of clinical guideline recommendations for patients with low-risk cancer managed with monitoring: Systematic review. Journal of Clinical Epidemiology. 2024:111280.*

Findings from this chapter were presented as oral presentations at the Preventing Overdiagnosis Conference in Copenhagen (2023) and the Cancer Primary Care Conference in Melbourne in (2024).

3.2 Background

Advanced imaging, cancer screening tests (e.g. PSA), and lower thresholds defining abnormality have led to an increase in the number of incidental, low-risk cancers diagnosed during routine clinical care (236-238). Prostate cancer is a prime example of this. Increased PSA testing may be contributing to the overdiagnosis of low-risk cancers. Low-risk prostate cancer was described in Chapter 1. While immediate treatment is critical for patients diagnosed with high-risk cancers, there is uncertainty about how to manage cancer that is unlikely to progress (low-risk cancer) (239-241). During monitoring or active surveillance patients undergo a series of tests over time (242). In the event of disease progression, patients receive immediate treatment, reducing over-treatment and minimising harm (242).

In this chapter, I examine the quality of clinical practice guidelines that provide recommendations on monitoring patients with low-risk cancer. As mentioned in the previous chapter, guidelines inform evidence-based decision-making, standardise quality of care, and drive clinical workload (243-245). Inconsistent and vague guidelines can lead to overuse or underuse of healthcare resources, negatively affecting costs and care quality (243).

Whilst the primary focus of this thesis is on PSA testing and retesting before a patient is diagnosed with prostate cancer, understanding how evidence is used to support monitoring strategies in the post-diagnosis setting for prostate cancer and for other cancer sites offer valuable context. This chapter examines how much detail clinical guidelines provide about monitoring strategies for patients diagnosed with low-risk cancer, and what type of evidence is considered sufficient to support the recommendations. It focuses on how guidelines define the following: low-risk cancer, which tests they recommend for monitoring, how often follow-up testing should occur, and when further investigation or treatment is advised if cancer progression is suspected.

This is important as the evidence for monitoring intervals is not only relevant to the early diagnosis of prostate cancer. In other disease areas, such as cardiovascular disease, monitoring intervals are often poorly specified and inconsistently defined (243). This has been suggested to contribute to variation in clinical practice and uncertainty among clinicians about optimal follow-up strategies. A similar gap appears to exist in oncology, where monitoring recommendations for patients with low-risk cancers are common but the evidentiary basis for the frequency of follow-up is rarely examined systematically.

To address this, this chapter includes guidelines from all cancer sites that provide recommendations for monitoring patients with a low-risk diagnosis. This broader approach ensures that potentially important lessons developed in other cancer contexts are not overlooked. Insights from this chapter are relevant across cancer care pathways, including prostate cancer. In particular, the personalised dynamic joint modelling risk

prediction approach described in Chapter 7 was developed for a low-risk prostate cancer cohort undergoing active surveillance. This highlights that questions about monitoring intervals span both early detection and post-diagnosis management, and that improving the evidence base for monitoring has implications across the cancer pathway. By examining prostate cancer alongside other cancer sites, this chapter aims to identify shared patterns, areas of uncertainty, and potential transferable lessons that may inform the development of evidence-based, risk-stratified PSA retesting strategies in primary care.

3.3 Objectives

The objectives of this chapter were to:

1) Summarise recommendations for monitoring patients with a diagnosis of low-risk cancer across different cancer sites.
2) Assess whether guidelines defined low-risk cancer, specified which tests to use, recommended monitoring intervals, and defined triggers for further intervention.
3) Examine the level of evidence cited to support each recommendation.
4) Summarise the quality of the guidelines using the AGREE II tool.

3.4 Methods

Following the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) (168) guidance, I conducted a systematic review of monitoring guidelines for patients with low-risk cancer. The protocol was registered on Figshare (https://doi.org/10.6084/m9.figshare.19049795.v1).

3.4.1 Search Strategy

I searched PubMed and adapted the search for the Turning Research into Practice (TRIP) database (169) for the most up-to-date guidelines between 2012 and 2023. I searched for guidelines written in English. Grey literature and specialist cancer care repositories were subsequently searched manually. The search strategy is provided in Table 3.1.

Table 3.1 Search Strategy

	Number of Guidelines	Updated Search Date*
PubMed		
(("Neoplasms"[Mesh]) OR (cancer*[Title/Abstract] OR neoplasm*[Title/Abstract] OR carcinoma*[Title/Abstract] OR sarcoma*[Title/Abstract] OR lymphoma*[Title/Abstract] OR leukaemia*[Title/Abstract] OR leukemia*[Title/Abstract])) AND (("Watchful Waiting"[Mesh]) OR ("active surveillance"[Title/Abstract] OR "active monitoring"[Title/Abstract] OR "watchful waiting"[Title/Abstract] OR "watch and wait"[Title/Abstract])) Filters: Guideline, Practice Guideline, from 2012 - 2023	65	08/09/2023
TRIP database		
("active surveillance" OR "active monitoring" OR "watchful waiting") AND (cancer OR neoplasms OR carcinoma OR sarcoma OR lymphoma OR leukaemia OR leukemia) - limited 2012-2023		
Australia & New Zealand	12	08/09/2023
Canada	42	09/09/2023
UK	42	10/09/2023
Other	49	11/09/2023
USA	125	12/09/2023
Europe	49	13/09/2023

**The original search outlined in the protocol included guidelines between 2011 and 2021and was run in 09/2022. We repeated the search in 09/2023 to include guidelines published between 2012- 2023.*

3.4.2 SELECTION PROCESS

Claire Friedemann Smith (CFS) and I independently screened and assessed full text for eligibility. Discrepancies were resolved through discussion. Guidelines were included if the monitoring recommendations were for patients with a confirmed low-risk cancer diagnosis, who had yet to start radical treatment. Guidelines were excluded if they only had recommendations for elderly/comorbid patients, were monitoring for cancer recurrence or monitoring pre-malignant cancers (246).

3.4.3 DATA EXTRACTION

I extracted the data into Excel. It was subsequently verified by CFS. Data extraction included: authorship, publication date, patient population, definition of low-risk cancer,

recommended tests, monitoring intervals, triggers for further intervention. Similar to Chapter 2, the Oxford Centre for Evidence-Based Medicine (OCEBM): Level of Evidence (173) hierarchy was used to rank the evidence underpinning each monitoring recommendation. The OCEBM evidence places systematic reviews of randomised trials and randomised trials as the highest levels of evidence, prospective and retrospective cohort, and modelling studies beneath them and other guidelines, expert opinion and no evidence as the lowest levels of evidence. When different evidence was cited for different monitoring tests, the evidence recommended for each test was presented.

3.4.4 Quality assessment (AGREE II)

The quality of each guideline was assessed using the AGREE II tool (174). Each guideline was independently scored by myself and another researcher. Details of the AGREE II tool can be found in Section 2.5.3.

3.4.5 Data synthesis

I considered whether the guidelines gave recommendations for:

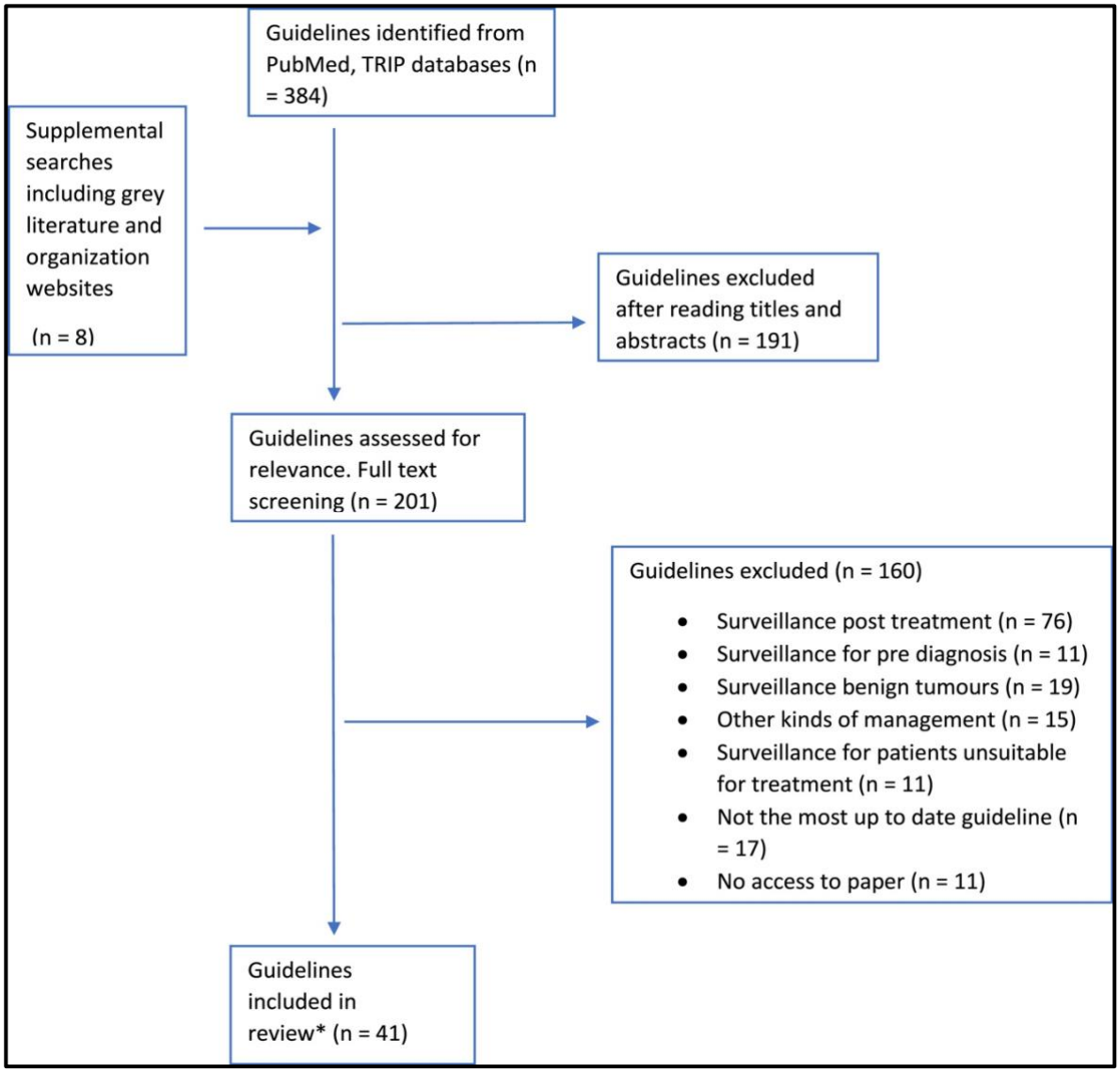
1) defining low-risk cancer,
2) which tests to use,
3) the monitoring interval, and
4) triggers for further intervention.

I then examined if each of those four categories of recommendations were specific (clinically useful) or non-specific (clinically not useful) (243). Non-specific recommendations were vague or provided more than one option. An example of a non-specific recommendation was “periodic clinical/imaging surveillance based on growth rate and shared decision making” (247). In contrast, specific recommendations were clear. For example, “imaging at month 3 and month 6, then every 6 months” (248). A Chi-squared test was used to determine whether there was a trend between specific recommendations and the quality of evidence referenced.

3.5 RESULTS

The initial search yielded 384 guidelines. After screening, 41 were eligible for data extraction (Figure 3.1)

Figure 3.1 Preferred Reporting Items for Systematic Reviews and Meta-analyses Diagram



Across the 41 published guidelines, 48 recommendations were identified: 15 (31%) for prostate cancer, 11 (23%) for renal cancer, 6 (12.5%) for thyroid cancer and 10 (21%) for blood cancer. The remaining 6 (12.5%) were for brain, gastrointestinal, oral cavity, bone and pheochromocytoma and paraganglioma cancer. When combining all guidelines, 48 (100%) stated which patients qualify for monitoring (defined low-risk), 31 (65%) specified which tests to use, 25 (52%) provided recommendations for surveillance intervals, and 23 (48%) outlined triggers to initiate further intervention (Table 3.2). Across all recommendations,

there was a strong positive trend with higher levels of evidence associated with an increased likelihood of a recommendation being specific (p = 0.001).

Table 3.2 Proportion of guidelines with recommendations for low-risk, test, intervals and triggers by cancer site

Cancer Site	Number of monitoring guidelines	Number (%) define low-risk	Number (%) define tests	Number (%) define monitoring intervals	Number (%) define triggers to stop monitoring or increase intervention
Prostate	15	15 (100%)	14 (93%)	12 (73%)	12 (73%)
Renal	11	11 (100%)	9 (82%)	7 (64%)	7 (64%)
Thyroid	6	6 (100%)	6 (100%)	5 (83%)	2 (33%)
Blood	10	10 (100%)	4 (40%)	2 (20%)	3 (30%)
Follicular Lymphoma	4	4 (100%)	2 (50%)	2 (50%)	2 (50%)
Hairy cell leukemia (HCL)	2	2 (100%)	NA	NA	NA
Mantle cell lymphoma	2	2 (100%)	NA	NA	NA
Chronic lymphocytic leukemia (CLL)	1	1 (100%)	1 (100%)	NA	1 (100%)
Non-gastric mucosa associated lymphoid tissue (MALT) lymphoma	1	1 (100%)	1 (100%)	NA	NA
Gastrointestinal**	2	2 (100%)	2 (100%)	2 (100%)	NA
Brain	1	1 (100%)	NA	NA	1 (100%)
Oral cavity	1	1 (100%	NA	NA	NA
Pheochromacytoma and paraganglioma (PPGL)	1	1 (100%)	NA	NA	NA
Bone Sarcomas	1	1 (100%)	1 (100%)	NA	NA
Total*	48	48 (100%)	36 (75%)	28 (58%)	52%)

**Total recommendations. Guidelines with recommendations for multiple cancer sites were included more than once*

*** Gastrointestinal stromal tumors and Gastroenteropancreatic neuroendocrine neoplasms.*

3.5.1 PROSTATE CANCER GUIDANCE

Fifteen (31%) guidelines were for monitoring patients with low-risk prostate cancer (96, 105, 249-261) (Table 3.2). Three of the 15 guidelines gave non-specific guidance on what constitutes low-risk (254, 257, 261) (Table 3.3). Low-risk was defined by PSA, Gleason and tumour, node and metastasis (TNM) staging but these recommendations varied across guidelines. Some recommended for PSA less than 10 ng/mL (249-251, 253, 258, 260) while others stated 20 ng/mL (96, 256) or PSA-D < 0.15 ng/mL/cc (105). Gleason scores were either 6 or 7, and TNM stage T1-T2a (Table 3.4). There was broad consistency across guidelines for which test could be considered for monitoring. Fourteen (93%) of recommendations suggested at least three of the following tests: PSA, digital rectal exam (DRE), multiparametric magnetic resonance imaging (mpMRI) and biopsy (96, 105, 249-260). There was inconsistency around how frequently these tests should be repeated. Most guidelines suggested PSA should be repeated every three or six months (96, 105, 250, 253, 255-260) and DRE annually or biennially (96, 105, 250, 253, 255, 257, 259, 260). Guidance on the frequency of mpMRI was mostly non-specific (105, 253, 254) and many guidelines recommended to "consider" mpMRI (250, 252, 255, 256) (Table 3.5). Most guidelines suggested biopsy as part of the surveillance protocol but mostly at longer intervals (every two-to-four years) (105, 250, 255-258). Recommendations for when monitoring should be stopped varied substantially with nearly every guideline offering a different set of criteria for what should be considered evidence of tumour progression. Patient preference was recommended in five (33%) guidelines (96, 253, 256, 258, 259).

Three randomised trials (240, 262, 263), involving over 3,000 patients and 64 years of follow-up, provided the primary evidence for monitoring prostate cancer. Trials had broadly similar inclusion criteria for low-risk (T1-T2 N0M0 with PSA <50) but recommendations in guidelines varied and did not always follow the trials' overall findings. For example, evidence from randomised trials does not support limiting monitoring to only patients with very low-risk prostate cancer which is what was recommended most of the guidelines.

The evidence for tests varied according to the type of test. Guidelines cited a range of evidence for all tests (Figure 3.2). While randomised trials exist for mpMRI and biopsy (231), their aim focused on cancer detection rather than monitoring. Monitoring in the Prostate Testing for Cancer and Treatment (ProtecT) trial (240) consisted of PSA testing every three-to-four months in the first year and six-to-twelve month thereafter but it was not specifically regulated and serial biopsies and mpMRI scanning were not completed.

No trials were identified that were designed to assess the value of different monitoring intervals for low-risk prostate cancer. Of the 12 prostate cancer guidelines that provided a recommendation on monitoring intervals, six (50%) (96, 105, 252, 253, 256, 258) cited expert opinion , four (33%) (250, 254, 259, 260) cited no evidence , and two (17%) cited prospective studies (255, 257) as evidence for monitoring intervals (Figure 3.2).

3.5.2 RENAL CANCER GUIDANCE

Eleven (23%) guidelines provided recommendations for monitoring renal cancer (247-249, 264-271) (Table 3.2). Three of the 11 guidelines gave non-specific recommendations defining low-risk (266, 269, 271) (Table 3.3). Definitions of low-risk were largely based upon the tumour size and TNM staging. Low-risk was defined by a solid renal mass of < 2cm (247, 248), < 3cm (270) or < 4cm (264, 265, 268) and TNM stage T1 to 3 (249, 264, 267) (Table 3.4). Non-specific recommendations included terms such as “small renal masses” (266) or “localised disease” (271). Eight (73%) made non-specific statements about which test should be used for monitoring (247, 249, 264-269). For instance, the American College of Radiology (265) suggested computed tomography (CT), magnetic resonance imaging (MRI) or ultrasound (US) but could not specify which test should be prioritised. Alberta Health (264) stated “biopsy is an option if it would alter management” (264). Other guidelines (247, 268) mentioned to image patients but were not clear on what imaging technique to use. The CUA (248) and the NCCN (267) recommended specific but different intervals (Table 3.5). Two guidelines (268, 269) did not recommend any surveillance intervals and five (247, 249,

264-266) recommended non-specific intervals. Recommendations for triggers to stop active surveillance were inconsistent or nonexistent (Table 3.5).

There were no randomised trials to support active surveillance over immediate treatment for low-risk kidney cancer (Figure 3.2). The Delayed Intervention and Surveillance for Small Renal Masses is the largest prospective study on renal cancer conducted to date, and has shown that most tumours have a slow growth rate (median less than 0.1 cm/year) (272). Five (45%) of guidelines (247, 248, 265, 268, 269) cited the same systematic review and pooled analysis (273) which established that a substantial proportion of small renal masses remained radiographically static. No studies were found that directly compared which tests to use for monitoring. For intervals, guidelines cited either no evidence (264, 266, 267), expert opinion (247, 248) or other guidance (249, 265). I found no studies that were specifically aimed at calculating the correct interval for monitoring. The only specific interval recommendation (267) was based on no evidence. Six of the seven triggers to stop monitoring were supported by other guidance or no evidence cited (247-249, 264, 269, 270).

3.5.3 THYROID CANCER GUIDANCE

Six (13%) guidelines provided recommendations for monitoring thyroid cancer (274-279) (Table 3.2). All six (100%) guidelines had specific definitions of low-risk (Table 3.3). Overall thyroid cancer guidelines consistently defined low-risk as a mass <1cm or T1aN0M0 (Table 3.4). Most suggested ultrasound between 6 and 12 months (275-278), with one guideline suggesting cross-sectional imaging (274) (Table 3.5).Second line tests that could be used to monitor were limited but included blood tests (279), neck palpation (276), or fine needle aspiration biopsy (FNA) (274). Three (50%) guidelines (275-277) recommended intervals of 6 to 12 months, two (33%) did not report any intervals (274, 278) and the National Institute for Health and Care Excellence (NICE) recommended the interval is based on clinical discretion (279). One (17%) guideline (277) offered specific recommendations on what should trigger referral or a change in management (Table 3.5).

No randomised trials for low-risk thyroid cancer were found (Figure 3.2). Observational evidence indicated lower mortality with surgery versus active surveillance in people with Stage 1 disease (279). Five (83%) guidelines cited Japanese prospective cohort studies (280-282). Tests for thyroid cancer were supported by systematic reviews, one (17%) (275), prospective studies, one (17%) (278), retrospective studies, two (33%) (277, 279), expert opinions, one (17%) (276). Evidence for intervals, across the four guidelines that provided an interval recommendation with referenced evidence, was equally split with one (25%) guideline citing expert opinion (276), no evidence (279), prospective studies (275) and retrospective studies (277). There were no studies cited by guidelines for when to stop monitoring.

3.5.4 OTHER CANCER GUIDANCE

Sixteen (33%) recommendations in ten individual guidelines were for monitoring other cancers (283-294) (Table 3.2). Nine (56%) gave non-specific guidance on what defines low-risk (Table 3.3). Eleven (69%) of recommendations mentioned either low tumour burden (286, 292) or asymptomatic patients (283, 284, 287, 288, 292, 294) (Table 3.4).

Eleven (69%) recommendations did not define what tests to use to monitor (284, 286-288, 291-293) (Table 3.2). When there was a recommendation, guidelines were mainly non-specific and recommended for either “imaging” (283, 290, 294) or “clinical assessment” (288, 289). Four (25%) recommended surveillance intervals were usually 3 to 6 months (283, 288-290). Eleven (69%) did not define triggers (284, 286-290, 292-294) (Table 3.5). If a trigger was defined it was either based on disease progression (288, 291) or patient symptoms (283, 285).

There were no randomised trials to support any of the recommendations for monitoring other low-risk cancers. The highest level of evidence to support the majority of the blood, gastrointestinal, brain and bone cancers was retrospective cohort studies (295-297). Some

blood cancer guidelines cited retrospective studies for tests, intervals, and triggers (297-299). However, these studies had very few patients (less than 250).

3.5.5 QUALITY ASSESSMENT

The domains considering the scope and purpose of guidelines and editorial independence scored highest overall (Table 3.6). The median for the scope and purpose domain was 78% (IQR: 68% to 89%). Editorial independence ranked high with four (10%) guidelines scoring below 50% (249, 254, 270, 271). The applicability domain had the lowest overall score with a median of 29% (IQR: 17% to 46%). Guidelines including monitoring recommendations rarely mentioned resource implications of their recommendations or barriers to the application of monitoring. Across all cancer sites, patient preferences and views were limited.

Table 3.3 Proportion of guidelines with completeness of monitoring recommendation for low-risk, test, intervals, and triggers by cancer site

Cancer Site	Completeness of monitoring recommendation												
	Number of Guidelines	Define low-risk cancer			Define which tests to use			Define the monitoring intervals			Define when to stop monitoring or increase interventions		
		Not reported	Non-specific*	Specific	Not reported	Non-specific*	Specific	Not reported	Non-specific*	Specific	Not reported	Non-specific*	Specific
Prostate	15	NA	3 (20%)	12 (87%)	1 (7%)	NA	14 (93%)	3 (20%)	6 (40%)	6 (40%)	3 (20%)	4 (27%)	8 (53%)
Renal	11	NA	3 (27%)	8 (73%)	2 (18%)	8 (73%)	1 (9%)	4 (36%)	6 (55%)	1 (9%)	4 (36%)	4 (36%)	3 (27%)
Thyroid	6	NA	NA	6 (100%)	NA	NA	6 (100%)	1 (17%)	2 (33%)	3 (50%)	4 (67%)	1 (17%)	1 (17%)
Blood	10	NA	7 (70%)	3 (30%)	6 (70%)	2 (20%)	2 (10%)	8 (80%)	1 (10%)	1 (10%)	7 (70%)	1 (10%)	2 (20%)
Follicular Lymphoma	4	NA	2 (50%)	2 (50%)	2 (50%)	2 (50%)	NA	2 (50%)	1 (25%)	1 (25%)	2 (50%)	1 (25%)	1 (25%)
HCL	2	NA	2 (100%)	NA	2 (100%)	NA	NA	2 (100%)	NA	NA	2 (100%)	NA	NA
Mantle cell lymphoma	2	NA	1 (50%)	1 (50%)	2 (100%)	NA	NA	2 (100%)	NA	NA	2 (100%)	NA	NA
CLL	1	NA	1 (100%)	NA	NA	NA	1 (100%)	1 (100%)	NA	NA	NA	NA	1 (100%)

Cancer Site	Completeness of monitoring recommendation												
Non-gastric MALT lymphoma	1	NA	1 (100%)	NA	NA	NA	1 (100%)	1 (100%)	NA	NA	1 (100%)	NA	NA
Gastrointestinal**	2	NA	NA	2 (100%)	1 (100%)	1 (100%)	NA	NA	1 (100%)	1 (100%)	1 (100%)	1 (100%)	NA
Brain	1	NA	NA	1 (100%)	1 (100%)	NA	NA	1 (100%)	NA	NA	NA	1 (100%)	NA
Oral Cavity	1	NA	NA	1 (100%)	1 (100%)	NA	NA	1 (100%)	NA	NA	1 (100%)	NA	NA
PPGL	1	NA	1 (100%)	NA	1 (100%)	NA	NA	1 (100%)	NA	NA	1 (100%)	NA	NA
Bone	1	NA	1 (100%)	NA	NA	1 (100%)	NA	1 (100%)	NA	NA	1 (100%)	NA	NA
Total***	48	NA	15 (31%)	33 (69%)	13 (27%)	12 (25%)	23 (48%)	20 (42%)	16 (33%)	12 (25%)	22 (46%)	12 (25%)	14 (29%)

* non-specific means clinically not useful

** Gastrointestinal stromal tumours and Gastroenteropancreatic neuroendocrine neoplasms

*** Clinical guidelines including >1 cancer site appear multiple times

Table 3.4 Monitoring recommendation with level of evidence by guideline and cancer site (definition of low risk)

Cancer (Ref)	Guideline Author	Year	Definition of Low-Risk				
			Biomarker	Radiology	Histology	Staging	Size
Prostate (249)	AIM	2021	PSA< 10 Î		Gleason 6 Î	T1-T2a Î	
Prostate (250)	Alberta Health Services	2022	PSA<10 Þ (300)		Gleason ≤6 Þ (300)	T1 or T2a/b Þ (300)	
Prostate (251)	American College of Radiology	2022	PSA <10 ♦ (259)		Gleason ≤6 ♦ (259)	T1-T2a ♦ (259)	
Prostate (252)	ASCO	2018			Gleason ≤7 ♦ (255)		T1-T2 ♦ (255)
Prostate (253)	American Urological Association, ASTRO, SUO	2022	PSA <10 ₭			Grade group one and T1-T2a ₭	
Prostate (254)	Cancer Australia	2021				Low-risk ♦ (256)	
Prostate (255)	Cancer Care Ontario	2014			Gleason ≤7 ₭ (301)	T1-T2 ₭(301)	
Prostate (256)	Cancer Council Australia	2015	PSA ≤ 20 ♦ (96)¥(302)		Gleason 6 ♦ (96, 302)	T1-T2 ♦ (96, 302) ¥	
Prostate (257)	EAU position statement	2018			Very low-risk and low-risk ₭ (303) ¥ (304)		
Prostate (105)	EAU, EANM, ESTRO, ESUR, ISUP, SIOG	2023	PSA < 10 and PSA-D < 0.15 ng/mL/cc ≠ (305)			ISUP grade 1, cT1c or cT2a ≠ (305)	

Cancer (Ref)	Guideline Author	Year	Definition of Low-Risk				
Prostate (258)	Department of Health	2022	PSA <10 **(306) ♦ (307)		Gleason ≤ 6 **(306) ♦ (307)	cT1 – T2a **(306) ♦ (307)	≤2 positive cores, minimal biopsy core ♦ involvement (<50% cancer per biopsy) ♦ (307)
Prostate (259)	NCCN	2023	PSA ♅ (303) <10		Grade ♅ (303) group 1	cT1-cT2a ♅ (303)	
Prostate (96)	NICE	2021	PSA <20 **(308)		Gleason 3+4 ** (308)	T1-T2 ** (308)	
Prostate (260)	SEOM	2012	PSA <10 ♦ (259)		Gleason <7 ♦ (259)	T1-T2a ♦ (259)	
Prostate (261)	International Society of Geriatric Oncology	2019				Low-risk ♆	
Renal (249)	AIM	2021				T1b ♦ (247) (267)	
Renal (264)	Alberta Health Services	2021		N0 ♦ (309)		T1-3, ♦ (309)	<4cm ♦ (309)
Renal (265)	American College of Radiology	2021		Confined to kidney ♦ (310) (311) ♄ (273)		T1a ♦ (310) (311) ♄ (273)	≤4cm ♦ (310) (311) ♄ (273)
Renal (247)	American Urological Association	2021					solid renal mass < 2cm, or those that are complex but predominantly cystic, (cT1a, ≤4cm) ♄(273)
Renal (266)	BAUS/BUG	2012				Small renal mass ♆	
Renal (267)	NCCN	2017				T1a **(312)	

Cancer (Ref)	Guideline Author	Year	Definition of Low-Risk				
Renal (268)	Canadian Association of Radiologists	2019					<4cm ҍ (273)
Renal (248)	Canadian Urological Association	2022					<2 or 2-4cm ҍ (273, 313)
Renal (269)	EAU	2022				Small renal mass ¥ (314) ҍ (273)	
Renal (270)	NHS England Greater Manchester	2014					<3cm ϯ
Renal (271)	NHS England West Midlands	2016				Localised disease ϯ	
Blood (283)	British Society for Haematology	2020				Low tumour burden (largest nodal or extra-nodal mass 3 cm, absence of systemic symptoms, no serous effusion, no substantial splenic enlargement, no risk of vital organ compression and no leukaemia or cytopenia , absence of B symptoms and normal LDH and b2 microglobulin) ¥ (315)	
Blood (284)	British Society for Haematology	2020				Cytopenias are minimal and patient is largely asymptomatic ϯ	

Cancer (Ref)	Guideline Author	Year	Definition of Low-Risk				
Blood (285)	Alberta Health Services	2021				Early stage †	
Blood (286)	ESMO	2021				Low tumour burden ¥ (316, 317)	
Blood (287)	NICE	2016				Localised asymptomatic gastric MALT lymphoma †	
Blood (287)	NICE	2016				Clinically non-progressive mantle cell lymphoma who are asymptomatic and for whom radiotherapy is not suitable †	
Blood (287)	NICE	2016				Stage IIA follicular lymphoma who are asymptomatic and for whom treatment with a single radiotherapy volume is not suitable †	
Blood (288)	Alberta Health Services	2021				Stage IA or IIA **(318)	
Blood (288)	Alberta Health Services	2021				Asymptomatic HCL †	
Blood (288)	Alberta Health Services	2021		Patient consent to forgo immediate therapy despite knowledge of	No adverse pathology features such as blastoid variant, Ki67>20% of cells, or complex cytogenetic changes	Non-nodal disease such as CLL-like presentation (lymphocytosis without associated cytopenias) or stage IAE marginal zone-like	

Cancer (Ref)	Guideline Author	Year	Definition of Low-Risk				
				demonstrated survival benefits of aggressive vs less aggressive therapy. Patient agreement to surveillance disease monitoring		presentation, asymptomatic ** (298)	
Thyroid (274)	American Thyroid Association	2015				Papillary microcarcinomas without clinically evident metastases or local invasion, and no convincing cytologic evidence of aggressive disease ¥ (282)	
Thyroid (275)	ESMO	2019				T1a ¥ (282)	Unifocal papillary microcarcinomas (10 mm) ь (319)
Thyroid (276)	European Thyroid Association	2022					<1cm ¥ (282)
Thyroid (277)	Japan Association of Endocrine Surgery	2021				T1aN0M0 low-risk papillary microcarcinomas ¥ (280)	≤10 mm ¥ (280)
Thyroid (278)	NCCN	2022					≤1cm ¥ (282)
Thyroid (279)	NICE	2022			N0M0	T1a – T2** (320)	

Cancer (Ref)	Guideline Author	Year	Definition of Low-Risk				
Gastro (289)	ESMO-EURACAN-GENTURIS	2022					Small submucosal gastric or duodenal nodules <2 cm ŧ
Gastro (290)	ESMO	2020					<2 cm or asymptomatic low-grade tumour with absence of morphological progression ŧ
Brain (291)	NICE	2018				Very low grade ** (296)	
PPGL (292)	ESMO-EURACAN	2020				Asymptomatic, have a low- to intermediate tumour burden and absence of localised complications of any mass ŧ	
Oral cavity (293)	EHNS-ESMO-ESTRO	2021				T1,N0 ŧ	<5mm ŧ
Bone sarcomas (294)	ESMO-EURACAN-GENTURIS-ERN	2021				Progressive and asymptomatic lesions ŧ	

ƙ randomised trial

ŧ no evidence cited

ƀ systematic review meta

ɨ other guidance

* Model

** retrospective study

⚕ expert opinion/clinical consensus/clinical principle

¥ Prospective cohort study

Table 3.5 Monitoring recommendation with level of evidence by guideline and cancer site (tests, intervals and triggers)

Cancer (Ref)	Guideline Author	Year	Monitoring Test (Monitoring Interval)				Trigger
			Test 1	Test 2	Test 3	Test 4	
Prostate (249)	AIM	2021	PSA ↑ (N/R)	DRE ↑ (N/R)	biopsy ₭ (321) (NR) ↑	mpMRI **(322) (consider) ⚕ (259)	N/R
Prostate (250)	Alberta Health Services	2022	PSA ↑ (6 monthly at physicians discretion) ↑	DRE ↑ (annually at physicians discretion) ↑	Biopsy ↑ (Year 2 and 3) ↑	mpMRI ₭(321) (consider) ↑	Gleason ≥4, progression from DRE, PSA doubling time < 3 years Ъ (323)
Prostate (251)	American College of Radiology	2022	PSA ↑ (N/R)	DRE ↑ (N/R)	Biopsy ¥(324) (N/R)	mpMRI Ъ (325) (N/R)	N/R
Prostate (252)	ASCO	2018	PSA ⚕ (255) (3-6 months) ⚕ (255)	DRE ⚕ (255) (annually) ⚕ (255)	Biopsy ⚕ (2 years and continuing surveillance biopsies) ⚕	mpMRI ⚕ (consider) ⚕	Gleason score ≥ 7 and/or significant increases in the volume of Gleason 6 tumour ⚕ (255)
Prostate (253)	American Urological Association, ASTRO, SUO	2022	PSA ¥ (326) (6 monthly) ⚕	DRE and symptoms ¥(326) (1-2 years) ⚕	Biopsy ¥ (326) (N/R)	mpMRI ¥(327) (more research needed for timings) ↑	Increase PSA, progression DRE, higher volume/grade of disease, patient preference * (328)
Prostate (254)	Cancer Australia	2021	PSA ¥ (329)(NR)	DRE ¥ (329)(N/R)	Biopsy ¥(329) (NR)	mpMRI ¥(329) (NR)	Disease progression ↑
Prostate (255)	Cancer Care Ontario	2014	PSA ¥ (330) (3-6 monthly) ¥ (331)	DRE ¥ (330)(annually) ¥ (331)	Biopsy ¥ (330) (6-12 months, 3-5 years) ¥(332)	mpMRI ¥ (333)(consider) ¥ (334)	Gleason >7 and/or significant increases in the volume of Gleason 6 tumour ⚕

Cancer (Ref)	Guideline Author	Year	Monitoring Test (Monitoring Interval)				Trigger
Prostate (256)	Cancer Council Australia	2015	PSA ǂ (3 monthly) ǂ	DRE ǂ (6 months) ǂ	Biopsy ǂ (6-12 months, 2-3 years) ǂ	mpMRI ǂ (consider) ǂ	Pathological progression, patient preference ǂ
Prostate (257)	EAU position statement	2018	PSA ǂ (6 monthly) ¥ (335)	DRE ǂ (annually) ¥ (335)	Biopsy ǩ (321) (3-5 years) ¥(335)	mpMRI ǩ (95, 321)(12 months after diagnosis and consider timings after that) ¥ (336)	Change in grade, or in the extent of cancer involvement at biopsy or in local stage >T2 ǂ (337)
Prostate (105)	EAU, EANM, ESTRO, ESUR, ISUP, SIOG	2023	PSA ƅ (305, 338)(6 monthly) ǂ (305)	DRE ǂ (305, 338)(annually) ǂ (305)	Biopsy ƅ (305, 339)(every 3 years for 10 years) ǂ (305)	mpMRI ¥ (340)(routinely) ǂ (305)	PSA progression, PSA kinetics if accompanied by change in histology ǂ (305)
Prostate (258)	Department of Health	2022	PSA ǂ (341) (3 monthly, 6 monthly second year) ǂ (341)	DREǂ (341) (6 monthly) ǂ (341)	Biopsy ǂ (341) (year 2, and 5) ǂ (341)	mpMRI ǂ (341) (consider) ǂ (307)	Change in PSA, change in DRE, increase core volume, increase Gleason score, increase positive cores, MRI progression, patient preference ǂ (342)
Prostate (259)	NCCN	2023	PSA ¥ (326) (6 monthly) ǂ	DRE ¥ (326) (annually) ǂ	Biopsy DRE ¥ (326) (annually) ǂ	mpMRI ƅ (325) (annually) ǂ	Increase in tumour volume, a rise in PSA density, as well as patient Anxiety, Grade Group ≥3 disease, or if tumour is found in a greater number of biopsy cores or in a higher percentage of a given biopsy core ǂ
Prostate (96)	NICE	2021	PSA ǩ (303)(3-4 monthly) and PSA kinetics (routinely) ǂ	DRE ǩ (303)(annually) ǂ	Biopsy ǩ (303) (N/R)	mpMRI ǩ (321)(12-18 monthly) ǂ	Patient preference ǂ

Cancer (Ref)	Guideline Author	Year	Monitoring Test (Monitoring Interval)				Trigger
Prostate (260)	SEOM	2012	PSA ↑ (3-6 monthly) ↑	DRE ↑ (6-12 monthly) ↑	Biopsy ↑ (sometimes) ↑		Cancer progression ↑
Prostate (261)	International Society of Geriatric Oncology	2019	N/R				N/R
Renal (249)	AIM	2021	CT or MRI ¥ (343) (individualised at discretion of physician) ⚱ (247) (267)				Tumour growth (size or infiltrative pattern) ↑
Renal (264)	Alberta Health Services	2021	Imaging ↑ (6 monthly) ↑	Biopsy ↑ (optional) ↑			Cancer progression ↑
Renal (265)	American College of Radiology	2021	CT or MRI ⚱ (247) (267) (6-12 monthly then annually) ⚱ (247) (267)	Ultrasound ⚱ (247) (267) (annually) ⚱ (247) (267)	Chest imaging ⚱ (247) (267) (annually or more frequently depending on clinical behaviour) ⚱ (247) (267)		N/R
Renal (247)	American Urological Association	2021	enhanced cross-sectional imaging ⚕ (3-6 months then periodic) ⚕	Ultrasound or chest x-ray ⚕ (annually) ⚕			Tumour size >3cm, stage progression, growth kinetics >5mm/year, clinical changes in patient/tumour factors, additional biopsy results, development of symptoms, progression to metastatic disease ⚕
Renal (266)	BAUS/BUG	2012	Biopsy ↑ (consider) ↑				N/R

Cancer (Ref)	Guideline Author	Year	Monitoring Test (Monitoring Interval)				Trigger
Renal (267)	NCCN	2017	CT MRI or US ** (344) (every 6 months for 2 years then annually for up to 5 years) ↑	History and physical exam ↑ (every 6 months for 2 years then annually for up to 5 years) ↑	Comprehensive metabolic panel ↑ (every 6 months for 2 years then annually for up to 5 years) ↑	Bone scan ↑ (as clinically indicated)	Progression ** (312)
Renal (268)	Canadian Association of Radiologists	2019	Imaging ↑ (N/R)				N/R
Renal (248)	Canadian Urological Association	2022	Ultrasound ⚕	Abdominal imaging ⚕ (3-6 monthly then 6-12 monthly) ⚕	CRX ⚕ (12 monthly or for-cause) ⚕		Growth >4 cm, growth rate >0.5 cm/year, progression to metastases, patient preference ⚕
Renal (269)	EAU	2022	Ultrasound, CT or MRI ♭ (273) ¥ (345) (N/R)				Clinical progression ↑
Renal (270)	NHS England Greater Manchester	2014	N/R				Cancer progression ↑
Renal (271)	NHS England West Midlands	2016	N/R				N/R
Blood (283)	British Society for Haematology	2020	Physical exam ↑ (3-6 monthly) ↑	Enquiry about symptoms ↑ (3-6 monthly) ↑	Imaging ↑ (consider) ↑		symptoms that suggest disease progression GELF ¥ (315)
Blood (284)	British Society for	2020	N/R				N/R

Cancer (Ref)	Guideline Author	Year	Monitoring Test (Monitoring Interval)				Trigger
	Haematology						
Blood (285)	Alberta Health Services	2021	Lymphocyte count ↑ (N/R)				Decision to initiate treatment should be based upon symptoms, advanced disease (bulky or symptomatic adenopathy/ splenomegaly or cytopenias), or evidence for rapid disease progression (e.g. lymphocyte count doubling within 6 months)Lymphocyte doubling within 6 months, symptoms ↑
Blood (286)	ESMO	2021	N/R				N/R
Blood (287)	NICE	2016	Biopsy ↑ (N/R)				N/R
Blood (287)	NICE	2016	N/R				N/R
Blood (287)	NICE	2016	N/R				N/R
Blood (288)	Alberta Health Services	2021	Clinical assessment **(318) (3-6 monthly) **(318)	CT **(318) (annually) **(318)			Disease progression **(318)
Blood (288)	Alberta Health Services	2021	N/R				N/R
Blood (288)	Alberta Health Services	2021	N/R				N/R

Cancer (Ref)	Guideline Author	Year	Monitoring Test (Monitoring Interval)				Trigger
Thyroid (274)	American Thyroid Association	2015	Serial cross sectional imaging ↑ (N/R)	FNA (on evidence of progression) ↑			Cancer progression ↑
Thyroid (275)	ESMO	2019	Ultrasound ♭ (319) (6-12 monthly) ♭ (319)				N/R
Thyroid (276)	European Thyroid Association	2022	Ultrasound ♯ (6-12 monthly) ♯	Neck palpation ♯ (6-12 monthly) ♯			N/R
Thyroid (277)	Japan Association of Endocrine Surgery	2021	Ultrasound **(346) (6 monthly for 1-2 years, then annually) **(346)				Tumour diameter 13mm, appearance new lymph node metastases, patient preference, appearance of other thyroid disease or parathyroid disease requiring surgery ↑
Thyroid (278)	NCCN	2022	Ultrasound ¥ (282) (N/R)				N/R
Thyroid (279)	NICE	2022	Ultrasound ** (320) (clinical discretion) ↑	Blood tests ** (320)(clinical discretion) ↑			N/R
Gastro (289)	ESMO-EURACAN-GENTURIS	2022	Assessment (3 monthly) ↑				N/R
Gastro (290)	ESMO	2020	Imaging (annually)) ↑				N/R
Brain (291)	NICE	2018	N/R				Radiological or clinical progression ↑
PPGL (292)	ESMO-EURACAN	2020	N/R				N/R

Cancer (Ref)	Guideline Author	Year	Monitoring Test (Monitoring Interval)				Trigger
Oral cavity (293)	EHNS-ESMO-ESTRO	2021	N/R				N/R
Bone sarcomas (294)	ESMO-EURACAN-GENTURIS-ERN	2021	Radiological monitoring ǂ (N/R)				N/R

ǩ randomised trial

ǂ no evidence cited

ƅ systematic review meta

ǿ other guidance

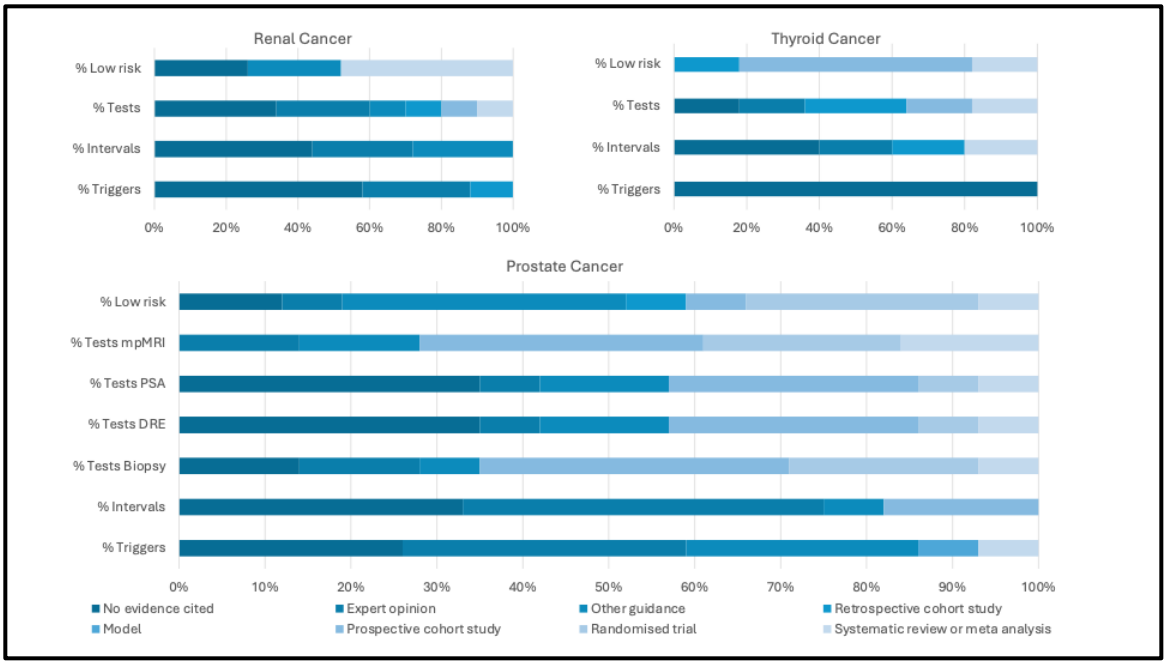
* Model

** retrospective study

ǂ expert opinion/clinical consensus/clinical principle

¥ Prospective cohort study

Figure 3.2 Levels of Evidence cited for each component of the monitoring strategy



Caption: Using renal cancer as an example, around 40% of the guidelines that had a recommendation for an interval cited no evidence, around 30% cited other guidance, and 30% cited expert opinion. Darker colours represent lower levels of evidence. Data is included in Appendix 1.

Table 3.6 Overall AGREE II scores

			AGREE II Tool: Overall results for each of the six domains						
Cancer Site	Guideline author	Year	Scope and Purpose	Stakeholder Involvement	Rigour of Development	Clarity of Presentation	Applicability	Editorial Independence	Overall
Prostate (249)	AIM Specialty Health	2021	78%	33%	42%	61%	63%	25%	50%
Prostate (250)	Alberta Health Services	2022	100%	53%	88%	83%	58%	100%	80%
Prostate (251)	American College of Radiology	2022	61%	72%	67%	83%	46%	92%	70%
Prostate (252)	ASCO	2018	100%	92%	54%	67%	25%	100%	73%
Prostate (253)	AUA, ASTRO, SUO	2022	89%	72%	77%	72%	42%	100%	75%
Prostate (254)	Cancer Australia	2021	83%	78%	40%	61%	46%	38%	58%
Prostate (255)	Cancer Care Ontario	2014	100%	72%	85%	89%	17%	100%	77%
Prostate (256)	Cancer Council Australia	2015	83%	72%	81%	89%	83%	100%	85%
Prostate (257)	EAU Position Statement	2018	83%	78%	65%	89%	21%	92%	71%
Prostate (105)	EAU, EANM, ESTRO, ESUR, ISUP, SIOG	2023	78%	78%	94%	72%	29%	100%	75%
Prostate (258)	Department of Health	2022	100%	89%	88%	83%	79%	100%	90%
Prostate (259)	NCCN	2023	56%	50%	79%	61%	46%	100%	65%
Prostate (96)	NICE	2021	94%	94%	86%	83%	75%	100%	89%

			AGREE II Tool: Overall results for each of the six domains						
Prostate (260)	SEOM	2012	61%	44%	29%	78%	21%	67%	43%
Prostate (261)	Society of Geriatric Oncology	2019	69%	61%	65%	67%	17%	100%	63%
Renal (249)	AIM Specialty Health	2021	72%	36%	44%	61%	58%	25%	49%
Renal (264)	Alberta Health Services	2021	92%	53%	65%	67%	25%	100%	67%
Renal (265)	American College of Radiology	2021	61%	61%	69%	78%	42%	92%	67%
Renal (247)	American Urological Association	2021	89%	69%	79%	78%	29%	100%	74%
Renal (266)	BAUS/BUG	2012	72%	39%	40%	72%	21%	100%	57%
Renal (267)	NCCN	2017	56%	61%	63%	61%	29%	100%	61%
Renal (268)	Canadian Association of Radiologists	2019	72%	64%	54%	61%	17%	58%	54%
Renal (248)	Canadian Urological Association	2022	72%	42%	69%	94%	54%	100%	72%
Renal (269)	EAU	2022	78%	78%	85%	67%	17%	100%	71%
Renal (270)	NHS England Greater Manchester	2014	89%	39%	25%	72%	17%	17%	43%
Renal (271)	NHS England West Midlands Expert Advisory Group for Urological Cancer	2020	72%	42%	35%	67%	17%	17%	42%
Blood (283)	British Society for Haematology	2020	67%	53%	58%	61%	33%	58%	55%
Blood (284)	British Society for Haematology	2020	61%	75%	54%	67%	17%	83%	60%
Blood (285)	Alberta Health Services	2021	89%	53%	58%	33%	38%	100%	62%
Blood (288)	Alberta Health Services	2021	94%	50%	73%	67%	54%	100%	73%
Blood (286)	EMSO	2021	56%	67%	51%	50%	17%	100%	57%
Blood (287)	NICE	2016	83%	94%	84%	67%	71%	100%	83%
Thyroid (274)	American Thyroid Association	2015	83%	83%	52%	78%	38%	83%	70%

			AGREE II Tool: Overall results for each of the six domains						
Thyroid (275)	ESMO	2019	72%	72%	53%	72%	17%	100%	64%
Thyroid (276)	European Thyroid Association	2022							67%
Thyroid (277)	Japan Association of Endocrine Surgery	2021	83%	61%	73%	67%	17%	100%	72%
Thyroid (278)	NCCN	2022	83%	67%	69%	78%	38%	100%	81%
Thyroid (279)	NICE	2022	94%	89%	83%	72%	50%	100%	70%
Gastro (289)	ESMO EURACAN GENTURIS	2022	72%	89%	71%	78%	33%	100%	74%
Gastro (290)	ESMO	2020	72%	89%	71%	78%	33%	100%	74%
Brain (291)	NICE	2018	94%	86%	71%	83%	17%	100%	75%
PPGL (292)	ESMO EURACAN	2020	56%	69%	29%	61%	17%	100%	55%
Oral cavity (excluding lip carcinoma) (293)	EHNS ESMO ESRTO	2021	64%	61%	56%	39%	17%	100%	56%
Bone Sarcomas (294)	ESMO EURCAN GENTURIS ERN	2021	67%	50%	58%	67%	17%	100%	59%

3.6 Discussion

3.6.1 Summary of findings

This chapter synthesised guideline recommendations for monitoring patients diagnosed with low-risk cancer. I found considerable variability in monitoring recommendations both between and within each cancer site, even when randomised trial evidence was available.

Prostate cancer was the only cancer site with randomised trial evidence to support the safety and patient eligibility for monitoring. When randomised trial evidence was absent for a particular cancer site, guidelines relied on prospective observational studies (280-282, 347) or systematic reviews of small studies (273). This was the case for low-risk renal and thyroid cancer. Cited studies compared the incidence of metastatic disease for patients opting for monitoring to patients receiving immediate treatment (272, 273). These non-randomised studies inform about the risk of progression in patients, but the lack of randomisation makes it challenging to draw definitive conclusions about safety and eligibility of monitoring because of confounding by indication.

The evidence to support what tests should be used to monitor was indirect and primarily aimed at cancer detection rather than monitoring. For example, in prostate cancer, while MRI-targeted biopsy is shown to be superior for detecting clinically significant prostate cancer (231), no direct evidence of the superiority of mpMRI over other tests (e.g. PSA) in the context of monitoring was cited in any guidance.

For all cancer sites, the quality of evidence was limited for surveillance intervals. Guidelines heavily relied on expert opinion. They either recommended specific surveillance intervals such as to monitor patients annually (96, 105, 252, 259) or every three to six months, which were based on expert opinion. Or, deferred the choice of monitoring intervals to the discretion of clinicians and recommended to “individually” (249, 267) monitor patients, or at intervals that were “up to clinical discretion” (250, 265).

Finally, the evidence underpinning what should trigger a change in management was limited, and the recommendations across guidelines varied significantly. Direct evidence did not exist for any cancer site although a randomised trial (PCASTt/SPCG-17) (257) is currently underway and compares standardised triggers for repeat biopsies and curative treatment in low-risk patients undergoing monitoring.

3.6.2 COMPARISON TO THE LITERATURE

Monitoring generally involves the scheduled repeated use of tests in an individual over time to make decisions about the management of the disease. It is central to the management of the patient. It takes up a significant part of the clinical workload and has associated costs. However in contrast the volume of published literature on the evaluation and use of tests specifically for monitoring is sparse (348).

Reviews of guidelines in other disease areas have also identified inconsistencies in monitoring interval recommendations and the use of evidence to support them. Moschetti (243) found wide variation in recommended intervals for monitoring chronic cardiovascular and respiratory conditions, with many guidelines relying on expert opinion. In this chapter, I found that the more relevant evidence available, the more specific the recommendations were. This was similar to findings from other health care guideline reviews (349, 350) and the results of Chapter 2 (159).

3.6.3 STRENGTH AND LIMITATIONS

The AGREE II tool was not designed to provide a comprehensive evaluation of the methodological rigor of evidence syntheses (351), therefore, I went further and summarised the recommendations and evidence for each recommendation of low-risk, tests, intervals and triggers for each cancer site.

In the rigour of development domain, prostate cancer guidelines performed better than other cancer sites. However, to obtain a high score in this domain, guideline developers are required to be transparent about the methods used to formulate their recommendations. Reviewers using AGREE II are asked to rank non-specific questions

from 1 to 7, so the tool does not account for whether guidelines are making recommendations that correctly follow the evidence. For example, monitoring in the ProtecT trial (240) did not include repeated biopsies but guidelines recommend biopsy intervals (105, 250, 255-258). My analysis provided an overarching perspective on the evidence underpinning monitoring recommendations. A limitation of this approach is that I was unable to focus on every detail within each cancer site.

Tools such as AGREE II are useful for assessing methodological rigour but do not evaluate the quality or appropriateness of the underlying evidence. The GRADE tool explicitly assesses evidence certainty and recommendation strength. Due to time constraints, I did not apply GRADE, which limits the ability to determine whether strong and specific recommendations were always justified. Future assessments could incorporate GRADE to more directly evaluate how well guidelines translate evidence into recommendations.

It is possible that inclusion of regional guidelines skewed the results and paints an unfavourable picture of the state of the evidence for monitoring low-risk cancer as they tend to be less specific and less evidence-based than international guidelines. This highlights a potential need for policy makers to consider whether it is worth making regional guidelines that are overall less consistent and helpful for policy makers compared to international guidance. Additionally, I included radiology-based guidelines, which also lowered the overall averages of guidelines as these were specific to imaging techniques. Finally, I did not include ductal carcinoma in situ as it is currently treated rather than monitored in clinical practice (352).

3.6.4 RESEARCH IMPLICATIONS

The development of the evidence that directly supports monitoring recommendations should be a priority for funders and researchers given the growing number of patients diagnosed with low-risk cancer. Evidence for monitoring strategies should be held to the same rigorous standard used to support screening programmes where randomised trials are required to prove effectiveness in reducing morbidity and mortality. This includes

assessing the complete monitoring program's clinical, social, and ethical acceptability, ensuring that benefits outweigh potential harms (353).

A robust monitoring strategy should include appropriate testing or imaging, conducted at defined intervals, with clear criteria for triggering intervention. To support such strategies, evidence should demonstrate that:

1) low-risk patients can be reliably distinguished from those at risk of progression;
2) monitoring is safe, cost-effective, and minimises unnecessary treatment and harm; and
3) delayed intervention does not lead to a significant increase in cancer-specific mortality beyond thresholds acceptable to patients and clinicians.

Ideally, this evidence would come from randomised trials comparing immediate treatment with active surveillance. In the absence of trials, well-designed observational studies may be acceptable if sufficient efforts are made to reduce bias. Where randomised trials are infeasible, evidence to support recommendations could be derived from carefully designed cohort studies, or modelling studies. However, these methods struggle to sufficiently control for known and unknown confounders that bias the results to favour more active intervention.

3.6.5 POLICY IMPLICATIONS

Guideline developers have been able to cite randomised trial evidence for prostate cancer and provide specific and strong recommendations. However, the recommendations do not fully align with the trial findings. For example, the Prostate Cancer Intervention versus Observation Trial (PIVOT) (263) and ProtecT (240) trial found no difference in cancer-specific mortality after 15-20 years of active surveillance or watchful waiting with fewer harms. These trials suggest a larger role for active surveillance or watchful waiting in prostate cancer management but recommendations continue to be conservative and for a limited group of patients. These risks continued overdiagnosis and overtreatment of prostate cancer. In addition, given the time it takes to complete randomised trials with mortality outcomes, the findings may not reflect

current clinical practice or patient demography when reported. For example, randomised trials in prostate cancer (240, 263) predated advances in technology, such as mpMRI, which have modified the detection of low-risk prostate cancer, potentially leading to improved health outcomes.

When randomised trial evidence is available, it is expected that guideline developers closely adhere to the results when making recommendations and if not provide justifications for deviations. When recommendations are reliant on expert opinion, this introduces potential conflicts of interest. While the AGREE II tool assesses the transparency of the development process, it was not built to detect this type of bias.

3.6.6 Clinical Implications

Due to heterogeneity among guidelines, clinicians considering monitoring as a treatment strategy may be uncertain as to which surveillance strategies to adopt. Healthcare providers rely on guidelines for decision-making and trust the recommendations are based on high-quality evidence, but this is not the case for monitoring patients with low-risk cancer. Until stronger evidence becomes available, shared decision-making and transparency about the limitations of current guidance will be essential to support informed care for patients with low-risk cancer.

3.7 Conclusion

With the exception of prostate cancer, the evidence base for monitoring low-risk cancer is weak and consequently recommendations in clinical guidelines are inconsistent. A lack of direct evidence supporting monitoring recommendations forces guideline developers to be reliant on expert opinion, alternative guidelines, or indirect evidence.
This chapter, in combination with Chapter 2 suggest that further research into retesting intervals is required. In Chapter 7, I use joint modelling to generate PSA retesting intervals. This method was not used in any of the evidence referenced in this chapter but this approach to modelling retesting intervals has been proposed as a method to individualise follow up testing intervals for active surveillance (354).

Chapter 4: Data Management

4.1 Background

Routinely collected primary care electronic health records have been used in epidemiological and medical research for over 35 years (355). These datasets contain longitudinal data on laboratory results, diagnoses, prescriptions, symptoms, and clinical activity recorded during routine healthcare interactions and consultations. In this chapter, describe how I managed the dataset in preparation for the following three analytical chapters.

4.2 Objectives

The objectives of this chapter were to:

1) Provide context of the use of electronic health records data in the UK.
2) Describe the management of variables used for the following three analytical chapters.

4.3 Summary of electronic health records databases in the UK

Primary care electronic health records are extracted from the clinical systems used in GP practices. In the UK, the structure of the National Health Service (NHS) makes these records unusually comprehensive. General practitioners (GPs) act as the gatekeepers to the NHS, and over 98% of the population is registered with one of around 6,419 practices in England (356). Because patients access the NHS through their GP, consultations, prescriptions, test results, and referrals are routinely documented in the GP's computer systems. While certain information generated in secondary care (such as blood tests performed in the hospital) may not always be fed back, the majority of each patient's health information is captured in the primary care records. Unlike claims-based systems, this produces a representative database reflecting patients' clinical histories rather than billing activity.

Partnerships between GP practices, academics, and for-profit companies that provide the software solutions have made electronic primary care health records available for research. Due to unique patient identifier (NHS Number), it is possible, with ethical project approval, to link primary care records to secondary and tertiary care settings. This provides a more holistic view on the patient's journey through different parts of the healthcare system throughout their lifetime. Linked data in this thesis includes prostate cancer diagnoses that are made in secondary care settings. This data comes from the National Cancer Registration Analysis Service (NCRAS) and the Hospital Episode Statistics (HES). Patient death records are available through the Office of National Statistics (ONS).

Primary care records relevant to this thesis include PSA tests results that occurred in primary care as well as diagnoses, symptoms and prescriptions. The primary use of this data is to help with the management of patients over time, although it can also be extracted and used for research purposes. There are three commercially supplied clinical software systems used in primary care practices in the UK. Currently, EMIS Health is the most common provider, and together with TPP covers more than 90% of practices in England (357).

The three software companies are as follows:

1) EMIS Health
2) SystmOne (provided by The Phoenix Partnership; TPP)
3) Vision (Cegedim Healthcare Solutions)

In 2023, a narrative review (357) provided details of the research databases that exist in the UK. Data included in these databases all come from one or multiple of the companies listed above. Before the COVID-19 pandemic, there were six main databases providing primary care records for research purposes; The Clinical Practice Research Datalink (CPRD) (355), QResearch (358), The Health Improvement Network (THIN) database (359), the Optimum Patient Care Research Database (OPCRD) (360), The Research and

Surveillance Centre (RCGP RSC) (361) and the Welsh Longitudinal General Practice Dataset hosted by SAIL Databank (362). During the COVID-19 pandemic, new electronic health records data resources were approved and designed as a response and as monitoring tools during the pandemic. These include the CVD-COVID-UK/COVID IMPACT Consortium (363) and OpenSAFELY (364). All eight of these data resources include records from between three and 58 million individuals with varying person follow-up time, varying abilities to provide linkages to other national databases, varying ethical procedures to gain access to the data and varying costs (357).

Initially, the major focus of electronic health records research was related to pharmaco-epidemiology (357), but now it encompasses other domains such as health services research, observational epidemiology, risk stratification, prediction modelling, health economics and clinical trials (365). The Prostate Cancer TRANSFORM trial in the UK is planning to explore the use of electronic primary care records to inform the control arm of the trial. In this thesis, I contributed to these developments by applying electronic health records to health services research in Chapter 5, observational epidemiology in Chapter 6, and risk stratification in Chapter 7.

4.4 CLINICAL PRACTICE RESEARCH DATALINK (CPRD)

CPRD is a UK government not-for-profit research service that supplies anonymised primary care data for public health research. CPRD Aurum includes data from GP practices in England that use the EMIS software. CPRD Aurum is considered representative of the broader English population in terms of geographical spread and deprivation (355). As Of December 2024 there were 37,033,788 acceptable patients in CPRD Aurum eligible for linkage (366). Linkage of CPRD primary care data with other patient level datasets is available for English practices who consented to participate in the linkage scheme. Datasets currently available for linkage to CPRD include: the Death Registration from the ONS, NCRAS Cancer Registration Tumour and Treatment data, NCRAS Systemic Anti-Cancer Therapy data, NCRAS National Radiotherapy Dataset, HES Admitted Patient Care data, HES Outpatient data, HES Accident and Emergency data, HES Diagnostic Imaging Dataset, Small area level data and other specific COVID-19 data

linkages. The Maternity Services Data Set will be released in the next update but as of August 2025, there were no reported timelines for its release (366).

4.5 THE BLOOD TEST TREND FOR CANCER DETECTION (BLOTTED) DATASET

I used data accessed under the approved CPRD protocol (ID: 22_001798; BLOTTED study) for the analyses presented in the following three results chapters. The protocol was designed to investigate the role of repeated blood test measurements in relation to cancer detection in patients attending primary care (12). As part of the study, CPRD Aurum data was linked with four additional datasets: the National Cancer Registration and Analysis Service (NCRAS), Hospital Episode Statistics (HES), the Office for National Statistics (ONS), and Small Area Level Data (355).

I contributed to the data specification for this project on PSA testing in primary care. The BLOTTED CPRD Aurum data cut included 28,496,162 patients from 1442 GP practices across England. These patients were all linked to NCRAS, HES, and the ONS and had at least 12 months of registration with their practice between 2000-01-01 and 2019-12-31. Of all ages, there were 13,936,821 male patients, 14,558,905 female patients and 436 patients with an unknown gender. Only patients with a coded male gender were included in this thesis. Although the BLOTTED protocol specifies 31 December 2019 as the end of the follow-up period, I restricted analyses to patients between 1 January 2000 and 31 December 2018. The restriction was necessary because the most recent NCRAS linkage was only available up to the 31 December 2018 (366). Further details on the study design and inclusion and exclusion criteria are described in the methods section of each chapter.

4.6 DATA MANAGEMENT

I managed and curated the datasets for the following three chapters using Structured Query Language (SQL). The files were provided directly from CPRD. Prior to my DPhil, I worked at Cegedim Healthcare Solutions, the company that owns the Vision electronic health record software. In this role, I helped manage data for the THIN database. This

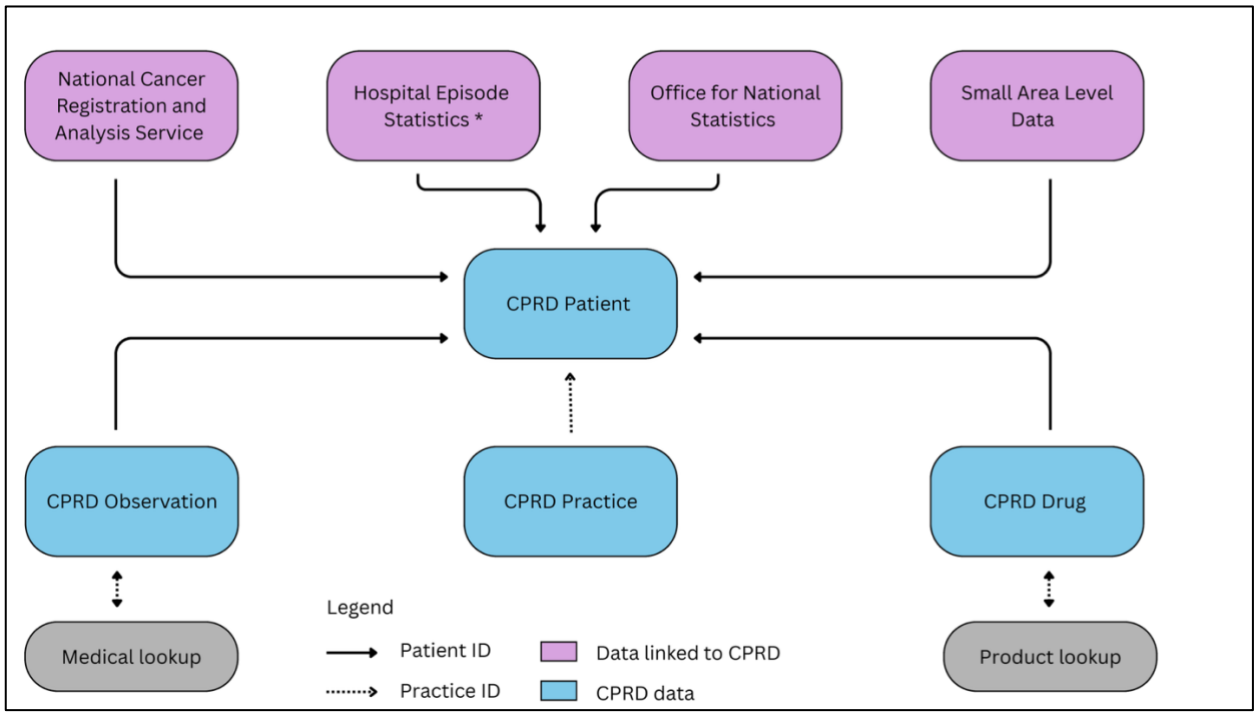
advanced my knowledge of SQL and gave me experience handling large datasets. SQL is more efficient than R when working with multi-million-row data. SQL uses on-disk indexing and a query optimiser, whereas R relies on in-memory processing, which can be slow and unstable when sufficient RAM is unavailable. The specific fields extracted from each CPRD table are summarised in Table 4.1. Figure 4.1illustrates how these tables were linked together.

Table 4.1: Description of data used in thesis

Table	Fields
Patient	Patient id, practice id, gender, year of birth, patient registration date, patient de-registration, CPRD date of death
Practice	Practice id, practice region, practice last collection date
Observation	Patient id, observation date, CPRD ethnicity, symptoms, PSA value, PSA unit
Drug issue*	Patient id, prescription
Office for National Statistics (ONS)	Patient id, date of death
Hospital Episode Statistics (HES)	Patient id, date of death, prostate cancer diagnosis, ethnicity
Small Area Level Data	Patient id, IMD quintile
National Cancer Registration and Analysis Service (NCRAS)	Patient id, prostate cancer diagnosis, Gleason primary, Gleason secondary, Gleason combined, stage best
Medical dictionary lookup table	Medcodeid, SNOMED CT, term, description
Product dictionary lookup	Productcodeid, product name, British National Formulary (BNF) chapter

** The product table was only used for sensitivity analyses to ensure including patients with a prescription of finasteride or dutasteride did not affect the overall results.*

Figure 4.1: Summary of data linkage



Caption: The dotted lines with two arrows indicate that the observation and drug tables are linked to their respective lookup tables. The observation table links via the medcodeid and the drug table links via the productcodeid. The dotted line with one arrow from practice to patient illustrates that the practice table is linked to the patient table via the practice identifier. The rest of the solid arrows indicate that the tables are linked to the patient table via the patient identifier. The blue boxes represent data from CPRD Aurum (EMIS Software), the purple boxes represent linked datasets, and the grey boxes are lookup tables.

** Hospital Episode Statistics data includes HES Admitted Patient Care data, HES Outpatient data and HES Accident and Emergency data.*

4.6.1 VARIABLES

For each variable below, I specified how it was cleaned in SQL. All variables described here are used in various analyses throughout Chapters 5, 6 and 7. All code lists for each variable were verified by a clinician (BDN) and are provided on my github page (https://github.com/kiana-k-collins).

4.6.1.1 Patient Identifier

Each individual patient in CPRD has a unique patient identifier. In the patient table, each patient has an associated year of birth, gender, registration date, de-registration date

and CPRD death date. To maintain patient confidentiality, CPRD only provides year of birth. To derive age, each patient's date of birth was imputed to the 1st of July of that year.

4.6.1.2 Practice Identifier

Each practice has a unique practice identifier. I retrieved the last collection date and the region for each practice from the practice table. The practice table links to the patient table via the practice identifier.

4.6.1.3 Date of Death

Date of death was taken from the ONS as the primary source. This linked to the patient table through the patient identifier. In HES, to find the patient's date of death I took the earliest discharged date from the Admitted Patient Care, Outpatient, and Accident & Emergency datasets, if the reason for discharge was that the patient died. In CPRD the date of death was provided by CPRD. If an ONS date of death was not available, the earliest date between the HES death record and the CPRD death record was used (367).

4.6.1.4 Prostate Cancer

Prostate cancer diagnoses were available from three sources: NCRAS, HES, and CPRD. In NCRAS and HES, cases were identified using ICD-10 code C61. The earliest diagnosis date was recorded for patients with a diagnosis in NCRAS. In HES, the earliest diagnosis date was taken across the Admitted Patient Care, Outpatient, and Accident & Emergency datasets. In CPRD, prostate cancer was identified using medcodeid values mapped to SNOMED CT codes in the observation table. The earliest recorded diagnosis date in CPRD was selected. For each patient, the overall first diagnosis date was assigned from NCRAS as the primary source. If no NCRAS record was available, the earliest diagnosis date between HES and CPRD was used.

Prostate cancer diagnoses were classified as either clinically significant or not clinically significant using Gleason score. Only patients with a diagnosis recorded in NCRAS could be assigned a Gleason score, as staging information is not available in CPRD or HES. The fields in NCRAS used to determine Gleason score were Gleason_Combined, Gleason_Primary, Gleason_Secondary and Stage_Best. Gleason_Combined was used

as the primary source of Gleason score. In total, 140,022 patients had a Gleason_Combined score. Of those, 21 patients had values greater than 10. These were recoded to Gleason 10, except in three cases where the Gleason primary and secondary were both 6 and the Stage_Best was 1 or 2. In those cases, the Gleason score was recoded to 6. It was not possible to give the other 50,440 patients a Gleason score as there was no information available. There were 1881 patients with a coded Stage 1 for Stage_Best of those 71 had Gleason_Primary coded as 3. These patients were assumed to be Gleason 6. The rest of the patients from NCRAS were categorised as having an unknown stage along those patients who only had a cancer diagnosis from HES or CPRD. Patients were then grouped into Gleason ≤6, Gleason ≥7 and unknown. This is similar to clinical significant category used in the ProsDetect Study that has not been published yet (CPRD Study Reference ID21_000609). This method allowed me to compare results to the relevant literature.

4.6.1.5 Ethnicity

Ethnicity was grouped into the following categories: White, Asian, Black, South Asian, Mixed, Other and Unknown. Ethnicity was primarily retrieved from the HES database. HES ethnicity was defined as the most frequently recorded value across the HES Admitted Patient Care, Outpatient, and Accident & Emergency datasets. If a patient had multiple ethnicities, the most frequent one was used. If it was a tie, a random ethnicity between the options available was chosen. There were 6,503,675 patients with an ethnicity code from HES. If ethnicity was not recorded in HES, I used medcodeids mapped from SNOMED CT codes to identify ethnicity in the Observation table in CPRD. There were 6,484,695 eligible patients who had an ethnicity in CPRD with an associated observation date. In CPRD, I used each patient's most recent record. The combined ethnicity from HES and CPRD has been shown to be comparable to the ethnicity distribution in the UK (368). Sixteen percent of ethnicity data was missing and treated as an unknown category. In March 2023 CPRD released an algorithm to determine ethnicity in CPRD Aurum and Gold. This was not available when I was managing ethnicity for this thesis. Their algorithm is similar to the approach I described above. One difference was that CPRD used the most common ethnicity that's recorded when combining both CPRD

and HES, whereas I took the most frequently recorded variable from HES as the primary source and if not recorded I used information from CPRD.

4.6.1.6 Family History of Prostate Cancer

Family history of prostate cancer is not coded consistently in primary care records (369), however, it is an important variable to consider as prostate cancer has a known hereditary link. For this variable, I used the medcodeid (Family history of prostate cancer ('2533391019') from the observation table.

4.6.1.7 Region

Region was taken from the practice table and linked back to the individual patient through the practice identifier. Region was the region of the practice. There were nine regions in England provided by CPRD. These were the following: South East, South West, London, North West, North East, East Midlands, West Midlands, Yorkshire and the Humber and East of England. Less than 1% of patients had missing region and these were grouped into an 'Unknown' category.

4.6.1.8 Index of Multiple Deprivation (IMD)

Patient-level index of multiple deprivation was retrieved from the linked small area dataset. The IMD in the small area dataset is produced by the UK Ministry of Housing, Communities and Local Government which is constructed using primarily administrative sources (e.g., welfare and benefit records) supplemented by census information (370). Socioeconomic status in CPRD was representative of the national distribution, with an average IMD decile of 5.52 in CPRD compared with 5.50 in the general English population (371). In the linked BLOTTED dataset, deprivation was provided in 20 bands of Index of Multiple Deprivation which I reduced into quintiles. Less than 0.2% were missing and categorised into an 'unknown category'.

4.6.1.9 PSA tests

PSA tests with associated dates and units were retrieved from the observation table in CPRD using medcodeids mapped to SNOMED CT codes. PSA tests with no associated value or with a negative value were not included. Tests were included if they occurred

between 2000-01-01 and 2018-12-31. For the patients with a prostate cancer diagnosis during follow up, PSA tests were not included after the patients first record of a prostate cancer diagnosis.

One PSA test per patient was assumed to be the maximum number of PSA tests a patient could have in a day. There were 47,412 (3%) patients with two or more PSA tests recorded on the same day. To ensure every patient only had one record per day the following rules were applied. If patients had a PSA value of 0.000 on the same day as a PSA test with a value above 0.000, I kept the result with the higher value. If a patient had two tests on the same day, and one had a null unit and one did not, I kept the PSA test value with a unit. If PSA tests occurred on the same day and one had a unit of ng/mL compared to another unit, I kept the PSA test with the unit of ng/mL. If a patient had three values on the same day I used the middle PSA result. If the patient did not have three tests I chose a random PSA result per patient.

Patients with a value of 0 were changed to a value of 0.001 to ensure statistical modelling could manage these values. Some studies (372) using PSA for monitoring progression use PSA + 1 to handle values that are 0. This is important for progression cohorts as if you have prostate cancer treatment and your PSA rises from 0 it may be a sign of progression. However, in a pre-diagnosis cohort of patients there is no clinical difference between a value of 0 and 0.001. In total, there were 8844 (0.2%) PSA tests that had a value of 0.001.

I considered removing patients with very high PSA values over 1000 ng/mL, however, most of them had a prostate cancer diagnosis. There were 1913 patients with at least one PSA test over 1000ng/mL who had a diagnosis of prostate cancer. There were less than 0.1% of PSA tests over 1000 ng/mL (Table 4.2).

Table 4.2: Number of PSA tests by very high PSA values and cancer

PSA range	Number of patients without prostate cancer during follow up	Number of patients with prostate cancer during follow up
≤1000 ng/mL	3,633,593	348,095
> 1000 ng/mL	708	2,199

4.6.1.10 Symptoms

The following seven symptom categories were included based on NICE NG12 (107): back pain, bone pain, fatigue, weight loss, haematuria, erectile dysfunction, and lower urinary tract symptoms. Symptoms and associated observation dates were retrieved from the observation table in CPRD Aurum based on medcodeids mapped from SNOMED CT codes. Symptoms were included in the analysis conducted in Chapter 5. Further details of this analysis can be found in the methods section of Chapter 5.

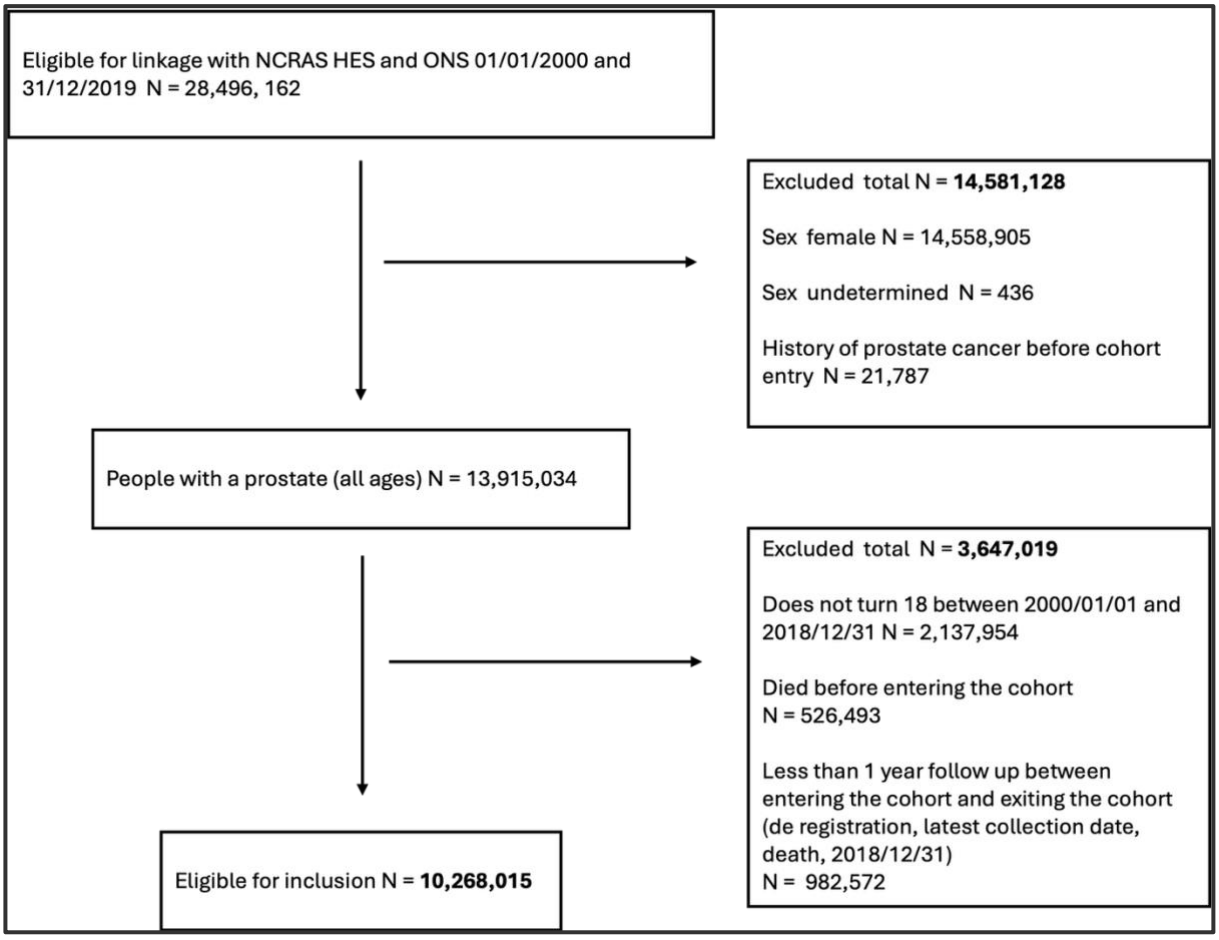
4.6.1.11 Prescriptions

Patients who were ever prescribed an alpha-a-reductase inhibitor (finasteride or dutasteride) was determined from the drug table. All patients with a PSA test who had at least one prescription of finasteride or dutasteride between 1995-01-01 and 2018-12-31 were flagged for a sensitivity analysis in Chapter 6. Productcodeid for these prescriptions can be found on Github, as described in Section 4.6.1.

4.7 RESULTS: DATA QUALITY CHECKS

All the counts and descriptions in the results section of this chapter represent the patient cohort eligible to contribute to one ,or all, of the next three analysis chapters. The study period was between 2000-01-01 and 2018-12-31. To be eligible for inclusion patients were required to be registered at English general practices for at least 12 months, linkable to NCRAS, HES, and ONS, male, did not have a prostate cancer diagnosis prior to entering the study, and aged over 18 years during the study period. The total number of eligible patients was 10,268,015 (Table 4.2). The total number of patients contributing to each study was dependent on the specific inclusion and exclusion criteria defined in each chapter.

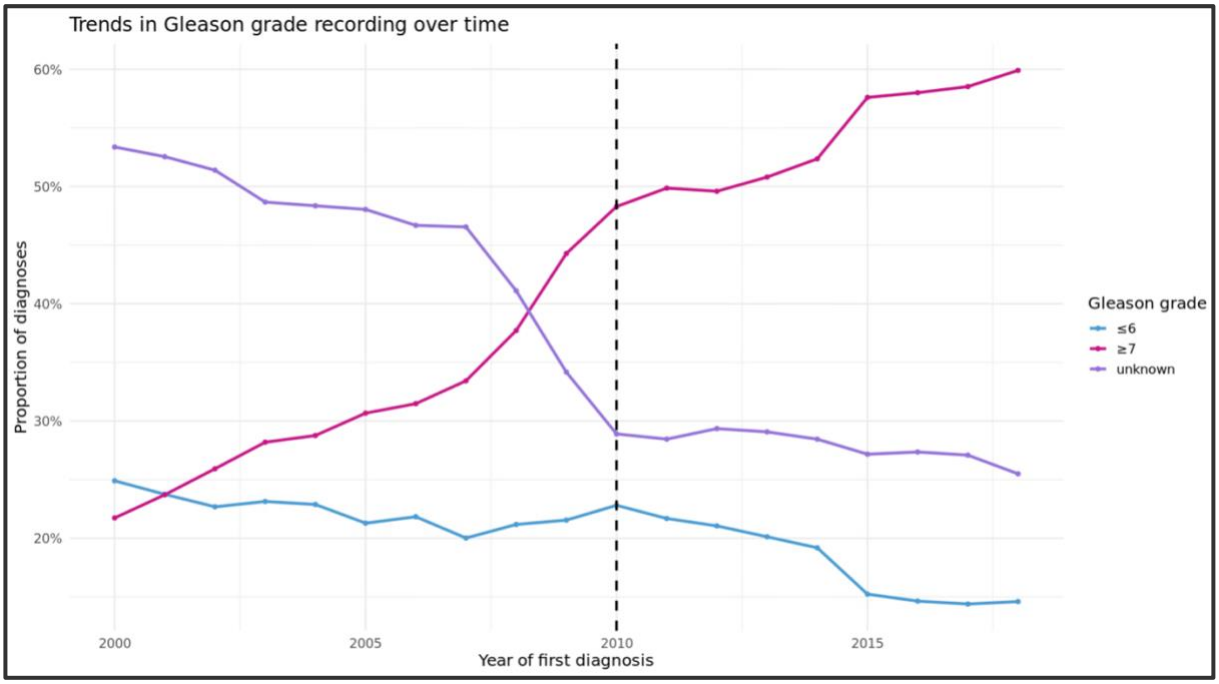
Figure 4.2: Patient inclusion flow chart



4.7.1 GLEASON SCORE

By Gleason score, there were 29,656 patients with Gleason 6, 65,798 patients with Gleason 7 and 54,311 with an unknown score. In 2010 there was an initiative to improve Gleason score coding in NCRAS data (373) as seen in the proportions of Gleason score coding over time (Figure 4.3).

Figure 4.3: Gleason score coding in NCRAS over time



4.7.2 PSA TESTS

Overall, there were 1,545,050 patients who together had a total of 3,984,595 PSA tests recorded during the study period (2000-01-01 and 2018-12-31). The total number of PSA tests in each study depended on the specific inclusion and exclusion criteria defined in each chapter. Table 4.3 summarises how many PSA tests there were per patient. Figure 4.4 shows the distribution of PSA tests by age at each test. Figure 4.5 shows that logged PSA values were close to normally distributed. Table 4.4 shows median (IQR) PSA values by age and cancer status.

Table 4.3: Number of PSA tests per patient

Number of PSA tests per patient	Number of patients (n = 1,545,050)
1	791,708 (53%)
2	305,739 (20%)
3	152,881 (10%)
4	88,294 (6%)
5	55,045 (4%)
6	36,782 (2%)
7	25,802 (2%)
8	18,813 (1%)
9	14,169 (1%)
10	10,921 (1%)
11 to 15	28,545 (2%)
16 to 20	9,943 (1%)
21 to 30	5,172 (<1%)
31+	1,236 (<1%)

Figure 4.4: Number of PSA tests by age

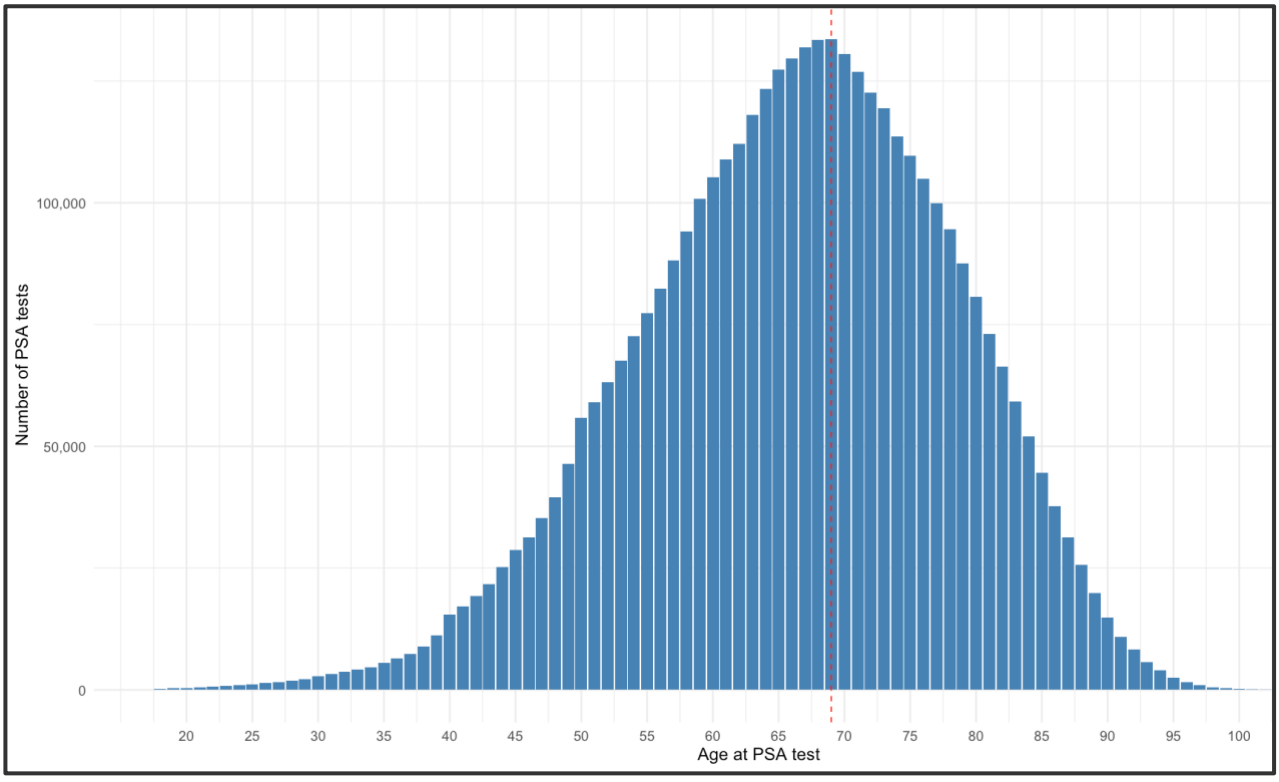


Figure 4.5: Histogram of log(PSA) values with normal curve

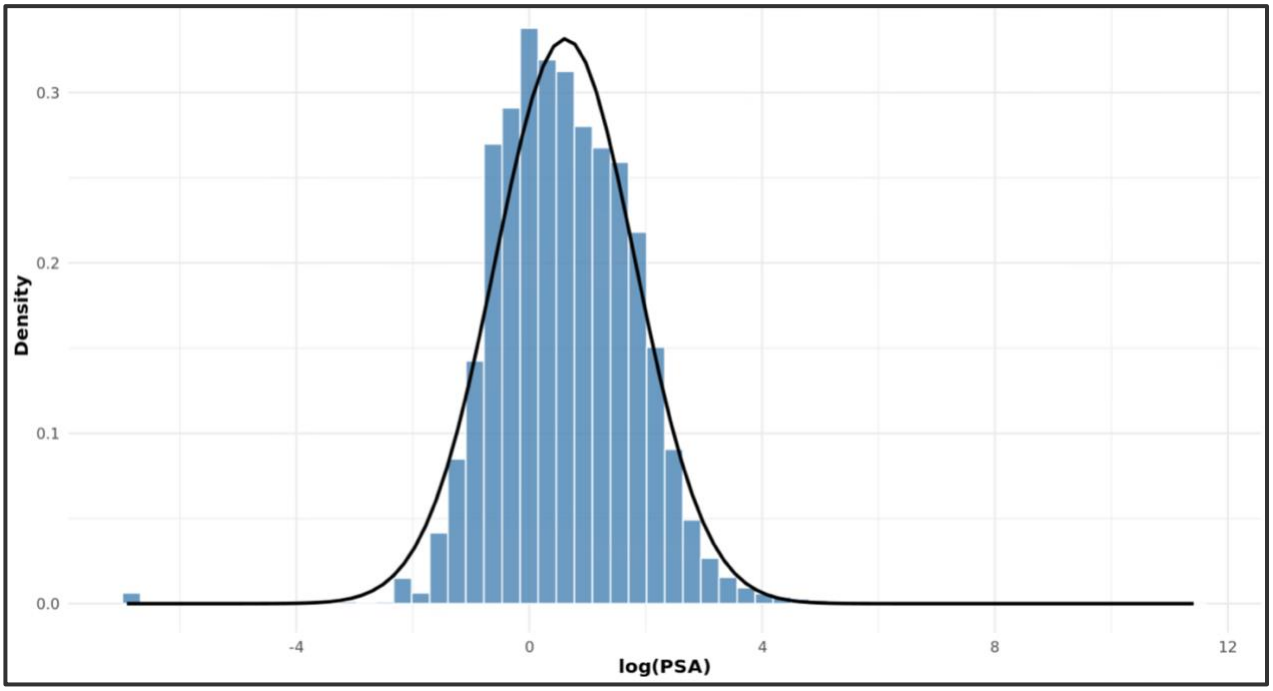


Table 4.4: Median PSA values by age and cancer diagnosis and Gleason score

Age at PSA test	No cancer Median (IQR) PSA ng/mL	All cancer Median (IQR) PSA ng/mL	Gleason ≤6 Median (IQR) PSA ng/mL	Gleason ≥7 Median (IQR) PSA ng/mL	Gleason unknown Median (IQR) PSA ng/mL
< 40	0.67 (0.47 to 0.96)	2.00 (1.11 to 3.83)	2.30 (1.40 to 4.60)	1.70 (1.00 to 3.20)	1.83 (0.90 to 7.00)
40 to 44	0.70 (0.50 to 1.06)	2.60 (1.42 to 4.20)	2.80 (1.60 to 4.03)	2.60 (1.50 to 4.31)	1.80 (1.00 to 3.20)
45 to 49	0.80 (0.50 to 1.20)	3.30 (1.90 to 5.50)	3.12 (2.00 to 4.60)	3.50 (2.00 to 6.20)	3.25 (1.58 to 5.32)
50 to 54	0.90 (0.58 to 1.50)	3.97 (2.30 to 6.30)	3.81 (2.44 to 5.60)	3.98 (2.20 to 6.90)	4.13 (2.30 to 6.72)
55 to 59	1.10 (0.65 to 2.20)	4.50 (2.80 to 7.16)	4.40 (3.00 to 6.40)	4.50 (2.70 to 7.60)	4.80 (2.70 to 7.90)
60 to 64	1.40 (0.79 to 3.01)	5.30 (3.30 to 8.40)	5.11 (3.50 to 7.30)	5.30 (3.20 to 8.80)	5.60 (3.20 to 10.00)
65 to 69	1.80 (0.90 to 3.90)	5.96 (3.90 to 9.60)	5.80 (4.10 to 8.30)	6.00 (4.00 to 10.00)	6.00 (3.40 to 11.00)
70 to 74	2.17 (1.00 to 4.50)	7.22 (4.57 to 12.30)	6.90 (4.80 to 10.10)	7.50 (4.90 to 12.90)	7.10 (3.50 to 14.14)
75 to 79	2.51 (1.10 to 5.33)	9.00 (5.40 to 17.10)	8.20 (5.60 to 12.90)	9.57 (6.13 to 18.10)	8.63 (4.20 to 18.50)
80 to 84	3.00 (1.25 to 6.50)	12.51 (6.50 to 26.50)	10.10 (6.60 to 17.30)	14.20 (8.05 to 28.01)	12.10 (5.70 to 27.10)
85 to 89	3.41 (1.30 to 7.80)	16.65 (7.40 to 38.20)	13.24 (7.10 to 23.85)	19.60 (9.92 to 39.30)	16.20 (7.00 to 38.60)
90+	3.84 (1.40 to 9.25)	20.80 (7.50 to 52.85)	18.92 (8.03 to 35.28)	24.60 (12.90 to 50.10)	20.50 (7.20 to 53.40)

4.8 MISSING DATA

Missing data on cancer stage was included as unknown. I considered the possibility of imputing this but there is no consensus on whether stage is missing at random or missing not at random. One study imputed metastatic prostate cancer using Swedish cancer registry data and found that the estimated incidence of metastatic cancer varied on imputation method. They found that combining deterministic imputation with multiple imputation provides plausible results that resembled the survival time for patients with known metastatic cancer (374). However, the study reported a large proportion of missing stage data (66% of metastatic stage and 76% of nodal stage). A study focused on imputation in English cancer registry records found that imputation would be possible for some patients but only with specific clinical imputations (375). Similar to the Swedish study, this study focused on imputing metastatic stage. To my knowledge, there are no studies published using multiple imputation to impute Gleason score using UK NCRAS data.

Patients with missing ethnicity were retained in the analysis by assigning an "unknown" category to avoid exclusion. Ethnicity in UK observational datasets is rarely missing at random (368). It was found that ethnicity recording varies systematically by age, gender, region, and clinician (376). A descriptive analysis of ethnicity category coding in English NHS hospital datasets was done to assess the completeness and consistency of ethnic coding. It explored variations between different groups of patients and found that minority ethnic groups were less likely to be coded consistently or assigned a specific category, and codes such as "other", "not stated", and "not known". It was also found that men aged 18 to 64 were more likely to have missing codes, that coding was more complete for patients who died in hospital compared with those discharged, and London had higher proportions of "not stated" or "other" compared with the rest of England (376).

Region and deprivation quintiles both had less than 1% of data missing. These variables were only used in the analysis of Chapter 5, where I described PSA testing and retesting across England. I retained these in the analysis as unknown categories, and I do not

expect them to impact the analysis. I did not want to exclude any patients as the aim of the chapter was to describe PSA testing in England.

4.9 Strengths and Limitations

A key strength of this dataset is its large sample size of over ten million male patients and 19 years of follow-up. Primary care records included not only PSA results but also symptoms, prescriptions, referrals, and comorbidities. Referrals and comorbidities could be used in future analysis alongside more detailed analysis on the effects of prescriptions. Linkage to hospital, cancer registry, and mortality data provides additional outcome information that improves completeness. These features together allowed me to conduct detailed longitudinal analyses of prostate cancer risk and testing patterns over the following three analytical chapters.

A limitation is that the cohort of patients must be s registered with their general practice for at least 12 months between 2000-01-01 and 2019-12-31. This creates an inherent bias by excluding those who may not be registered with a GP or those who had a PSA test and died within the year of having their first test. In total, there were 89 distinct patients who entered the cohort in 2000 and had a diagnosis of prostate cancer and died within the year. I report 14 individual patients who entered the cohort in 2000 and died within the year who had a confirmed prostate cancer diagnosis in the year 2000 and had at least one PSA test before their diagnosis. Of these 14 patients there were 20 PSA tests. The median value of PSA tests for this group of patients was high at 85.0 ng/mL (IQR 19.8 to 595.0). There were 147,007 patients who did not contribute a full year of follow-up between 2000 and 2018. Of the 147,007 patients there were 162 PSA tests not removed. 65,799 of the 147,007 patients turned 18 in 2018 and 14 of those patients had a PSA test value 0.60 ng/mL (0.3 to 1.2).

The categorisation of clinically significant cancer is a limitation. Patients were grouped into broad categories of clinical significance (Gleason ≤6 and Gleason ≥7). This was the best available approximation of clinically significant disease possible within the NCRAS dataset and has been used in other ongoing studies such as ProsDetect. While this

approach allows broad stratification, it is not possible to distinguish patients who have Gleason 3+4 disease versus Gleason 4+3. A patient with a Gleason score of 7 that comes from adding 3 + 4 is thought to have a less aggressive cancer than someone with a Gleason score of 7 that comes from adding 4 + 3. This clinical significance of this difference is important. Based on consensus from the International Society of Urological Pathology in 2014 developed a simple, intuitive grading system that has been accepted by clinicians and improves stratification of patients into distinct grade groups, which have implications for treatment. Gleason 6 is equal to Grade Group 1, Gleason 3 + 4 falls under Grade Group 2, and Gleason 4 + 3 indicates Grade Group 3 (Section 1.5.3). This new grading system has not yet been incorporated into NCRAS data, and further research is needed to address variation in coding and improve the consistency of classifying clinically significant prostate cancer.

Further to these specific limitations around the data management of primary care records, in each of the following analytical chapters, I describe the limitations relevant to the specific study design and relevant variables utilised in each chapter.

4.10 Conclusion

In this chapter, I summarised electronic medical health records data available in the UK and described how I managed each variable from the BLOTTED dataset. These variables are used for the subsequent analysis in Chapters 5, 6, and 7.

Chapter 5: PSA Retesting Intervals and Trends in England: A Population-based Cohort Study

5.1 Dissemination

The work presented in this chapter was published in the British Medical Journal (2025) (377).

***Collins KK**, Oke JL, Virdee PS, Perera R, Nicholson BD. Prostate specific antigen retesting intervals and trends in England: population-based cohort study. Bmj. 2025;391:e083800.*

The findings in this chapter were presented as a poster at the Cancer Research UK Early Diagnosis Conference in Birmingham (2024). They were presented as an oral presentation at the Cancer Primary Care Conference in Manchester (2025). They also won Best Oral Presentation at the South West Society of Academic Primary Care in Oxford (2025).

Findings from this chapter received international media coverage across television, radio, and print outlets, including *BBC Breakfast*, *BBC Radio 4*, *BBC News*, and *The Independent*. Copies of all media reports are provided in Appendix 2.

5.2 Background

As described in Chapter 1 (Section 1.12 and Section 1.13), in England there is conflicting guidance for PSA testing making it difficult to determine whether PSA testing is encouraged or discouraged. For asymptomatic patients, the PCRMP recommends shared decision making and the NSC recommends against PSA testing. Additionally, there is separate guidance for symptomatic patients (NICE NG12). Importantly, none of these guidelines provide recommendations on PSA retesting intervals.

In Chapter 2, I reported that internationally, the recommended PSA retesting interval ranges from one to ten years (159). This variation in PSA retesting intervals in clinical guidelines reflects the lack of direct evidence for PSA retesting intervals. Reasons for retesting PSA in primary care are largely unknown other than to confirm a raised PSA value (378). It is possible that patients with persisting symptoms are retested (379). Repeating a PSA test for asymptomatic patients as part of routine of annual screening increases the risk of prostate cancer overdiagnosis and overtreatment (110, 380).

PSA testing in the UK has been evaluated in several cross-sectional (381, 382) and longitudinal studies (369). However, these studies had short timeframes or used survival analyses methods focussed on the risk of having one PSA test. Increased rates of PSA testing over time and inequalities in the UK around the cumulative risk of having a PSA test have been shown (369, 381, 382). It is established that PSA testing is higher in the South of England and in lower areas of deprivation (110).

Patterns of PSA retesting intervals, rates of PSA testing by PSA result, and the impact of symptom presentation in primary care in England are unknown. In this chapter, I characterise how PSA testing was utilised in primary care between 2000 and 2018 before a patient is diagnosed with prostate cancer. I describe population-based trends in PSA testing over time and examine individual patient variation in both the rates of PSA testing and the length of PSA retesting intervals. I also evaluate associations with region, deprivation, ethnicity, age, family history of prostate cancer, PSA test results, and symptom presentation to explore if the variation in overall PSA testing rates are driven by differences in how frequently patients are retested.

5.3 OBJECTIVES:

The objectives of this chapter were to:

1) Determine temporal trends in PSA testing between 2000 and 2018.
2) Determine to what extent PSA testing was driven by symptom presentation, family history, PSA test result, ethnicity, region, age or deprivation.
3) Describe the length of PSA retesting intervals in primary care.

4) Determine whether the length of PSA retesting intervals varied by symptom presentation, family history, PSA test result, ethnicity, region, age, or deprivation.

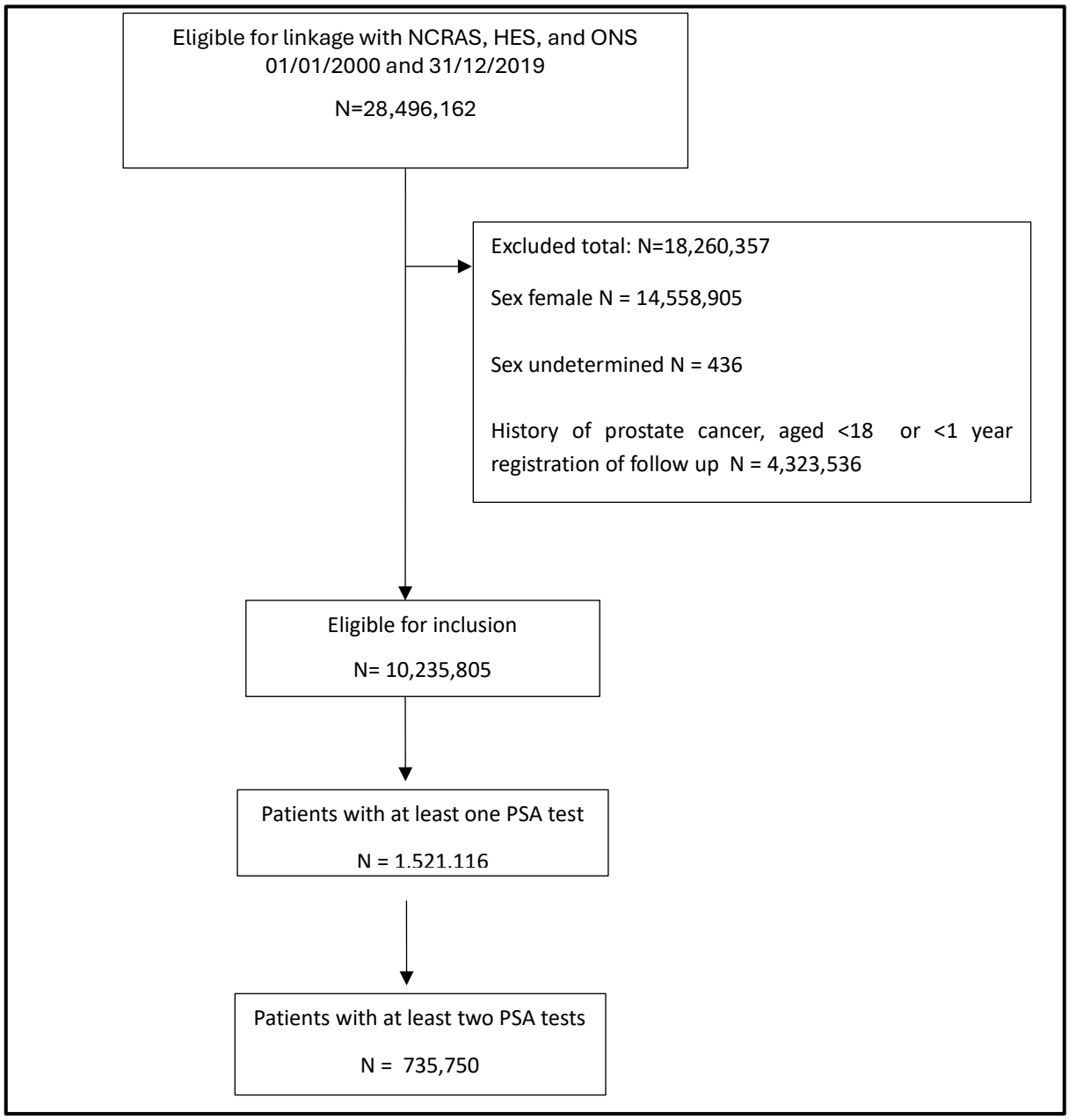
5.4 METHODS

5.4.1 STUDY POPULATION

I conducted an open population-based cohort study of routinely collected electronic health records data. The data used was previously described in Chapter 4. All results in this chapter are reported according to the Reporting of studies Conducted using Observational Routinely Collected health Data (RECORD) extension to the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines for observational studies.

Eligible patients (Figure 5.1) were registered at English general practices between 2000 and 2018, linkable to NCRAS, HES, and ONS, male, contributed at least one year of follow up, did not have a prostate cancer diagnosis prior to entering the study, and aged over 18 years during the study period. Patients entered the cohort at the latest of date of the start of the study (2000-01-01), registration with the practice, or 18th birthday. Patients exited the cohort at the earliest of date of the end of the study (2018-12-31), first prostate cancer diagnosis, death, transferred out of the practice, or last data download for that practice.

Figure 5.1: Flow chart of participant selection



5.4.2 VARIABLES

PSA tests for all patients that occurred before the patient entered the cohort or after the patient exited the cohort were excluded. For the patients with a prostate cancer diagnosis during follow-up, I included PSA tests occurring before the patient's earliest cancer diagnosis date. Each PSA test record was defined as being either above or below an "age-specific threshold." This was based on the NICE NG12 age-specific PSA thresholds for patients with symptoms of prostate cancer (107). PSA values were

categorised as above the age-specific threshold if the patient's age was between 18 to 49 and PSA value >2.5 ng/mL, age 50 to 59 and PSA value >3.5 ng/mL, age 60 to 69 and PSA value > 4.5 ng/mL and aged 70+ and PSA value over 6.5 ng/mL.

I included seven symptom categories based on NICE NG12 (107): back pain, bone pain, fatigue, weight loss, haematuria, erectile dysfunction and lower urinary tract symptoms. Symptoms were retrieved from the patients' primary care record (CPRD Aurum) based on SNOMED-CT codes. PSA tests were paired with a symptom if the symptom occurred in the 90 days before the PSA test date. If PSA tests occurred in the first three months of the year 2000, I retrieved symptoms occurring in the 90 days prior. If multiple PSA tests were taken within the 90-day time window, or multiple symptoms were recorded in the 90-day window, the closest symptom to the PSA test was included. If two symptoms were recorded on the same day was chosen at random. Ethnicity groupings, region, family history and Index Multiple Deprivation (IMD) quintiles were previously described in Chapter 4.

5.4.3 PATIENT CHARACTERISTICS

Individual patient characteristics determined at the date of study entry were age groups (18 to 29, 30 to 39, 40 to 49, 50 to 59, 60 to 69, 70 to 79, 80 to 89, 90+ years), ethnicity, family history of prostate cancer, whether the patient had a diagnosis of prostate cancer during follow-up, region, and IMD quintile.

5.4.4 STATISTICAL ANALYSIS

After completing the data management in SQL as described in Chapter 4, further analyses was conducted using R version 4.4.2.

5.4.4.1 PSA testing trends overtime

Population-based crude PSA testing rates were calculated by dividing the number of tests ordered per 1000 person-years of follow-up overall and by year. Age-standardised testing rates were estimated using direct standardisation with 2018 as the reference population. Temporal trends of PSA testing rates between 2000 and 2018 were stratified

by age at PSA test, region, IMD quintile, ethnic group, family history, PSA test above/below the age-specific threshold and presence of at least one symptom paired with a PSA test. I did not replace any missing data as the aim was to describe patterns of PSA testing recorded in primary care.

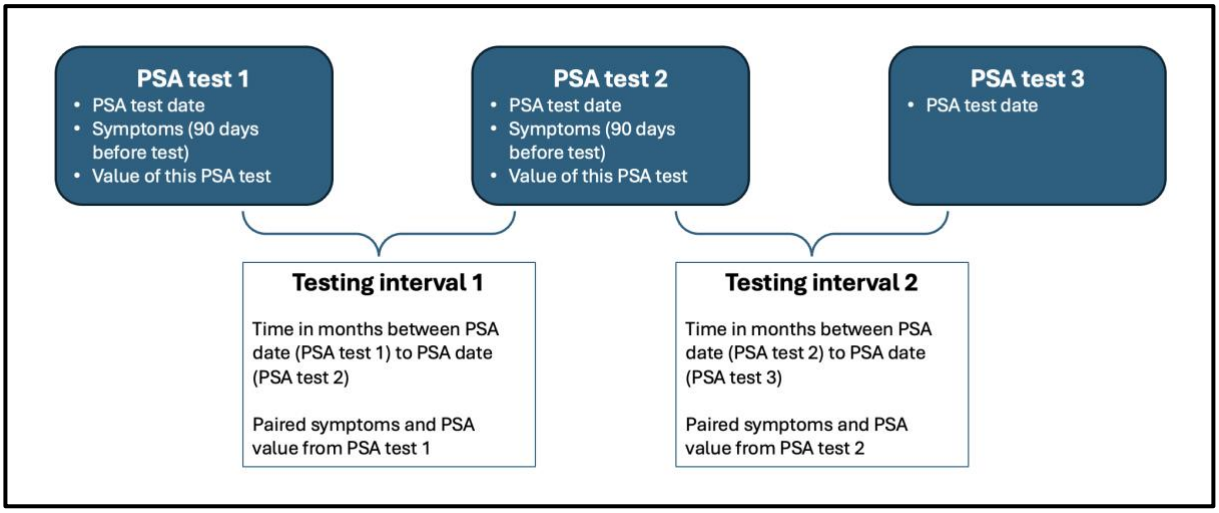
5.4.4.2 PSA testing rates

To model individual PSA testing rates, based on peer review suggestions from the BMJ, I used univariate and multivariable mixed-effects negative binomial regression models with an offset term for the log of person-years of follow-up. Fixed effects included: age range, ethnicity, IMD, region, family history of prostate cancer, if the patient ever had a symptom paired with a PSA test and if the patient ever had a PSA value above the age-specific threshold. A random intercept for general practice was included to account for clustering at the practice level. Rate ratios (RRs) for the number of PSA tests were obtained by exponentiating the model coefficients.

5.4.4.3 PSA retesting intervals

Descriptive statistics were used to summarise PSA retesting intervals in months. If a patient had three PSA tests they contributed two intervals. I used symptoms and PSA test value that were paired with the PSA test at the start of the interval. The patients last recorded PSA test result and associated symptoms were not included in the interval calculation because details of subsequent testing were unknown (Figure 5.2).

Figure 5.2: Illustration of how PSA retesting intervals were defined



Caption: Construction of PSA retesting intervals. Intervals were calculated as the time (months) between consecutive PSA tests (e.g., test 1→ test 2, test 2→ test 3). Symptoms and PSA values for each interval were taken from the earlier test using the PSA value at that test and symptoms recorded in the preceding 90 days.

Univariate and multivariable linear mixed-effects regression models were used to identify patient factors associated with the log-transformed length of the PSA retesting interval (in months). Nested random intercepts for patients within practices accounted for both the non-independence of repeated measures within patients and the clustering within general practices. Fixed effects were the same as described above. Expected months between PSA tests were calculated by exponentiating the model intercept, representing the log-geometric mean interval for the reference group and multiplying this by the exponentiated fixed effect for each covariate level.

95% confidence intervals and a two-sided significance level of 5% were estimated for all analyses. The following characteristics were used as the reference group: Age 60 to 69, White ethnicity, IMD 1, no family history of prostate cancer, no symptom paired with a PSA test, and never had PSA test with a value above the age-specific threshold.

5.4.5 Subgroup analysis

After discussions with the Strategic Evidence Team at Cancer Research UK, I conducted a subgroup analysis to investigate associations between the length of PSA retesting

intervals in patients without prostate cancer who had multiple PSA tests but never had a PSA test result above the age-specific threshold.

5.4.6 SENSITIVITY ANALYSES

I also conducted two sensitivity analyses. First, to assess the impact on PSA retesting intervals by including only PSA tests that were over one month apart to remove bias from having a repeat PSA test to confirm first raised PSA. Second, I ran the analysis on cohorts who had more than six years of follow-up from study entry to exit to assess the impact of restricting to patients with over six years of follow-up to mitigate potential censoring bias. Sensitivity analyses are included in Appendix 3.

5.5 RESULTS

A total of 10,235,805 male patients from 1442 practices contributed 81,742,938 person-years of observation (Table 5.1). The median follow-up was 5.9 years (IQR 2.9 to 12.4) with a maximum of 19 years. There were 1,521,116 patients who had at least one PSA test, and 3,835,440 PSA tests were performed overall. Nineteen percent (729,923) of 3,835,440 PSA tests were for patients aged 50 to 59 years, 31% (1,187,800) for 60 to 69, 28%(1,076,797) for 70 to 79, and 12% (467,291) for 80 to 89. Forty-eight percent (735,750/1,521,116) of patients had at least two PSA tests recorded in the study period (Table 5.1).

Table 5.1 Patient characteristics

	Overall study cohort (N = 10,235,805)		Patients with at least 1 PSA test (N = 1,521,116)		Patients with at least 2 PSA tests (N = 735,750)		Patients sub-group analysis* (N = 535,990)	
Number of practices	1442		1441		1438		1438	
Median Follow Up Years (IQR)	5.9 (2.9 to 12.4)		14.3 (7.9 to 19.0)		16.4 (10.4 to19.0)		17.2 (11.1 to 19.0)	
Person years observation	81,742,938		19,843,625		10,557,563		7,899,475	
Demographic categories	Number	%	Number	%	Number	%	Number	%
Ethnicity								
White	7,019,072	68.6	1,289,012	84.7	641,174	87.1	463,142	86.4
Black	402,798	3.9	51,383	3.4	23,653	3.2	17,071	3.2
Asian	304,061	3.0	20,068	1.3	8,848	1.2	7,225	1.3

	Overall study cohort (N = 10,235,805)		Patients with at least 1 PSA test (N = 1,521,116)		Patients with at least 2 PSA tests (N = 735,750)		Patients sub-group analysis* (N = 535,990)	
Mixed	118,876	1.2	8,542	0.6	3,447	0.5	2,617	0.5
South Asian	478,353	4.7	46,970	3.1	21,586	2.9	18,180	3.4
Other	264,970	2.6	21,982	1.4	9,236	1.3	7,330	1.4
Unknown	1,647,675	16.1	83,159	5.5	27,806	3.8	20,425	3.8
Region								
East Midlands	302,747	3.0	38,485	2.5	18,725	2.5	13,501	2.5
East of England	404,147	3.9	75,548	5.0	37,425	5.1	26,933	5.0
London	2,366,313	23.1	252,147	16.6	115,415	15.7	87,594	16.3
North East	291,735	2.9	39,887	2.6	16,564	2.3	11,957	2.2
North West	1,700,935	16.6	270,221	17.8	131,290	17.8	96,860	18.1
South East	2,055,582	20.1	346,579	22.8	174,295	23.7	126,795	23.7
South West	1,202,150	11.7	188,471	12.4	91,470	12.4	63,080	11.8
West Midlands	1,526,812	14.9	258,948	17.0	126,852	17.2	92,260	17.2
Yorkshire and The Humber	377,935	3.7	50,358	3.3	23,575	3.2	16,917	3.2
Unknown	7,449	0.1	472	0.0	139	0.0	93	0.0
Index of multiple deprivation								
1 (least deprived/most affluent)	1,930,388	18.9	372,309	24.5	193,930	26.4	139,142	26.0
2	2,026,539	19.8	344,821	22.7	173,569	23.6	125,612	23.4
3	2,035,452	19.9	301,805	19.8	146,258	19.9	106,207	19.8
4	2,244,264	21.9	273,790	18.0	124,324	16.9	91,717	17.1
5 (most deprived/least affluent)	1,986,414	19.4	226,883	14.9	96,972	13.2	72,795	13.6
Unknown/Missing	12,748	0.1	1,508	0.1	697	0.1	517	0.1
Age at study entry								
18 to 29	3,853,853	37.7	37,778	2.5	5,124	0.7	4,591	0.9
30 to 39	2,328,096	22.7	169,384	11.1	47,111	6.4	40,827	7.6
40 to 49	1,522,747	14.9	322,808	21.2	136,510	18.6	109,803	20.5
50 to 59	1,105,127	10.8	406,124	26.7	220,923	30.0	160,777	30.0
60 to 69	746,148	7.3	336,184	22.1	197,430	26.8	136,534	25.5
70 to 79	461,472	4.5	191,741	12.6	104,780	14.2	69,237	12.9
80 to 89	188,368	1.8	52,777	3.5	22,632	3.1	13,564	2.5
90+	29,994	0.3	4,320	0.3	1,240	0.2	657	0.1
Family history of prostate cancer								
yes	34,200	0.33	19,245	1.3	11,337	1.5	8430	1.6

**Patients who never had PSA values above the age-specific threshold and who did not have a prostate cancer diagnosis during follow-up. Above the threshold included if age 18 to 49 and PSA value >2.5 ng/mL, age 50 to 59 and PSA value >3.5 ng/mL, age 60 to 69 and PSA value > 4.5 ng/mL and aged 70+ and PSA value over 6.5 ng/mL.*

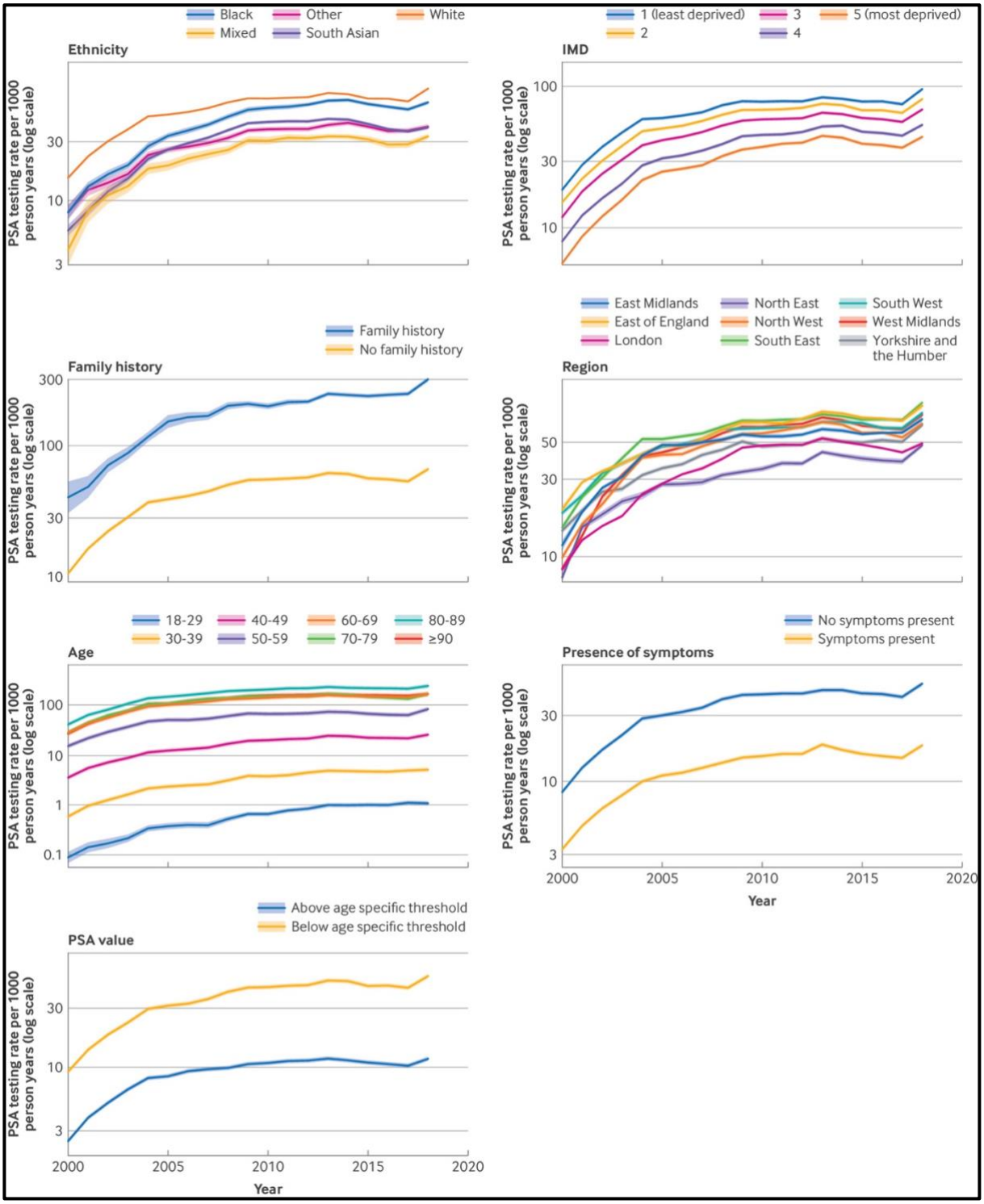
5.5.1 PSA TESTING TRENDS OVER TIME AT THE POPULATION LEVEL

The age-standardised rate of PSA testing increased over 5-fold from 11.8 (95% CI 11.7 to 12.0) in 2000 to 69.7 (69.5 to 70.0) in 2018. Rates slightly declined between 2014 to 2017. This trend was broadly similar across all sociodemographic characteristics (Figure 5.3).

Over time testing rates were consistently higher in patients aged 70 to 89 years. By year, testing rates for patients aged 70 to 79 years were three times higher than those aged 50 to 59 years (Figure 5.3). The rate of testing was highest for patients of White ethnicity had the highest rate of testing 55.9 (55.9 to 56.0). Testing rates were highest in the South East 58.3 (58.2 to 58.4) and the lowest in the North East 31.3 (31.1 to 31.5). Testing rates were more than twice as high in the least deprived quintiles compared to the most deprived quintiles (Figure 5.3).

A 30% greater increase occurred in PSA values below the age-specific thresholds (from 9.30 to 57.83 per 1,000 person-years) compared to those falling above the threshold (from 2.53 to 11.89). In 2018, the absolute rate of PSA testing for values below the referral threshold was 4.9 times higher than for values above it. Rates for PSA testing patients with a family history of prostate cancer were 3.6 times higher than for those without a family history in 2000 and increased to 4.8 times by 2018. Testing rates overall were two to three times higher in asymptomatic patients (35.1 (35.2 to 35.2) per 1,000 person-years) than in symptomatic patients (12.9 (12.9 to 12.9)). Between 2017 and 2018 the standardised rate of PSA testing increased by 26.4% in asymptomatic patients and 19.6% in patients with symptoms recorded (Figure 5.3).

Figure 5.3: Age-standardised rates per 1000 person years between 2000 to 2018 (logarithmic scale)



Caption: Age-standardised PSA testing rates per 1,000 person-years by patient characteristics (ethnicity, deprivation, family history, region, age group, symptom presence, and PSA value) from 2000 to 2018. Rates are shown with 95% confidence intervals on a logarithmic scale. An interactive version of this figure that illustrates rates on a logarithmic scale and a linear scale is available online at [https://kiana-k-collins.shinyapps.io/bmj_shiny_app_v2/].

PSA values were categorised as above the age-specific threshold if age 18 to 49 and PSA value >2.5 ng/mL, age 50 to 59 and PSA value >3.5 ng/mL, age 60 to 69 and PSA value > 4.5 ng/mL and aged 70+ and PSA value over 6.5 ng/mL.

5.5.2 PSA TESTING RATES BY INDIVIDUAL CHARACTERISTICS

Characteristics that were statistically significantly (p <0.001) associated with the likelihood of undergoing PSA testing were age, ethnicity, region, deprivation, family history of prostate cancer, ever having a PSA value above the age-specific threshold, and ever having a symptom prior to a PSA test (Table 5.2).

Patients who were of an ethnicity other than White were more likely than White patients to undergo PSA testing with rate ratios (RR) ranging from 1.03 (95%CI 1.01 to 1.04) for patients of Asian ethnicity to 1.39 (1.37 to 1.40) for patients of Black ethnicity (P<0.001) (Table 5.2). Patients in the North East were less likely than patients in the South East to be tested with PSA, RR 0.63 (0.55 to 0.72) (P<0.001). Patients in the most deprived areas of England were tested less than patients' in the least deprived areas RR 0.75 (0.74 to 0.75) (Table 5.2). Having ever had a PSA value above the age-specific threshold increased the RR of PSA testing to 3.84 (3.82 to 3.85). Family history of prostate cancer increased the RR of PSA testing to 3.24 (3.19 to 3.29).

The strongest association was for ever having a symptom recorded prior to a PSA test RR 4.92 (4.90 to 4.94) (Table 5.2). Overall, 46% (696,103) of patients with at least one PSA test also had at least one symptom recorded in the prior 90 days to one of their PSA tests and 27% (1,029,253) of all PSA tests were paired with a symptom. Of these tests, 57% (582,652) were paired with lower urinary tract symptoms, 15% (149,274) with back pain, and 10% (103,873) with haematuria. Of the 785,366 patients who only had one test during the study period, 35% (273,442) were paired with a symptom. Of the 735,750 patients with multiple PSA tests, 24% (177,815) of the PSA tests were paired with a symptom.

Table 5.2: Rate ratios of PSA testing: Univariate and multivariable mixed-effects negative binomial regression models

	Univariable Models			Multivariate Models		
	Rate Ratio	95% CI	P value	Rate Ratio	95% CI	P value
Region (reference South East)			<0.001			<0.001
Intercept (rate)*	0.05	0.04 to 0.05		0.07	0.06 to 0.07	
East Midlands	0.78	0.64 to 0.96		0.85	0.73 to 0.99	
East of England	1.00	0.82 to 1.22		0.89	0.77 to 1.03	
London	0.60	0.54 to 0.67		0.9	0.83 to 0.97	
North East	0.57	0.48 to 0.69		0.63	0.55 to 0.72	
North West	0.77	0.7 to 0.86		0.86	0.8 to 0.93	
South West	0.95	0.83 to 1.08		0.88	0.8 to 0.97	
West Midlands	0.83	0.74 to 0.92		0.91	0.84 to 0.98	
Yorkshire and Humber	0.67	0.55 to 0.81		0.74	0.64 to 0.86	
Unknown	0.28	0.12 to 0.66		0.39	0.21 to 0.74	
Age range (reference 60 to 69)			<0.001			<0.001
Intercept (rate) *	0.12	0.12 to 0.13		-	-	
18 to 29	0.01	0.01 to 0.01		0.04	0.03 to 0.04	
30 to 39	0.09	0.09 to 0.09		0.18	0.18 to 0.18	
40 to 49	0.3	0.3 to 0.3		0.44	0.44 to 0.44	
50 to 59	0.67	0.67 to 0.67		0.77	0.76 to 0.77	
70 to 79	0.99	0.98 to 0.99		1.02	1.02 to 1.03	
80 to 89	0.77	0.76 to 0.77		1.01	1.01 to 1.02	
90+	0.47	0.45 to 0.48		0.89	0.86 to 0.91	
Ethnicity (reference White)			<0.001			<0.001
Intercept (rate) *	0.04	0.04 to 0.04		-	-	
Asian	0.64	0.63 to 0.65		1.03	1.01 to 1.04	
Black	1.18	1.17 to 1.19		1.39	1.37 to 1.4	

	Univariable Models			Multivariate Models		
Mixed	0.59	0.58 to 0.6		1.08	1.06 to 1.1	
Other	0.71	0.7 to 0.72		1.12	1.11 to 1.14	
South Asian	0.79	0.78 to 0.8		1.16	1.15 to 1.17	
Unknown	0.27	0.27 to 0.27		0.47	0.47 to 0.48	
Index of multiple deprivation (reference 1 least deprived)			<0.001			<0.001
Intercept (rate) *	0.05	0.05 to 0.05		-	-	
2	0.88	0.88 to 0.89		0.93	0.92 to 0.93	
3	0.78	0.78 to 0.79		0.87	0.87 to 0.88	
4	0.70	0.7 to 0.71		0.82	0.82 to 0.82	
5	0.62	0.61 to 0.62		0.75	0.74 to 0.75	
Unknown	0.57	0.54 to 0.61		0.78	0.74 to 0.82	
PSA value ever above age-specific threshold (reference no)**			<0.001			<0.001
Intercept (rate) *	0.03	0.03 to 0.03		-	-	
Yes	12.53	12.44 to 12.61		3.84	3.82 to 3.85	
Family history (reference no)			<0.001			<0.001
Intercept (rate) *	0.03	0.03 to 0.04		-	-	
Yes	4.11	4.01 to 4.21		3.24	3.19 to 3.29	
Symptom ever present before a PSA test (reference no)			<0.001			<0.001
Intercept (rate) *	0.02	0.02 to 0.02		-	-	
Yes	12.50	12.45 to 12.55		4.92	4.9 to 4.94	

Caption: Rate ratios (RR) were estimated from a mixed-effects negative binomial regression model with a log link function. The model included a random intercept for general practice and was adjusted for all covariates listed. Reference categories: South East (region), IMD 1 (least deprived), White (ethnicity), age 60 to 69, no family history of prostate cancer, never had a symptom recorded in the 90 days before any PSA test and never had a PSA test with a value above the age-specific threshold.

** Multivariate model intercept shows baseline rate for the reference categories: (South East (region), IMD 1 (least deprived), White (ethnicity), age 60 to 69, no family history of prostate cancer, never had a symptom recorded in the 90 days before any PSA test, and*

never had a PSA test with a value above the age-specific threshold) all other values are rate ratios versus this baseline. Univariable model intercepts examine each factor separately.

****Above the threshold included if age 18 to 49 and PSA value >2.5 ng/mL, age 50 to 59 and PSA value >3.5 ng/mL, age 60 to 69 and PSA value > 4.5 ng/mL and aged 70+ and PSA value over 6.5 ng/mL.*

5.5.3 PSA RETESTING INTERVALS

Of the 735,750 patients with at least two PSA tests, there were 3,050,074 PSA tests creating 2,314,324 retesting intervals. The median retesting interval before adjustment was 12.6 months (IQR 6.2 to 27.5) (Table 5.3).

Table 5.3: Median intervals split by region, IMD, ethnicity, age, PSA value above/below the referral threshold symptoms (Overall patients with at least two PSA tests (N = 735,750)

Category	Number of distinct patients	Number PSA retesting intervals	Median months until next test	Interquartile range (IQR)
Region				
East Midlands	18,725	61,601	12.12	5.98-25.85
East of England	37,425	117,456	13.07	6.47-28.38
London	115,415	325,729	13.86	7.46-28.32
North East	16,564	43,510	13.21	5.98-34.62
North West	131,290	412,233	12.52	6.08-27.17
South East	174,295	573,183	12.65	6.34-27.27
South West	91,470	309,641	11.86	5.75-25.76
West Midlands	126,852	398,842	12.84	6.41-27.99
Yorkshire and The Humber	23,575	71,841	12.61	6.18-28.32
Age at PSA test				
18 to 29	895	1,248	13.27	3.94-33.32
30 to 39	9,111	11,544	26.92	10.51-60.59
40 to 49	71,511	103,503	26.31	11.96-54.43
50 to 59	214,999	400,944	18.82	9.17-40.54
60 to 69	312,535	790,047	12.94	6.54-27.73
70 to 79	253,800	717,284	11.66	5.91-21.68
80 to 89	103,866	269,459	9.63	4.86-17.71
90+	10,147	20,295	7.26	3.61-14.29
Ethnicity				
Asian	8,848	25,037	13.57	7.36-27.37
Black	23,653	63,741	14.16	7.39-28.06
Mixed	3,447	9,446	13.73	6.93-29.07
Other	9,236	25,561	13.83	7.23-28.48
South Asian	21,586	61,127	13.76	7.49-28.29
Unknown	27,806	68,628	12.22	5.98-24.90
White	641,174	2,060,784	12.61	6.21-27.56
Index of multiple deprivation (IMD)				

Category	Number of distinct patients	Number PSA retesting intervals	Median months until next test	Interquartile range (IQR)
1	193,930	671,011	12.48	6.24-26.61
2	173,569	575,797	12.45	6.21-26.77
3	146,258	458,767	12.65	6.21-27.33
4	124,324	355,329	13.04	6.31-28.58
5	96,972	251,373	13.63	6.47-30.26
Unknown	697	2,047	13.04	6.67-28.45
Above age-specific threshold				
yes	172,752	540,270	5.75	2.69-10.81
no	655,159	1,774,054	15.60	9.23-33.11
Family history				
yes	11,337	40,052	13.12	7.36 – 26.08
no	724,413	2,271,937	12.65	6.24 – 27.56
Erectile dysfunction (ED)				
no	725,123	2,265,450	12.65	6.24-27.30
yes	41,645	48,874	16.89	7.88-37.12
Haematuria				
no	724,689	2,261,587	12.65	6.27-27.40
yes	43,719	52,737	12.48	4.60-31.50
Back Pain				
no	720,165	2,234,883	12.61	6.24-27.27
yes	66,964	79,441	15.47	7.26-34.10
Bone Pain				
no	735,523	2,312,725	12.65	6.24-27.53
yes	1,556	1,599	12.65	6.24-27.46
Lower urinary tract symptoms (LUTS)				
no	662,726	1,987,002	12.42	6.21-26.25
yes	220,397	327,322	15.93	6.96-34.95
Unexpected weight loss (UWL)				
no	732,712	2,301,846	12.65	6.24-27.50
yes	11,410	12,478	14.49	6.37-32.29
Fatigue				
no	729,740	2,282,481	12.65	6.24-27.40
yes	28,485	31,843	15.57	7.13-33.34

Once adjusted, the estimated geometric mean interval between tests ('months') was 19.3 months (Table 5.4). Patients aged 40 to 49 had the longest estimated mean interval at 29.5 months and the interval decreased with age from age 40 (Table 5.4). All ethnic groups had shorter PSA retesting intervals when compared to patients of White ethnicity ranging from 1.79 months shorter for patients of South Asian ethnicity (17.55 vs 19.34 months) to 2.34 months shorter for those of Mixed ethnicity (17.00 vs 19.34 months). Regional variation was modest with only one month longer or shorter intervals across regions. Compared to the South East, the North East had the longest retesting interval at

0.91 months longer (20.25 vs 19.34 months). Deprivation showed minimal variation, with a significant but small difference of under a month between quintiles (Table 5.4).
The strongest predictor of a shorter retesting interval was a PSA value above the age-specific threshold, which reduced the retesting interval by over 13 months. Family history of prostate cancer reduced the retesting interval by three months (3.16 months) (Table 5.4).

PSA tests paired with erectile dysfunction, back pain and lower urinary tract symptoms had significantly longer PSA retesting intervals whereas PSA tests paired with unexpected weight loss and haematuria had significantly shorter intervals. Haematuria had the largest effect and reduced the PSA retesting interval by 1.16 months (Table 5.4).

*Table 5.4 Linear mixed effect models for length of PSA retesting intervals: Multivariable Models**

	Multivariable model overall				Multivariable model sub-group analysis			
	Interval ratios	95% CI	Expected interval (months)*	P value	Interval ratios	95% CI	Expected interval (months)*	P value
Intercept**	19.34	18.92 to 19.69		<0.001	21.60	21.17 to 22.03		<0.001
Region (reference South East)				<0.001				<0.001
East Midlands	0.98	0.93 to 1.03	18.89		1.01	0.96 to 1.07	21.81	
East of England	1.03	0.99 to 1.08	19.96		1.03	0.98 to 1.08	22.18	
London	0.98	0.96 to 1.01	19.04		0.94	0.92 to 0.97	20.37	
North East	1.05	1.00 to 1.10	20.25		1.06	1.01 to 1.11	22.82	
North West	0.95	0.93 to 0.98	18.41		0.97	0.95 to 1.00	21	
South West	1.02	0.99 to 1.05	18.89		1.06	1.03 to 1.09	22.89	
West Midlands	1.05	1.02 to 1.07	20.22		1.03	1.00 to 1.06	22.28	
Yorkshire and Humber	0.97	0.93 to 1.02	18.85		0.99	0.94 to 1.04	21.36	
Unknown	0.93	0.72 to 1.20	17.93		0.90	0.67 to 1.21	19.41	
Age range (reference 60 to 69)				<0.001				<0.001

	Multivariable model overall				Multivariable model sub-group analysis			
18 to 29	0.80	0.75 to 0.85	15.39		0.78	0.73 to 0.83	16.78	
30 to 39	1.42	1.39 to 1.45	27.49		1.40	1.37 to 1.43	30.21	
40 to 49	1.53	1.52 to 1.54	29.54		1.49	1.48 to 1.50	32.14	
50 to 59	1.26	1.26 to 1.27	24.44		1.25	1.25 to 1.26	27.1	
70 to 79	0.77	0.76 to 0.77	14.83		0.77	0.77 to 0.77	16.64	
80 to 89	0.68	0.68 to 0.68	13.16		0.62	0.61 to 0.62	13.29	
90+	0.57	0.56 to 0.58	10.95		0.44	0.43 to 0.46	9.59	
Ethnicity (reference White)				<0.001				<0.001
Asian	0.88	0.87 to 0.90	17.10		0.86	0.85 to 0.88	18.61	
Black	0.89	0.88 to 0.90	17.27		0.87	0.86 to 0.88	18.77	
Mixed	0.88	0.85 to 0.90	17.00		0.87	0.84 to 0.89	18.72	
Other	0.90	0.88 to 0.91	17.37		0.88	0.86 to 0.89	18.9	
South Asian	0.91	0.90 to 0.92	17.55		0.89	0.87 to 0.90	19.14	
Unknown	0.87	0.86 to 0.88	16.83		0.82	0.81 to 0.83	17.77	
Index of multiple deprivation (reference 1 least deprived)				<0.001				<0.001
IMD 2	1.00	0.99 to 1.00	19.28		0.99	0.99 to 1.00	21.42	
IMD 3	0.99	0.99 to 1.00	19.19		0.98	0.97 to 0.99	21.18	
IMD 4	0.98	0.97 to 0.99	18.97		0.97	0.96 to 0.98	20.88	
IMD 5	0.97	0.96 to 0.98	18.75		0.95	0.94 to 0.95	20.41	
Unknown	1.02	0.96 to 1.09	19.71		1.02	0.94 to 1.09	21.92	
PSA value ever above age-specific threshold (reference no)***				<0.001	-	-		<0.001
Yes	0.32	0.32 to 0.33	6.27		-	-	-	
Family history				<0.001				<0.001

	Multivariable model overall				Multivariable model sub-group analysis			
Yes	0.84	0.82 to 0.85	16.18		0.83	0.82 to 0.85	18.03	
Fatigue (reference no)				0.13				0.16
Yes	0.99	0.98 to 1.00	19.17		0.99	0.98 to 1.00	21.4	
Bone pain (reference no)				0.23				0.22
Yes	0.97	0.92 to 1.02	18.74		0.96	0.91 to 1.02	20.8	
Back pain (reference no)				<0.001				<0.001
Yes	1.03	1.02 to 1.04	19.92		1.04	1.03 to 1.04	22.35	
Unexpected weight loss (reference no)				<0.001				<0.001
Yes	0.96	0.94 to 0.98	18.51		0.94	0.92 to 0.96	20.38	
Haematuria (reference no)				<0.001				<0.001
Yes	0.94	0.93 to 0.95	18.18		0.96	0.95 to 0.97	20.72	
Erectile dysfunction (reference no)				<0.001				<0.001
Yes	1.04	1.03 to 1.05	20.12		1.04	1.03 to 1.05	22.44	
Lower urinary tract symptoms (reference no)				<0.001				<0.001
Yes	1.02	1.02 to 1.03	19.76		1.04	1.04 to 1.05	22.52	

**Univariable models are provided in Appendix 3*

*** The intercept represents the estimated geometric mean interval in months between PSA tests for the reference category (patients aged 60 to 69, White, IMD 1, South East, no family history, no symptoms, never above PSA age-specific threshold). In the overall model this was 19.34 months (95% CI: 18.92 to 19.69) and in the subgroup model 21.60 months (95% CI: 21.17 to 22.03)."*

****Above the threshold included if age 18 to 49 and PSA value >2.5 ng/mL, age 50 to 59 and PSA value >3.5 ng/mL, age 60 to 69 and PSA value > 4.5 ng/mL, and aged 70+ and PSA value over 6.5 ng/mL.*

Caption: "Months" refers to the estimated geometric mean time between repeat PSA tests. For each covariate level, values were calculated by multiplying the reference interval by the exponentiated fixed effect, giving the estimated interval in months while holding all other covariates at their reference level.

5.5.4 SUBGROUP ANALYSIS

Seventy-three percent (535,990/735,750) of patients who had multiple PSA tests never presented with a PSA value above the age-specific threshold. These patients were included in the sub analysis and contributed 7,899,475 person-years of observation, with a median follow-up time of 17.2 years (IQR 11.1 to 19.0) (Table 5.1). There were 1,887,390 tests performed, providing 1,351,400 retesting intervals. The median interval between tests was 17.8 months (IQR 10.8 to 36.2) (Table 5.5). Similar trends for ethnicity in the main retesting intervals analysis were found in the sub-analysis but with a greater effect (Table 5.4). Regional variation increased with intervals ranging from 1.22 months longer in the North East, compared to the South East (22.82 vs 21.60 months), to 1.23 months shorter in London (20.37 vs 21.60 months) (Table 5.4).

Table 5.5: Median intervals split by region, IMD, ethnicity, age, PSA value above/below the age-specific threshold symptoms (Subgroup analysis: Patients with at least two tests and never had a PSA result above the age-specific threshold and do not have prostate cancer (N = 535,990))

Category	Number distinct patients	Number PSA retesting intervals	Median months until next test	Interquartile range (IQR)
Region				
East Midlands	13,501	34,545	16.92	9.92-36.14
East of England	26,933	68,094	18.53	11.07-36.89
London	87,594	212,460	17.28	10.55-33.61
North East	11,957	24,919	21.98	11.10-45.93
North West	96,860	246,367	17.28	10.51-35.58
South East	126,795	334,600	17.51	10.74-35.97
South West	63,080	157,051	18.56	10.91-38.37
West Midlands	92,260	232,247	18.17	11.04-36.63
Yorkshire and The Humber	16,917	40,973	18.13	11.04-38.11
Age at PSA test				
18 to 29	830	1,144	14.90	5.49-35.24
30 to 39	8,283	10,234	29.53	12.35-63.40

Category	Number distinct patients	Number PSA retesting intervals	Median months until next test	Interquartile range (IQR)
40 to 49	61,437	84,336	29.89	14.26-57.98
50 to 59	166,333	273,663	24.18	12.61-47.11
60 to 69	217,996	450,057	18.40	11.33-36.27
70 to 79	171,017	396,982	14.09	9.13-28.19
80 to 89	62,973	127,414	12.88	7.39-24.61
90+	4,926	7,570	11.73	6.04-20.37
Ethnicity				
Asian	7,225	18,065	16.10	9.66-31.47
Black	17,071	39,129	17.84	10.61-33.15
Mixed	2,617	5,988	18.05	10.68-35.53
Other	7,330	17,323	17.21	10.35-33.51
South Asian	18,180	46,143	15.90	9.43-31.80
Unknown	20,425	41,612	16.33	10.12-32.95
White	463,142	1,183,140	17.94	10.84-36.70
Index of multiple deprivation (IMD)				
1	139,142	380,109	17.58	11.01-35.94
2	125,612	331,422	17.44	10.78-35.81
3	106,207	265,805	17.77	10.74-36.14
4	91,717	213,606	18.17	10.58-36.56
5	72,795	159,266	18.43	10.35-37.02
Unknown	517	1,192	19.91	11.50-37.48
Family history				
yes	8,430	25,206	16.49	11.27-31.77
no	527,560	1,326,194	17.81	10.74-36.23
Erectile dysfunction (ED)				
no	526,715	1,317,394	17.67	10.74-36.01
yes	29,987	34,006	22.04	11.53-43.43
Haematuria				
no	528,115	1,323,893	17.71	10.78-36.07
yes	24,274	27,507	20.60	9.72-43.10
Back Pain				
no	522,540	1,297,107	17.67	10.74-36.01
yes	47,249	54,293	20.20	10.91-40.21
Bone Pain				
no	535,798	1,350,377	17.77	10.78-36.17
yes	1,004	1,023	16.33	9.44-34.31
Lower urinary tract symptoms (LUTS)				
no	477,689	1,140,788	17.08	10.58-35.12
yes	151,295	210,612	21.81	11.60-41.75
Unexpected weight loss (UWL)				
no	533,472	1,342,645	17.77	10.78-36.17
yes	8,164	8,755	18.30	9.17-36.97
Fatigue				
no	530,823	1,329,646	17.74	10.78-36.14
yes	19,867	21,754	20.01	10.61-38.86

5.6 Discussion

5.6.1 Summary of findings

Between 2000 and 2018, of the 10,235,805 male patients in primary care in England older than 18 years of age, 15% (1,521,116) had at least one PSA test, increasing to 33% 1,313,394 for those older than 50 years (3,938,402). Half of these patients (735,750/1,521,116) had multiple PSA tests and 73% (535,990/735,750) of them never presented with a PSA value above the age-specific threshold (107). The median retesting interval overall was 12.6 months (IQR 6.2 to 27.5). Testing rates varied by region, deprivation, ethnicity, family history, age, PSA value above the age-specific threshold, and whether patients ever had a symptom before any PSA test ($p < 0.001$). Once tested, patients had shorter retesting intervals if they were older, belonged to any ethnic group other than White, had a family history of prostate cancer, or had previously elevated PSA levels ($p < 0.001$). Despite considerable variation in testing rates by region and deprivation, the length of retesting intervals was similar across these groups.

5.6.2 Strengths and limitations

I conducted a comprehensive analysis of PSA testing rates and the length of PSA retesting intervals in English primary care. Unlike earlier studies focussed on first PSA tests, I used mixed-effects modelling to account for clustering by practice and examined repeat testing. Data linkages with HES, ONS and NCRAS enabled me to investigate data from across the healthcare network. Using data from 1.5 million patients with at least one PSA test over 19 years of follow-up, I reported novel insights into the factors and symptoms linked to PSA testing and the length of retesting intervals.

Studies using routinely collected primary care data have limitations, as analyses depend on what clinicians choose to record and code. Data on symptom presentation can be recorded in the free-text of primary care records but are not accessible for research in CPRD at present. In the National Prostate Cancer Audit both coded and free-text data are available and it was found that only 19% of prostate cancer diagnoses were for

asymptomatic patients (383). Without access to free-text, I, with the help of BDN, inferred the general practitioner's (GP) reasons for PSA testing from coded symptoms.

PSA interval analyses were limited to patients with at least two PSA tests during follow-up. This raises the possibility of censoring bias, which was highlighted by some of the BMJ reviewers. The sample is inherently biased toward individuals who were already engaged in regular testing and due to follow-up constraints, the estimated retesting intervals may be shorter than the true intervals for the broader population. To assess this, I ran two sensitivity analyses restricted to patients with at least six years of follow-up (the median). The first analysis defined follow-up from cohort entry. The estimated interval was 19.3 months in the full cohort, compared to 19.8. The direction and magnitude of associations remained consistent across models, suggesting the main findings are robust, but they reflect testing patterns among patients already undergoing repeat PSA testing, rather than the full population of PSA tested patients.

PSA tests were not included if they occurred before the patient was registered with the current GP practice as I did not know where the patient was registered prior to joining the contributing CPRD GP practice. As a result, I excluded 157,938 (3%) PSA tests that were recorded between 2000 and 2018. As this proportion is quite small, I do not expect it to have an impact on the findings and conclusions made. Additionally, in the negative binomial model, I adjusted for ever having a raised PSA, which lies on the causal pathway to increased PSA testing. This may reduce observed associations with patient factors. Given that elevated PSA levels appropriately trigger repeat testing, including this variable helps capture the real-world patterns of PSA monitoring.

5.6.3 COMPARISON WITH THE LITERATURE

I reported similar population-based PSA testing rates over time as those previously reported (369, 382, 384). PSA testing increased rapidly in the early 2000s, followed by a plateau and decline in the mid-to-late 2010s. As mentioned in Chapter 2, the USPSTF changed its recommendation in 2012 from encouraging PSA testing to advising against it (102). These trends may reflect shifts in English clinical practice in response to changes

in international PSA testing guidance despite no material change in English guidelines. In France between 2006 and 2018, it was found that 50% of men had received five PSA tests with the first test between the ages of 65 to 75. High PSA test use has been found in Canada (385), France (386) Ireland (387) and Sweden where 75% of men aged 60 to 70 had a PSA test in the preceding decade (388). Australian PSA testing rate increased by 9% per year between 2002 and 2007 and then decreased by 5% per year to 2018 (389).

My results are consistent with the findings from other longitudinal primary care studies conducted in the UK that identified similar associations between PSA testing and age, ethnicity, level of deprivation, family history and region (369, 381, 382, 390, 391). I reported that patients of Black ethnicity were more likely to be PSA tested than patients of White ethnicity and had shorter PSA retesting intervals (2.07 months) (Table 3). In another large English primary care database (QResearch), it was found that rates of opportunistic PSA screening were significantly associated with Black ethnicity (369). I found practice-level variation in PSA testing rates, which was smaller but comparable to the 13% variation in asymptomatic PSA testing found using Prostate Cancer Audit data (383). I observed less practice variation when examining the length of retesting intervals.

Finally, I found 27% (1,029,235) of all PSA tests (3,835,440) were paired with a recorded symptom. A study (369), focused on assessing opportunistic PSA screening in the UK identified 65% of all first PSA tests in the study period were deemed to be for screening. I know of no other studies focussing on symptoms in primary care records before a PSA test.

5.6.4 POLICY IMPLICATIONS

In early 2018, British media personalities Bill Turnbull and Stephen Fry publicly announced their prostate cancer diagnoses and shared their PSA testing and treatment journeys. Between 2017 and 2018, PSA testing rates increased substantially. Between 2017 and 2018, PSA testing rose by 26.4% for asymptomatic and 19.6% for symptomatic patients, contrasting with declines of over 4% for both symptomatic and asymptomatic patients the year before. Similar patterns have been observed internationally. For

example, Angelina Jolie's disclosure that she has the BRCA1 led to increased genetic testing (392). While it is unclear if increased PSA testing led to more clinically significant prostate cancer diagnoses, Lovegrove (2020) reported a 30% increase in two-week wait referrals and more diagnostic multiparametric MRIs (mpMRIs) and biopsies (393). These findings suggest that public health-seeking behaviours may shift during periods of high-profile media attention and health systems should anticipate for potential unpredictable surges in PSA testing, overtesting, and associated costs.

5.6.5 RESEARCH IMPLICATIONS

In this chapter, I found considerable variation in PSA testing rates but less variation in the length of PSA retesting intervals. While many patients were never tested with PSA, suggesting possible undertesting, others were tested only once, which may be insufficient for those at risk. I also identified a cohort of patients with low PSA values, who underwent frequent testing beyond guideline recommendations, raising concerns about overtesting. The benefit of retesting and ad hoc screening remains uncertain and requires further research to determine evidence-based retesting intervals that balance the benefits of early detection with the harms of overdiagnosis.

Unlike structured bowel or breast cancer screening, there is no consistent guidance on PSA retesting, for patients with low PSA results. This raises concerns about equity and psychological impacts of PSA testing for patients and their families, possibly leading to confusion and mistrust, with patients left to seek testing or interpret uncertain advice. Shared decision making promotes a patient-centered approach to navigate the trade-offs between the benefits and harms of PSA testing. With shared decision making the decision to undergo PSA testing is often patient-driven and factors such as education level and health literacy significantly influence these choices (227, 394). It is important that all patients understand the harms and benefits to make their own decisions on whether to engage with testing. Sweden has organised approach to PSA testing, described in Chapter 1, and patients still report a need for clearer communication and support (395). Research is required to understand patient and practitioners'

perspectives on PSA testing and retesting to develop strategies for shared decision making to mitigate the impact of unclear clinical consensus on the use of PSA.

Community based PSA testing is becoming more common in England. These are often via mobile PSA testing clinics run by charities such as CHAPS, a prostate cancer charity who run three to six PSA testing events a month in different locations (396) and The Prostate Project's "Man Van" initiative (397). As these PSA tests are delivered outside of NHS primary care, I may have underestimated how frequently patients are PSA tested in the community. If a patient had a high PSA at a separate clinic, I expect the patient would consult a GP and have the test repeated, but if not this could mean many patients have already had PSA tests or I am missing those with low values who do not present to their GP. Future research should link PSA testing data from community-based initiatives with primary care and hospital records to ensure complete capture of PSA testing episodes, enabling more accurate assessments of testing frequency, follow-up patterns, and subsequent diagnostic or treatment pathways.

No guidance for PSA retesting intervals or when to stop testing exists in England, as found in Chapter 2 (159). Testing is typically offered to patients who present with symptoms or request a PSA test. Over 70% of 735,750 patients with multiple PSA tests never exceeded the age-specific threshold . The subgroup analysis was done on this cohort of patients. Their median unadjusted retesting interval was 17.6 months (IQR 10.6 to 36.1). This interval is shorter than guideline-recommended frequencies of two-to-four years for higher-risk patients and represents frequent testing for lower risk patients who could safely be tested at much longer intervals. Research is needed to determine when it is safe to stop PSA testing considering age and PSA history. While some countries have established guidance on discontinuing PSA testing at age 70 (103, 104, 181-183) or based on life expectancy (103, 105, 176, 179, 180, 183), these recommendations rely mainly on European screening trials (185, 188) or American cohorts (187), highlighting the need for either evidence from primary care data in England or for guideline developers to consider this evidence as sufficient.

5.6.6 CLINICAL IMPLICATIONS

I confirm that PSA testing is closely aligned with changes in prostate cancer incidence. I found that PSA testing rates in England declined sharply in 2015, with an annual percentage change of -7%, mirroring a similar drop in prostate cancer incidence (398). Declines in PSA testing may either reduce overdiagnosis and overtreatment or conversely risk delayed identification of clinically significant prostate cancers.

I found a cohort of younger patients, outside the typical eligibility criteria for screening trials, that were tested with PSA. There were 63,903 PSA tests performed in patients under 40, involving 56,914 individuals. Most of these patients (83% 47,010) had a single test. Of the tests in this age group, 43% (27,333) were paired with symptoms, most commonly lower urinary tract symptoms , erectile dysfunction, and back pain. With home-based PSA testing kits now available through private providers, we anticipate increased testing in this age range. This represents an important cohort of patients who may experience harms of overtesting.

PSA testing rates were three times higher in patients in their 70s and 80s compared to those in their 50s, with retesting intervals up to a year shorter, even after accounting for PSA levels, symptoms, and demographics. Patients over 70 are the least likely to benefit from repeat testing, they account for an estimated 40% of overdiagnoses (155) and many countries advise against testing this group (103, 104, 181-183). Some of the increased testing in older patients may reflect symptom presentation, which is consistent with guidance. Despite UK recommendations to limit PSA testing to symptomatic patients or after GP discussion, I still observed considerable testing in asymptomatic patients. Current practice may not effectively target testing to those most likely to benefit, raising concerns about overdiagnosis.

5.7 CONCLUSION

PSA testing in primary care is varied. Among patients who underwent multiple tests, many were tested more frequently than recommended, raising concerns about overtesting. PSA retesting is occurring in patients without recorded symptoms and for

those with previous with low PSA values. To ensure maximum patient benefit while reducing the risk of overtesting there is an urgent need for research to determine appropriate evidence-based PSA retesting intervals. In the following two chapters, I generate population-based PSA retesting intervals based on population risk (Chapter 6) and test the feasibility of joint modelling to determine individualised PSA retesting intervals based on predicted individual risk of cancer (Chapter 7).

Chapter 6: Population-based Static PSA Retesting Intervals

6.1 Dissemination

The findings from this chapter were presented as an oral presentation at the CRUK Early Detection Conference in Portland (2025).

6.2 Background

In Chapter 2, I reported that international recommendations for PSA retesting intervals ranged from one to ten years. Most guidelines with recommended retesting intervals, advised that asymptomatic patients over the age of 50 could be retested with PSA every two-to-four years if their baseline PSA was between 1 and 3 ng/mL. Some guidance recommended that for those with a PSA less than 1 ng/mL, the retesting interval could be safely extended to between four and ten years (159). In England, there is no guidance on when or if patients should be retested with PSA.

In Chapter 5, I found that recorded PSA testing rates in England are varied, likely reflecting the lack of consistent guidance available. I found that some patients may be overtested while others may be undertested. I reported 48% of patients with one PSA test were retested. Of those patients, more than 75% had no symptoms recorded, and 73% never had a PSA value above the recommended threshold. For those who never had a PSA test value above the age-specific threshold, the median retesting interval was 1.5 years (IQR 0.9 to 3) (377). This is more frequent than international guidelines recommend based on the findings of Chapter 2.

The most recent European Association of Urology (EAU) 2025 guideline (399) recommended a risk-adapted approach to PSA testing. For patients under the age of 60 with a PSA below 1 ng/mL, a retesting interval of eight to ten years was advised. For patients considered initially at risk (PSA greater than 1 ng/mL at age 40 or PSA between 1

and 2 ng/mL at age 60) the EAU recommends biennial retesting. This guideline is similar to other international guidelines discussed in Chapter 2, and was based on indirect evidence from studies investigating a single PSA value, assessments of risk of prostate cancer progression, or data from randomised screening trials primarily aimed at mortality reduction, rather than retesting intervals (159). Although indirect, these studies were considered sufficiently robust to support this guidance (175, 188, 400, 401). The evidence cited by the EAU included European clinical trial data (402), observational Swedish data (175, 185) and observational Norwegian data (400). To my knowledge, no similar studies using English primary care data exist. It remains unknown whether the distribution of first PSA values in England is consistent with international studies.

In this chapter, I assess whether English primary care records of PSA testing align with findings from international studies that describe baseline PSA values (403). I generate population-level recommendations for PSA retesting intervals for patients attending primary care based on the risk of prostate cancer stratified by baseline PSA value and age. The retesting intervals presented in this chapter are population-level estimates rather than personalised. The estimates are based on a single baseline PSA test per patient, rather than incorporating each patient's full testing history. The results help to place English primary care data within the broader context of international evidence and establishes a foundation for the development of the joint model presented in Chapter 7.

6.3 OBJECTIVES

The objectives of this chapter were to:

1) Describe the distribution of baseline PSA values by age group at first test in a primary care population.
2) Calculate the positive and negative predictive values of baseline PSA categories for both overall and clinically significant prostate cancer.
3) Determine risk of prostate cancer overall and clinically significant prostate cancer by PSA value, age, family history, ethnicity, deprivation, and region.
4) Estimate population-based PSA retesting intervals based on a risk threshold stratified by baseline PSA category and five-year age bands.

6.4 METHODS

I performed a retrospective cohort study of routinely collected electronic health records data from the Clinical Practice Research Datalink (CPRD). The dataset and linkages were previously described in Chapter 4. All results are reported according to the REporting of studies Conducted using Observational Routinely Collected health Data (RECORD) extension to the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines for observational studies.

6.4.1 STUDY POPULATION

Eligible patients were male, aged over 40 years at the time of their first PSA test, had no prior prostate cancer diagnosis before entering the study, were registered with a general practice in England for at least one year, and had linked data available in NCRAS, HES, and ONS datasets. Patients entered the cohort if the date of their first PSA test occurred during the study period. Patients exited the cohort at the earliest of the following dates: date of the end of the study period (2018-12-31), first prostate cancer diagnosis, death, transfer out of the practice, or last data download for that practice.

6.4.2 VARIABLES

All variables used in this study were previously described in Chapter 4. In this chapter, clinically significant prostate cancer was defined as Gleason ≥ 7. Gleason < 7 was categorised as low-risk cancer. PSA results were grouped in the following categories: (< 1, 1 to 1.9, 2 to 2.9, 3 to 3.9, 4 to 4.9, ≥ 5 ng/mL). Each patient's first PSA test was used as the baseline test. Age at each PSA test was categorised into five-year age bands from age 40 to 90. There was no missing data for PSA and age. The missing indicator method was used for deprivation, ethnicity and region.

For the secondary outcome of clinically significant prostate cancer, Gleason score was used. Clinically significant cancer was defined as Gleason ≥ 7, and no clinically significant prostate cancer was defined as Gleason ≤ 6, unknown grade, or no cancer. Gleason score recording was incomplete and categorised as unknown for approximately 30% of all cancer cases and the proportion of unknown cases was particularly higher

before 2010 (Figure 4.3). As a result, there was incomplete classification of Gleason score and potential misclassification of diagnoses before 2010 (373). Sensitivity analyses were performed for patients with a first PSA test and subsequent prostate cancer diagnosis post 2010.

6.4.3 OUTCOMES

The primary outcome was a diagnosis of prostate cancer during follow-up. The secondary outcome was diagnosis of clinically significant prostate cancer, defined as Gleason score ≥ 7.

6.4.4 STATISTICAL ANALYSIS

All analyses were conducted using R version 4.4.2

6.4.4.1 Descriptive statistics

Baseline demographic and clinical characteristics were summarised as of the date of each patient's first PSA test and stratified by baseline PSA category. Counts and percentages were reported for baseline characteristics. Median follow-up times and first PSA value were reported with interquartile ranges (IQR).

The positive predictive value represents the proportion of patients with a positive test who have the disease of interest. Positive predictive values (PPV) and negative predictive values (NPV) were calculated for prostate cancer overall and clinically significant prostate cancer for patients across baseline PSA categories.

6.4.4.2 Cox proportional hazards model

A Cox proportional hazards regression model was fitted to estimate hazard ratios for prostate cancer overall and clinically significant prostate cancer by baseline PSA category, adjusting for five-year age bands, ethnicity, family history, region, and Index of Multiple Deprivation (IMD) quintile. Patients with a baseline PSA less than 1 ng/mL and aged 60 to 64 years served as the reference group. To account for clustering of patients within general practices, robust standard errors were calculated using the practice

identifier as the clustering variable. Likelihood ratio tests were used to assess the contribution of each variable. Results are presented as hazard ratios with 95% confidence intervals.

6.4.4.3 Estimating retesting intervals

To estimate population-based PSA retesting intervals, Kaplan–Meier survival curves were used to calculate the probability of remaining prostate cancer–free. Differences in time to prostate cancer diagnosis between baseline PSA categories were assessed using log-rank tests. Patients who did not develop prostate cancer were censored at the earliest of death, deregistration from their general practice, or the end of data collection. Additional cumulative incidence curves by age at first PSA test are provided in Appendix 4.

To illustrate how retesting intervals could be defined, I used the ten-year cumulative incidence from the Kaplan-Meier curves. Ten years was selected because ten years represents the maximum retesting interval recommended in the literature and clinical guidelines, as found in Chapter 2 (159). This timeframe also ensured adequate follow-up for robust estimation, as the median follow-up time in this cohort was 5.3 years (IQR: 2.1 to 9.5) after a baseline PSA test. Based on ten-year survival after a baseline PSA test, retesting intervals were defined as the time point at which the risk of prostate cancer remained below 1% in the following year. The 1% cumulative incidence threshold used in this chapter illustrates how retesting intervals could be derived from population-level risk estimates. It aligns with approaches in other screening domains where retesting intervals are defined by risk-based thresholds. A similar 1% threshold was applied in breast cancer (404), and other prostate cancer studies (185). The estimation of retesting intervals in this chapter would differ based on a threshold of 0.5% or 2%, as described in Section 6.6.6.

6.4.4.4 Sensitivity analyses

Four sensitivity analyses were performed. Firstly, Kaplan-Meier survival curves by age were generated based on every patient's last PSA test as a check to compare to the joint model results presented in Chapter 7. Secondly, I restricted the analysis to patients with more than five and ten years of follow-up post first PSA test to ensure the analysis was

not biased by available follow up time. Thirdly, I excluded patients with a prescription of an alpha-reductase inhibitor to determine if baseline PSA values changed. Finally, NCRAS prostate cancer grading data was more robust after 2010, so I restricted the analysis on a cohort of patients who had their first PSA test in 2010 and followed them up until 2018. Results of the sensitivity analyses are in Appendix 4, Appendix 4.2, and Appendix 4.3 .

6.5 RESULTS

A total of 1,389,568 patients were included, with a median follow-up from baseline PSA test of 5.3 years (IQR: 2.1 to 9.5). The median baseline PSA result was 1.2 ng/mL (0.7 to 2.7). Fifty-eight percent (799, 484) of patients had their first PSA test between the ages of 50 and 69.

6.5.1 DESCRIPTIVE RESULTS: PSA VALUE, AGE AND CANCER

Forty percent (557,866) of all patients had a baseline PSA less than 1 ng/mL, followed by 27% (365,195) with PSA 1 to 1.9 ng/mL, and 13% (183,066) with PSA greater or equal to 5 ng/mL. Fifteen percent of patients had their first PSA test between the ages of 40 and 49, 29% between 50 and 59, 29% between 60 and 69, and 28% were aged 70 years or older. The distribution of PSA values varied by age. For patients aged between 40 and 44, 72% (55,722) had a first PSA less than 1 ng/mL and 1% (1,031) had a first PSA ≥ 5 ng/mL. In contrast, for those aged between 65 and 69, 30% (56,914) had a first PSA less than 1 ng/mL and 16% (30,461) had a first PSA ≥5 ng/mL. Similar trends were observed across older age groups with 37% (40,749) of patients aged over 85 at first PSA test had a PSA value greater or equal to 5 ng/mL (Table 6.1).

Table 6.1: Patient characteristics by PSA value at first PSA test (ng/mL)

	< 1	1 to 1.9	2 to 2.9	3 to 3.9	4 to 4.9	≥ 5	Total
Number of patients	557,866 (40%)	365,195 (27%)	148,684 (11%)	82,648 (6%)	52,097 (4%)	183,066 (13%)	1,389,556 (100%)
Follow-up from first PSA (IQR years)	5.6 (2.5 to 9,7)	5.8 (2.6 to 10.1)	5.7 (2.5 to 9.8)	5.4 (2.4 to 9.5)	4.9 (2.0 to 9.1)	2.5 (0.3 to 6.9)	5.3 (2.1 to 9.5)
Age at first PSA							
40 to 44	55,722 (72%)	18,213 (23%)	2,358 (3%)	795 (1%)	372 (0%)	1,031 (1%)	78,491 (6%)
45 to 49	81,737 (65%)	33,200 (26%)	6,108 (5%)	2,121 (2%)	996 (1%)	2,546 (2%)	126,708 (9%)
50 to 54	106,196 (56%)	53,865 (29%)	13,669 (7%)	5,581 (3%)	2,862 (2%)	6,605 (4%)	188,778 (14%)
55 to 59	95,558 (46%)	61,921 (30%)	21,527 (10%)	10,210 (5%)	5,747 (3%)	13,905 (7%)	208,868 (15%)
60 to 64	77,485 (37%)	61,571 (29%)	26,573 (13%)	14,162 (7%)	8,563 (4%)	22,809 (11%)	211,163 (15%)
65 to 69	56,914 (30%)	51,975 (27%)	26,304 (14%)	15,299 (8%)	9,712 (5%)	30,461 (16%)	190,665 (14%)
70 to 74	38,179 (25%)	37,744 (25%)	21,467 (14%)	13,439 (9%)	8,845 (6%)	33,502 (22%)	153,176 (11%)
75 to 79	24,379 (21%)	24,971 (22%)	15,884 (14%)	10,597 (9%)	7,494 (6%)	32,149 (28%)	115,474 (8%)
80 to 84	14,336 (19%)	14,727 (20%)	9,889 (13%)	6,827 (9%)	4,899 (6%)	24,806 (33%)	75,484 (5%)
85+	7,360 (18%)	7,008 (17%)	4,905 (12%)	3,617 (9%)	2,607 (6%)	15,252 (37%)	40,749 (3%)
Ethnicity							
Asian	8,804 (52%)	4,451 (26%)	1,420 (8%)	722 (4%)	411 (2%)	1,224 (7%)	17,032 (1%)
Black	20,573 (46%)	11,441 (25%)	4,030 (9%)	2,159 (5%)	1,321 (3%)	5,522 (12%)	45,046 (3%)
Mixed	3,579 (49%)	1,883 (26%)	629 (9%)	362 (5%)	202 (3%)	648 (9%)	7,303 (1%)
Other	9,379 (50%)	4,892 (26%)	1,647 (9%)	851 (5%)	505 (3%)	1,366 (7%)	18,640 (1%)
South Asian	21,854 (55%)	9,866 (25%)	3,311 (8%)	1,609 (4%)	900 (2%)	2,532 (6%)	40,072 (3%)
Unknown	28,484 (38%)	19,797 (26%)	8,238 (11%)	4,771 (6%)	3,088 (4%)	11,474 (15%)	75,852 (5%)
White	465,193 (39%)	312,865 (26%)	129,409 (11%)	72,174 (6%)	45,670 (4%)	160,300 (14%)	1,185,611 (85%)
Index of Multiple Deprivation Quintile							
IMD 1	133548 (39%)	91195 (27%)	38027 (11%)	21087 (6%)	13212 (4%)	44796 (13%)	341,865 (25%)

	< 1	1 to 1.9	2 to 2.9	3 to 3.9	4 to 4.9	≥ 5	Total
IMD 2	122885 (39%)	84697 (27%)	34555 (11%)	19218 (6%)	12194 (4%)	42421 (13%)	315,970 (23%)
IMD 3	109776 (40%)	72088 (26%)	29502 (11%)	16508 (6%)	10291 (4%)	36893 (13%)	275,058 (20%)
IMD 4	102551 (41%)	64078 (26%)	25797 (10%)	14302 (6%)	9154 (4%)	32317 (13%)	248,199 (18%)
IMD 5	88569 (43%)	52753 (25%)	20658 (10%)	11458 (6%)	7203 (4%)	26459 (13%)	207,100 (15%)
IMD unknown	537 (39%)	384 (28%)	145 (11%)	75 (6%)	43 (3%)	180 (13%)	1,364 (0%)
Region							
North East	14,304 (47%)	9,968 (33%)	4,030 (13%)	2,306 (8%)	1,526 (5%)	5,468 (18%)	37,602 (3%)
North West	102,009 (42%)	65,280 (27%)	26,471 (11%)	14,656 (6%)	9,054 (4%)	32,316 (13%)	249,786 (18%)
Yorkshire and The Humber	18,719 (40%)	11,376 (25%)	4,873 (11%)	2,740 (6%)	1,759 (4%)	6,357 (14%)	45,824 (3%)
East Midlands	13,735 (43%)	9,217 (29%)	3,850 (12%)	2,099 (7%)	1,258 (4%)	4,776 (15%)	34,935 (3%)
West Midlands	88,703 (40%)	67,080 (30%)	26,426 (12%)	15,019 (7%)	9,559 (4%)	33,359 (15%)	240,146 (17%)
East of England	27,687 (41%)	17,693 (26%)	7,519 (11%)	4,242 (6%)	2596 (5%)	9,385 (14%)	69,122 (5%)
London	98,637 (41%)	57,773 (24%)	21,646 (9%)	11,725 (5%)	7,232 (3%)	24,668 (10%)	221,681 (16%)
South East	129,021 (41%)	81,697 (26%)	34,042 (11%)	18,928 (6%)	11,936 (4%)	40,448 (13%)	316,072 (23%)
South West	64,909 (40%)	45,009 (28%)	19,773 (12%)	10,904 (7%)	7,156 (4%)	26,177 (16%)	173,928 (13%)
Unknown region	142 (31%)	102 (22%)	54 (12%)	29 (6%)	21 (5%)	112 (24%)	460 (0%)
Family history of prostate cancer							
Family history (no recorded)	550,432 (40%)	360,189 (26%)	147,012 (11%)	81,844 (6%)	51,612 (4%)	181,884 (13%	1,372,973 (99%)
Family history Yes	7,434 (44%)	5,006 (30%)	1,672 (10%)	804 (5%)	485 (3%)	1,182 (9%)	16,853 (1%)
Prostate Cancer diagnosis during follow-up							
Prostate cancer No	553,567 (43%)	356,762 (28%)	140,025 (11%)	74,515 (6%)	44,178 (3%)	113,443 (9%)	1,282,490 (92%)
Prostate cancer Yes	4,299 (4%)	8,433 (8%)	8,659 (8%)	8,133 (8%)	7,919 (7%)	69,623 (65%)	107,066 (8%)
Gleason Score							
Gleason ≤ 6	873 (4%)	1,974 (9%)	2,195 (10%)	2,263 (10%)	2,407 (11%)	12,321 (56%)	22,033 (21%)
Gleason ≥ 7	1,522 (3%)	4,252 (8%)	4,531 (9%)	3,969 (8%)	3,632 (7%)	34,419 (66%)	52,325 (49%)

	< 1	1 to 1.9	2 to 2.9	3 to 3.9	4 to 4.9	≥ 5	Total
Gleason unknown	1,904 (6%)	2,207 (7%)	1,933 (6%)	1,901 (6%)	1,880 (6%)	22,883 (70%)	32,708 (30%)

PPVs for prostate cancer were low for baseline PSA values below 2 ng/mL (1% to 2%), and highest for PSA greater than or equal to 5 ng/mL (37%). PPVs ranged between 6% and 15% across the intermediate PSA ranges of 2 to 4.9 ng/mL. Eighty five percent (44,178) of patients with a first PSA between 4 to 4.9ng/mL, and 62% (113,443) of patients with a first PSA greater or equal to 5 ng/mL were not diagnosed with prostate cancer during follow-up (Table 6.2).

Table 6.2: Positive predictive value (PPV) for prostate cancer and clinically significant prostate cancer (Gleason ≥7) by baseline PSA range

PSA range at baseline PSA (ng/mL)	Total patients	Any prostate cancer	Gleason ≥7	PPV (any prostate cancer)	PPV (Gleason ≥7)
<1	557,866	4,299	1,522	1%	0%
1 to 1.9	365,195	8,433	4,252	2%	1%
2 to 2.9	148,684	8,659	4,531	6%	3%
3 to 3.9	82,648	8,133	3,969	10%	5%
4 to 4.9	52,097	7,919	3,632	15%	7%
≥ 5	183,066	69,623	34,419	38%	19%
Total	1,389,568	107,067	52,325	-	-

Table 6.3: Negative predictive value (NPV) for prostate cancer and clinically significant prostate cancer (Gleason ≥7) by baseline PSA range

PSA range at baseline PSA (ng/mL)	Total patients	No prostate cancer	No Gleason ≥7	NPV (any prostate cancer)	NPV (Gleason ≥7)
<1	557,866	553,567	556,344	99%	100%
1 to 1.9	365,195	356,762	360,943	98%	99%
2 to 2.9	148,684	140,025	144,153	94%	97%
3 to 3.9	82,648	74,515	78,679	90%	95%
4 to 4.9	52,097	44,178	48,465	85%	93%
≥5	183,066	113,443	148,647	62%	81%
Total	1,389,556	1,282,490	1,337,231	–	–

6.5.2 FACTORS ASSOCIATED WITH PROSTATE CANCER

PSA value was a strong predictor of prostate cancer risk when age, region, family history, deprivation, and ethnicity were controlled for. Compared with the *reference of patients*

aged 60 to 64 years with a PSA < 1 ng/mL, White ethnicity, IMD 1, from the South East, with no family history of prostate cancer, the hazard ratio (HRs) for prostate cancer was HR 2.70 (95% CI 2.58 to 2.84) for patients with a baseline PSA of 1 to 1.9 ng/mL. This increased to PSA HR 58.18 (55.61 to 60.89) for patients with a PSA ≥ 5 ng/mL. The intermediate PSA categories (2 to 4.9 ng/mL) showed progressively higher risks of prostate cancer (Figure 6.1).

Compared with the reference of age 60 to 64 and other factors described above, younger patients had lower HRs for overall cancer. Patients aged 45 to 49 had a HR 0.52 (0.50 to 0.56) compared to those aged 60 to 64. Risk increased slightly for some older groups. The HR was 1.02 (0.99 to 1.03) for ages 65 to 69, but the HR's were generally lower for those aged over 70 (Figure 6.1). When analysis was restricted to clinically significant prostate cancer (Gleason ≥7), the magnitude of association with PSA value was stronger. HRs increased to 3.90 (3.66 to 4.19) for PSA 1 to 1.9 ng/mL. Age also had a noticeable difference in the pattern as seen in Figure 6.1. Patients above the age of 80 were less likely to be diagnosed with clinically significant disease if they had their first PSA test over the age of 80. The HR for 80 to 84 was 0.47 (0.45 to 0.49) and for ages 85+ the HR was 0.27 (0.24 to 0.28) (Table 6.4).

Deprivation and region showed a consistent impact on risk in both the overall prostate cancer analysis and the clinically significant cancer analysis. Patients with a Black ethnic background had higher risk compared with White patients HR 1.49 (1.44 to 1.56) for overall prostate cancer and 1.64 (1.56 to1.75) for clinically significant disease. Asian and South Asian patients had substantially lower risks HR 0.64 (0.58 to 0.70) and 0.66 (0.61 to 0.70), respectively) (Table 6.4, Figure 6.1).

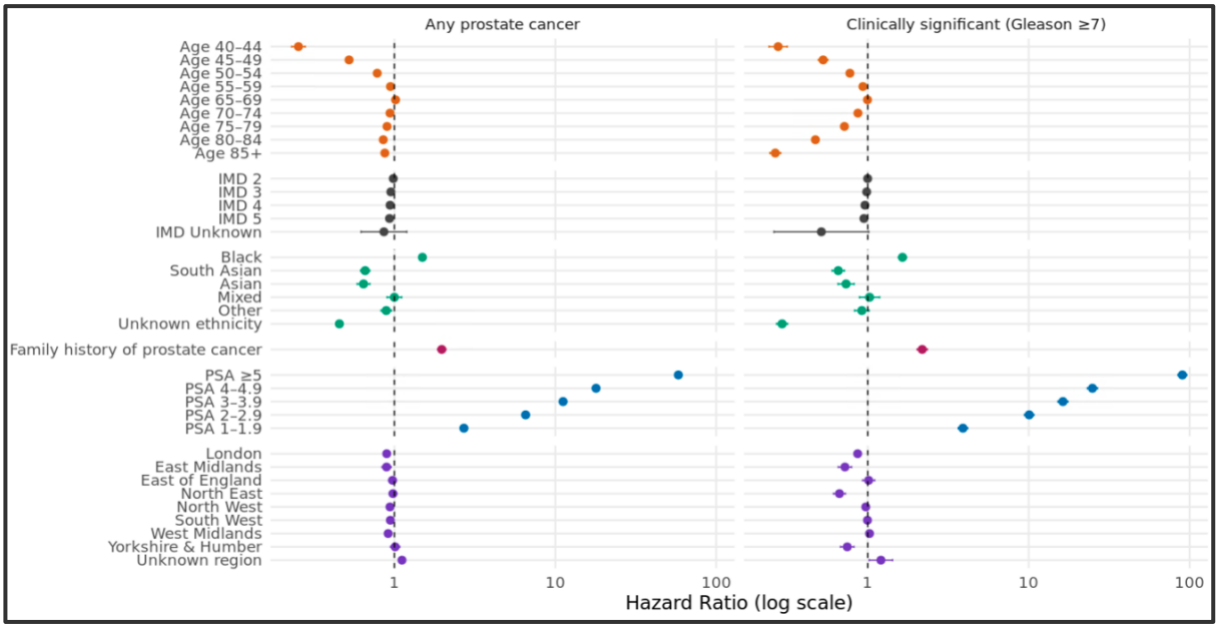
Table 6.4: Multivariable cox model results

Variable	All cancer HR (95% CI)	P value	Clinically significant cancer HR (95%CI)	P value
PSA range (ref < 1 ng/mL)		< 0.001		< 0.001
1 to 1.9	2.70 (2.58 to 2.84)		3.90 (3.66 – 4.19)	
2 to 2.9	6.54 (6.24 to 6.89)		10.07 (9.44 – 10.82)	
3 to 3.9	11.17 (10.65 to 11.78)		16.31 (15.23 – 17.57)	

Variable	All cancer HR (95% CI)	P value	Clinically significant cancer HR (95%CI)	P value
4 to 4.9	17.92 (17.06 to 18.90)		24.88 (23.19 – 26.82)	
≥ 5	58.18 (55.61 to 60.89)		90.10 (84.53 – 96.05)	
Age group (ref 60 to 64)		< 0.001		< 0.001
40 to 44	0.25 (0.23 – 0.29)		0.28 (0.25 – 0.32)	
45 to 49	0.52 (0.50 – 0.56)		0.53 (0.50 – 0.57)	
50 to 54	0.78 (0.75 – 0.82)		0.77 (0.75 – 0.82)	
55 to 59	0.95 (0.93 – 0.97)		0.93 (0.91 – 0.97)	
65 to 69	1.02 (0.99 – 1.03)		1.00 (0.96 – 1.02)	
70 to 74	0.94 (0.91 – 0.96)		0.87 (0.84 – 0.89)	
75 to 79	0.90 (0.87 – 0.92)		0.72 (0.69 – 0.73)	
80 to 84	0.85 (0.82 – 0.87)		0.47 (0.45 – 0.49)	
85+	0.87 (0.84 – 0.90)		0.27 (0.24 – 0.28)	
Ethnicity (ref White)		< 0.001		< 0.001
Asian	0.64 (0.58 – 0.70)		0.73 (0.65 – 0.82)	
Black	1.49 (1.44 – 1.56)		1.64 (1.56 – 1.75)	
Mixed	1.00 (0.90 – 1.11)		1.03 (0.89 – 1.19)	
Other	0.89 (0.83 – 0.96)		0.92 (0.83 – 1.02)	
South Asian	0.66 (0.61 – 0.70)		0.66 (0.60 – 0.71)	
Unknown	0.46 (0.44 – 0.47)		0.29 (0.27 – 0.32)	
Region (ref South East)		< 0.001		< 0.001
East Midlands	0.89 (0.84 – 0.95)		0.72 (0.66 – 0.79)	
East of England	0.97 (0.92 – 1.03)		1.01 (0.93 – 1.10)	
London	0.90 (0.87 – 0.93)		0.86 (0.82 – 0.91)	
North East	0.98 (0.93 – 1.03)		0.67 (0.61 – 0.72)	
North West	0.94 (0.91 – 0.97)		0.97 (0.93 – 1.02)	
South West	0.94 (0.91 – 0.98)		1.00 (0.95 – 1.04)	
Unknown	1.11 (1.04 – 1.23)		1.21 (0.98 – 1.57)	
West Midlands	0.91 (0.88 – 0.95)		1.03 (0.98 – 1.07)	
Yorkshire & Humber	1.01 (0.95 – 1.08)		0.75 (0.68 – 0.82)	
IMD (ref 1)		< 0.001		0.002
2	0.98 (0.96 – 1.00)		1.00 (0.97 – 1.02)	
3	0.95 (0.93 – 0.97)		0.98 (0.95 – 1.01)	
4	0.94 (0.92 – 0.96)		0.96 (0.93 – 0.99)	
5	0.93 (0.91 – 0.95)		0.94 (0.91 – 0.98)	
Unknown	0.86 (0.62 – 1.19)		0.51 (0.26 – 1.01)	
Family history of prostate cancer	1.97 (1.86 – 2.08)	< 0.001	2.18 (2.03 – 2.34)	< 0.001

Caption: Reference is patients with a baseline PSA < 1 ng/mL, aged 60 to 64, White ethnicity, IMD 1, and the South East, and no family history of prostate cancer.

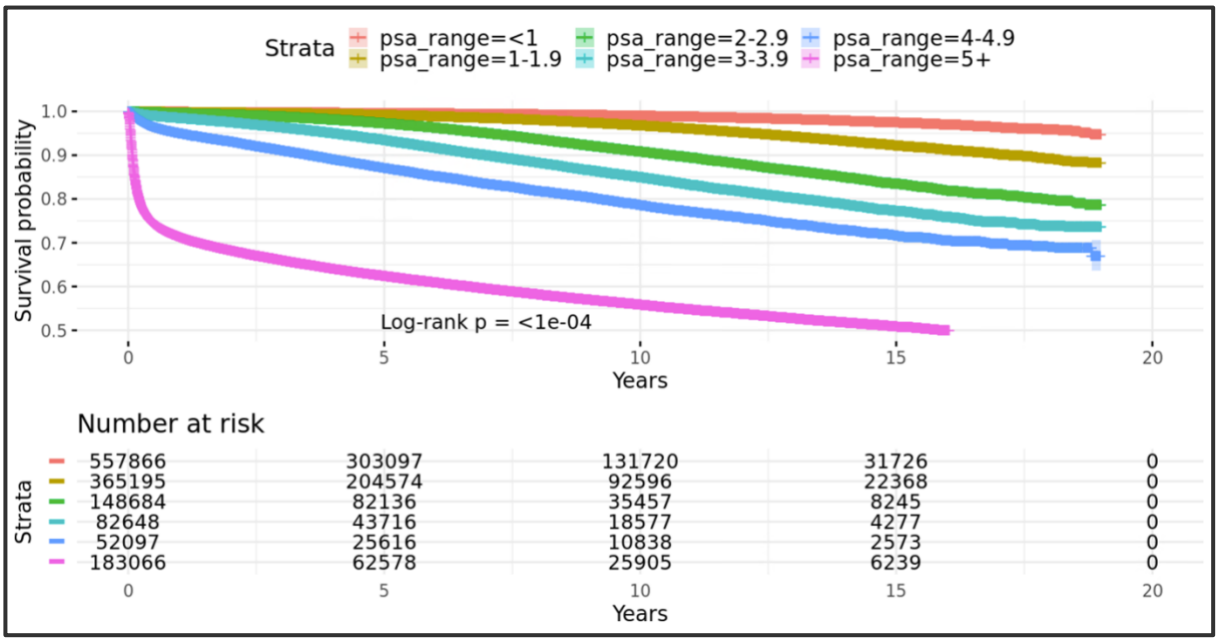
Figure 6.1: Hazard ratios and 95% CI's for risk factors of prostate cancer



6.5.3 CUMULATIVE RISK OF CANCER

Estimates from Kaplan-Meier curves illustrated that the cumulative incidence of prostate cancer for all ages combined increased over time across all PSA categories (Figure 6.2). Patients under the age of 60, had low cumulative ten-year risk of prostate cancer. For those aged 40 to 59 with a first PSA below 1 ng/mL, ten-year risk ranged from 0.2% (95%CI 0.1 to 0.2) to 0.7% (0.7 to 0.8). Risk increased with age and was highest in those aged 85 and older. For patients aged between 60 and 64 with a PSA less than 1 ng/mL at their first PSA test, the risk of cancer in 10 years was 1.2% (1.1 to 1.3) and for those 65 to 69 it was 1.6% (1.5 to 1.8). For patients with PSA 1 to 1.9 ng/mL, the ten-year cumulative incidence increased from 1.9% (0.8 to 1.3) in patients aged 40 to 44 to 3.7% (3.5 to 4) in patients aged 65 to 69 and remained at this risk consistently across older age ranges. Five-year cumulative incidence for patients aged 65 to 69 with a PSA 1 to 1.9ng/mL was 1% (0.9 to 1.1). Patients of all ages with PSA greater than 2 ng/mL had 10-year risks of cancer exceeding 10%. Patients with a PSA ≥5 ng/mL had the highest risks, with 10-year cumulative incidences of 48.2% (47.5 to 48.8) between ages 65 to 69. Survival estimates by age and PSA value are provided in Appendix 4.1.

Figure 6.2: Kaplan-Meier survival curves for risk of prostate cancer by baseline PSA category



Caption: Kaplan–Meier estimates of prostate cancer–free survival by baseline PSA category at first PSA test. Patients were stratified into six groups: < 1, 1 to 1.9, 2 to 2.9, 3 to 3.9, 4 to 4.9, and ≥5 ng/mL. The number of patients at risk over time is shown below each curve. Each curve represents survival time for all ages stratified by PSA category. Further analysis for each age range by PSA category is in Appendix 4.

6.5.4 Estimation of retesting intervals

To illustrate the feasibility of translating population-based cumulative incidence of prostate cancer into retesting intervals, a threshold of 1% cumulative incidence was applied. For each age and baseline PSA group, if the cumulative incidence of prostate cancer exceeded 1%, the corresponding retesting interval was defined as the year preceding the point at which the 1% threshold was crossed. Based on this, the recommended interval for the patients' next test varied by age group and baseline PSA (Table 6.5).

Patients aged between 40 to 59 with a baseline PSA less than 1 ng/mL did not cross the 1% threshold over ten years. Patients aged 60 to 64 with a PSA less than 1 ng/mL crossed the threshold at nine years. For patients aged 40 to 45, with a first PSA 1 to 1.9 the threshold was crossed at seven years and in year one for patients of the same age with a first PSA of 2 to 2.9 ng/mL. For patients aged 60 to 69, the estimated time to next PSA test

ranged from seven to nine years for PSA less than 1 ng/mL and decreased with increasing PSA levels. Patients of all ages with a first PSA greater or equal to 5 ng/mL crossed the 1% threshold within the first year after their PSA test. This was similar for patients younger than 64 with a PSA greater or equal to 3 ng/mL. Referral to secondary care may be warranted for these patients. If patients are aged over 65 waiting one year to retest may be justified for those with a PSA value 3 to 3.9 ng/mL.

When focussing on patients with a diagnosis of clinically significant cancer, retesting intervals were generally longer for patients with a PSA below 4 ng/mL and for patients aged over 80 (Table 6.6). For patients of all ages with a PSA below 2 ng/mL the 1% threshold was crossed between five to ten years for patients aged over 75 and four years for patients aged 74 or below. All patients aged 85+ with a PSA value below 4 ng/mL were not likely to be diagnosed with clinically significant prostate cancer in the following ten years.

Table 6.5: Estimated time to next PSA test (years) corresponding to a 1% cumulative incidence of prostate cancer, by age, and baseline PSA group (overall prostate cancer)

Age range at first PSA test	PSA < 1 ng/mL	PSA 1 to 1.9 ng/mL	PSA 2 to 2.9 ng/mL	PSA 3 to 3.9 ng/mL	PSA 4 to 4.9 ng/mL	PSA ≥ 5 ng/mL
40 to 44	>10	9	2*	Refer	Refer	Refer
45 to 49	>10	7	1*	Refer	Refer	“
50 to 54	>10	6	2	Refer *	Refer	“
55 to 59	>10	6	2	Refer *	Refer	“
60 to 64	9	5	3	Refer	Refer *	“
65 to 69	7	5	2	1	Refer *	“
70 to 74	5	4	2	1	Refer	“*
75 to 79	3	3	2	1	Refer	“*
80 to 84	2	3	2	1	1	“*
85+	1	2	2	1	Refer	“*

Caption: Full Kaplan–Meier survival probabilities by year, age, and PSA category are provided in Appendix 4.1

** Patient recommended to be referred based on NICE NG12 PSA age-specific threshold guidance for patients presenting to primary care with symptoms*

Table 6.6: Estimated time to next PSA test (years) corresponding to a 1% cumulative incidence of prostate cancer, by age, and baseline PSA group (clinically significant prostate cancer)

Age range at first PSA test	PSA < 1	PSA 1 to 1.9	PSA 2 to 2.9	PSA 3 to 3.9	PSA 4 to 4.9	PSA ≥ 5
40 to 44	>10	>10	4	Refer	Refer	Refer
45 to 49	>10	>10	4	Refer	Refer	"
50 to 54	>10	8	4	Refer	Refer	"
55 to 59	>10	8	4	Refer	Refer	"
60 to 64	>10	8	4	2	Refer	"
65 to 69	>10	7	4	2	Refer	"
70 to 74	>10	7	4	3	1	"
75 to 79	>10	>10	5	3	1	"
80 to 84	>10	>10	>10	6	5	"
85+	>10	>10	>10	>10	6	"

Caption: Kaplan–Meier survival probabilities with the outcome as time to clinically significant (Gleason ≥ 7) diagnosis. (N = 49,365).

6.5.5 SENSITIVITY ANALYSES

There were 707,858 patients with a first PSA test between 2010 and 2018. Median follow up time was 3.4 years (IQR 1.4 to 5.8). The distribution of PSA tests by year for these patients was the same as the 2000 cohort (median PSA 1.1ng/mL 0.63 to 2.4). The risk of prostate cancer diagnosis from first PSA was similar in low PSA ranges (1 to 2.9 ng/mL) and higher in the patients with elevated first PSA test results (3 to ≥ 5 ng/mL). In the 2010 cohort, the HR for PSA 1 to1.9 ng/mL was 2.87 (95%CI 2.72 to 3.03) compared with 3.13 (2.84 to 3.45) in the 2000 cohort, and for PSA 4 to 4.9 ng/mL it was HR 47.78 (43.81 to 52.14) versus 21.59 (20.65 to 22.57). The higher HR reflects shorter follow-up, where the relative risks between PSA categories was larger because fewer cancers occurred among patients with a first PSA less 1 ng/mL in the nine years following their first PSA test (Appendix 4.3). No meaningful differences were found in other sensitivity analyses.

6.6 DISCUSSION

6.6.1 SUMMARY OF FINDINGS

This chapter examined PSA values in a cohort of 1,389,556 patients between the ages of 40 and 90 who had a first PSA test recorded in primary care between 2000 and 2018. it

was found that 67% (923,061) of patients had a first PSA test value less than 2 ng/mL and 40% (557,866) had a PSA less than 1 ng/mL. PSA category was the strongest predictor of prostate cancer. The risk of cancer increased with increasing PSA categories. Using a 1% cumulative incidence threshold as an example, population based retesting intervals varied by PSA and age. Patients aged 40 to 59 with a PSA less than 1 ng/mL could safely wait ten years before retesting. This decreased to seven to nine years for patients in their 60s with a PSA less than 1 ng/mL. If patients had a PSA value between 1 and 1.9 ng/mL the retesting interval ranged from four to nine years for those under the age of 75 with shorter intervals for older patients. For patients with a PSA 2 to 2.9 ng/mL, based on this threshold, retesting would be recommended every two years for most ages. The estimated retesting intervals are entirely dependent on the chosen threshold. Further research is required to pick a threshold that balances the harms of overtesting with the benefits of early diagnosis.

6.6.2 Comparison to literature

The results from this chapter align closely with international evidence on prostate cancer risk by baseline PSA value (Table 6.7). In an American study of 126,000 men aged 40 to 55 years (405), the long-term risk of lethal prostate cancer for those with baseline PSA values below 2 ng/mL ranged between 1.5% and 2%. The findings reported are similar as the cumulative incidence of prostate cancer in ten years for patients with a baseline PSA between the ages of 40 and 55 was 0.2 to 0.5% for PSA < 1 ng/mL and 1.1 to 2.5% for PSA 1 to 1.9 ng/mL. Other examples reporting risk of prostate cancer from baseline PSA include studies conducted in Norway (400), United States (208, 405, 406), Sweden (175), Europe (402) and Switzerland (403). The risk of prostate cancer death was more than ten-fold higher in men with a baseline PSA level of 3 to 3.9 ng/mL than in men with a PSA level of < 0.5 ng/mL) (400). In this chapter, I found that patients with a baseline PSA of 3 to 3.9 ng/mL had over 11 times the risk of prostate cancer diagnosis compared with those with PSA less than 1 ng/mL.

By ethnicity, the HR of cancer risk was consistent with an American study (405) where the HR for lethal prostate cancer for patients of Black ethnicity compared to those of

White ethnicity was 1.77(1.52 to 2.07). I found that for clinically significant prostate cancer the HR was 1.64 (1.56 to 1.75) compared to those of White ethnicity (Table 6.4).

The distribution of PSA values reported in this chapter using English primary care data aligned with international findings. In a Swiss cohort of patients (403) from the European Randomized Study of Screening for Prostate Cancer (ERSPC) trial, 88.2% of 4,932 patients aged 55 to 70 years had an initial PSA value of less than 3 ng/ml and 56% of those had a baseline PSA value below 1 ng/mL, 32% had a PSA 1 to 1.9 and 13% had a PSA 2 to 2.9. In the same age range (55 to 70), a study in Finland (407), of 20,268 patients found similar results when analysing a cohort of patients with PSA values below 3 ng/mL. They reported of patients with a baseline PSA value below 3ng/mL, 53% had a results less than 1 ng/mL, 35% had a result between 1 to 1.9 and 13% had a result between 2 to 2.9 ng/mL (407). In English data from this study, I found 642,415 patients with a first PSA test between the ages of 55 and 70. Of those patients 79% (506,763) had a first PSA below 3 ng/mL. Of these patients, 48% (242,062) had a PSA below 1 ng/mL, 37% (186,132) had a PSA 1 to 1.9 ng/mL and 16% (78,569) had a PSA of 2 to 2.9 ng/mL (Table 6.1).

Table 6.7: Comparison of proportion of age and baseline PSA values across international studies

	Prop of all patients with PSA < 3 ng/mL	PSA <1 out of patients with PSA < 3 ng/mL	PSA 1-1.9 out of patients with PSA < 3 ng/mL	PSA 2-2.9 out of patients with PSA < 3 ng/mL
Swiss study ages 55 to 70	88%	56%	32%	13%
Finland study ages 55 to 70	-	53%	35%	13%
This study using ages 55 to 70	79%	48%	37%	16%
CAP trial ages 50 to 69	89%	-	-	-

In a Norwegian (400), Swedish (185), German (408) and American (208) cohorts of patients, it was found that over 70% of patients had a first PSA result below 2 ng/mL. The Norwegian Prostate Cancer Consortium study of 176,099 men aged 40 to 69, found that 84% had a baseline PSA below 2 ng/mL (400). This was similar to the findings from the PLCO trial in the United States where 83% of those aged 55 to 60 had a baseline PSA of less than 2 ng/mL (208). In a Swedish population-based cohort study among patients

who had a baseline PSA between the ages of 57.5 to 62.5, 71.7% (1,646/2,295) had a PSA value below 2 ng/mL (185). In the PROBASE trial 89% of screened patients in Germany had a baseline PSA of less than 1.5 ng/mL (408). Data on the proportions of patients by PSA category in England are similar. I found that of the 417,270 patients aged between 55 and 64 in this study, 72% (299,159) had a PSA below 2 ng/mL.

Internationally and within the UK, screening cohorts report lower baseline PSA values than those found from the general primary care population. This reflects more opportunistic or symptom-driven testing practices in primary care (409), where the proportion of patients with elevated PSA values by PSA category and age are slightly higher than what was reported in the CAP and ProtecT trials. In this chapter, I found that of the 793,627 patients who had a first PSA test between the ages of 50 and 69, 83% (655,280) had a baseline PSA less than 3 ng/mL. and the median first PSA was 1.1 ng/mL (IQR 0.7 to 2.2). The CAP trial had 64,436 patients aged 50 to 69 in the intervention group with a first PSA result. Of them, 89% (57,579) patients had a value less than 3 ng/mL. In the ProtecT trial the median PSA result of those collected (n=58 542) was 0.99 ng/mL (IQR 0.60–1.70). One other study based on UK data (391) reported proportions of PSA test result by value and age. It used CPRD data between 2002 and 2011, for patients between 45 and 69, and found that 78% of patients had a PSA value of below 3 ng/mL. It was confirmed in this chapter that this proportion held true using data from 2000 to 2018. For all ages combined, 77% of patients had a baseline PSA value less than 3 ng/mL.

6.6.3 Strengths and Limitations

A strength of this chapter is the large dataset of PSA values over a period of 19 years and over 1.38 million patients with a first PSA test value. Primary care electronic health records provide real-world insights about patients who present to their GP. Although similar studies have been done in other countries, I know of one other UK based observational study looking at PSA value, age and subsequent cancer risk in primary care data (391). This study only used data from 2002 to 2011. More recent primary care UK based PSA testing studies have focussed on the rates of PSA testing (369) instead of describing PSA values.

6.6.3.1 Routinely collected health records

A limitation of this study is that the outcome of a prostate cancer diagnosis relies on routine clinical practice. In practice, patients with low PSA values are not referred for further investigation. This introduces verification bias which occurs when the probability of confirming disease depends on the initial test result. In this context, because cancers are mostly diagnosed among patients with higher PSA values (above the referral threshold), it is unknown how many undiagnosed cancers there are in patients with low PSA values. As a result, the negative predictive value for low PSA levels is likely to be inflated.

Another limitation of using electronic health record data is that practices may refer patients based on NICE NG12 age-specific thresholds or the PCRMP threshold of 3 ng/mL. One study found ten discrete referral models from 16 cancer networks in England and Wales (410). PPV estimates for elevated PSA values are likely to be more accurate than NPV results, as patients with higher PSA levels are generally referred for further testing in routine care. However, unlike in trial settings where referral thresholds are standardised, the thresholds used in this study are unknown. A patient aged 63 with a PSA of 4.2 ng/mL would be referred based on PCRMP for further investigations but would not be referred using the NICE NG12 age specific thresholds.

The median follow-up time following a patients first PSA test in this study was 5.3 years. This may have biased the results to lengthen PSA retesting intervals as patients in the study were not followed up for long enough post first PSA test. Patients with first PSA values in the range less than 1 ng/mL to 4 ng/mL had higher median follow up as they were less likely to be diagnosed with cancer and leave the study cohort. The median follow-up for these patients was 5.6 (IQR 2.5 to 9.8 years). To mitigate this potential selection bias, I ran a sensitivity analysis of patients with at least five and ten years of follow-up**.** No meaningful difference in the relative trends across low PSA ranges was found. The PPV for PSA greater than five was lower in the sensitivity analysis due to survivor effects (Appendix 4.3).

6.6.3.2 Factors influencing PSA values

PSA values may be over or underestimated depending on patients presenting with symptoms, if the patient was taking an alpha-reductase inhibitors or if pathology labs used different inter-assays. Firstly, symptoms were not accounted for in this chapter. As a result, some elevated PSA results may reflect benign conditions such as urinary tract infection or benign prostatic hyperplasia rather than prostate cancer. This would underestimate the PPV by inflating the number of false-positive PSA results. For example, among 82,648 patients with a first PSA value of 3 to 3.9 ng/mL, 10% (8,133) were subsequently diagnosed with prostate cancer, indicating a high false-positive burden at this threshold. Future analyses could address this limitation by conducting a sensitivity analysis restricted to asymptomatic patients.

Secondly, finasteride and dutasteride are prescriptions which reduce a patient's serum PSA level by half (88). In this cohort of patients over 10% were found to have been prescribed finasteride or dutasteride at some point in their history. Further sensitivity analyses excluding 181,265 with a prescription found that the median first PSA result was slightly lower 1.1 ng/mL (IQR 0.6 to 2.3) compared to was 1.2 (0.7 to 2.6).

Finally, measurement errors in PSA assays present a challenge. Studies show that total PSA values can differ by between 15 and 20% between assays (89). Different assays are used throughout England and it is not possible to know which PSA tests were done using which assay (411). Different assays could over or underestimate PSA values.

6.6.3.3 Cancer stage coding

The coding of clinically significant prostate cancer is another limitation. I used a crude definition of Gleason < 7 or ≥7 as this is the best staging data currently available in NCRAS. There were no differences in the results other than PSA value was a stronger risk factor for clinically significant disease compared to overall prostate cancer. I found higher PSA values were associated with higher HR's of clinically significant cancer. Around 30% of the cancer diagnoses had missing data on stage. In 2010 there was an effort to improve Gleason score coding in NCRAS data (373). A sensitivity analysis was

run for patients with cancer diagnoses post 2010. In this cohort of patients there were 36,960 prostate cancer diagnoses and only 20% of the stage data was missing with 62% Gleason ≥ 7 and 18% Gleason < 7. PSA value increased a patients risk of clinically significant cancer in this 2010 cohort more than in the 2000 cohort although this could be due to less follow up time as the max follow up was nine years instead of 19.

6.6.4 Clinical implications

Based on a 1% threshold, the patients aged 40 to 59 with a baseline PSA < 1 ng/mL could wait over ten years until their next PSA test. Applying this interval alone would reduce retesting for 24% (339,213) of all patients with a first PSA test. This percentage rises to over 70% for patients between the ages of 40 to 44 (Table 6.1). A five-to-nine-year interval is estimated for patients aged between 60 and 74 with a first PSA < 1 ng/mL or for all patients under the age of 70 with a first PSA between 1 and 1.9 ng/mL. These two intervals would reduce retesting for an additional 33% (453,323) of all patients. Together, they indicate that at least 57% of patients could safely wait five years or longer before their next test.

Across all ages I reported that 11% (148,684) of patients had a first PSA test value between 2 and 2.9 ng/mL. This is a grey zone and 9% of clinically significant cancers detected were in patients with a first PSA in this range. This underscores the heterogeneity of risk and the need for additional stratification. Retesting patients with a first PSA between PSA 2 to 2.9 ng/mL would be recommended every two years based on population-level estimates, with a 1% threshold as presented in this chapter. The use of mpMRI scanners in this cohort of patients has the potential to reduce unnecessary biopsies and can be helpful to monitor these patients with PSA values falling in this grey zone.

NICE NG12 guidelines as described Section 1.13, recommends considering PSA testing for patients presenting with symptoms of prostate disease (2). If the patients' PSA value is above an age-specific threshold (2), referral to secondary care is advised. The age specific thresholds are outlined in Section 1.13. Results from this chapter slightly differ

from those in NICE NG12. For patients aged 40 to 49 with a PSA between 2 to 2.9 ng/mL NICE recommends considering referral to secondary care. The estimates in this chapter recommend retesting patients in 1-to-2 years as their risk of cancer is not above 1%. However, it may be worth considering a lower threshold for these men such as 0.5%. For other age specific referral thresholds recommended by NICE, earlier referral may be warranted. For patients aged 60 to 69, NICE NG12 recommends referring if their PSA is greater than 4.5 ng/mL. However, it is possible that patients in this age range may require more intensive follow-up or should consider closer monitoring. In this chapter, all patients with a first PSA greater than 4 ng/mL crossed the 1% within the year after their first PSA test except for those over 80. For patients aged 60, following PCRMP guidelines and referring patients if their PSA is greater than 3 ng/mL may be more appropriate.

6.6.5 POLICY IMPLICATIONS

This chapter provides reassurance that the EAU risk-stratified retesting algorithm (105) could be safely adopted in England, as the distribution of baseline PSA values and ages in this population closely matches those reported in the American, Swiss, and Swedish studies (Section 6.6.2). These studies underpin the EAU's interval recommendations of eight-to-ten years for patients with low PSA values such as PSA less than 1 ng/mL (175, 186, 193). They also recommend that patients aged 60 with a PSA less than 1 ng/mL require no further testing based on 15-year cancer risk (159, 185). Although this evidence is indirect, it has been considered sufficient to guide European policies for retesting. Practically, this is a simple policy implication and would be easily implemented into English guidance as proportions of PSA by baseline value and age are consistent.

For patients at increased risk defined by the EAU as patients with a PSA greater than 1ng/mL at age 40 or PSA greater than 2 ng/mL at age 60, biennial retesting intervals are recommended (105). Based on results from this chapter, biennial intervals are recommended for patients with a PSA greater than 2 but longer intervals may be safe for those with a between PSA 1 and 1.9 ng/mL.

Finally, most international guideline recommendations reported in Chapter 2, recommend to stop PSA testing at age 70 or when life expectancy is less than 10 years. This is not currently recommended in English guidance. In this Chapter, 28% of all patients had their first PSA test over the age of 70. Policymakers should be aware that this is a cohort of patients with the highest risk of overdiagnosis of prostate cancer (228).

6.6.6 RESEARCH IMPLICATIONS

The estimation of retesting intervals in this chapter is based on a 1% cumulative incidence threshold and there is no consensus on the most appropriate risk threshold for PSA retesting. Evidence from previous studies suggests that longer intervals may be safe for patients with low PSA values. These recommendations are based on different thresholds of risk. For example, a Swiss study (403) recommended an eight-year interval for men with baseline PSA less than 1 ng/mL, reporting a 0.21% incidence of Gleason ≥7 prostate cancer after eight years and a 0.66% ten-year probability of any prostate cancer diagnosis. Similarly, results from ERSPC trial found an overall prostate cancer detection rate of 0.47% during an eight-year period (186), although this was only 1327 patients. Other prostate cancer studies have used higher thresholds, recommending retesting after six years for patients with PSA between 1 and 1.9 ng/mL, corresponding to an 11% cumulative risk of prostate cancer (412). Comparable risk threshold approaches have been used in other cancer sites. In cervical cancer, the retesting interval was extended for patients without HPV to five year as the cumulative incidence rate of CIN3+ after six years for women negative for HPV at baseline was 0.27% (95% CI 0.12 to 0.45) (221).

There is no consensus for a “correct” threshold and this would depend on the individual, healthcare systems, cancer site, treatments, and resources. To illustrate how retesting intervals change based on the applied threshold, retesting intervals based on a 0.5% cumulative incidence threshold are demonstrated in Table 6.8. A systematic review of risk thresholds that are recommended as evidence to lengthen retesting intervals is essential and it may be helpful to do a more formal comparison in different cancer sites. Further work to determine an acceptable threshold should incorporate patient, clinician,

policy, and health economic perspectives, supported by simulation modelling to evaluate potential clinical and population-level impacts.

Table 6.8: Estimation of retesting intervals based on a 0.5% risk threshold

Age range at first PSA test	PSA < 1ng/mL	PSA 1 to 1.9 ng/mL	PSA 2 to 2.9 ng/mL
40 to 44	>10	7	1
45 to 49	>10	5	-
50 to 54	>10	5	1
55 to 59	8	4	1
60 to 64	6	4	1
65 to 69	4	3	1
70 to 74	2	2	1
75 to 79	1	1	-
80 to 84	-	1	-
85+	-	-	-

Captions: unfilled intervals indicate that the risk of cancer crossed 0.5% within one year for the age group with a baseline PSA in the specific range.

Further research into individualised risk stratification is required to better understand how to manage patients who fall into the PSA “grey zone”. The analysis in this chapter focused on baseline PSA levels and future prostate cancer risk. Although this provides an estimate of when it may be safe to retest after an initial PSA measurement, it does not address subsequent retesting intervals. Additionally, the findings presented in this chapter are descriptive and based on population-level groupings, which may not reflect variation at the individual level. Further research to develop more dynamic approaches which integrate each patient’s longitudinal PSA history with their evolving risk of prostate cancer may provide more individualised retesting interval estimates. Joint modelling may provide more accurate risk stratification at an individual level for these patients.

Research to ensure data collection and reporting is essential for risk-stratification models. As part of the NHS 10-year Long Term Plan published in July 2025, there is a strong emphasis on unlocking health data for research to support earlier diagnosis and better patient outcomes. A key factor that should be prioritised in this is accurate and

complete staging data for patients with a diagnosis of prostate cancer. In this chapter, there was over 30% missing stage data in NCRAS which limited the results to use overall prostate cancer diagnosis instead of clinically significant disease. In the future it will be important to undertake similar baseline PSA studies with more accurate prostate cancer staging data. Particularly, it is necessary to have the data to accurately separate Gleason 3+4 and Gleason 4+3 or present analyses by grade groups as described in Section 1.5.3.

Finally, further research with electronic health records is necessary to understand baseline PSA and future risk of prostate cancer when accounting for symptoms. This would help determine if symptoms combined with baseline PSA assist in the risk prediction of prostate cancer or if symptoms increase PSA values and associated false positive results. Additionally, further research to understand the reasons patients are having PSA tests would assist with understanding PSA measurements and risk of cancer.

6.7 Conclusion

In this chapter, I replicated the findings from European data that patients with a PSA less than 1 ng/mL under 60 can safely wait ten years before a repeat test. This chapter provides reassurance that the EAU risk stratified retesting algorithm would be safe to follow in England and would be a practical short-term solution. Joint modelling, described in Chapter 7, extends this approach by testing the feasibility of individualised dynamic risk predictions to generate evidence for retesting intervals.

Chapter 7: Estimation of Individualised Dynamic PSA Retesting Intervals

7.1 Background

Previously in this thesis I showed that for both the early detection of prostate cancer (Chapter 2) and the monitoring of low-risk disease (Chapter 3), recommended retesting or surveillance intervals are not based on evidence from randomised trials with the aim of evaluating repeat testing schedules. As outlined in Chapter 3, the safety of active surveillance is supported by randomised trials which demonstrate that there is no difference in overall mortality between low-risk patients managed with surveillance compared to low-risk patients who receive radical treatment. However, the specific timing of surveillance intervals recommended in guidelines is largely based on expert consensus (86).

Similarly, in Chapter 2 (159), I described how PSA screening trials evaluate whether screening with PSA compared with no screening reduces prostate cancer specific or overall mortality. I highlighted that guidance for retesting is largely informed by studies that estimate prostate cancer risk and mortality from a single baseline PSA measurement at a given age. The methods used are typically logistic regression, Cox regression or Kaplan-Meier analyses (185, 188, 217). In Chapter 6, I replicated this baseline PSA approach using English primary care data to estimate prostate cancer-free survival by baseline PSA and age. Although this analysis generated useful population-level estimates, it does not account for repeat PSA measurements or reflect an individual patient's evolving risk.

In this chapter, I assess the feasibility of using joint modelling to predict an individual's cumulative risk of prostate cancer. Unlike population-based baseline PSA risk approaches, joint modelling incorporates each patient's longitudinal PSA testing history and dynamically updates the cumulative risk predictions as new data become available.

This provides a potential framework for generating evidence-based, individualised PSA retesting intervals.

7.2 OBJECTIVES

The objectives of this chapter were to:

1) Describe joint modelling as a method for dynamically estimating an individual's cumulative risk of prostate cancer.
2) Develop and internally validate a joint model using longitudinal PSA values and age.
3) Simulate the feasibility of using survival predictions from joint models as evidence for repeat PSA testing intervals by applying a risk threshold.

7.3 SUMMARY OF METHODS TO DETERMINE RETESTING INTERVALS

Frequency of surveillance intervals has been studied in other disease areas such as cardiovascular disease (413, 414), osteoporosis (415, 416), diabetes (417) and other cancer sites (418, 419). For example, in the UK breast cancer screening is currently offered every three years for women aged between 50 and 70. This is a fixed, one-size-fits-all schedule. A limitation of fixed schedules is that they do not account for individual differences in risk. To address this, a range of modelling approaches have been developed to design more, risk-adapted testing intervals that better reflect each patient's likelihood of disease.

Most existing studies use simulation-based approaches. A review of cancer screening studies from 2021 (420) found that the most common evaluated cancer types were breast (25%) and colorectal (24%) cancer. It found that the most common methodological approaches for modelling cancer screening were Markov models which simulate how people transition through health states (421). Markov models can be implemented at the individual level (microsimulation) or at the cohort level.

Markov models are one type of simulation model. Simulation studies can be used to compare different screening strategies. For example, screening every two, three, or five

years. The aim of these models is to determine which schedule minimises expected costs, maximises quality-adjusted life years gained, and reduces rates of overdiagnosis. One example of a simulation-based approach is provided by Mandelblatt et al (422). They developed a 17-state Markov model to estimate cost-effectiveness across 18 different screening strategies for cervical cancer. Simulation studies are valuable alternatives to long, expensive randomised trials because they can evaluate many hypothetical policies and identify those offering the greatest potential benefit at an acceptable cost. Interestingly, guideline recommendations for PSA retesting only occasionally cited this type of evidence (159). In Chapter 2, I found that only American (NCCN (178), AUA (176), and French guideline (179) referenced simulation studies. Of the 37 studies cited as evidence over all guidelines, four (11%) of them were simulation studies. Three were microsimulation studies (189-191) and one was a Monte Carlo simulation based on a Markov model (192).

In contrast to simulation studies, several analytical approaches have been proposed to determine the length of retesting intervals (423-425). Kirch and Klein (426) proposed that the optimal interval between screening tests is proportional to the square root of the age-specific incidence of disease. Their model assumed a test had perfect screening sensitivity and a fixed “preclinical period” during which disease is detectable, but when the patient is still asymptomatic. Zelen (427) expanded this proposing to maximise a utility-based approach that accounted for imperfect test sensitivity and random variability in the duration of the preclinical period. Lee and Zelen (428) subsequently incorporated age-specific disease incidence, assumed that the natural history of disease follows a progressive course, and the benefit of earlier detection arises from a shift in the stage distribution at diagnosis.

More recently, Markov decision processes have become popular. Specifically partially observable Markov decision processes (POMDPs) which (429) can be used to study sequential decisions made in uncertain environments. They are useful for studying systems in which the true state of the system is not known. Unlike standard Markov or microsimulation models that compare a fixed set of predefined strategies, POMDPs identify optimal testing policies when the true underlying disease state is unknown.

While POMDPs can be implemented through simulation, they are fundamentally analytical frameworks that model how decisions should evolve as new information becomes available. No guidelines included in Chapter 2 referenced analytical approaches or POMDP models as evidence for PSA retesting intervals. Instead, seven of the eleven (64%) guidelines with recommended PSA retesting intervals cited at least one study that used baseline PSA value to estimate future risk of prostate cancer (159).

A limitation to the modelling methods described above is that that it is impossible to simulate all or individualised options. Any simulation is dependent on assumptions and are dependent on an estimation of the natural progression of disease based on the average population risk of disease. Most decision-analytic frameworks (cohort/individual Markov models, POMDPs) condition decisions on the patient's current state based on their most recent test result, with little or no use of a patient's full longitudinal history. They also assume the natural history of disease by using population-level transition distributions.

For prostate cancer, average transitions are particularly problematic because disease trajectories are heterogeneous. Some tumours remain indolent while others metastasise and lead to death. A single set of average transitions is unlikely to accurately represent all patients. The simulation frameworks mentioned are often referred to as personalised approaches. However, they are more similar to risk-stratified approaches rather than personalised testing intervals and are contingent on population-level groupings of risk. Both Joint modelling and landmarking are more personalised approach that uses longitudinal patient-level data.

Landmarking is a method used to predict a patient's cumulative risk of disease based on longitudinal data (430, 431). Both joint modelling and landmarking aim to incorporate evolving patient information to update risk, but they differ fundamentally. Landmarking obtains individual survival probabilities from a Cox model fitted to patients who are still at risk at a specific time; biomarker information accrued up to this time (the landmark time) is incorporated as an additional predictor. By selecting a series of landmark time points, such models can produce a sequence of survival predictions to focus on events

occurring in the specified timeframe (432). Studies comparing joint modelling to landmarking generally favour results from joint models (433-435). The rest of this chapter focusses only on joint modelling.

7.4 SUMMARY OF JOINT MODELLING

In this section, I provide a brief overview of joint modelling and outline how it works conceptually. In the methods section, I describe how I developed a joint model to generate evidence for individualised PSA retesting intervals.

Joint models for longitudinal and time-to-event data are established as a method for calculating dynamic, individualised predictions for longitudinal and survival outcomes (436-438). Joint models are patient-specific as they use individual-level random effects from the longitudinal data (439). They also provide updated risk predictions over time as extra longitudinal information becomes available. As a result, they have different levels of predictive accuracy at different specified follow-up times when incorporating different lengths of the individual patient's history.

The four attributes listed below are important to consider when building prediction models. Simpler statistical models can incorporate one or two of the attributes, but joint modelling is able to account for all four attributes simultaneously. These attributes are:

1) Measure longitudinal outcomes that are continuous or binary, measured with error and are correlated with one another (e.g. PSA measurements for the same patient).
2) Overcome the fact that typically patients with disease progression have more adverse measurement values leading up to the diagnosis (e.g. raised PSA values leading up to a diagnosis of prostate cancer).
3) Account for censoring.
4) Provide risk estimates for survival outcomes (diagnosis of cancer).

A model that can account for these four attributes is important in prostate cancer, where disease progression differs not only between patients but also within the same patient over time (440). Joint modelling can incorporate repeated biomarkers (PSA) alongside other parameters of interest. The theory underpinning longitudinal and time-to-event models is described below in Sections 7.4.1and 7.4.2, and how these two models are linked together to form a joint model is explained in Section 7.4.3.

7.4.1 JOINT MODELS: LONGITUDINAL SUBMODEL

Mixed effects models (439) are used to model repeat measurements from the same patient overtime and can manage if the measurements are not equally spaced or recorded at the same time. They assume measurements for the same patient are positively correlated whereas other statistical models such as a t-test or linear regression models assume that the observations are independent from one another. Mixed effect models are the current standard longitudinal submodel in joint modelling (441). They combine population-level effects (fixed effects) with subject-specific effects (random effects) to determine how measurements change over time (Equation 1). There are many extensions of the longitudinal submodel that can be used in joint modelling. Examples include linear mixed effect models for continuous outcomes, logistic mixed effects models for categorical outcomes with different options for covariances, variance functions and nested or crossed random effect designs, or generalised mixed-effects variants for non-Gaussian outcomes. All of these types of mixed modes can be used in joint modelling (442), but none of them, on their own, are able to handle event times or censoring.

Equation 1: Standard linear mixed effects model

$$y_i(t) = m_i(t) + \varepsilon_i(t)$$

$$m_i(t) = \chi_i^{\mathrm{T}}(t)\beta + \mathrm{Z}_i^{\mathrm{T}}(t)b_i$$

$$\varepsilon_i(t) \sim \mathcal{N}(0, \sigma^2)$$

Where:

$y_i(t)$ is the longitudinal outcome for patent i at time t.

$x_i(t)$ and β are the fixed effects

$z_i(t)$ and are the random effects and b_i are the subject-specific random effects

$\varepsilon_i(t)$ is the measurement error

7.4.2 JOINT MODELS: TIME-TO-EVENT SUBMODELS

The Cox proportional hazard model is commonly used as the time-to-event submodel of a joint model (443) (Equation 2). Cox models are semi-parametric and rely on the assumption of proportional hazards where the covariates have a constant impact on the hazard of the event over time. They also accommodate for right censored event times. Other models (442) that could be used as the time-to-event submodel of a joint model include fully parametric models (444), accelerated failure time models (445) and relative risk models (446). In all these models, including the Cox proportional hazards model, covariates are fixed at a certain time point and repeated measurements per patient are not accounted for.

Equation 2: Standard Cox proportional hazards model

$$h_i(t) = h_0(t)\ exp\ \{\gamma^{\mathrm{T}}\omega_i\}$$

Where:

$h_i(t)$ is the survival probability for patient i at specific time t

$h_0(t)$ is the baseline hazard

$\omega_i(t)$ are the covariates

γ are the log hazard ratios

7.4.2.1 Time varying Cox proportional hazards models

Therneau and Grambsch (447) extended the Cox model to include time varying covariates that update over a follow-up period. In this extension, time varying covariates are included as a piecewise constant process. The last observation for the patient is carried forward until the next measurement occurs. As seen in Figure 7.1, this is a step function. The circle illustrates that between time 0 and 1.8, the PSA trajectory is expected to be 2.4 which is likely an underestimation, but at 3.8 years it is an overestimation. This approach is only suitable for exogenous (external) variables, which change over time but are not influenced by the disease process or the event. For example, age increases over time and is associated with prostate cancer risk, but it is not affected by whether or not a patient develops prostate cancer. PSA is an endogenous variable because it both influences and is influenced by the disease process leading to prostate cancer. For instance, PSA levels rise as cancer progresses and so PSA shares the same biological mechanisms that drives the risk of prostate cancer. Modelling this as a time-varying covariate violates the independence assumption of the Cox model. Instead, joint modelling approaches estimate the underlying biomarker trajectory over time (depicted as the green curve in Figure 7.1), rather than assuming a stepwise pattern (the blue line in Figure 7.1.

Further challenges with using a time varying Cox model are that time-varying covariates in Cox models assume that covariates are measured without error, that values are not related to the event, and are not correlated to one another. Repeated biomarkers in electronic health records data, such as PSA, violate these assumptions as they are observed at irregular times with measurement errors. The Cox model assumes that the exact values of the explanatory variables are known for all the individuals who are at risk at each event time. Treating biomarkers as standard time-varying covariates in Cox models can bias effect estimates and attenuate predictive performance because Cox models do not account for measurement error or incorporate historical trajectories of the biomarker (448, 449).

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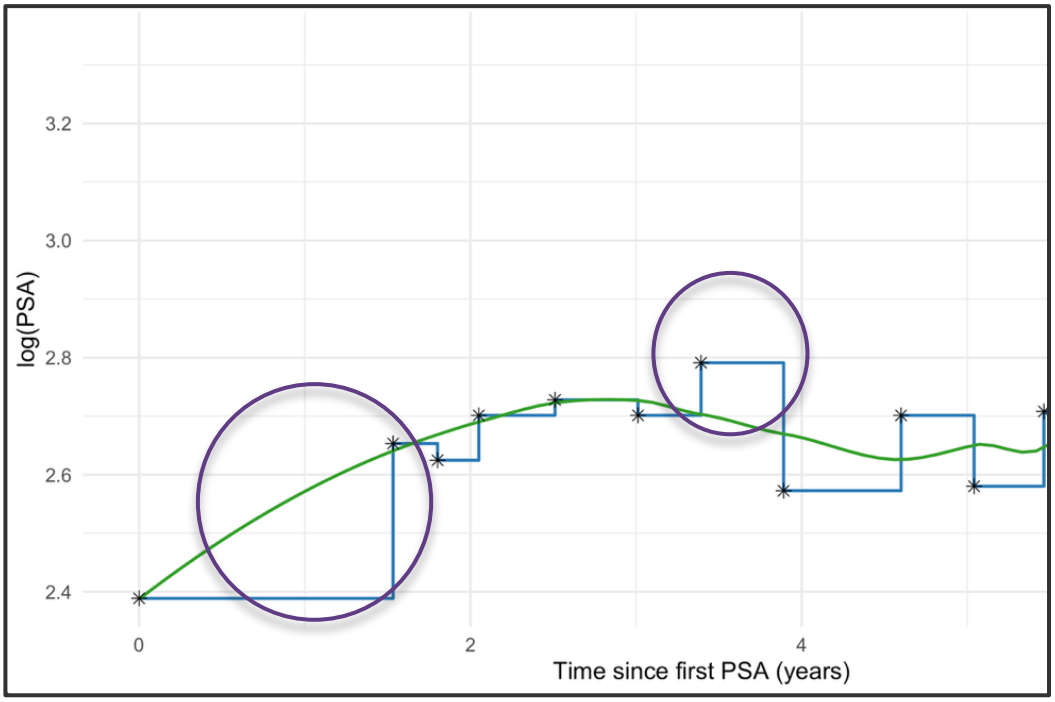
Figure 7.1: Log(PSA) trajectory for an example patient



*Caption: Illustration of an example patient's PSA results over time. * are the patient's individual PSA test results. The blue line represents the step function which is used from modelling this example patient's PSA trajectory over time in a time varying Cox proportional hazards model. The green line is the joint distribution that would be modelled by a joint model. The purple circles are examples of where the step function over or underestimates the patient's PSA trajectory.*

7.4.3 JOINT MODELS: LINKING LONGITUDINAL AND TIME-TO-EVENT MODELS

Joint models combine a longitudinal submodel with repeat measures data with a time-to-event submodel for the outcome (Equation 3). The two models are linked by patient-specific random effects that characterise the trajectory of the longitudinal repeated measures, and include them in the survival estimates (430). This described structure is a shared parameter model where the longitudinal predictors are modelled through a linear mixed model (or variants, described Section 7.4.1), and survival outcomes are modelled by the Cox model (or variants, described in Section 7.4.2). The association between the longitudinal and the survival processes is explained by the shared random effects. The patient level random effects represent the underlying state of disease, as well as act as the common source of correlation between different outcomes for an individual patient.

A key assumption of joint models is full conditional independence. In a shared-parameter framework, the random effects explain all interdependencies between the longitudinal and time-to-event processes. The repeated longitudinal measurements for each individual are correlated through their subject-specific random effects, while the longitudinal and survival submodels are linked through the shared random effects. Additionally, in joint models the baseline hazard needs to be assumed. There are two main approaches for this. The first is a more commonly understood frequentist framework (442) which uses a maximum likelihood approach as the standard estimation approach (450). A second is a less interpretable Bayesian approach that allows for a more flexible estimation (442) where the estimated parameters of the joint model are based on Markov chain Monte Carlo (MCMC) methods. There have been developments with other estimation methods (451-453), but a systematic review of 65 joint modelling studies found that over 90% of studies used either a frequentist or Bayesian approach (441).

Equation 3: Standard joint model

$$h_i\left(t \mid \mathcal{M}_i(t)\right) = h_0(t)exp\{\gamma^{\mathrm{T}}\omega_i + \alpha m_i(t)\}$$

$$y_i(t) = m_i(t) + \varepsilon_i(t)$$

$$m_i(t) = \chi_i^{\mathrm{T}}(t)\beta + \mathrm{Z}_i^{\mathrm{T}}(t)b_i$$

$$\mathcal{M}_i(t) = \{m_i(s), 0 \leq s < t\}$$

Where:

$h_i\left(t \mid \mathcal{M}_i(t)\right)$ is the hazard for patient i at time t, conditional on the longitudinal history $\mathcal{M}_i(t)$

$\mathcal{M}_i(t)$ is the observed longitudinal outcome history up to time t

α quantifies the association between the time varying covariate and the risk of an event

$m_i(t)$ is the latent error free trajectory from the mixed model

7.4.4 JOINT MODELS: DYNAMIC PREDICTIONS

Dynamic survival predictions are obtained by conditioning on a patient's biomarker history up to a given time t. For patient i in Equation 4, this represents the probability of surviving from time t to a future time u given that the patient i has survived event-free

until t, their observed biomarker trajectory, and the dataset on which the joint model was fitted. In practical terms this means that for an individual patient who has not had the event by the specific time of interest the model conditions on their survival up to that point. As additional PSA tests are conducted, the model updates that patient's predicted risk of prostate cancer at a future point based on their individual PSA testing results and the data used to fit the joint model. Below I describe a simple example of how dynamic predictions could work for two hypothetical patient scenarios. (Patient A and Patient B).

Patient A

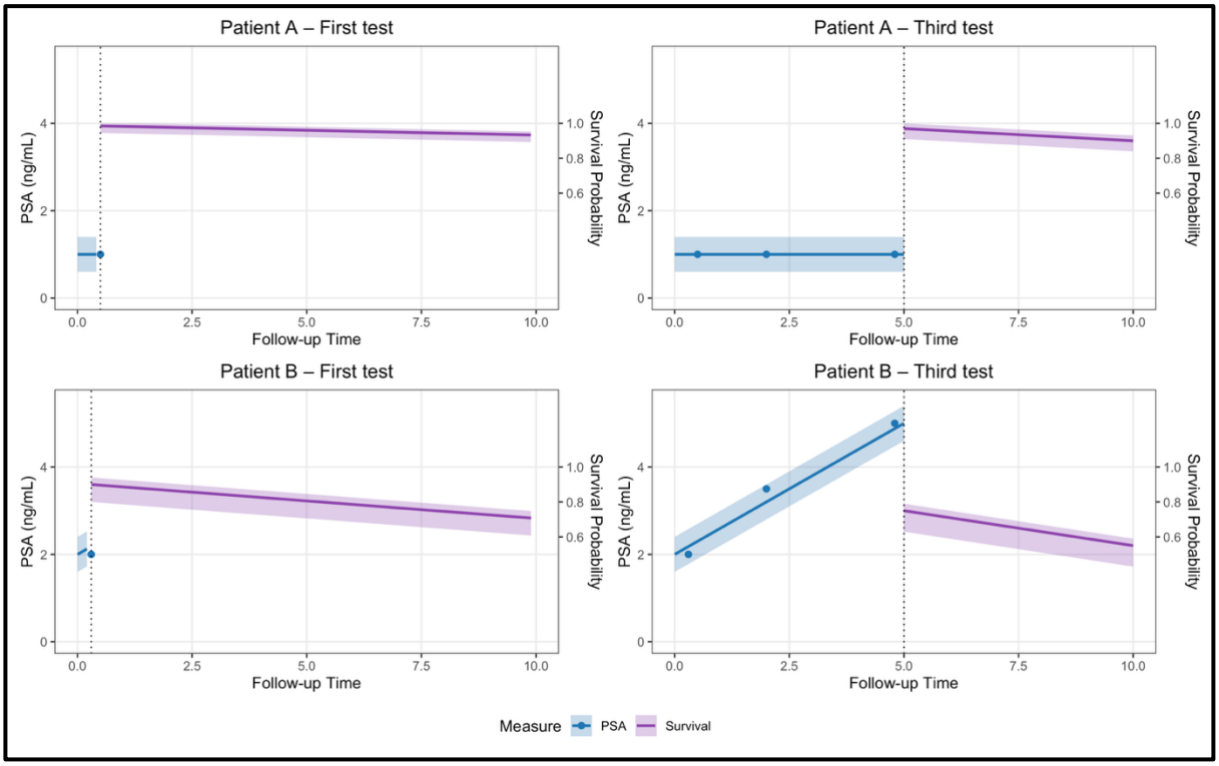
Patient A is a 55-year-old man who had three PSA tests in the last five years from the ages of 50 to 55. All PSA results were around 1.0 ng/mL. At year five, his predicted probability of remaining cancer-free in the next 10 is very high (e.g. 97%).

Patient B

Patient B is another 55-year-old man who also had three PSA tests in the last five years. His PSA results increased from 2.0 to 5.0 ng/mL. At year five, his predicted probability of remaining cancer-free to year 10 is lower (e.g. 75%).

Both patients are the same age and cancer free at year five, but their future risk is different because the model conditions on their PSA history. As each new test is added, predictions update so recommendations for retesting can adapt over time rather than relying on a single baseline measurement. Figure 7.2 illustrates how survival estimates change based on each patient's first PSA test value versus their third PSA test value. Future cancer risk can be predicted using any length of PSA history (e.g., one to four years) and for any chosen time horizon (e.g., five or ten years). This flexibility means the model can provide personalised risk estimates based on the data available for each patient.

Figure 7.2: Illustrative example of Patient A and B



Equation 4: Dynamic Survival Prediction

$$y_j(t) = \{y_j(s), 0 \leq s \leq t\}$$

$$\pi_j(u|t) = Pr\{T_j^* \geq u \mid T_i^* > t, y_j(t), \mathcal{D}_n\}$$

Where:

$u > t$ defines the future prediction horizon

T_j^* is the true event time (prostate cancer diagnosis)

$\mathcal{D}_n$ is the dataset the joint model was fitted on

$y_j(t)$ is the patient's biomarker history

7.5 Methods

In the methods section, I apply the theory of joint modelling described above to the specific model development conducted in this chapter. All results are reported according to the Transparent Reporting of a multivariable prediction model for Individual

Prognosis or Diagnosis (TRIPOD) guidelines (454). Statistical significance was defined as a two-sided *p*-value < 0.001.

7.5.1 DATA

The dataset and variables (outcomes and predictors) used were previously described in Chapter 4. Data from the BLOTTED study (455) were used to both develop and internally validate the predictions from the joint model. Development and validation datasets are described in Figure 7.6 and Table 7.2.

7.5.2 STUDY POPULATION AND DESIGN

The study population in this chapter is identical to the previous chapter except that instead of only using each patient's baseline (first) PSA test, I used all PSA tests that occurred for each patient between 2000 and 2018 or until they died, left the practice, or had a prostate cancer diagnosis. Eligible patients were those who had their first PSA test ever in primary care on record between 2000-01-01 and 2018-12-31 and who were between the ages of 40 and 90 at their first test. I originally chose to include patients who had at least two PSA tests, but due to challenges with the stability of the joint model, patients were required to have at least three PSA tests during follow-up. This is further discussion in Section 7.7.3.

7.5.3 OUTCOME

The main outcome was a diagnosis of overall prostate cancer. This included both those with low-risk disease and clinically significant disease.

7.5.4 PREDICTORS

Age and PSA values were chosen as the only predictors. This decision was made to test the feasibility of joint modelling as a method. The computational power required for only two predictors was intensive on its own. Age and PSA were the top two factors associated with a prostate cancer diagnosis found in the results of the Cox model from Chapter 6 Figure 6.1. Although family history of prostate cancer is also important, it is poorly recorded in primary care records and was. not used in tis chapter.

7.5.5 MISSING DATA

There was no missing data relevant in this chapter. To be included, all patients must have had at least three PSA test results. In CPRD Aurum, year of birth is available for all patients. An additional benefit of joint models is that patients do not need to have measurements at the same intervals. The joint model (green line in Figure 7.1) can predict the biomarker if the true value is missing at the specific timepoint. Missing PSA data is therefore handled automatically by the joint model under the assumption that it is missing at random and may depend on previous observed responses (437).

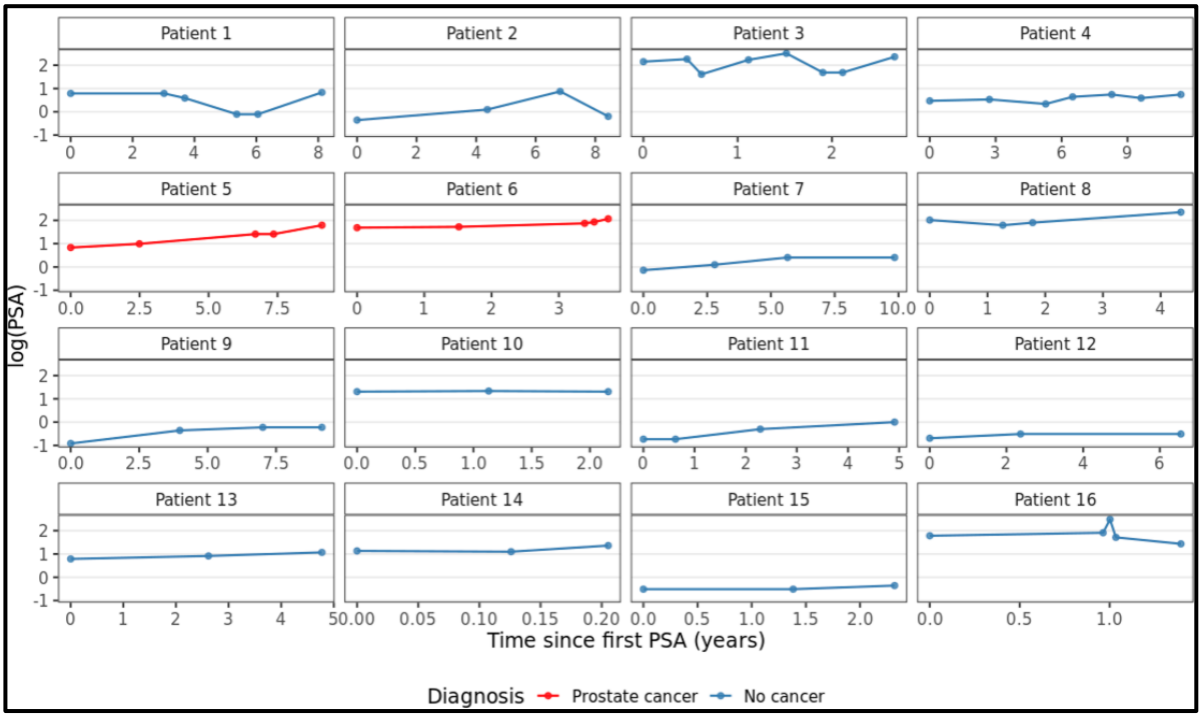
7.5.6 MODEL DEVELOPMENT

I developed a multivariate joint model of longitudinal and time-to-event data. I used the joint modelling package JMbayes2 version 0.5.7 in R version 4.5.1 (440, 456). I did this after attending a training course on joint modelling run by Professor Dimitris Rizopoulos, who developed the package. JMbayes2 estimates parameters of the joint model using Markov chain Monte Carlo (MCMC) methods under a Bayesian framework.

7.5.6.1 Model development: Longitudinal submodel

I used a linear mixed effects model as the longitudinal submodel. The lme function of the nlme package 3.1.168 in R was used to derive the linear mixed effects model that modelled trends in individual patient's log(PSA) values over time. Log(PSA) was the outcome measure and was modelled as a continuous variable. Log(PSA) was normally distributed based on Figure 4.5 presented in Chapter 4. PSA trajectories were not linear for every patient. Figure 7.3 depicts PSA trajectories for 16 random patients. To handle the non-linearity of PSA, I extended the mixed effects model by including natural cubic splines.

Figure 7.3: Individual PSA trajectories for 16 random patients with or without prostate cancer



Caption: Patients with ID 5 and 6 with red trajectories were diagnosed with prostate cancer during follow-up. All other patients did not have a cancer diagnosis during follow-up. Patients presented with different numbers of PSA tests. Patient 4 is an example of a patient with seven tests over ten years. Patient 10 is an example of a patient with three tests over two years.

7.5.6.1.1 Natural Cubic Splines

Natural cubic splines with two degrees of freedom were used for the effect of time in both the fixed and random effects of the linear mixed effect model. Boundary knots were set to the range of follow up times between 0 and 18.8 which was the maximum follow-up time from first PSA test. To determine whether to include splines in the linear mixed effect model, I ran models with no splines, two splines and three splines. These three models were compared using Akaike Information Criterion (AIC), Bayesian Information Criterion (BIC) and LogLik statistics, presented in Table 7.1. Models were run for a random selection of 30,000 patients, 60,000 patients and the development cohort of 80,000 patients. Models with two natural cubic splines for time consistently achieved lower AIC and BIC values. Models with three splines slightly reduced the residual SD but at the cost of worse AIC and BIC values. The standard deviation of the residuals and the effect of age were stable across within test sets with splines and across test sets.

Table 7.1: Model fit statistics for longitudinal sub-models by spline specification and sample size

Dataset	Model	Number of distinct patients	Number of PSA tests	AIC	BIC	logLik	Residual SD	Age effect (β, p)
Test set 1 (Random sample)	No spline	30,000	125,552	274,866	274,934	-137,426	0.484	0.036, p<0.001
	2-spline knots	30,000	125,552	273,607	273,685	-136,796	0.460	0.036, p<0.001
	3-spline knots	30,000	125,552	274,903	275,000	-137,441	0.451	0.036, p<0.001
Test set 2 (Random sample)	No spline	60,000	250,849	558,100	558,173	-279,043	0.497	0.037, p<0.001
	2-spline knots	60,000	250,849	555,886	555,969	-277,935	0.474	0.037, p<0.001
	3-spline knots	60,000	250,849	557,557	557,662	-278,769	0.464	0.037, p<0.001
Test set 3 (Development cohort)	No spline	80,000	457,345	969,539	969,616	-484,763	0.497	0.0367 p<0.001
	2-spline knots	80,000	457,345	962,864	962,952	-481,424	0.472	0.038, p<0.001
	3-spline knots	80,000	457,345	963,171	963,282	-481,576	0.459	0.038, p<0.001

7.5.6.1.2 Fixed and Random Effects

The fitted linear mixed-effects model accounted for both population-level effects, fixed effects, and patient-level random effects (Equation 5). Fixed effects included age at first PSA test and natural cubic splines with two degrees of freedom for time since first PSA test. Random effects included a random intercept, and for each patient, a spline term with 2 degrees of freedom spline terms for time since first PSA. Following discussions with Professor Dimitris Rizopoulos, a diagonal covariance structure was used (pdDiag()), so the random intercept and spline terms were estimated independently to improve model convergence.

Equation 5: Fitted linear mixed effects model

$$\log(PSA_{ij}) = m_i(t_{ij}) + \varepsilon_{ij}$$

$$m_i(t_{ij}) = \beta_0 + \beta_1 Age_i + \beta_2 ns_1(t_{ij}) + \beta ns_2(t_{ij})$$

$$+ b_{0i} + b_{1i} ns_1(t_{ij}) + b_{2i} ns_2(t_{ij})$$

$$\varepsilon_i(t) \sim \mathcal{N}(0, \sigma^2)$$

Where:

$\log(PSA_{ij})$ is the log transformed PSA value for patient i at visit j

Age_i is the patients age at their first PSA test

$ns_1(t_{ij})$ and $ns_2(t_{ij})$ are the two natural splines for time at since first PSA test (knots at 0 and 18.8 years)

b_{0i} b_{1i} and b_{2i} are the patient specific random effects and random spline terms

ε_{ij} is the residual error

7.5.6.2 Model development: time to event sub model

The coxph () function from the survival package version 3.8.3 in R was used to fit a Cox proportional hazards model. It estimated the time from first PSA to prostate cancer diagnosis and adjusted for age at first PSA test (Equation 6). Patients without a prostate cancer diagnosis were censored at the earliest of the date of death, deregistration with the practice, or end of the study period.

The proportional hazards assumption was assessed using Schoenfeld residuals. Age at first PSA violated the assumption as the risk of cancer increases by age (p <0.001). However, inspection of the scaled Schoenfeld residuals plot (Figure 7.4) indicated that the estimated effect of age remained stable up to 15 years of follow-up. After this the curve trended upwards, likely due to limited follow up time available for all patients. Given the large sample size of 80,000 patients, visual evaluation of Schoenfeld residuals, and the limited number of patients contributing data beyond 15 years, I assumed that the proportional hazards violation was unlikely to bias the results.

Equation 6: Fitted Cox proportional hazards model

$$h_i(t) = h_0(t)\ exp\ \{y_1 Age_i\}$$

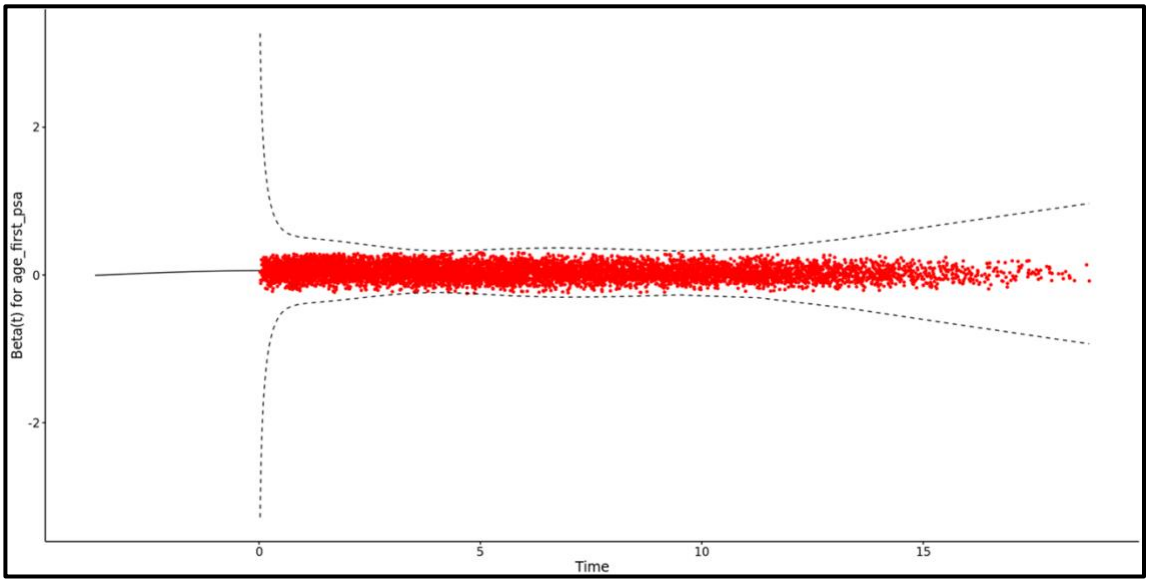
Where:

$h_i(t)$ is the hazard of prostate cancer for patient i at time t

$h_0(t)$ is the baseline hazard function

Age_i is patient $i's$ age at their first PSA test

Figure 7.4: Schoenfeld Residuals

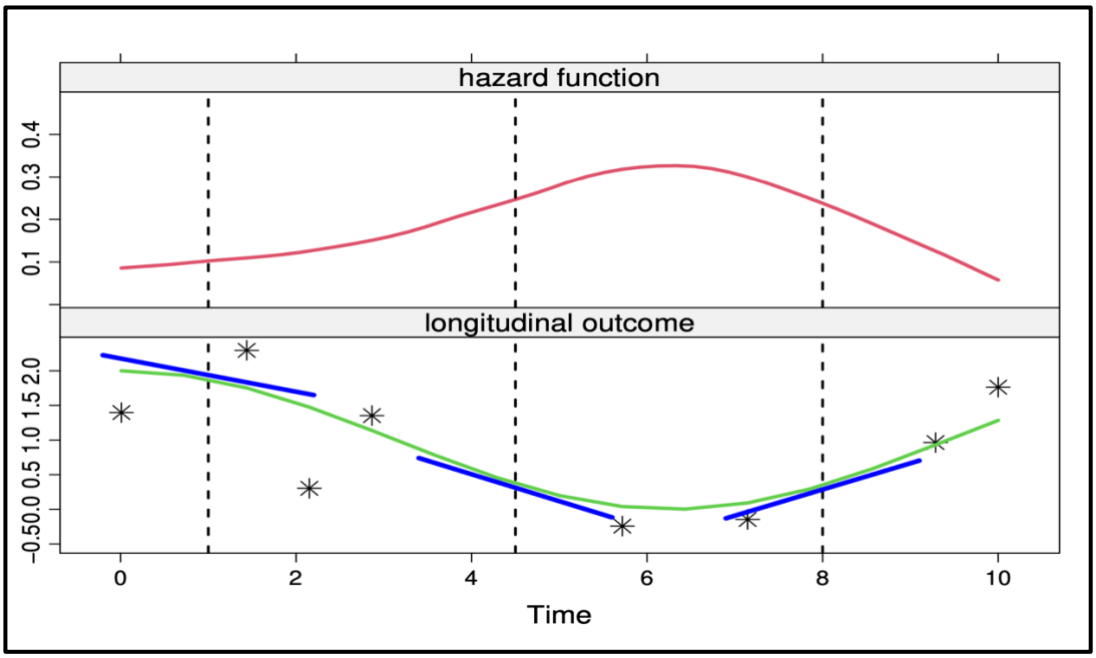


7.5.6.3 Model development: Joint model

Joint models were fitted using the R package JMbayes2 (R version 4.5.1 and JMbayes2 version 0.5.7). The joint model (Equation 7) combined both the linear mixed effects model (Equation 5) and the Cox proportional hazard model (Equation 6) by shared random effects.

I extended the standardised joint model (Equation 3) by including the slope functional form which incorporated the rate of change of the true PSA longitudinal trajectory. This is important to include when the direction and strength of the trend of the biomarker in question (PSA) is as informative as its level at a particular time point (457). The addition of slope in the joint model is illustrated by Equation 7 and Figure 7.5. It allows for each patient to have their own intercept of the longitudinal outcome, and their own slope, making it possible for trajectories to differ in both level and trend of the longitudinal outcome.

Figure 7.5: Visual of the hazard function, biomarker value, and slope in a joint model



Caption: This figure was presented in Joint Models for Longitudinal and Time-to-Event Data Course: August 18-22, 2025 Rotterdam. Available from: https://www.drizopoulos.com/

Equation 7: Fitted joint model

$$h_i\big(t \mid \mathcal{M}_i(t)\big) = h_0(t)exp\{\gamma_{age}Age_i + \alpha_1 m_i(t) + \alpha_2 m_i'(t)\}$$

Where:

Age_i is the patient's age at first PSA test

$m_i(t)$ is the log(PSA) trajectory

$m_i'(t)$ is the slope

γ_{age} is the log hazard ratio for age

α_1 and α_2 are the association parameters for PSA and slope

7.5.6.4 Model Development: Dynamic predictions using a joint model

Dynamic predictions were determined using the predict() function within the JMbayes2 package. The predictions estimate each patient's cumulative risk of a prostate cancer diagnosis at specified future times, conditional on their PSA history up to the time specified. The argument process = "event" ensures that predictions are for the survival (event) outcome rather than the longitudinal process. The times = seq() argument specifies the future time points for which predictions are made, defining how far into the future the model estimates risk based on each patient's available PSA history. Predictions were generated at equally spaced time points within the follow-up period. In addition to predicting an individual patient's cumulative risk of cancer, JMbayes2 can also predict longitudinal trajectories over time, although this was not used in this thesis.

7.5.6.5 Model development: Convergence

Convergence of the model was evaluated by inspecting trace plots, which are time-series plots showing sampled values of model parameters across successive Markov Chain Monte Carlo (MCMC) iterations. This was because JMbayes2 package is for joint modelling under a Bayesian framework. I ensured that the Gelman-Rubin convergence diagnostic $\widehat{R}$, or Rhat scores were ≤ 1.1 (458). The Rhat score compares the variance between multiple MCMC chains to the variance within each chain. Values greater than 1 indicate lack of convergence, while values close to ≤ 1.1 suggest there was adequate convergence (459).

7.5.6.6 Model development: Challenges

Model convergence, slope stability, and computational memory limitations were all significant challenges to overcome during model development.

Rhat scores were used as the main indicator of model convergence. I began running joint models on two different cohorts of 30,000 individuals and one cohort of 80,000. After three attempts on these different cohorts of patients, effect estimates for age and log(PSA) value were continuously stable. With effect sizes remaining between -0.0260 and -0.0163 for age at first PSA and between 1.3027 and 1.4583 for log(PSA); with Rhat scores all less than 1.06. Results of these models can be found in Appendix 5.

While age at first PSA test and log(PSA) were both stable, the slope in each model (using different sample sizes) had varying effect sizes from 0.1 to 1.6 (Appendix 5). The Rhat scores were > 1.1, and occasionally the estimated JMbayes2 P values for slope were not significant (p > 0.001). The default number of chains and iterations in JMbayes2 is three chains, 3500 iterations per chain and 500 burn-in per chain. To reduce the Rhat scores in the models on 30,000 patients, I increased the number of iterations and chains. I increased the number of iterations to 8500 and the burn-in to 3500 based on the tutorial given by Dimitris Rizopolous. This reduced Rhat scores to below 1.1 but, it doubled the time for the model to run (over 8 hours), and the effect of the slope remained unstable.

To overcome the varied effects of the slope, I ran the joint model on a larger set of patients. This resulted in computational memory challenges. After accessing a separate R Studio server with 500 GB of RAM, I was able to develop the joint models on a selection of 80,000 patients. This was the maximum number of patients possible with the computational power available. The slopes in the models converged (Rhat < 1.1) and they were significant (*p <0.001*). However, the estimate of the effect of the slope was still varied due to the fact that many patients had limited longitudinal records. I started off developing the joint model on patients who had at least two PSA tests. Once I limited the cohort to patients who had a minimum of three PSA tests, the models converged and the

slopes were stable and significant. The results of this joint model are presented in this chapter.

7.5.7 VALIDATION DATASETS

Validation of prediction models is important as poorly developed models could be harmful or exacerbate health care outcomes (460). Validation of the models should ideally be carried out in a representative population who will be benefiting from the model. Splitting the data at the time of development should be avoided (460). Validation techniques include the following: random sample splitting, k-fold cross validation, bootstrapping, internal-external cross validation, external validation, temporal validation and spatial validation. Although bootstrapping or k-fold validation are the gold standard techniques for internal validation, they require high computational capacity. These techniques are favoured as they use all the available data. For the joint model development in this thesis, I did not have sufficient computational memory to fit the joint model on the entire dataset. When datasets are so large and include many geographical regions, like in this chapter, spatial validation is a pragmatic comprise (460).

Therefore, spatial validation was used, similar to other studies (461). This validation method splits the data into development and validation datasets by region (462). I used the South of England to develop the joint model, which included the following regions: South East, South West, East of England, London and East Midlands. Validation was done on patients in the North East, North West, West Midlands and Yorkshire and The Humber.

7.5.8 MODEL PERFORMANCE

Discrimination and calibration were used to determine model performance. Discrimination is a measure of how well the model separates patients who do and do not have the outcome (463). Calibration measures the agreement between observed and predicted outcomes. Discrimination was assessed using the Area Under the Curve (AUC). AUCs were derived for different groups of cancer trends and future cancer predictions. The trend was calculated based on data from 1, 2, 3, and 5 years, and future

predictions were made for 2, 4, and 10 years for all trend calculations. Calibration was evaluated through calibration plots at time horizons for three years of history (trend calculation) and two years of cancer risk (prediction).

The overall performance of the model was assessed using the Brier score. A lower Brier score means the prediction was more accurate. It summarises the difference between the observed and predicted outcomes, accounting for censoring using model-based weights in JMbayes2. These were calculated based on the best and worst performing AUCs.

7.5.9 THRESHOLDS FOR RETESTING INTERVALS ESTIMATION

In this chapter, to illustrate the feasibility of translating the outcomes of joint models into personalised retesting intervals, I applied a predicted risk threshold of 3%. This was chosen to be consistent with the NICE NG12 suspected cancer referral guidelines (107). NICE recommends referral to secondary care if the patient has a positive predictive value of over 3%.

7.5.10 SENSITIVITY ANALYSIS

A sensitivity analysis was run to determine what combination of trend and future risk best predicted results in ten years.

7.6 RESULTS

A total of 409,674 patients were eligible for inclusion. Due to computational resource constraints, 80,000 patients were randomly sampled for model development and 80,000 for internal validation (Figure 7.6). Development cohort was patients from the South East, South West, East of England, London and East Midlands. The validation cohort included patients from the North East, North West, West Midlands and Yorkshire and The Humber. In the development cohort, 7,502 (9.4%) were diagnosed with prostate cancer during follow-up compared with 7,133 (8.9%) in the validation cohort. The proportion with cancer is slightly higher than in Chapter 6, reflecting that repeated PSA testing may occur in patients with a higher underlying risk or with persistent concern about cancer. Given

the limited specificity of PSA, greater testing increases the probability of a cancer diagnosis. Patient characteristics are summarised in Table 7.2, and PSA test distributions are described in Table 7.3.

Figure 7.6: Participant flow diagram

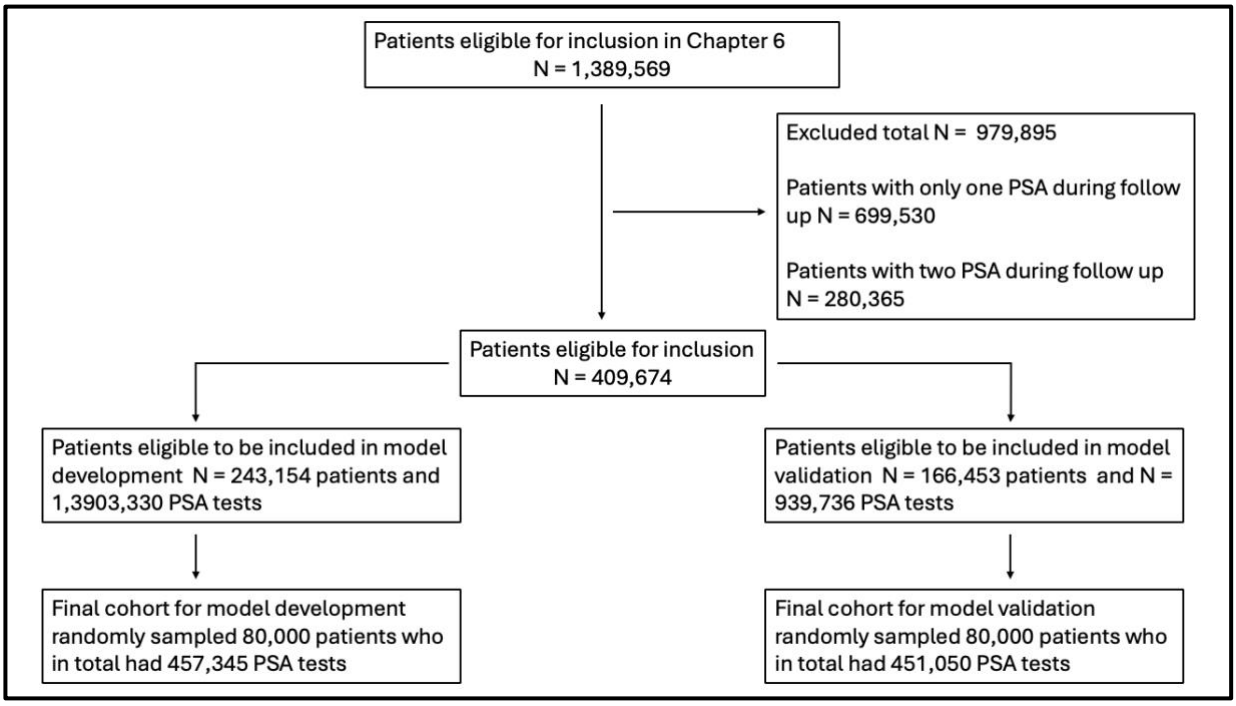


Table 7.2: Patient characteristics of the development and validation cohorts

	Development Cohort			Validation Cohort		
	Prostate cancer	No prostate cancer	Overall	Prostate cancer	No prostate cancer	Overall
Number of patients	7,502	72,498	80,000	7133	72,867	80,000
Median age at first PSA test (IQR), years	66.1 (59.6 to 73.2)	63.4 (56.3 to 71.1)	63.7 (56.6 to 71.3)	66.0 (60.0 to 72.5)	63.7 (56.7 to 70.9)	63.9 (57.0 to 71.0)
Median PSA value first test	4.1 (2.2 to 7.3)	1.4 (0.7 to 3.2)	1.6 (0.8 to 3.7)	4.2 (2.3 to 7.4)	1.4 (0.8 to 3.4)	1.6 (0.8 to 3.8)
Number of PSA tests per patient	5 (3 to 7)	4 (3 to 7)	4 (3 to 7)	4 (3 to 7)	4 (3 to 6)	4 (3 to 6)
Median follow-up from first PSA test (IQR), years	5.6 (2.8 to 9.5)	9.8 (6.4 to 13.2)	9.5 (6.0 to 13.0)	5.6 (2.6 to 9.1)	9.9 (6.6 to 13.3)	9.6 (6.2 to 13.1)

Table 7.3 Summary of PSA tests in the development and validation cohorts

	Development Cohort			Validation Cohort		
	Prostate cancer	No prostate cancer	Overall	Prostate cancer	No prostate cancer	Overall
Number of tests	45,400	411,945	457,345	42,382	408,668	451,050
Median PSA (IQR), ng/mL	5.9 (3.5 to 10.1)	2.0 (0.9 to 4.6)	2.3 (1.0 to 5.2)	6.0 (3.7 to 9.8)	2.0 (0.9 to 4.6)	2.3 (1.0 to 5.2)

7.6.1 LONGITUDINAL MODEL RESULTS

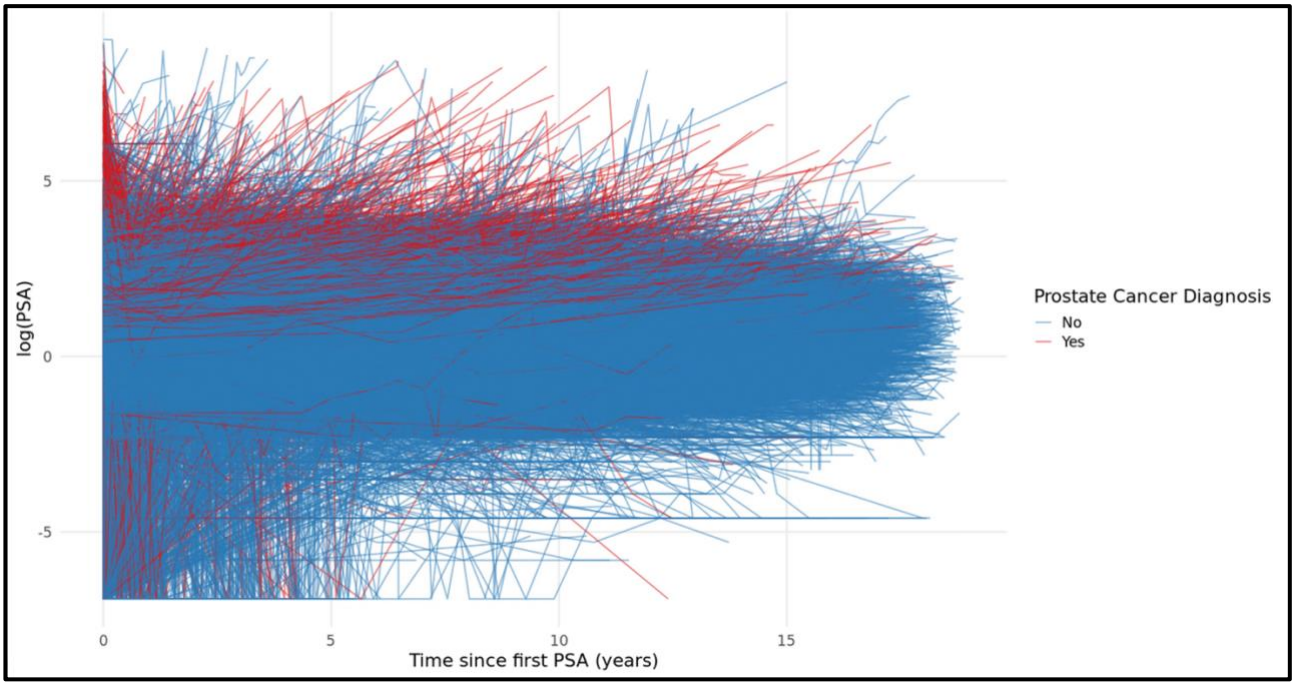
The results from the longitudinal mixed-effects model with two spline terms are presented in Table 7.4. The model captured patient-specific PSA trajectories over time. Nonlinearity in PSA (log(PSA)) was flexibly modelled using natural splines. Both spline terms were positive (0.62 and 0.53), indicating increasing PSA levels over time. Older age at first PSA was associated with higher baseline PSA values and each additional year of age increased the log(PSA) by 0.038 per year (95C% 0.037 to 0.038 p<0.001). For example, the model predicts that a patient at age 40 would have a log(PSA) of -0.343 (about 0.7 ng/mL). This is consistent with the observed median PSA at that age.

There was variation between patients when considering both baseline PSA levels and individual patient trajectories. Random-effects standard deviation for the intercept was 0.992, and spline coefficients were 1.403 and 1.530. Figure 7.7 illustrates the PSA trajectories of all 80,000 individuals included in the development cohort.

Table 7.4: Linear mixed effects model

Term	Estimate	Std. Error	95% CI	DF	p value
Intercept	-1.899	0.023	-1.949 to -1.859	377,343	<0.001
Spline (time) component 1	0.623	0.007	0.609 to 0.637	377,343	<0.001
Spline (time) component 2	0.534	0.012	0.510 to 0.558	377,343	<0.001
Age at first PSA (per year)	0.038	0.000	0.037 to 0.038	79,998	<0.001

Figure 7.7: PSA trajectories for 80,000 patients in the development cohort (log scale)



Caption: Plot for the patients in the validation cohort is included in the Appendix 5.

7.6.2 TIME-TO-EVENT MODEL RESULTS

In the univariate Cox proportional hazards model, age at first PSA was associated with the risk of prostate cancer diagnosis (Table 7.5). Each additional year of age increased the hazard of a cancer diagnosis by 3.9% HR 1.039 (95%CI 1.037 to 1.042, $p < 0.001$).

The size of the age coefficient (0.039) is similar to that from the longitudinal submodel (0.038), but the interpretation is different. In the longitudinal model illustrated in Table 7.6, age was associated with higher baseline PSA values, whereas in the Cox model described in Table 7.5, age was associated with increased risk of prostate cancer over time. This univariate Cox model formed the time-to-event submodel, which was subsequently combined with the longitudinal PSA trajectory in the joint model.

Table 7.5: Cox proportional hazards model

	β (Coef)	SE	HR (expβ)	95% CI	P value
Age at first PSA	0.039	0.001	1.039	1.037 to 1.042	<0.001

7.6.3 JOINT MODEL RESULTS

The results from the joint model are presented in Table 7.6 and Table 7.7. Results from joint models are interpreted in the same way as the interpretations for the individual submodels. The joint model linked patient-level PSA trajectories with time to prostate cancer diagnosis. The associations between age and PSA levels were broadly consistent with the separate longitudinal and Cox models presented above.

The longitudinal submodel confirmed rising PSA levels with age and time as both spline components were positive (Table 7.6). Age at first PSA was positively associated with higher PSA levels. In the survival submodel, higher PSA values and positive PSA slope were both predictive of prostate cancer risk (Table 7.7). A one-unit increase in log(PSA) was associated with a hazard ratio (HR) of 3.74 (95% Crl: 3.65 to 3.84), while the slope of PSA (rate of change in log (PSA)) was associated with HR 3.32 (2.54 to 4.34). Increasing age at first PSA was associated with a lower risk of prostate cancer. This contrasts with the positive age effect observed in the linear mixed effects model and the Cox model. This is because once PSA level and trajectory are included, higher age is associated with lower cancer risk. Older patients tend to have higher PSA values, so for the same PSA level and slope, a younger patient is more likely to be diagnosed with prostate cancer.

Table 7.6: Longitudinal submodel results

Term	Mean	SD	2.5%*	97.5%*	Rhat**
Intercept	-1.9043	0.0233	-1.9495	-1.8587	0.9999
Spline (time) component 1	0.6477	0.0075	0.6328	0.6618	1.0015
Spline (time) component 2	0.5604	0.0126	0.5349	0.5851	1.0124
Age at first PSA	0.0378	0.0004	0.0371	0.0385	1.0004
Residual SD (σ)	0.4719	0.0006	0.4707	0.4731	1.0056

** Ranges obtained from the posterior distribution of the parameter (MCMC Bayesian Methods). Roughly equivalent to a 95% Confidence Interval (Crl).*

*** Rhat (Gelman–Rubin diagnostic) compares variance between and within MCMC chains; values ≤ 1.1 indicate adequate convergence.*

Table 7.7: Survival submodel results

Term	Mean	SD	2.5%*	97.5%*	JMbayes2 estimated P value	Rhat**	HR (exp[Mean])
Age at first PSA (per year)	-0.0225	0.0018	-0.0259	-0.0191	<0.001	1.0011	0.98
Value log (PSA)	1.3192	0.0129	1.2947	1.3447	<0.001	1.0079	3.74
Slope: d/dt log-PSA	1.1986	0.1355	0.9335	1.4678	<0.001	1.0066	3.32

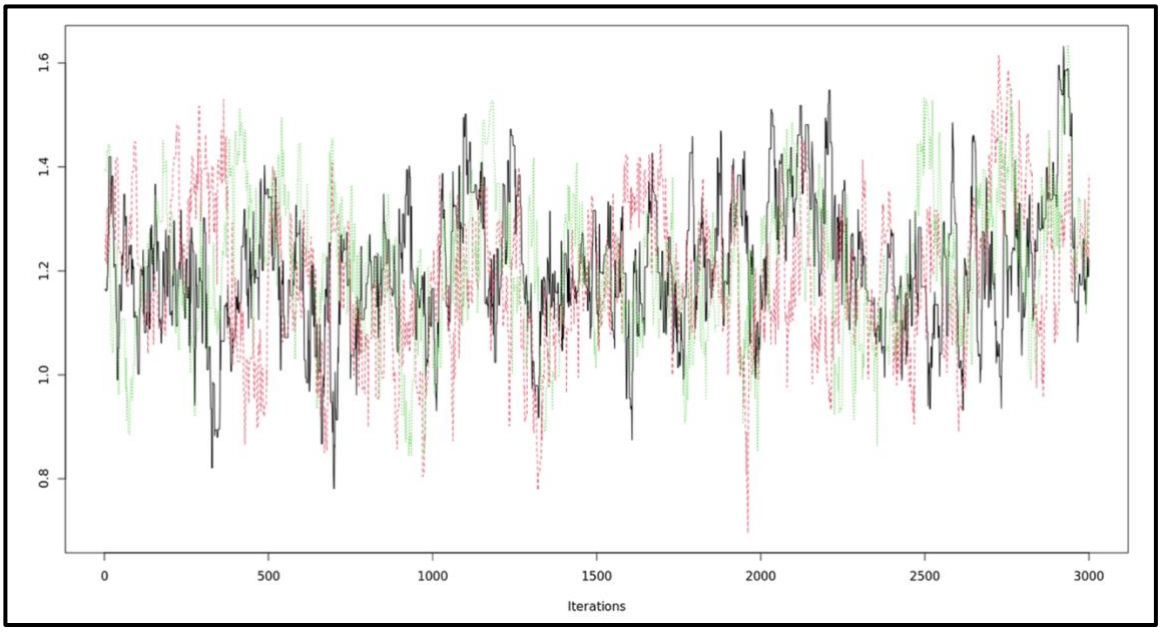
** Ranges obtained from the posterior distribution of the parameter (MCMC Bayesian Methods). Roughly equivalent to a 95% Confidence Interval (Crl).*

*** Rhat (Gelman–Rubin diagnostic) compares variance between and within MCMC chains; values ≤ 1.1 indicate adequate convergence.*

7.6.4 Model Convergence

The model converged well as shown by the trace plot depicted in Figure 7.8. There are multiple chains showing overlapping lines. This is further confirmed by the Rhat scores, which were all below 1.01 (Table 7.6 and Table 7.7).

Figure 7.8: Joint model trace plot



Caption: Overlapping lines indicate the model converged well.

7.6.5 Model Performance

All model performance scores were calculated using the validation cohort of 80,000 patients from the North of England. Since the joint model is dynamic, predictions are updated at each specified time point, based on all longitudinal PSA measurements observed up to that point for patients who are still alive at the time point. Consequently, the model performance varies depending on how much longitudinal history is incorporated and how far into the future cancer risk predictions are made.

7.6.5.1 Discrimination

Discrimination was best for short-term predictions (Table 7.8). AUCs ranged from 0.84 to 0.86 for predictions of cancer in the subsequent two years based on a one-year or two-year trend of PSA data. Estimates based on a two-year trend gave a strong prediction of cancer in the following four years with an AUC of 0.83. Similarly, a three-year trend gave good discrimination with the prediction of either two or four years of cancer into the future, showing an AUC of 0.80.

Performance declined as the predictions became further into the future. Longer than 10-year predictions had AUCs between 0.77 to 0.79. Including longer PSA histories did not improve accuracy. Predictions based on longer history of PSA data had a more limited ability to discriminate between those with cancer and without cancer. These results reflect the dynamic nature of the joint model (different discrimination abilities at different times). There was a strong short-term discrimination but weaker performance when extrapolated further into the future.

Table 7.8 Discrimination performance of the joint model by PSA history length and prediction horizon

Years of PSA history	Cancer risk prediction horizon*	Final prediction time**	Patients at risk	AUC
1	2	3	42,086	0.86
1	4	5	42,086	0.83
1	10	11	42,086	0.79
2	2	4	28,742	0.84

Years of PSA history	Cancer risk prediction horizon*	Final prediction time**	Patients at risk	AUC
2	4	6	28,742	0.83
2	10	12	28,742	0.78
3	2	5	20,146	0.80
3	4	7	20,146	0.80
3	10	13	20,146	0.77
5	2	7	9,341	0.77
5	4	9	9,341	0.78
5	10	15	9,341	0.77

** Prediction horizon refers to the number of years into the future for which cancer risk was predicted, conditional on surviving the period of PSA history.*

*** A patient with 5 years of PSA history contributes PSA data up to year 5 (years of PSA history) The model then predicts their risk of prostate cancer over the next 2 years (cancer risk prediction horizon = 2). Therefore, the model is predicting risk between years 5 and 7 from the patient first PSA test.*

7.6.5.2 Calibration

Figure 7.9 illustrates the calibration performance of the joint model using both PSA testing history of 1 or 5 years to predict 2, 4 and 10-year prostate cancer risk. The red line is the observed probability of prostate cancer against the model-predicted probability. The dashed diagonal line indicates perfect calibration. The solid grey line is the density curve which indicates that the majority of predictions fall below 0.2. This reflects the predicted risk in this population.

The model using 1 year of PSA testing history with 2 and 4 years prediction of future cancer was well-calibrated for very low-risk patients with a predicted risk less than 0.05. Between a predicted risk of 0.05 and 0.15 there was a slight underestimation where the observed probabilities were slightly higher than the predicted risk probabilities. This underestimation stabilised as predicted risk increased to 0.2.

The model with 1 year of PSA testing history and 10 years of future cancer risk slightly overestimated risk when predicted risk was less than 0.1 and very slightly underestimated risk between 0.1 to 0.3. This model was generally well calibrated but overpredicted risk when predicted risk was greater than 0.3.

The model using 5 years of PSA testing history with 2 and 4 years prediction of future cancer underestimated the risk for low-risk patients as the observed probabilities were higher than the predicted probabilities.

The model using 5 years of PSA testing history to predict cancer 10 years into the future was better calibrated for low-risk patients with a predicted risk between 0 and 0.1. For patients with a predicted risk between 0.15 to 0.3 the model underestimated risk and then overpredicted when predicted risk was greater than 0.3

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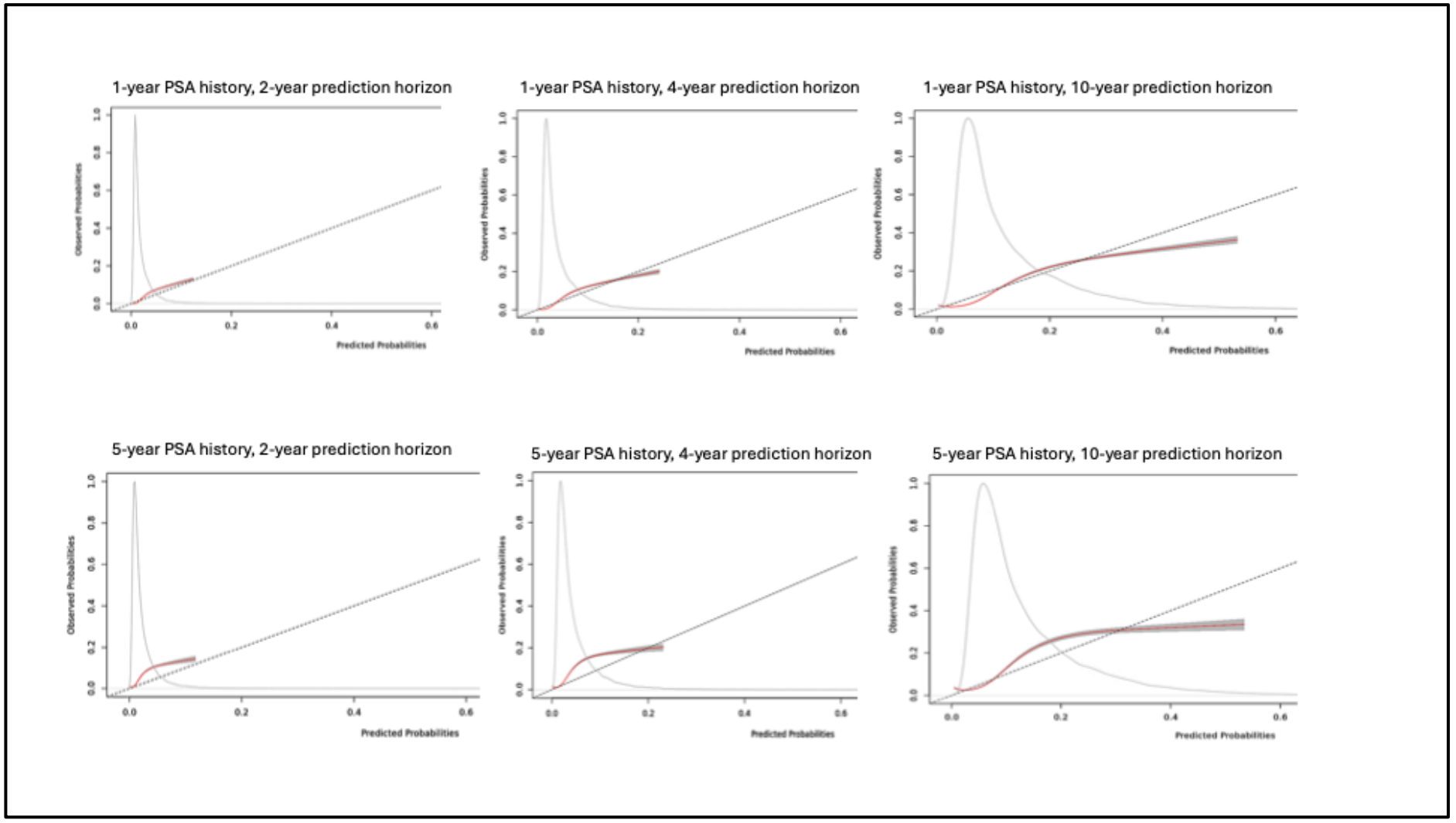
Figure 7.9 Series of calibration plots for 1 and 5 years of PSA history and 2,4, and 10 years prediction horizon



7.6.5.3 Brier Scores

Brier scores combine discrimination and calibration into a single accuracy measure increased with prediction horizon. At three years the Brier score was 0.0187 and this rose to 0.0334 at five years and 0.0809 at 11 years (Table 7.9). When using PSA testing history at five years, the short-term Brier score at seven years was 0.0335 with 2,035 events and 23,842 censored observations in this interval (five to seven years). These results indicate the model is well-calibrated and accurate in the short term but loses precision when predicting events further into the future similar to the AUC results.

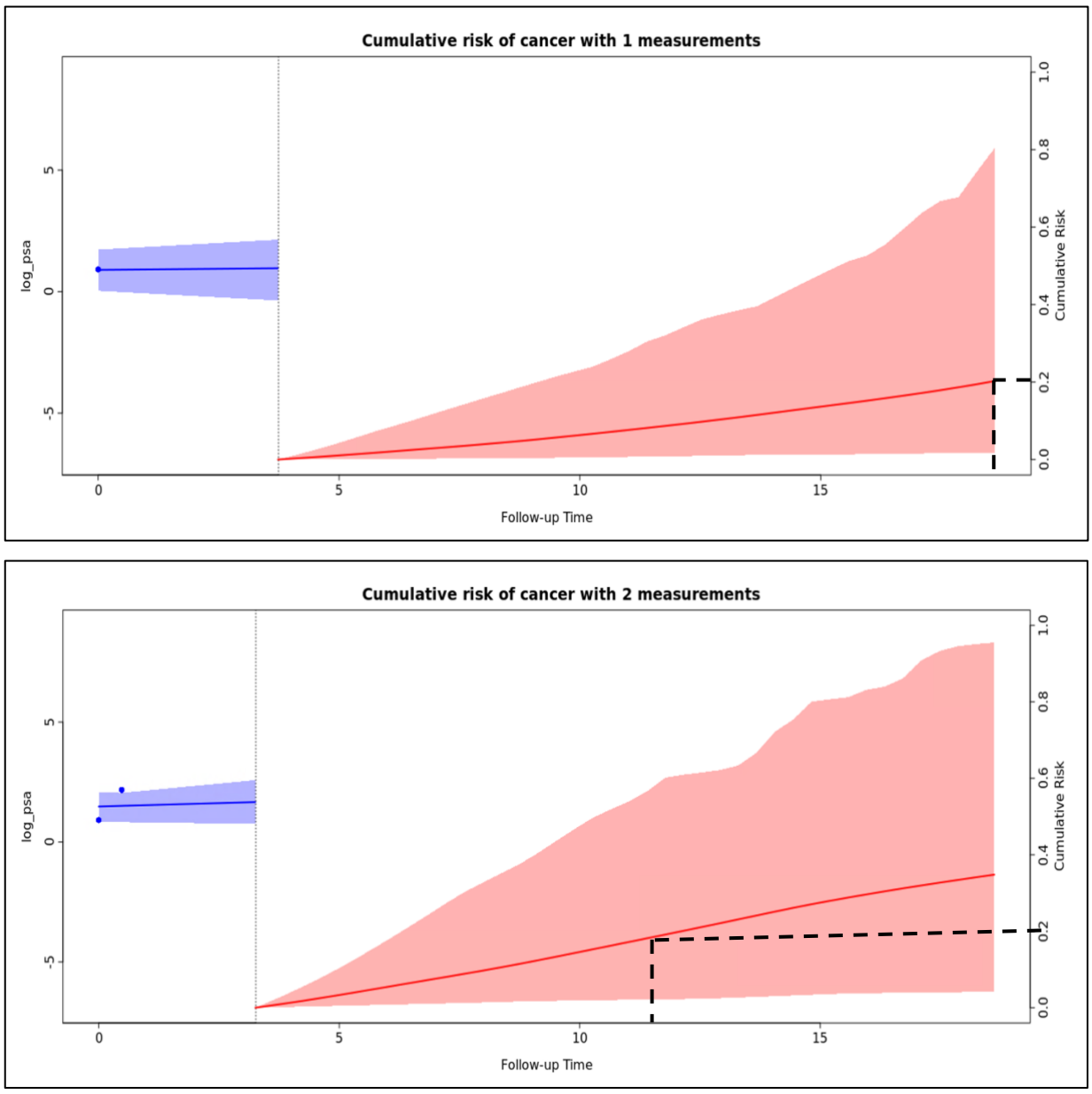
Table 7.9: Brier Scores

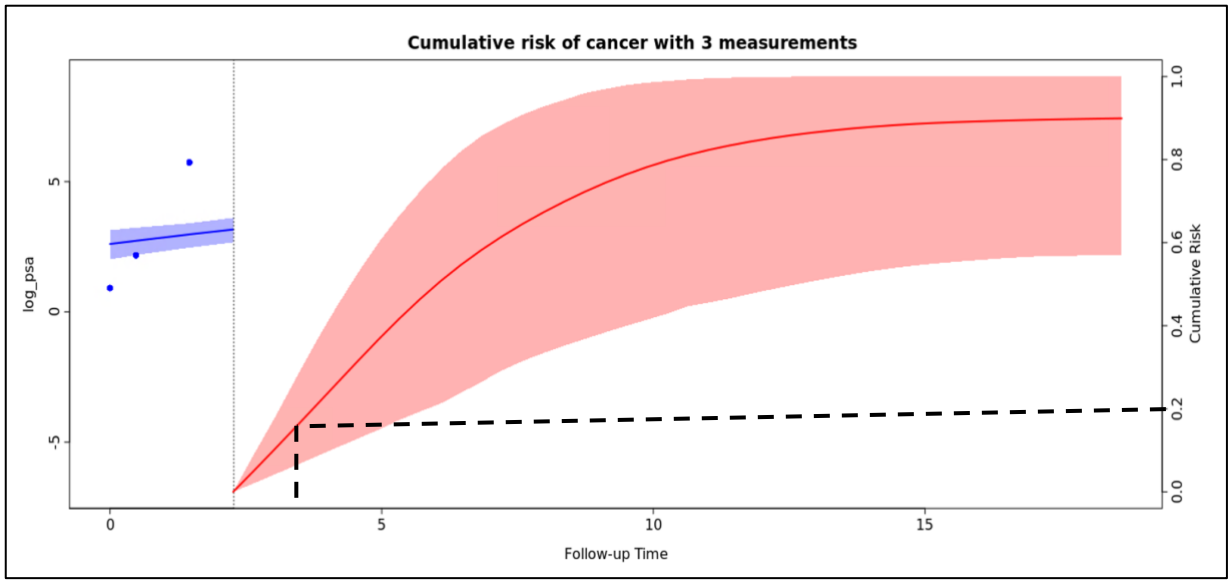
PSA testing history (years)	Prediction Horizon (years)	Final time (years)	Subjects at risk	Events (in interval)	Censored (in interval)	Brier score
1	2	3	78,822	1,492	4,469	0.0187
1	4	5	78,822	2,610	11,532	0.0334
1	10	11	78,822	5,314	43,173	0.0809
5	2	7	66,005	2,035	23,842	0.0335
5	4	9	66,005	2,889	35,884	0.0527
5	10	15	66,005	3,815	58,183	0.1025

7.6.6 DYNAMIC PREDICTIONS

Dynamic predictions allow the conditional probability of prostate cancer diagnosis to be updated as new longitudinal PSA measurements are observed. Figure 7.10 illustrates this process by presenting the result of the developed joint model prediction for one example patient. As each additional longitudinal PSA value is added (the blue line), the cumulative risk of survival (red line) dynamically adjusts to the new available information. The model considers each patient's age, PSA value and their slope of PSA. The black dotted line is drawn where the patients cumulative risk passes 0.2. This was done purely to illustrate how the survival prediction changes as more PSA tests are included.

Figure 7.10: Series of figures of the outcome from the joint model for longitudinal PSA measurements and associated survival predictions for an example patient





7.6.7 Dynamic retesting intervals

Dynamic retesting intervals can be derived directly from a patient's predicted cumulative incidence (risk) of prostate cancer. To demonstrate how joint modelling could be used to individualise PSA follow-up, a 3% risk threshold was applied (as described in Section 7.5. Based on this threshold, three example patients are presented. Each patient's PSA testing history and retesting interval recommendation are provided in Table 7.10, Table 7.12 and Table 7.11.

Example patient scenarios:

- Patient 1: low-risk, stable PSA over time
- Patient 2: intermediate-risk, PSA gradually rising
- Patient 3: high-risk, persistently elevated PSA

These examples illustrate how the timing of repeat PSA tests could be guided by individual risk predictions rather than fixed schedules. The joint model recommends longer intervals for low-risk patients, reducing unnecessary testing, and shorter intervals for those with rising PSA values, potentially enabling earlier detection. Unlike fixed schedules (e.g. every two years), the joint model adapts to each patient's evolving PSA history. A patient could be recommended to be retested at five years, then two years, then four years. However, the length of the interval still depends on the chosen risk

threshold. Setting this threshold too high could delay cancer detection compared with fixed testing, whereas setting it too low could increase testing frequency without substantial benefit. None of the three patients used in these results were part of the development of the joint model. An example full prediction output is provided in Appendix 5.

7.6.7.1 Example Patient 1 (low-risk)

Table 7.10: Patient 1 PSA testing history and joint model retesting interval prediction

PSA test number	Age	PSA Date	PSA Value (ng/mL)	Joint model 3% threshold crossed
1	45	2003-08-07	0.80	3% predicted risk within the next 8 years
2	52	2010-12-14	0.66	3% predicted risk within the next 8 years
3	53	2011-11-24	0.68	3% predicted risk within the next 8 years
4	55	2013-04-02	1.26	3% predicted risk within the next 6 years
5	57	2015-05-07	0.97	3% predicted risk within the next 6 years
6	59	2017-07-27	1.10	Not crossed within the next 5 years*

**The patients last PSA test was 13 years after their first PSA test. The joint model can only predict survival until 18.8 years from each patients' first PSA test. Therefore, from this patient's test in 2017 the model can only predict five years beyond.*

Patient 1: Real-world PSA and diagnosis

Patient 1 was 45 at their first PSA test in 2003 (0.8 ng/mL) and remained cancer-free for 14 years of follow-up. Six PSA tests were performed: 0.66 (2010), 0.68 (2011), 1.26 (2013), 0.97 (2015), and 1.10 (2017). All test results were low.

Patient 1: Model-predicted retesting pattern

Using the joint model, the predicted risk exceeded 3% eight years after the first test, suggesting to retest at age 53. When updated with data from the second test, the model again predicted a further eight-year interval before crossing the 3% threshold.

Patient 1: Comparison real world versus joint model

In practice, six tests were performed over 14 years. The joint model approach would have recommended three tests at approximately ages 45, 53 and 61. This patient never developed cancer and longer intervals would not have delayed diagnosis. Three tests could have been avoided.

7.6.7.2 Example Patient 2 (intermediate-risk)

Table 7.11: Patient 2 PSA testing history and joint model retesting interval prediction

PSA test number	Age	PSA Date	PSA Value (ng/mL)	Joint model risk prediction
1	63	2009-10-01	0.90	3% predicted risk within the next 3 years
2	64	2010-06-07	1.00	3% predicted risk within the next 4 years
3	65	2011-10-11	1.33	3% predicted risk within the next 3 years
4	68	2014-12-22	5.90	3% predicted risk within the next 1 year

Patient 2: Real-world PSA and diagnosis

Patient 2 had PSA tests at ages 63 (0.9 ng/mL), 64 (1.0 ng/mL), 65 (1.33 ng/mL) and 68 (5.9 ng/mL). They were diagnosed with Gleason 3+3 (cancer) in 2015, five years after their first test.

Patient 2: Model-predicted retesting pattern

The joint model predicted that the 3% risk threshold would be crossed approximately three years after the first test, recommending retesting around age 66.

Patient 2: Comparison real world versus joint model

In practice, Patient 2 was retested annually (2010, 2011) and then again in 2014. In 2014 their PSA increased to 5.9 ng/mL. The joint model would have recommended a retest between 2012 and 2013, but it is unknown what the PSA result would have been. However, this does precede the actual diagnosis date. Based on results from the joint model, the cancer would have been detected at the same time or slightly earlier and one unnecessary test would have been avoided.

7.6.7.3 Example patient 3 (high-risk)

Table 7.12: Patient 3 PSA testing history and joint model retesting interval prediction

PSA test number	Age	PSA Date	PSA Value ng/mL	Joint model risk prediction
1	65	2005-10-11	8.97	6% predicted risk within the next year
2	66	2006-08-25	12.00	9% predicted risk within the next year
3	66	2006-11-02	12.00	7% predicted risk within less than a year
4	66	2006-11-22	12.60	7% predicted risk within less than a year

Patient 3: Real-world PSA and diagnosis

At age 65 in 2005, Patient 3 had a first PSA with a result of 8.97 ng/mL. Follow-up tests occurred in 2006 and were 12.0, 12.0 and 12.6 ng/mL. Patient 3 was diagnosed with Gleason ≥ 7 prostate cancer in November 2006 after the last test.

Patient 3: Model-predicted retesting pattern
The joint model predicted that the cumulative risk would exceed 3% within the first year after the baseline PSA, indicating the need for an early repeat test.

Patient 3: Comparison real world versus joint model
In this case, the joint model would have recommended a repeat test earlier than what occurred in practice. The joint modelling approach would have detected cancer either at the same time or earlier than what happened.

7.7 DISCUSSION

7.7.1 SUMMARY OF FINDINGS

In this chapter, I described the theory of joint modelling, and I developed a joint model to predict an individual's risk of prostate cancer. The model was developed using longitudinal PSA test records combined with age and time to prostate cancer diagnosis from 80,000 patients from the South of England. It was validated in a separate cohort of 80,000 patients from the North of England.

The linear mixed-effects submodel captured patient-specific PSA trajectories. Older age at first PSA and rising PSA values over time were both associated with higher risk of prostate cancer. There was considerable heterogeneity between patients in both their baseline PSA levels and PSA trajectories over time. The time-to-event submodel confirmed that each additional year of age increased a patient's risk of prostate cancer. Results from the joint model indicated that higher PSA values HR 3.74 (95% CI 3.29 to 3.84) and steeper PSA slopes HR 3.32 (2.54 to 4.34) were predictive of prostate cancer. The model performed better in the short-term (less than seven years) with AUCs of over 0.8 and Brier scores less than 0.035. Predictive accuracy declined when including longer historical trends or predicting events further into the future.

To translate the joint model results into practical PSA retesting recommendations, I demonstrated how predicting an individual's cumulative prostate cancer risk may be a feasible approach to generate an evidence-based retesting interval. This approach is important because it accounts for how predicted risk changes over time within the same patient and between different patients. A 3% risk threshold was applied to illustrate the feasibility of how retesting intervals could account for each patient's individual PSA testing history. I provided three examples of retesting intervals, for a low-risk, intermediate-risk and high-risk patient. This approach extends the population-based recommendations developed in Chapter 6 by showing how dynamic, patient-specific retesting intervals could be derived.

7.7.2 Comparison to literature

Joint modelling has been proposed as a method to determine personalised screening intervals with longitudinal biomarker data (436) and has been used to derive personalised screening intervals in other disease areas (444, 457, 464-466). For example, Schuurman (466) optimised testing schedules for glomerular and tubular biomarkers in patients with chronic heart failure using data from the Bio-SHiFT study. For each patient at every follow-up visit, a joint model was used to identify the time point at which the patient's cumulative risk of a cardiac event reached 7.5%. This time point defined the personalised retesting interval, and both fixed and personalised screening strategies were then simulated for comparison.

To my knowledge, there are no studies using joint modelling before a patient is diagnosed with prostate cancer. However, there are several studies that use longitudinal PSA data and joint modelling to predict prostate cancer recurrence after treatment (354, 438, 467, 468) and to predict prostate cancer progression in patients with a low-risk cancer diagnosis who are monitored on active surveillance protocols (469, 470). In this chapter, I found, PSA value, PSA slope and age were all significant predictors of a patient's future risk of prostate cancer. These conclusions were confirmed in other joint modelling studies that predicted recurrence or progression (372, 435, 468, 471).

As described in Section 1.10.3, PSA is more effective at detecting prostate cancer recurrence post treatment than it is for detecting low risk cancer progression or early cancer detection. However, in this chapter, I show it may be possible to use joint modelling to assist with the timing of PSA retesting intervals in primary care before a patient is diagnosed with prostate cancer.

7.7.2.1 Joint models related to the prostate cancer pathway

Tomer et al (469) applied joint modelling to optimise biopsy intervals during active surveillance and showed that personalised schedules could substantially reduce unnecessary biopsies compared with fixed annual testing. Another study (470) used an interval-censored cause-specific joint model that incorporated competing risks such as early treatment, reducing biopsies per patient by 41to 52%. The joint model developed in this chapter only included PSA and age but it could be expanded to account for competing events. Future simulation studies are required to estimate how many unnecessary PSA tests could be avoided with individualised retesting balanced with the number of recommended tests from using fixed schedules.

7.7.3 STRENGTHS AND LIMITATIONS

The primary strength of this chapter lies in its novel approach used to predict dynamic risk for prostate cancer. To my knowledge, no other studies using joint modelling to predict prostate cancer based on primary care data. The advantage of joint modelling is its ability to derive a risk prediction for an individual patient by using all observed longitudinal measurements available for that patient. Another strength is the size of the dataset which was large enough to develop and use spatial validation to validate the joint model. A third strength is that joint modelling allows for PSA to be used as a continuous longitudinal outcome instead of being grouped into a category, which is commonly the case in screening simulation studies that use Markov Decision Process to estimate retesting intervals. A final advantage of joint modelling is the fact that retesting intervals are not the same for each patient, instead, they dynamically adapt in the same patient if that patient's risk changes over time. For example, the recommended interval may be

ten years for a patient at age 50 and could change to five years by age 60 if their risk increases.

There are important limitations to consider. Joint models are limited by the length of follow-up in the data used to build them. In the BLOTTED dataset, the maximum follow-up was 19 years (2000 to 2018). The median follow up overall was 9.5 years (6.0 to 13.0) after the first PSA test and 5.6 years (2.8 to 9.5) for those diagnosed with prostate cancer. Predictions made further into the future were less accurate, possibly due to reduced follow-up data. This was reflected by lower AUC values. For example, using one year of PSA history to predict two years ahead produced an AUC of 0.86 with, compared with 0.77 when using five years of history to predict two years into the future. This likely because a patient must have been contributing data for the whole PSA history timeframe without a diagnosis of cancer and have follow up in the years after the years of trend. For patients with one-year of PSA history there were 42,086 patients at risk compared to 9,441 patients with a five-year history. The joint model prediction is conditional on the patient surviving the whole history period after a PSA test without a diagnosis of cancer or leaving the study. Data with long follow up is specifically important in the case of prostate cancer, as it is generally a slow-growing disease. The ERSPC trial only saw a small positive screening result after 15 years of follow-up, this increased in the recent results of the 23-year follow up. It may be possible to improve the joint model using the ORCHID-E database which has primary care data available from 2000 to the end of 2024.

A second limitation is that the joint model was developed using the outcome of overall prostate cancer instead of clinically significant disease. This was because accurate stage of prostate cancer is better defined post 2010, based on the results of Chapter 4. Based on the sensitivity analysis in Chapter 6 where both overall and clinically significant disease were presented, results were different when considering the length of follow-up. As this chapter is only illustrating the feasibility of joint modelling as an approach, it was decided that including longer follow-up was the priority. It will be important to consider stage in the future when more accurate data is available.

A third limitation is that the joint model was developed using data from patients with at least three PSA tests. These individuals may represent a higher-risk group who were monitored more closely, though this cannot be confirmed in primary care data. The proportion of patients with a prostate cancer diagnosis was 9.3% of the cohort. This was higher than in Chapter 6 where 7.7% of the patients with at least one test were subsequently diagnosed with prostate cancer. Conversely, in model development, patients with a first or second high PSA and then a diagnosis of cancer which may limit the model's ability to predict cancer for those whose first or second test was high. The calibration plot (Figure 7.9) illustrated that the model underestimated risk in high-risk individuals. Future work should extend joint modelling to include patients with fewer than three PSA tests.

Finally, although individualised retesting intervals are conceptually attractive, a limitation is that they may be difficult to implement in clinical practice. Joint modelling has high computational demands. The models took on average 12 hours to run, and I had to overcome many challenges with the R studio server crashing due to lack of memory. A model using 80,000 patients was the limit I was able to run using the memory available (500 GB). Once validated, it is possible the joint model could be translated into a web-based calculator. Further research will be essential to test out this implementation technique.

7.7.4 RESEARCH IMPLICATIONS

Model development and external validation are the next steps required following the analysis in this chapter. In Chapter 8, I discuss other research implications of retesting generally, such as the importance of choosing an appropriate risk threshold, stakeholder perspectives and possible implementation approaches.

7.7.4.1 Model development

Further research should extend the model development. This could include trialling different functional forms that are built into the JMbayes2 package to improve prediction. The use of different splines in the survival model may improve prediction. For example,

some studies on prostate cancer have used B Splines (372). Other variables, such as ethnicity or polygenetic risk scores, could be included in the model. With the addition of more computing power, it may be possible to incorporate other biomarkers available in primary care data.

Further research also is required to determine whether joint models can converge when fewer than three PSA tests are available per patient. In this chapter, models that did not include the PSA slope as a functional form converged successfully when using patients with at least two PSA tests. Convergence challenges occurred when including the slope function form. To overcome this model development was done using patients with at least three PSA tests per patient. Future model development should also evaluate whether joint models can be developed when some patients only have one PSA test. This would allow more patients to be included and would better reflect real world situations where patients may only have one PSA test. To be able to develop a model using patients with fewer than three tests further work is needed to assess whether including the PSA slope into the model does meaningfully improve the model performance enough to justify the additional complexity and computing power required. It is possible that a simpler joint model using only age and log(PSA) could achieve similar predictive accuracy with lower computational cost. If this is true, additional validation is needed to determine whether predictions differ substantially between models requiring three PSA tests per patient and those developed on patients with fewer measurements.

A final implication for model development is that joint models can also predict future longitudinal PSA values, rather than cumulative risk which was done in this chapter. In JMbayes2, the predict() function can be used to forecast a patient's expected PSA trajectory over time instead of predicting their probability of survival. This approach could inform retesting based on the patient's predicted PSA value rather than predicted cancer risk. For example, a clinician could schedule the next PSA test when the model predicts the patient's PSA will reach 3 ng/mL, or an age-specific referral threshold. This may offer a more intuitive and clinically actionable way to individualise follow-up.

7.7.4.2 External validation

External validation of the joint model is required. Data from the UK Biobank would be a good first option considering the availability of additional genetic data. Other countries such as PSA data from Sweden, data from the ERSPC or the ORCHID E dataset are potential external validation cohorts. I expect the model will validate well as the proportion of PSA values described in Chapter 6 were similar to international cohorts of patients (Section 6.6.2).

7.7.5 CLINICAL IMPLICATIONS

7.7.5.1 Individualised risk thresholds

The retesting intervals recommended in this chapter should be interpreted as a feasibility study. Similar to Chapter 6, retesting intervals are contingent on a risk threshold. The findings from this chapter illustrate the possibility of defining clinically meaningful individual thresholds for PSA retesting. Applying a fixed prediction threshold, such as 3%, provides a simple framework for identifying patients who may benefit from more frequent repeat testing. However, thresholds do not need to be fixed. Dynamic or patient-specific threshold that are adjusted for age, comorbidity, or individual risk tolerance may better reflect real-world clinical decision-making. For example, older patients may accept a higher threshold when balancing biopsy risks against potential benefits, while younger men may prefer a more conservative retesting approach. Additionally, an individual patient's risk threshold may change over time. Incorporating predicted risk trajectories from joint models into clinical tools could assist with shared decision-making between patients and clinicians, ensuring that retesting intervals are both evidence-based and preference-sensitive. In Chapter 8, illustrate how the interval would be shorter if a 1% threshold was used similar to the threshold used in Chapter 6.

7.7.5.2 Reducing unnecessary testing for low-risk patients

Unnecessary repeat PSA testing can be reduced by limiting retesting for patients with very low baseline PSA values (less than 1 ng/mL). Chapter 6 illustrated that risk-based intervals derived from baseline PSA alone can identify this group. The joint model

provides further support for reducing retesting in low-risk patients. Individualised risk prediction may offer a more acceptable approach for patients because intervals are updated as new PSA results become available rather than being fixed indefinitely for an average group of patients. For example, instead of advising patients that they "never need another test," as on average patients in their age and PSA category are unlikely to develop prostate cancer, clinicians could safely inform patients that their next PSA is due in around eight to ten years, and that their next retesting interval after that will be reviewed based on their updated risk. An example of this is described this in Section 7.6.7.1. Patient 1 had six PSA tests, beginning at age 45, that were consistently low (0.66 to 1.26 ng/mL). Using the joint model for this patient, their predicted risk of cancer crossed the 3% threshold eight years after the first test, and again eight years after their second test. Therefore, two PSA tests at ages 53 and 61 would have been sufficient. This would reduce six PSA tests to three and is consistent with Vickers (2013), who suggested that low-risk patients need only three lifetime PSA tests: one in the mid-40s, mid-50s, and mid-60s (175).

7.7.5.3 Adapting retesting intervals for patients who become higher risk

Joint modelling could improve on the population-based retesting intervals from screening programs for high-risk patients. Retesting intervals derived from joint modelling are adaptive and change within the same patient over time. In the ERSPC trial the retesting intervals were fixed until a patient presented with a PSA high enough to trigger referral. Joint modelling, instead, allows the retesting interval to adjust based on the patient's PSA trajectory. This provides the opportunity for more flexible, risk-based follow-up. For example, if a patient was first retested at an 8-year interval and their PSA increased their next retesting interval would adjust to be in a shorter timeframe. An example of this is described by Patient 2 (intermediate risk patient) (Section 7.6.7.2) where the retesting interval shortened as the patient's risk increased. Furthermore, with the addition of mpMRI, the risk of overtreatment from earlier or more frequent testing is reduced, making adaptive PSA retesting more feasible in the diagnostic pathway. Whether or not this improves patient outcomes compared to fixed schedules in screening programs would require further simulation studies.

7.7.5.4 Ensuring high risk patients are treated as high risk

It is important patients are referred for further investigations if necessary. Patient 3 (Section 7.6.7.3) was 65 at the time of his first PSA test in October 2005 which was 8.97 ng/mL. Their PSA test was repeated about ten months later. For this patient, the joint model predicted a cumulative risk of cancer passed 3% in the first year after the patient's first PSA test. Following either PCRMP or NICE NG12 guidance, this patient would have been referred. It is possible the joint model could provide clinicians with more reassurance that referral is required.

7.7.5.5 Improving targeting and consistency in current practice

Current PSA screening policies that encourage patients to make their own decisions about PSA testing is exacerbating harms and reduce benefits of PSA testing (228). As shown in Chapter 5, PSA testing rates are low among patients in their 50 who are most likely to benefit from early detection and highest among patients over 70, who are most likely to be overdiagnosed. Age at the first PSA screening has a particularly strong influence on the effectiveness of screening. One study found that the initiation of testing at age 50 years resulted in risk reductions that are more than double those among men who start testing at age 60, which is the median age of the first PSA screening test in the ERSPC (472). Joint modelling provides a possible solution to safely test patients from a younger age with the correct follow up in place to reduce the risk of overtesting. Joint modelling could support a more consistent, risk-stratified approach to PSA testing, ensuring that patients are retested according to their individual risk. This evidence for retesting intervals may help improve the varied rates of PSA testing occurring in practice.

7.8 CONCLUSION

Joint modelling has the potential to provide individualised risk predictions for prostate cancer that adapt throughout a patient's lifetime. Further research is required to externally validate the models and determine an appropriate risk threshold for retesting. This approach, although in its inception, may help reduce unnecessary testing in patients unlikely to benefit, and at the same time encourage appropriate testing in those most likely to benefit from it.

Chapter 8: Discussion

8.1 Reflections

In this thesis, I aimed to generate research that directly informs three practical, policy-relevant questions. What is the guidance for PSA retesting in primary care? How often are patients being retested with PSA in primary care? And how often should patients be retested with PSA in primary care?

Throughout the DPhil, I came to appreciate the complexity of producing evidence that can easily translate into policy. Policymakers require pragmatic answers, yet the realities of academic research mean that generating robust findings that directly answer the question of interest is both challenging and full of nuances. This tension is particularly evident in prostate cancer, where biological variability, a long natural history, and increasing public awareness have created polarising perspectives on when and how often PSA retesting should occur. Despite the differing perspectives on PSA testing generally, the shared goal of improving patient outcomes remains the same. Achieving that, requires bridging the gap between research and actionable policy.

Over the past four years, I have learned that, perhaps unsurprisingly, nothing is as straightforward as it first appears. At the same time, I discovered the opposite is also true: evidence can be made both accessible and useful for policy, even if initially it seems too complicated to translate into a meaningful solution. Chapter 5 of this thesis has already been picked up by international media outlets, who did interpret the main messages correctly. As a result, I experienced what it feels like to have my research ideas make an impact. I have developed an appreciation of evidence-based policy development from the academic perspective. Perhaps the biggest accomplishment is that, despite the challenges, complexities, and mix of small, medium, and occasional big wins along the way, I am finishing these four years more committed than ever to producing research that is both robust and relevant to real-world decision-making.

8.2 SUMMARY OF FINDINGS

While I have made important contributions to the literature, it is still unclear what the optimal use of the PSA test is in primary care. In this section, I summarise the three objectives of the thesis and the contributions that I made to the literature.

The three objectives of this thesis are as follows:

1) Summarise recommendations and the evidence referenced in clinical practice guidelines for retesting intervals.
2) Characterise how PSA tests are currently used in English primary care for patients without a prostate cancer diagnosis.
3) Generate new evidence to inform optimal repeat testing intervals patients who have a PSA test in primary care.

8.2.1 OBJECTIVE 1: SUMMARISE RECOMMENDATIONS AND EVIDENCE CITED IN CLINICAL PRACTICE GUIDELINES FOR RETESTING INTERVALS.

Within England, there is no guidance on whether or how often patients should be retested with PSA. International guideline recommendations for PSA retesting reflect this uncertainty, as they recommend varying lengths of PSA retesting intervals. In Chapter 2, I provided a comprehensive summary of international guideline recommendations. I examined the variation across guidelines, assessed the quality of each guideline, and explored the applicability and methods of the studies cited as evidence for retesting intervals. Most guidelines recommended some form of risk-based retesting, however the definition of risk groups for stratification varied between age, PSA, and other risk factors such as family history or ethnicity. Recommended PSA retesting intervals ranged from one to ten years. The most common retesting interval was between two and four years.

When summarising the evidence that the guidelines used to support their recommendations, I found that in the absence of randomised trials for PSA retesting intervals (219), guideline developers relied on modelling, cohort studies and retrospective analyses of data from PSA screening trials. These cohort studies often

focused on prostate cancer risk or mortality based on a single PSA measurement at a specific point in time (175, 185, 187, 188, 193, 195, 201, 203, 205-209, 217), rather than calculating retesting intervals. Modelling studies simulated screening strategies, but their results rarely translated into an explicit interval recommendation. Additionally, alignment between the cited evidence and guideline recommendations varied with most guidelines extrapolating beyond what the evidence supported or recommending shorter retesting intervals than what the evidence recommended.

Alongside the guideline review on PSA retesting intervals, in Chapter 3, I reviewed guideline recommendations for monitoring patients with a diagnosis of low-risk cancer. I found variation in recommendations both across and within cancer sites. Evidence was strongest for prostate cancer, where randomised controlled trials support the safety of monitoring. For renal and thyroid cancer, guidance was based on observational series and small studies. Across all cancer sites, evidence to guide monitoring intervals and triggers for treatment was sparse. Most guidance relied heavily on expert opinion or left decisions to clinical judgement. Together, these reviews highlighted that both PSA retesting and monitoring intervals are poorly defined in different parts of the cancer pathway and only occasionally reflects the available evidence.

8.2.2 Objective 2: Characterise how PSA tests are currently used in England primary care for patients without a prostate cancer diagnosis.

After completing two systematic reviews, the remainder of the thesis was based on a series of three studies that used electronic health records data from CPRD Aurum as part of the BLOTTED Study (455). CPRD Aurum provides valuable longitudinal data on PSA tests, symptoms, diagnoses, and treatment. Management of the data was described and reported in Chapter 4. In that chapter, I described the dataset and highlighted strengths and challenges of using routinely collected primary care data. The BLOTTED dataset included over 10 million male patients over the age of 18 and of those over 1.5 million patients had at least one PSA test recorded.

To understand how the PSA test is used in primary care in England, in Chapter 5 I described trends in PSA testing over time and examined individual patient variation in both the rates of PSA testing and the length of PSA retesting intervals. I evaluated associations with region, deprivation, ethnicity, age, family history of prostate cancer, PSA test results, and symptom presentation to explore whether variation in overall testing rates was driven by differences in retesting frequency. One quarter of all tests were paired with a symptom of prostate cancer. Among patients with multiple PSA tests, over 70% never presented with a raised PSA value (above the age-specific threshold) and more than two thirds of PSA tests were repeated within two and a half years. Median retesting intervals were 12.6 months (IQR 6.2 to 27.5). Retesting intervals were shorter for older patients, those from non-White ethnic groups, or those with a family history of prostate cancer. Despite differences in testing rates by region and deprivation, that have been reported in the last decade, the length of retesting intervals was consistent across these subgroups.

8.2.3 Objective 3: Generate new evidence to inform repeat testing intervals for those opting for PSA testing in primary care.

In the final part of this thesis, I used English primary care data to generate evidence for PSA retesting intervals. I evaluated the risk of prostate cancer diagnosis by baseline PSA values. Baseline PSA was the strongest predictor of cancer risk. Sixty-seven percent of all patients between the ages of 40 and 90 had a baseline PSA under 2 ng/mL and these patients had a low overall risk of cancer (1.4% throughout the follow-up period). Based on Kaplan Meier survival plots, using a 1% risk of cancer threshold, I estimated retesting intervals. When the risk of a prostate cancer diagnosis was more than 1% in the following year for a given group of patients with a baseline PSA value at a specific age, retesting was recommended. I found that younger patients (ages 40 and 59) with a baseline PSA less than 1 ng/mL could safely wait up to ten years. Retesting was recommended in the following two years for all patients over the age of 40 with PSA values ≥2 ng/mL. These results provided a descriptive population-level framework for retesting recommendations based on observational data and confirmed the proportion of patients presenting with PSA values below 1ng/mL is consistent with studies done internationally.

I extended this approach further by developing a joint model to incorporate an individual's longitudinal PSA history. This was done to test the feasibility of individualised dynamic retesting interval predictions. The model combined PSA trajectories with age and produced dynamic, patient-specific future risk estimates. Higher baseline PSA and steeper PSA increases predicted greater risk of cancer. The joint model performed well for short-term risk prediction but accuracy declined over longer time periods. I illustrated how these models could be translated into patient-specific retesting intervals, based on a risk threshold of 3%. Examples for a low, medium, and high-risk patient demonstrated the feasibility of moving beyond population-based intervals to personalised, evidence-based recommendations.

External validation is required for both of these techniques and further research is needed to ensure patients are neither over nor under tested with PSA. A balance is required between the length of the retesting interval and the number of cancers potentially diagnosed late. Together, the analyses in Chapter 6 and 7 contribute new observational evidence to inform further research into both population-level and personalised PSA retesting intervals in primary care.

8.3 STRENGTHS OF THE THESIS

The strengths of each individual study have been described within the respective chapters. In this section, I summarise the overall strengths of this thesis.

8.3.1 POLICY RELEVANT SERIES OF ANALYSES

In this thesis, I presented a comprehensive series of analyses on PSA testing and monitoring intervals. These analyses combined several methodological approaches, including two systematic reviews of international clinical practice guidelines (Chapters 2 and 3), a descriptive analysis of PSA testing patterns in English primary care (Chapter 5), a population-based analysis of prostate cancer risk following a baseline PSA test (Chapter 6), and the development of a dynamic joint model to estimate individualised, risk-based retesting intervals (Chapter 7).

Together, these studies examine PSA retesting from several perspectives. They illustrate what guidance currently recommends, what evidence supports those recommendations, how testing is carried out in practice, and how evidence for retesting intervals could be generated from routinely collected data. The first two chapters laid the foundation by summarising existing guideline recommendations and the quality of evidence underpinning them. These findings helped shape the design of the later chapters that focused on PSA testing practices and development of PSA retesting intervals. By structuring the thesis in this way, I aimed to generate findings that are both clinically meaningful and useful for improving policies for PSA retesting.

8.3.2 LARGE PRIMARY CARE DATA WITH LINKAGE TO HOSPITAL RECORDS AND THE CANCER REGISTRY

Using a large, representative electronic health records database linked to the Cancer Registry, Hospital Episode Statistics, and the Office for National Statistics, I conducted an epidemiological study to confirm that PSA retesting is an area that warrants future research as current practices are varied. The size of the dataset also allowed me to develop and internally validate a risk prediction model. Further refinement of the model is possible as not all the data available was utilised. In Chapter 6, I show the proportion of patients with a PSA test by PSA value and age. Currently in England, this information is only available from the CAP trial which included 400,000 patients (99). I had access to over 1.3 million individuals who had their first ever PSA test in the timeframe between 2000 and 2018, confirming the strength of observational level electronic primary care records. I was able to generate evidence for both population based and dynamic individualised retesting strategies. The joint modelling approach proposed in Chapter 7 represents a novel approach for PSA retesting, and to my knowledge, has only been used previously in prostate cancer recurrence and active surveillance cohorts. The size of the database provided the resource to develop both a robust population-based testing strategy and an individualised prediction strategy.

8.3.3 Involvement of Policy-based Stakeholders

Another important strength was the sustained involvement of policy stakeholders who consistently contributed throughout the project. I worked closely with the Strategic Evidence Team at Cancer Research UK. We met regularly over the four years. Chapter 5 includes a subgroup analysis of patients who never presented with a PSA value above the NICE NG12 threshold. This subgroup analysis was suggested by the charity, which was interested in understanding how much PSA testing is ongoing within GP practices and what the results of the PSA tests were in relation to presented symptoms. The collaboration with CRUK ensured that the research questions in this thesis were aligned with policy priorities and provided a channel that helped to maximise the impact of my findings.

8.3.4 Involvement of patient and public members and academic collaborations

Patient and public contributors were actively engaged throughout this research, strengthening its translational relevance. Their input highlighted the challenges of communicating overdiagnosis, the uncertainty surrounding PSA testing, and the need for clearer, more consistent guidance for patients. A dedicated PPI group was established early in the project and provided input into Chapters 2, 5, 6 and 7, particularly around the interpretation of findings and how they relate to patient decision-making. During the development of Chapters 6 and 7, I worked with two dedicated PPI leads while preparing a grant application for future research on PSA retesting intervals. The project further benefited from insights shared by patients, urologists and academics during national and international conferences , in Copenhagen, Melbourne, San Francisco, Birmingham, Manchester, Oxford, and Portland. Further input came through collaborative activities such as CRUK/Oxford research sharing day, which I organised, and a statistics teaching workshop designed for patient contributors. Collectively, this engagement helped ensure that the research remained relevant to both patients and those implementing prostate cancer testing policy.

8.3.5 OPEN SOURCED AND TRANSPARENT

The findings from this thesis are open sourced, transparent and reproducible. My analytical code and a description of the methods are provided on Github (https://github.com/kiana-k-collins). In addition to make the research accessible to the public, Figure 5.3, in Chapter 5 that depicts PSA testing rates in the UK is available online as a dynamic dashboard (https://kiana-k-collins.shinyapps.io/bmj_shiny_app_v2/). All of the publications so far from this thesis (Chapters 2, 3 and 5) are published in Open Access journals. I plan to publish Chapters 6 and 7 in the future.

8.4 LIMITATIONS OF THE THESIS

Limitations specific to each study are reported in the respective chapters. This section describes the overarching limitations of the thesis.

8.4.1 RETESTING METHODS FOCUSSED ON EVIDENCE CITED IN GUIDELINES

I focused on clinical practice guidelines to understand what PSA retesting intervals are recommended and on what types of studies the retesting interval recommendations were based. While this approach provided a practical and policy-relevant overview, it meant that other methodological studies proposing other statistical or simulation-based solutions to retesting intervals were not captured if they were not cited by the guidelines included in the two systematic reviews. Other types of methodologies for calculating retesting intervals were mentioned briefly in the introduction of the thesis, but they were not explored systematically or in detail. This decision was deliberate, to keep the review aligned with what clinicians and policymakers currently use, however it limits the breadth of methodological insight.

8.4.2 USE OF NHS ELECTRONIC HEALTH RECORDS

All analytical analyses in this thesis are based on English primary care data. While this represents the best data to address the question in Chapter 5, which was a descriptive epidemiological study to determine retesting intervals, data from a large randomised trial with longer follow-up would have been more suitable, or biobanks linked to longitudinal

cohort databases with PSA test results. Instead, in this thesis, I captured actual practice over nearly two decades. The reason a patient has a PSA test is not recorded in primary care electronic health records data. It could reflect clinical concern or patient preferences which are generally influenced by wider social and economic factors, private healthcare, at-home tests, media coverage, or international guideline shifts. As there are no PSA testing trials in the UK that examine repeat PSA testing, relying on observational data was the best option. This means that evidence presented here reflects NHS primary care practice, not testing occurring privately or independently. With the TRANSFORM trial beginning recruitment in 2025, it will be important to see how the analysis from Chapter 6 and 7 compares to the data collected in TRANSFORM.

Primary care data are also limited by inconsistent GP coding practices. Some GPs code comprehensively while others rely on free-text notes that are not captured in any available research databases. There is no national standard for coding PSA testing rationale or results. Verification bias is also an inherent challenge as only patients who had a PSA test can enter the diagnostic pathway. Consequently, cancers in patients who are never tested, or who are not referred for further investigation following an abnormal result remain unobserved. This verification bias may lead to underestimation of prostate cancer prevalence and inflation of the negative predictive value of PSA.

8.4.3 CHANGES IN THE PROSTATE CANCER DIAGNOSTIC PATHWAY

All analyses in this thesis uses data collected up to 2018. This is before the NICE approval of mpMRI scanners for prostate cancer detection and their full roll out into the NHS. The introduction of mpMRI and transperineal MRI-guided biopsies has improved diagnostic accuracy and enabled more precise identification of clinically significant cancers (231, 473). Consequently, cancer stage data in this study reflect pre-mpMRI diagnostic practices may underestimate the detection of clinically significant prostate cancer compared with current pathways. The use of the overall cancer outcome has mitigated this risk but this has also included many patients with low-risk cancer. This may have led to an overestimation of the association between PSA and any prostate cancer diagnosis.

8.4.4 LIMITED QUALITATIVE ANALYSIS

Apart from input directly from stakeholders and PPI participants, this thesis is limited by the absence of a formal qualitative analysis. It was designed this way as it was thought that the first step was to determine if the methods suggested for retesting intervals were viable. Further research should incorporate input from clinicians', patients', urologists' and policymakers' on these methods for calculating patient risk and associated retesting intervals by simulating the benefits of early detection with the harms of overdiagnosis.

8.5 POPULATION BASED VS INDIVIDUALISED DYNAMIC RETESTING INTERVALS

In this section, I describe the differences between the population-based retesting interval discussed in Chapter 6 and the individualised dynamic retesting intervals illustrated in Chapter 7. Both approaches translate an estimated risk of prostate cancer into a recommended interval for retesting. However, they differ fundamentally in terms of the methods used and the data subset that each model was built upon. In Section 8.5.1 and Section 8.5.2 I outline the differences in how risk is calculated (Design/Method), and which populations are represented (Data). In section 8.5.3, I discuss how these results can be applied in a clinical setting.

Conceptually, population-based retesting intervals describe the average risk of prostate cancer within defined groups of age and baseline PSA level. In contrast, individualised dynamic intervals estimate a patient-specific risk that evolves over time as new PSA information becomes available. In both designs, a risk threshold must be chosen to determine when retesting should occur. For illustrative purposes, to compare models, a 1% threshold was applied. In practice, a different threshold could be chosen (higher or lower). A higher threshold would lengthen the recommended interval and increase the likelihood of interval cancers being missed. A lower threshold would shorten the interval, reducing missed cancers but increasing the potential for overdiagnosis.

8.5.1 DESIGN/METHOD

The population-based analysis in Chapter 6 was descriptive. It quantified the observed cumulative incidence of prostate cancer within ten years of a patient's first PSA test and was stratified by five-year age bands (between ages 40 and 90) and by baseline PSA categories (< 1, 1-1.9, 2-2.9, 3-3.9, 4-4.9 and 5+ ng/mL). This design assumes that risk remains static within each group, and it provides a single retesting recommendation for all patients sharing the same baseline characteristics.

In contrast, the joint-model framework utilised in Chapter 7 is predictive and estimates a patient's future risk of developing prostate cancer conditional on their age and individual PSA history. The model dynamically updates risk predictions as each new PSA result is obtained. This allows the risk and the recommended retesting interval to recalibrate over time.

Importantly, the 1% threshold in Chapter 6 (population-based approach) reflects the proportion of cancers that actually occurred in the observational data, whereas in Chapter 7 (individual approach) the 3% thresholds represents a predicted probability of cancer derived from the joint model.

8.5.2 POPULATION (DATA INCLUDED IN EACH MODEL)

The risk estimates are based on different populations as different subsets of the BLOTTED data were used for each model. Chapter 6 included all patients aged 40 to 90 years with at least one PSA test recorded in primary care. Chapter 7 applied the same age range but required each patient to have at least three PSA tests to be able to model PSA trajectories. The proportion of patients diagnosed with prostate cancer therefore differed. In Chapter 6, 7.7% of the cohort was diagnosed with cancer during follow-up (107,067/1,389,568) compared to 9.4% of the cohort utilised in Chapter 7 (7,502/80,000) This was likely due to more PSA testing being linked to increased likelihood of finding a cancer, or the patient being at higher risk of cancer. As the underlying populations differ, the resulting risk estimates are not directly comparable. A formal comparison would

require simulation study or a prospective study. This is an opportunity for future research discussed in Section 8.8.

8.5.3 CLINICAL INTERPRETATION AND APPLICABILITY

Due to the differences outlined in Sections 8.5.1 and 8.5.2, the clinical applications of the population-based and individualised dynamic retesting approaches are distinct. In practice, the population-based and individualised dynamic models address different but complementary aspects of PSA testing and could serve different purposes within the prostate cancer diagnostic pathway.

8.5.3.1 Population-based model (Chapter 6)

The population-based model is most relevant when only a single baseline PSA measurement is available. It provides one recommended retesting interval following the patient's first test and assigns the same interval to all patients within a given age and PSA stratum. Its simplicity is both a strength and a limitation. It is straightforward to apply in primary care and ideal for guideline-based recommendations, and it is easy to communicate ("patients aged 60 to 64 with a PSA between 1 and 1.9 ng/mL can safely wait five years before having another PSA test"). However, it assumes that all patients within that group share the same risk trajectory. It cannot account for subsequent changes in PSA or for patient-specific factors that emerge over time.

8.5.3.2 Individualised dynamic model (Chapter 7)

The individualised dynamic model, developed using joint modelling, provides patient-specific risk predictions that adapt as new PSA results are recorded. Unlike the population-based approach, which fixes risk at baseline age group and PSA category, the joint model updates the predicted probability of prostate cancer each time a patient is retested and can handle an unlimited number of PSA tests per patient. The recommended interval can lengthen or shorten depending on whether PSA values remain stable, rise, or decline. Clinically, this model likely mirrors how GPs interpret serial PSA results in the context of age, prior values, and clinical history. The dynamic model could support personalised follow-up schedules, guiding when to retest a patient

or refer for further assessment. It is not restricted by predefined age bands or PSA categories. Instead, it produces continuous, individualised risk predictions.

8.5.3.3 Applications

Although the two models address different questions, both highlight ways in which PSA testing data could support clinical decision-making and contribute to the overall PSA testing evidence base. The population-based model is best suited for public health and policy applications particularly were patients have one PSA test. In contrast, the individualised model could enhance clinical decision-making for ongoing monitoring, providing risk estimates that evolve as new PSA results become available.

Together, these models demonstrate how population-level prediction and personalised predictions can complement each other within the prostate cancer testing pathway. Population-based intervals support efficient resource allocation and patient reassurance, while dynamic individualised predictions allow follow-up to be tailored to individual risk profiles and changes in those profiles overtime. The ethics surrounding population versus individual medicine generally is outside the scope of this thesis. While the retesting interval recommendations made from both models, for illustrative purposes, rely on the same underlying risk threshold (1%), the interpretation is different. One is based on observed cumulative incidence, the other on predicted probability. This distinction has direct implications for how retesting recommendations are communicated to patients and operationalised in primary care.

8.5.4 ILLUSTRATIVE EXAMPLES

Figure 8.1 demonstrates how the cumulative risk curve for a patient aged 60 to 64 years with a first PSA between 1 to 1.9 ng/mL differs when estimating risk when using the static population-based Kaplan–Meier method (A) versus the dynamic joint model method (B). The Kaplan-Meier approach provides a single observed cumulative risk for the entire group, shown by the solid line. The joint model produces a distribution of predicted risks for individual patients whose risk trajectories diverge as their PSA histories unfold. In Figure 8.1, the static approach, on the left, is based on a patient's baseline PSA value (A). On the right, graph (B) depicts the distribution of risk for 15 patients who had a baseline

PSA between the ages of 60 to 64 with a value of between 1 to 1.9 ng/mL. However, instead of using the first PSA test the risk projections are based on the each of the 15 patient's last PSA record to show how risk distributions change as more PSA values are included.

Figure 8.1: Comparison of population-based risk compared to individualised based risk for patients between the ages of 60 and 64 with a first PSA between 1 and 1.9ng/mL

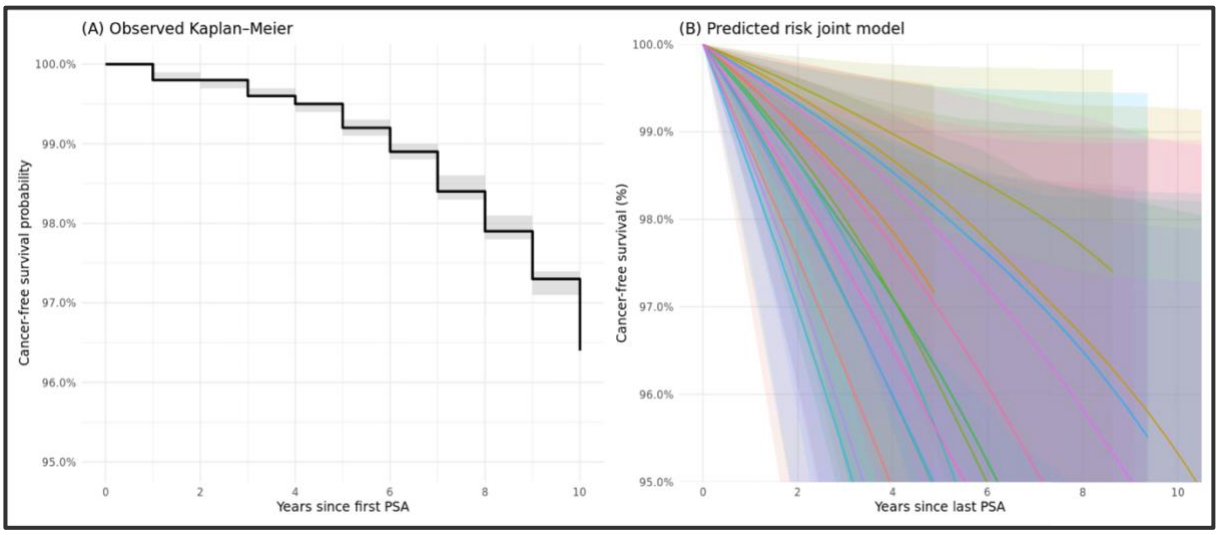


Figure 8.2 and Figure 8.3 illustrate for the same 15 patients how the joint model predicts cumulative risk of prostate cancer per patient.

Figure 8.2 is the survival predictions from first PSA test result, for all patients with a baseline PSA 1 to 1.9 between the ages of 60 and 64. And Figure 8.3 depicts the predicted risk for the same patients based on all of their PSA tests to date.

Figure 8.2: Cumulative incidence predictions for patients between the ages of 60 and 64 with a first PSA between 1 and 1.9 ng/mL based on each patient's first PSA test

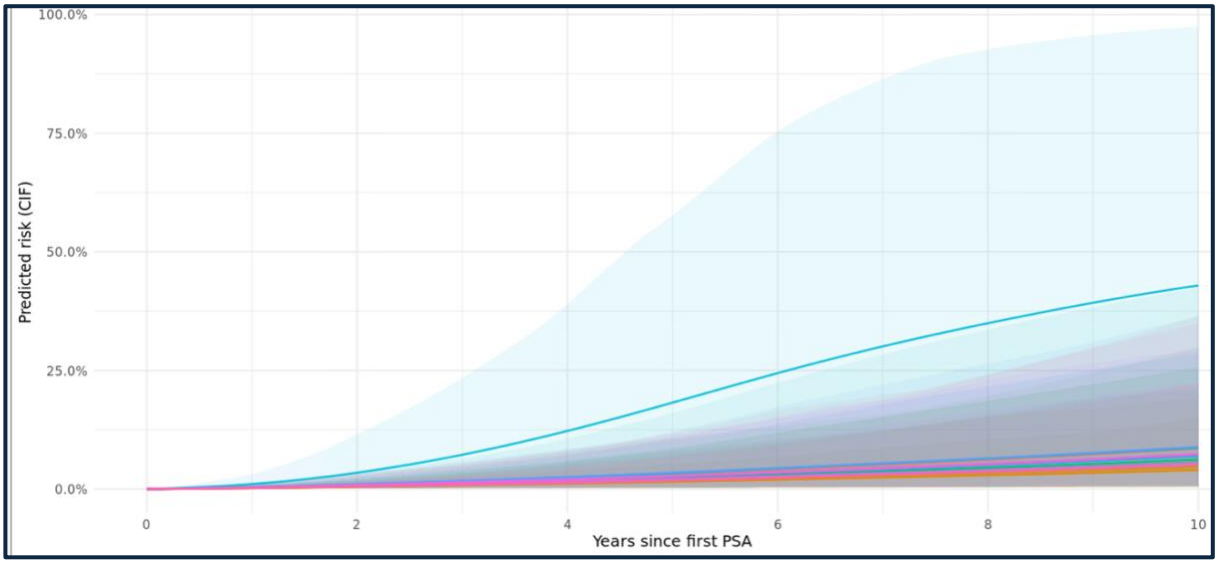
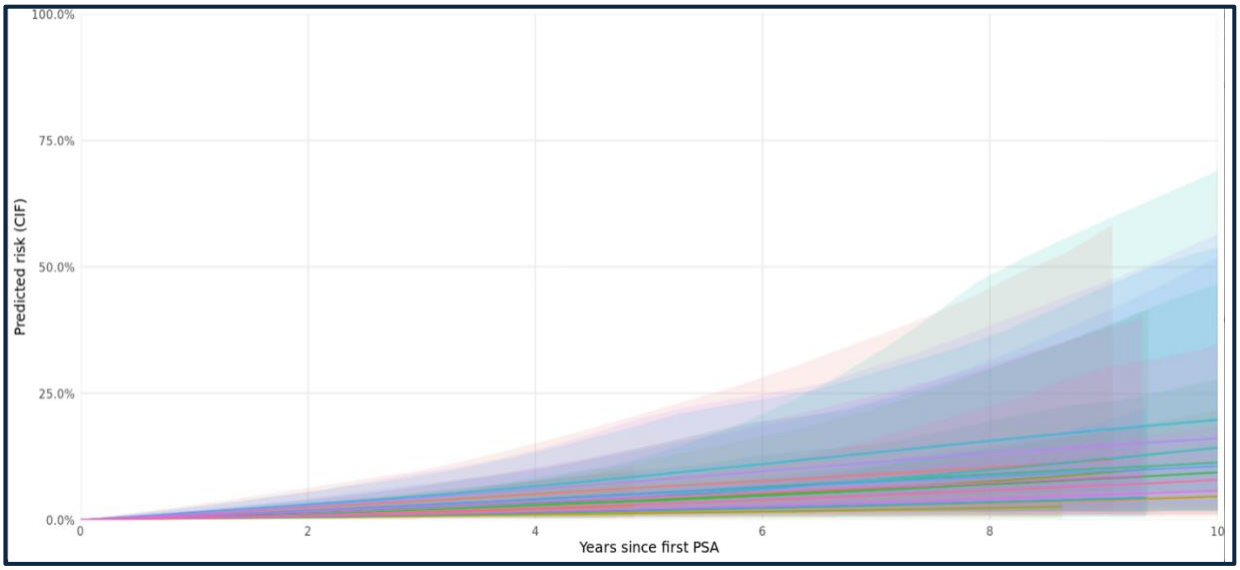


Figure 8.3: Cumulative incidence predictions for patients between the ages of 60 and 64 with a first PSA between 1 and 1.9 ng/mL based on each patient's last PSA test



To further understand how retesting intervals could look in practice, Table 8.1 illustrates the differences between the six baseline PSA level categories for patients aged 60 to 64. Table 8.2 depicts the risk predictions for the same three patients (low, intermediate, and high risk) reported in Chapter 7. To understand how different thresholds have an impact on the length of the retesting interval recommendation, I included estimates for retesting intervals using a 1% and 3% risk from the joint model. The population-based approach

assumes that all patients with similar baseline PSA (e.g. 1 to 1.9 ng/mL at ages 60 to 64) should be retested in five years, regardless of how their PSA values evolve. In contrast, the dynamic approach updates each individual's predicted prostate cancer risk as new PSA results become available. This allows retesting intervals to shorten or lengthen depending on a patient's observed PSA trajectory. For reference, NICE NG12 guidance recommends referring patients who are between the ages of 60 to 64 if their PSA value is above 4.5 ng/mL.

Table 8.1: Comparison population based and joint model retesting intervals recommendations for patients aged 60 to 64 with a first PSA test by each range in Chapter 6

Patient	Age PSA test	PSA value	Estimated retesting interval in years (Joint model Dynamic 1% risk threshold)	Estimated retesting interval in years (Joint model Dynamic 3% risk threshold)	Estimated retesting interval in years (Static Model Baseline PSA 1% risk threshold)
1	60	0.5	6	> 10 (13)	9
1	60	0.7	6	> 10 (13)	
1	62	0.55	7	> 10 (14)	
1	63	0.72	6	> 10 (13)	
2	60	1.7	3	5	5
2	64	1.1	4	8	
2	66	1.7	3	6	
2	67	1.2	3	6	
3	60	2.1	2	4	3
3	63	2.2	2	4	
3	65	1.7	3	5	
3	68	2.2	2	4	
4	60	3.7	1	2.5	< 1 (Refer)
4	61	4.7	1	2	
4	65	4.93	< 1 (Refer)	1	
4	66	3.9	1	2	
5	60	4.1	1	2	< 1 (Refer)
5	61	13.9	< 1 (Refer)	< 1 (Refer)	
5	63	9.4	< 1 (Refer)	< 1 Refer)	
6	60	10.2	< 1 (Refer)	< 1 (Refer)	< 1 (Refer)

Table 8.2: Three patient examples from dynamic retesting intervals section reported in Chapter 7

Patient	Age PSA test	PSA value	Joint model Dynamic 1% risk threshold	Joint model Dynamic 3% risk threshold	Static Model Baseline PSA (1%)
Low risk patient	45	0.8	4	8	> 10
“	52	0.66	4	8	-
“	53	0.68	4	8	-
“	55	1.26	3	6	-
“	57	0.97	3	6	-
Intermediate risk patient	63	0.9	2	3	9
“	64	1.00	2	3	-
“	65	1.33	1	3	-
“	68	5.9	1	2	-
High risk patient	65	8.97	< 1 (Refer)	< 1 (Refer)	< 1 (Refer)

8.6 CLINICAL IMPLICATIONS

This thesis has several implications for clinical practice. Specific implications are described in each chapter. This section highlights three key overarching clinical implications.

8.6.1 LACK OF EVIDENCE-BASED GUIDANCE FOR PSA RETESTING

Clinicians currently lack evidence-based frameworks to help guide repeat PSA testing decisions. In England, neither NICE nor the PCRMP provide guidance on retesting, and international recommendations vary widely from every two-to-four years (AUA) (176) to up to ten years (EAU) (105) (Table 2.2). Only a few countries, such as Sweden, Lithuania, and the Czech Republic, have implemented structured retesting programmes, yet none are supported by direct evidence for retesting intervals.

The importance of PSA retesting is becoming clearer. An update with the results of the 23-year follow up of the ERSPC trial was published in October 2025. Results from the ERSPC trial (135), as mentioned in Chapter 1, highlight that repeated PSA testing led to a 13% relative reduction in prostate cancer mortality after 23 years of follow-up. It was reported that retesting with PSA prevented one death per 456 patients invited to screening and one per 12 patients diagnosed with cancer. In the ERSPC trial patients

were offered a minimum of two and a maximum of eight PSA testing invitations. Most centres implemented a four-year interval between retesting. Sweden and France used a two-year interval, and Belgium applied a seven-year interval. In contrast, the CAP trial (99), described in Chapter 1, only offered a single PSA test to patients. There was 40% participation and a smaller relative reduction in prostate cancer mortality of 8% with an absolute reduction of 0.09% after 16 years. When viewed together, these findings may indicate that repeat PSA testing could improve clinical benefit compared to a single PSA test (135). However, the frequency of repeat tests must be determined.

In Chapters 6 and 7, I show how population-based and/or dynamic joint modelling approaches could provide an evidence base for retesting intervals. Until validated and published, clinicians should approach retesting with caution and use PSA history, age, and individual risk factors when advising patients on when to have a repeat PSA test if they have already made a shared decision to have a first test. Joint modelling offers a framework to determine PSA retesting intervals that are not only individualised but to also change overtime as the patient's risk increases or decreases. This could provide accurate risk stratification at an individual level to ensure patients are receiving the benefits of repeat testing while minimising the harms of overdiagnosis associated with testing too frequently.

8.6.2 PSA TESTING IS CURRENTLY NOT TARGETED TO THOSE WHO BENEFIT MOST

Unregulated PSA retesting increases the risk of overdiagnosis and overtreatment of prostate cancer. It also does little to identify cancers that are likely to cause harm (228). In Chapter 5, I found that PSA testing is often not targeted at patients most likely to benefit. Some patients are overtested, particularly patients with previous low PSA values, no symptoms, or those aged over 70. Others who could benefit from retesting may be missed, such as those at high risk of prostate cancer with a family history or high PSA values. I found that approximately half (48%) of patients with one PSA test were retested between 2000 and 2018, and 73% of patients with multiple PSA tests never had a raised PSA value. The retesting interval for these patients was a median of 17 (IQR 11.1

to 19.0) months. This finding suggests that a form of “annual” screening may be occurring for some patients that does not follow clinical trial evidence or the guideline recommendations specified in Chapter 2.

Clinicians should prioritise PSA retesting for the patients most likely to benefit. In Chapter 6, I found that patients between the ages of 40 and 70 with a first PSA less than 1 ng/mL can safely defer retesting for seven to ten years. This is over 40% of patients who presented to the GP and had a PSA test. The cumulative incidence of prostate cancer ten years after a first PSA less than 1 ng/mL between the ages of 40 and 59 was below 0.7%. This finding highlights an opportunity for clinicians to reduce unnecessary testing in low-risk patients. Those with a PSA < 1 ng/mL between the ages of 40 to 59 to ten years and those between the ages of 60 and 70 between seven and nine years. Clinicians should encourage shared decision-making and help patients weigh the balance between the benefits of testing compared to the harm and overdiagnosis and prioritise repeating PSA tests for those that need it.

8.6.3 INDIVIDUALISED PSA RETESTING APPROACHES

Evidence for PSA retesting intervals remains limited and is a major gap in the literature. A BBC article following publication of my work highlighted that “the benefit of re-testing and ad hoc screening remains uncertain and requires further research to determine evidence-based re-testing intervals that balance the benefits of early detection with the harms of overdiagnosis”(474). Similarly, a consensus paper by Prostate Cancer UK (149) identified the frequency of PSA retesting as a key area requiring further study.

In Chapter 7, I illustrated the feasibility of moving away from a one-size-fits-all schedule and towards an individualised risk-based approach. Although not ready for routine clinical use, this approach provides a foundation for decision-support tools that could guide personalised retesting strategies in primary care. Whether or not the dynamic approach will introduce more or less testing overall depends on the chosen risk threshold for retesting. In this Chapter 7, I illustrated the retesting interval based on a threshold of 3% in alignment with NICE Guidance. In this chapter, I demonstrated the difference in length of the recommended retesting intervals when using a 1% compared

to a 3% threshold. Regardless of the threshold chosen, some patients will be tested more often, while some will be tested less often. This joint modelling approach could help clinicians identify patients who would benefit from more or less testing if they decide to have their first PSA test after a shared decision with their clinician.

8.7 POLICY AND STAKEHOLDER IMPLICATIONS

8.7.1 RAISING AWARENESS OF OVERTESTING AND IMPROVING COMMUNICATION

This research has already contributed to national awareness about PSA testing and the harms of overtesting. Following publication of the results from Chapter 5 in the *BMJ* (377), and a linked editorial (475), the findings were written up by the BBC. I discussed my findings on BBC Breakfast and BBC Radio 4, drawing public and policy attention to the importance of targeted PSA use and the potential harms of unnecessary repeat testing. All media articles published by the end of October 2025 are provided in Appendix 2.

Effective communication about retesting intervals is critical, particularly as home-based PSA tests and private health checks become increasingly available. Policymakers, charities, and public health agencies must ensure that messages around PSA testing are evidence-based and balanced, helping the public understand that more frequent testing does not necessarily equate to better health outcomes. I hope this media attention has encouraged more balanced conversations between clinicians and patients about when PSA testing is appropriate. The coverage, along with public responses on social media, reinforced the message that retesting should be evidence-based. For example, a widely shared tweet captured this: *"Why can't I get an appointment with my GP? One reason: we are doing too many low-value tests because some charities are giving poor/misleading information to men. The NHS is a cake. We all have a responsibility to use it fairly."* While all the blame should not be directed at charities, this tweet reflects a growing public recognition that excessive testing can have both individual-level harms such as unnecessary biopsies, anxiety, and side effects in addition to population-level

consequences, such as strain on GP services and misallocation of limited NHS resources.

8.7.2 Balancing population and individualised testing strategies

The thesis raises important policy questions about the future direction of prostate cancer testing. If the decision is to proceed with targeted risk-stratified PSA testing, should national strategies adopt population-level intervals as described in Chapter 6 or should health systems invest in personalised tools (Chapter 7). At a population level, results from Chapter 6 suggest that an EAU style risk-adapted approach could be feasible in England, with most men under 70 and with PSA less than 1 ng/mL able to defer retesting for seven to ten years. However, Chapter 7 demonstrates that dynamic, individualised approaches using longitudinal PSA data and joint modelling could refine these estimates over time. Policymakers will need to balance the scalability and simplicity of population-level intervals with the precision and resource demands of personalised models. Establishing evidence-based thresholds that minimise both over and undertesting will be critical for implementing safe and efficient PSA retesting strategies for the NHS. Importantly, all decisions about future PSA testing in England should try to avoid interference with the control arm of the TRANSFORM trial.

8.7.3 Data infrastructure

National data programmes such as Get Data Out provide valuable open-source information on cancer diagnoses, but they are unable to offer insights into primary care practices**.** At present, there is no systematic national way to access primary care data without research ethics and a large fee. Before I conducted this research, it was unknown who receives PSA tests, or how often patients are retested. This thesis highlights the importance of using evidence from primary care databases to address questions such as describing PSA testing rates, symptom patterns, and retesting intervals across England. Chapter 5 highlights PSA testing activity, and Chapter 6 provides new evidence on the distribution of baseline PSA values in primary care. These findings establish a foundation for better national monitoring of testing behaviour and highlight the importance of improving data linkage between primary care, diagnostic, and cancer

registry datasets. However, BLOTTED data was only available until 2018. More recent primary care data with linkage to the cancer registry is essential to monitor PSA testing policies in the future. For policymakers, this illustrates the importance of data and the importance of investing in stronger data infrastructure where coded anonymised data is available to the public. Doing so would allow the NHS and research community to evaluate changes in practice, identify inequalities, and measure the impact of any future testing or retesting guidance.

In addition to the need for accessible coded primary care databases, policymakers could look for solutions to make free-text information securely available for research. Free-text is the uncoded data available in the GP records from the clinicians notes. The results presented in this thesis, and all other research using electronic primary care records, are limited to coded primary care data. Currently it is not possible to understand the reasons behind PSA testing decisions. Securely accessible free-text data, specifically for research purposes, would provide essential context for interpreting testing behaviour. For example, whether PSA tests are being ordered following shared decision-making, in response to patient anxiety, or due to clinical symptoms. If large numbers of GPs are being pressured by patients to perform unnecessary tests, this would signal a clear gap for public education and communication. If free-text was available for research this may help inform more specific and effective interventions.

8.8 FUTURE RESEARCH

The findings from this thesis provide several avenues for future research.

8.8.1 MODEL DEVELOPMENT

Methodologically, further research should assess whether incorporating historical PSA trajectories meaningfully improves prediction beyond baseline PSA alone, and whether other routinely collected primary care data (e.g. comorbidities, medications such as alpha-a reductase, ethnicity) enhance predictive performance. Other data could be included, such as polygenic risk scores or mpMRI results if patients were referred then sent back to primary care with no cancer diagnosis. Extending joint models to include

competing risks, such as death or diagnosis of other cancers, would make them more realistic for use in older populations. The use of artificial intelligence to assist radiologists in reading mpMRI images is expected to improve cancer staging for patients by ensuring inexperienced radiologists are reporting the same findings as experienced radiologists (476). Data from these updated diagnostics could further improve the use of PSA in these models.

8.8.2 DEFINING AND EVALUATING RISK THRESHOLDS

Although Chapters 6 and 7 present new methods to estimate prostate cancer risk at the population and individual level, they do not directly answer the question, "how often should patients have a PSA test?" Both methods, in this chapter, relied on a risk threshold set at 1%, to translate risk into an interval. This threshold was chosen to illustrate the feasibility of the retesting intervals design. The optimal threshold and associated retesting interval remain undetermined.

A key next step is to evaluate how best to define and apply dynamic or absolute risk thresholds for PSA retesting. For instance, follow-up could be triggered when an individual's predicted probability of prostate cancer exceeds a certain level, such as 20% within five years or the threshold could be based on risk in every year and retesting could be triggered if the threshold crosses 1% to 3% within the year. Simulation studies to evaluate the trade-offs between earlier detection, overdiagnosis, and test burden are required. It is possible different thresholds could be used in different age ranges or based on patient preferences.

Determining appropriate thresholds for retesting also has ethical and policy considerations which will require a combination of mixed methods research and health economics. The chosen thresholds represent trade-offs between the risk of overtesting versus delayed detection. These trade-offs are not purely statistical. They reflect societal and individual values about acceptable risk. Policymakers, clinicians, and patient advocacy groups will need to define these thresholds transparently. This could be informed by evidence presented in this thesis. Patients and health systems differ in their

preferences for the balance between overdiagnosis and over testing and the costs each is willing to pay to achieve this balance.

8.8.3 Evaluating population baseline PSA risk versus individualised retesting strategies

Further work is needed to explore how population-based strategies, such as those recommended by the EAU, compare with individualised risk-based approaches when implemented at scale. Comparative effectiveness studies or microsimulation modelling could assess cost-effectiveness, feasibility, and equity implications of each strategy. Such analyses would inform whether a hybrid model, population-based at first test and dynamic thereafter, offers an optimal balance between efficiency and precision.

8.8.4 Patient, clinician, and ethical perspectives

Understanding how patients and clinicians perceive different retesting strategies is critical. Qualitative and behavioural research could explore acceptability, communication, and trust in risk-based intervals. This is important when the evidence suggests that less testing could be safe as this is not immediately intuitive. Future work should investigate how to convey these messages in the context of media narratives that often equate “more testing” with better care, and how to support shared decision-making in primary care.

8.8.5 Implementation and system integration

Translating risk-based retesting into practice will require attention to workflow, data and software infrastructure**,** and usability of the tool. Integration of dynamic risk models into electronic health records could provide automated prompts for clinicians, but such tools must be tested for impact on consultation time, clinician workload, and patient outcomes. Implementation studies co-designed with clinicians and patients will be essential to ensure feasibility and acceptability. Clinicians already struggle with keeping appointments to ten minutes and their time with patients is suffering. It has been previously reported that too many open screens impacts the time with patients and this has been compared to a check in desk at the airport (477). Future studies could examine

whether the added value of a risk-based model outweighs the practical inconvenience of using it in clinical consultations, compared with the current uncertainty about when or whether to repeat a PSA test. Providing a publicly accessible online tool to estimate individual PSA retesting intervals could offer a more feasible and user-friendly solution. If built in RShiny interaction with the tool could be monitored as an implementation study.

8.9 Conclusion

In this thesis, I provide new evidence on how often PSA retesting occurs in primary care in England. I highlight that PSA retesting interval recommendations are both varied in guidelines and inconsistently applied in practice. I demonstrate how population and individualised risk-based approaches may be feasible to inform retesting strategies when a patient chooses to have a PSA test in primary care. I hope this research will first help ensure that the right patients are tested at the right intervals at the risk threshold deemed appropriate by policy makers. And second, enable clinicians, patients and the public to use or not use PSA testing with greater confidence, guided by evidence rather than uncertainty.

APPENDIX 1

Appendix 1: Table 1: Data for *Figure 8.4 - Levels of Evidence cited for each component of the monitoring strategy*

Prostate Cancer								
Outcome	No evidence cited	Expert opinion	Other guidance	Retrospective cohort study	Model	Prospective cohort study	Randomised trial	Systematic review or meta-analysis
% Triggers	25	32	25	0	9	0	0	9
% Intervals	32	41	9	0	0	18	0	0
% Tests Biopsy	13	13	9	0	0	35	21	9
% Tests DRE	35	9	12	0	0	26	9	9
% Tests PSA	35	9	12	0	0	26	9	9
% Tests mpMRI	0	15	15	0	0	32	23	15
% Low risk	11	9	30	9	0	9	23	9
Renal Cancer								
Outcome	No evidence cited	Expert opinion	Other guidance	Retrospective cohort study	Model	Prospective cohort study	Randomised trial	Systematic review or meta-analysis
% Triggers	58	30	0	12	0	0	0	0
% Intervals	44	28	28	0	0	0	0	0
% Tests	34	26	10	10	0	10	0	10
% Low risk	26	0	26	0	0	0	0	48
Thyroid Cancer								
Outcome	No evidence cited	Expert opinion	Other guidance	Retrospective cohort study	Model	Prospective cohort study	Randomised trial	Systematic review or meta-analysis
% Triggers	100	0	0	0	0	0	0	0
% Intervals	40	20	0	20	0	0	0	20

% Tests	18	18	0	28	0	18	0	18
% Low risk	0	0	0	18	0	64	0	18

APPENDIX 2

Appendix 2 Table 1: Summary of media dissemination

News outlet	Title
BBC Breakfast	PSA testing segment
BBC Radio 4	Morning show on prostate cancer
BBC (478)	Possible over-testing for prostate cancer
The Independent (479)	Researchers warn doctors could be "overtesting" for prostate cancer
The Times (480)	Suffering stars add to worries about prostate cancer 'overtesting'
MedPage Today(481)	Men Unlikely to Benefit Are Getting PSA Testing Anyhow – Study from across the pond reflects a common U.S. problem
News Medical (482)	Many men receive frequent prostate cancer tests without symptoms
Raw News (483)	Prostate testing may not target those most likely to benefit, warn experts
Bioengineer (484)	Experts caution that prostate testing may miss targeting those who would benefit most

This table represents all the English news articles I could find about the results published from Chapter 5.

The BMJ Press release is available from this link: https://bmjgroup.com/prostate-testing-may-not-target-those-most-likely-to-benefit-warn-experts/

APPENDIX 3

Appendix 3 Table 1: Overall age-standardised rate of PSA tests per 1,000 person years by year (N = 10,235,805)

Year	Crude Rate (per 1,000 person years)	Standardised rate (per 1,000 person years)	95% CI	% change from previous year
2000	11.10	11.83	11.71 -11.95	
2001	16.74	17.92	17.78 - 18.06	51%
2002	22.37	24.03	23.87 - 24.19	34%
2003	28.28	30.47	30.30 - 30.65	27%
2004	36.15	39.05	38.85 - 39.25	28%
2005	38.28	41.43	41.23 - 41.64	6%
2006	40.27	43.60	43.39 - 43.81	5%
2007	43.76	47.14	46.92 - 47.35	8%
2008	49.27	52.72	52.49 - 52.95	12%
2009	53.70	57.28	57.04 - 57.51	9%
2010	54.14	57.60	57.36 - 57.83	1%
2011	55.75	59.01	58.78 - 59.24	2%
2012	56.71	59.81	59.58 - 60.04	1%
2013	62.21	64.99	64.75 - 65.24	9%
2014	61.07	63.37	63.13 - 63.60	-3%
2015	57.33	59.17	58.94 - 59.39	-7%
2016	56.86	58.54	58.32 - 58.76	-1%
2017	54.51	55.95	55.73 - 56.16	-4%
2018	69.72	69.72	69.49 - 69.96	25%

Appendix 3 Table 2: Temporal trends PSA age-standardised testing rates by year and age per 1000 person-years between 2000 and 2018

Age range	Year	Standardised rate	Lower CI 95%	Upper CI 95%
18-29	2000	0.09	0.07	0.11
30-39	2000	0.56	0.51	0.62
40-49	2000	3.30	3.17	3.45
50-59	2000	14.33	14.03	14.64
60-69	2000	30.33	29.80	30.85
70-79	2000	39.20	38.48	39.92
80-89	2000	38.70	37.49	39.94
90+	2000	25.81	23.03	28.84
18-29	2001	0.14	0.11	0.17
30-39	2001	0.93	0.86	0.99
40-49	2001	5.25	5.08	5.43
50-59	2001	21.20	20.84	21.57
60-69	2001	45.48	44.85	46.11

Age range	Year	Standardised rate	Lower CI 95%	Upper CI 95%
70-79	2001	60.08	59.21	60.95
80-89	2001	59.10	57.70	60.53
90+	2001	40.36	37.17	43.75
18-29	2002	0.17	0.14	0.20
30-39	2002	1.23	1.15	1.30
40-49	2002	6.84	6.65	7.03
50-59	2002	28.41	27.99	28.83
60-69	2002	61.61	60.88	62.34
70-79	2002	80.40	79.40	81.41
80-89	2002	78.61	77.04	80.22
90+	2002	55.58	51.91	59.44
18-29	2003	0.21	0.18	0.24
30-39	2003	1.59	1.51	1.68
40-49	2003	8.50	8.29	8.71
50-59	2003	34.97	34.51	35.43
60-69	2003	77.17	76.36	77.98
70-79	2003	104.36	103.22	105.50
80-89	2003	103.03	101.24	104.83
90+	2003	72.79	68.69	77.07
18-29	2004	0.33	0.29	0.37
30-39	2004	2.07	1.97	2.17
40-49	2004	10.61	10.38	10.84
50-59	2004	45.08	44.57	45.60
60-69	2004	99.64	98.73	100.55
70-79	2004	132.15	130.87	133.43
80-89	2004	131.51	129.52	133.53
90+	2004	100.97	96.19	105.92
18-29	2005	0.38	0.34	0.42
30-39	2005	2.33	2.23	2.44
40-49	2005	11.87	11.63	12.11
50-59	2005	47.66	47.13	48.19
60-69	2005	103.49	102.57	104.40
70-79	2005	141.07	139.76	142.40
80-89	2005	142.68	140.62	144.76
90+	2005	103.16	98.33	108.17
18-29	2006	0.41	0.36	0.45
30-39	2006	2.41	2.31	2.52
40-49	2006	12.66	12.42	12.91
50-59	2006	47.74	47.21	48.27
60-69	2006	109.03	108.10	109.96

Age range	Year	Standardised rate	Lower CI 95%	Upper CI 95%
70-79	2006	151.78	150.41	153.14
80-89	2006	151.46	149.37	153.57
90+	2006	117.56	112.45	122.85
18-29	2007	0.38	0.34	0.43
30-39	2007	2.63	2.53	2.74
40-49	2007	13.44	13.19	13.69
50-59	2007	51.24	50.70	51.79
60-69	2007	118.05	117.11	119.00
70-79	2007	164.59	163.18	166.01
80-89	2007	165.88	163.73	168.06
90+	2007	123.48	118.30	128.84
18-29	2008	0.52	0.48	0.57
30-39	2008	3.01	2.89	3.13
40-49	2008	15.86	15.59	16.12
50-59	2008	58.10	57.52	58.69
60-69	2008	131.31	130.33	132.29
70-79	2008	183.43	181.95	184.91
80-89	2008	181.17	178.95	183.42
90+	2008	135.02	129.57	140.64
18-29	2009	0.63	0.58	0.69
30-39	2009	3.72	3.59	3.85
40-49	2009	18.27	17.98	18.55
50-59	2009	65.23	64.62	65.84
60-69	2009	140.63	139.63	141.64
70-79	2009	197.10	195.57	198.63
80-89	2009	190.60	188.35	192.87
90+	2009	146.46	140.83	152.26
18-29	2010	0.65	0.60	0.71
30-39	2010	3.65	3.52	3.78
40-49	2010	18.96	18.67	19.24
50-59	2010	63.33	62.73	63.93
60-69	2010	141.59	140.59	142.59
70-79	2010	199.97	198.44	201.50
80-89	2010	194.43	192.18	196.70
90+	2010	153.68	148.17	159.34
18-29	2011	0.77	0.72	0.83
30-39	2011	3.99	3.86	4.13
40-49	2011	20.11	19.82	20.41
50-59	2011	64.67	64.07	65.27
60-69	2011	143.80	142.80	144.80

Age range	Year	Standardised rate	Lower CI 95%	Upper CI 95%
70-79	2011	202.37	200.84	203.92
80-89	2011	204.71	202.42	207.02
90+	2011	160.14	154.80	165.62
18-29	2012	0.82	0.76	0.88
30-39	2012	4.42	4.28	4.56
40-49	2012	20.60	20.30	20.90
50-59	2012	65.56	64.97	66.16
60-69	2012	143.32	142.33	144.32
70-79	2012	206.78	205.24	208.34
80-89	2012	209.30	207.01	211.61
90+	2012	157.90	152.78	163.15
18-29	2013	0.99	0.93	1.06
30-39	2013	4.74	4.59	4.89
40-49	2013	23.93	23.61	24.25
50-59	2013	71.91	71.30	72.53
60-69	2013	154.44	153.42	155.47
70-79	2013	225.15	223.55	226.75
80-89	2013	220.42	218.08	222.78
90+	2013	165.78	160.60	171.09
18-29	2014	0.99	0.93	1.05
30-39	2014	4.79	4.64	4.94
40-49	2014	23.42	23.10	23.74
50-59	2014	69.81	69.21	70.40
60-69	2014	147.76	146.77	148.76
70-79	2014	220.82	219.27	222.38
80-89	2014	221.35	219.03	223.69
90+	2014	162.74	157.70	167.90
18-29	2015	0.98	0.92	1.05
30-39	2015	4.58	4.44	4.72
40-49	2015	21.63	21.33	21.94
50-59	2015	63.43	62.88	63.99
60-69	2015	137.40	136.45	138.35
70-79	2015	207.48	206.00	208.97
80-89	2015	213.54	211.29	215.81
90+	2015	157.56	152.68	162.55
18-29	2016	0.98	0.92	1.05
30-39	2016	4.65	4.51	4.79
40-49	2016	21.52	21.21	21.82
50-59	2016	63.48	62.93	64.02
60-69	2016	132.82	131.89	133.75

Age range	Year	Standardised rate	Lower CI 95%	Upper CI 95%
70-79	2016	207.61	206.16	209.08
80-89	2016	211.32	209.11	213.55
90+	2016	158.79	153.99	163.70
18-29	2017	1.07	1.01	1.14
30-39	2017	4.73	4.59	4.87
40-49	2017	20.98	20.68	21.28
50-59	2017	60.77	60.24	61.30
60-69	2017	125.18	124.28	126.08
70-79	2017	198.38	196.99	199.77
80-89	2017	203.46	201.32	205.61
90+	2017	150.15	145.55	154.85
18-29	2018	1.07	1.01	1.14
30-39	2018	4.97	4.83	5.12
40-49	2018	25.17	24.84	25.51
50-59	2018	81.30	80.69	81.92
60-69	2018	161.55	160.53	162.58
70-79	2018	240.31	238.80	241.82
80-89	2018	238.41	236.10	240.74
90+	2018	164.23	159.43	169.14

Appendix 3 Table 3: Temporal trends PSA age-standardised testing rates by year and ethnicity per 1,000 person-years between 2000 and 2018

Ethnicity	Year	Standardised rate	Lower CI 95%	Upper CI 95%
Asian	2000	5.44	4.64	6.62
Black	2000	7.86	7.06	8.83
Mixed	2000	3.87	2.92	5.94
Other	2000	7.85	6.91	8.95
South Asian	2000	5.58	5.04	6.18
Unknown	2000	5.45	5.29	5.61
White	2000	14.96	14.79	15.15
Asian	2001	7.69	6.81	8.75
Black	2001	12.86	11.82	14.02
Mixed	2001	8.20	6.82	10.34
Other	2001	12.09	10.97	13.35
South Asian	2001	8.28	7.70	8.92
Unknown	2001	8.16	7.97	8.36
White	2001	22.52	22.31	22.72
Asian	2002	11.41	10.37	12.58
Black	2002	16.00	14.89	17.22

Ethnicity	Year	Standardised rate	Lower CI 95%	Upper CI 95%
Mixed	2002	10.80	9.30	12.67
Other	2002	13.83	12.69	15.06
South Asian	2002	11.81	11.13	12.54
Unknown	2002	10.11	9.89	10.33
White	2002	30.05	29.82	30.28
Asian	2003	13.38	12.33	14.54
Black	2003	19.07	17.93	20.30
Mixed	2003	13.02	11.44	14.85
Other	2003	16.27	15.09	17.53
South Asian	2003	14.91	14.17	15.68
Unknown	2003	12.59	12.34	12.85
White	2003	37.69	37.44	37.94
Asian	2004	18.90	17.69	20.20
Black	2004	27.36	26.09	28.70
Mixed	2004	17.84	16.06	19.83
Other	2004	23.27	21.90	24.70
South Asian	2004	21.54	20.69	22.44
Unknown	2004	15.29	15.00	15.58
White	2004	47.65	47.38	47.92
Asian	2005	21.84	20.60	23.14
Black	2005	33.05	31.74	34.43
Mixed	2005	18.96	17.21	20.88
Other	2005	25.84	24.45	27.29
South Asian	2005	25.93	25.03	26.87
Unknown	2005	15.41	15.11	15.72
White	2005	49.66	49.40	49.93
Asian	2006	24.18	22.95	25.48
Black	2006	36.59	35.29	37.94
Mixed	2006	21.63	19.84	23.55
Other	2006	27.49	26.11	28.92
South Asian	2006	28.62	27.70	29.58
Unknown	2006	15.20	14.88	15.52
White	2006	51.66	51.39	51.92
Asian	2007	25.73	24.51	27.00
Black	2007	40.66	39.34	42.02
Mixed	2007	23.45	21.66	25.36
Other	2007	28.80	27.45	30.21
South Asian	2007	31.97	31.03	32.94
Unknown	2007	14.89	14.55	15.24
White	2007	55.44	55.17	55.71

Ethnicity	Year	Standardised rate	Lower CI 95%	Upper CI 95%
Asian	2008	28.44	27.22	29.71
Black	2008	47.29	45.93	48.68
Mixed	2008	25.61	23.83	27.49
Other	2008	32.15	30.78	33.58
South Asian	2008	36.83	35.84	37.84
Unknown	2008	15.06	14.70	15.43
White	2008	61.67	61.39	61.95
Asian	2009	32.78	31.52	34.09
Black	2009	53.55	52.15	54.97
Mixed	2009	30.62	28.74	32.61
Other	2009	36.65	35.23	38.11
South Asian	2009	41.73	40.71	42.78
Unknown	2009	15.97	15.58	16.37
White	2009	66.36	66.08	66.65
Asian	2010	32.69	31.48	33.94
Black	2010	55.83	54.46	57.24
Mixed	2010	30.54	28.72	32.45
Other	2010	37.51	36.13	38.92
South Asian	2010	42.29	41.29	43.31
Unknown	2010	15.54	15.14	15.95
White	2010	66.32	66.03	66.60
Asian	2011	33.25	32.08	34.45
Black	2011	57.41	56.07	58.79
Mixed	2011	32.01	30.22	33.89
Other	2011	37.84	36.50	39.22
South Asian	2011	43.36	42.37	44.36
Unknown	2011	16.67	16.24	17.10
White	2011	67.51	67.23	67.80
Asian	2012	33.38	32.26	34.54
Black	2012	59.06	57.74	60.40
Mixed	2012	31.46	29.74	33.25
Other	2012	38.16	36.86	39.49
South Asian	2012	43.12	42.17	44.09
Unknown	2012	16.92	16.48	17.37
White	2012	68.22	67.94	68.50
Asian	2013	33.84	32.75	34.96
Black	2013	63.67	62.35	65.00
Mixed	2013	32.33	30.65	34.08
Other	2013	40.74	39.45	42.07
South Asian	2013	45.47	44.52	46.44

Ethnicity	Year	Standardised rate	Lower CI 95%	Upper CI 95%
Unknown	2013	18.90	18.42	19.38
White	2013	74.01	73.72	74.30
Asian	2014	34.19	33.13	35.28
Black	2014	65.25	63.97	66.55
Mixed	2014	32.49	30.88	34.17
Other	2014	41.59	40.33	42.88
South Asian	2014	44.90	43.98	45.82
Unknown	2014	19.25	18.77	19.75
White	2014	71.62	71.34	71.91
Asian	2015	30.99	30.02	31.99
Black	2015	60.16	58.98	61.36
Mixed	2015	30.59	29.09	32.16
Other	2015	38.64	37.48	39.83
South Asian	2015	41.33	40.48	42.19
Unknown	2015	17.68	17.22	18.15
White	2015	66.91	66.64	67.18
Asian	2016	30.13	29.21	31.07
Black	2016	57.27	56.16	58.39
Mixed	2016	28.33	26.94	29.78
Other	2016	36.05	34.97	37.16
South Asian	2016	38.04	37.25	38.84
Unknown	2016	17.90	17.44	18.36
White	2016	66.49	66.23	66.76
Asian	2017	28.88	28.02	29.77
Black	2017	54.22	53.17	55.27
Mixed	2017	28.82	27.47	30.22
Other	2017	36.11	35.07	37.16
South Asian	2017	35.22	34.48	35.97
Unknown	2017	16.77	16.34	17.21
White	2017	63.53	63.27	63.79
Asian	2018	30.70	29.82	31.59
Black	2018	61.65	60.55	62.76
Mixed	2018	32.89	31.48	34.35
Other	2018	40.36	39.28	41.45
South Asian	2018	39.39	38.62	40.17
Unknown	2018	21.70	21.21	22.19
White	2018	80.17	79.88	80.47

Appendix 3 Table 4: Temporal trends PSA age-standardised testing rates by year and IMD quintile per 1,000 person-years between 2000 and 2018

IMD Quintile	Year	Standardised rate	Lower CI 95%	Upper CI 95%
1	2000	18.77	18.43	19.11
2	2000	15.16	14.86	15.47
3	2000	12.03	11.77	12.31
4	2000	8.11	7.90	8.32
5	2000	5.64	5.46	5.82
1	2001	28.15	27.74	28.56
2	2001	22.73	22.38	23.09
3	2001	18.40	18.08	18.73
4	2001	12.45	12.20	12.70
5	2001	8.76	8.54	8.98
1	2002	37.85	37.38	38.31
2	2002	30.38	29.97	30.79
3	2002	24.44	24.08	24.81
4	2002	16.43	16.15	16.72
5	2002	12.14	11.89	12.39
1	2003	47.60	47.08	48.11
2	2003	38.36	37.90	38.81
3	2003	30.86	30.45	31.27
4	2003	20.80	20.49	21.13
5	2003	16.09	15.80	16.38
1	2004	59.31	58.74	59.88
2	2004	48.68	48.17	49.19
3	2004	38.80	38.35	39.26
4	2004	27.75	27.39	28.12
5	2004	22.01	21.68	22.35
1	2005	59.66	59.10	60.23
2	2005	50.80	50.29	51.32
3	2005	41.94	41.47	42.41
4	2005	30.94	30.55	31.33
5	2005	24.94	24.59	25.30
1	2006	62.27	61.70	62.84
2	2006	53.23	52.71	53.75
3	2006	44.37	43.89	44.85
4	2006	32.74	32.34	33.13
5	2006	26.35	25.99	26.71
1	2007	66.81	66.23	67.40
2	2007	57.87	57.33	58.41
3	2007	47.93	47.43	48.42

IMD Quintile	Year	Standardised rate	Lower CI 95%	Upper CI 95%
4	2007	35.38	34.98	35.79
5	2007	28.45	28.08	28.83
1	2008	74.22	73.61	74.83
2	2008	64.65	64.10	65.22
3	2008	53.37	52.86	53.89
4	2008	39.30	38.88	39.73
5	2008	32.68	32.28	33.08
1	2009	79.08	78.46	79.71
2	2009	68.98	68.41	69.55
3	2009	58.27	57.74	58.80
4	2009	44.45	44.01	44.91
5	2009	36.06	35.64	36.48
1	2010	78.13	77.52	78.74
2	2010	68.71	68.14	69.28
3	2010	58.40	57.87	58.93
4	2010	45.26	44.81	45.71
5	2010	37.86	37.43	38.29
1	2011	79.56	78.95	80.18
2	2011	70.21	69.64	70.78
3	2011	59.90	59.37	60.43
4	2011	46.33	45.88	46.78
5	2011	39.43	38.99	39.86
1	2012	79.01	78.41	79.62
2	2012	70.87	70.31	71.44
3	2012	60.79	60.26	61.32
4	2012	48.23	47.77	48.69
5	2012	40.33	39.89	40.76
1	2013	84.58	83.96	85.20
2	2013	76.26	75.67	76.84
3	2013	66.13	65.58	66.68
4	2013	53.08	52.61	53.56
5	2013	45.02	44.56	45.48
1	2014	82.49	81.88	83.09
2	2014	74.23	73.67	74.80
3	2014	64.23	63.70	64.77
4	2014	52.24	51.78	52.71
5	2014	43.61	43.16	44.05
1	2015	78.86	78.28	79.44
2	2015	68.85	68.31	69.39
3	2015	59.84	59.33	60.35

IMD Quintile	Year	Standardised rate	Lower CI 95%	Upper CI 95%
4	2015	48.53	48.09	48.98
5	2015	39.64	39.22	40.06
1	2016	79.61	79.03	80.19
2	2016	68.24	67.72	68.78
3	2016	58.88	58.38	59.38
4	2016	46.94	46.51	47.38
5	2016	38.86	38.46	39.28
1	2017	75.52	74.96	76.07
2	2017	65.45	64.94	65.96
3	2017	56.53	56.05	57.01
4	2017	44.93	44.52	45.35
5	2017	37.21	36.82	37.61
1	2018	96.99	96.36	97.62
2	2018	82.53	81.96	83.10
3	2018	70.22	69.69	70.76
4	2018	54.34	53.89	54.80
5	2018	44.37	43.94	44.81

Appendix 3 Table 5: Temporal trends PSA age-standardised testing rates by year and region per 1,000 person-years between 2000 and 2018

Region	Year	Standardised rate	Lower CI	Upper CI
East Midlands	2000	11.65	10.95	12.39
East Midlands	2001	19.53	18.65	20.45
East Midlands	2002	25.85	24.84	26.90
East Midlands	2003	30.80	29.70	31.93
East Midlands	2004	43.73	42.41	45.09
East Midlands	2005	41.76	40.48	43.08
East Midlands	2006	41.70	40.43	43.01
East Midlands	2007	49.44	48.07	50.83
East Midlands	2008	52.09	50.71	53.51
East Midlands	2009	55.83	54.41	57.28
East Midlands	2010	54.30	52.92	55.71
East Midlands	2011	54.53	53.16	55.93
East Midlands	2012	56.11	54.73	57.51
East Midlands	2013	60.08	58.67	61.53
East Midlands	2014	59.49	58.10	60.90
East Midlands	2015	56.61	55.29	57.96

Region	Year	Standardised rate	Lower CI	Upper CI
East Midlands	2016	56.72	55.42	58.05
East Midlands	2017	57.04	55.76	58.35
East Midlands	2018	69.52	68.11	70.96
East of England	2000	19.56	18.82	20.32
East of England	2001	28.61	27.74	29.50
East of England	2002	33.60	32.67	34.55
East of England	2003	37.38	36.41	38.37
East of England	2004	41.83	40.81	42.86
East of England	2005	48.06	46.99	49.16
East of England	2006	47.91	46.84	48.99
East of England	2007	53.14	52.03	54.26
East of England	2008	60.14	58.98	61.33
East of England	2009	65.47	64.27	66.69
East of England	2010	66.81	65.60	68.03
East of England	2011	65.46	64.28	66.66
East of England	2012	70.15	68.94	71.38
East of England	2013	77.68	76.41	78.96
East of England	2014	75.95	74.71	77.21
East of England	2015	71.29	70.10	72.49
East of England	2016	70.02	68.86	71.19
East of England	2017	67.34	66.22	68.48
East of England	2018	83.44	82.18	84.71
London	2000	8.52	8.30	8.74
London	2001	12.66	12.40	12.92
London	2002	15.35	15.07	15.64
London	2003	17.69	17.39	18.00
London	2004	24.52	24.17	24.88
London	2005	27.90	27.52	28.28
London	2006	31.98	31.58	32.39
London	2007	34.81	34.39	35.23
London	2008	39.96	39.51	40.41
London	2009	46.65	46.16	47.13
London	2010	48.65	48.16	49.14
London	2011	50.26	49.77	50.75
London	2012	48.45	47.97	48.93
London	2013	51.18	50.70	51.68
London	2014	52.36	51.87	52.85
London	2015	47.57	47.12	48.03
London	2016	46.24	45.81	46.68
London	2017	43.11	42.70	43.53

Region	Year	Standardised rate	Lower CI	Upper CI
London	2018	49.54	49.10	49.98
North East	2000	7.65	7.13	8.21
North East	2001	15.53	14.82	16.27
North East	2002	18.17	17.41	18.97
North East	2003	22.00	21.16	22.87
North East	2004	23.53	22.67	24.43
North East	2005	27.72	26.80	28.67
North East	2006	27.80	26.89	28.74
North East	2007	28.60	27.69	29.54
North East	2008	31.57	30.62	32.55
North East	2009	33.21	32.25	34.20
North East	2010	34.56	33.59	35.56
North East	2011	37.06	36.06	38.08
North East	2012	37.37	36.38	38.38
North East	2013	43.64	42.58	44.73
North East	2014	41.58	40.55	42.63
North East	2015	39.68	38.68	40.70
North East	2016	38.99	38.01	40.00
North East	2017	37.98	37.02	38.96
North East	2018	48.37	47.29	49.47
North West	2000	9.81	9.56	10.06
North West	2001	15.47	15.16	15.78
North West	2002	21.14	20.78	21.49
North West	2003	29.35	28.94	29.77
North West	2004	40.07	39.59	40.55
North West	2005	41.58	41.10	42.06
North West	2006	42.52	42.04	43.01
North West	2007	46.90	46.40	47.41
North West	2008	52.59	52.06	53.12
North West	2009	55.65	55.11	56.19
North West	2010	56.97	56.43	57.51
North West	2011	59.36	58.81	59.91
North West	2012	61.14	60.59	61.70
North West	2013	66.98	66.41	67.56
North West	2014	63.96	63.40	64.52
North West	2015	57.44	56.92	57.96
North West	2016	57.38	56.87	57.90
North West	2017	53.11	52.62	53.60
North West	2018	64.83	64.29	65.37
South East	2000	15.11	14.81	15.41

Region	Year	Standardised rate	Lower CI	Upper CI
South East	2001	23.59	23.22	23.95
South East	2002	30.43	30.02	30.84
South East	2003	40.32	39.85	40.79
South East	2004	52.26	51.74	52.80
South East	2005	52.58	52.05	53.11
South East	2006	54.77	54.24	55.30
South East	2007	57.02	56.49	57.56
South East	2008	62.92	62.36	63.47
South East	2009	68.59	68.02	69.17
South East	2010	68.18	67.62	68.75
South East	2011	68.69	68.13	69.26
South East	2012	69.67	69.11	70.24
South East	2013	75.33	74.75	75.91
South East	2014	72.49	71.92	73.05
South East	2015	68.90	68.36	69.44
South East	2016	70.55	70.01	71.09
South East	2017	68.57	68.05	69.10
South East	2018	87.42	86.82	88.02
South West	2000	18.11	17.69	18.54
South West	2001	23.90	23.43	24.38
South West	2002	32.12	31.58	32.67
South West	2003	37.48	36.90	38.07
South West	2004	42.72	42.10	43.33
South West	2005	46.73	46.09	47.37
South West	2006	49.00	48.35	49.65
South West	2007	53.60	52.94	54.28
South West	2008	60.16	59.46	60.86
South West	2009	60.57	59.88	61.28
South West	2010	59.88	59.19	60.57
South West	2011	61.07	60.38	61.76
South West	2012	62.25	61.56	62.94
South West	2013	67.02	66.31	67.73
South West	2014	67.07	66.37	67.78
South West	2015	65.79	65.10	66.49
South West	2016	61.05	60.40	61.71
South West	2017	61.32	60.67	61.97
South West	2018	78.51	77.78	79.25
West Midlands	2000	8.25	8.01	8.50
West Midlands	2001	13.65	13.35	13.96
West Midlands	2002	23.34	22.95	23.74

Region	Year	Standardised rate	Lower CI	Upper CI
West Midlands	2003	32.23	31.78	32.69
West Midlands	2004	41.39	40.87	41.90
West Midlands	2005	43.77	43.25	44.30
West Midlands	2006	46.34	45.81	46.88
West Midlands	2007	49.81	49.26	50.36
West Midlands	2008	56.12	55.54	56.70
West Midlands	2009	61.81	61.21	62.41
West Midlands	2010	61.51	60.92	62.11
West Midlands	2011	63.64	63.04	64.25
West Midlands	2012	65.06	64.46	65.67
West Midlands	2013	71.55	70.92	72.18
West Midlands	2014	68.40	67.80	69.01
West Midlands	2015	63.04	62.47	63.61
West Midlands	2016	61.89	61.33	62.45
West Midlands	2017	57.92	57.39	58.46
West Midlands	2018	74.73	74.12	75.34
Yorkshire and The Humber	2000	14.41	13.73	15.14
Yorkshire and The Humber	2001	19.17	18.40	19.97
Yorkshire and The Humber	2002	24.67	23.81	25.56
Yorkshire and The Humber	2003	25.97	25.10	26.87
Yorkshire and The Humber	2004	31.45	30.50	32.42
Yorkshire and The Humber	2005	34.92	33.94	35.93
Yorkshire and The Humber	2006	36.89	35.89	37.91
Yorkshire and The Humber	2007	41.99	40.94	43.07
Yorkshire and The Humber	2008	44.88	43.80	45.98
Yorkshire and The Humber	2009	51.02	49.88	52.18
Yorkshire and The Humber	2010	47.04	45.95	48.14
Yorkshire and The Humber	2011	48.22	47.13	49.34
Yorkshire and The Humber	2012	48.03	46.94	49.13
Yorkshire and The Humber	2013	53.51	52.38	54.67
Yorkshire and The Humber	2014	50.98	49.89	52.09
Yorkshire and The Humber	2015	49.39	48.34	50.46
Yorkshire and The Humber	2016	52.19	51.12	53.28
Yorkshire and The Humber	2017	50.14	49.11	51.19
Yorkshire and The Humber	2018	64.67	63.50	65.86

Appendix 3 Table 6: Temporal trends PSA age-standardised testing rates by year and PSA value above or below the age-specific threshold per 1,000 person-years between 2000 and 2018

Above or below the age-specific threshold	Year	Standardised rate	Lower CI	Upper CI
Above the age-specific threshold	2000	2.53	2.47	2.58
Above the age-specific threshold	2001	3.88	3.81	3.94
Above the age-specific threshold	2002	5.17	5.10	5.25
Above the age-specific threshold	2003	6.68	6.59	6.76
Above the age-specific threshold	2004	8.31	8.21	8.40
Above the age-specific threshold	2005	8.54	8.45	8.64
Above the age-specific threshold	2006	9.40	9.31	9.50
Above the age-specific threshold	2007	9.85	9.75	9.95
Above the age-specific threshold	2008	10.12	10.02	10.22
Above the age-specific threshold	2009	10.85	10.75	10.95
Above the age-specific threshold	2010	11.04	10.94	11.14
Above the age-specific threshold	2011	11.47	11.36	11.57
Above the age-specific threshold	2012	11.58	11.48	11.69
Above the age-specific threshold	2013	12.01	11.91	12.12
Above the age-specific threshold	2014	11.58	11.48	11.68
Above the age-specific threshold	2015	11.06	10.96	11.15
Above the age-specific threshold	2016	10.77	10.68	10.87
Above the age-specific threshold	2017	10.44	10.35	10.54
Above the age-specific threshold	2018	11.89	11.80	11.99
Below the age-specific threshold	2000	9.30	9.20	9.40
Below the age-specific threshold	2001	14.04	13.92	14.16
Below the age-specific threshold	2002	18.85	18.71	19.00
Below the age-specific threshold	2003	23.80	23.64	23.95
Below the age-specific threshold	2004	30.75	30.57	30.92
Below the age-specific threshold	2005	32.89	32.71	33.08
Below the age-specific threshold	2006	34.19	34.01	34.38
Below the age-specific threshold	2007	37.29	37.10	37.48
Below the age-specific threshold	2008	42.60	42.39	42.80
Below the age-specific threshold	2009	46.43	46.22	46.64
Below the age-specific threshold	2010	46.55	46.35	46.76
Below the age-specific threshold	2011	47.54	47.33	47.75
Below the age-specific threshold	2012	48.23	48.02	48.44
Below the age-specific threshold	2013	52.98	52.77	53.20
Below the age-specific threshold	2014	51.78	51.57	52.00
Below the age-specific threshold	2015	48.11	47.91	48.31
Below the age-specific C threshold	2016	47.76	47.57	47.96
Below the age-specific threshold	2017	45.50	45.31	45.69
Below the age-specific threshold	2018	57.83	57.62	58.05

Caption: PSA values were categorised as above the age specific threshold if patients were aged 18-49 years with a PSA value >2.5 ng/mL, 50-59 years with a PSA value >3.5 ng/mL, 60-69 years with a PSA value >4.5 ng/mL, and ≥70 with a PSA value >6.5 ng/mL

Appendix 3 Table 7: Temporal trends PSA age-standardised testing rates by year and symptom presentation per 1,000 person-years between 2000 and 2018

Symptom present 90 days before PSA test (Yes/No)	Year	Standardised rate	Lower CI	Upper CI
Symptoms present	2000	3.33	3.26	3.39
No symptoms present	2000	8.50	8.40	8.60
Symptoms present	2001	4.91	4.84	4.99
No symptoms present	2001	13.00	12.88	13.12
Symptoms present	2002	6.58	6.49	6.66
No symptoms present	2002	17.45	17.31	17.59
Symptoms present	2003	8.21	8.11	8.30
No symptoms present	2003	22.27	22.12	22.42
Symptoms present	2004	10.15	10.05	10.25
No symptoms present	2004	28.90	28.73	29.08
Symptoms present	2005	11.13	11.03	11.24
No symptoms present	2005	30.30	30.13	30.48
Symptoms present	2006	11.51	11.40	11.62
No symptoms present	2006	32.09	31.91	32.27
Symptoms present	2007	12.59	12.48	12.71
No symptoms present	2007	34.54	34.36	34.73
Symptoms present	2008	13.64	13.53	13.76
No symptoms present	2008	39.08	38.88	39.27
Symptoms present	2009	14.85	14.73	14.97
No symptoms present	2009	42.42	42.22	42.62
Symptoms present	2010	15.36	15.24	15.48
No symptoms present	2010	42.24	42.04	42.44
Symptoms present	2011	16.00	15.87	16.12
No symptoms present	2011	43.01	42.82	43.21
Symptoms present	2012	16.23	16.11	16.35
No symptoms present	2012	43.58	43.38	43.78
Symptoms present	2013	18.36	18.23	18.49
No symptoms present	2013	46.63	46.43	46.84
Symptoms present	2014	17.41	17.29	17.53
No symptoms present	2014	45.96	45.76	46.16
Symptoms present	2015	15.92	15.80	16.03
No symptoms present	2015	43.25	43.06	43.44

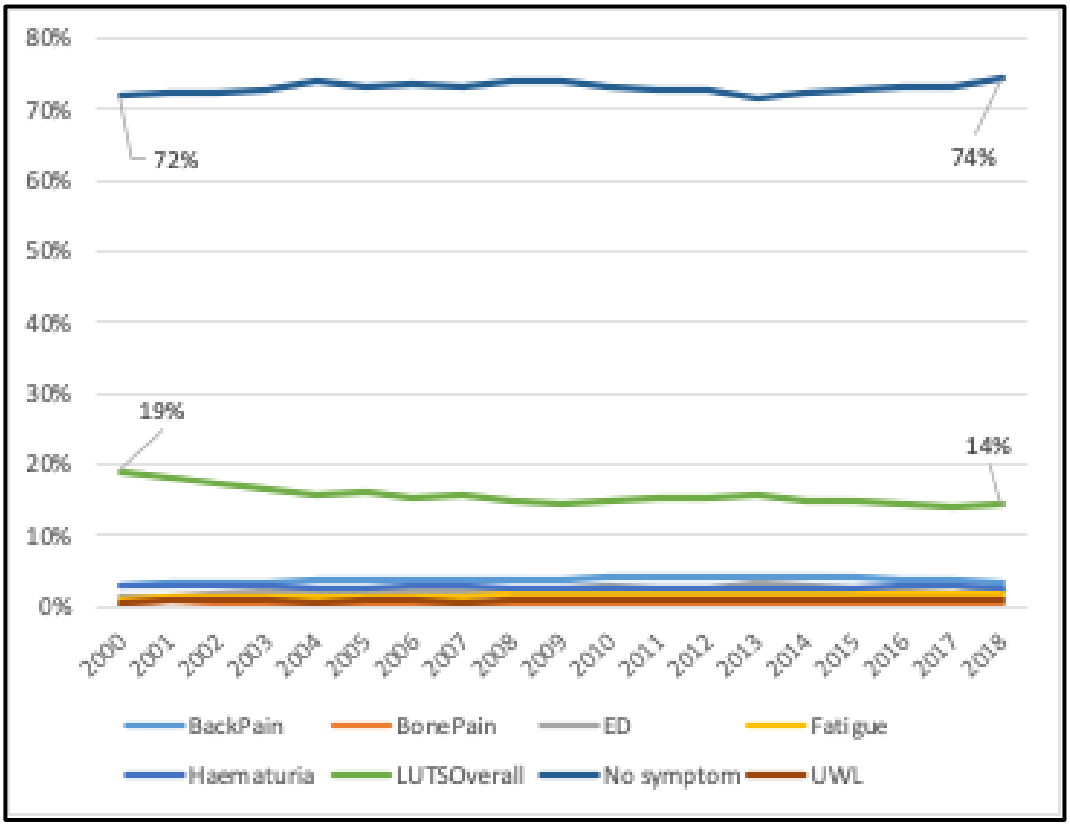
Symptom present 90 days before PSA test (Yes/No)	Year	Standardised rate	Lower CI	Upper CI
Symptoms present	2016	15.68	15.57	15.79
No symptoms present	2016	42.86	42.67	43.05
Symptoms present	2017	14.98	14.87	15.09
No symptoms present	2017	40.97	40.79	41.15
Symptoms present	2018	17.92	17.80	18.05
No symptoms present	2018	51.80	51.60	52.00

Appendix 3 Table 8: Temporal trends PSA age-standardised testing rates by year and family history of prostate cancer per 1,000 person-years between 2000 and 2018

Family history of prostate cancer	Year	Standardised rate	Lower CI	Upper CI
No family history	2000	11.77	11.65	11.89
Family history	2000	42.52	33.69	55.02
No family history	2001	17.83	17.69	17.97
Family history	2001	50.59	42.46	61.36
No family history	2002	23.90	23.74	24.06
Family history	2002	72.45	63.90	82.86
No family history	2003	30.31	30.13	30.49
Family history	2003	89.90	81.04	99.99
No family history	2004	38.83	38.63	39.03
Family history	2004	117.36	108.06	127.59
No family history	2005	41.14	40.93	41.35
Family history	2005	151.36	138.82	170.89
No family history	2006	43.25	43.04	43.46
Family history	2006	162.47	152.83	175.69
No family history	2007	46.75	46.54	46.97
Family history	2007	166.97	158.12	177.49
No family history	2008	52.22	52.00	52.45
Family history	2008	196.51	187.66	206.42
No family history	2009	56.72	56.49	56.95
Family history	2009	204.39	196.15	213.14
No family history	2010	57.04	56.80	57.27
Family history	2010	194.28	186.84	202.11
No family history	2011	58.37	58.13	58.60
Family history	2011	208.23	200.97	215.76
No family history	2012	59.12	58.89	59.35
Family history	2012	211.52	204.60	218.66
No family history	2013	64.13	63.89	64.37
Family history	2013	242.31	235.33	249.47

Family history of prostate cancer	Year	Standardised rate	Lower CI	Upper CI
No family history	2014	62.48	62.25	62.72
Family history	2014	236.68	230.12	243.41
No family history	2015	58.26	58.04	58.48
Family history	2015	230.57	224.38	236.91
No family history	2016	57.55	57.33	57.77
Family history	2016	237.26	231.27	243.37
No family history	2017	54.89	54.68	55.11
Family history	2017	239.37	233.57	245.28
No family history	2018	68.34	68.11	68.58
Family history	2018	305.92	299.44	312.50

Appendix 3 Figure 2: Proportion of PSA tests with a symptom recorded in the 90 days before the test by symptom between 2000 and 2018



The proportion of PSA tests with symptoms recorded 0-90 days before the test remained stable throughout the 19 years of follow up, except LUTS declined from 19% - 14%.

Chapter 5: Sensitivity analysis 1

The impact on PSA retesting intervals if only considered PSA tests that were over one month apart to remove bias from having a repeat PSA test to confirm first raised PSA

N = 720,403 distinct patients and 2,228,291 intervals between PSA tests

Appendix 3 Table 9: Linear mixed effect models for length of PSA retesting intervals: Multivariable Models*

	Interval ratios	95% CI	Expected months	P value
Intercept*	18.38	(18.08–18.68)		<0.001
Region (ref South East)				<0.001
East Midlands	0.97	(0.93–1.01)	17.76	
East of England	1.02	(0.98–1.06)	18.70	
London	1.02	(1.00–1.04)	18.74	
North East	1.09	(1.05–1.13)	20.04	
North West	0.98	(0.96–1.00)	18.05	
South West	0.96	(0.94–0.99)	17.70	
West Midlands	1.03	(1.00–1.05)	18.87	
Yorkshire & Humber	0.98	(0.94–1.02)	18.07	
Unknown	0.87	(0.69–1.09)	16.00	
Age range (ref 60–69)				<0.001
18–29	0.51	(0.47–0.55)	9.28	
30–39	0.72	(0.70–0.73)	13.13	
40–49	0.96	(0.96–0.97)	17.72	
50–59	1.04	(1.04–1.05)	19.19	
70–79	0.93	(0.92–0.93)	17.02	
80–89	0.97	(0.97–0.98)	17.84	
90+	1.11	(1.09–1.12)	20.35	
Ethnicity (ref White)				<0.001
Asian	0.95	(0.94–0.97)	17.54	
Black	0.97	(0.96–0.98)	17.78	
Mixed	0.99	(0.96–1.02)	18.17	
Other	0.98	(0.97–1.00)	18.05	
South Asian	0.97	(0.96–0.98)	17.76	
Unknown	0.89	(0.88–0.90)	16.33	
IMD (ref 1)				<0.001
2	1.00	(0.99–1.00)	18.38	
3	1.00	(0.99–1.00)	18.32	
4	0.99	(0.98–1.00)	18.22	
5	0.99	(0.98–1.00)	18.17	
Unknown	1.03	(0.97–1.10)	18.95	
PSA above threshold				<0.001
Yes	0.59	(0.59–0.60)	10.92	
Family history				<0.001
Yes	1.01	(0.99–1.02)	18.46	
Symptoms (ref No)				
Fatigue	1.22	(1.20–1.23)	22.32	
Bone Pain	1.12	(1.07–1.16)	20.51	
Back Pain	1.19	(1.18–1.19)	21.77	<0.001
UWL	1.18	(1.16–1.20)	21.70	<0.001
Haematuria	1.20	(1.19–1.21)	22.11	<0.001
ED	1.18	(1.17–1.19)	21.74	<0.001
LUTS	1.26	(1.25–1.26)	23.08	<0.001

"Months" refers to the estimated geometric mean time between repeat PSA tests. The intercept represents the mean interval for the reference group (age 60-90, White, IMD1, South East, no symptoms, no raised PSA, no family history). For each covariate level, values were calculated by multiplying the reference interval by the exponentiated fixed effect, giving the estimated interval in months while holding all other covariates at their reference level.

Findings: When restricting the analysis to PSA tests conducted at least one month apart (to remove the influence of repeat testing performed to confirm an initial elevated result), the impact on retesting intervals was most pronounced for PSA levels themselves. In this analysis, having a previous elevated PSA reduced the interval by approximately 7.5 months, compared to a 13-month reduction observed in the main analysis. Age also showed some differences, although the overall patterns and direction of associations remained consistent.

Chapter 5: Sensitivity analysis 2

The impact of restricting to patients with over six years of follow-up to mitigate potential censoring bias. We ran analysis on cohorts who had more than six years of follow up from study entry to exit.

N = 660,312 distinct patients and 2,176,547 retesting intervals

Appendix 3 Table 10: Linear mixed effect models for length of PSA retesting intervals: Multivariable Models*

	Interval ratios	95% CI	Expected months	P value
Intercept*	20.00	(19.60–20.40)		
Region (ref South East)				<0.001
East Midlands	0.98	(0.93–1.03)	19.5	
East of England	1.03	(0.98–1.07)	20.5	
London	0.99	(0.97–1.02)	19.8	
North East	1.04	(0.99–1.08)	20.7	
North West	0.95	(0.92–0.97)	18.9	

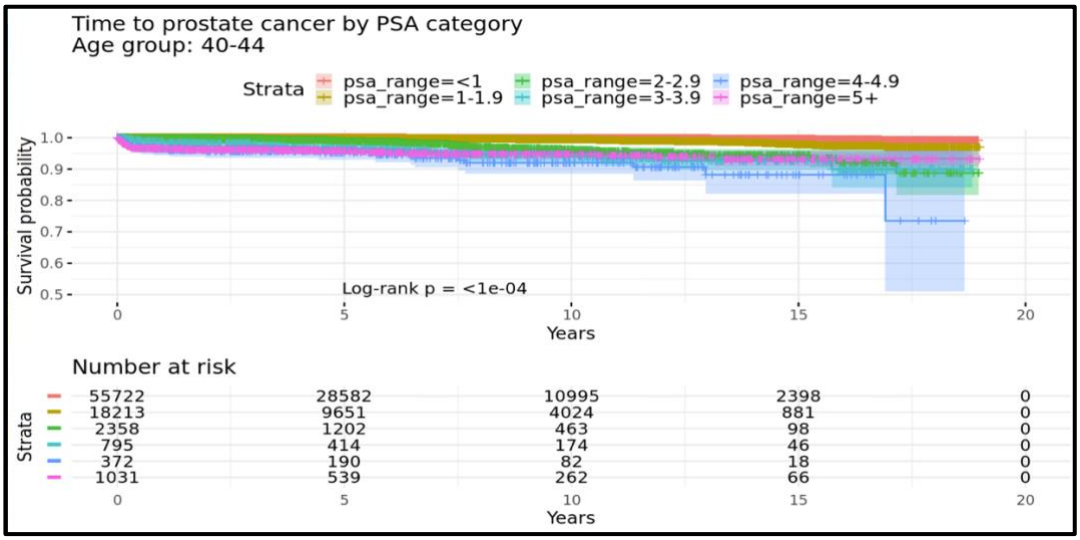
	Interval ratios	95% CI	Expected months	P value
South West	1.02	(0.99–1.05)	20.4	
Unknown	0.97	(0.75–1.25)	19.3	
West Midlands	1.04	(1.01–1.07)	20.8	
Yorkshire & Humber	0.97	(0.93–1.02)	19.5	
IMD (ref 1)				<0.001
2	1.00	(0.99–1.01)	20.0	
3	1.00	(0.99–1.00)	20.0	
4	0.99	(0.98–1.00)	19.8	
5	0.99	(0.98–1.00)	19.7	
Unknown	1.01	(0.94–1.08)	20.2	
Ethnicity (ref White)				<0.001
Asian	0.90	(0.88–0.91)	17.9	
Black	0.90	(0.89–0.91)	18.0	
Mixed	0.89	(0.86–0.91)	17.7	
Other	0.91	(0.89–0.93)	18.2	
South Asian	0.91	(0.90–0.92)	18.2	
Unknown	0.93	(0.92–0.94)	18.6	
Age range (ref 60–69)				<0.001
18–29	0.94	(0.87–1.01)	18.8	
30–39	1.57	(1.53–1.60)	31.4	
40–49	1.56	(1.55–1.58)	31.2	
50–59	1.27	(1.27–1.28)	25.4	
70–79	0.76	(0.76–0.77)	15.3	
80–89	0.68	(0.67–0.68)	13.5	
90+	0.56	(0.55–0.57)	11.3	
Family history				<0.001
Yes	0.84	(0.82–0.85)	16.7	
PSA value above age-specific threshold				<0.001
Yes	0.33	(0.33 – 0.33)	6.6	
Symptoms				
Fatigue	1.00	(0.99–1.01)	19.9	
Haematuria	0.95	(0.94–0.96)	19.0	<0.001
Bone Pain	0.99	(0.93–1.04)	19.7	
Back Pain	1.04	(1.03–1.05)	20.7	<0.001
UWL	0.97	(0.95–0.99)	19.4	<0.001
ED	1.05	(1.04–1.06)	20.9	<0.001
LUTS	1.03	(1.02 – 1.03)	20.5	<0.001

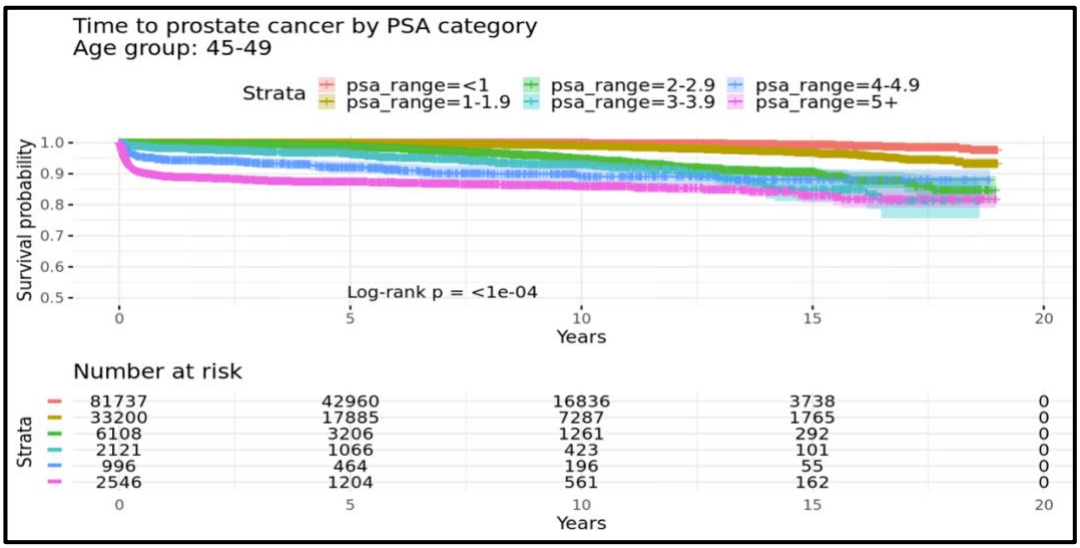
"Months" refers to the estimated geometric mean time between repeat PSA tests. The intercept represents the mean interval for the reference group (age 60-90, White, IMD1, South East, no symptoms, no raised PSA, no family history). For each covariate level, values were calculated by multiplying the reference interval by the exponentiated fixed effect, giving the estimated interval in months while holding all other covariates at their reference level.

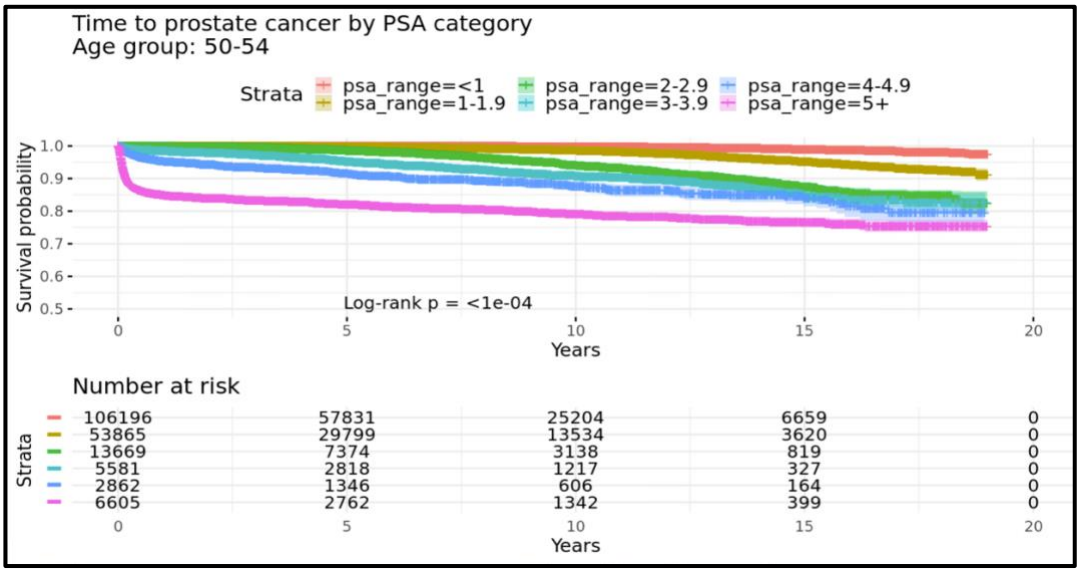
Findings: The intercept is over a month longer than in the overall cohort, while all other model results and directions remain similar.

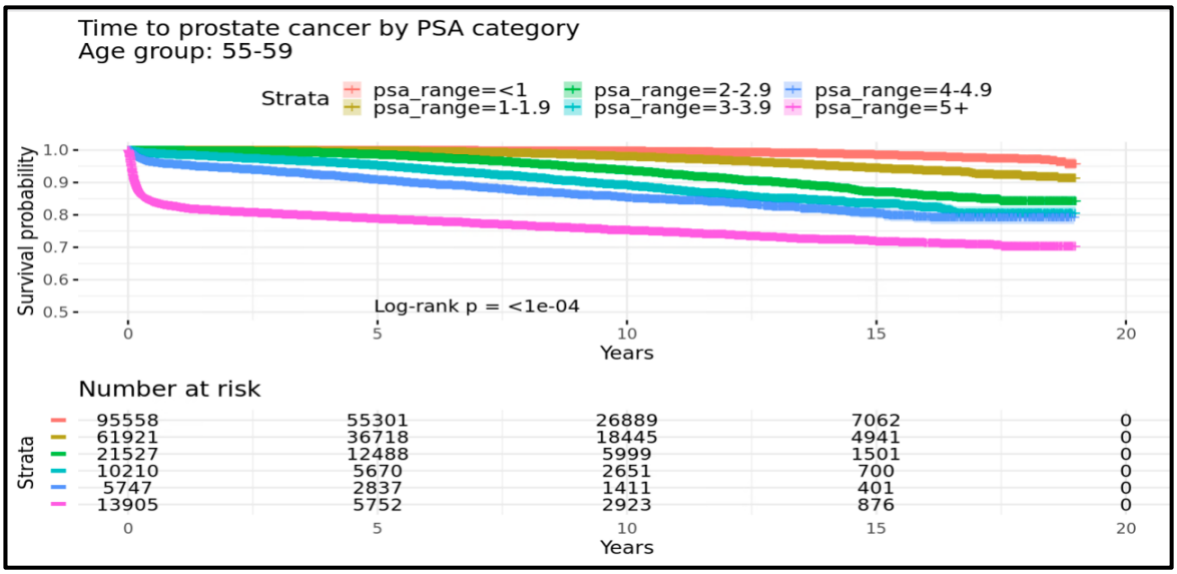
APPENDIX 4

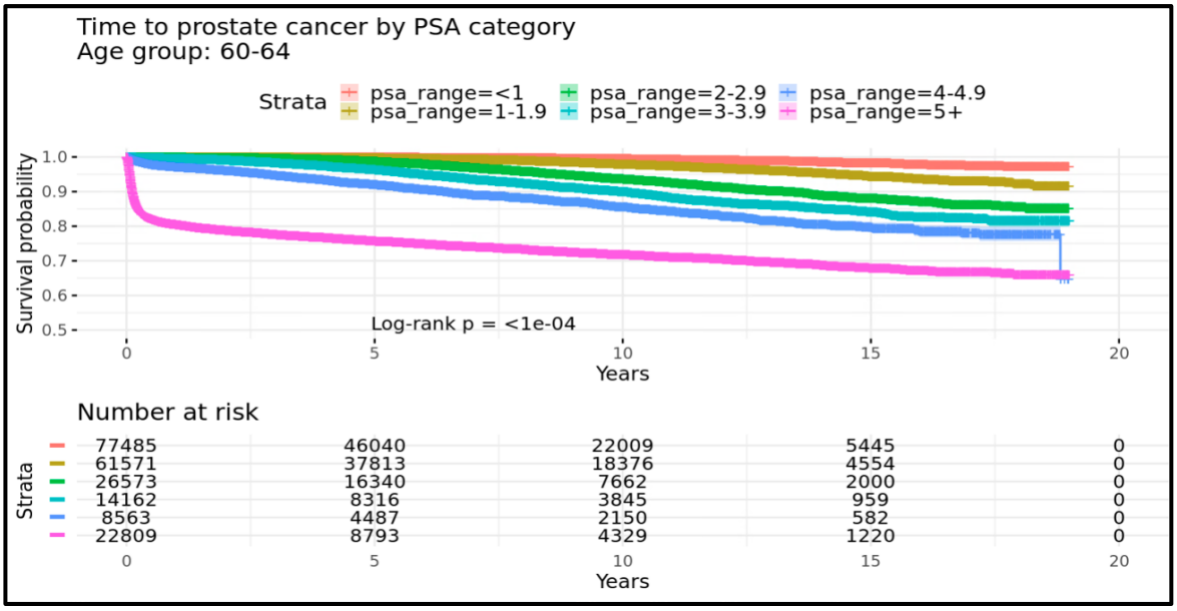
Kaplan-Meier plots by age range at and PSA at baseline test

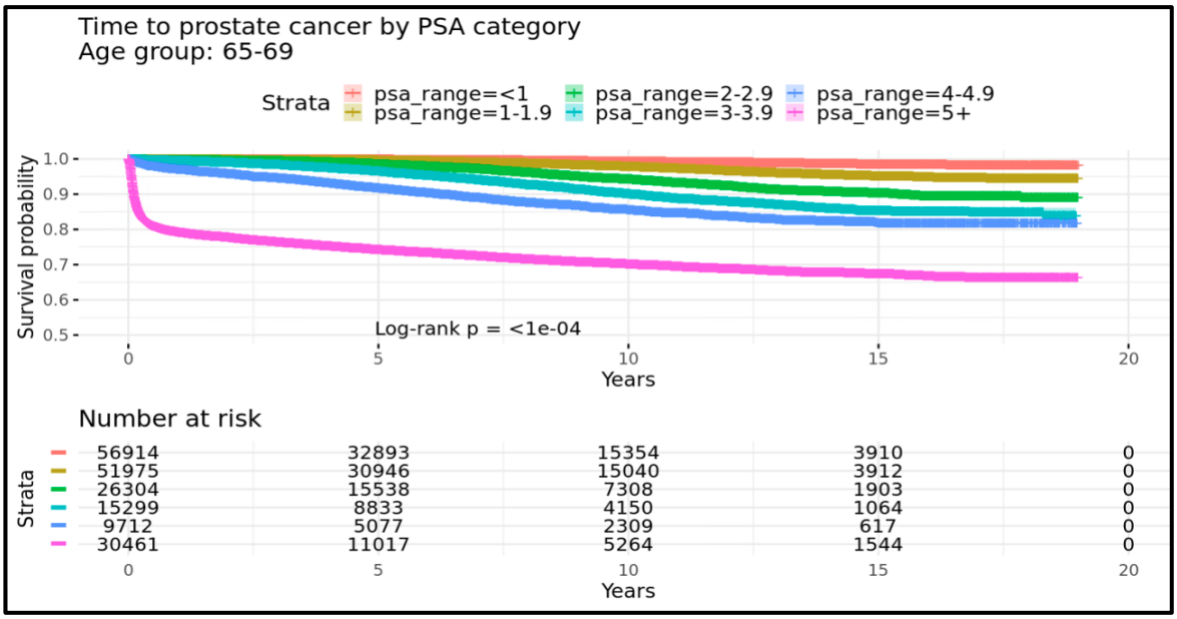


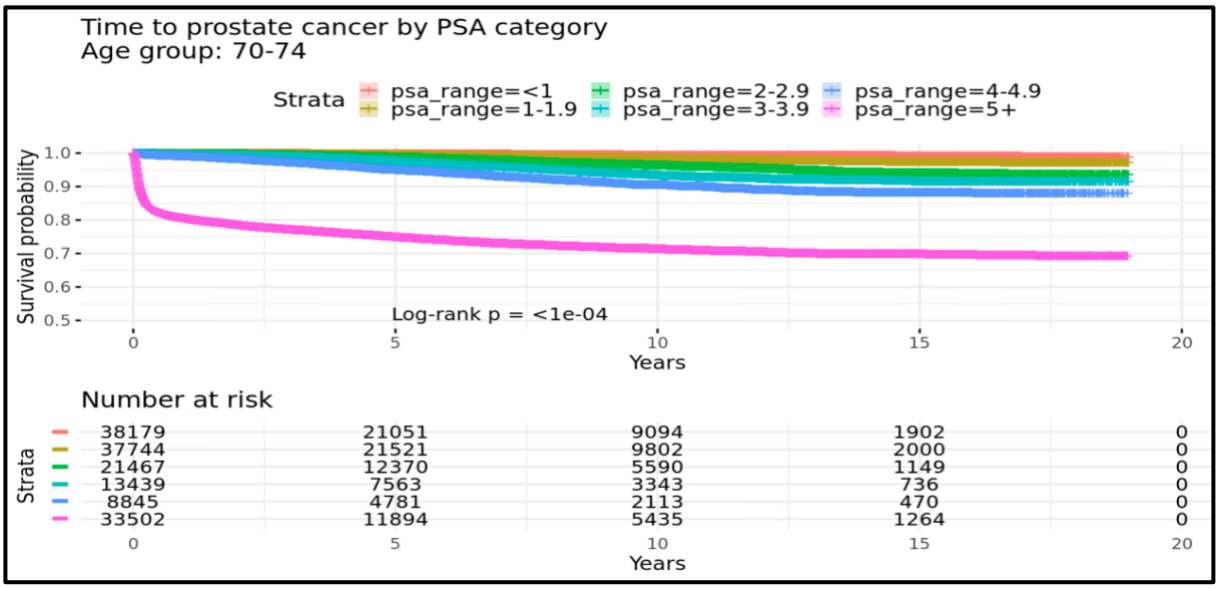


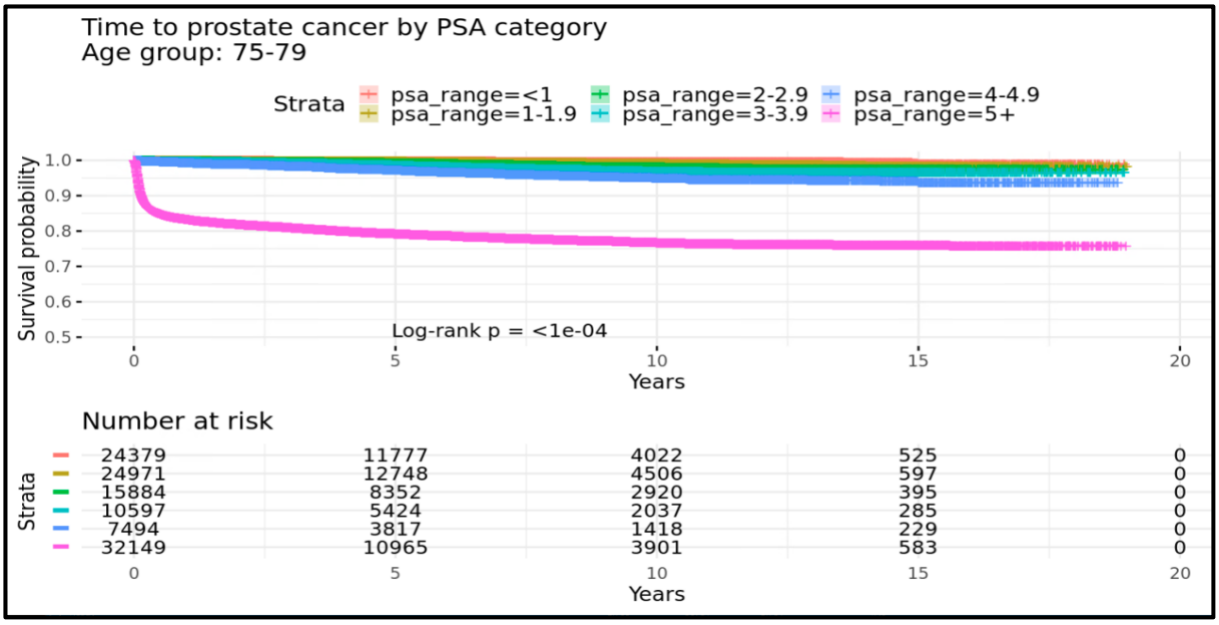


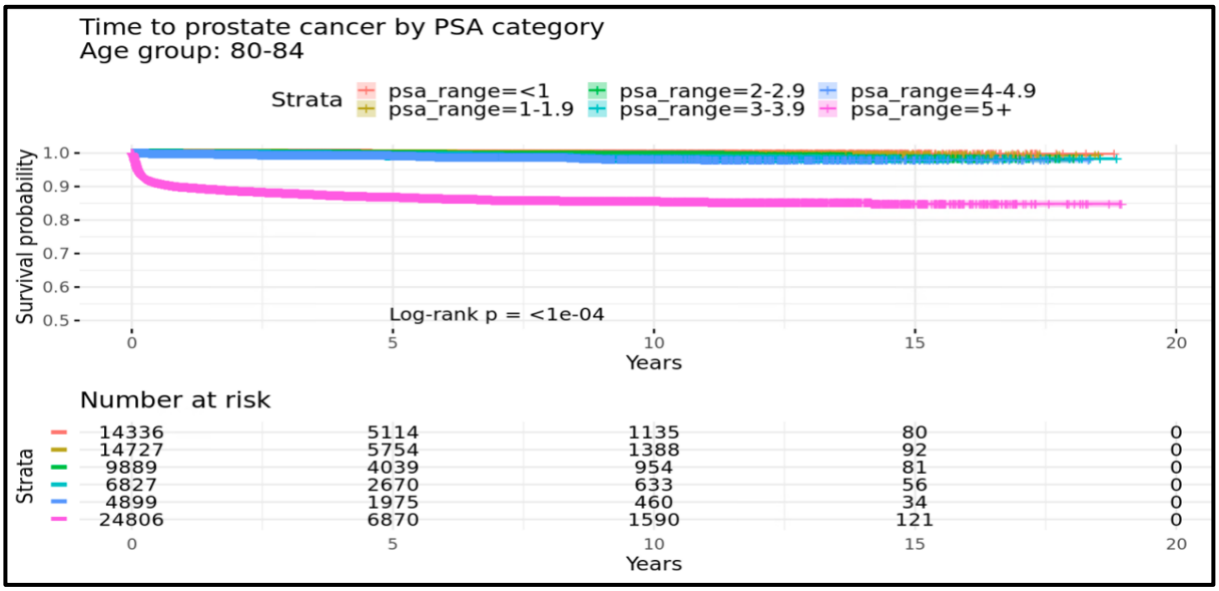

Time to prostate cancer by PSA category
Age group: 55-59
Strata
psa_range=<1
psa_range=1-1.9
psa_range=2-2.9
psa_range=3-3.9
psa_range=4-4.9
psa_range=5+
Survival probability
1.0
0.9
0.8
0.7
0.6
0.5
Log-rank p = <1e-04
0
5
10
15
20
Years
Number at risk
Strata
95558 55301 26889 7062 0
61921 36718 18445 4941 0
21527 12488 5999 1501 0
10210 5670 2651 700 0
5747 2837 1411 401 0
13905 5752 2923 876 0
0
5
10
15
20
Years

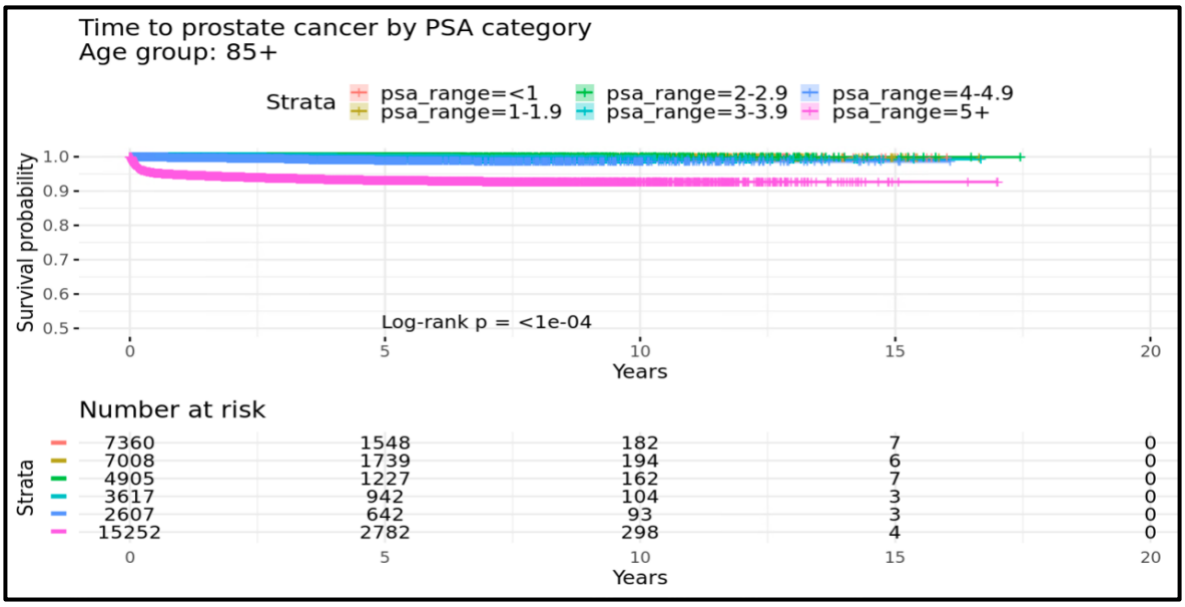

Time to prostate cancer by PSA category
Age group: 60-64
Strata
psa_range=<1
psa_range=1-1.9
psa_range=2-2.9
psa_range=3-3.9
psa_range=4-4.9
psa_range=5+
Survival probability
1.0
0.9
0.8
0.7
0.6
0.5
Log-rank p = <1e-04
0
5
10
15
20
Years
Number at risk
Strata
77485 46040 22009 5445 0
61571 37813 18376 4554 0
26573 16340 7662 2000 0
14162 8316 3845 959 0
8563 4487 2150 582 0
22809 8793 4329 1220 0
0
5
10
15
20
Years


Time to prostate cancer by PSA category
Age group: 65-69
Strata
psa_range=<1
psa_range=1-1.9
psa_range=2-2.9
psa_range=3-3.9
psa_range=4-4.9
psa_range=5+
Survival probability
1.0
0.9
0.8
0.7
0.6
0.5
Log-rank p = <1e-04
0
5
10
15
20
Years
Number at risk
Strata
56914 32893 15354 3910 0
51975 30946 15040 3912 0
26304 15538 7308 1903 0
15299 8833 4150 1064 0
9712 5077 2309 617 0
30461 11017 5264 1544 0
0
5
10
15
20
Years

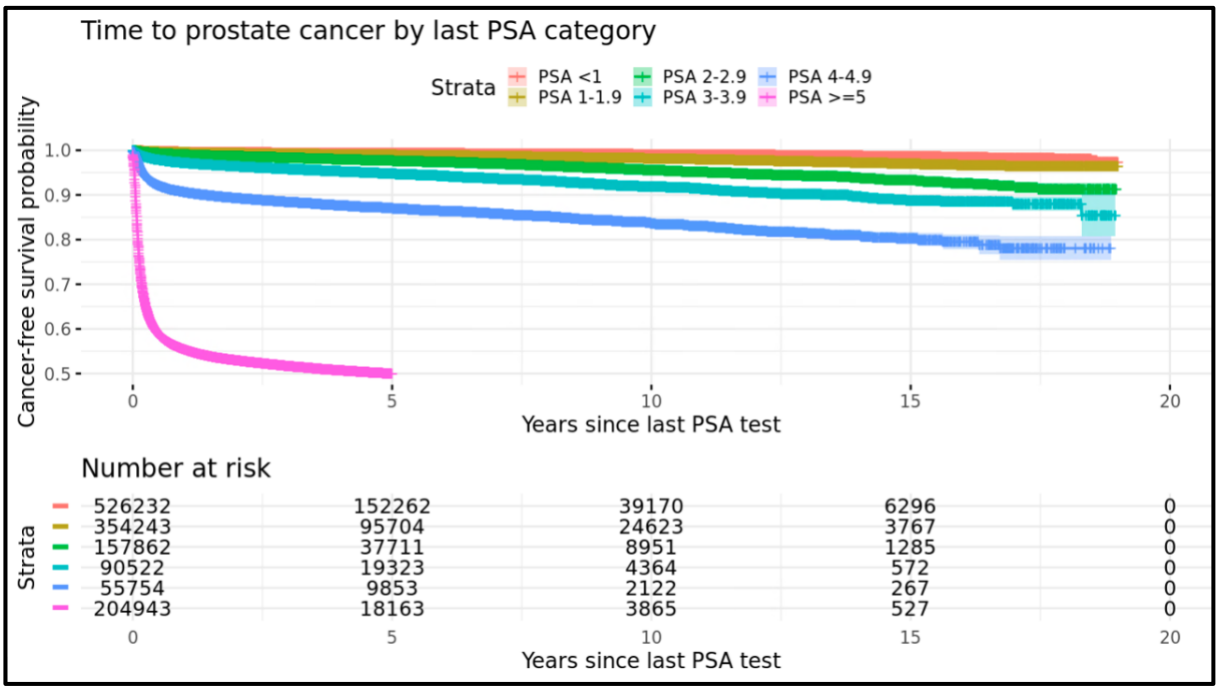

Time to prostate cancer by PSA category
Age group: 70-74
Strata
psa_range=<1
psa_range=1-1.9
psa_range=2-2.9
psa_range=3-3.9
psa_range=4-4.9
psa_range=5+
Survival probability
1.0
0.9
0.8
0.7
0.6
0.5
Log-rank p = <1e-04
0
5
10
15
20
Years
Number at risk
Strata
38179 21051 9094 1902 0
37744 21521 9802 2000 0
21467 12370 5590 1149 0
13439 7563 3343 736 0
8845 4781 2113 470 0
33502 11894 5435 1264 0
0
5
10
15
20
Years


Time to prostate cancer by PSA category
Age group: 75-79
Strata
psa_range=<1
psa_range=1-1.9
psa_range=2-2.9
psa_range=3-3.9
psa_range=4-4.9
psa_range=5+
Survival probability
1.0
0.9
0.8
0.7
0.6
0.5
Log-rank p = <1e-04
0
5
10
15
20
Years
Number at risk
Strata
24379 11777 4022 525 0
24971 12748 4506 597 0
15884 8352 2920 395 0
10597 5424 2037 285 0
7494 3817 1418 229 0
32149 10965 3901 583 0
0
5
10
15
20
Years


Time to prostate cancer by PSA category
Age group: 80-84
Strata
psa_range=<1
psa_range=1-1.9
psa_range=2-2.9
psa_range=3-3.9
psa_range=4-4.9
psa_range=5+
Survival probability
1.0
0.9
0.8
0.7
0.6
0.5
Log-rank p = <1e-04
0
5
10
15
20
Years
Number at risk
Strata
14336 5114 1135 80 0
14727 5754 1388 92 0
9889 4039 954 81 0
6827 2670 633 56 0
4899 1975 460 34 0
24806 6870 1590 121 0
0
5
10
15
20
Years



Kaplan-Meier plots by age range at and PSA at last test



Appendix 4 Table 1: PSA retesting intervals from last PSA test

Age range at first PSA test	PSA < 1	PSA 1 to 1.9	PSA 2 to 2.9	PSA 3 to 3.9	PSA 4 to 4.9	PSA ≥ 5
40 to 44	>10	>10	4	Refer	Refer	Refer
45 to 49	>10	>10	Refer	"	"	"
50 to 54	>10	>10	3	"	"	"
55 to 59	>10	8	2	"	"	"

Age range at first PSA test	PSA < 1	PSA 1 to 1.9	PSA 2 to 2.9	PSA 3 to 3.9	PSA 4 to 4.9	PSA ≥ 5
60 to 64	>10	5	1	“	“	“
65 to 69	8	3	1	“	“	“
70 to 74	3	1	-	“	“	“
75 to 79	1	1	-	“	“	“
80 to 84	-	1	-	“	“	“
85+	-	-	-	“	“	“

APPENDIX 4.1

Appendix 4.1 Table 1 Baseline PSA < 1 Ten-year survival by age

time	40-44	45-49	50-54	55-59	60-64	65-69	70-74	75-79	80-84	85+
0	100% (100–100)	100% (100–100)	100% (100–100)	100% (100–100)	100% (100–100)	100% (100–100)	100% (100–100)	100% (100–100)	100% (100–100)	100% (100–100)
1	100% (100–100)	100% (100–100)	100% (100–100)	99.9% (99.9–100)	99.9% (99.9–99.9)	99.8% (99.7–99.8)	99.6% (99.6–99.7)	99.5% (99.5–99.6)	99.4% (99.3–99.5)	99% (98.7–99.2)
2	100% (100–100)	100% (100–100)	99.9% (99.9–100)	99.9% (99.9–99.9)	99.8% (99.8–99.8)	99.7% (99.6–99.7)	99.5% (99.4–99.6)	99.4% (99.2–99.5)	99.1% (98.9–99.2)	98.3% (98–98.6)
3	100% (100–100)	100% (100–100)	99.9% (99.9–99.9)	99.9% (99.8–99.9)	99.8% (99.7–99.8)	99.6% (99.5–99.6)	99.4% (99.3–99.5)	99.1% (99–99.3)	98.8% (98.6–99)	97.7% (97.3–98.1)
4	100% (100–100)	100% (99.9–100)	99.9% (99.9–99.9)	99.8% (99.8–99.9)	99.7% (99.7–99.7)	99.5% (99.4–99.5)	99.3% (99.2–99.3)	98.9% (98.8–99.1)	98.5% (98.2–98.7)	96.9% (96.4–97.5)
5	100% (99.9–100)	100% (99.9–100)	99.9% (99.9–99.9)	99.8% (99.7–99.8)	99.6% (99.6–99.7)	99.4% (99.3–99.5)	99.1% (99–99.2)	98.6% (98.4–98.7)	98.2% (97.9–98.5)	96.4% (95.8–97)
6	99.9% (99.9–100)	99.9% (99.9–100)	99.8% (99.8–99.9)	99.7% (99.7–99.8)	99.5% (99.4–99.5)	99.3% (99.2–99.3)	98.9% (98.8–99)	98.3% (98.1–98.5)	98% (97.7–98.3)	95.6% (94.8–96.4)
7	99.9% (99.9–99.9)	99.9% (99.9–99.9)	99.8% (99.7–99.8)	99.6% (99.6–99.7)	99.4% (99.3–99.4)	99.1% (99–99.2)	98.8% (98.6–98.9)	98.1% (97.9–98.3)	97.6% (97.2–98)	95% (94.1–95.9)
8	99.9% (99.9–99.9)	99.9% (99.9–99.9)	99.7% (99.7–99.8)	99.5% (99.5–99.6)	99.2% (99.1–99.3)	98.9% (98.8–99)	98.5% (98.4–98.7)	97.8% (97.5–98.1)	97.3% (96.9–97.7)	94.2% (93.1–95.4)
9	99.9% (99.8–99.9)	99.9% (99.8–99.9)	99.6% (99.6–99.7)	99.4% (99.4–99.5)	99% (98.9–99.1)	98.6% (98.5–98.8)	98.2% (98.1–98.4)	97.5% (97.2–97.8)	96.8% (96.3–97.4)	93.5% (92.1–94.9)
10	99.8% (99.8–99.9)	99.7% (99.7–99.8)	99.5% (99.5–99.6)	99.3% (99.2–99.3)	98.8% (98.7–98.9)	98.4% (98.2–98.5)	97.9% (97.7–98.1)	97.2% (96.9–97.6)	96.5% (96–97.1)	93% (91.4–94.7)

Appendix 4.1 Table 2 Baseline PSA 1 to 1.9 Ten-year survival by age

time	40-44	45-49	50-54	55-59	60-64	65-69	70-74	75-79	80-84	85+
0	100% (100–100)	100% (100–100)	100% (100–100)	100% (100–100)	100% (100–100)	100% (100–100)	100% (100–100)	100% (100–100)	100% (100–100)	100% (100–100)

time	40-44	45-49	50-54	55-59	60-64	65-69	70-74	75-79	80-84	85+
1	100% (99.9–100)	100% (99.9–100)	99.9% (99.9–100)	99.9% (99.9–99.9)	99.8% (99.8–99.9)	99.8% (99.7–99.8)	99.7% (99.6–99.7)	99.6% (99.5–99.7)	99.5% (99.4–99.7)	99.4% (99.2–99.6)
2	99.9% (99.9–100)	99.9% (99.9–99.9)	99.9% (99.8–99.9)	99.8% (99.8–99.9)	99.8% (99.7–99.8)	99.7% (99.6–99.7)	99.5% (99.4–99.6)	99.4% (99.3–99.5)	99.3% (99.1–99.4)	99.1% (98.9–99.4)
3	99.9% (99.9–100)	99.9% (99.8–99.9)	99.8% (99.8–99.9)	99.7% (99.7–99.8)	99.6% (99.6–99.7)	99.5% (99.4–99.6)	99.3% (99.2–99.4)	99.1% (99–99.3)	99% (98.8–99.2)	98.8% (98.5–99.1)
4	99.9% (99.8–99.9)	99.8% (99.7–99.8)	99.7% (99.6–99.7)	99.6% (99.5–99.6)	99.5% (99.4–99.5)	99.3% (99.2–99.4)	99.1% (99–99.2)	98.9% (98.7–99)	98.7% (98.5–98.9)	98.5% (98.2–98.9)
5	99.7% (99.7–99.8)	99.7% (99.6–99.7)	99.5% (99.4–99.6)	99.4% (99.4–99.5)	99.2% (99.1–99.3)	99% (98.9–99.1)	98.8% (98.6–98.9)	98.6% (98.5–98.8)	98.4% (98.1–98.6)	98.1% (97.6–98.5)
6	99.6% (99.5–99.7)	99.4% (99.3–99.6)	99.2% (99.1–99.3)	99.1% (99.1–99.2)	98.9% (98.8–99)	98.7% (98.6–98.8)	98.5% (98.3–98.6)	98.2% (98–98.4)	97.9% (97.6–98.3)	97.4% (96.8–98)
7	99.5% (99.3–99.6)	99.3% (99.1–99.4)	98.9% (98.8–99)	98.7% (98.6–98.9)	98.4% (98.3–98.6)	98.2% (98–98.3)	98.1% (97.9–98.3)	97.7% (97.4–97.9)	97.6% (97.2–97.9)	96.7% (95.9–97.5)
8	99.4% (99.2–99.5)	98.9% (98.7–99.1)	98.5% (98.3–98.6)	98.2% (98.1–98.3)	97.9% (97.8–98.1)	97.6% (97.4–97.8)	97.6% (97.4–97.8)	97.3% (97–97.6)	97.1% (96.7–97.6)	96% (95–97)
9	99.1% (98.9–99.3)	98.5% (98.3–98.7)	98% (97.8–98.2)	97.4% (97.3–97.6)	97.3% (97.1–97.4)	96.9% (96.7–97.1)	97.2% (96.9–97.4)	96.8% (96.5–97.2)	96.6% (96–97.1)	95.7% (94.6–96.9)
10	98.9% (98.7–99.2)	98% (97.8–98.3)	97.5% (97.3–97.7)	96.6% (96.4–96.8)	96.4% (96.2–96.7)	96.3% (96–96.5)	96.6% (96.3–96.8)	96.3% (95.9–96.7)	96.1% (95.5–96.7)	95.3% (93.8–96.7)

Appendix 4.1 Table 3: Baseline PSA 2 to 2.9 Ten-year survival by age

time	40-44	45-49	50-54	55-59	60-64	65-69	70-74	75-79	80-84	85+
0	100% (100–100)	100% (100–100)	100% (100–100)	100% (100–100)	100% (100–100)	100% (100–100)	100% (100–100)	100% (100–100)	100% (100–100)	100% (99.9–100)
1	99.5% (99.2–99.8)	99.1% (98.9–99.3)	99.8% (99.7–99.9)	99.7% (99.6–99.7)	99.7% (99.6–99.8)	99.6% (99.5–99.7)	99.4% (99.3–99.5)	99.4% (99.3–99.5)	99.4% (99.3–99.6)	99.6% (99.4–99.8)
2	99.3% (98.9–99.6)	98.9% (98.6–99.1)	99.4% (99.3–99.6)	99.3% (99.2–99.4)	99.4% (99.3–99.5)	99.2% (99.1–99.3)	99.1% (99–99.2)	99.1% (98.9–99.2)	99.1% (98.9–99.3)	99.1% (98.8–99.4)
3	98.9% (98.4–99.4)	98.4% (98.1–98.8)	98.8% (98.6–99)	98.8% (98.6–98.9)	99% (98.9–99.1)	98.8% (98.7–98.9)	98.7% (98.5–98.9)	98.6% (98.4–98.8)	98.8% (98.6–99)	98.8% (98.4–99.1)

time	40-44	45-49	50-54	55-59	60-64	65-69	70-74	75-79	80-84	85+
4	98.5% (97.9–99.1)	97.9% (97.5–98.3)	97.9% (97.6–98.2)	97.9% (97.7–98.1)	98.4% (98.2–98.5)	98.1% (97.9–98.3)	98.1% (97.9–98.3)	98.2% (97.9–98.4)	98.4% (98.1–98.7)	98.3% (97.8–98.8)
5	98% (97.3–98.6)	97.1% (96.6–97.6)	96.8% (96.5–97.2)	96.8% (96.5–97)	97.4% (97.2–97.6)	97.2% (97–97.4)	97.5% (97.2–97.7)	97.7% (97.5–98)	97.8% (97.5–98.2)	97.5% (96.8–98.1)
6	97.4% (96.6–98.2)	96.1% (95.5–96.7)	95.7% (95.3–96.1)	95.3% (95–95.7)	96.1% (95.8–96.4)	96.3% (96.1–96.6)	96.8% (96.5–97.1)	97.2% (96.8–97.5)	97.1% (96.6–97.5)	97.2% (96.5–97.9)
7	96.1% (95–97.2)	94.7% (93.9–95.4)	94.1% (93.6–94.7)	93.7% (93.3–94.1)	94.6% (94.3–95)	95.2% (94.9–95.5)	95.8% (95.5–96.2)	96.5% (96.1–96.8)	96.5% (96–97.1)	97% (96.2–97.8)
8	94.7% (93.3–96)	93.2% (92.3–94.1)	92.5% (91.9–93.1)	92.1% (91.7–92.6)	93.1% (92.7–93.5)	93.7% (93.3–94.1)	94.7% (94.3–95.1)	95.6% (95.2–96.1)	95.9% (95.3–96.5)	96% (94.8–97.2)
9	94.2% (92.8–95.7)	92% (91–93)	90.6% (89.9–91.4)	90.2% (89.7–90.8)	91.4% (90.9–91.8)	92.1% (91.6–92.5)	93.9% (93.4–94.3)	94.7% (94.2–95.2)	95.3% (94.6–96)	95.3% (93.9–96.8)
10	93.7% (92.2–95.3)	90.5% (89.3–91.6)	88.6% (87.8–89.5)	88.5% (87.9–89.1)	89.7% (89.2–90.2)	90.8% (90.3–91.3)	93% (92.6–93.5)	94% (93.4–94.6)	94.5% (93.6–95.4)	94.9% (93.2–96.6)

Appendix 4.1 Table 4: Baseline PSA 3 to 3.9 Ten-year survival by age

time	40-44	45-49	50-54	55-59	60-64	65-69	70-74	75-79	80-84	85+
0	100% (100–100)	100% (100–100)	100% (99.9–100)	100% (100–100)	100% (100–100)	100% (100–100)	100% (100–100)	100% (100–100)	100% (100–100)	100% (100–100)
1	97% (95.8–98.2)	95.4% (94.5–96.3)	96.4% (95.9–96.9)	96.8% (96.5–97.2)	98.9% (98.7–99.1)	99% (98.8–99.1)	99.2% (99–99.3)	99.3% (99.1–99.5)	99.2% (99–99.4)	99.4% (99.1–99.6)
2	96.4% (95.1–97.8)	94% (92.9–95)	95% (94.5–95.6)	95.2% (94.7–95.6)	97.8% (97.5–98)	98% (97.8–98.2)	98.4% (98.2–98.7)	98.7% (98.5–98.9)	98.8% (98.5–99.1)	98.7% (98.3–99.1)
3	96.1% (94.7–97.5)	93% (91.8–94.1)	93.3% (92.6–94)	93.5% (93–94)	96.3% (96–96.6)	96.7% (96.4–97)	97.6% (97.3–97.9)	98% (97.7–98.3)	98.1% (97.8–98.5)	98% (97.4–98.6)
4	94.8% (93.1–96.5)	91.9% (90.7–93.2)	91.6% (90.8–92.4)	92% (91.4–92.6)	94.5% (94.1–94.9)	95.1% (94.7–95.4)	96.6% (96.2–96.9)	97.2% (96.9–97.6)	97.6% (97.2–98)	97.4% (96.7–98.1)
5	94.4% (92.6–96.2)	90.6% (89.2–92)	89.3% (88.4–90.3)	90.2% (89.5–90.8)	92.5% (92–93)	93.5% (93–93.9)	95% (94.6–95.4)	96.4% (96–96.8)	96.9% (96.4–97.4)	97.1% (96.3–97.8)
6	93.4% (91.4–95.4)	88.8% (87.2–90.4)	87.3% (86.3–88.4)	87.9% (87.1–88.6)	90.1% (89.5–90.7)	91.5% (91–92)	93.5% (93–94)	95.4% (95–95.9)	96.5% (96–97.1)	96.4% (95.4–97.3)

time	40-44	45-49	50-54	55-59	60-64	65-69	70-74	75-79	80-84	85+
7	91.7% (89.4–94.1)	87.1% (85.3–88.8)	85.9% (84.8–87)	86% (85.2–86.8)	87.9% (87.2–88.5)	89.5% (88.9–90.1)	92.1% (91.5–92.6)	94.4% (93.9–95)	95.3% (94.6–96.1)	96% (95–97.1)
8	90.1% (87.4–92.8)	85.6% (83.7–87.5)	83.9% (82.7–85.1)	83.9% (83.1–84.8)	85.9% (85.2–86.6)	87.7% (87–88.3)	90.6% (89.9–91.2)	93.3% (92.7–94)	94.4% (93.5–95.2)	94.5% (92.9–96.1)
9	90.1% (87.4–92.8)	84.4% (82.4–86.5)	82% (80.6–83.3)	82.1% (81.1–83)	84% (83.2–84.8)	85.7% (85–86.5)	89.1% (88.4–89.8)	91.8% (91.1–92.6)	93.1% (92–94.2)	94.5% (92.9–96.1)
10	89.6% (86.7–92.5)	84.1% (82.1–86.2)	80.4% (78.9–81.9)	80.3% (79.3–81.3)	82.2% (81.3–83)	83.8% (83–84.6)	87.7% (86.9–88.5)	90.6% (89.7–91.5)	92.3% (91–93.5)	93.2% (90.8–95.6)

Appendix 4.1 Table 5: Baseline PSA 4 to 4.9 Ten-year survival by age

time	40-44	45-49	50-54	55-59	60-64	65-69	70-74	75-79	80-84	85+
0	100% (100–100)	99.9% (99.7–100)	100% (99.9–100)	100% (99.9–100)	100% (99.9–100)	100% (100–100)	100% (99.9–100)	100% (100–100)	100% (100–100)	100% (99.9–100)
1	95.5% (93.4–97.7)	89.8% (88–91.8)	89.1% (87.9–90.3)	89.7% (88.9–90.5)	92.9% (92.3–93.4)	94% (93.5–94.5)	98% (97.7–98.3)	98.5% (98.2–98.8)	99% (98.7–99.3)	98.9% (98.5–99.3)
2	94.9% (92.6–97.2)	88.8% (86.8–90.8)	86.4% (85.1–87.7)	87.3% (86.4–88.1)	90.2% (89.6–90.9)	91.6% (91–92.1)	96.4% (96–96.8)	97.4% (97.1–97.8)	98.2% (97.8–98.6)	98.2% (97.6–98.7)
3	94.2% (91.7–96.7)	87.2% (85–89.3)	84.5% (83.2–85.9)	84.8% (83.9–85.8)	87.7% (87–88.5)	88.9% (88.2–89.5)	94.3% (93.8–94.8)	96.2% (95.8–96.7)	97.4% (96.9–97.9)	97.3% (96.5–98)
4	94.2% (91.7–96.7)	86.2% (84–88.5)	82.9% (81.4–84.4)	82.2% (81.2–83.3)	85% (84.2–85.8)	86.3% (85.5–87)	92.5% (91.9–93.1)	94.8% (94.3–95.4)	96.6% (96–97.2)	96% (95–97)
5	93.7% (91.1–96.4)	84.7% (82.3–87.2)	80.6% (79–82.2)	79.9% (78.8–81.1)	82.7% (81.8–83.6)	83.9% (83–84.7)	90.5% (89.8–91.2)	93.6% (92.9–94.2)	95.8% (95.1–96.5)	94.5% (93.3–95.9)
6	93.2% (90.4–96)	83.3% (80.7–86)	78.4% (76.7–80.2)	77.7% (76.5–78.9)	80.2% (79.3–81.2)	81.8% (80.9–82.7)	88.8% (88–89.6)	92.6% (91.8–93.3)	94.4% (93.5–95.2)	93.5% (92–95)
7	92% (88.8–95.3)	81.5% (78.7–84.4)	77.1% (75.4–78.9)	76% (74.7–77.2)	78% (77–79.1)	79.6% (78.7–80.5)	87.1% (86.3–88)	91.3% (90.5–92.1)	93.6% (92.6–94.6)	92.3% (90.5–94.2)
8	90.5% (86.9–94.4)	80.2% (77.2–83.2)	75.9% (74.1–77.8)	73.9% (72.6–75.3)	76.4% (75.4–77.5)	77.6% (76.6–78.6)	85.6% (84.7–86.5)	90.3% (89.4–91.2)	92.3% (91.2–93.5)	90.9% (88.7–93.2)
9	90.5% (86.9–94.4)	79.2% (76.1–82.5)	74.5% (72.5–76.4)	72.7% (71.3–74.1)	74.6% (73.5–75.8)	76.3% (75.2–77.3)	84.4% (83.4–85.4)	88.8% (87.8–89.8)	90.5% (89–91.9)	88.9% (86–91.9)

time	40-44	45-49	50-54	55-59	60-64	65-69	70-74	75-79	80-84	85+
10	90.5% (86.9–94.4)	78.5% (75.2–81.8)	73.1% (71–75.2)	70.9% (69.5–72.4)	72.6% (71.4–73.8)	74.7% (73.6–75.8)	82.5% (81.5–83.6)	87.4% (86.3–88.6)	88% (86.2–89.9)	86.6% (82.7–90.5)

Appendix 4.1 Table 6: Baseline PSA 5+ Ten-year survival by age

time	40-44	45-49	50-54	55-59	60-64	65-69	70-74	75-79	80-84	85+
0	100% (100–100)	99.9% (99.7–100)	99.9% (99.8–100)	99.9% (99.8–99.9)	99.8% (99.8–99.9)	99.9% (99.8–99.9)	99.8% (99.8–99.9)	99.7% (99.7–99.8)	99.6% (99.6–99.7)	99.5% (99.4–99.6)
1	94.2% (92.8–95.6)	83.2% (81.8–84.7)	75.6% (74.5–76.6)	71.7% (70.9–72.4)	68.5% (67.9–69.1)	66.9% (66.3–67.4)	68.6% (68.1–69.1)	71.1% (70.6–71.6)	76% (75.5–76.6)	78.3% (77.7–79)
2	93.5% (92–95.1)	82.1% (80.6–83.7)	73.5% (72.4–74.6)	68.8% (68–69.6)	65.4% (64.8–66.1)	63.9% (63.4–64.5)	65.2% (64.7–65.7)	68% (67.5–68.5)	72.8% (72.2–73.4)	74.8% (74.1–75.6)
3	93.2% (91.6–94.7)	81% (79.5–82.6)	72.2% (71.1–73.3)	67% (66.2–67.8)	63.3% (62.7–64)	61.5% (61–62.1)	62.7% (62.2–63.3)	65.9% (65.4–66.4)	70.4% (69.8–71)	71.9% (71.1–72.7)
4	92.9% (91.3–94.5)	80.5% (78.9–82.1)	71.1% (69.9–72.2)	65.7% (64.8–66.5)	61.6% (60.9–62.2)	59.6% (59–60.2)	60.7% (60.1–61.2)	64% (63.4–64.5)	67.8% (67.2–68.4)	69.1% (68.2–69.9)
5	92.4% (90.7–94.1)	80.1% (78.5–81.7)	70% (68.9–71.2)	64.5% (63.6–65.3)	60% (59.3–60.7)	58% (57.4–58.5)	59% (58.5–59.6)	62.3% (61.7–62.9)	65.8% (65.2–66.5)	66.3% (65.3–67.2)
6	91.9% (90.1–93.7)	79.5% (77.8–81.1)	68.7% (67.6–69.9)	63.3% (62.5–64.2)	58.8% (58.1–59.4)	56.6% (56–57.2)	57.6% (57–58.2)	60.7% (60.2–61.3)	63.6% (62.9–64.3)	64% (63–65.1)
7	91.2% (89.3–93.2)	78.9% (77.2–80.6)	67.9% (66.7–69.1)	62% (61.2–62.9)	57.5% (56.8–58.2)	55.3% (54.7–55.9)	56.2% (55.6–56.8)	59.2% (58.6–59.8)	61.5% (60.7–62.3)	61.5% (60.4–62.7)
8	91.2% (89.3–93.2)	78.6% (76.9–80.4)	67.3% (66.1–68.6)	61% (60.1–61.9)	56.4% (55.7–57.1)	53.9% (53.3–54.5)	55.1% (54.5–55.7)	57.7% (57.1–58.3)	59.8% (59–60.6)	59.3% (58–60.7)
9	90.9% (89–93)	78.1% (76.4–79.9)	66.5% (65.2–67.8)	59.8% (58.9–60.8)	55.3% (54.6–56)	52.8% (52.2–53.5)	54% (53.4–54.6)	56.2% (55.6–56.9)	57.9% (57.1–58.8)	57.1% (55.6–58.6)
10	90.9% (89–93)	77.7% (75.9–79.5)	65.4% (64.1–66.7)	58.8% (57.9–59.8)	54.3% (53.6–55.1)	51.8% (51.2–52.5)	53.1% (52.4–53.7)	54.8% (54.1–55.5)	56.1% (55.1–57)	54.5% (52.6–56.4)

APPENDIX 4.2

Analysis form 2010 onwards

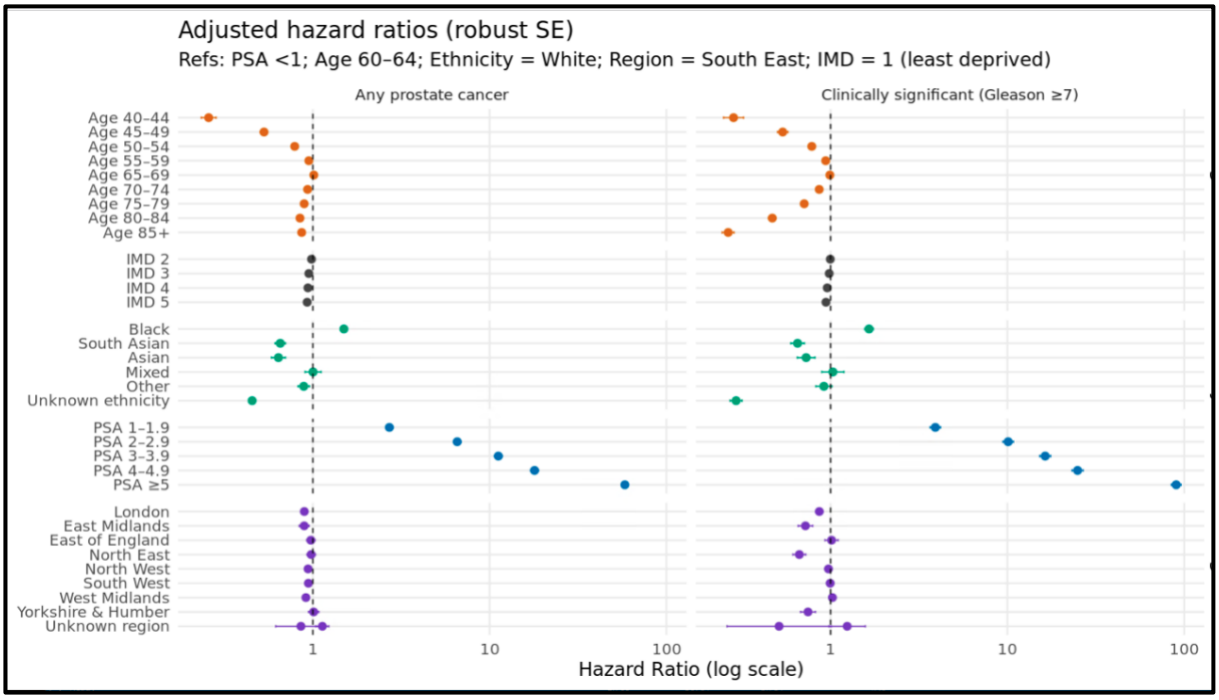
Number of patients: 707,858

Median age at first PSA 60 (IQR 52 to 69)

Median baseline PSA value 1.1ng/mL (IQR 0.63 to 2.4)

Median follow-up from baseline PSA 3.4 years (IQR 1.4 to 5.8), min 0 and max 9

Number of patients	Gleason 6	Gleason ≥ 7	Unknown
668,238	6,897	24,343	8,380



Appendix 4.2 Table 1: Cox model for patients post 2010

Variable	All cancer HR (95% CI)	P value	Clinically significant cancer HR (95% CI)	P value
PSA range (ref < 1 ng/mL)		< 0.001		< 0.001
1 to 1.9	2.87 (2.72 – 3.03)		5.32 (4.46 – 6.34)	
2 to 2.9	9.45 (8.94 – 9.99)		22.89 (19.70 – 26.60)	
3 to 3.9	22.59 (21.07 – 24.23)		54.91 (47.70 – 63.22)	
4 to 4.9	47.78 (43.81 – 52.14)		115.37 (99.43 – 133.90)	
≥ 5	196.13 (180.92 – 212.64)		542.36 (466.85 – 630.00)	
Age group (ref 60 to 64)		< 0.001		< 0.001
40–44	0.29 (0.25 – 0.33)		0.26 (0.22 – 0.31)	
45–49	0.56 (0.51 – 0.61)		0.53 (0.47 – 0.59)	

Variable	All cancer HR (95% CI)	P value	Clinically significant cancer HR (95% CI)	P value
50–54	0.78 (0.73 – 0.83)		0.76 (0.70 – 0.83)	
55–59	0.93 (0.89 – 0.98)		0.93 (0.88 – 0.98)	
65–69	1.04 (1.00 – 1.08)		1.08 (1.03 – 1.14)	
70–74	0.98 (0.94 – 1.02)		1.00 (0.95 – 1.06)	
75–79	0.90 (0.86 – 0.95)		0.82 (0.76 – 0.88)	
80–84	0.75 (0.70 – 0.80)		0.41 (0.36 – 0.47)	
85+	0.71 (0.66 – 0.76)		0.17 (0.15 – 0.19)	
Ethnicity (ref White)		< 0.001		< 0.001
Asian	0.61 (0.54 – 0.70)		0.66 (0.57 – 0.76)	
Black	1.39 (1.31 – 1.48)		1.48 (1.37 – 1.60)	
Mixed	0.90 (0.78 – 1.04)		0.89 (0.73 – 1.09)	
Other	0.93 (0.83 – 1.05)		0.93 (0.81 – 1.08)	
South Asian	0.61 (0.55 – 0.68)		0.61 (0.53 – 0.70)	
Unknown	0.40 (0.36 – 0.45)		0.33 (0.28 – 0.38)	
Region (ref South East)		< 0.001		< 0.001
East Midlands	0.95 (0.88 – 1.02)		0.91 (0.83 – 1.00)	
East of England	0.89 (0.83 – 0.96)		0.88 (0.79 – 0.98)	
London	0.86 (0.81 – 0.92)		0.77 (0.71 – 0.84)	
North East	0.99 (0.92 – 1.06)		0.86 (0.76 – 0.97)	
North West	0.97 (0.92 – 1.02)		1.00 (0.92 – 1.08)	
South West	0.90 (0.85 – 0.96)		0.85 (0.78 – 0.93)	
Unknown	0.82 (0.57 – 1.17)		0.78 (0.33 – 1.83)	
West Midlands	0.92 (0.87 – 0.98)		0.93 (0.86 – 1.01)	
Yorkshire & Humber	1.08 (0.98 – 1.19)		1.03 (0.92 – 1.16)	
IMD (ref 1 – least deprived)		< 0.001		0.023
2	0.99 (0.96 – 1.02)		1.01 (0.96 – 1.06)	
3	0.95 (0.92 – 0.98)		0.97 (0.93 – 1.02)	
4	0.94 (0.91 – 0.97)		0.95 (0.90 – 1.00)	
5	0.91 (0.88 – 0.95)		0.92 (0.87 – 0.98)	
Unknown	0.72 (0.51 – 1.01)		0.55 (0.27 – 1.12)	
Family history of prostate cancer	1.82 (1.69 – 1.96)	< 0.001	1.81 (1.65 – 1.99)	< 0.001

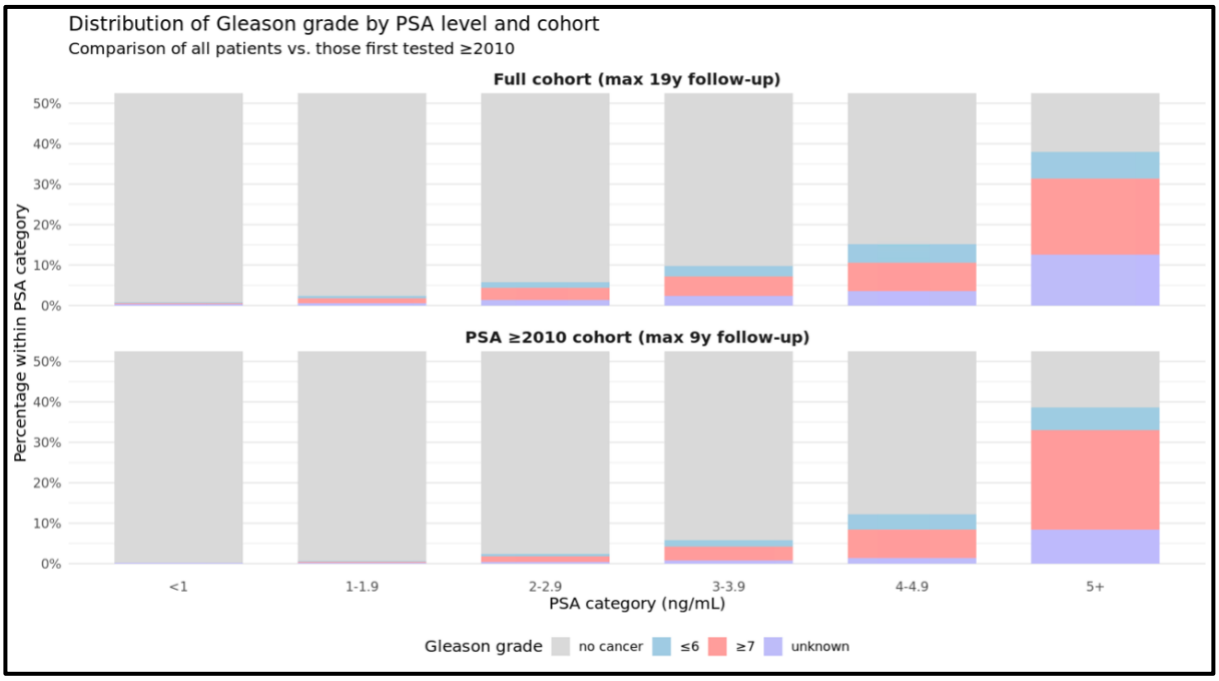
Appendix 4.2 Table 2:Cancer diagnosis cohort of patients from 2010 onwards

PSA range	No cancer	≤6	≥7	Unknown
<1	308,188 (48.7%)	161 (1.7%)	170 (0.7%)	362 (2.3%)
1–1.9	184,670 (29.2%)	370 (3.9%)	598 (2.5%)	346 (2.2%)
2–2.9	69,924 (11.1%)	443 (4.7%)	1,042 (4.4%)	289 (1.8%)
3–3.9	35,846 (5.7%)	646 (6.8%)	1,308 (5.5%)	292 (1.9%)
4–4.9	20,642 (3.3%)	861 (9.1%)	1,647 (7.0%)	349 (2.2%)
5+	48,968 (7.7%)	4,416 (46.7%)	19,578 (80.0%)	6,742 (41.5%)
Total	668,238 (100%)	9,017 (100%)	24,343 (100%)	16,380 (100%)

Appendix 4.2 Table 3:Cancer diagnosis cohort of patients included in main analysis

PSA range	No cancer	≤6	≥7	Unknown
<1	553,567 (43.2%)	873 (5.3%)	1,522 (2.4%)	1,904 (2.2%)
1 to 1.9	356,762 (27.8%)	1,974 (12.0%)	4,252 (6.7%)	2,207 (2.5%)
2 to 2.9	140,025 (10.9%)	2,195 (13.3%)	4,531 (7.2%)	1,933 (2.2%)
3 to 3.9	74,515 (5.8%)	2,263 (13.7%)	3,969 (6.3%)	1,901 (2.2%)

PSA range	No cancer	≤6	≥7	Unknown
4 t4.9	44,178 (3.4%)	2,407 (14.6%)	3,632 (5.8%)	1,880 (2.1%)
5+	113,443 (8.9%)	12,321 (74.1%)	34,419 (55.5%)	22,883 (26.7%)
Total	1,282,490 (100%)	16,033 (100%)	62,325 (100%)	32,708 (100%)



Appendix 4.2 Table 4:PPV 2010 onwards

PSA range at baseline PSA (ng/mL)	Total patients	Any prostate cancer	Gleason ≥7	PPV (any prostate cancer)	PPV (Gleason ≥7)
<1	308,881	693	170	0%	0%
1 to 1.9	185,984	1,314	598	1%	0%
2 to 2.9	71,698	1,774	1,042	2%	1%
3 to 3.9	38,092	2,246	1,308	6%	3%
4 to 4.9	23,499	2,857	1,647	12%	7%
≥5	79,704	30,736	19,578	39%	25%
Total	707,858	39,620	24,343	–	–

APPENDIX 4.3

Results with minimum 5 and 10 years of follow up

Appendix 4.3 Table 1:PPV Five year follow-up

PSA range at baseline PSA (ng/mL)	Total patients	Any prostate cancer	Gleason ≥7	PPV (any prostate cancer)	PPV (Gleason ≥7)
<1	303,097	2,586	1,231	1%	0%
1–1.9	204,574	6,211	3,560	3%	2%
2–2.9	82,136	5,687	3,252	7%	4%
3–3.9	43,716	4,007	2,117	9%	5%
4–4.9	25,616	2,437	1,213	10%	5%
≥5	62,578	6,353	2,411	10%	4%
Total	721,717	27,281	13,784	–	–

Appendix 4.3 Table 2:PPV 10 year follow-up

PSA range at baseline PSA (ng/mL)	Total patients	Any prostate cancer	Gleason ≥7	PPV (any prostate cancer)	PPV (Gleason ≥7)
<1	131,720	1,350	709	1%	1%
1–1.9	92,596	2,885	1,730	3%	2%
2–2.9	35,457	1,906	1,118	5%	3%
3–3.9	18,577	1,128	577	6%	3%
4–4.9	10,838	642	300	6%	3%
≥5	25,905	1,599	584	6%	2%
Total	315,093	9,510	5,018	–	–

Appendix 4.3 Table 3:NPV five year follow-up

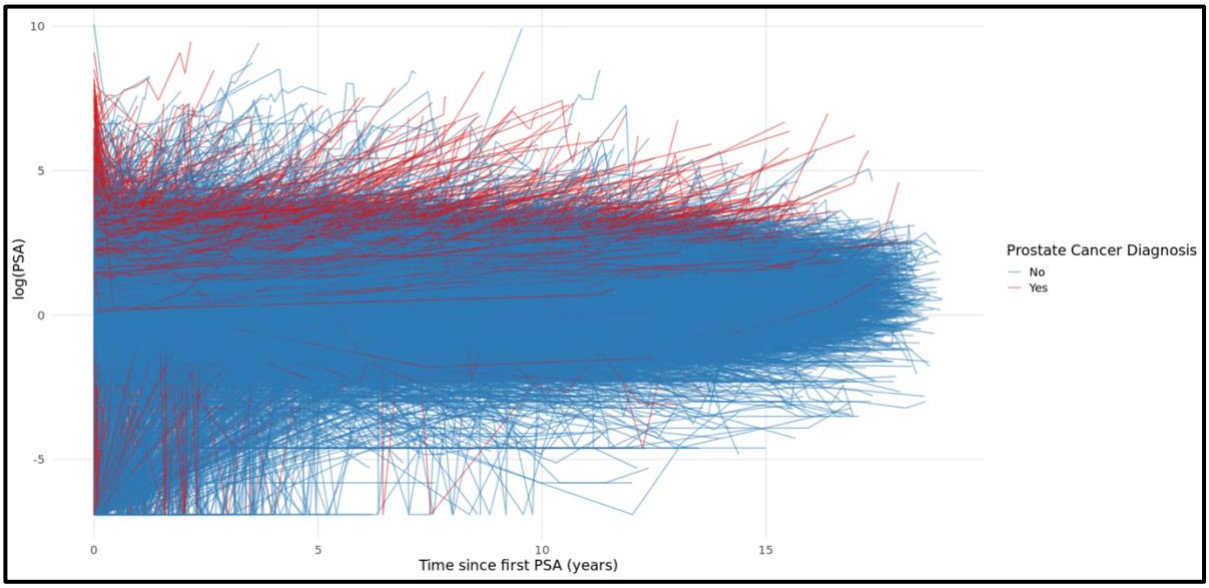
PSA range at baseline PSA (ng/mL)	Total patients	No prostate cancer	No Gleason ≥7	NPV (any prostate cancer)	NPV (Gleason ≥7)
<1	303,097	300,511	301,866	99%	100%
1–1.9	204,574	198,363	201,014	97%	98%
2–2.9	82,136	76,449	78,884	93%	96%
3–3.9	43,716	39,709	41,599	91%	95%
4–4.9	25,616	23,179	24,403	90%	95%
≥5	62,578	56,225	60,167	90%	96%
Total	721,717	694,436	707,933	–	–

Appendix 4.3 Table 4:NPV 10 year follow-up

PSA range at baseline PSA (ng/mL)	Total patients	No prostate cancer	No Gleason ≥7	NPV (any prostate cancer)	NPV (Gleason ≥7)
<1	131,720	130,370	131,011	99%	99%
1–1.9	92,596	89,711	90,866	97%	98%
2–2.9	35,457	33,551	34,339	95%	97%
3–3.9	18,577	17,449	18,000	94%	97%
4–4.9	10,838	10,196	10,538	94%	97%
≥5	25,905	24,306	25,321	94%	98%
Total	315,093	305,583	310,075	–	–

APPENDIX 5

PSA trajectories validation cohort



Appendix 5 Table 1:AUC ten-year total

Years of PSA history	Cancer risk prediction horizon*	Final prediction time	Subjects at risk	AUC
1	9	10	42,086	0.80
2	8	10	28,742	0.80
3	7	10	20,146	0.79
4	6	10	14,021	0.79
5	5	10	9,341	0.78
6	4	10	6,007	0.77
7	3	10	3,894	0.77
8	2	10	2,563	0.74
9	1	10	1,666	0.61

Appendix 5 Table 2:joint model results first 30k cohort

Submodel	Term	Mean	SD	2.5%	97.5%	p-value	Rhat
Survival model	age_first_psa	−0.0163	0.0032	−0.0225	−0.0099	<0.001	1.01
	value(log_psa)	1.3058	0.0221	1.2632	1.3458	<0.001	1.06
	slope(log_psa)	0.1126	0.2414	−0.3451	0.5826	0.63	1.05
Longitudinal model (log-PSA)	(Intercept)	−1.8577	0.0371	−1.9309	−1.7840	<0.001	1.00
	$n(2,B=c(0,18.7))_1$	0.5776	0.0137	0.5502	0.6047	<0.001	1.08
	$n(2,B=c(0,18.7))_2$	0.5420	0.0251	0.4915	0.5896	<0.001	1.07
	age_first_psa	0.0363	0.0006	0.0352	0.0374	<0.001	1.00
	σ	0.4590	0.0012	0.4565	0.4614	<0.001	1.01

Submodel	Term	Mean	SD	2.5%	97.5%	p-value	Rhat
Model fit	DIC = 295,958	WAIC = 296,016	LPML = −148,011				

Appendix 5 Table 3:joint model results second 30k cohort

Submodel	Term	Mean	SD	2.5%	97.5%	p-value	Rhat
Survival model	age_first_psa	−0.0260	0.0034	−0.0326	−0.0197	<0.001	1.01
	value(log_psa)	1.4583	0.0245	1.4107	1.5049	<0.001	1.02
	slope(log_psa)	0.6077	0.3112	0.0380	1.2530	0.032	1.04
Longitudinal model (log-PSA)	(Intercept)	−1.8813	0.0372	−1.9535	−1.8070	<0.001	1.00
	$n(2,B=c(0,18.8))_1$	0.5852	0.0134	0.5584	0.6113	<0.001	1.01
	$n(2,B=c(0,18.8))_2$	0.5031	0.0247	0.4521	0.5489	<0.001	1.03
	age_first_psa	0.0365	0.0006	0.0353	0.0376	<0.001	1.00
	σ	0.4720	0.0013	0.4696	0.4746	<0.001	1.01
Model fit	DIC = 301,374	WAIC = 301,417	LPML = −150,712				

Appendix 5 Table 4: joint model 80k cohort

Submodel	Term	Mean	SD	2.5%	97.5%	p-value	Rhat
Survival model	age_first_psa	−0.0179	0.0021	−0.0220	−0.0140	<0.001	1.02
	value(log_psa)	1.3027	0.0131	1.2772	1.3293	<0.001	1.03
	slope(log_psa)	1.3037	0.1415	1.0263	1.5889	<0.001	1.03
Longitudinal model (log-PSA)	(Intercept)	−1.9177	0.0224	−1.9613	−1.8736	<0.001	1.00
	$n(2,B=c(0,18.8))_1$	0.5843	0.0083	0.5682	0.6004	<0.001	1.01
	$n(2,B=c(0,18.8))_2$	0.5285	0.0148	0.4988	0.5574	<0.001	1.02
	age_first_psa	0.0372	0.0003	0.0365	0.0379	<0.001	1.00
	σ	0.4591	0.0008	0.4576	0.4606	<0.001	1.01
Model fit	DIC = 790,808	WAIC = 790,887	LPML = −395,443				

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