Individualising prognostic stratification in non-metastatic prostate cancer: the development, validation and clinical impact assessment of the Predict *Prostate* tool.

David Robert Thurtle

This thesis is submitted for the degree of Doctor of Medicine

November 2021

St Catharine's College
University of Cambridge

Declaration

This thesis is the result of my own work and includes nothing which is the outcome of work done in collaboration except as declared in the Preface and specified in the text. I further state that no substantial part of my thesis has already been submitted, or, is being concurrently submitted for any such degree, diploma or other qualification at the University of Cambridge or any other University or similar institution except as declared in the Preface and specified in the text. It does not exceed the prescribed word limit for the relevant Degree Committee

David Robert Thurtle

Department of Surgery, School of Clinical Medicine, University of Cambridge and Cambridge University Hospitals NHS Foundation Trust

30th November 2021

The Summary

Individualising prognostic stratification in non-metastatic prostate cancer: the development, validation and clinical impact assessment of the Predict *Prostate* tool.

David Thurtle

Decision-making around treatment for non-metastatic prostate cancer is complex, with radical treatment associated with significant potential morbidity despite some tumours being relatively indolent. Prognostic stratification should therefore help inform management. However, models currently used in clinical practice have significant flaws. This thesis sets out the rationale for a new individualised prognostic model, describes the development and validation of a novel model called Predict *Prostate*, and then evaluates the impact of this model in clinical practice.

Chapter 1 introduces the topic and includes a systematic review of existing tools, including a collaborative screening process of 6,597 records. Very few individualised prognostic tools were identified, and those found were considered inadequate by failing to include treatment effect, and disregarding non-cancer mortality. Chapter 2 describes the development of an algorithm to estimate individualised 15-year prostate cancer-specific, non-prostate cancer, and overall mortality. Data on 10,089 men from the UK National Cancer Registration and Analysis Service were split into model-development and validation cohorts. An additional validation was performed in a small international cohort. Chapter 3 describes the updating and large external validation of the model in a geographically independent cohort of 69,206 men from the Swedish Prostate Cancer database. Overall the model was well calibrated, and discriminatory performance of the model generally exceeded existing models. Chapters 4 and 5 evaluate the application of the model. First, model estimates were presented to health care professionals in a randomised online format using hypothetical clinical vignettes. Clinicians were found to overestimate cancer lethality, and were less likely to recommend radical treatment when shown Predict *Prostate* estimates. Chapter 5 describes the multi-centre randomised controlled trial assessing the impact of the model among newly diagnosed prostate cancer patients. Here, the model was shown to shift perceptions around prognosis, reduce decisional conflict and uncertainty, and was popular with patients. Chapter 6 summates and concludes the thesis.

Acknowledgements

I am grateful to a wide group of colleagues, collaborators and co-authors from whom I have received a great deal of advice and support, and without whom this work would not have been possible. I am grateful to the clinical department of urology and the wider prostate cancer MDT, who provided constructive feedback while also supporting my ongoing clinical training. I am particularly grateful to Kelly Leonard, Priya Tamer and the rest of the Cambridge Urology Translational Research and Clinical Trials (CU-TRACT) team for their general support and especially for their assistance with the patient study.

I thank Professor Sir David Spiegelhalter, Dr Alex Freeman, Mike Pearson and others from The Winton Centre for Risk and Evidence Communication who have been important supporters of this work. From our first meeting, they have each provided significant positivity and advice, alongside exceptional ability in web-development and design which considerably enhanced this project.

This project was enabled by primer-funding and research scholarship funding from The Evelyn Trust and The Urology Foundation respectively. I am grateful to both for their trust, foresight and support throughout.

Finally, I am indebted to the support provided by Professor Vincent Gnanapragasam and Professor Paul Pharoah as supervisors of my MD. Both have always made themselves available and approachable, encouraged me to progress as a clinical academic and taken significant time to guide and nurture my development.

Preface

Parts of this thesis have already been published in peer-reviewed journals. Any published work related to a specific chapter has been cited early within that chapter, with no further self-citations. Extracts of text, tables and figures have been used from some of these cited articles – which were all led and written myself and for each of which I was the lead author. As per the authorship lists of these publications, much of this work has been a collaborative process and I am very grateful for the help of all my co-authors and collaborators throughout this project. Specifically, in Chapter 1, the help of two other junior clinical academics was sought to help screen results, but otherwise was done independently.

Chapters 2 and 3 cover work all done myself, under the supervision of both my MD supervisors. Some of the methodology and design used in Chapters 4 and 5 was informed by additional informal supervision by Dr Val Jenkins from the University of Sussex. I was grateful to have some administrative support to help in study delivery, particularly helping to coordinate additional sites and maintain study documentation.

Table of contents

List of abbreviations:

ACM – All cause mortality

AJCC – American Joint Committee on Cancer

AS – Active surveillance

AUC – Area under the curve

AUA – American Urological Association

Bh – Baseline hazard

CAPRA – University of California San Francisco Cancer of the Prostate Risk Assessment score

CCI – Charlson Comorbidity Index

C-index – Concordance index

CPG – Cambridge Prognostic Groups

CUH – Cambridge University Hospitals

DCS – Decisional Conflict Scale

DMPQ – Decision-Making Preference Questionnaire

EAU – European Association of Urology

FP – Fractional Polynomial

GG – Grade group

ISUP – International Society of Urological Pathologists

MSKCC – Memorial Sloane Kettering Cancer Centre

NCCN – National Comprehensive Cancer Network

NICE – National Institute for Health and Care Excellence (UK)

NPCM – Non-prostate cancer mortality

O:E ratio – Observed: expected ratio

PCa – Prostate cancer

PCBaSe – Prostate cancer database Sweden

PCSM – Prostate cancer specific mortality

PIRADS – Prostate imaging reporting and data system

PIVOT – Prostate cancer intervention versus observation trial

PPC – Proportion of positive cores

ProtecT – Prostate testing for cancer and Treatment trial

PSA – Prostate-specific antigen

RCT – Randomised controlled trial

RP – Radical Prostatectomy

RT – Radiotherapy

SD – Standard Deviation

SEER – The Surveillance, Epidemiology and End Results Program of the National Cancer Institute (USA)

SOC – Standard of Care

STAI – State Trait Anxiety Index

T-stage – Tumour-stage

UK – United Kingdom

95% CI – 95% Confidence Interval

1 Chapter 1: Background, review of existing models, rationale for a novel model and objective-setting

This chapter provides an overview of non-metastatic prostate cancer, its management and the established uses of risk-stratification and prognostication in managing the disease. The existing literature on prognostic models is explored in a formalised way, as described. This chapter expands upon a previously published review (1). Informed by this review of the literature, the chapter concludes by outlining the aims and objectives for this thesis – to develop a more useful tool to inform clinical practice.

1.1 Background

1.1.1 Non-metastatic prostate cancer

Prostate cancer (PCa) is the commonest male cancer and its incidence is increasing with more than 48,000 men diagnosed annually in the UK, and 1.3 million estimated new cases globally in 2018 (2, 3). Incidence is rising due to an ageing male population and increased testing. In the UK alone, the incidence is projected to rise by 69% by 2030 (4). Over 84% of UK men have non-metastatic disease at presentation – localised or locally advanced disease without detectable metastases on conventional imaging. More than half of these men diagnosed with non-metastatic PCa in the UK are classified as low or intermediate-risk using traditional three-strata risk criteria – representing a significant healthcare and economic burden (5, 6).

PCa is an age-related disease with the peak rate of diagnosis between age 75 and 79 years, and peak rate of PCa death above 90 years (7). Outcomes for many men with the condition are very favourable; indeed presence of the disease can often be an incidental finding. This is borne out in cadaveric studies where a recent review estimated the mean PCa prevalence at autopsy among men aged over 79 years was as high as 59% (95%CI: 48-71) (8). The lifetime risk of being diagnosed with PCa has been reported to be 13.4%, considerably higher than the risk of dying from the disease at 4.3% reflecting both the potentially indolent nature of the disease in some men, as well as the competing risks of mortality in this older age group (9).

1.1.2 Management of non-metastatic prostate cancer

Unlike many other new cancer diagnoses, there are several valid treatment modalities for localised PCa including radiotherapy, prostatectomy and conservative management. Differentiating aggressive tumours that require upfront treatment from those that are indolent, and avoiding the associated morbidity of overtreatment has been identified as a top priority in PCa research (10). Treatment decisions in this growing group of men therefore are notoriously complex with the risk of progression and psychological impact of a cancer diagnosis balanced against significant potential morbidity associated with treatment. These latter problems can be very significant with rates of erectile dysfunction reported to be as high as 79% and 66% 3 years after prostatectomy and radiotherapy respectively, and incontinence rates of around 20% and 3% respectively (11). Partly as a result of this, the uptake of conservative management strategies is increasing, alongside increasing confidence in using 'active surveillance' for some cases (12, 13). 'Active surveillance' (AS) refers to the close monitoring of the disease, usually under secondary care, with serial PSA monitoring, MRI, clinical review and re-biopsy to detect any progression expediently. 'Watchful waiting' is another conservative management strategy, used more widely in older or comorbid patients, whereby intervention is only considered if the disease becomes symptomatic. Work performed during the timeframe of this thesis has demonstrated the safety of active surveillance, and relatively low rates of pathological progression or conversion to radical treatment within our unit in Cambridge (14).

Level 1 randomised trial evidence has underlined the complexity in decision-making by demonstrating non-inferiority of conservative management compared to radical therapy in many early cancers in both the American PIVOT and UK ProtecT trials (15, 16). In the latter study, PCa-specific mortality was found to be very low across a median of 10 years follow up irrespective of treatment modality, with only minor reductions noted in shorter term outcomes such as development of metastases or disease progression with radical treatment (16).

Given the relative equipoise between treatment options in early or favourable-risk disease, the predominant decision dilemma is therefore at the point of diagnosis when men have to decide between upfront radical treatment with its associated potential morbidity, or active surveillance or other conservative approaches. The long-term impacts from this decision are not limited to survival differences or treatment-related

morbidity, but include psychological impacts. A recent large UK study of over 17,000 men diagnosed with PCa in the preceding 5 years reported that 63% of men reported mild, moderate or severe decisional regret; and importantly that this was strongly related to health-related quality of life (17). Levels of regret correlated both with adverse effects related to treatment, and with lower levels of perceived involvement in the decision-making process (17). These impacts may not be short-lived with an American study of predominantly low-risk men followed up 15-years after diagnosis finding that 15% still expressed decisional regret, with a much higher percentage reported among those undergoing active treatment than conservative treatment. The authors conclude that better-informing patients about all treatment options may help to mitigate this negative outcome (18).

1.1.3 Treatment decision-making

In view of the complexities around managing PCa outlined above, it is not surprising that a number of tools are available to assist in treatment decision-making. Most national guidelines currently risk-stratify men according to modified versions of the three-stratum D'Amico classification system, first proposed in 1998 (19). This used biochemical recurrence as the primary outcome from a cohort of men all managed by radical treatment. However, biochemical recurrence is known to be a poor surrogate for survival and many men will no longer undergo radical treatment (12, 13, 20). The value of this system is therefore questionable, especially given its use has moved from predicting radical therapy outcomes to counselling men at diagnosis about whether to have radical treatment or surveillance. Alternative risk models have been proposed to delineate smaller groups using standard variables (PSA, Gleason score, T-stage) or which integrate additional parameters, such as biopsy characteristics (21-23). However, many are built around single-centre data, using PSA-screened and heavily radically-treated populations, making them less applicable to the fundamental decision dilemma of whether treatment is needed in the first place (24, 25). Other attempts at developing survival models have focussed solely on men undergoing radical treatment, and have not been appropriately validated (26, 27). Most models are derived from American data such that the generalisability is also deficient, particularly to the UK population, with a different healthcare structure and where no formal PSA screening exists. Rather, UK guidelines currently rely upon a modified D'Amico classification

which stratifies men into 'low', 'intermediate' or 'high' risk groups (19, 28, 29). These three stratification groups are too broad to provide individualised outcome prospects. However, a lack of an obvious alternative necessitates the current reliance on this three stratum approach. More recently, extensions to these three-stratum models have sought to validate performance against cancer mortality and have increased the number of stratification groups (28, 30-32). Although these extensions add granularity they remain too heterogeneous for modern individualised medicine approaches.

Rather than using biochemical recurrence as an outcome, prognostic models, according to the American Joint Committee on Cancer, should use survival itself as an endpoint, which is less equivocal and more robust (33). Using survival is especially important in PCa given the slow natural history of the disease. In other tumour-types, high quality prognostic models using long term survival are already integrated in to routine practice and endorsed by the AJCC (34). However, no prognostic model for PCa has yet been endorsed, nor to our knowledge, is any such model widely-used in routine clinical practice. Models integrating the impact of radical treatment compared to conservative management would be particularly powerful.

To further assess the existing literature and guide further work, a rigorous systematic review was designed to try to identify more individualised prognostic models built around long-term patient survival, available for use at the point of a new diagnosis of primary non-metastatic PCa. Given the predominant decision dilemma of deciding between treatment or conservative management, studies including men exclusively undergoing one treatment type were excluded. Prognostic models, including more than one variable were sought, rather than studies exploring the prognostic significance of a single parameter, as these could not inform the individualised decision dilemma outlined above.

1.1.4 Review aims

The review aims were to establish:

(i) What models were available to inform the decision dilemma at the point of PCa diagnosis

(ii) model accuracy in terms of discrimination and calibration

(iii) model generalisability, external validation and clinical utility.

1.2 Review of existing tools: Methods

1.2.1 Design and selection criteria

The study protocol followed the recommendations of Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines (35). The review aim, search strategy and study inclusion and exclusion criteria were framed using the CHecklist for critical Appraisal and data extraction for systematic Reviews of prediction Modelling Studies (CHARMS) (36). The search strategy was informed by previous similar studies, including publications which tested and recommended search terms for risk-prediction models (37, 38). The full systematic review protocol was pre-specified and registered through PROSPERO, reference CRD42018086394 (https://www.crd.york.ac.uk/prospero/) and is available in the appendix.

In summary, this was a review of studies reporting multi-variable long term survival models for use at the point of diagnosis for men newly diagnosed with non-metastatic PCa. Long term survival was defined as at least 5 years following diagnosis. We focused on publications subsequent to January 2000 to increase relevance to modern practice. For inclusion, studies needed to include men undergoing more than one treatment type and models including more than one variable. Models for either cancer-specific or overall survival outcomes were potentially eligible, and any eventual model-types were allowable. Both model development and model validation studies were eligible. Single-parameter or single-treatment studies were excluded. Comprehensive study inclusion and exclusion criteria are shown in Table 1.1.

Study Inclusion Criteria All of the following inclusion criteria must be met: • Studies reporting models based on men with non-metastatic prostate cancer • Studies evaluating 'long-term' (≥5 years) cancer-specific or overall survival outcomes. • Studies reporting models in screened or non-screened populations. • Studies including men undergoing more than one treatment option • Models available for use at the point of diagnosis – i.e. pre-treatment. • The model includes more than one parameter, i.e. multi-variable.
Study Exclusion Criteria Any of the following is a reason to exclude a study: • Any article that is not an original study (e.g. reviews, commentary, editorials, corrigendums, letters) • Conference proceeding or abstract from poster/oral communication only • Study where data cannot be derived to contribute to a primary or secondary outcome of this systematic review • Studies pertaining only to men with advanced/metastatic disease • Studies pertaining exclusively to men **after** an active treatment option eg. after radical prostatectomy. • Studies of single biomarkers or single parameters only • Studies including men exclusively undergoing a single treatment type.

Table 1.1 Eligibility criteria for systematic review study inclusion and exclusion

1.2.2 Information sources and data management

Studies were identified by searching Medline, Embase and Cochrane Library from 1st January 2000 to 28th February 2018. Detailed search strategies for each database are available in the appendix published online alongside the published review (1). Word derivations were used to maximize capture of relevant articles, informed by previous similar publications and locally sought guidance. For example rather than simply searching for 'prostate cancer' the following search strategy was used:

(prostat* adj3 (neoplasm* or cancer* or carcinoma* or tumor* or tumour* malignanc*)).ti. OR prostatic neoplasms (MESH) (focus) (medline) OR Prostate cancer (MESH) (focus) (embase)

Highly relevant but excluded articles were recorded, collated and their references analysed for additional studies to be included.

Search results were exported into Covidence software, an online screening platform endorsed by Cochrane (covidence.org). Title and abstract screening and full-text screening were sequentially performed by a team of 3 reviewers. Prior to screening, a pilot screening process was conducted for calibration of screening between reviewers. Reviewers were not blinded to study authors, institution, publication journal or year of publication.

1.2.3 Data items

The full list of data items extracted from each included study is recorded in the protocol. These were informed by the CHARMS checklist (36) and included:

- Study design
- Characteristics of study participants
- Outcomes
- Candidate predictors
- Sample size
- Missing data
- Statistical methods
- Model performance and evaluation
- Usability.

Model performance, assessed by discrimination, was the principal summary measure.

1.2.4 Bias assessment

To assess the validity of eligible studies, individual studies were assessed for bias using the new Prediction model Risk Of Bias ASsessment Tool (PROBAST) (39). The PROBAST tool assesses both risk of bias and applicability of both model development studies and validation studies (40).

1.3 Review of existing tools: Results

1.3.1 Study selection

The search of Cochrane, Medline and Embase yielded 6,581 studies after deduplication. Sixteen additional studies were identified by reviewing the references of excluded but relevant studies. A total of 12 studies were eligible for inclusion in the final review (25-27, 41-49). Two of these had not been summarised in previous reviews (26, 45). The PRISMA flow diagram is shown in Figure 1.1, including the reasons for exclusion at full-text screening. Only one reason for exclusion was assigned to each study, when multiple reasons may have been present. Nine of the final 12 included studies were model development studies, 3 were model validation studies. Two of these external validations were of models already included as model development studies (48, 49). One study related to an external validation of the Cancer of the Prostate Risk Assessment (CAPRA) score against mortality (25). The original CAPRA model development study however did not meet the eligibility criteria as it was

developed against the outcome of biochemical recurrence rather than long-term survival (22).

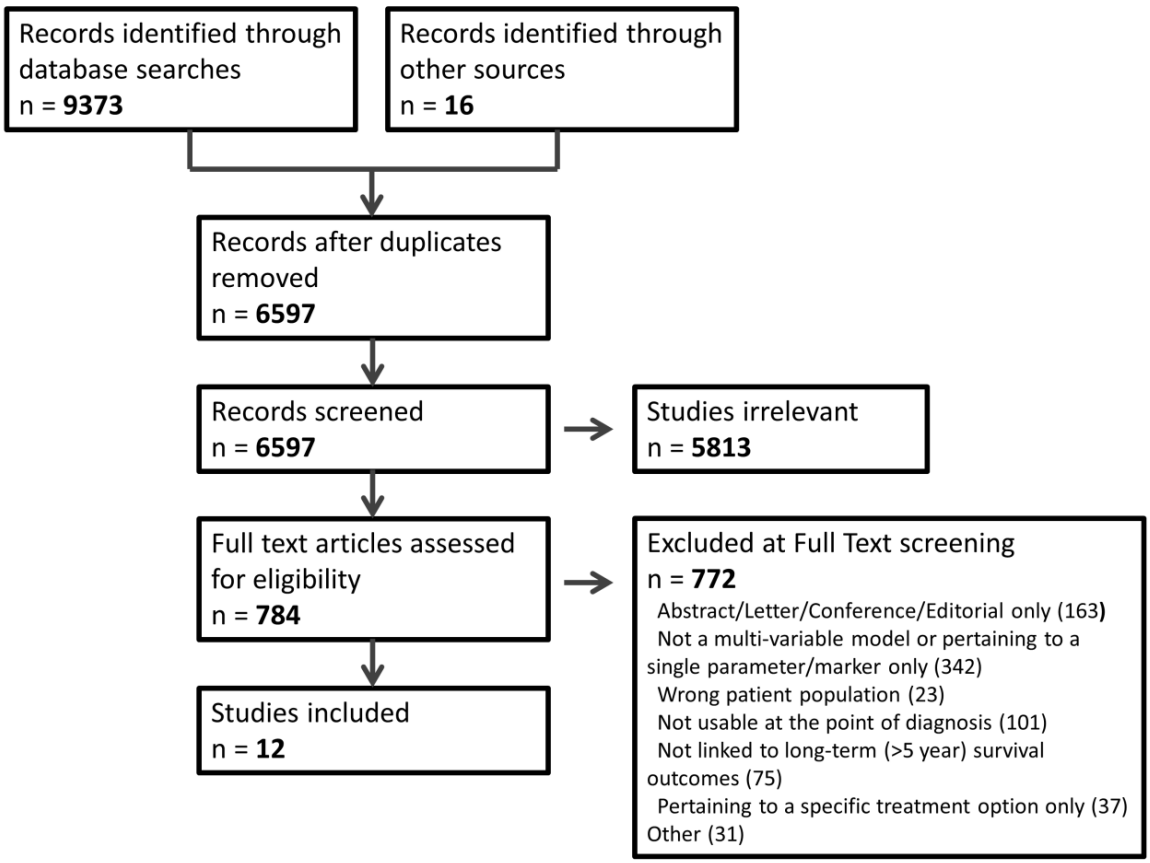


Figure 1.1 PRISMA flow diagram depicting the flow of information through the different phases of the review.

1.3.2 Study characteristics

Characteristics of the included studies' participants and settings are summarized in Table 1.2. The model development studies used data from over 231,888 men. However, 2 studies used analytical cohorts from the same registry (Surveillance, Epidemiology and End Results (SEER))(43, 47). Two studies used data from single US centres, 2 used data from groups of 4 hospitals, and 5 were from regional or national multi-centre registries. Eligibility criteria of patients into studies varied significantly, with some models using very specific or selected sub-cohorts only. For example Nguyen *et al.* included only consenting men, undergoing RT or RP, with at least one intermediate or high risk feature but ≤T3b disease (42). The treatment cohorts included, and whether treatment effect was a parameter in the final model was highly

variable. Only 6 of the 9 models included any men who had been managed conservatively (including 'watchful waiting' or 'conservative management'); none of the models described or defined a specific 'active surveillance' cohort (41, 43-47). Only 3 of the 9 models included treatment as a predictor variable - none of which were externally validated (27, 44, 46). Median follow-up was relatively short within all model development cohorts, with the longest reported follow-up being 7.6 years (26).

1.3.3 Results of individual studies

The final results of individual studies are summarized in Table 1.2 and Table 1.3. The primary outcome was cancer-specific mortality only in 1 study (45), and was overall-survival only in another study (44) - the remainder reported measures of both. The study designs, model-types and performance metrics varied markedly. We therefore focused on describing the studies, results, applicability and model availability. Significant heterogeneity in the question being asked and statistical methods of validation between studies meant that attempts to meta-analyse data would not have been appropriate. Modelling techniques varied, with the majority of studies using a proportional hazards model (Cox or Fine and Gray) although none reported assessing whether the proportional hazards assumption was valid. Included studies did not report any flexible parametric approaches to deal with continuous variables, and the majority used group categorizations of these variables. Reporting of model accuracy was inconsistent. Considering AUC and c-indices synonymously, 6 out of 9 studies reported some measure of discrimination with values ranging from 0.63 to 0.90 for PCa survival outcomes, although this higher figure was derived within a small elderly sub-cohort (43, 46) and 0.58 to 0.73 for overall outcomes (43, 44). Only 4 out of 9 studies reported assessing calibration in some capacity (26, 43-45). Relative performance within particular sub-populations were not generally reported.

Study	Source of data	Country	Years of diagnosis	Eligibility summary	Overall (n)	Number of PCa deaths	Number of overall deaths	Treatment cohorts included	Median follow-up
Margel 2014(41)	Registry (Ontario Cancer Registry)	Canada	1994-2008	Aged 66+, with diabetes prior to PCa diagnosis and pathology reports available	4001	321	1395	Surgery, RT, WW, ADT	4.7 years
Nguyen 2009(42)	Hospital data (4 centres)	USA	1965-2002	Consenting men who had RP or RT or RT+ADT for up to T3b PCa at 4 centres with at least one Int/High risk factor (PSA>10, GL7+, t2b+, PSAV>2.0ng/ml/yr)	1063	178	NR	Surgery, RT, RT+ADT	5.6 years
Feuer 2012(43)	Registry (SEER)	USA	1995-2005	PCa, aged 40-96, with complete information and cause of death (and linked medicare data if aged 66+)	203546	NR	NR	All	NR
Kutikov 2012(27)	Registry (CaPSURE)	USA	NR	Localised PCa, undergoing RT or RP	6091	167	983	Surgery, RT	4.4 years
Cowen 2006(44)	Hospital data (single Centre)	USA	1987-1989	Clinically localised PCa (<cT3) with known initial treatment strategy	506	NR	321	Surgery, RT, Other (inc CM, Cryo)	NR
Kerkmeijer 2016(26)	Hospital data (4 Centres)	Belgium & Holland	1989-2008	Treated PCa patients only	3383	149	628	Surgery, RT, Brachytherapy	7.6 years
Gnanapragasam 2016(45)	Registry (NCRS Eastern)	UK	2000-2010	All clinically localised PCa with intact data for included variables	10139	462	1557	Surgery, RT, CM, Brachy	6.9 years
Tewari 2004(46)	Hospital data (single centre)	USA	1990-1997	Men under 75 with localised PCa, negative bone scan, and intact data including zip code	3159	NR	NR	Surgery, RT, CM	6.2 years
Howlader 2014(47)	Registry (SEER)	USA	1992-2009	All PCa patients (the model including co-morbidity includes men aged 66+ only)	NR	NR	NR	All	NR

Table 1.2 Study characteristics of model development studies – participants and setting. NR = not recorded RT = radiotherapy CM = conservative management WW = watchful waiting

Study	Outcome(s) or Endpoint(s)	Time frame of predictions	Model type	Statistical methods	Included predictors	Missing data handling	Number of groups	Internal validation method	Discrimination results (c-index or AUC)	Calibration results	Model availability
Margel 2014(41)	PCSM and ACM	5-year	N/A	Nested Cox model	2 models: 1= age, comorbidity group, year of entry, socioeconomic and housing status. 2= as above + Gleason grade and cancer volume.	Complete case analysis	N/A	Bootstrapping	Admin data only model: ACM c-index 0.70 PCSM 0.76 Extended model ACM 0.74, PCSM: 0.85	NR	No
Nguyen 2009(42)	PCSM and ACM	5-year	Group-based stratification	Fine & Gray	PSA, PSAV, Stage, Gleason	NR	4 groups	KM curves only	NR	NR	Yes - paper
Feuer 2012(43)	PCSM, OCM and LE	3- 5- and 10- year	Nomogram	Cox model	Preclinical model: stage, Gleason, age, race, marital status, (comorbidity if 66+)	Complete case analysis	'Individualised'	Time dependent AUC	10 year AUCs: Pre-Rx model: <66yrs PCSM 0.82 OCM 0.69, 66+yrs PCSM 0.87 OCM 0.61	Plots	No
Kutikov 2012(27)	PCSM and NPCM	10-year	Nomogram	Fine & Gray	Age, race, comorbidity, primary treatment (RT vs RP), receipt of ADT and modified CAPRA SCORE	Imputed mean values	Nomogram	NR	NR	NR	Yes - paper
Cowen 2006(44)	Overall survival	5, 10 and 15 years and median LE	Nomogram	Cox model	Age, Charlson, performance status, angina, BMI, smoking, marital status, PSA, Gleason, treatment	Imputation	260 points	Within complete case sub-cohort	c-index 0.73	Plots	Yes - paper
Kerkmeijer 2016(26)	DSS and OS	10-year DSS	Nomogram	Cox model	T-stage, grade(on 1-3 scale) PSA, Age	Single imputation	16 points - 5 groups	Bootstrapping	c-index 0.78 DSS, 0.68 OS	Plots	Yes - paper
Gnanapragasam 2016(45)	PCSM	N/A	Group-based stratification	Cox model	PSA, grade group, T-stage integers	Complete case analysis	5 groups	Random validation cohort	c-index 0.75 (95%CI 0.72-0.77) for PCSM	Plots	Yes - paper and online model
Tewari 2004(46)	PCSM and ACM	10-year	Look up tables	Cox model	Age, grade (3 groups), PSA, treatment, comorbidity, race	Complete case analysis	n/a	Unclear	0.63 PCSM, 0.69 OS	NR	Yes - paper
Howlader 2014(47)	OS, PCa/ other death	5-year	Look up tables	Unclear	Age, stage, comorbidity	NR	n/a	NR	NR	NR	Yes - paper

Table 1.3 Study characteristics of model development studies: analysis and model output. PCSM = Prostate cancer specific mortality OCM = other cause mortality ACM = all-cause mortality LE = life expectancy NR = not recorded AUC = area under the curve DSS = disease specific survival OS = overall survival

Study	Source of data	Country	Years of diagnosis	Eligibility summary	Overall (n)	Number of PCa deaths	Number of overall deaths	Treatment cohorts included	Median follow-up
Gnanapragasam 2018(49)	Registry (PCBaSe) & Hospital data (single Singapore centre)	Sweden & Singapore	2000-2010	All non-metastatic PCa with intact data on included variables	Sweden: 72337 Singapore: 2550	7162 (Sweden) 142 (Singapore)	23083 (Sweden) 408 (Singapore)	All	7 years Sweden, 4.1 years Singapore
Feuer 2014(48)	Hospital data (single US centre)	USA	2001-2008	Aged 40-94, intact staging details & 1 year of information prior to diagnosis	1102	NR	NR	All	NR
Cooperberg 2009(25)	Registry (CaPSURE)	USA	<July 2007	Localised PCa (<T3b), with >6/12 follow-up, treatment known and intact data	10627	NR	1833	All	5.9 years

Table 1.4 Study characteristics of external validation studies: participants and setting. NR = not recorded

Study	Outcome(s) or Endpoint(s)	Time frame of predictions	Model type	Statistical methods	Included predictors	Missing data handling	Number of groups	Discrimination results	Calibration results	Model availability
Gnanapragasam 2018(49)	PCSM	10-year mortalities	5 groups	N/a	PSA, grade group, T-stage integers	Complete case analysis	5 groups	c-index 0.81 for PCSM in Sweden, 0.79 in Singapore	NR	Yes - papers and online
Feuer 2014(48)	DSS and OS	1, 3, 5, 7, 10 years	nomogram - online	As per development study [30]	Grade (3 categories), stage, marital status, age, race, year of diagnosis and comorbidity score	Complete cases + weighted averages for marital status	'individualised'	AUCs (5-year:) 0.81 PCSM, 0.81 OCM, (10 year:) 0.77 PCSM 0.76 OCM	Curves	No
Cooperberg 2009(25)	PCSM and ACM	5 and 10-year survival	Score	Cox prop hazards	CAPRA (& primary treatment, age and comorbidity in multivariable analysis)	Mixed	10 groups	PCSM 0.80 OM 0.71	NR	Yes - papers and online

Table 1.5 Study characteristics of external validation studies: analysis and model output. PCSM = Prostate cancer specific mortality OCM = other cause mortality ACM = all-cause mortality LE = life expectancy NR = not recorded AUC = area under the curve DSS = disease specific survival OS = overall survival

1.3.4 Validation

Seven of the 9 model development studies reported internal validation. Two reported using bootstrapping, and one used a separate 40% random sample of the original dataset for internal validation (26, 41, 45). An additional 3 external validation papers were included (Table 1.4). Of note, each of these included the author of the original model within their author list, suggesting these were not completely independent validations. These 3 models each used large numbers of subjects over comparable timeframes to their model development study. Discrimination of the Cambridge Prognostic Groups, SEER Cancer Survival Calculator, and CAPRA scores were comparable for PCSM at 0.81, 0.81 and 0.80 respectively over 5 years (25, 48, 49) (Table 1.5). Discriminative performance was lower for overall mortality at 0.71 in the latter study. These external validation papers performed quite well on individual bias assessment (Table 1.6). In the CAPRA validation paper estimates were reported to be 'adjusted' for age and treatment type, such that it is unclear whether the reported accuracy reflects that of the usable model (25).

1.3.5 Risk of bias

Risk of bias within studies is summarized on an individual study level in Table 1.6 and across all 12 studies in Figure 1.2 Bias assessment summary (across both the model development and model validation studies). Frequent concerns were observed with respect to participant selection and inclusion, particularly with respect to reporting or allowing for missing data. The outcome of death was well-defined and unambiguous in the majority of studies. Every included study had at least one parameter for which there was high concern of bias – leading to a high overall judgement of bias in the PROBAST tool. Concerns about applicability to the review question were present in more than half of the studies.

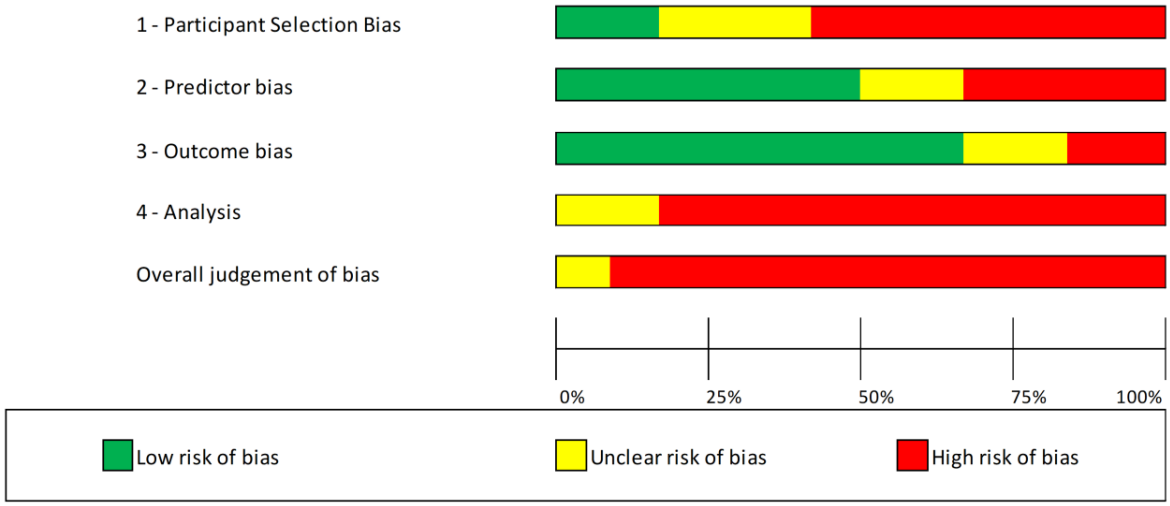


Figure 1.2 Bias assessment summary (across both the model development and model validation studies)

Study	Risk of bias				Concern regarding applicability			Overall	
	Participants	Predictors	Outcome	Analysis	Participants	Predictors	Outcome	Risk of bias	Applicability
Model development studies									
Margel 2014(41)	high	high	low	high	high	high	low	high	high
Nguyen 2009(42)	high	high	high	high	high	low	high	high	high
Feuer 2012(43)	high	unclear	low	high	high	low	low	high	high
Kutikov 2012(27)	unclear	low	low	high	low	high	low	high	high
Cowen 2006(44)	high	unclear	unclear	high	unclear	low	low	high	unclear
Kerkmeijer 2016(26)	low	low	high	unclear	low	low	low	high	low
Gnanapragasam 2016(45)	high	low	low	high	low	low	low	high	low
Tewari 2004(46)	high	low	low	high	unclear	low	low	high	unclear
Howlader 2014(47)	unclear	high	low	high	high	low	low	high	high
External validation studies									
Gnanapragasam 2018(49)	high	low	low	high	low	low	low	high	low
Feuer 2014(48)	unclear	low	unclear	unclear	low	low	low	unclear	low
Cooperberg 2009(25)	low	high	low	high	low	low	low	high	high

Table 1.6 Individual study bias and applicability summary using the PROBAST tool.

1.3.6 Usability

All of the included studies reported models that were nomograms, look-up tables or grouping stratifications. Seven of the 9 studies were clinically usable through the publication itself. One was also available in a dedicated website (49). The SEER Cancer Survival Calculator was never launched online, and the publication itself does not provide sufficient detail to use the model (43). The model by Margel *et al.* was available but not usable as it included year of entry as a predictor variable, making the model usable only on retrospective series rather than in future individual cases. Indeed, this model was developed to answer the question of whether pathological information adds to a prognostic model, rather than being intended for use at diagnosis (41).

1.4 Review of existing tools: Discussion

1.4.1 Principal findings

Treatment decisions at the point of diagnosis of non-metastatic PCa should be informed by the likely prognosis of the disease. Despite finding a number of published prognostic models in this systematic review, there remains a lack of well-validated, unbiased, generalisable models for use at the point of diagnosis. In particular, there was a lack of external validation and dearth of models that compare outcomes between conservative management and radical treatment; where the predominant decision dilemma exists. Existing models have also been built around relatively short-term survival data, and their generalisability to UK patients is relatively untested.

1.4.2 Prior evidence

A number of previous reviews have assessed "prediction" or "risk" models in the broader sense (50-52). Shariat *et al*. previously published a thorough catalogue of available predictive models in PCa – predicting everything from detecting PCa in the initial biopsy setting to survival (51). Other reviews have focused exclusively on outcomes following radical prostatectomy or radiotherapy (53, 54). Lughezzani *et al.* in 2010 for example summarised models predicting Gleason score upgrading, pathological stage, life expectancy, perioperative mortality, post-operative biochemical recurrence or functional outcomes in addition to PCSM after prostatectomy (53). The paucity of models using mortality as an outcome was particularly noted in the study, which concluded that no tools were capable of quantifying the benefit of RP relative to other treatment modalities (53). In 2009, a

separate review by Shariat *et al*. summarised available models into 8 groups (50). One of these groups was of models predicting survival. This group included only 4 models, all of which related to advanced or metastatic disease requiring hormonal therapy, or androgen-insensitive disease (50). Green *et al*. explored more historic literature from 1966 until 2012 (52). They included 4 studies which looked at life expectancy in men with localised PCa, two of which were included in our study (44, 46). The other two were models from Albertsen *et al.* in 1996 which was prior to our study dates, and from Walz et al in 2007 which focused exclusively on non-cancer mortality and therefore did not meet our eligibility criteria (55, 56). A recent review into decision-making tools again took an overview of tools available for use at different points in the patient pathway (57). Here, the only mentioned models that predicted survival were all post-prostatectomy models (57). In 2015 Kent and Vickers reported on 'gross deficiencies' in current tools for prediction of non-PCa death and concluded that they were unable to identify a suitable life expectancy tool (58). These previous reviews all suggest there is a lack of focus upon and availability of good quality survival models.

1.4.3 Interpretation of findings

Although a number of previous reviews have been published, our systematic review represents the most systematic and contemporary work focused towards the decision dilemma that patients and clinicians face, as it includes only models that are available at the pre-treatment stage and that are not treatment-specific. This review demonstrates that only a very small number of models for this setting have been published using long-term survival as an endpoint, and only 3 have been externally validated. However, the number of events reported in these 3 validation studies were, at least, in excess of the 100 suggested as the minimum number needed for adequate validation (59). Within the external validations, model discrimination of up to 0.81 was reported for disease related mortality (48, 49). The included studies highlight the potential for using large datasets to develop prognostic models. These have the advantage of providing data from 'real-world' settings, outside of the clinical trial context or using data exclusively from specialised centres. Our included studies commonly used elements of good study design that would be in keeping with the AJCC acceptance criteria for risk models (33). For example, criteria that were seen in all studies, were that the prognostic time-zero was well-defined, and that model developments

have been published in well regarded peer-reviewed journals. However, other criteria were lacking such as reporting measures of discrimination, assessing calibration, and thorough reporting of missing data in validation work. The inadequacies of existing models are evident by the fact that the American Joint Committee on Cancer (AJCC) have not endorsed a single prognostic model for non-metastatic PCa (60).

The most robust tools we found were the three that have been externally validated – namely the Cambridge Prognostic Groups, The SEER Cancer Survival Calculator and the UCSF Cancer of the Prostate Risk Assessment (CAPRA) score. However, the SEER calculator has never been released for public use. Of note, the Cambridge Prognostic Group stratification criteria has not previously been summarized in prior reviews, as both its development and validation have been published in the last few years (45, 49). Both the CAPRA and Cambridge Prognostic Group models do still have significant shortcomings if considering application to clinical practice due to their disregard of treatment effect, focusing only on disease-specific mortality and ignoring comorbidity. Importantly, each of the three external validation studies also had potential flaws in their design, using predominantly complete-case analyses and non-independent authors (25, 48, 49).

Many of the included studies used historic cohorts. This is a necessity when using long-term survival as an outcome, but, raises issues of generalisability to men diagnosed in the contemporary setting. The uptake of pre-biopsy multi-parametric MRI and targeted biopsies, may for instance impact upon the type of PCa detected and affect generalisability of previous models to current practice (61). Another issue was of small cohorts and low numbers of events in some cases, often as a result of relatively short follow up. The value of 5-year outcomes themselves is questionable given RCT data on survival in non-metastatic PCa would suggest cancer-specific survival over this timeframe is incredibly high (16). An important feature of any prognostic model should be its usability and applicability to a man diagnosed today. However, with unquantified missing data this applicability becomes less clear. Dealing with PCSM in isolation may also be problematic, not least because of the importance of competing risks of death in a disease that affects older men (62). In this review we see that all but 2 included models were derived from North American data, such that generalisability to European or UK men could be questioned, with differing approaches to PSA-testing and different healthcare contexts. This is particularly relevant with regards to screening, whereby historic American cohorts are likely to have been detected through PSA

screening, such that issues of lead time bias and detection of cancers that would not be considered clinically-significant may affect model generalisability to modern practice.

Access for clinicians and patients to know about and use models should be easy with modern web-based software. However, we found models were often only available in paper nomograms published with the article. Rather than online resources increasing the availability of models, there is the suggestion of the opposite occurring, with sites such as www.nomogram.org and www.clinicriskcalculators.org which were previously cited in reviews no longer being available online (53). Indeed, the SEER Cancer Survival Calculator, one of the most promising models we explored, which was also externally validated, was never made available online or for clinical use (43, 48). The UCSF CAPRA score (www.urology.ucsf.edu) and Cambridge Prognostic Groups (www.cambridgeprognosticgroup.com) on the other hand are freely available online. Difficulty in accessing models, or a reluctance to fully share model coefficients may partly explain the lack of external validations by researchers outside of the original models' authorship group.

Another hurdle to acceptance of any model will be their 'face validity'. For example, in any PCa prognostic model clinicians would likely expect grade, PSA and stage to be incorporated as a minimum set of variables; each of which has been shown to be independently prognostic (63-65). However, two of the models based on the largest dataset failed to include PSA which is inadequately recorded in the SEER database (43, 48). A number of the other models used 3-strata grade classifications, rather than the full Gleason grade system, or the contemporary grade group system, which would again seem inadequate for a modern PCa model (66).

A key step in the development of any prognostic model, following validation, should also be a clinical impact study to quantify whether the model's use improves decision-making and patient outcomes within a comparative design (67). Reviewing clinical impact studies was beyond the scope of this formalized review, but no such studies were found on simple literature review. These studies not only assess whether use of the model is an improvement upon standard care, but also enable the study of factors that may affect implementation into care, such as the acceptability and ease of use to clinicians or patients, which can be difficult to assess in a review such as this (67). Impact studies can also help to

bridge the gap between clinical validity and clinical utility, as utility of a model is not proportional to its prognostic capabilities. This has recently been explored further in a review on the UCSF CAPRA score, which confirmed its prognostic capacities but was unable to demonstrate clinical usefulness – particularly when deliberating between different treatment strategies (68).

1.4.4 Strengths and limitations of systematic review

This review of the literature had particular strengths in its broad coverage and search strategy, however, it has potential limitations. Although we assessed bias within individual studies we recognise that risk of bias will also exist across studies, driven particularly by publication bias and selective reporting within studies which we were unable to assess. Other limitations may relate to our timeframe of inclusion of studies only from the year 2000 onwards. Models developed prior to this time may have undergone more thorough testing or validation and clinical impact assessment. However, our rationale for focusing on this contemporary time period was to investigate models appropriate to modern management; with significant changes having taken place in patient management and diagnostic practice since that time (61, 66). It should also be noted that validation studies published subsequent to the year 2000 would have been included, even if the original model was published earlier.

Notably, our inclusion criteria meant that the Memorial Sloan Kettering Cancer Center (MSKCC) prostate cancer nomograms, predominantly derived from Kattan nomograms, were omitted from inclusion in this review as too were the Partin nomograms(69, 70). These are some of the more established and widely used tools – particularly in America. However, the predominant MSKCC nomogram uses biochemical recurrence as the outcome, rather than survival, and indeed was published prior to our inclusion dates, hence it failed to meet our inclusion criteria (70). In more recent years, the MSKCC website has included a tool which includes predictions around cancer survival after surgery – no formal publication relating to this model could be found, nor would it necessarily meet our inclusion criteria – in that it would be specific to only one treatment type. Given the wide use of these tools, further comparison to them would have been insightful, and hence it is a limitation that these models were not included.

We recognize that exciting developments are also underway to propose genomic or biomarker-based prognostic indicators (71). Many of these are currently reported as single parameter studies, rather than being incorporated into existing models. As such these would not meet the eligibility criteria for this review. As others have suggested, any incremental value of these models should be assessed against 'a gold-standard multivariable clinical prognostic model'(72).

1.4.5 Prognostication in other tumour types

The systematic review outlined above demonstrated the inadequacies of models specific to the PCa setting. This lack of a useful clinical tool is further emphasised by the finding that only a small proportion of clinicians regularly use a prognostic tool. As part of our clinician study, outlined later in Chapter 4, health care professionals were asked whether they used any form of prediction tool in their regular practice. Overall, only 46% of the 190 respondents reported using any tool whatsoever. Figure 1.3 shows the percentage of respondents that used each of the named tools. Only 19% used a prognostic tool as such, i.e. based upon survival outcomes (marked in red in the figure).

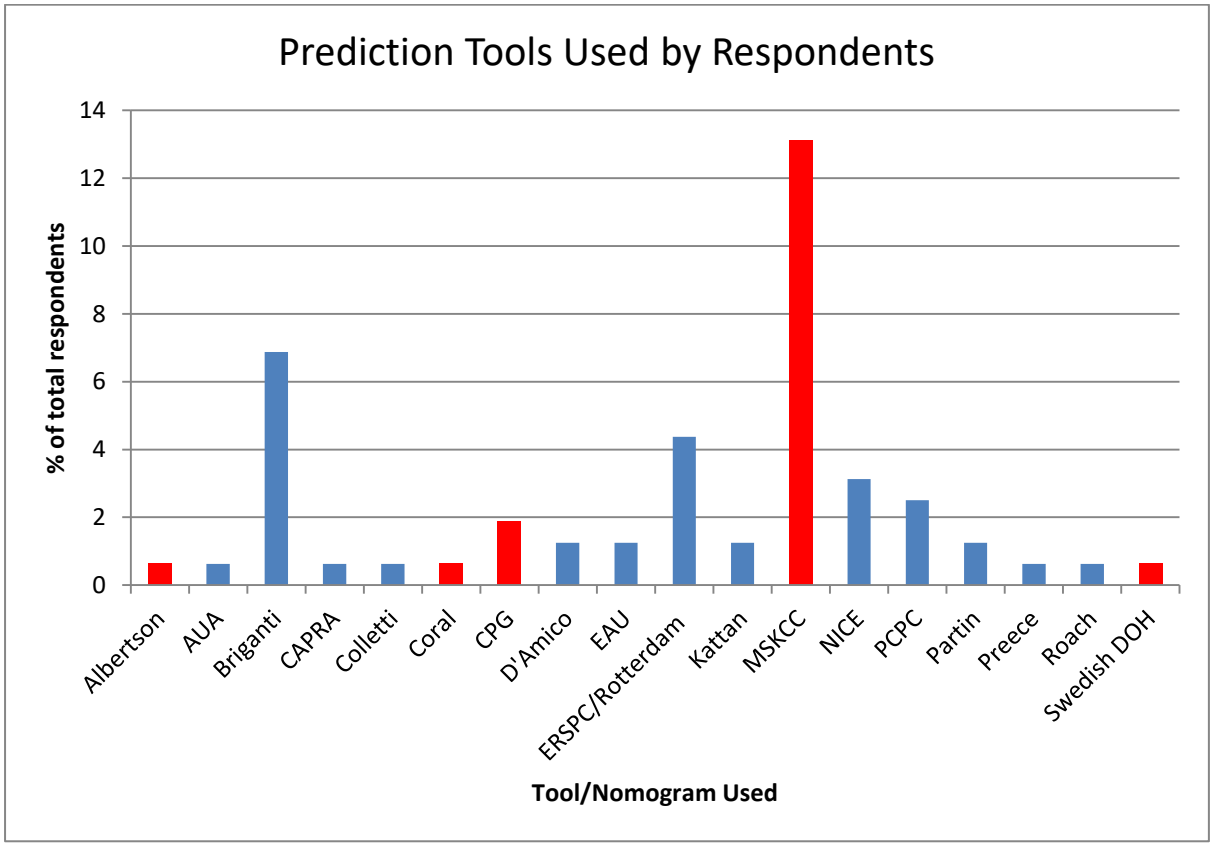


Figure 1.3. Chart demonstrating the risk prediction tools clinicians reported using in their current practice at the point of diagnosis. Those known to be predictive of survival outcomes are highlighted in red. n=160 AUA = American Urology Association stratification criteria. CAPRA = UCSF Cancer of the prostate risk assessment score. CPG = Cambridge Prognostic Groups. EAU = European Association of Urology stratification criteria. ERSPC = European randomised study for screening in prostate cancer. MSKCC = Memorial Sloane Kettering Cancer Centre nomograms. NICE = UK National Institute for health and care excellence risk stratification criteria. PCPC = Prostate cancer prevention trial calculator. DOH = Department of Health.

In other tumour-types, there are examples of prognostic models of higher quality which are already integrated in to routine clinical practice. Pioneering work in Cambridge addressed many similar themes in breast cancer in the past, with the development of the PREDICT model (34). This web-based prediction tool, first published in 2010, was built using cancer registry data from the East of England. PREDICT has grown in popularity over time to become the predominant decision tool used in UK breast cancer MDTs; particularly to guide decision-making around the use of adjuvant chemotherapy. The use of PREDICT is now recommended as part of the NICE Guidelines on breast cancer, and its website hosts over twenty-thousand sessions per month, with the model hosted on an NHS website (www.predict.nhs.uk). PREDICT allows both patients and healthcare professionals to model survival outcomes, based on potential treatment modalities, and has evolved over time with the addition of contemporary biomarkers and therapeutic agents (73, 74).

1.5 Conclusions

As shown by the thorough review outlined above, very few long-term prognostic models previously existed to inform the predominant decision dilemma of whether to undergo treatment or not at the point of diagnosis of non-metastatic prostate cancer. Existing models were limited by inadequate external validation and fell short of many of the expectations of an unbiased, high-quality prognostic model (33). The most robust clinically-available tools are the Cambridge Prognostic Groups and the UCSF Cancer of the Prostate Risk Assessment (CAPRA) score. However, both have significant shortcomings and are limited in their applicability at diagnosis by failing to include treatment effect, and by disregarding non-cancer mortality. Both use categorical risk stratification groups, which remain broad and heterogeneous, rather than providing individualised outcome estimates.

A need has been made evident for prognostic models built on long-term survival outcomes which maximally utilise available clinico-pathological information and contextualize PCa mortality within a patient's own context of competing-risks. High quality multivariable models including treatment effect are overdue, and crucial if both under and over-treatment of prostate cancer is to be minimised. Further work in this thesis to design and develop an individualized multi-variable model was inspired by the findings of the systematic review outlined above.

1.6 Objectives for this research

The need for a novel prognostic tool for localised prostate cancer has been identified. This should be based upon contemporary UK data that uses mortality as an outcome measure rather than inadequate surrogates and is usable at the point of diagnosis when the decision dilemma exists between radical and conservative treatment. Furthermore, as outlined in Chapter 1.4.5 an example of a clinically-useful tool in another tumour-type already exists, and has demonstrated the potential to inform practice and gain widespread adoption. In this project therefore, some of the local expertise that enabled PREDICT was harnessed but adapted for the specific context of PCa, informed by the review outlined above. The over-riding aim was to create a model which can be implemented into an online, simple to use, risk communication tool, which provides users with cancer-specific and overall mortality risks at diagnosis, while concurrently modelling the impacts of different treatments on these

outcomes. It should counter the inadequacies of previous models – highlighted in the review described in this chapter.

Hypothesis

This thesis is designed around the hypothesis that a validated, individualised, prognostic tool for non-metastatic prostate cancer can be developed, that accurately stratifies men according to survival outcomes, and that this tool can be successfully integrated into clinical practice.

Objectives:

1. Establish a contemporary database of UK men with non-metastatic prostate cancer and use these data to develop an individualised prognostic model that estimates overall and prostate cancer-specific survival, and the impact of different treatment modalities upon these outcomes.
2. Externally validate the model and develop it into a web-based tool for real-time clinical decision making.
3. Clinically test the tool among both clinicians and patients to assess its value and potential clinical impact.

2 Development of a novel individualised prognostic model for prostate cancer

This chapter describes the development of a novel multi-variable prognostic model using data from the East of England. Parts of this work have been published previously (75).

2.1 Introduction

As outlined in Section 1.1.1, prostate cancer is the commonest cancer affecting males and a leading cause of cancer-related morbidity (7). Treatment decisions among men with non-metastatic disease are complex with the risk of cancer related mortality balanced against the potential morbidity associated with treatment, as well as competing mortality risks. Estimating prognosis within these contexts is therefore highly important, with over 40,000 consultations for newly diagnosed PCa every year in the UK alone (5). Despite this importance, as outlined in Chapter 1, there are very few prognostic models and no high-quality individualised models available for clinical counselling and decision-making around treatment.

The objectives for this section of the thesis were to develop and validate an individualised prognostic model for non-metastatic PCa. The aim was to produce a model that was able to contextualise the relative PCa-specific and overall survival outcomes for an individual with newly diagnosed disease, and that allows modelling of the potential benefit of treatment upon these outcomes. The mathematical model should then be translated into a usable presentation format for use in clinical practice.

2.2 Methods

Study design was informed by the AJCC criteria for model adoption (33). The methodology for this model development study is reported throughout as per the Transparent Reporting of a multivariable Prediction model for individual prognosis or Diagnosis (TRIPOD) guideline, with the TRIPOD checklist recorded in the appendix (76).

2.2.1 Study population and definition of variables

Following institutional review, fully-anonymised data were retrieved from the Office for Data Release from Public Health England (ODR1617/171). Information on all men diagnosed with non-metastatic PCa in secondary care in Eastern England, UK, between 2000 and 2010 was collected prospectively by the National Cancer Registration and Analysis Service [NCRAS] Eastern Region. Men with recorded nodal or metastatic disease at diagnosis were excluded, along with men diagnosed only by endoscopic resection and any remaining men with PSA ≥100ng/ml – as a surrogate for occult metastatic disease (6, 77). Only men with intact information on key candidate predictors – age, PSA (ng/ml), histological grade group, T-stage and primary treatment were included. From a potential cohort of 15,335 men, 5,246 (34.2%) were excluded for missing information in at least one of these variables leaving a final analytic cohort of 10,089. Charlson comorbidity scores, derived from inpatient hospital episode statistics (HES) data were also included. These are based on clinical coding of inpatient episodes in a 2-year period between 27 and 3 months prior to PCa diagnosis, thus excluding PCa from any comorbidity score. Vital status was ascertained at the end of March 2017 with all analyses censored at the end of September 2016 to allow for a lag-time of up to 6 months for non-cancer deaths through the National Health Service Strategic Tracing Service. Death was considered 'PCa-specific' when PCa was listed in 1a, 1b or 1c of the death certificate.

Potential variables entered into the primary model were age, PSA, clinical T-stage, histological grade, ethnicity, comorbidity and primary treatment type. Information from NCRAS was that recorded at the time of diagnosis. T-stage was simplified to T1, T2, T3 or T4 as subcategories were rarely available and are likely to have limited impact in determining prognosis (78). Histological grade groups (1-5) were used in keeping with modern practice, as defined by the international Society of Urological Pathologists (ISUP) (66). PSA (ng/ml) refers to the value at diagnosis, prior to biopsy or treatment. Primary treatment refers to the first definitive treatment the patient received in the first 12 months. Here we have used the term 'conservative management' to cover both active surveillance and watchful waiting as registry data did not discriminate between the two during this time period. As previously published, the majority of men receiving radiotherapy (RT) in this period were on concomitant hormone therapy which represents current best practice for this treatment modality (12).

2.2.2 Model Development

The primary (UK) cohort was split randomly in a 70:30 ratio into model development (n=7062) and validation cohorts (n=3027) (Table 1). Within the development cohort separate models were built for PCa-specific mortality (PCSM) and non-PCa mortality (NPCM). The general approach to modelling was similar to that used for the PREDICT breast cancer prognosis and treatment benefit model (79). Cox proportional hazards models were utilised to estimate hazard ratios associated with each candidate predictor. Follow up time was censored at time to death, time to last follow up or 15 years, which ever came first. Each variable was assessed through uni- and multi-variable analysis with the proportional hazards assumption tested using the estat phtest function in Stata. For some variables, data were categorised for this purpose. A backwards elimination technique was used for variable selection with a 5% significance level. Risk-relationships between continuous variables were modelled using multivariable fractional polynomials, with continuous data retained wherever possible to maximise predictive information. T-stage, histological grade group, and primary treatment type were modelled as factor variables. Radical treatments (radiotherapy (RT) or radical prostatectomy (RP)) were combined, as explained later. After fitting the multi-variable models, smoothed functions for the baseline hazard of PCSM and NPCM were calculated. The baseline cumulative hazard was estimated for each patient, then the logarithmic value of the baseline hazard was regressed against time using a univariate fractional polynomial function (79).

2.2.3 Competing risks adjustment

Beta coefficients for each prognostic factor in the two Cox models were used to derive a prognostic index for PCSM(piPCSM) and NPCM (piNPCM) for each patient. The absolute risk (hazard(H)) of PCa death (H_{PCa}) and non-PCa (H_{NPC}) death until time *t*, if there were no competing mortalities, are estimated by the following formulae respectively:

$$H_{PCa} = 1 - \exp(-\exp(piPCSM)*bhPCSM(t)) \text{ and}$$

$$H_{NPC} = 1 - \exp(-\exp(piNPCM)*bhNPCM(t)).$$

Where bhPCSM(*t*) and bhNPCM(*t*) are the cumulative baseline hazards of PCSM or NPCM at time *t* respectively. However, as these risks compete against each other, the cumulative risk (R) of overall mortality (OM) at time *t* is :

$$R_{OM}(t) = 1 - (1-H_{PCA}(t))*(1-H_{NPC}(t).$$

Therefore the formulae for cumulative risk (R) of PCa death and non-PCa death at time *t* are:

$R_{PCa}(t) = R_{OM}(t) * (H_{PCa}(t) / (H_{PCa}(t)+H_{NPC}(t))$ and

$R_{NPC}(t) = R_{OM}(t) * (H_{NPC}(t) / (H_{NPC}(t)+H_{PCa}(t))$ respectively.

The source code for replicating the model's output has been made available online, including this competing risk adjustment, and is recorded in the appendix of this thesis (80).

2.2.4 Internal validation and comparison to existing models

Model calibration and goodness-of-fit was first investigated in the UK validation cohort by comparing observed and predicted deaths within quintiles of predicted mortality and within strata of other prognostic variables. For assessing calibration, we integrated the predicted outcomes across all follow-up times to allow for cases with follow-up of less than 10 or 15 years. Thus the calibration corresponds to a range of different follow-up times. A simplified χ^2 goodness-of-fit (GOF) test was performed using the method of May and Hosmer, whereby a p value of less than 0.05 would suggest a significant difference between the expected and observed number of events, assessed up to 10 years or 15 years (81). Calibration curves were also visually assessed. Model discrimination was evaluated by estimating 10 and 15-year cumulative mortality risk. Harrell's concordance statistic (C-index) was then calculated for PCa-specific, non-PCa and overall deaths. This accounts for right-censored data, i.e. cases with less than 10 or 15 years follow-up respectively. All analyses were performed using Stata 14 (StataCorp, College Station, TX, USA), with the exception of C-index which was performed using '*rcorr.cens*' within the '*Hmisc*' package of R (82).

Comparisons against existing models were made by calculating C-indices for 3 well-known tools used at the point of diagnosis internationally – namely the UCSF Cancer of the Prostate Risk Assessment (CAPRA) score, the updated NCCN criteria and the three-tier EAU criteria – akin to the UK NICE criteria (22, 30, 32). Available information was used to calculate these with no imputation of missing data. Where T stage sub-classification was unknown, integer T-stages were used do lineate risk categories.

2.2.5 Inclusion of biopsy information as a variable and revalidation

Previous risk criteria have included diagnostic biopsy information as a potentially important prognostic variable, as a surrogate for tumour burden. To investigate this we undertook an additional sub-cohort analysis on men diagnosed at Addenbrooke's Hospital, Cambridge for whom biopsy characteristics were available, and were within our overall cohort (n=1451).

Pathological information was retrospectively retrieved and transcribed. During the time period of inclusion the routine method of prostate biopsy was systematic trans-rectal prostate biopsy, typically using 12 cores with an 18Gauge tru-cut biopsy needle.

For this analysis we used percentage of positive cores (PPC = number of cores positive for cancer/total number of cores taken). PPC was regressed against PCSM, offset against all parameters within the base model. PPC was modelled continuously and categorically. Likelihood ratio χ^2tests, Akaike (AIC) and Bayesian information criterion (BIC) were used to determine best fit. The eventual parameter was weight-adjusted and incorporated in to the model. Performance of the extended model, including the PPC parameter, was then re-assessed within the Singaporean cohort – for which biopsy information was available – using the same methodology as outlined above.

2.2.6 External validation

External validation of both the baseline model (excluding biopsy information) and the extended model (including biopsy information) was assessed using a geographically and ethnically independent cohort of men from Singapore General Hospital, diagnosed between 1990 and 2015. PCa cases and deaths amongst cohort members were recorded by linkage of the cohort database with the population-based Singapore Cancer Registry and the Singapore Registry of Births and Deaths (49). Intact data requirements resulted in the exclusion of 310 cases. No follow-up information was available for a further 389 men leaving an analysable cohort of 2,546 (Table 1). Data amongst this cohort had been recorded on a prospective basis including the same parameters as the primary cohort with the addition of biopsy information, but did not include comorbidity information. NPCM estimates therefore assumed the same prevalence of comorbidity as the primary dataset (10.21%) spread evenly across the cohort. Vital status was ascertained via the Singapore Ministry of Home Affairs, with data censored 30th June 2017. Model performance was assessed using the same methods described above. Ethics for use of these data was covered by ref. 2009/1053/D approved by the SingHealth Centralised Institutional Review Board.

2.2.7 Model presentation and translation into a web-based tool

Following development of the algorithm, presentation of the model in a usable format was considered. We expect that primary utility will be among men for whom conservative management and radical treatment might both be appropriate options. Early collaboration

was sought with colleagues at The Winton Centre for Risk and Evidence Communication at the University of Cambridge. Presentation of the model estimates in a number of different formats was developed, in collaboration, to cater to the varied needs of potential users, including patients themselves and health care professionals. Five different presentation styles were prepared, namely curves, charts, icons, tables and text. In each presentation style we sought to convey the uncertainty around the estimates generated, using gradations of colour, or by reporting 95% confidence-intervals for the tabular outputs.

Separate to this thesis, colleagues at The Winton Centre were undertaking a thorough user-centred design-process in redeveloping the Predict Breast cancer web-interface (83). The work employed focus groups, usability-testing, online surveys and meetings to maximise the benefit of prognostic models (83). Many of the insights gained were also applied to the eventual Predict *Prostate* web interface (prostate.predict.nhs.uk). The site was developed in an iterative process between ourselves and the Winton Centre team. Importantly, alongside the potential survival benefits of treatment, it was felt necessary to also present potential adverse effects of different treatment approaches. The derivation of these data are outlined on the website, and are extracted from previously published studies, and as such are not individualised to patients (11, 84). The intention behind the web-interface was to develop a site that can be accessible to patients directly, with explanatory toggles on most buttons for the tool, transparent explanations with regard to the model development, disclosure of related publications, a thorough 'frequently asked questions' section and online publication of the underlying algorithm itself (85).

2.3 Results

2.3.1 Participants

The model development cohort consisted of 7,063 men with mean age of 69.9 years. 842 and 1,821 men died from PCa and other causes within 15 years respectively. The UK validation cohort consisted of 3,026 men with mean age 39.9 years; 360 and 806 died from PCa and other causes respectively. Median follow-up was 9.8 years for both cohorts with 82,887 person-years of follow-up in total (Table 2.1). Importantly, the UK cohort included significant numbers of patients who had undergone conservative management (n=1997). Only 114 (5.7%) of these men converted to radical treatment over total study follow-up. Trends across the inclusion period, including increased incidence rates of PCa each year, more rapid increases in intermediate-risk disease, increasing proportions of T1 disease and increasing uptake of conservative management have been identified previously within a similar cohort (6, 12).

		Total UK Cohort		UK Model Development Cohort		UK Validation Cohort		Singapore Validation cohort	
Total Subjects		10,089		7,063		3026		2546	
Time at risk (years)		82,887		58,138		24,750		13,416	
Median follow-up (years)		9.8	Range 0-16	9.8	Range 0-16	9.8	Range 0-16	5.1	Range 0-26
10 year outcomes:			%		%		%		%
PCa deaths		1030	10.2	712	10.1	317	10.5	105	4.1
Non PCa deaths		2246	22.3	1555	22.0	691	22.8	225	8.8
Any-cause death		3276	32.5	2267	32.1	1008	33.3	330	13.0
Observations censored before 10 years		3770	37.4	2667	37.8	1103	36.5	1930	75.8
15-year outcomes:									
PCa deaths		1202	11.9	842	11.9	360	11.9	133	5.2
Non PCa deaths		2627	26.0	1821	25.8	806	26.6	283	11.1
Any-cause death		3829	38.0	2663	37.7	1166	38.5	416	16.3
Observations censored before 15 years		6000	59.5	4212	41.7	1788	59.1	2063	81.0
Crude PCS mortality rate (per patient year)		1.46		1.46		1.46		0.99	
Annual overall mortality rate (per patient year)		4.64		4.6		4.72		3.1	
Age (mean, SD)		69.9	8.30	69.9	8.34	69.9	8.29	66.1	7.96
PSA (mean, SD)		18.4	17.5	18.5	17.5	18.2	17.6	15.7	16.6
Gradegroups			%		%		%		%
	1	3328	33.0	2317	32.8	1011	33.4	1126	44.2
	2	3017	29.9	2125	30.1	892	29.5	723	28.4
	3	1486	14.7	1057	15.0	429	14.2	326	12.8
	4	1032	10.2	710	10.1	322	10.6	170	6.7
	5	1226	12.2	854	12.1	372	12.3	201	7.9
Tumour-stage									
	1	5421	53.7	3761	53.2	1660	54.9	1625	63.8
	2	3213	31.8	2270	32.1	943	31.2	660	25.9
	3	1378	13.7	977	13.8	401	13.3	244	9.6
	4	77	0.8	55	0.8	22	0.7	17	0.7
Primary Treatment									
Radical Prostatectomy		1419	14.1	995	14.1	424	14.0	1012	39.7
Radiotherapy		3495	34.6	2457	34.8	1038	34.3	823	32.3
Hormone Monotherapy		3178	31.5	2226	31.5	952	31.5	164	6.4
Conservative Management		1997	19.8	1385	19.6	612	20.2	538	21.1
Missing		na		na		na		9	0.4
Ethnicity									
White		7804	77.4	5464	77.4	2340	77.3	36	1.4
Missing/unknown		2136	21.2	1491	21.1	641	21.3	0	0.0
Asian		50	0.5	35	0.5	15	0.5	2435	95.6
Other		99	1.0	108	1.5	26	0.9	73	2.9

Table 2.1 Baseline cohort characteristics in the UK cohort overall, model development and validation cohorts and the external Singapore cohort.
PCa = prostate cancer SD= standard deviation

2.3.2 Model development and specification

Age, PSA, histological grade group, clinical stage and primary treatment type were all independent predictors for PCSM in the development cohort, both in univariate and multivariate analysis (Table 2.2). Ethnicity was excluded for failing to show prognostic significance; there was also minimal variation with >98% of known ethnicity being Caucasian, and significant amounts of missing data for this parameter. No significant breach of the proportional hazards assumption was observed on either non-adjusted or adjusted assessment of included variables. Example proportional hazard plots against PCSM are shown in Figure 2.1.

.

Comorbidity had a predictive effect in relation to NPCM but not PCSM. Age was also independently prognostic for NPCM. In the final model, comorbidity was modelled as a binary variable (0 or ≥1), due to small numbers of observations with comorbidity score 2 or above. The hazard ratios and fractional polynomial (FP) functions for prognostic factors in the final model are shown in Table 2.2. Associated FP functions for age and PSA are plotted in Figure 2.2. These allow more flexibility in relationships for continuous variables.

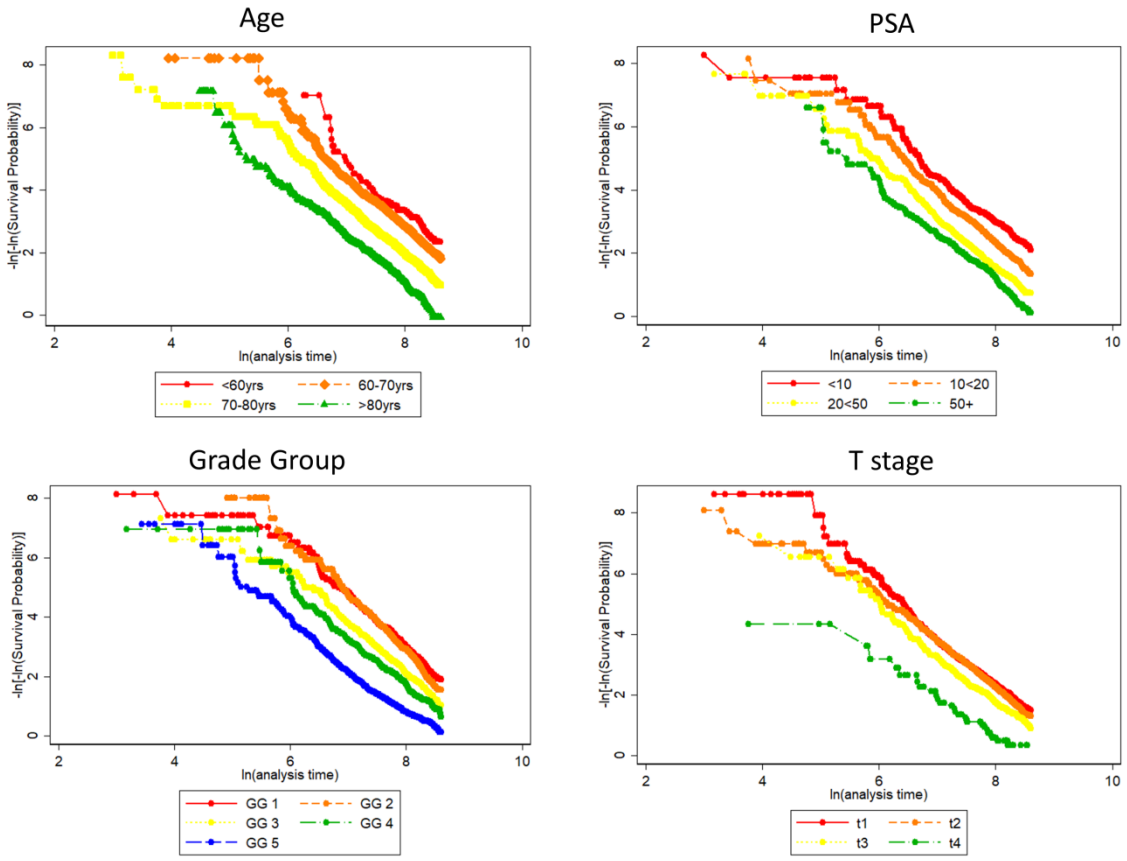


Figure 2.1 Proportional hazard plots for Age, PSA, Grade Group and T stage, against PCSM without adjustment. Categorisation of variables was used, as shown. GG = Grade group T = tumour PSA = Prostate specific antigen

Baseline hazard

The estimated baseline survival functions at time *t* days for PCSM and NPCM are:

Baseline hazard PCSM : exp(-16.40532 + 1.653947*(ln(*t*)) + 1.89e-12*(*t*^3)), range (0 5479)

Baseline hazard NPCM: exp(-12.4841 + 1.32274*(ln(*t*)) + 2.90e-12*(*t*^3)), range (0 5479)

These functions are plotted against actual baseline PCSM and NPCM in Figure 2.3 and Figure 2.4 respectively.

		Prostate Cancer Specific Mortality		
		HR	95%CI	P
Age FP (age/10)^3 -341.16		1.003	1.002-1.003	<0.001
PSA FP ln((psa+1)/100)+1.6364		1.204	1.092-1.328	<0.001
Grade group				
	1	1.00	-	-
	2	1.32	1.06-1.65	0.014
	3	1.73	1.36-2.19	<0.001
	4	2.10	1.63-2.69	<0.001
	5	3.93	3.15-4.89	<0.001
T stage				
	1	1.00	-	-
	2	1.18	1.01-1.37	0.042
	3	1.49	1.23-1.80	0.000
	4	1.88	1.14-3.13	0.014
Primary Treatment				
	Conservative management	1.00	-	-
	Radical treatment (RP/RT)	0.50	0.38-0.67	<0.001
	Hormone monotherapy	2.48	1.92-3.20	<0.001
		Non Prostate Cancer Mortality		
Age FP age-69.87		1.13	1.12-1.14	<0.001
Comorbidity Score				
	1+	1.89	1.67-2.14	<0.001

Table 2.2 The hazard ratios and p values of the variables included in each of the prostate cancer specific mortality and non-prostate cancer mortality models.
FP = fractional polynomial HR = hazard ratio CI = confidence interval

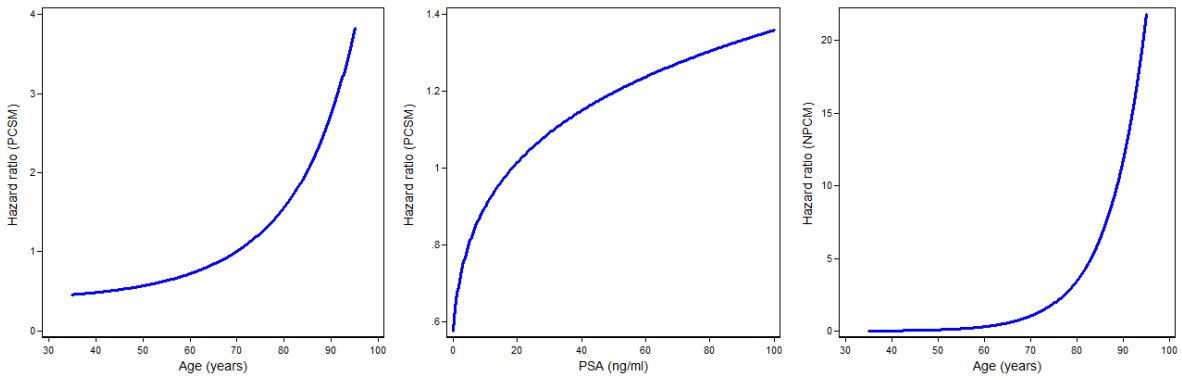


Figure 2.2 Prostate cancer-specific mortality (PCSM) hazard ratio functions for age (left) and PSA (centre), and non-PCa mortality (NPCM) hazard ratio function for age (right). Each derived from the model development data.

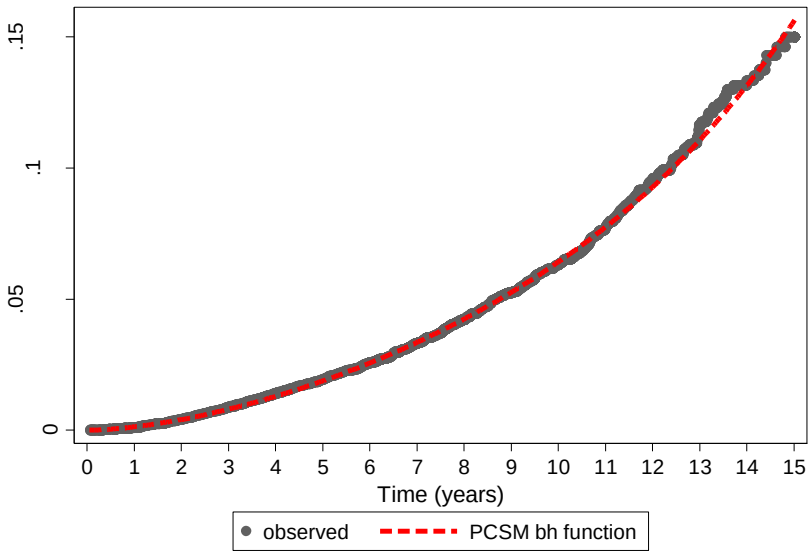


Figure 2.3 Baseline hazard (bh) function for PCSM plotted against observed cumulative PCSM within the UK development cohort across 15 years.

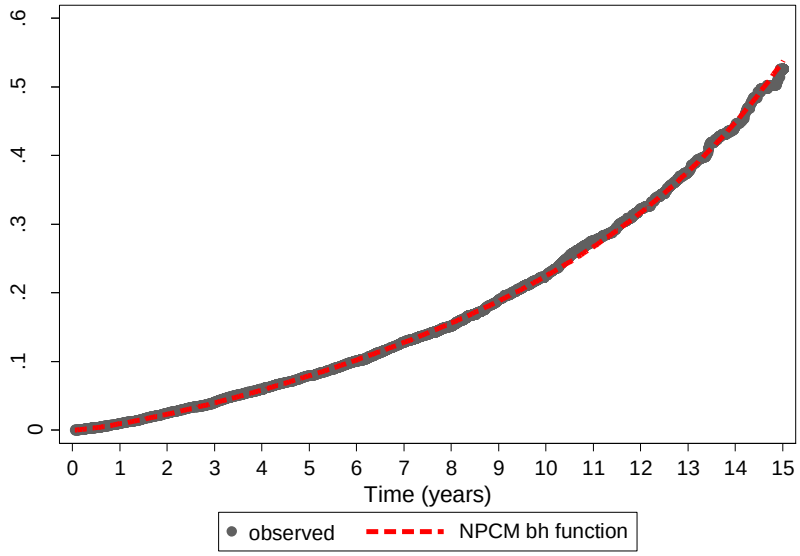


Figure 2.4 Baseline hazard (bh) functions for NPCM plotted against observed cumulative NPCM within the UK development cohort across 15 years.

2.3.3 UK validation

The model was well-calibrated within the East of England validation cohort with absolute differences between observed and predicted PCa-specific and overall deaths less than 1% at 10 years (Table 2.3). The goodness of fit (GOF) tests suggested the model fitted well across different quintiles of risk, as shown by the calibration curves (Figure 2.5) with no significant difference in observed and predicted PCa-specific (p=0.19) or overall deaths (p=0.43) over 10 years (Table 2.3) . Model discrimination was good, particularly for PCa-specific mortality, with C-index 0.84 (95%CI 0.82-0.86) and 0.84 (95%CI: 0.82-0.86) over 10 and 15 years follow

up respectively (Table 2.3). Calibration was again seen to be good across 15 years (Table 2.4). Within the UK cohort, model discrimination was superior (p<0.001) to the current EAU, NCCN and CAPRA risk-stratification criteria for both PCSM and overall mortality (Table 2.5).

	Predicted	Observed	Difference (%)	χ^2 GOF p value	C-index	95%CI
10 years follow-up						
PCa Deaths	343	317	-0.86	0.19	0.84	0.82-0.86
Non-PCa deaths	641	691	1.65	0.19	0.74	0.72-0.77
Overall deaths	986	1008	0.73	0.43	0.77	0.75-0.78
15 years follow-up						
PCa Deaths	413	360	-1.75	0.04	0.84	0.82-0.86
Non-PCa deaths	751	806	1.82	0.02	0.71	0.69-0.72
Overall deaths	1165	1166	0.03	0.63	0.77	0.75-0.78

Table 2.3 Observed and predicted deaths over 10 and 15 years in the UK validation cohort (n=3026). Goodness of fit (GOF) and C-index are shown for each cause of death.

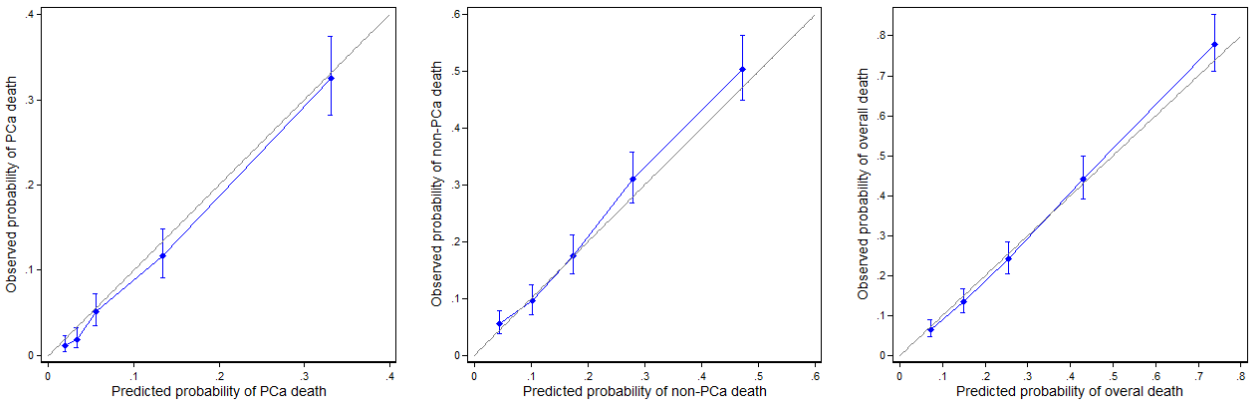


Figure 2.5 Calibration curves comparing observed and predicted probability of prostate cancer(PCa) (left), non-PCa (centre) and overall (right) deaths at 10 years by quintile of risk within the UK validation cohort.

	Predicted	Observed	Difference (%)	χ^2 GOF p value	AUC	95%CI
Prostate Cancer Deaths	413	360	-1.75	0.04	0.84	0.82-0.86
1st quintile	13	6	-1.16			
2nd quintile	24	18	-0.99			
3rd quintile	43	42	-0.17			
4th quintile	101	90	-1.82			
5th quintile	232	204	-4.63			
Non Prostate Cancer Deaths	751	806	1.82	0.02	0.71	0.69-0.72
1st quintile	30	37	1.16			
2nd quintile	72	76	0.66			
3rd quintile	126	124	-0.33			
4th quintile	201	191	-1.65			
5th quintile	322	378	9.26			
Overall Deaths	1165	1166	0.03	0.63	0.77	0.75-0.78
1st quintile	48	46	-0.33			
2nd quintile	105	97	-1.32			
3rd quintile	187	176	-1.82			
4th quintile	316	313	-0.50			
5th quintile	509	534	4.13			

Table 2.4 Observed and predicted deaths across quintiles of risk within the UK validation cohort across 15 years (n=3026). χ2 goodness of fit (GOF) and Harrell's C-indices are shown for each cause of death

	PCSM			Overall Mortality		
Model	C-index	95% CI	p	C-index	95% CI	p
PREDICT	0.843	0.824-0.862	-	0.766	0.753-0.780	-
EAU	0.688	0.665-0.711	<0.001	0.628	0.613-0.643	<0.001
NCCN	0.720	0.695-0.744	<0.001	0.644	0.628-0.659	<0.001
CAPRA	0.754	0.728-0.779	<0.001	0.656	0.640-0.672	<0.001

Table 2.5 Discrimination of the model, compared to other existing models amongst the UK validation cohort over 15 years maximum follow-up (n=3026).
EAU = European Association of Urology NCCN = National Comprehensive Cancer Network CAPRA = Cancer of the Prostate Risk Assessment (UCSF)

Calibration remained good across various sub-categories of patients, as demonstrated in Table 2.6. Importantly, predictions for both PCa and non-PCa deaths amongst men undergoing either conservative management or radical therapy were within 2%. The GOF tests amongst this treatment sub-cohort continued to demonstrate no significant difference between predicted and observed PCa-specific (p=0.23) or overall deaths (p=0.11) over 10 years.

Category	Number of	PCa deaths			NPCa Deaths			Overall deaths		
Age at diagnosis	cases	Predicted	Observed	Diff. (%)	Predicted	Observed	Diff. (%)	Predicted	Observed	Diff. (%)
<60	317	10.9	11	0.0	10.7	12	0.4	21.6	23	0.4
60-69	1,121	68.8	72	0.3	118.8	131	1.1	187.7	203	1.4
70-79	1,207	166.1	152	-1.2	329.1	342	1.1	495.2	494	-0.1
≥80	381	100.9	82	-5.0	189.1	206	4.4	290.0	288	-0.5
PSA (ng/ml)										
0<10	1,176	68.6	56	-1.1	180.5	166	-1.2	249.1	222	-2.3
10<20	1,025	106.6	90	-1.6	237.7	255	1.7	344.3	345	0.1
20<50	597	111.5	106	-0.9	168.5	207	6.4	280.0	313	5.5
≥50	228	60.1	65	2.1	61.0	63	0.9	121.0	128	3.1
T Stage										
1	1,660	160.8	143	-1.1	366.7	389	1.3	527.4	532	0.3
2	943	115.9	94	-2.3	202.7	222	2.0	318.6	316	-0.3
3	401	63.0	70	1.7	72.9	75	0.5	136.0	145	2.2
4	22	7.0	10	13.6	5.4	5	-1.8	12.4	15	11.8
Grade Group										
1	1,011	63.3	61	-0.2	206.9	216	0.9	270.1	277	0.7
2	892	62.6	33	-3.3	165.5	163	-0.3	228.1	196	-3.6
3	429	55.8	45	-2.5	102.3	99	-0.8	158.1	144	-3.3
4	322	58.9	53	-1.8	84.2	108	7.4	143.1	161	5.6
5	372	106.2	125	5.1	88.8	105	4.4	195.0	230	9.4
Primary treatment										
Conservative Management	612	36.8	28	-1.4	148.7	144	-0.8	185.5	172	-2.2
RT/RP	1,462	57.7	51	-0.5	204.3	177	-1.9	262.0	228	-2.3
Hormone monotherapy	952	252.2	238	-1.5	294.7	370	7.9	546.9	608	6.4
Comorbidity										
Nil	2,696	299.8	278	-0.8	527.0	563	1.3	826.7	841	0.5
≥1	330	47.0	39	-2.4	120.7	128	2.2	167.8	167	-0.2

Table 2.6 Calibration between observed and predicted PCSM, NPCM and overall mortality at 10 years for sub-groups within the UK validation cohort.

2.3.4 Model extension with the inclusion of diagnostic biopsy information

1,451 men diagnosed at Addenbrooke's Hospital, for whom percentage positive cores (PPC) information was available, made up the sub-cohort used to explore PPC. The unadjusted rates of PCSM within ten categories of PPC in this sub-cohort are shown in Figure 2.6. A step-change in poorer prognosis was observed with PPC ≥50%, as is also demonstrated by the relative hazard ratios for PCSM for categories above 50% (Figure 2.7). PPC was modelled using several different categorisations, including using these data continuously. PPC split dichotomously using a cut-off of either ≥48%, ≥49% or ≥50% fit these data equally well as demonstrated in Figure 2.8, a value of ≥50% PPC was therefore selected and tested against other PPC categorisations. As demonstrated by the lower values using the penalized likelihood criteria of AIC and BIC, this simple dichotomous variable around 50% PPC was most likely to be nearest the true model in these data (Table 2.7). KM curves demonstrated the prognostic significance persisted even after adjustment for all other included variables within the model (Figure 2.9).

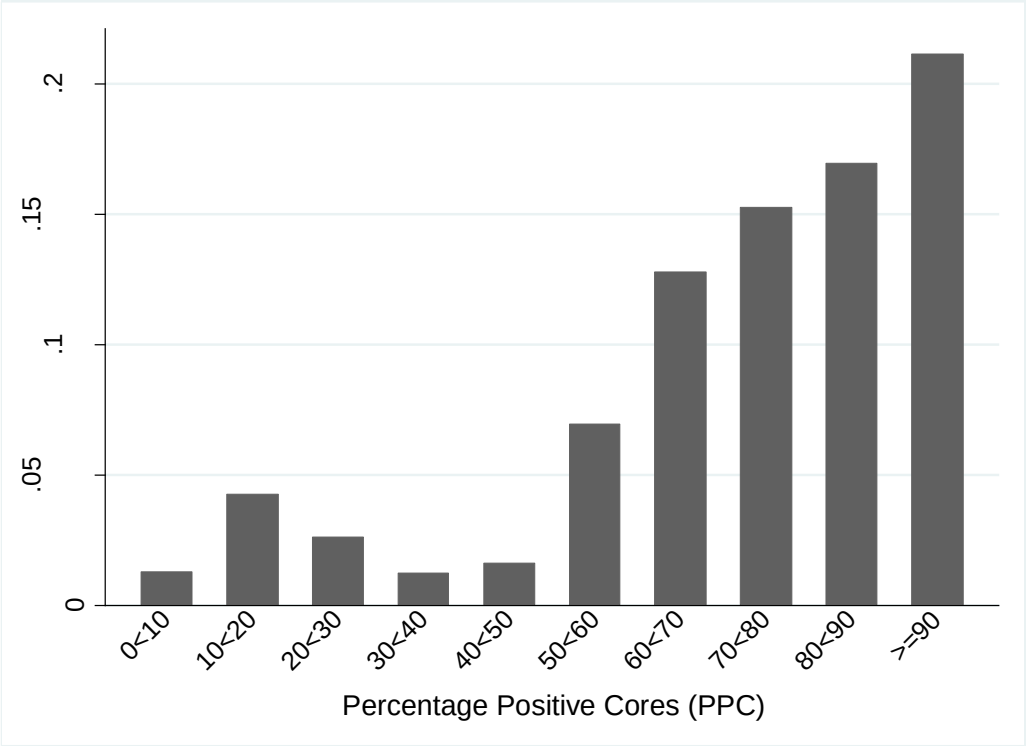


Figure 2.6 Proportion of men dying from prostate cancer within each decile of percentage positive cores (PPC), without any adjustment for other parameters.

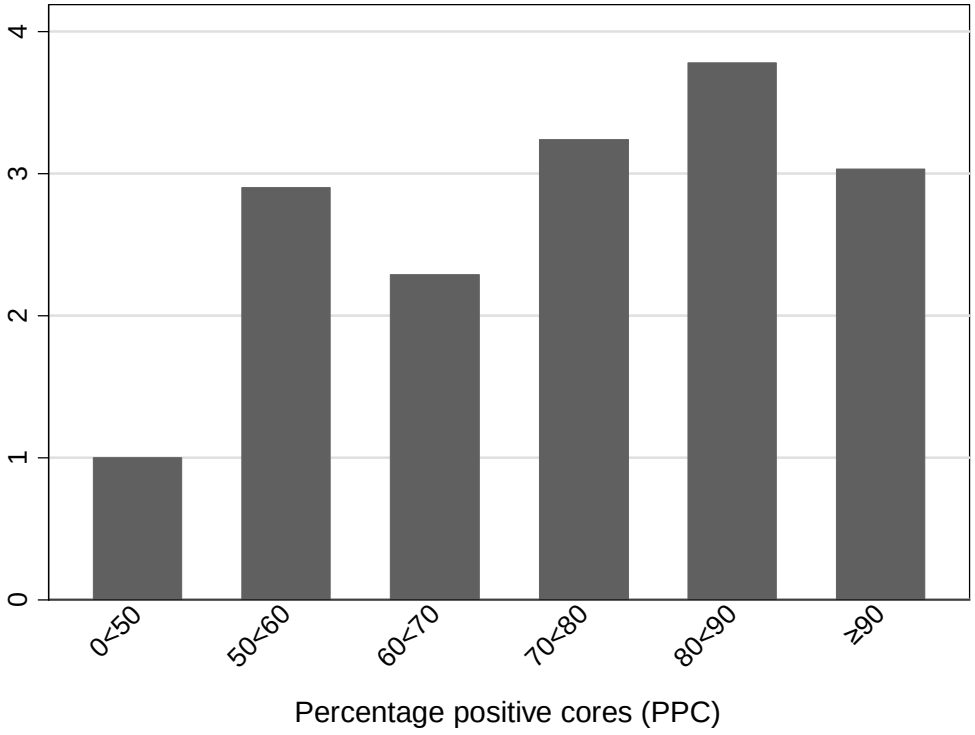


Figure 2.7 Hazard ratios for PCSM within deciles of percentage positive cores (PPC), following full adjustment for parameters included in the model.

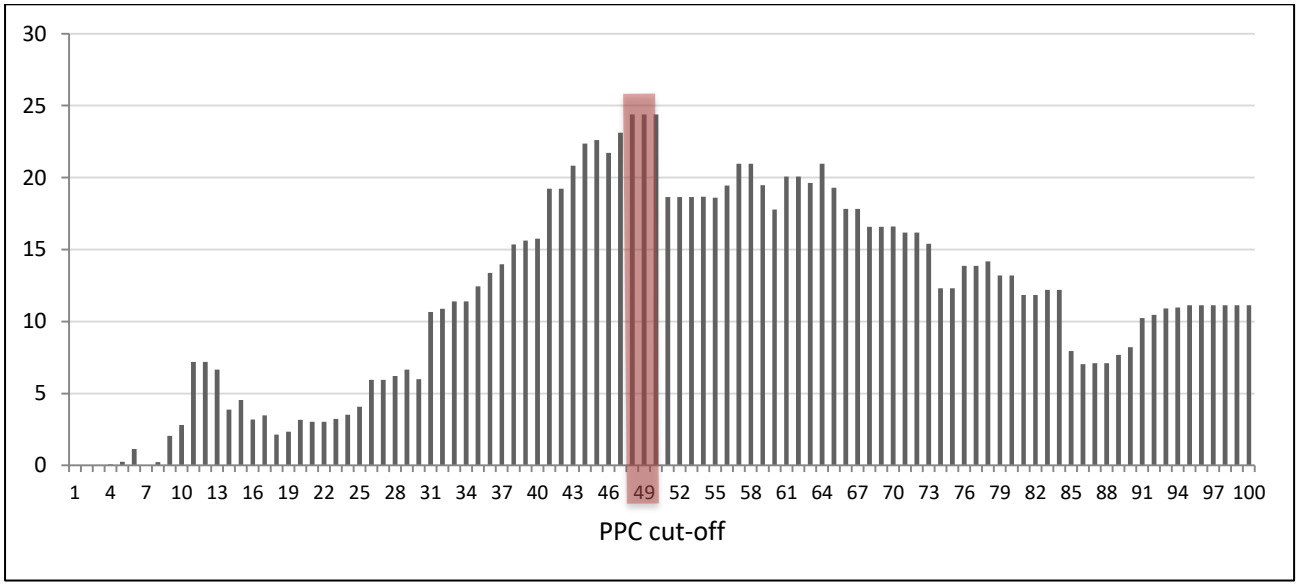


Figure 2.8 Likelihood-Ratio Chi squared values assessing every potential value of PPC as a cut-off for a dichotomous variable. The highest figures were for ≥48, ≥49 or ≥50% PPC (highlighted red).

Categorisation	AIC	BIC
PPC (continuous)	1160.0	1165.3
Logit transformation of PPC	1162.3	1167.6
<50% vs ≥50%	1154.8	1160.0
<50% vs 50<75% vs 75-100%	1156.5	1167.1
<33% vs 33-67% vs 67-100%	1318.2	1328.9

Table 2.7 Akaike (AIC) and Bayesian information criterion (BIC) for various categorisations of PPC.

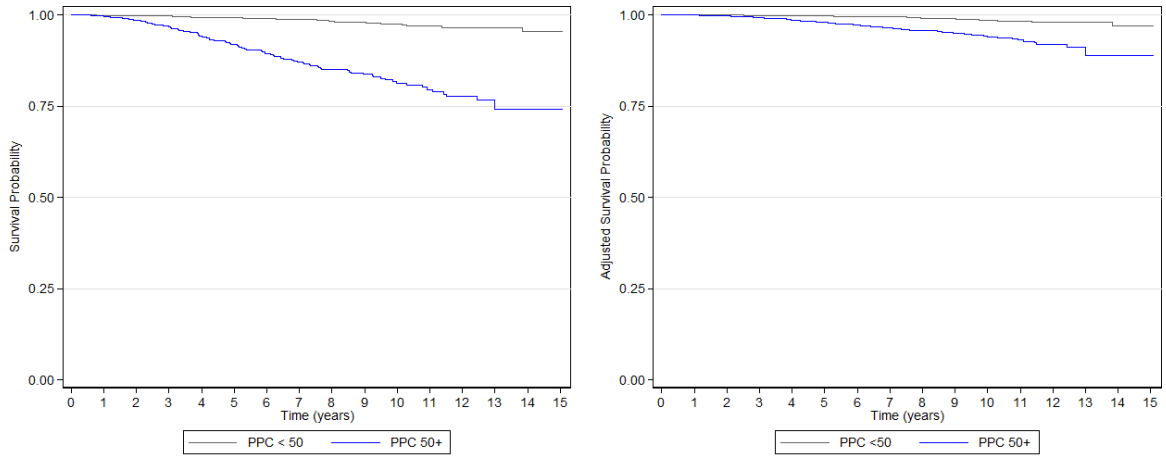


Figure 2.9 Kaplan Meier curves showing the differences in survival for men with percentage positive biopsy cores (PPC) of 50% or greater compared to those with less than 50% PPC. The left graph is unadjusted, whereas the right graph shows the curve adjusted for all other prognostic variables for prostate cancer specific mortality within the multi-variable model

In this sub-cohort, 939 (63.0%) and 552 (37.0%) men had <50% and ≥50% PPC respectively. The hazard ratio (HR) for PCSM was 3.31 for those with ≥50% PPC compared to 1.0 for those with PPC <50% (Table 2.8), after adjustment for all other variables in the model. However, to incorporate PPC into the model these hazard ratios required adjustment for the relative proportions of the two groups, such that the net effect remains a hazard of 1.0. Therefore the 'biopsy effect' is only activated if PPC is known. If PPC is unknown, predictions are as per the baseline model (excluding PPC). Core involvement was weight-adjusted according to these relative proportions of PPC, as shown in Table 2.8. First the HR is multiplied by the proportion to calculate the 'weighting'. Next, the 'adjusted HR' is calculated by dividing the HR by the sum of the two weightings. The coefficients, for inclusion in the model, are calculated by taking the log of the adjusted HR, in the usual way. The final composition of the extended model including PPC, is shown in Table 2.9.

PPC	Unadjusted HR	Frequency	Proportion	Weighting (HR*proportion)	Weight-adjusted HR
<50%	1	939	0.63	0.630	**0.54**
≥50%	3.31	552	0.37	1.225	**1.78**
				Sum: 1.855	

Table 2.8 The unadjusted hazard ratios (HR) for prostate cancer specific mortality (PCSM) for the two PPC categories are shown. These are adjusted according to the proportion of men in each PPC category to provide a weight-adjusted HR.

	Prostate Cancer Specific Mortality		
	HR	95%CI	P
Age FP (age/10)^3 -341.16	1.003	1.002-1.003	<0.001
PSA FP ln((psa+1)/100)+1.6364	1.204	1.092-1.328	<0.001
Grade group			
1	1.00	-	-
2	1.32	1.06-1.65	0.014
3	1.73	1.36-2.19	<0.001
4	2.10	1.63-2.69	<0.001
5	3.93	3.15-4.89	<0.001
T stage			
1	1.00	-	-
2	1.18	1.01-1.37	0.042
3	1.49	1.23-1.80	0.000
4	1.88	1.14-3.13	0.014
Percentage positive cores (PPC)			
<50%	0.54	--	<0.001
Unknown	1.00		
≥50%	1.78	--	<0.001
Primary Treatment			
Conservative management	1.00	-	-
Radical treatment (RP/RT)	0.50	0.38-0.67	<0.001
Hormone monotherapy	2.48	1.92-3.20	<0.001
	Non Prostate Cancer Mortality		
Age FP age-69.87	1.13	1.12-1.14	<0.001
Comorbidity Score			
1+	1.89	1.67-2.14	<0.001

Table 2.9 The hazard ratios and p values of the variables included in each of the prostate cancer specific mortality and non-prostate cancer mortality models, including incorporation of the percentage positive cores (PPC) variable. FP = fractional polynomial HR = hazard ratio CI = confidence interval

2.3.5 External validation of models excluding and including biopsy information

Accuracy of the baseline model, and the extended model including the PPC variable, was assessed using the Singaporean cohort (n=2,546). Here, median follow-up was 5.1 years, with 133 and 283 PCa and non-PCa deaths respectively (Table 2.1).

Model discrimination of the baseline model amongst this cohort was promising with C-index 0.83 (95%CI: 0.79 – 0.87) and 0.76 (95%CI 0.73-0.78) for PCSM and overall mortality respectively (Table 2.10). Differences between observed and predicted deaths were less than 1% over 10 and 15-years, albeit within a small cohort. GOF analysis showed no significant differences between observed and predicted non-PCa deaths, but the model appeared to slightly underestimate PCSM and overall deaths (Table 2.10).

	Predicted	Observed	Difference (%)	GOF p value	C-index	95%CI
10 years follow-up						
PCa Deaths	89	105	0.63	0.01	0.83	0.79-0.87
Non-PCa deaths	236	225	-0.43	0.10	0.74	0.70-0.77
Overall deaths	325	330	0.20	0.01	0.76	0.73-0.78
15 years follow-up						
PCa Deaths	112	127	0.59	0.00	0.82	0.78-0.86
Non-PCa deaths	279	273	-0.24	0.08	0.72	0.69-0.76
Overall deaths	391	400	0.35	0.01	0.75	0.72-0.78

Table 2.10 Observed and predicted deaths over 10 and 15 years in the Singaporean validation cohort using the baseline model (n=2546). Goodness of fit (GOF) and C-index are shown for each cause of death.

Accuracy of the extended model, including PPC, was assessed using the Singaporean cohort, for whom biopsy information was available (Table 2.1). Here, model discrimination amongst this cohort was slightly better with C-index 0.85 (95%CI: 0.82 – 0.88) and 0.76 (95%CI 0.73-0.79) for PCSM and overall mortality respectively (Table 2.11).

	Predicted	Observed	Difference (%)	GOF p value	C-index	95%CI
10 years follow-up						
PCa Deaths	92	105	0.51	0.11	0.85	0.82-0.86
Non-PCa deaths	236	225	-0.43	0.23	0.74	0.70-0.77
Overall deaths	328	330	0.08	0.01	0.76	0.73-0.78
15 years follow-up						
PCa Deaths	114	127	0.51	0.08	0.84	0.80-0.87
Non-PCa deaths	278	273	-0.20	0.17	0.72	0.68-0.75
Overall deaths	393	400	0.27	0.01	0.76	0.73-0.78

Table 2.11 Observed and predicted deaths over 10 and 15 years in the Singaporean validation cohort using the extended model, incorporating biopsy information (n=2546). Goodness of fit (GOF) and C-index are shown for each cause of death.

Differences between observed and predicted deaths were less than 1% over 10 and 15-years, albeit within a small cohort (Table 2.11). GOF analysis showed no significant difference between observed and predicted PCa-related deaths (p=0.11) although the model appeared to continue to slightly underestimate PCSM in higher-risk tumours (Figure 2.10).

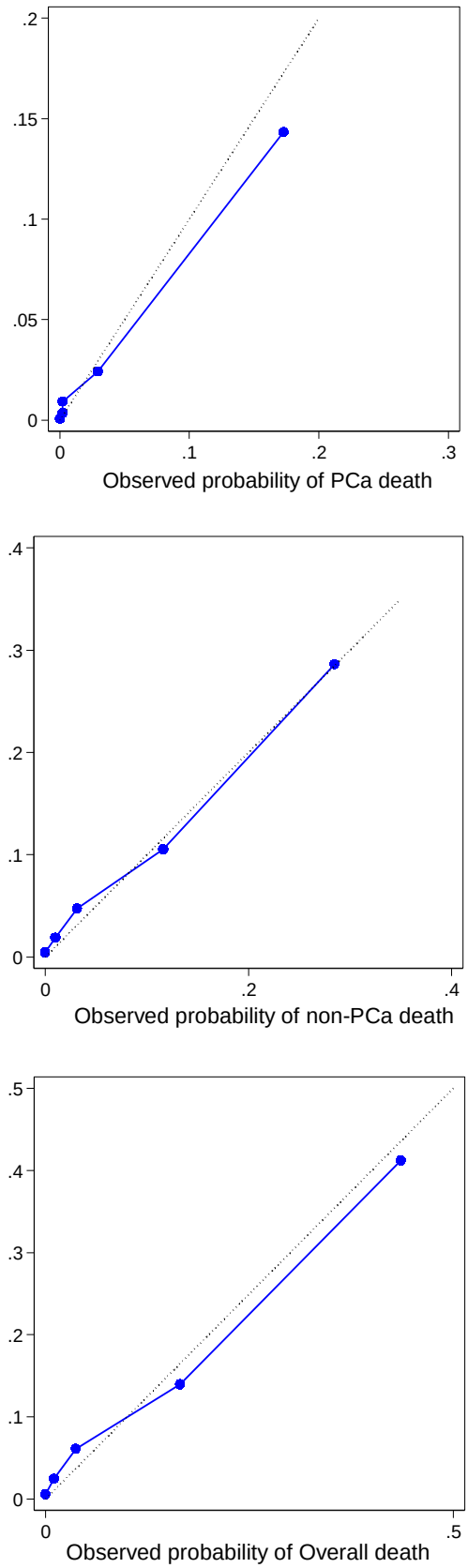


Figure 2.10 Calibration curves comparing observed and predicted prostate cancer (PCa) (top), non-PCa (middle) and overall (bottom) deaths at 10 years by quintile of risk amongst the Singapore dataset.

Calibration within subgroups (Table 2.12) suggested the model particularly underestimated PCSM in the context of very high-risk characteristics: grade group 5 (predicted: 30.6, observed: 36), t-stage 4 (predicted: 4.1, observed: 8) and PSA >50g/ml (predicted: 21, observed: 25). Calibration however was improved with the use of the extended model including PPC coefficients, particularly for PCSM as demonstrated in Figure 2.11.

		Prostate cancer deaths			**Non prostate cancer deaths**			**Overall deaths**		
Category	Number of cases	Predicted	Observed	Diff. (%)	Predicted	Observed	Diff. (%)	Predicted	Observed	Diff. (%)
Age at diagnosis										
<60	501	5.8	10	0.8	8.0	10	0.4	13.8	20	1.2
60-69	1,196	27.0	31	0.3	65.5	66	0.0	92.5	97	0.4
70-79	737	39.9	46	0.8	116.3	106	-1.4	156.3	152	-0.6
≥80	112	19.4	18	-1.3	45.2	43	-2.0	61.0	64.6	3.2
PSA (ng/ml)										
0<10	1,344	19.6	17	-0.2	90.0	94	0.3	109.6	111	0.1
10<20	677	23.4	30	1.0	71.1	57	-2.1	94.5	87	-1.1
20<50	380	28.2	33	1.3	51.3	50	-0.3	79.4	83	0.9
≥50	145	21.0	25	2.8	22.8	24	0.8	43.7	49	3.7
T Stage										
1	1,625	34.2	29	-0.3	139.4	123	-1.0	173.7	152	-1.3
2	660	30.5	41	1.6	66.8	74	1.1	97.3	115	2.7
3	244	23.3	27	1.5	25.6	26	0.2	48.8	53	1.7
4	17	4.1	8	22.9	3.3	2	-7.6	7.4	10	15.3
Grade Group										
1	1,126	17.6	14	-0.3	99.2	82	-1.5	116.9	96	-1.9
2	723	17.0	18	0.1	56.1	62	0.8	73.1	80	1.0
3	326	15.9	23	2.2	31.8	33	0.4	47.7	56	2.5
4	170	11.0	14	1.8	19.6	20	0.2	30.6	34	2.0
5	201	30.6	36	2.7	28.5	28	-0.2	59.0	64	2.5
Primary Treatment										
Conservative Management	538	18.9	12	-1.3	69.7	66	-0.7	88.6	78	-2.0
RT/RP	1,836	35.6	60	1.3	133.1	123	-0.6	168.7	183	0.8
Hormone Monotherapy	164	37.6	33	-2.8	32.2	36	2.3	69.9	69	-0.5
Ethnicity										
Chinese	2,155	77.4	84	0.3	205.1	194	-0.5	282.5	278	-0.2
Other	391	14.7	21	1.6	30.1	31	0.2	44.8	52	1.8

Table 2.12 Calibration between observed and predicted prostate cancer specific deaths, non-prostate cancer deaths and overall deaths at 10 years for sub-groups within the Singapore validation cohort.

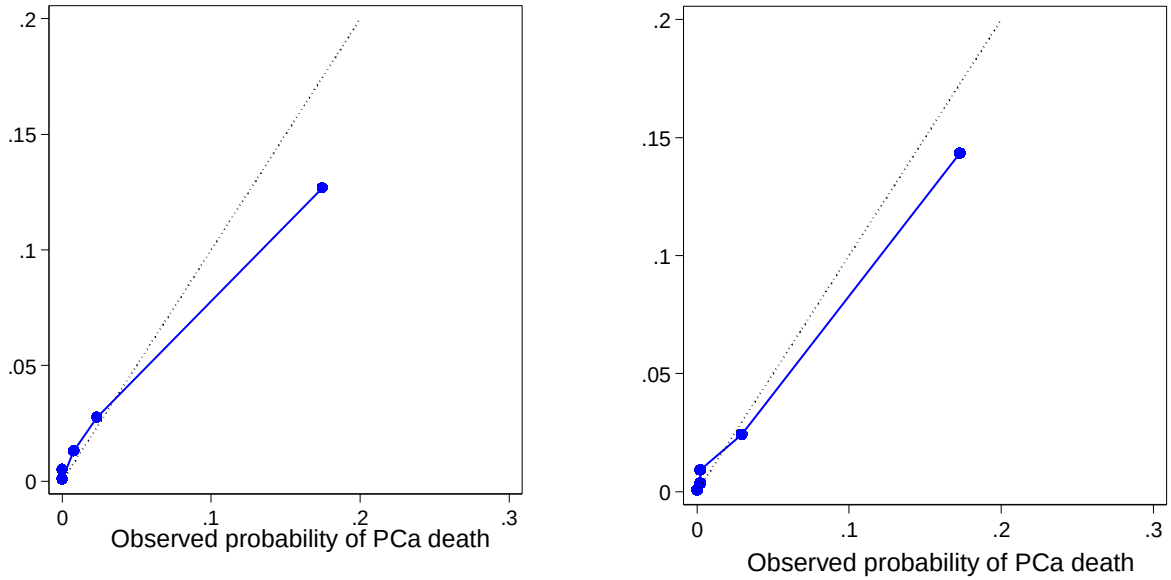


Figure 2.11 PCSM calibration in the Singapore cohort excluding (left) and including (right) the PPC variable, by quintile of risk.

Next, within this external cohort, we compared accuracy of our extended model, including PPC, to other existing PCa models. For PCSM, the model performed significantly better compared to the EAU stratification criteria (P<0.001) (Table 2.13). Improved C-indices were observed for PCSM compared to the CAPRA and NCCN criteria although these were under-powered to reach significance. However the model out-performed all of these existing models in predicting overall mortality (p<0.001) (Table 2.13).

	PCSM			**Overall**		
Model	C-index	95% CI	p	C-index	95% CI	p
PREDICT	0.838	0.804-0.872	-	0.756	0.728-0.784	-
EAU	0.763	0.732-0.794	0.001	0.637	0.606-0.667	<0.001
NCCN	0.804	0.767-0.841	0.182	0.649	0.616-0.682	<0.001
CAPRA	0.822	0.785-0.860	0.530	0.671	0.638-0.704	<0.001

Table 2.13 Discrimination of the extended model including PPC, compared to other existing models amongst the Singaporean cohort over 15 years maximum follow-up (n=2546).
EAU = European Association of Urology NCCN = National Comprehensive Cancer Network CAPRA = Cancer of the Prostate Risk Assessment (UCSF)

Finally, we limited the cohort to only men who received conservative management or radical treatment, to model contemporary practice where primary hormone therapy is less commonly used (12). Again, the model showed superior discrimination compared to other models (Table 2.14). Here, the discrimination was superior to the comparator models for

PCSM, NPCM and Overall mortality within the UK cohort, and performed very favourably in the Singaporean cohort also (Table 2.14).

	UK			Singapore		
PCSM	C-index	95%CI	p	C-index	95%CI	p
PREDICT	0.759	0.706-0.812	-	0.814	0.772-0.856	-
EAU	0.608	0.549-0.665	<0.001	0.756	0.716-0.796	0.052
NCCN	0.640	0.579-0.701	<0.001	0.785	0.733-0.837	0.395
CAPRA	0.667	0.607-0.727	0.024	0.797	0.748-0.846	0.607
NPCM						
PREDICT	0.719	0.692-0.746	-	0.722	0.684-0.760	-
EAU	0.557	0.529-0.585	<0.001	0.564	0.521-0.607	<0.001
NCCN	0.565	0.536-0.594	<0.001	0.557	0.513-0.601	<0.001
CAPRA	0.572	0.543-0.601	<0.001	0.575	0.530-0.620	<0.001
Overall						
PREDICT	0.721	0.698-0.744	-	0.733	0.700-0.766	-
EAU	0.567	0.542-0.592	<0.001	0.613	0.578-0.648	<0.001
NCCN	0.579	0.553-0.605	<0.001	0.615	0.577-0.653	<0.001
CAPRA	0.590	0.564-0.616	<0.001	0.632	0.594-0.670	<0.001

Table 2.14 Comparison of PREDICT to other models across 15 years within the UK and Singapore validation cohort, excluding all men managed with primary hormone monotherapy.
PCSM = Prostate cancer specific mortality NPCM = Non prostate cancer mortality

2.3.6 Proposed clinical utility of the model and web-presentation

Hereafter, we refer to the developed model, including biopsy information, as 'Predict *Prostate*'. This first iteration of the model was published in PLoS Medicine, representing the initial public version of the tool. Example outputs from the prototype web-interface for the tool for 3 hypothetical vignettes are demonstrated in Figure 2.12. The age and comorbidity status at diagnosis are altered within each case to demonstrate the impact of competing risks on treatment benefit. With increasing age and comorbidity, reductions in PCSM achieved by radical treatment are attenuated by increased rates of NPCM as the risks of PCSM and NPCM compete against one another. For example a 72 year-old with comorbidity and the disease characteristics shown in Case B has an estimated 19.6% 15-year risk of PCa death when conservatively managed. Although the estimated PCSM is reduced to 11.1% by treatment, the overall survival improves by only 3.8%, whereas for a younger fitter man, far more of the reduction in PCSM translates into overall survival benefit (Figure 2.12). In these examples 'range of potential treatment benefit' is presented in the light blue colour, to represent uncertainty abound the estimate.

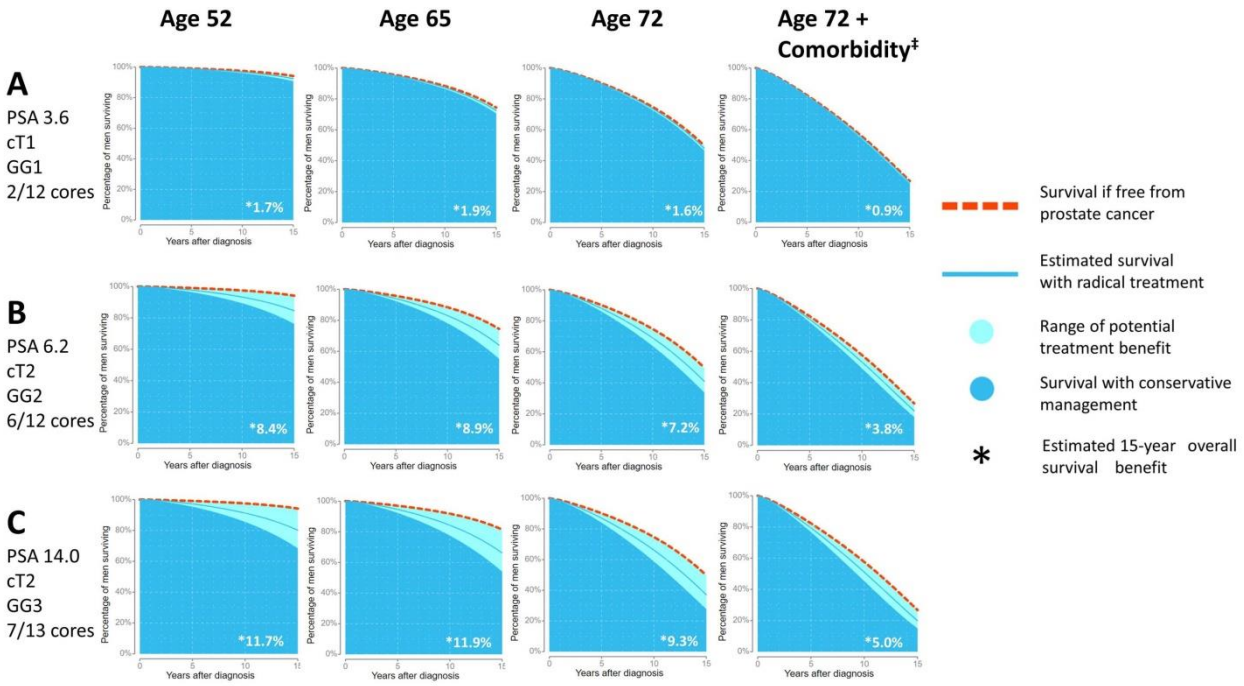


Figure 2.12 Example model outputs using 15-year overall survival curves for three hypothetical vignettes A, B and C. Only age and comorbidity status has been changed between each column to demonstrate the reduction in benefit from radical treatment when competing risk increases. PSA = Prostate specific antigen cT = clinical tumour stage GG = histological grade group ‡ Comorbidity refers to a patient with Charlson score of 1 or more who has been admitted to hospital in the 2 years prior to prostate cancer diagnosis.

A new Predict *Prostate* logo was developed to accompany the web-development and model dissemination (Figure 2.13). This emulated some of the design features of the Breast cancer tool for consistency. The 'i' was replaced by a geometric icon depicting a male – intended to symbolise an individualised approach as compared to a symmetrical depiction, and to avoid confusion with a symbol synonymous with an established PCa charity. The original Predict *Prostate* website homepage is displayed in Figure 2.14.

predictprostate

Figure 2.13 Predict *Prostate* logo

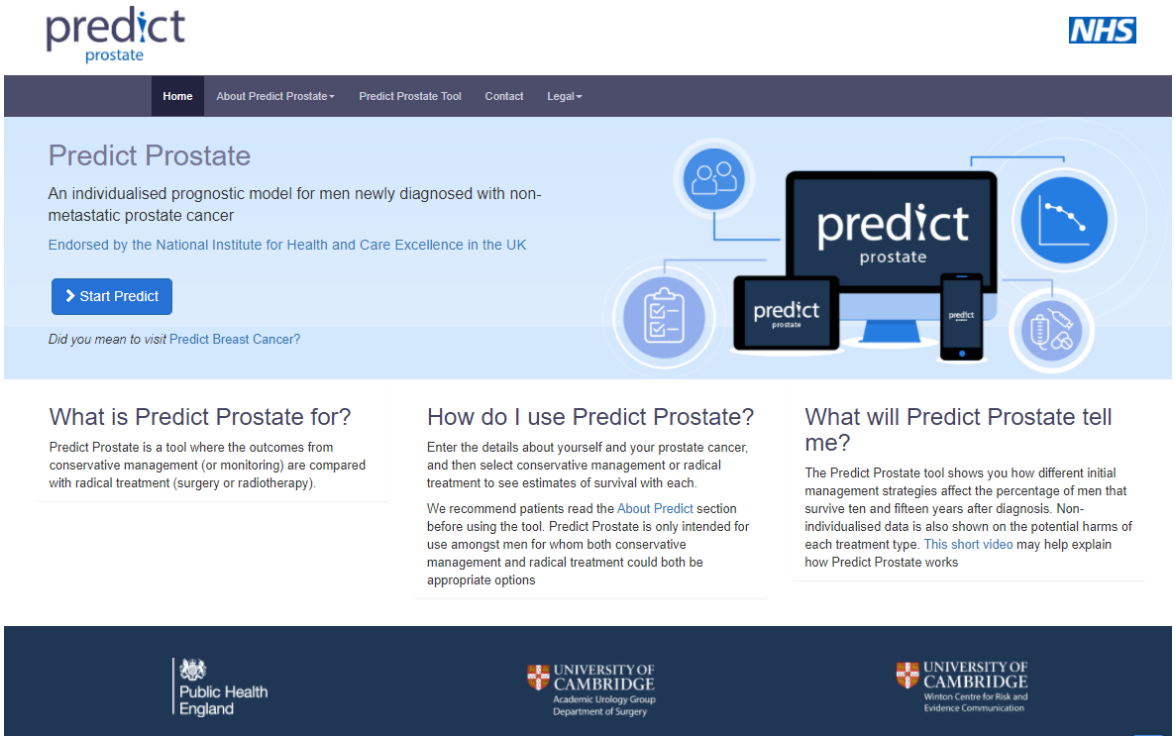


Figure 2.14 Predict *Prostate* homepage. Available at prostate.predict.nhs.uk

2.4 Discussion

2.4.1 Principal Findings

In developing Predict *Prostate*, to our knowledge, we presented the first individualised multivariable prognostic model for non-metastatic PCa built and validated in an unscreened, pre-treatment, primary diagnostic cohort. We showed that this model, is able to derive predictions for PCa and overall mortality with a high degree of concordance by using routinely available diagnostic clinico-pathological data, and it appears to outperform existing models, albeit within small validation cohorts. By incorporating biopsy information the calibration of the model appears improved. Importantly, the model incorporates the impact of radical therapy, which allows comparison to be made against the option of conservative management within the context of an individual's competing risks. The model appears to particularly work well among men with more favourable features, or treated with surveillance or radical therapy, among whom the model is intended for use. Use of this model does not require any additional tests or information beyond what is routinely available at the point of diagnosis. The model was designed such that it could be refined in the future if additional independent factors with proven prognostic value are established, or with updated datasets - as indeed we see later in this thesis.

2.4.2 Interpretation of Findings

As outlined in Chapter 1, PCa incidence is rising and level 1 evidence shows that many men with favourable disease characteristics will not necessarily benefit from immediate radical therapy (15, 16). Additionally, radical treatment is associated with risks of significant adverse effects including incontinence, impotence, bowel dysfunction and long-term decisional regret (11, 18). Unsurprisingly, conservative management or active surveillance is therefore becoming increasingly popular in low-risk disease, and emerging evidence also suggests very favourable outcomes in intermediate-risk disease (86). Identifying men appropriate for initial conservative management and conveying this information to an individual within their own context of competing mortality is currently an imprecise exercise, with a lack of objective data on potential outcomes. Instead, most current prognostication is directed by categorisation of men into risk-stratified criteria and discussions with clinicians who may or may not be PCa-specialists and are potentially conflicted by a bias to a treatment they offer (28, 31, 32, 87). Predict *Prostate* was

conceived to address this critical gap in clinical need and better inform and standardise the decision-making process.

As shown through this chapter, Predict *Prostate* was built around long-term actual survival data and this study design and the model itself were developed to address all AJCC criteria for adoption (33). The parameters used within Predict *Prostate* for PCSM are well established independent variables such as histological Grade Group, PSA and T Stage (63-65). Here, they have been combined in a novel way and by utilising fractional polynomials to maintain as much predictive information as possible. Indeed, it is intuitive that a man with PSA of 9.9 would have a different prognosis to someone with PSA of 0.9, although current stratification criteria would fail to differentiate these two. Predict *Prostate* is also distinctive in estimating the competing risks of both PCSM and NPCM to accurately model overall mortality – as was shown by its improved discriminatory performance compared to other models. The model deliberately uses histological grade groups (1-5) as we collectively standardise practice towards this more-intuitive scale (66). Biopsy information was integrated as an optional variable into Predict *Prostate* as biopsy quantification is accepted as a surrogate for tumour volume. However, no consensus on the best methodology for its assessment yet exists, with few studies exploring its relationship with long-term survival (88). Hence we used a pragmatic assessment of this by using the simplest common denominator, the number of positive cores divided by the overall biopsy cores taken (PPC). Our data showed an independent prognostic impact around the dichotomous cut-off of <50% versus ≥50% PPC. Incidentally, this is the same cut-off reported in two American studies exploring survival, where effect size was comparable. This cut-off has now also been integrated into the latest NCCN risk-criteria to differentiate 3-risk groups in to 5 (32, 89, 90). PPC thus maintains simplicity and facilitates ease of interpretation (although the model can function without biopsy information). During the study period routine practice was to perform 12-core systematic trans-rectal biopsy. However, contemporary practice in prostate biopsy is evolving with the use of more image-targeting (61). It is unknown how these changes will alter the prognostic value of biopsy involvement. In the meantime, it is recommended, as per the AUA guidelines, that any number of biopsies from a single target are considered as a single core if taken as part of a 'target and systematic' biopsy approach (31). This is so as not to artificially inflate the PPC by using all cores from a target.

A key question when first developing Predict *Prostate* was whether to use data-derived coefficients for treatment effect or published trial data. Ultimately the data-derived coefficient for the effect of either radical treatment type (RP or RT) was used, with a hazard ratio of 0.50 (95%CI 0.38-0.67) for PCSM. This is in fact very similar to published randomised controlled trial data of treatment effect, albeit these studies failed to demonstrate significance. For example in PIVOT (RP vs AS: HR 0.63 95%CI: 0.36-1.09) and the ProtecT trials (RT vs active monitoring: HR 0.51 95%CI: 0.15-1.69. RP vs active monitoring: 0.63 95%CI: 0.21-1.93) (15, 16). In the web-based presentation of the model, uncertainty around this treatment effect is demonstrated by displaying treatment benefit from 0-100% of PCSM around the estimated survival (Figure 2.12). Separate presentation of RT and RP outcomes was not explored as no adequate randomised data yet shows a survival difference between the two treatment approaches, and even in a multivariable model it would be difficult to fully exclude selection bias, which we know is likely to favour RP (16, 91). One caveat in the clinical utility of Predict *Prostate* is that primary androgen deprivation, used in a proportion of our study cohorts, is now seldom used as a first line therapy. Indeed, within this cohort the poor prognosis apparently associated with primary androgen deprivation is likely to reflect a selection bias towards men unfit for other treatment options, or with potentially occult metastatic disease. Our model however is primarily for use among men deciding between conservative management and radical treatment – where decision dilemmas are most acute. Indeed, as shown in Table 2.6 and Table 2.12, calibration of this model was best amongst men with low to intermediate-risk features where this model would be most useful and appropriate in clinical decision-making. Using disease status information from the National Prostate Cancer Audit, this may represent up to 47% of all newly diagnosed prostate cancers (5).

2.4.3 Strengths and limitations

Particular strengths of Predict *Prostate* include its derivation from a large cohort from a geographical area straddling 2 academic centres and 9 general hospitals. These data were collected prospectively by an independent cancer registry using mortality as the primary outcome, rather than shorter-term surrogates and linked with national records to ensure accurate death certificate notification - avoiding many potential biases associated with single-centre studies. Indeed, the accuracy of UK PCa cause of death reporting is known to

be very reliable (92). The model maximises usability by using routinely-available clinico-pathological data, and reflects real-world data from a non-screened, primary diagnostic cohort, including a significant number of men treated conservatively. Crucially, the model also allows adjustment for competing mortalities by incorporating both cancer-specific and non-cancer survival outcomes to contextualise treatment effect, within a risk communication tool. The performance metrics already outlined in the small external validation described herewith, already meet many of the criteria set out by the AJCC (33). Abundant literature shows that better decision aids contribute to more knowledgeable, informed patients and that this improves clinician-patient communication (93, 94). Therefore, it is anticipated this model can be highly impactful, although formal clinical impact assessments will be undertaken to test this, as per Chapters 4 and 5 of this thesis (67).

However, we do acknowledge limitations in the development of this model outlined within this chapter, and with the model itself. Foremost of these, are the drawbacks and limitations resulting from the composition of the primary cohort itself. Our UK cohort had a higher proportion of higher-risk cancers than might be expected from other UK cohorts, it was composed almost exclusively of Caucasian men, and a large proportion received primary hormone monotherapy. The amount of missing data, although quantified in broad terms, could not be described in detail by NCRAS who supplied these data. These potential deficiencies the in the source data, draw into question the generalisability of our findings to a large UK or global audience.

In terms of input variables, we did not have data on MRI-defined lesions nor radiological stage, which are recognised to be of increasing importance in the PCa pathway generally. However, it is yet unknown if these data will improve prognostic ability with MRI primarily used to guide biopsies rather than offer prognostic information. Indeed, the additional value of MRI in detecting missed cancers is debatable given that men with a missed cancer using non-imaging approaches have extremely low rates of PCa death (95). The model presented at this stage also does not currently integrate genomic tests or molecular markers. However, the most established tools such as Prolaris CCP and Oncotype DX GPS have predominantly been tested against shorter-term outcomes in very selected groups, particularly in the post-treatment setting (96, 97). When these expensive tools have been assessed against PCSM, concordance has been shown to be very similar to our model. For

example the Decipher genomic classifier alongside CAPRA showed an AUC of 0.78 (95%CI 0.68-0.87) for 10-year PCSM following prostatectomy (98). As Dr Cooperberg MD from UCSF suggests, that good data should be sought as to whether any such marker truly adds independent prognostic information beyond a gold-standard multivariable model (72), such that these markers should be compared to a model such as Predict *Prostate*. As with MRI, if one or more marker does show independent prognostic value in the future it can be integrated into future refinements to Predict *Prostate*(73). By using real world data, our treatment categories were based upon actual treatments received as opposed to assigned treatments as can be problematic in randomised trials (16). However, our analysis cannot account for the impact of delayed conversions to treatment beyond 1 year, albeit the number of men switching from conservative management was very small within this cohort (5.7%). A final potential limitation of the model is the lack of t-stage sub-classifications. However, it is accepted that T stage is often inaccurately assigned in localised disease (78).

In terms of statistical approach, it is recognised that more complex and flexible parametric survival modelling frameworks exist. However, we have used an established methodology, which in other tumour types could not be improved upon by other approaches (99). Indeed, in a recent collaborative study with researchers from the Cambridge Centre for Artificial Intelligence in Medicine, using a complex novel machine-learning framework only led to very minor improvements in terms of discrimination (100). On completing this initial model development work, it was appreciated that the external validation cohort used was relatively small, and different from the model development dataset; although the performance within a cohort of differing ethnicity and tumour characteristics could be seen as a positive. Finally, our comparisons to the EAU, NCCN and CAPRA stratification criteria are pragmatic but potentially unfair. These models are intended to delineate patients into groups of risk, rather than offering predictions of 10- or 15-year risk. Indeed they are not intended to stratify men according to NPCM or overall mortality so any such comparisons are unfair, but help to demonstrate the existing lack of clinically usable models in this field for these outcomes. These are still widely used clinical models such that these comparisons may be of interest to PCa specialists, particularly in the absence of equivalent models to compare against, as shown in Chapter 1.

2.5 Conclusions

In conclusion, this chapter presents the initial development of an individualised prognostication tool, brief external validation and translation into a risk communication tool for use at the point of PCa diagnosis. For the first time, this simultaneously presented individualised estimates of cancer-specific and overall survival outcomes and can model the impact of treatment upon these outcomes. The accuracy of the model appeared promising across populations, and provided encouraging levels of discrimination in two small validation cohorts. This initial model underpins the web-based tool and decision-aid Predict *Prostate,* first launched in 2019 aimed at informing the decision-making process for patients and clinicians (85). Based on the work in this chapter, further external validation is warranted to explore accuracy and generalisability across other contexts and in larger populations over longer follow up times.

3 External validation study, model updating and comparative performance

This chapter explores the external validation of Predict *Prostate* within a large Swedish dataset, including an update on how biopsy information is used within the model and comparison to existing tools. The chapter expands upon work which has been published previously (101).

3.1 Introduction

As outlined in Chapter 1, there was a lack of multivariable prognostic tools to guide the predominant decision dilemma for men with non-metastatic prostate cancer, namely the decision between radical treatment and initial conservative management. Chapter 2 described the development of a novel individualised prognostic tool called Predict *Prostate*. Using data from over 10,000 UK men Predict *Prostate* provides cancer-specific and overall percentage survival estimates for up to 15 years. Internal validation and accuracy within a small external Singaporean population were promising as outlined in Chapter 2, and these findings were published in March 2019 (80). Thereafter, in May 2019 the model was endorsed in the UK by the National Institute for Health and Care Excellence (NICE) as an 'endorsed resource' as they felt it supports recommendations in the NICE PCa guidelines (102). However, external validation in large independent cohorts, ideally from a different location, is vital to demonstrate generalisability and accuracy of a multivariable prognostic model (33).

The Prostate Cancer database Sweden (PCBaSe) is one of the largest and most comprehensive PCa cohorts world-wide and thus was well-suited to allow external validation of Predict *Prostate* (67). This chapter describes the external validation of the tool, within this large dataset. The aims in this section of the thesis were to externally validate Predict *Prostate* in this separate population, compare performance to existing models and consider updating or improving the model.

3.2 Methods

3.2.1 Source of data

Data from PCBaSE 3.0 were used, according to a pre-specified project outline available in the appendix. PCBaSe was created by the combination of the National Prostate Cancer Register of Sweden with other national healthcare and demographic databases (103). The capture rate of this register is 98% of all incident PCa cases compared to the Swedish Cancer Registry – to which registration is mandated by law (104). Cause of death information is updated from the Cause of Death Registry which captures all deaths in Sweden. The agreement between recorded cause of death and reviewed medical records is considered to be very good, and has been reported previously at 86% (95% CI: 85-87%) (105).

3.2.2 Participants and predictors

Men within PCBaSe diagnosed with PCa between January 1st 2000 and 31st December 2010 were included, with no evidence of metastatic disease and prostate specific antigen (PSA) <100ng/ml. This mirrored inclusion criteria used in the model development cohort described in Chapter 2. Cases were censored at death, migration or 31st December 2016, whichever event occurred first. Data were available for 82,936 men. Outcome events were 'PCa death' or 'any cause death' from which 'non-PCa death' was derived. Intact data were required for variables mandatory within the model: age, PSA, T-stage, histological grade-group, primary treatment type and comorbidity. This led to the exclusion of 13,730 (16.6%) cases, leaving a final analysable dataset of 69,206 (Table 3.1). Missing data were most abundant for histological grade group (n=8117), as primary and secondary Gleason grade were not always registered, particularly preventing differentiation of Grade Group 2 and 3 disease. Data were also missing on PSA (n=2124), T-stage (n=1364), age (n=4) and primary treatment (n=3960). Some men had missing data for more than one variable. All variables were determined at the time of diagnosis. Biopsy characteristics are an optional variable in the Predict *Prostate* model, therefore missing data on proportion of positive cores ([PPC] = number of cores with any cancer/number of cores taken) were tolerated. Primary treatment was defined as the radical treatment received up to 12 months after the date of diagnosis, or conservative management. The same definition of comorbidity was used as in the model development study: the combination of both Charlson Comorbidity Index of 1 or greater

(excluding PCa) and a hospital admission in the 2 years preceding PCa diagnosis (80). Up to 2008, the treatment strategies of active surveillance and watchful waiting were reported as conservative management within this cohort. After 2008 these strategies were registered as separate entities, but were still combined for the sake of this study. A small, well-defined active surveillance group was separately analysed as a sub-cohort however.

3.2.3 Outcome measures

The Predict *Prostate* model estimates 10 and 15-year prostate cancer-specific mortality (PCSM), non-PCa mortality (NPCM) and overall, or all-cause mortality (ACM), calculated from the time of diagnosis. It provides estimates following conservative management and radical treatment (by either radical prostatectomy or radiotherapy).

3.2.4 Statistical analysis methods

Analytical methods were broadly the same as outlined in Chapter 2.2.6. Beta coefficients for each prognostic factor in the model were applied to derive prognostic indices for PCSM and NPCM for each patient. These were used in combination with the model's baseline hazard functions and time-at-risk to create individual estimates of unadjusted PCSM and NPCM over 15 years. These estimates were adjusted for the competing risks between the two causes of death to generate ACM estimates. To assess discrimination, 15-year estimates were generated. Harrell's concordance index (c-index) was then applied using the 'Hmisc' package in R (82). Discrimination using Predict *Prostate* was compared to the EAU and NCCN stratification systems, and the UCSF CAPRA score (22, 29, 32). Sub-classification of stage T2 was not available; therefore T2 was assumed to be T2a for the sake of these alternative classifications. When PPC was unknown, it was assumed to be <34% in the CAPRA model. Adjusted predictions of cumulative PCSM, NPCM and ACM were generated using available follow-up for assessment of model calibration. Calibration was assessed using a Chi-square goodness of fit (GOF) across quintiles of risk using the method of May and Hosmer (81). Calibration was also assessed within treatment sub-groups. All data analyses were performed in Stata™ 14, unless otherwise stated above.

3.2.5 Biopsy sub-analysis and model updating

Biopsy parameterisation using percentage of positive cores (PPC) was re-explored within a large 'biopsy sub-cohort' of 44,163 men from PCBase for whom biopsy data were available. PPC was explored against PCSM with and without adjustment for other prognostic variables

for PCSM within the model. Re-parameterisation of PPC using fractional polynomials (FP) was then performed as per the methodology described in Chapter 2.2.5. The Predict *Prostate* model without biopsy information, using the 50% PPC cut-off, or incorpariting the FP function of PPC were then applied to both the whole PCBase cohort and the biopsy sub-cohort. Discrimination and calibration was compared between versions of the model.

3.3 Results

3.3.1 Participants

69,206 men were included with 13.9 years median follow-up. The Swedish population attributes at baseline are compared to the UK model development cohort in Table 3.1. Patient characteristics were similar in both cohorts, with a larger proportion of grade group 1 disease in the Swedish cohort. A larger proportion of men underwent surgery as opposed to radiotherapy in the Swedish cohort, and a smaller proportion were treated with primary androgen deprivation therapy in this time period. Cross-tabulation of the patients by EAU risk categories, and treatment type is reported in Table 3.2 (30). The proportion of patients with a recorded comorbidity was similar in both cohorts.

		UK Model Development Cohort		Sweden PCBase Cohort	
Total Subjects		7,063		69,206	
Time at risk (years)		58,138		589,733	
Median follow-up (years)		9.8	Range 0-16	13.9	Range 0-17
Age (mean, SD)		69.9	8.34	68.8	8.83
PSA (mean, SD)		18.5	17.5	15.7	17.0
Gradegroups			%		%
	1	2317	32.8	36992	53.5
	2	2125	30.1	14015	20.3
	3	1057	15.0	7774	11.2
	4	710	10.1	6345	9.2
	5	854	12.1	4080	5.9
T-stage					
	1	3761	53.2	35700	51.6
	2	2270	32.1	22478	32.5
	3	977	13.8	10295	14.9
	4	55	0.8	733	1.1
Primary Treatment					
Radical Prostatectomy		995	14.1	20936	30.3
Radical Radiotherapy		2457	34.8	11906	17.2
Androgen Deprivation Monotherapy		2226	31.5	15980	23.1
Conservative Management		1385	19.6	20384	29.5
Comorbidity					
No recorded comorbidity		6363	90.1	62173	89.8
Comorbidity (Charlson≥1)		700	9.9	7033	10.2
10 year outcomes:					
PCa deaths		712		6993	
Non PCa deaths		1555		15122	
Any-cause death		2267		22115	
Overall outcomes:					
PCa deaths		846		8151	
Non PCa deaths		1829		18003	
Any-cause death		2675		26154	
Crude PCS mortality rate (per patient year)		1.46		1.38	
Annual overall mortality rate (per patient year)		4.60		4.43	

Table 3.1 Baseline cohort characteristics in the original UK model development cohort and Prostate Cancer database Sweden (PCBaSe) cohort. (PCa = prostate cancer SD= standard deviation NA = Not available)

EAU Risk Group	UK Conservative (AS/WW)	RT	RP	ADT	Sweden Conservative (AS/WW)	RT	RP	ADT
Low	433	220	80	64	8501	1825	7066	375
Intermediate	776	1045	526	579	8060	5015	11209	3004
High	176	1192	389	1583	3823	5066	2661	12601
Total	1385	2457	995	2226	20384	11906	20936	15980

Table 3.2 Breakdown of patients within the UK model development cohort and Swedish PCBaSe cohort, according to EAU risk stratification group, and primary treatment type. (AS = active surveillance, WW = watchful waiting, RT = radiotherapy, RP = radical prostatectomy, ADT = androgen deprivation therapy)

3.3.2 Model performance

Overall discrimination of Predict *Prostate* was very good with C-indices 0.85 (95% CI 0.85-0.86) for PCSM and 0.79 (95% CI 0.79-0.79) for overall mortality (Table 3.3). Overall calibration of the model was excellent with 25,925 deaths predicted and 25,850 deaths observed in PCBaSe. This equates to an overall observed:expected (O:E) ratio of 1:1.003. Calibration across quintiles of risk is shown in Figure 3.1 and Table 3.4. Although the O:E ratio for any-cause death was very close to 1, expected numbers of PCa deaths were slightly higher than observed (O:E 0.897) , and expected numbers of non-PCa deaths were lower than observed (O:E 1.060), particularly in the highest risk quintiles (Table 3.4).

			PCSM			Overall		
	N	Tool	C-index	SD	p	C-index	SD	p
Conservative Management	20384	**PREDICT**	**0.810**	**0.010**		**0.740**	**0.0057**	
	20384	EAU	0.746	0.0115	<0.001	0.636	0.0061	<0.001
	20384	NCCN	0.760	0.0118	<0.001	0.643	0.0063	<0.001
	20384	CAPRA	0.765	0.0125	<0.001	0.643	0.0064	<0.001
Radical Treatment	32842	**PREDICT**	**0.784**	**0.0122**		**0.670**	**0.0077**	
	32842	EAU	0.742	0.0113	<0.001	0.606	0.0077	<0.001
	32842	NCCN	0.769	0.0106	0.063	0.617	0.0081	<0.001
	32842	CAPRA	0.780	0.0116	0.475	0.625	0.0082	<0.001
Overall	69206	**PREDICT**	**0.852**	**0.0038**		**0.792**	**0.0028**	

Table 3.3 Discrimination of Predict *Prostate* (PREDICT) within treatment subgroups and comparison to other existing tools. (EAU = European Association of Urology criteria, NCCN = National Cancer Care Network criteria, CAPRA = UCSF Cancer of the prostate risk assessment criteria, SD = standard deviation

	n	Quintile	**Predict *Prostate*** Observed	Expected
PCSM	13842	1	83	152
	13841	2	316	366
	13841	3	773	832
	13841	4	2123	2037
	13841	5	4786	5625
	69206		**8081**	**9012**
NPCM	13842	1	679	628
	13841	2	1398	1420
	13841	3	2628	2587
	13841	4	4745	4558
	13841	5	8394	7645
	69206		**17844**	**16838**
ACM	13842	1	780	890
	13841	2	1827	1970
	13841	3	3638	3676
	13841	4	7412	7199
	13841	5	12268	12115
Overall	**69206**		**25925**	**25850**

Table 3.4 Overall calibration of the Predict *Prostate* model. Observed numbers of deaths are compared to expected numbers of deaths predicted by the model. (PCSM = Prostate cancer specific mortality. NPCM = Non prostate cancer mortality. ACM = All cause mortality)

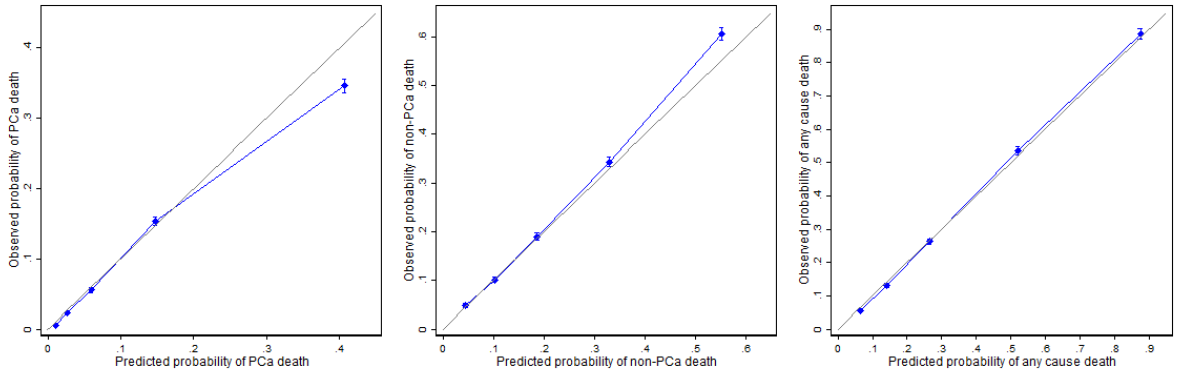


Figure 3.1 Calibration curves demonstrating observed and expected 15-year probability of death within the PCBaSe cohort across quintiles of risk for prostate cancer (PCa) death (left), non-PCa death (centre) and any cause death (right).

3.3.3 Treatment Subgroups

Overall, 20,384 men underwent conservative management and 32,842 received radical treatment within the PCBase cohort. Within these groups c-indices remained good, with c-index for 15-year PCSM 0.81 (95%CI 0.80-0.82) for those receiving conservative management and 0.78 (95% CI 0.77-0.80) for radical treatment (Table 3.3).

Among men on well-defined active surveillance, C-indices were higher at 0.88 for PCSM and 0.75 for overall mortality (Table 3.6). Calibration also remained good within treatment groups with differences between observed and predicted numbers of overall deaths 1.4%, 2.2% and 3.1% among men who received active surveillance, radiotherapy, and prostatectomy, respectively (Table 3.5). The model overestimated PCSM and underestimated NPCM within the subgroup which received androgen deprivation monotherapy by as much as 8% – but remained within 2% for overall death (Table 3.5).

		PCa Death			Non-PCa death			Overall death		
	n	Obs	Pred	% Diff	Obs	Pred	% Diff	Obs	Pred	% Diff
'Active surveillance'	6224	195	191	0.06	850	940	1.44	1045	1131	1.38
'Watchful waiting'	2745	239	198	1.49	942	915	0.98	1181	1112	2.51
Other conservative	11415	1358	1373	0.13	4906	4535	3.25	6264	5908	3.12
Radical prostatectomy	20936	550	703	0.73	1919	2403	2.31	2469	3107	3.05
Radiotherapy	8953	737	560	1.94	1591	1594	0.03	2318	2155	2.18
ADT	15980	4809	5798	6.19	7215	5993	7.65	12024	11792	1.45

Table 3.5 Calibration of Predict *Prostate* mortality estimates with observed (Obs) and predicted (Pred) numbers of deaths within treatment groups

			PCSM			NPCM			Overall		
	n	Tool	C-index	SD	p	C-index	SD	p	C-index	SD	p
'AS'	**6224**	**PREDICT**	**0.876**	**0.0232**		**0.710**	**0.0187**		**0.747**	**0.0165**	
		EAU	0.752	0.0370	<0.001	0.611	0.0189	<0.001	0.635	0.0171	<0.001
		NCCN	0.775	0.0382	<0.001	0.617	0.0199	<0.001	0.644	0.0180	<0.001
		CAPRA	0.795	0.0386	<0.001	0.624	0.0204	<0.001	0.653	0.0184	<0.001
'WW'	**2745**	**PREDICT**	**0.765**	**0.0310**		**0.621**	**0.0188**		**0.686**	**0.0165**	
		EAU	0.710	0.0314	0.013	0.568	0.0182	<0.001	0.595	0.0161	<0.001
		NCCN	0.732	0.0318	0.137	0.580	0.0191	0.006	0.609	0.0169	<0.001
		CAPRA	0.761	0.0334	0.9	0.574	0.0196	0.002	0.609	0.0172	<0.001
'RP'	**20936**	**PREDICT**	**0.774**	**0.0210**		**0.641**	**0.0133**		**0.655**	**0.0116**	
		EAU	0.734	0.0200	0.006	0.537	0.0128	<0.001	0.581	0.0114	<0.001
		NCCN	0.769	0.0204	0.7	0.543	0.0139	<0.001	0.593	0.0123	<0.001
		CAPRA	0.784	0.0197	1.5	0.548	0.0141	<0.001	0.600	0.0125	<0.001
EBRT	**7108**	**PREDICT**	**0.734**	**0.0205**		**0.623**	**0.0168**		**0.611**	**0.0137**	
		EAU	0.672	0.0168	<0.001	0.495	0.0159	<0.001	0.555	0.0127	<0.001
		NCCN	0.699	0.0174	0.009	0.496	0.0164	<0.001	0.565	0.0133	<0.001
		CAPRA	0.715	0.0197	0.181	0.508	0.0173	<0.001	0.579	0.0140	0.003
Brach	**1845**	**PREDICT**	**0.755**	**0.0509**		**0.755**	**0.0509**		**0.651**	**0.0285**	
		EAU	0.722	0.0433	0.3	0.722	0.0444	0.328	0.596	0.0277	0.006
		NCCN	0.747	0.0410	0.8	0.747	0.0493	0.821	0.604	0.0286	0.019
		CAPRA	0.758	0.0433	1	0.759	0.0518	1	0.619	0.0284	0.112

Table 3.6 Discrimination within treatment sub-groups and comparison to existing models. EAU = European Association of Urology NCCN = National Comprehensive Cancer Network CAPRA = UCSF Cancer of the Prostate Risk Assessment

3.3.4 Comparison to existing models

Predict *Prostate* significantly outperformed the comparator models when predicting overall mortality, both overall and within every major treatment sub-group (Table 3.3 + Table 3.6). Discriminatory performance was significantly better for PCSM overall (Table 3.3). Across all treatment sub-groups, the model outperformed the 3-stratum EAU risk categories (Table 3.3). Improvements in discrimination failed to reach significance for PCSM in some comparisons against the NCCN and CAPRA score, but in only one incidence was the c-index better for one of these comparator models (CAPRA score for PCSM among RP patients, Table 3.6).

3.3.5 Biopsy parameter sub-analysis and model updating

Biopsy parameterisation using percentage of positive cores (PPC) was explored within a group of 44,163 men who had this information registered, where mean PPC was 41.9% (SD 27.6). Within this cohort, PCSM was positively correlated to PPC categorised by deciles (Figure 3.2). The relationship was far smoother, than the apparent jump in PCSM seen above a cut-off of ≥50% in our smaller UK sub-cohort data (Figure 2.7). Indeed, when modelling was assessed around the ≥50% PPC cut-off, offset for all other variables for PCSM

the hazard ratio for ≥50% PPC compared to <50% PPC was 2.13 (95%CI 1.96-2.32) in the PCBase cohort as compared to 3.31 in the UK development cohort (Table 2.8). As demonstrated in Figure 3.3, following adjustment for all other factors included in the PCSM model, the relationship between PPC and PCSM appeared more linear.

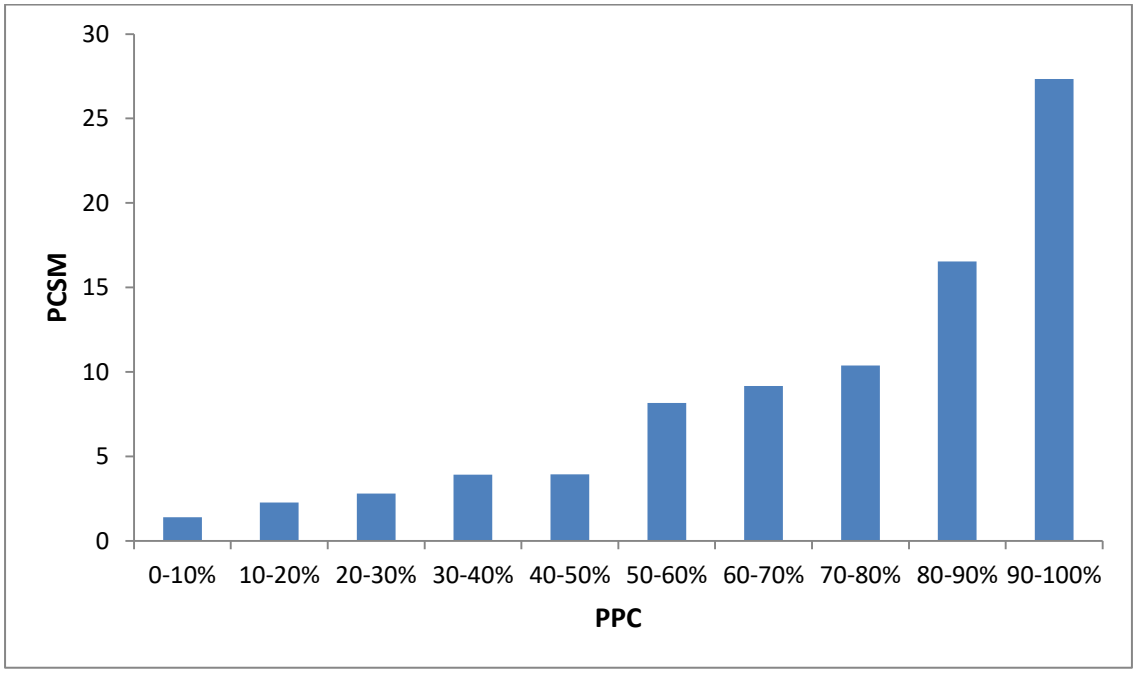


Figure 3.2 Relationship between unadjusted 15-year prostate cancer-specific mortality (PCSM) and percentage of positive biopsy cores (PPC) within the PCBase biopsy sub-cohort

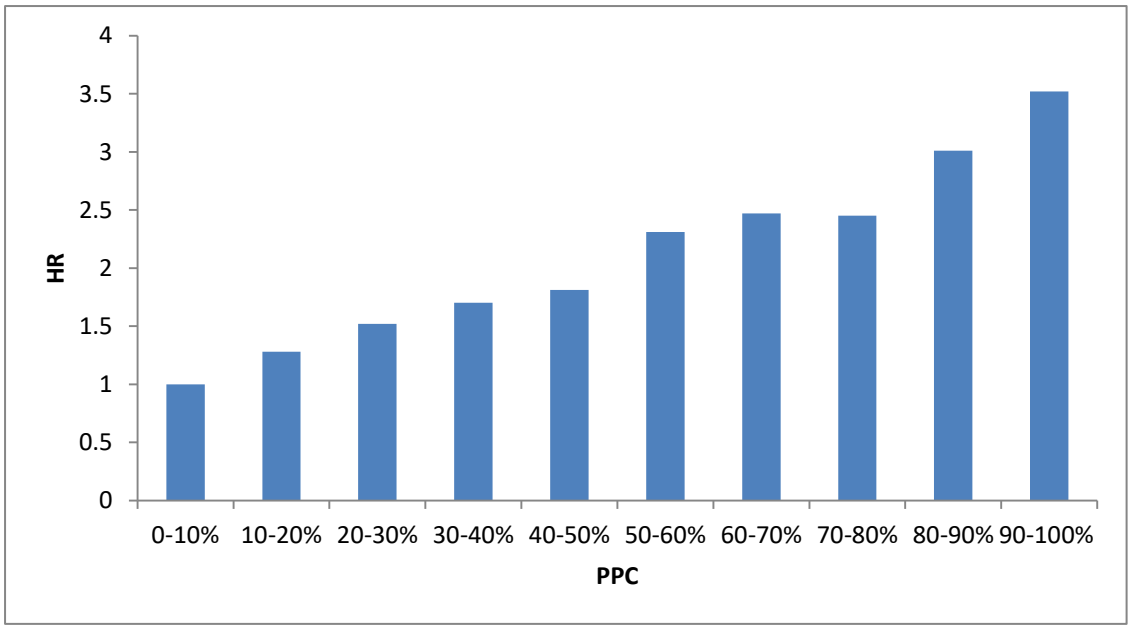


Figure 3.3 Graph showing the relationship between percentage of positive biopsy cores (PPC) and hazard ratio (HR) for prostate cancer specific mortality in the PCBase biopsy sub-cohort, following adjustment for all other factors associated with PCSM in the model

Rather than using the dichotomous outcome used previously, PPC was re-fit against PCSM allowing the flexibility of fractional polynomials (FP) (Figure 3.4). As per Figure 3.4 the relationship remained almost linear

The final FP equation for PPC was:

+1.890134*(((*PPC*+0.1811159)/100)^.5-.649019)

Applying this new parameterisation to our PCBase biopsy cohort (n=44163), the mean hazard ratio was 1.01 such that further adjustment of the model was not felt necessary.

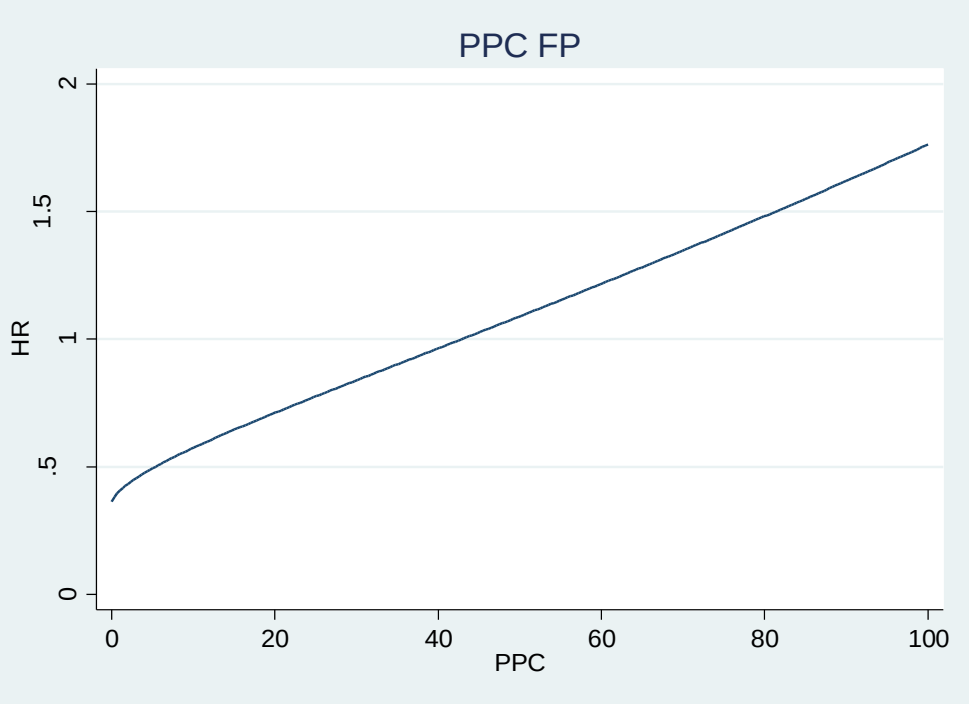


Figure 3.4 Prostate cancer-specific mortality (PCSM) hazard ratio function, using fractional polynomials (FP) for percentage positive biopsy cores (PPC) derived from the PCBase biopsy sub-cohort. HR = hazard ratio

Inclusion of biopsy characteristics did not significantly alter the discriminatory performance of the model when reapplied to the overall PCBase cohort (Table 3.7) or the biopsy sub-cohort, either by using a dichotomous cut-off around 50% PPC or by using PPC more continuously in our FP function (Table 3.9). However, inclusion of biopsy information did improve calibration across lower-risk quintiles of risk for PCSM, which had been highlighted as an issue during model validation (Figure 3.5 and Table 3.8). Calibration for any-cause death was good regardless of inclusion of biopsy information (Table 3.8 & Figure 3.5).

		Predict *Prostate* (Exc Biopsy coef.)			Predict *Prostate* (Inc Biopsy coef.)		
	Model	C-index	SD		C-index	SD	P value
PCSM	PREDICT	0.853	0.0039		0.852	0.0038	
	EAU	0.767	0.0041	<0.001	0.767	0.0041	<0.001
	NCCN	0.787	0.0044	<0.001	0.787	0.0044	<0.001
	CAPRA	0.791	0.0048	<0.001	0.791	0.0048	<0.001
NPCM	PREDICT	0.744	0.0036		0.742	0.0036	
	EAU	0.624	0.0041	<0.001	0.624	0.0041	<0.001
	NCCN	0.626	0.0043	<0.001	0.626	0.0043	<0.001
	CAPRA	0.625	0.0044	<0.001	0.625	0.0044	<0.001
Overall	PREDICT	0.791	0.0028		0.792	0.0028	
	EAU	0.669	0.0032	<0.001	0.669	0.0032	<0.001
	NCCN	0.677	0.0034	<0.001	0.677	0.0034	<0.001
	CAPRA	0.678	0.0035	<0.001	0.678	0.0035	<0.001

Table 3.7 Comparison of discrimination within the PCBase cohort, using the Predict *Prostate* model excluding and including the effect of the biopsy coefficient. EAU = European Association of Urology NCCN = National Comprehensive Cancer Network CAPRA = UCSF Cancer of the Prostate Risk Assessment

			Excluding Bx coef.		Including Bx coef.	
	n	Quintile	Obs	Pred	Obs	Pred
PCSM	13842	1	101	236	83	152
	13841	2	287	458	316	366
	13841	3	818	801	773	832
	13841	4	2082	1858	2123	2037
	13841	5	4793	5246	4786	5625
	69206					
NPCM	13842	1	673	827	679	628
	13841	2	1406	1418	1398	1420
	13841	3	2622	2587	2628	2587
	13841	4	4735	4581	4745	4558
	13841	5	8408	7679	8394	7645
	69206					
ACM	13842	1	828	930	780	890
	13841	2	1834	1979	1827	1970
	13841	3	3610	3624	3638	3676
	13841	4	7395	6975	7412	7199
	13841	5	12258	11983	12268	12115
	69206					

Table 3.8 Assessment of calibration within the PCBase cohort across quintiles of risk. Comparison is made between the Predict prostate model excluding and including the biopsy parameter. Bx = biopsy

	Exc Bx Info C-index	Biopsy50 C-index	PPC FP C-index
PCSM	0.8608	0.8629	0.8559
NPCM	0.7374	0.7337	0.7322
ACM	0.7786	0.7830	0.7840

Table 3.9 Discrimination across the biopsy sub-cohort using three different biopsy categorisation methods: Excluding biopsy information completely (Exc Bx Info), Using a cut-off of >=50%PPC (Biopsy50), or using a fractional polynomial of PPC (PPC FP). PPC = percentage of positive cores

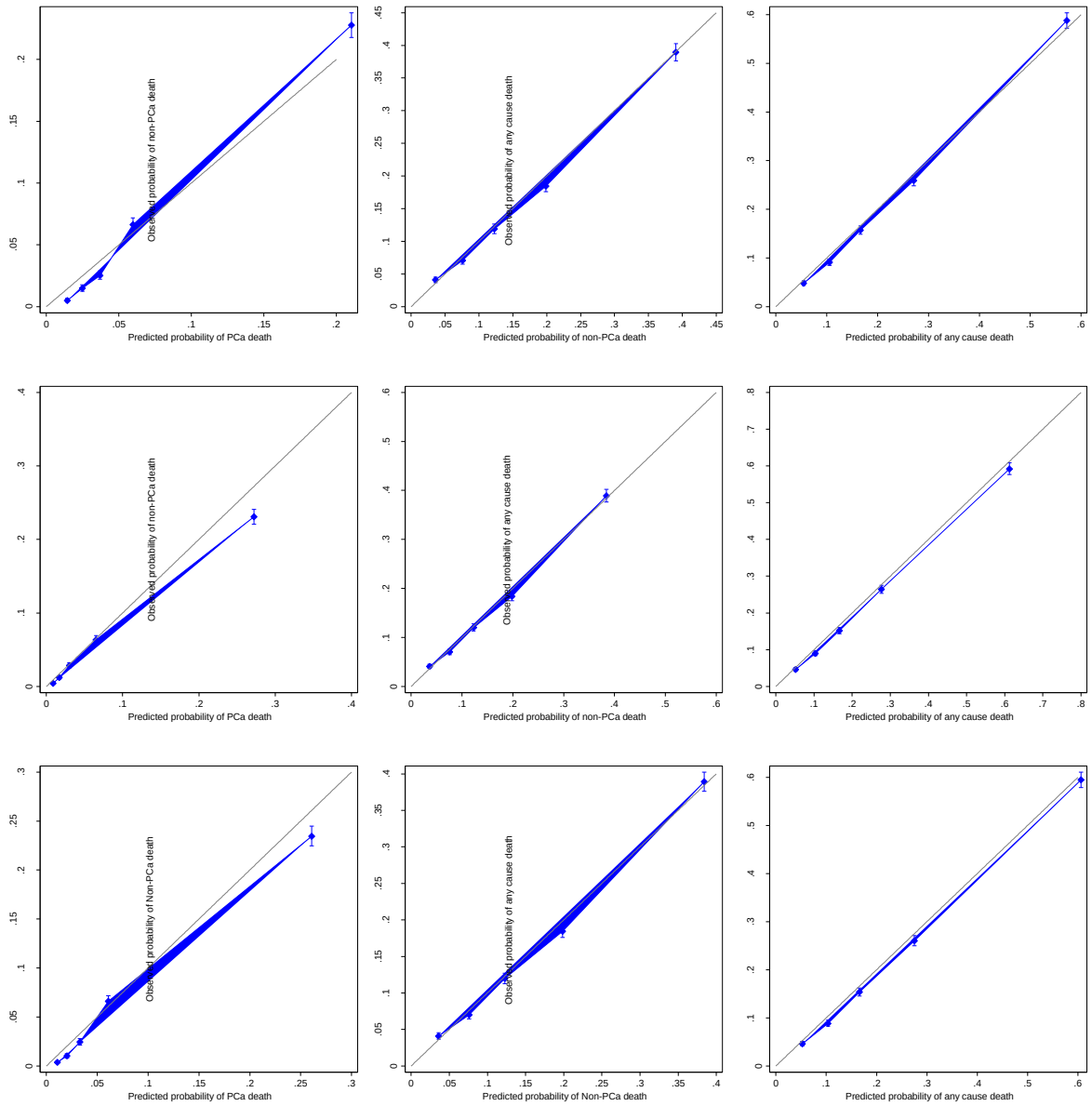


Figure 3.5 Calibration curves demonstrating observed and expected 15-year probability of death across quintiles or risk for PCa death (left), non-PCa death (centre) and any cause death (right) within the biopsy sub-cohort, using no biopsy parameter (top row), the 50% cutoff parameter (middle row) and the PPC FP parameter (bottom row).

3.4 Discussion

3.4.1 Summary of findings

In this large external validation of the Predict *Prostate* tool, the model was demonstrated to be a robust and generalisable long-term prognostic model. Discriminatory performance and calibration was as good as within the development cohort, within this geographically independent cohort almost ten times larger than the original cohort. Model performance was reassuringly good within treatment sub-groups, particularly among men managed conservatively or by radical therapy, for whom the model is primarily intended. A new more intuitive parameterisation of biopsy information was also developed using these external data.

3.4.2 Interpretation of findings

Conveying information to an individual about their disease prognosis within their own context of competing mortality has historically been an imprecise exercise with little objective data available. Predict *Prostate,* as justified in Chapter 1, was conceived to address this gap in clinical need and to standardise the decision-making process (80). As explained in Chapter 2, the tool is built around long-term actual survival data and has been designed to address all AJCC criteria (33).

During model development, C-indices were 0.84 for PCSM and 0.77 for overall mortality within the UK validation cohort (Chapter 2.3.3). External validity was also assessed within a Singaporean cohort. However, this cohort was small (n=2,546) and follow-up was short (5.1 years). In this chapter, it is shown that in a cohort of >69,000 men with longer median follow-up that discrimination was actually slightly better with c-indices of 0.85 for PCSM and 0.79 for overall mortality, with excellent overall calibration. A marginal overestimation of PCSM was noted, which was contrary to the slight underestimation of PCSM observed in the Singaporean external validation described in the previous chapter. Given that the model was very well calibrated for all-cause mortality, this apparent overestimation of PCSM (and corresponding underestimation of NPCM) is likely to be a result of differences in cause of death classification, reporting or recording practices. Overall mortality is the key outcome of interest, and a more unequivocal endpoint, against which this model performs very well.

When compared to existing models in this cohort, Predict *Prostate* consistently out-performed the three-stratum risk classification system used in the EAU, D'Amico and NICE

stratification criteria (19, 28, 32). We recognise that comparisons against these risk stratification criteria are limited, and that they are not designed to be prognostic nomograms, however, they are widely used in clinical practice to inform treatment decisions. Benefits of Predict *Prostate* were also seen against the NCCN and CAPRA scores, which add more granularity but ultimately retain a grouping system rather than individual estimates (22, 32). This was the first time comparisons had been made between Predict *Prostate* and the NCCN criteria. For the outcome of PCSM, the UCSF CAPRA score performed similarly well for some treatment groups, particularly in men treated with prostatectomy. This may be unsurprising, as the model was originally built around prostatectomy patients only (106). It should be noted, that Predict *Prostate* is not a treatment-specific tool, therefore by assessing discrimination within treatment sub-groups its discriminatory performance is inevitably reduced. Nonetheless, Predict *Prostate* performed significantly better in predicting overall mortality and PCSM in most treatment groups.

This validation within the Swedish cohort also confirmed that incorporating biopsy data to the model improved performance. Any incremental benefit on discriminatory ability was marginal, however calibration was improved, countering some of the concerns about over-estimation of PCSM in lower-risk patients. Furthermore, in addition to demonstrating that including biopsy information improves calibration, in this large biopsy sub-cohort from PCBase re-parameterisation of biopsy effect on PCSM was performed. Fractional polynomials were used for PPC, using a similar approach to other continuous variables within our original model development study as outlined in Chapter 2.3.4. Using PPC as a continuous variable maximises use of prognostic information, and allows for a more intuitive relationship between proportion of positive cores and PCSM, rather than a sharp categorical step-change in estimated mortality around a value of 50% PPC, as was used in our original model development. The incorporation of this updated variable into Predict *Prostate* demonstrates how the model can be flexible over time, with the amendment or addition of further parameters as and when variables are shown to have independent prognostic effects, or as further data mature or become available (85). The inclusion of biopsy effect remains an optional variable, such that the model will function with or without biopsy information, and the code for each model is publicly available (85). This ability to incorporate other parameters has been demonstrated with the Predict Breast cancer model previously, since its inception (73).

3.4.3 Strengths and Limitations

This external validation work has numerous strengths, given the large sample size, long follow-up and high levels of complete data in PCBaSe (107). However, we recognise limitations inherent to using registry data. 17% of men were excluded due to missing data and we cannot exclude this introducing some bias. A large proportion of men within this validation dataset had low grade disease, such that PCa mortality rates were relatively low, which may affect discriminatory performance. Men diagnosed within the inclusion period may also not be representative of contemporary practice with changes in PCa diagnosis and treatment. For instance, we recognise that primary hormone therapy is now rarely used in the context of non-metastatic PCa. This is partly why we included subgroup analyses within other treatment groups. We also appreciate that multi-modal therapies are increasingly used in higher risk cases, which we were not able to assess in this study due to the inclusion dates, and data availability limitations of our datasets. Another particular concern is the lack of information from magnetic resonance imaging (MRI). However, as explained earlier, the current focus for MRI is on tumour-detection rather than prognostication and it is unknown if MRI lesion characteristics (Likert or PIRAD scoring) impact upon survival itself. Unfortunately comparative information on biopsy technique and number of cores taken was also not recorded in our exported dataset, so comparisons on biopsy outcomes were difficult, and the differences seen between this, and our original Addenbrooke's cohort cannot be fully explained. Our model also cannot account for subsequent transitions to different treatments. However, in our UK dataset, conversions to active treatment from conservative management were less than 6% across total follow-up (80).

The same limitations exist with regards to the comparisons to the EAU, NCCN and CAPRA scores, namely the lack of T-stage sub-classification in this dataset. We also recognise that other endpoints of interest exist, particularly development of metastases and commencement of hormone therapy. The model is untested against these endpoints due to a lack of reliable data in either our UK cohort or this Swedish cohort. Indeed these would be problematic endpoints as their recording will be variable, and especially with regards to bone metastases will be strongly influenced by the timing and frequency of imaging. Our model development and testing has been calibrated against the more robust endpoint of death itself.

One key issue going forward is the validation of this model in non-Caucasian and screened populations. Although in Chapter 2 the model was tested in Singaporean men, Predict *Prostate* remains untested in men of African descent or other ethnicities. Independent validations within screened populations, and within other prospectively collected or randomised datasets, would be helpful. Finally, we recognise that other nomograms are available, against which direct comparisons would be very insightful. These were not possible within the design of this study, or the limitations of these data, particularly with regards to comorbidity.

3.5 Conclusions

This large external validation again demonstrates the accuracy of Predict *Prostate*, and here demonstrates its robustness to perform similarly in an independent population. This external validation should increase confidence in using the model, which has the potential to significantly improve shared decision-making for PCa management. However, testing of the model within clinical practice is required to understand its usability and potential impact. Further, independent external validations would also be useful, especially in populations of different ethnicities.

4 Impact assessment of Predict Prostate among clinicians

This chapter describes a clinical impact assessment of Predict *Prostate* among health care professionals, as well as an exploration of their perceptions around survival following diagnosis with non-metastatic PCa. This chapter expands upon a short paper published previously in the British Journal of Cancer (108).

4.1 Introduction

As outlined in Chapter 1, decision-making around treatment for non-metastatic prostate cancer (PCa) is complex. Shared decision-making depends upon both clinician and patient having a good understanding of the benefits and harms of different management options, including survival. Estimation of life expectancy has previously been shown to be poor among PCa specialists (109, 110). That said, PCa patients are known to desire survival and life expectancy information and estimation (111). However, clinician understanding around disease lethality and benefits of treatment are not well known, and may be variable as is evident by the significant effect clinician specialty has upon treatment decision-making (87). How perceptions around survival affect treatment recommendations had not previously been explored prior to this work.

In Chapters 2 and 3 the development and validation of Predict *Prostate* as a new risk communication tool was described. This is based upon a prognostic algorithm developed, and subsequently validated, within cohorts numbering over 80,000 PCa patients in total (80, 101). The model provides unbiased and personalised 15-year cancer-specific and overall survival estimates, alongside estimates of survival benefit from radical therapy compared with conservative management. Predict *Prostate* can thus inform decisions with a quantifiable reference for prognosis. In the study described in this chapter, the model was used as a standardised reference to compare against clinician estimates of prognosis; and the potential impact of exposure to the model on treatment recommendations was assessed.

Impact studies are an important step in the development and introduction of risk prediction models (67). In this study we therefore sought to both establish current understanding and decision-making practices, and assess the model's potential impact upon clinical practice. A deliberate decision was made to first assess the model among health care professionals

working in the PCa field, as most should be familiar with the use of prognostic models or risk-prediction tools, and are aware of the complexities around decision-making in PCa. The study was designed using hypothetical clinical vignettes, rather than being used in clinical practice, and was delivered prior to the online publication of the Predict *Prostate* webtool (85). This was used, in part, to guide the model's continued development.

Our objectives for this impact study among clinicians were to:

-Assess PCa specialists' current usage of prognostic models

-Assess specialists' perceptions of disease-specific and overall mortality in men newly diagnosed with non-metastatic PCa and compare these to a well-validated prognostic model.

-Review the potential impact of Predict *Prostate* estimates on treatment recommendations.

-Gain qualitative feedback on the Predict *Prostate* tool.

4.2 Methods

4.2.1 Study design

A randomised online questionnaire-based study was developed using Qualtrics® research software (Utah, USA). Respondents completed a set of common questions on their practice, including questions assessing their exposure to PCa patients and current usage of prediction models. Respondents were then randomised into group A or B. Those in group A were presented with 6 hypothetical 'A' vignettes with clinical diagnostic information only, then 6 'B' vignettes with clinical details in addition to presentation of Predict *Prostate* survival estimates. Those randomised to group B saw the 'B' vignettes with clinical information alone, then the 'A' vignettes alongside Predict *Prostate* estimates (Figure 4.1). Randomisation was performed in a 1:1 ratio automatically within the Qualtrics software, without researcher influence. After randomisation, questions assessed clinicians perceptions of cancer-specific and non-cancer mortality over 15 years. Additional questions assessed the perception of potential survival benefit from radical treatment compared to conservative management. In all cases, clinicians were asked "on a scale from 0 (certainly not) to 100 (certainly) how likely would you be to recommend radical treatment?" For cases where Predict *Prostate* estimates were shown alongside the vignettes, respondents were not asked to estimate survival but rather they were asked how the estimates compared to

their expectations. Finally, respondents were asked to comment on the usefulness of Predict *Prostate* and provide written feedback on the tool. The full questionnaires are available in the appendix. Each case vignette was designed to represent scenarios in which use of the Predict *Prostate* tool might be appropriate (Figure 4.2). Survey progression was uni-directional – preventing respondents from amending previous answers. Progression through the study was prevented if questions were left unanswered, but partially completed responses were analysed. Responses were closed and submitted if no activity was recorded for 2 weeks. Responses were anonymised.

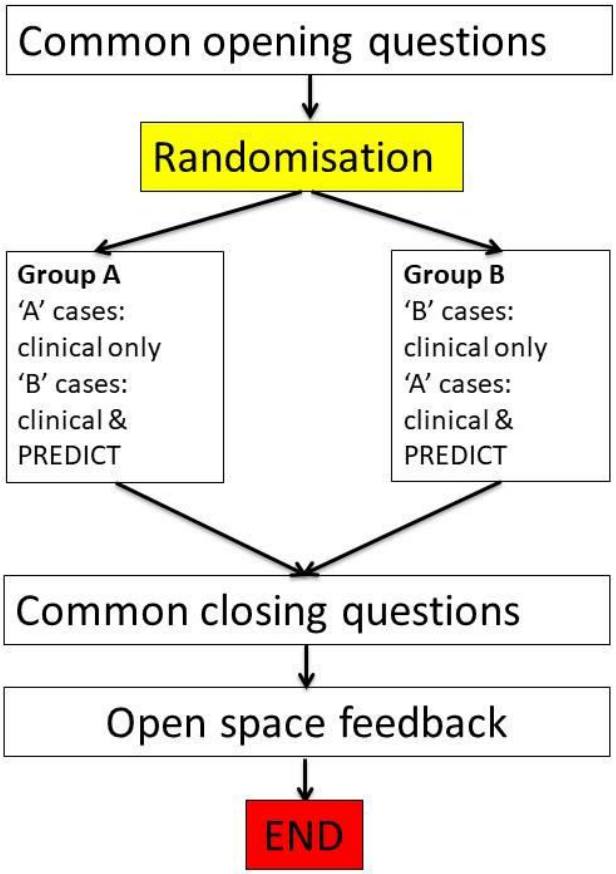


Figure 4.1 Study flow chart for the Predict *Prostate* clinician impact study

Case A1 64yo, PSA 23, GG4, T3, 3/12bx, Otherwise well	**Case B1** 75yo PSA 5.1 GG2 2/12bx T1 Otherwise well
Case A2 72yo, PSA 8.2, GG1, T2, 3/14bx, Myocardial infarction 1 year ago	**Case B2** 57yo, PSA 12, GG3, T2, 10/12bx, Otherwise well
Case A3 54yo, PSA 14.0, GG3, T2, 2/12bx, Otherwise well	**Case B3** 71yo, PSA 9.0, GG1, T2, 3/12bx, Otherwise well
Case A4 68yo, PSA 13.4, GG3, T2, 8/16bx, Co=0 Otherwise well	**Case B4** 58yo, PSA 15.3, GG3, T2, 7/14bx, Otherwise well
Case A5 60yo, PSA 6.4, GG2, T1, 2/12Bx Otherwise well	**Case B5** 61yo, PSA 6.1, GG2, T3, 2/12bx, Otherwise well
Case A6 83yo, PSA 24, GG2, T1, 1/12Bx Peripheral vascular disease	**Case B6** 81yo, PSA 6.1, GG2, T1, 1/12Bx, Connective tissue disease

Figure 4.2 Details of the 12 hypothetical clinical vignettes used within the study

4.2.2 Recruitment and data collection

Prostate cancer specialists were invited to participate predominantly through professional mailing lists, including via the British Uro-oncology Group and British Association of Urological Surgeons, between June and September 2018. Respondents were also encouraged to share the survey link with colleagues, and the link was shared via social media platforms. No incentive was offered for participation.

4.2.3 Statistical analysis

Clinician estimates of 15-year survival outcomes were compared to Predict *Prostate* estimates. The likelihoods of recommending treatment were compared between the two randomisation groups. Data analyses were performed using Stata 14 (Texas, USA). Comparison of mean likelihood of treatment recommendation between groups was performed using the non-parametric Mann-Whitney U Test, as data were often skewed to 0 or 100. This was an exploratory study of current practice. Approximate a priori sample size calculations were generated around the outcome of likelihood of recommending radical treatment. Studies in other tumour-types have demonstrated changes in treatment choice in 23%-25% of cases when using a decision aid (112, 113). Using a figure of 20% change in

treatment recommendation, standard deviation of 30%, alpha 0.05 and power of 80% the minimum sample size required was 74 (37 per group).

4.3 Results

4.3.1 Respondents and model usage

190 responses were received from 121 urologists (64% [85 consultants, 36 trainees]), 32 oncologists (17% [29 consultants, 3 trainees), 25 PCa specialist nurses (13.2%) and 12 other professionals (6%); henceforth collectively referred to as 'clinicians'. Sixty percent of respondents reported working in specialist cancer centres and 82% reported counselling men with PCa at least weekly. 81% and 19% of respondents reported working in a UK, and non-UK centre respectively. Forty-six percent of respondents reported using a 'risk prediction model' in their routine practice. The tools and nomograms they reported using were shown previously in Chapter 1 in Figure 1.3. In total, only 19% of all respondents appeared to be using a prediction for survival (either cancer-specific survival or overall survival). Most respondents reported not using a tool whatsoever, or using stratification tools such as the AUA, EAU, D'Amico or NICE risk criteria.

4.3.2 Clinician Estimates

Clinician estimates of 15-year PCSM varied significantly and exceeded Predict *Prostate* estimates in most cases (83%) (Table 4.1 and Figure 4.3). Mean clinician estimates of PCSM across all 12 cases were 1.9-fold greater than Predict *Prostate* estimates. Perceptions of survival benefit from upfront radical treatment at 15 years were similarly much higher, with mean clinician estimates of survival benefit 5.4-fold greater than the matched Predict *Prostate* estimates (Table 4.1).

Clinician estimates of non-prostate cancer mortality (NPCM) were closer to Predict *Prostate* estimates with mean NPCM estimates across all 12 vignettes only 1.2-fold greater than Predict *Prostate* estimates. Clinicians appeared to slightly overestimate NPCM among men aged under 70 years, but underestimated NPCM in 3 older cases aged 72 (case A2), 83 (case A6) and 81 (case B6) (Table 4.1), when compared to Predict *Prostate* estimates.

Clinician estimates of survival benefit from radical treatment over 15 years were strikingly similar to their estimates of 15-year PCSM. In 10/12 cases, clinician estimates of treatment benefit were more than 75% of the estimated PCSM. In 4/12 vignettes mean estimated survival benefit from radical treatment actually exceeded the mean estimated PCSM over 15 years (Table 4.1).

	Clinician estimates			PREDICT Prostate estimates		
Case	15year PCa deaths	15year Non-PCa deaths	Extra men alive with radical treatment	15year PCa deaths	15year Non-PCa deaths	Extra men alive with radical treatment
	Mean (95%CI)	Mean (95%CI)	Mean (95%CI)			
Case A1	58.4 (91.5-98.7)	31.4 (25.9-36.9)	40.0 (33.9-46.0)	17.8	20.6	7.2
Case A2	12.3 (8.9-15.7)	62.8 (56.4-69.1)	15.9 (9.9-21.9)	8.0	67.6	1.2
Case A3	44.9 (38.5-51.2)	22.6 (16.9-28.2)	42.3 (35.0-49.5)	9.2	7.1	4.3
Case A4	40.7 (34.8-46.6)	40.9 (34.8-46.5)	31.6(25.1-38.1)	32.0	28.4	11.1
Case A5	23.7 (18.4-29.1)	29.9 (23.8-36.0)	23.0 (16.3-29.8)	6.2	14.1	2.7
Case A6	15.3 (11.0-19.5)	82.0 (76.9-87.1)	7.7 (4.6-10.8)	11.8	87.8	0.1
Case B1	14.7 (11.8-17.6)	61.7 (56.6-66.8)	19.8 (14.1-25.5)	9.4	57.9	1.8
Case B2	41.9 (35.7 - 48.1)	18.4 (14.5-22.2)	38.7 (31.4-46.0)	27.2	9.7	11.9
Case B3	9.8 (6.8-12.8)	50.1 (43.6-56.6)	19.0 (11.5-26.6)	8.0	42.7	2.3
Case B4	38.3 (32.0-44.6)	21.4 (16.9-26.0)	33.3 (26.6-40.4)	28.6	10.7	12.3
Case B5	32.2 (25.9-38.6)	26.2 (21.4-31.0)	31.0 (23.4-38.6)	9.1	15.5	3.9
Case B6	8.9 (4.9-12.9)	79.6 (74.3-84.9)	12.1 (5.7-18.5)	10.3	88.1	0.1
All cases	**24.0**	**43.3**	**25.5**	**15.3**	**37.8**	**5.3**

Table 4.1. Mean 15-year mortality estimates from prostate cancer professionals and from PREDICT *Prostate* for each of the 12 hypothetical clinical vignettes. The final row shows weighted mean values across all cases.

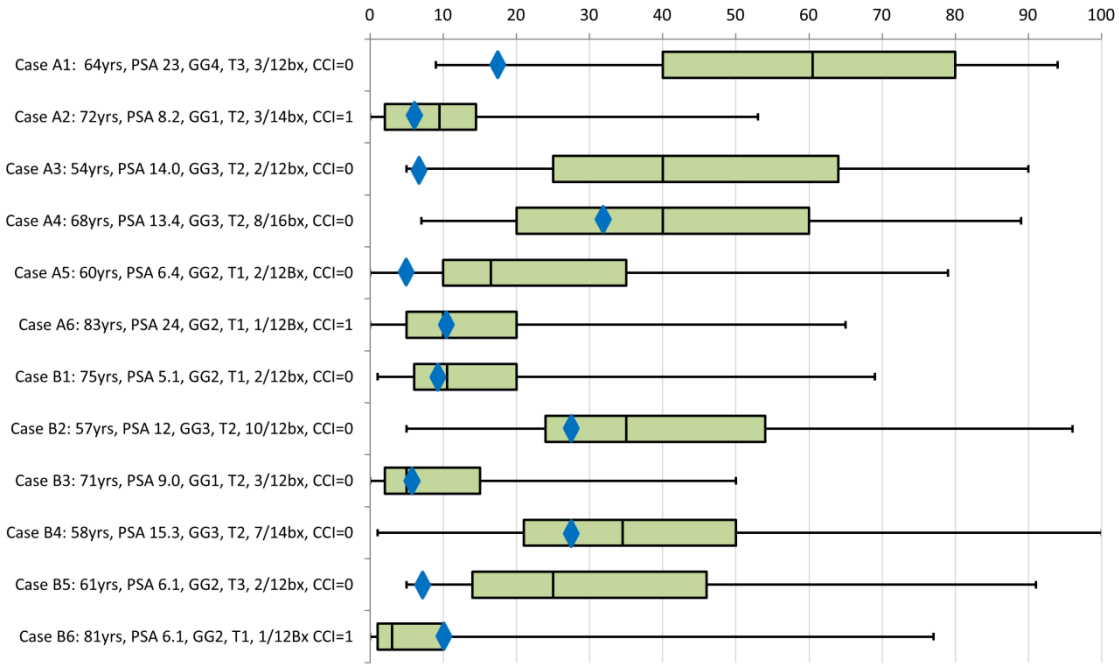


Figure 4.3 Boxplots showing the median, IQR and range of clinician estimated percentages of men dying of prostate cancer by 15 years after diagnosis without radical treatment for each of 12 case vignettes. For comparison the PREDICT Prostate estimates for prostate cancer death by 15 years is shown by a blue diamond. PSA = Prostate specific antigen; T = clinical tumour stage' GG = grade group; Bx = biopsy cores; CCI = Charlson Comorbidity Index.

4.3.3 Impact of Predict *Prostate* on treatment recommendations

Likelihood of recommending treatment, using clinical information alone correlated with clinician estimates of PCSM and with traditional three-stratum risk stratification criteria (Table 4.2). It was also strongly influenced by patient age, with treatment recommendations particularly high (>80%) in younger men (<65years) with any 'high risk' features (29). For example, in cases A3 and B2 the likelihood of recommending radical treatment was >90% - corresponding to men aged 54 and 57 with grade group 3 disease. Whereas, the likelihood of recommending radical treatment to men aged 83 and 81 with low-risk characteristics were both below 15% (cases A6 and B6).

	Likelihood of Recommending Upfront Radical Treatment			
	Clinical Information only Mean (SD)	Clinical information + PREDICT Prostate Mean (SD)	% Decrease	p
Case A1: 64yrs, PSA 23, GG4, T3, 3/12bx, Co=0	95.1(14.3)	78.5(28.2)	17.46	0.000
Case A2: 72yrs, PSA 8.2, GG1, T2, 3/14bx, Co=1	16.2(24.8)	11.1(15.4)	31.48	0.574
Case A3: 54yrs, PSA 14.0, GG3, T2, 2/12bx, Co=0	91.0(15.7)	66.2(29.5)	27.25	0.000
Case A4: 68yrs, PSA 13.4, GG3, T2, 8/16bx, Co=0	87.0(16.2)	87.7(15.8)	-0.80	0.867
Case A5: 60yrs, PSA 6.4, GG2, T1, 2/12Bx Co=0	47.1(29.6)	36.4(28.4)	22.72	0.079
Case A6: 83yrs, PSA 24, GG2, T1, 1/12Bx Co=1	13.8(20.0)	4.3(11.2)	68.84	0.003
Case B1: 75yrs, PSA 5.1, GG2, T1, 2/12bx, Co=0	32.5(28.0)	19.1(2.80)	41.23	0.009
Case B2: 57yrs, PSA 12, GG3, T2, 10/12bx, Co=0	93.2(18.3)	86.7(19.8)	6.97	0.002
Case B3: 71yrs, PSA 9.0, GG1, T2, 3/12bx, Co=0	20.0(23.8)	19.3(20.9)	3.50	0.757
Case B4: 58yrs, PSA 15.3, GG3, T2, 7/14bx, Co=0	92.7(15.7)	86.6(20.4)	6.58	0.010
Case B5: 61yrs, PSA 6.1, GG2, T3, 2/12bx, Co=0	81.1(24.6)	58.7(29.9)	27.62	0.000
Case B6: 81yrs, PSA 6.1, GG2, T1, 1/12Bx Co=1	7.2(13.6)	5.8(11.3)	19.44	0.500

Table 4.2 Likelihood of recommending radical treatment for each case, comparing the two randomisation groups. PSA = Prostate specific antigen GG = Grade group T = T-stage Bx = biopsy Co=comorbidity SD = standard deviation

Concomitantly viewing estimates from Predict *Prostate* led to lower likelihood of recommending radical treatment in 11/12 (92%) vignettes (Table 4.2) with significant differences ($p<0.05$) in 7/12 (58%). Percentage decreases were most evident in intermediate risk cases, older patients (>70 years) and in the presence of comorbidity (Figure 4.5). For example, in a 75-year old man with PSA 5.1 and Gleason 3+4 disease in 2/12 biopsy cores (Case B1), the mean likelihood of recommending treatment was 32.5% with clinical information alone, compared to 19.1% among the group where Predict Prostate estimates were also shown to clinicians ($p=0.009$) (Figure 4.4).

Although reported likelihood of recommending treatment differed substantially between the two groups, the vast majority of respondents in the Predict *Prostate* group felt the model estimates were 'similar to' what they expected (Figure 4.6). Overall, 62% of responses reported that Predict *Prostate* estimates of treatment benefit were similar to what they expected. 31% and 7% reported that the model estimates for treatment benefit were less than and greater than they expected respectively. Figure 4.6 demonstrates how these responses differed by case. Predict *Prostate* estimates for treatment benefit were noticeably lower than clinician expectations in cases A3 and B5. These were two cases of low-volume intermediate-risk disease in younger patients. Indeed, as per Table 4.1, mean clinician estimates of survival benefit were nearly 10-fold greater than Predict *Prostate* estimates in these cases.

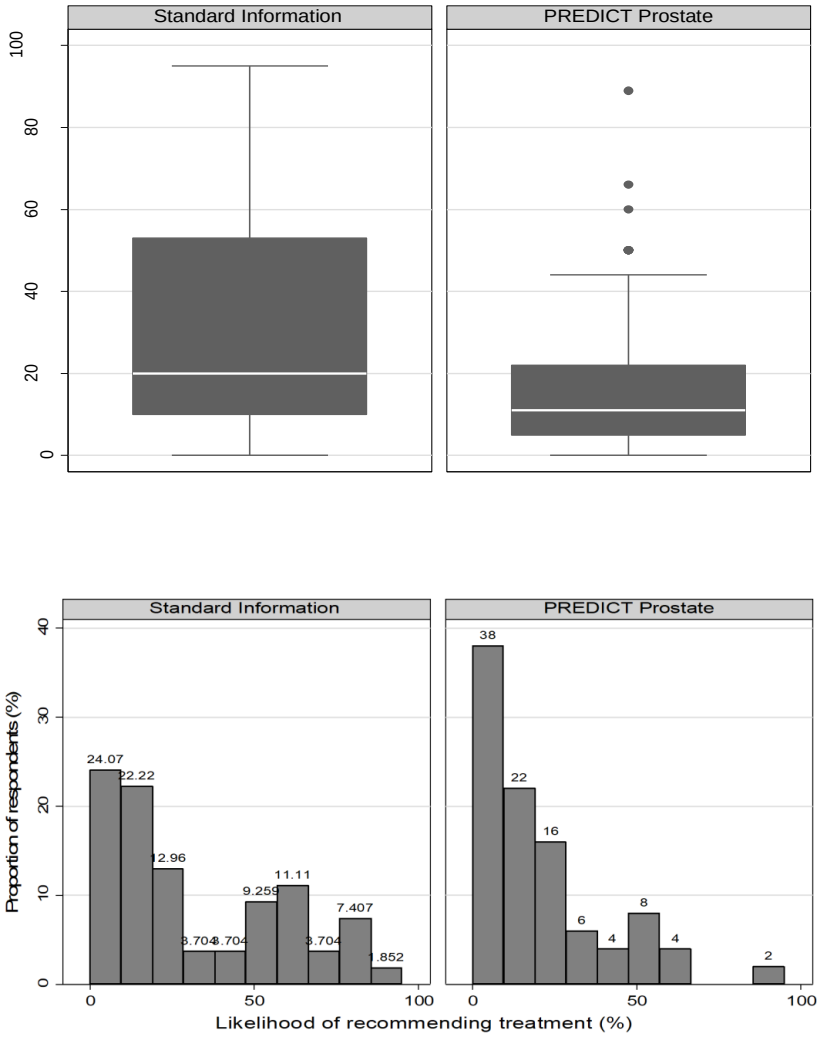


Figure 4.4 Plots demonstrating the reported likelihood of recommending radical treatment for case B1 (75 years old , PSA 5.1ng/ml, grade group 2, T1, 2/12 cores, otherwise well) when given clinical information alone, or in addition to Predict Prostate estimates.

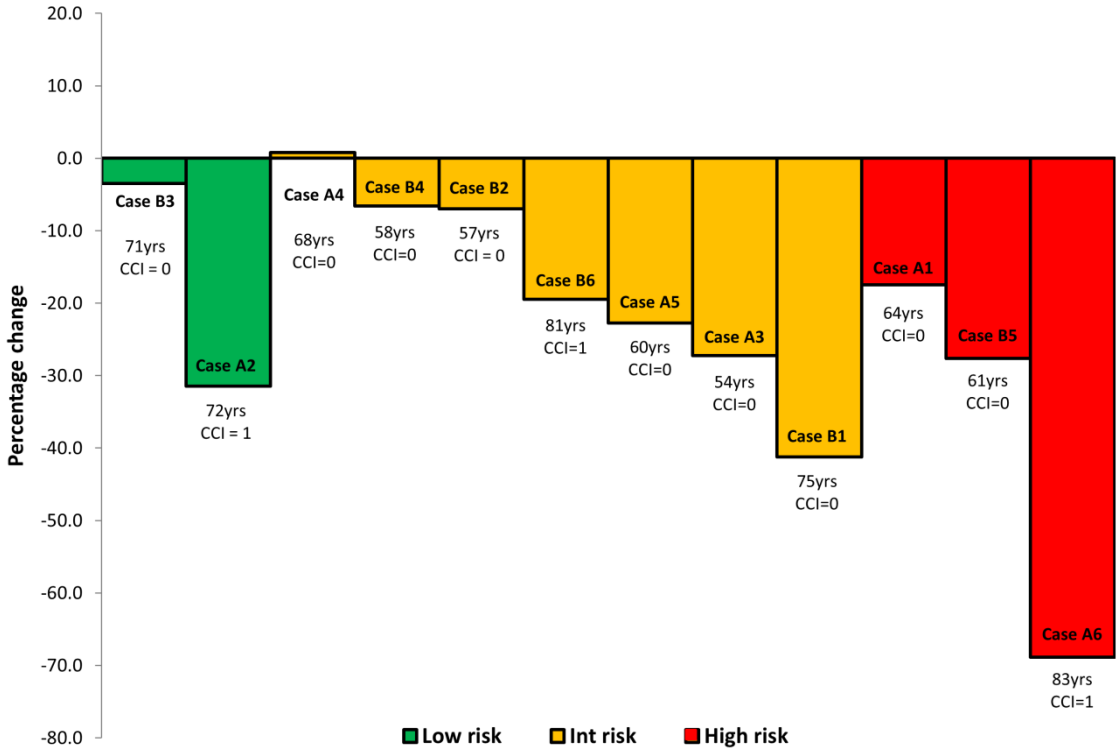


Figure 4.5 Mean difference in clinician likelihood of recommending radical treatment when shown Predict *Prostate* estimates in addition to routine diagnostic clinical information alone. Results for all 12 hypothetical cases are shown, sorted by EAU risk group. The case number, age and Charlson Comorbidity Index (CCI) is reported. Further case details are shown in Figure 4.3.

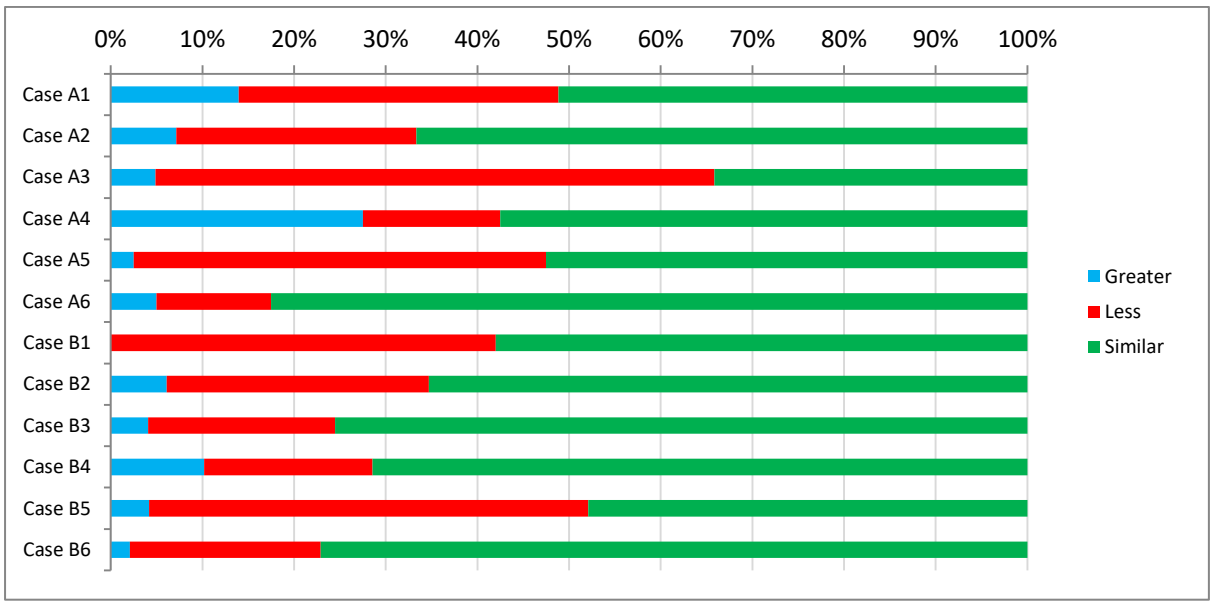


Figure 4.6 The proportion of respondents that thought the Predict *Prostate* estimates for 15-year survival benefit from radical treatment were greater, less or similar to what they expected for each case vignette.

4.3.4 Clinician feedback

Overall, 81% of respondents felt Predict *Prostate* would be a useful clinical tool. The remainder (19%) stated they were 'unsure' and no one answered that it would not be useful. Individual written feedback was recorded by 29 respondents, this is summarised in Table 4.3 under 3 categories: 'complimentary', 'concerns/reservations' and 'suggestions'. Written feedback was generally positive with recurrent themes being that this would be a useful tool for both clinicians and patients, particularly the graphical presentations. Reported concerns or inadequacies were that the model ignored 'non-death' but important endpoints such as metastases or switching to hormone therapy – with its associated morbidity. Others found fault with the terminology used in the study itself, namely that clinicians do not recommend treatments, but rather they present options to a patient. Suggestions for improvement included further stratification by location or lifestyle and using the term 'active surveillance' rather than conservative management.

Complimentary

'Excellent tool'

'Impressive stuff'

'Looks class'

'This tool is URGENTLY needed to prevent overtreatment'

'Potentially very useful tool to aid decision making in both outpatient and MDT settings'

'Any tool is useful. This is nicely validated. '

'Very useful tool'

'Excellent to have a UK based database.'

'I will use it.'

'Good resource especially for the educated patient.'

'This would be a useful tool to help educate and counsel patients.'

'The 15 year graphs are very helpful'

'This data will help patients to decide what matters to them'

'Useful way of pictorially representing the potential benefits (or not) of radical treatment to improve the decision making process'

'Fantastic instrument. Graphical representation is really helpful for clinicians and I expect patients too.'

Concerns/Reservations

'Some cases appear to have overly high survival with conservative management'

'Unable to understand the graphs'

'Treatment is not all about survival - may be provided for local control to reduce later symptoms'

'Non-death variables are ignored - such as hormone therapy side effects'

'Needs MRI information to be incorporated or adjusting for the MRI era.'

'Non-survival endpoints are important but ignored.'

'Treatment is ever changing and the model won't be relevant to all'

'Needs active surveillance option'

'May increase radical treatment being offered as showing pts that there is always a small increase in survival'

'We don't 'recommend' treatment options, we put them to the patient.'

Suggestions

'Need to consider web based tool and mobile App.'

'User-interface and marketing are key. This isn't about science, it's about marketing.'

'The information would be better presented as statements'

'Need to take into account biopsy approach'

'Alternative endpoints to survival would improve the model'

'Needs to mention active surveilance'

'Can you stratify life expectancy by UK postcode?'

'Could you take into account smoking history?'

'Needs an active surveillance option.'

'Needs external validation'

Table 4.3 Summary of written feedback on PREDICT Prostate categorised into 3 groups. 29 respondents wrote feedback, sections of feedback from one respondent may be under more than 1 category.

4.4 Discussion

4.4.1 Summary of findings

The clinician study outlined in this chapter suggests PCa professionals generally overestimate cancer-related mortality. The results also suggest that clinicians' perceptions of treatment effectiveness are generally over-optimistic; well in excess of a 75% improvement in cancer-specific mortality which does not correlate with direct evidence from RCTs (16, 114). Predict *Prostate*, by providing individualised and contextualised prognostic information may challenge current understanding of prognosis and lead to increased consideration of conservative management strategies – and most clinicians considered it to be a useful tool.

4.4.2 Interpretation of findings

Clinician understanding of PCa prognosis in non-metastatic disease is not well-explored in the literature. However, estimates of overall life expectancy in patients with PCa among urologists, oncologists and other health professionals are known to suffer from 'inaccuracy, imprecision and inconsistency'(109, 110). It is also widely accepted that there is inadequate recognition of competing risks in the clinical community more widely, with this issue being particularly relevant in PCa (115). Over-treatment also remains a significant issue in PCa management, with up to 24% of men with low-risk disease still being managed with radical therapy in some centres in the UK (5).

In this chapter we see that clinicians consistently overestimate PCSM compared to a validated prognostic model. NPCM estimates were fairly accurate, but still slightly overestimated mortality, which has been reported previously (116). Clinicians also appeared to consider radical treatment to be curative in the vast majority of cases. Although this may seem intuitive for a disease which is not metastatic, it does not correlate with RCT data such as from the ProtecT or SPCG trials. ProtecT reported non-significant hazard ratios (HR) for PCa death over 10 years, while SPCG reported a cancer-specific HR of 0.56 (95%CI 0.41-0.77) when radical treatment is compared to watchful waiting across 23 years of follow up (16, 114). Here, treatment was associated with only modest, and non-significant reductions in PCSM (16).

These findings, that clinicians recommend radical treatment in most intermediate or high

risk PCa, are unsurprising with the current reliance on a three-tier risk-stratification system. These have been integrated into patient management for many years and adopted by numerous guideline panels to direct management decisions (28, 29). However, growing evidence supports the judicious use of surveillance in some men with intermediate-risk disease, and more individualised approaches are being sought (117). Indeed, the latest NICE guidelines suggest considering active surveillance is reasonable in intermediate-risk disease (118).

This chapter reports the first impact assessment of Predict *Prostate* itself. As per Professor Karel Moons *et al*. a prognostic model "is of no benefit if it is not generalizable or does not change behaviour"(67). Indeed, despite being a free tool, many stakeholders would expect to see evidence of the clinical utility of Predict *Prostate* prior to adoption. This work has shown that the model has face validity, and is considered to be useful by most clinicians. This work suggests the model may encourage more consideration of a conservative management approach, particularly in cases of intermediate-risk disease. As was seen in Figure 4.5 this may be particularly true for older patients, or those with comorbidities. These cases most obviously demonstrate how overall survival benefits from treatment are adjusted for competing risks in the Predict *Prostate* model, rather than relying upon cancer-specific survival alone. Clearly, it is difficult to assess whether the lower reported likelihoods of recommending radical treatment are as a result of the lower than expected PCSM, or lower than expected survival benefit of treatment. The apparent reduction in recommending treatment in the context of seeing Predict *Prostate estimates,* across all vignettes, suggests a paradigm shift in the thinking of clinicians on reviewing these estimates. However, differences in likelihood of recommending treatment were more overt in intermediate-risk cases.

Decisions around treatment should clearly be shared decisions – with the predominant stakeholder being the patient. Indeed we recognise that in modern practice clinicians do not generally 'recommend' treatment strategies, but rather they discuss these with the patient. However, even recent studies have demonstrated that treatment decisions are determined largely by clinician recommendations (119), with numerous previous studies demonstrating a bias among clinicians towards their own expertise as the optimum management strategy (120). Prognostic models rely upon the assumption that more accurate predictions and a better-informed patient leads to 'better' decision making. Indeed, in a large study of over

1500 men with PCa, researchers in the US reported that more active involvement, and greater relevant knowledge, were associated with reduced decisional conflict and higher decision-making satisfaction (121). A recent wide-reaching Cochrane review similarly reported that decision aids improve patient's knowledge, understanding of risk, and ability to participate in their clinical care (122). In the PCa context, a Dutch study found that the use of a decision aid significantly reduced the number of men undecided about which treatment to have for PCa (123). Additionally to these benefits, decision aids have also been shown to allow patients to ask more narrow technical questions about potential treatments (124).

The complexities around clinical decision-making are appreciated, where the patients' views are central to the outcomes, and therefore these hypothetical scenarios are rather artificial. It should also be considered that differences in reported likelihood of recommending radical treatments may not translate into changes in practice, but may allow or inform more open discussions with patients about their options. Our results suggest that by providing individualised and contextualised prognostic information, Predict *Prostate* may prompt clinicians to re-evaluate prognosis estimation and increase consideration of non-interventional strategies.

4.4.3 Strengths and limitations

This study amongst clinicians has many strengths as it represents the reported behaviour of a diverse spectrum of prostate cancer professionals within a randomised design and where the pre-defined sample size was exceeded. The capture of information from a combination of urologists, oncologists and specialist nurses reflects current practice where multi-disciplinary patient counselling is increasingly widespread. However, we recognise the study limitations inherent to questionnaire-based research. These findings were from a predominantly UK context and stated change in treatment recommendations may not equal actual change in practice. The findings may not be generalisable outside of the UK. The reported profession of respondents cannot be confirmed, nor their experience quantified, and the final response rate, as a proportion of potential respondents cannot be determined due to the method of recruitment. Some respondents, may rarely manage patients with the localised PCa characteristics described in the vignettes, however, all would be likely to partake in PCa multi-disciplinary team (MDT) meetings. The survival endpoint of 15-years

may also be unfamiliar to many clinicians, with most studies focussing on 10-year outcomes, or shorter time-periods. However, Predict *Prostate* was deliberately developed to extend beyond 10 years as it is widely appreciated that non-metastatic PCa outcomes up to 10 years are very favourable regardless of treatment (16). As outlined above, it is acknowledged that clinicians may recommend a therapy but final treatment decisions are made by the patient himself. Nonetheless, physician recommendations do remain very important in guiding patients' decisions (125). Further exploration of the impact of the tool among actual patients, embedded within clinical practice, is needed to help contextualise these results, and this is explored in Chapter 5. Finally, this study cannot represent clinician feedback of the web-model more broadly, as only small sections of the web-design were presented herewith, further investigation was not within the scope of this particular part of the project. Indeed, the work outlined in this chapter was performed prior to the online publication of the tool, and used the earlier version of the model outlined in Chapter 2, rather than the model incorporating the PPC FP update.

4.5 Conclusions

In summary, this clinician impact study suggests that PCa specialists tend to overestimate PCa-related mortality and the survival benefits of radical treatment for non-metastatic PCa. Using a freely available tool such as Predict *Prostate* can provide individualised and contextualised prognostic information which may help to reduce variability in treatment recommendations among clinicians. The model appeared popular among respondents, many of whom felt it was a necessary tool. Use of the model should lead to more informed clinician-patient discussions. In turn this may reduce overtreatment of good prognosis disease while also increasing the confidence that radical treatment, when needed, will confer a survival benefit and justify the risks of side effects. At the very basic level it should enhance knowledge of risks and benefits among clinicians, and therefore patients.

5 Impact assessment of Predict Prostate among newly diagnosed patients

This chapter describes the integration of Predict *Prostate* into clinical practice among patients newly diagnosed with PCa, within a multi-centre randomised controlled trial design. The full protocol was published online, and parts of the write-up have been published previously (126, 127).

5.1 Introduction

As outlined in the preceding chapters, the majority of PCa presents as non-metastatic localised or locally advanced disease (128). Treatment decisions are complex, particularly for men with earlier stage disease with the risk of progression and psychological impact of a cancer diagnosis balanced against potential morbidity associated with radical treatment. Unsurprisingly, decisional anxiety and regret are well-recognised issues for many newly diagnosed men (18). There is also significant regional variation in the proportion of men undergoing radical treatment, particularly for favourable intermediate-risk disease (129). Prognostic stratification should therefore be useful in guiding management and treatment decision-making.

Predict *Prostate* (prostate.predict.nhs.uk) was launched in May 2019 as a freely-available online personalised risk communication tool based on an internationally-validated prognostic model for men with newly diagnosed, non-metastatic PCa. Its development and validation has been described in Chapters 2 and 3 of this thesis and in peer reviewed articles (80, 101, 102). The model has been demonstrated to be accurate within two separate external validations, and shown to be able to discriminate better between patients, compared to more commonly used existing models. Chapter 4 of this thesis described previous work which evaluated the tool's impact upon clinician perceptions and treatment recommendations (108). The clinician study, performed before the online web-interface of the model had been completed, used Predict *Prostate* estimates in isolation, around hypothetical vignettes, in a virtual randomised setting. Prior to the patient impact study outlined in this chapter, no formalised patient assessment of the website had been

performed; nor had the clinical utility of any similar risk communication tool embedded within an interactive web interface been assessed among newly diagnosed PCa patients.

The underlying assumption that accurate outcome estimates lead to improved patient decision-making requires testing. 'Impact studies' such as outlined in this chapter, seek to quantify whether using a prognostic model improves decision-making within a comparative design. Impact analyses are an important element of prognostic model development and should include comparisons to a control group who receive standard care (67). They help assess what clinical benefit a model might have, however accurate it might be in validation studies. Indeed, many stakeholders will expect to see evidence of clinical utility prior to adoption. In assessing the clinical utility among patients we hoped to quantify any potential benefit of using the model compared to current standard practice. Impact studies can also be useful to study issues that may affect acceptability and uptake of a model in regular care as well as usability (67).

The ideal assessment outcomes of survival or long term decisional regret were not viable options, therefore we sought to assess the effect of the model on shorter term outcomes such as decision-certainty, decisional conflict, anxiety, and perceptions of disease severity. In this impact study, we also assessed whether or not using Predict *Prostate* affected patient decision-making within a multi-centre randomised controlled trial design. Our primary objectives were to:

- Assess the impact of the Predict *Prostate* risk communication tool on decisional conflict, uncertainty and anxiety among men newly diagnosed with non-metastatic PCa.

Secondary objectives were to:

- Assess patients' perceptions of their survival and survival benefits of treatment, and how Predict *Prostate* survival estimates compared to and impacted upon these.
- Retrieve feedback on the tool and assess whether certain men may benefit more from using the tool.

In addressing these objectives, the trial was designed around the primary outcome measure of patient scores on the decisional conflict scale (DCS) (130). Secondary outcome measures included patient scores on state-anxiety measured on the State-Trait Anxiety Inventory

(STAI-Y) (131), reported treatment preference and actual treatment decided upon or received.

5.2 Methods

5.2.1 Trial design

The study was approved by the Cambridge South Research Ethics Committee (REC 18/EE/0254). The design was a prospective UK multi-centre randomised controlled trial. Ethical approval documents are available in the appendix. The full protocol is available online (ISRCTN 28468474) and in the appendix to this thesis(126). In summary, men aged 35-80 with newly diagnosed non-metastatic PCa, in whom either surveillance or upfront radical treatment were both deemed potentially appropriate, were invited to participate (Table 5.1). Study participation was integrated into the patient's clinical pathway, without delays in standard management pathways. Participants, already aware of their PCa diagnosis were invited to a study appointment. All participants were informed and counselled according to the SOC in their centre's normal practice, which we did not standardise across centres. However, all centres should follow governing guidelines from the National Institute for Health and Care Excellence (NICE), which include that information and decision-support should be available to all patients (118). In UK practice, SOC should include discussion within a dedicated multi-disciplinary team, then a diagnosis appointment where a patient is informed of the biopsy results by a consultant alongside a specialist nurse; potential treatment options would ordinarily be introduced at this point. Further written information and signposting to other resources are provided alongside contact details for a named clinical nurse specialist who is available for further discussion. Indeed, nationalised audit data has reported that 87% of men across England and Wales had a named clinical nurse specialist (132). Additional consultations are arranged with oncologists or other specialists for discussion as appropriate, and a follow-up consultation is arranged. The study appointment in this trial was organised between the diagnosis appointment, and follow-up appointment, and followed a cooling-off period of at least 24-hours after introduction of the study. Where possible, study appointments were arranged on the day of, but prior to, follow-up appointments, to avoid the need for an additional trip for the patient.

The study appointment was performed face-to-face. During this appointment men were randomised to either the control (standard of care (SOC)) arm or the intervention (Predict *Prostate)* arm of the trial. Randomisation was achieved by block random allocation within each site (with random block sizes between 4-6), using sealed envelopes sent from the coordinating centre (CUH) (133). Recruitment took place between November 2018 and March 2020. The study closed to recruitment at the outbreak of the Covid-19 outbreak in the UK, as non-Covid research studies were suspended, and additionally we felt the pandemic may have materially changed patient expectations around their diagnosis or survival. Men in the SOC arm were directly allocated to complete the questionnaire. Those in the intervention arm were exposed to a structured presentation of the Predict *Prostate* tool on a PC by a trained researcher, then completed the questionnaire (Figure 5.1). The researchers presented the tool by directing the participant through the website in a structured manner, without offering any additional clinical advice or input, using prescribed terminology as set out in the study appointment protocol (Appendix). The patient's individual details were entered into the model and the results explained to them using positive and negative terms, and expressing uncertainty. For example "out of 100 patients with the same age and disease characteristics as you, 16 are expected to die from prostate cancer in the next 10 years, 10 are expected to die from other causes, and 74 are expected to still be alive. At this moment we cannot say to which group you will belong." Graphs, charts, text, icons and actual numbers were presented to the participants showing the estimated outcomes with conservative management and radical treatment – following the design of the website (85). Adverse effects information were also presented through the website, alongside an explanation of their providence. All patients saw a clinician in a follow-up appointment as part of their clinical pathway soon after completing the questionnaire, and had access to a specialist nurse at any point, as per their local SOC practice.

As trial recruitment took place both prior to, and after, the public launch of the Predict *Prostate* tool, an additional question was added to the questionnaire via an amendment. This questioned whether the patient had prior exposure to the tool.

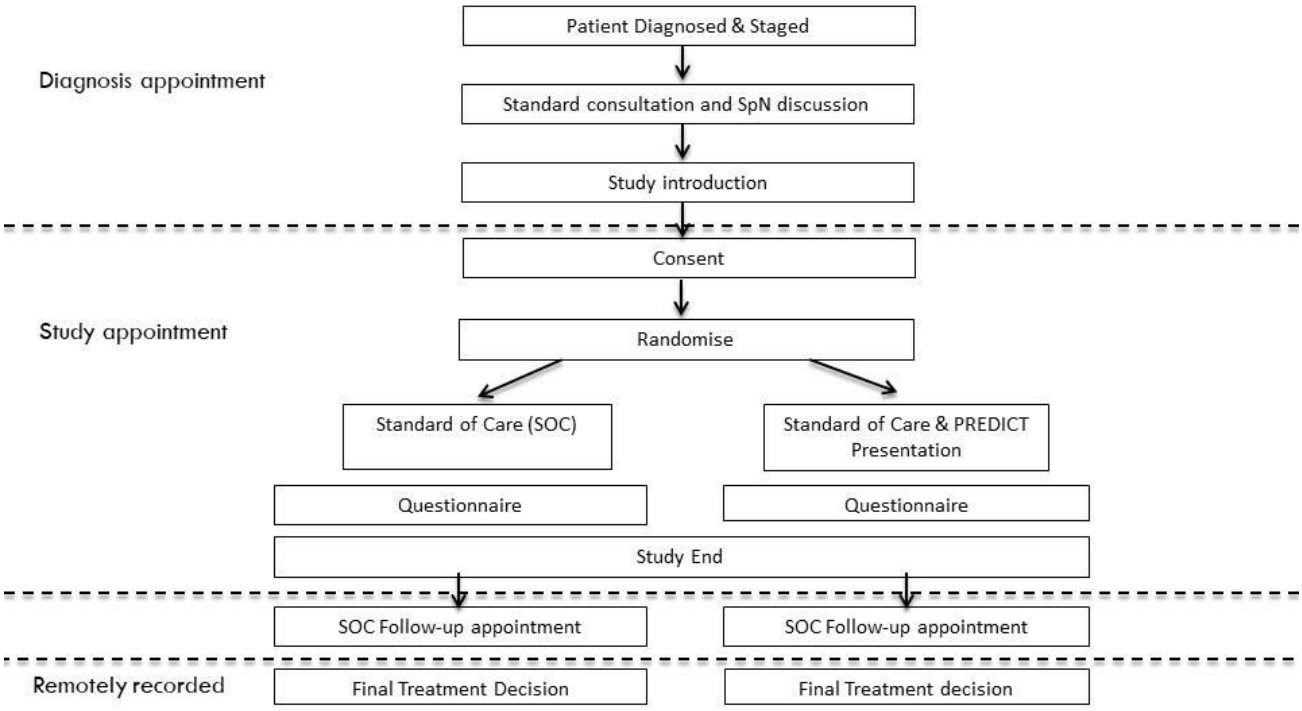


Figure 5.1 Patient study flow chart

5.2.2 Study eligibility and recruitment

Eligible subjects were identified from prostate diagnostic clinics and multi-disciplinary team meetings (MDTs). Patients were identified by the PI, the patient's responsible urology consultant or another member of the patient's existing clinical care team. There were no posters, adverts, websites or other active recruitment techniques. No payments were made to participants of the study. Participation did not routinely require any additional travel, visits or diversion from the clinical pathway.

Inclusion criteria • Men newly diagnosed with primary non-metastatic PCa. • Men for whom either active surveillance or radical treatment (prostatectomy +/- radiotherapy) are felt to be appropriate by the diagnosing clinician. • Age 35-80 years • Able to understand and provide informed consent
Exclusion criteria • Known to have a condition, which affects their ability to see, read or understand the decision aid • Any other condition, which in the opinion of the investigator makes the subject unsuitable for study participation. • Unable to comprehend English. (Predict *Prostate* was only available in English at the time of the trial)

Table 5.1 Study eligibility criteria

5.2.3 Data collection and assessment measures

Case report forms (CRF) were completed by a researcher for all study participants at study entry. Questionnaires were completed by all study participants on the day of the study appointment. Copies of these questionnaires, which were designed using the input of a patient and public involvement group are included in the appendix.

Impact of the decision aid may depend upon both patient and tumour characteristics as these may affect patient understanding, and perceptions about disease management. Therefore, data were collected on patient demographic and tumour details. Details of tumour characteristics were entered using details from the hospital electronic record systems, where possible. The importance of various factors in decision-making were also assessed such as survival, bowel function, urinary function and burden of treatment itself. Methodology for this purpose has been published previously (123).The scoring systems used within the questionnaire were validated scales that have been used widely in clinical research, namely the Decisional Conflict Scale (DCS) (130), Decision Making Preference Questionnaire (DMPQ) (134) and the State-Trait Anxiety Inventory (STAI-Y) (131). Questions explored perceptions around cancer-specific and overall mortality. Patients in the intervention (Predict *Prostate*) arm completed additional questions on the model, including how the estimates compared to their expectations, and were given the option to provide written feedback. The patient's final treatment decision was recorded from the medical notes; ethical approval allowed collection of this data-point up to 12 months from the study appointment. Any one who by that point had not yet decided upon an alternative treatment was considered to have chosen conservative management.

5.2.4 Statistical analysis

A priori information of impact on DCS and an accepted size of impact deemed clinically relevant was not available. Mirroring outcomes from a study using changes in actual treatment choices, we estimated that a reduction in DCS of 20% would be a clinically meaningful outcome (135). The minimum required sample size (SD 20, α 0.05, β 0.80) was therefore 32. To capture potential lower impact results, we expanded our target sample size to 150, which would detect DCS reductions of 10%. The impact of the intervention was tested within an intention-to-treat analysis. DCS, DCS subscales, and STAI scores were compared between groups using independent samples t-test, as pre-specified in the protocol. Data analyses were performed in

Stata™ 14 (StataCorp, Texas, US). Participants' feedback and comments were collated and summarised. Analyses were performed separately for the whole cohort, and the whole cohort excluding those men who reported prior exposure to Predict *Prostate*.

5.3 Results

5.3.1 Patient characteristics

Recruitment began at Cambridge University Hospitals NHS Foundation Trust, as a single-site study in November 2018. 7 further sites joined the study after HRA approval in March 2019. In total, 156 patients were included from 8 UK centres, representing a mixture of larger academic centres and smaller district general hospitals. 11/156 (7%) patients had exposure to the Predict *Prostate* tool prior to partaking in the study, (intervention group n=6; control group n=5) and were excluded from this analysis, leaving a final analytical cohort of 145 (Table 5.2). 75 patients were randomised into the Predict *Prostate* arm of the study and 70 to the SOC arm. Distribution of characteristics across the two arms were similar; median age was 67 years and PSA 6.8ng/L (Table 5.3). Other patient and tumour characteristics were predominantly consistent with low or intermediate-risk disease, according to NICE or EAU criteria (Table 5.3)(29). More than 99% of patients were diagnosed following a pre-biopsy MRI and the majority had both targeted and systematic prostate biopsies. Transperineal biopsies were performed in 56% of cases. Additional educational and social characteristics of the patients are recorded in Table 5.4, with no differences noted between the groups.

Centre	Completed study
City Hospitals Sunderland, Sunderland	4
Cambridge University Hospitals (CUH), Cambridge	37
Dartford and Gravesham, Dartford	36
North Bristol, Bristol	35
Queen Elizabeth Hospital, Kings Lynn	4
Royal Liverpool and Broadgreen, Liverpool	4
Surrey and Sussex Healthcare, Redhill	18
Weston General Hospital, Weston-Super-Mare	7
Total	**145**

Table 5.2 Recruiting centres and number of men completing the trial at each site

		Predict *Prostate* arm (n=81)		SOC arm (n= 75)	
Variable		**Median**	**IQR**	**Median**	**IQR**
Age		67	61-73	67	61-71
PSA		6.7	5.1-8.6	7.1	5.0-9.7
Biopsy cores taken		16	12-24	14	12-24
Biopsy cores positive		4	2-5	4	2-6
		n	**%**	**n**	**%**
Grade Group	1	32	43	26	37
	2	35	47	36	51
	3	6	8.0	8	11
	4	2	2.7	0	0
cT stage	cT1	24	32	19	28
	cT2	47	63	45	65
	cT3	4	5.3	5	7.3
Risk Category	Low	24	32	25	36
	Int	46	61	42	60
	High	5	6.7	3	4.3
Biopsy route	TP	41	57	37	54
	TR	31	43	31	46
Biopsy approach	T&S	32	43	41	59
	S only	33	45	24	35
	T only	9	12	4	5.7
Pre-biopsy MRI	Yes	74	99	69	100
	No	1	1.3	0	0

Table 5.3 Patient and tumour characteristics within the intervention and SOC arm, and overall. Comparison is made between study arms. SOC = standard of care PSA = Prostate-Specific Antigen cT stage = clinical tumour stage TP = Transperineal TR = Transrectal T&S = Targeted and systematic T only = Targeted only S only = Systematic only

		Predict N (%)	SOC N (%)
Work status	Employed	16 (22)	16 (23)
	Not in paid employment	1 (1.3)	2 (2.9)
	Retired	46 (62)	39 (56)
	Self-employed	11 (15)	12 (17)
	Not recorded	1 (1.3)	1 (1.4)
Highest Educational level	School	21 (28)	22 (31)
	College	28 (37)	21 (30)
	University	8 (11)	12 (17)
	Post-graduate	10 (13)	10 (14)
	Not recorded	8 (11)	5(7.1)
Relationship status	Living with partner	62 (83)	53 (75.7)
	Single	4 (5.3)	14 (20)
	Widower	2 (2.7)	2 (2.9)
	Not recorded	7 (9.3)	1 (1.4)
Family status	1 or more children	58 (77)	56 (80)
	No children	11 (14.7)	13 (19)
	Not recorded	6 (8.0)	1 (1.4)

Table 5.4 Social characteristics of trial participants in each randomisation group. SOC = Standard of care.

5.3.2 Decision-making preferences

Most patients wanted decision-making to be a collaborative process, with 56% preferring to 'make treatment decisions with their doctor' and 37% preferring to 'make decisions after hearing their doctors' opinion' (Table 5.5). Dying from PCa was reported to be either an 'important' or 'very important' factor when decision-making by 83% of men. Incontinence (76%) and bowel problems (77%) were also considered important; fewer felt that sexual dysfunction (49%) or the burden of treatment itself (56%) were important (Table 5.6).

DMPQ Statement	Predict n (%)	SOC n (%)	Overall n (%)
I prefer to make treatment decisions on my own	2 (2.7)	3 (4.3)	5 (3.4)
I prefer to make treatment decisions after hearing my doctor's opinion	29 (39)	25 (36)	54 (37)
I prefer to make treatment decisions with my doctor	40 (54)	41 (59)	81 (56)
I prefer my doctor to make treatment decisions after talking to me	3 (4.0)	1 (1.4)	4 (2.8)
I prefer my doctor to make treatment decisions on his/her own	0	0 (0)	0 (0)
Not recorded	1 (1.3)	0 (0)	1 (0.7)

Table 5.5 Responses to the decision-making preference questionnaire (DMPQ). Choose statement the participant most agrees with. SOC = Standard of care

	Not important	*Slightly important*	*Mode-rately important*	*Important*	*Very important*	**Important OR Very Important**
	n	n	n	n	n	**%**
Chance of dying from prostate cancer	1	10	13	27	92	**83**
Risk of bowel problems	2	8	23	67	44	**77**
Risk of urinary problems	2	7	26	72	37	**76**
Thought of living with untreated cancer	7	22	26	32	57	**62**
Burden of treatment itself	10	20	34	56	24	**56**
Risk of sexual problems	25	12	36	43	28	**49**

Table 5.6 Reported importance of factors in participants' decision-making around treatment. Scored on a 5-point scale using the terms at the heading of each column. The final column combines 'important' and 'very important'.

5.3.3 Impact of Predict *Prostate* on survival perceptions

Patient perceptions of 15-year PCSM, non-PCa mortality (NPCM) with conservative management, and survival benefit from radical treatment were all considerably lower among men who had seen the Predict tool (Table 5.7). This was most striking for PCSM where patient-perceived 15-year risk of mortality was 43.1% among men in the control group, and 20.1% in the PREDICT group (p<0.0001). This was despite there being no differences between the two groups in terms of prognosis, as demonstrated by mean Predict *Prostate* estimates (Table 5.7). Although the patient-perceived PCSM and survival benefit from treatment were lower among those in the Predict group, they continued to be much higher than Predict *Prostate* estimates, whereas patients' perceptions of NPCM were similar to Predict *Prostate* estimates.

Men in the Predict *Prostate* arm also reported that the mortality estimates differed from their expectations, especially for PCSM where 57% of men reported the estimates were lower than they expected. Only 7% reported the Predict estimates for PCSM were higher than they expected. Most men (73%) felt that the NPCM estimates were similar to their expectations (Figure 5.2).

	SOC % Mean (SD)	**Predict** % Mean (SD)	p	Mean difference (95% CI)
Chance of dying from PCa over 15 years without treatment				
Patient perception	43.1 (28.0)	20.1 (19.8)	<0.0001	
Predict estimates	7.96 (4.7)	7.11 (3.1)	0.197	
Difference	35.2 (27.7)	13.0 (19.0)	<0.001	22.2 (14.5 to 28.0)
Chance of dying from other (non-PCa) causes over 15 years				
Patient perception	49.9 (23.2)	33.7 (26.3)	0.0001	
Predict estimates	33.9 (20.1)	35.2 (22.0)	0.7	
Difference	16.1 (25.6)	-1.52 (27.2)	<0.001	17.6 (8.89 to 26.3)
Extra men alive following radical treatment (vs CM) over 15 years				
Patient perception	52.9 (31.4)	34.1 (33.3)	0.0009	
Predict estimates	3.77 (2.0)	3.44 (1.4)	0.25	
Difference	49.2 (31.3)	60.6 (33.1)	<0.001	18.5 (7.94 to 29.1)

Table 5.7 Comparison of perceived 15-year Prostate cancer (PCa) mortality, non-PCa mortality, and survival benefit from radical treatment for men in the standard of care (SOC) group and those who saw the Predict Prostate tool. Mean Predict Prostate estimates are also recorded and compared between each randomisation group. P values relate to the comparison using independent group t-test.

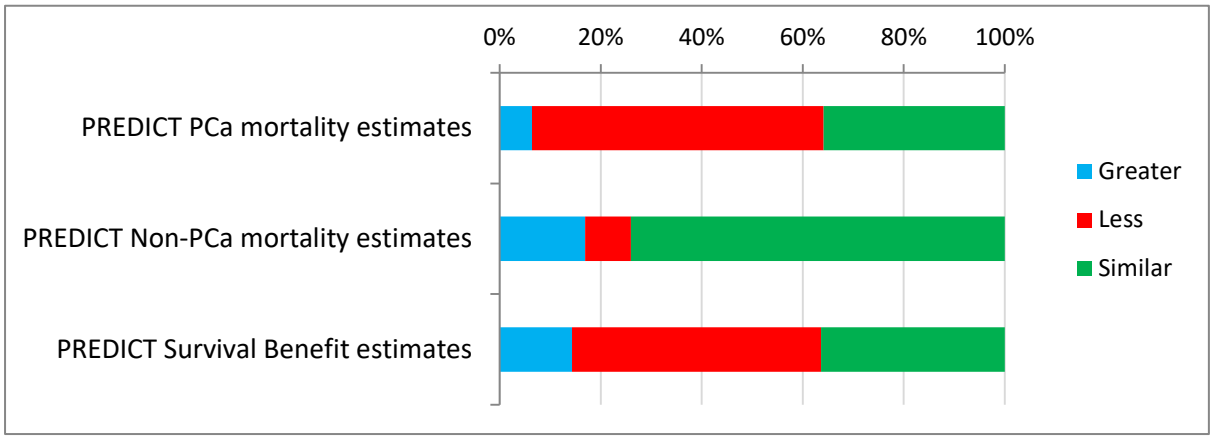


Figure 5.2 Participant-reported comparison of PREDICT estimates to their perceptions. Assessed only among the group shown the PREDICT model (n=75)

5.3.4 Impact of Predict *Prostate* on decision-making

Mean composite decisional conflict scores were 21.7 and 16.1 for the SOC and Predict groups respectively, representing 26% lower overall decisional conflict score values among those who saw the Predict *Prostate* tool (p=0.03) (Figure 5.3). This improvement was observed across nearly all of the DCS subscales including the 'uncertainty' and 'values clarity' subscales (Table 5.8). The proportion of men with an overall DCS below 25 was 73% in the Predict group and 55% in the SOC group. There were no significant differences between either group in terms of trait (p=0.6) or state (p=0.19) of anxiety (Table 5.9).

Measure	SOC (n=75) Mean (SD)	Predict (n=81) Mean (SD)	P value	Mean Difference (95%CI)
DCS Informed Subscale	16.4 (14.3)	13.3 (12.1)	0.16	3.14 (-1.23 to 7.50)
DCS Values Clarity Subscale	21.3 (16.1)	14.7 (15.0)	0.013	6.53 (1.36 to 20.5)
DCS Support Subscale	15.7 (16.7)	10.7 (12.5)	0.046	4.97 (0.09 to 9.9)
DCS Uncertainty Subscale	32.6 (23.0)	21.1 (23.0)	0.029	8.49 (0.86 to 16.1)
DCS Effective Decision Subscale	23.5 (18.4)	17.7 (18.6)	0.067	5.77 (-0.41 to 12.0)
Decisional Conflict Scale Overall	**21.7 (15.3)**	**16.1 (14.3)**	**0.027**	**5.51 (0.64 to 10.4)**

Table 5.8 Decisional conflict scale (DCS) and pre-defined subscale results for the control and Predict study arms. p values relate to the comparison using independent group t-test.

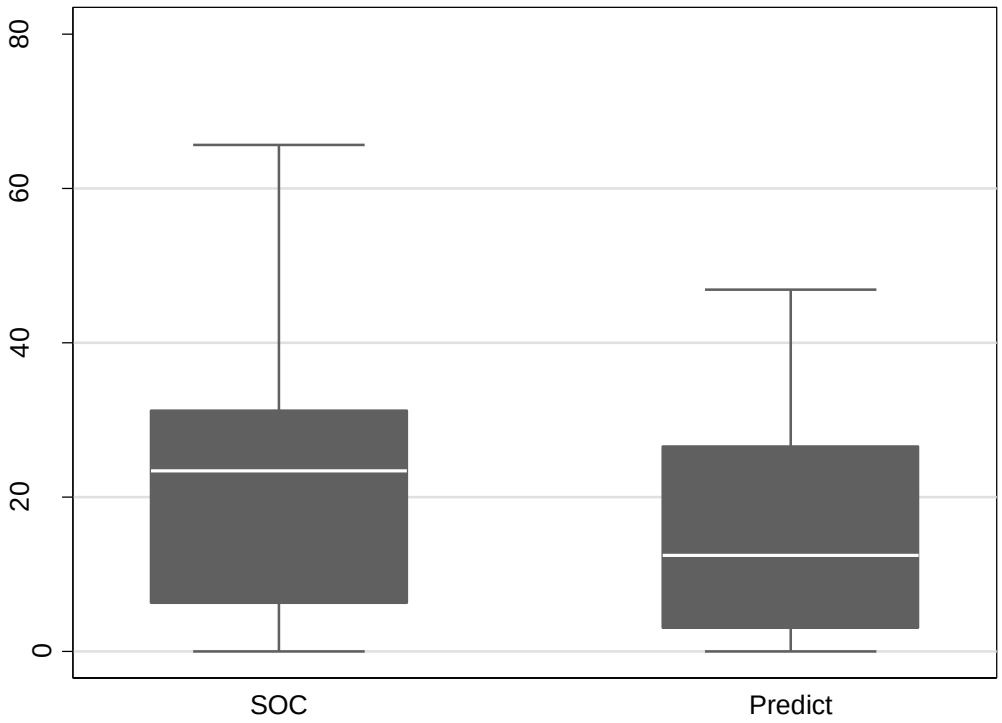


Figure 5.3 Comparison of mean overall decisional conflict scale results between the standard of care (SOC) group and Predict Prostate group (Predict). p=0.01

Measure	n	SOC (n=70) Mean (95% CI)	PREDICT (n=74) Mean (95% CI)	P value	Mean Difference (95%CI)
STAI Y1 Score (***State*** of anxiety)	144	37.7 (34.9 - 40.4)	35.2 (32.6 - 37.7)	0.19	-1.23 to 6.25
STAI Y2 score (**Trait** of anxiety)	144	34.0 (31.6 - 36.3)	33.1 (30.7 - 35.6)	0.6	-2.5 to 4.2

Table 5.9 Comparison of total state trait anxiety inventory (STAI) scores for the control group and PREDICT group. Accepted values for: low (20-37), medium (38-44) and high (45-80). SOC = Standard of care

5.3.5 Impact of Predict Prostate on treatment decisions

When asked whether seeing the Predict model would make them more or less likely to choose radical treatment, 1 in 3 men (36%) reported it would make them less likely to choose radical treatment. 37% felt it would not change their decision, and only 15% felt Predict would make them more likely to choose radical treatment (Table 5.12). Overall, there were no differences in terms of reported treatment preferences (Table 5.10) or the final treatment received between the two groups (Table 5.11). 61% of men in the SOC group opted for initial surveillance, and 59% in the Predict group. When sub-stratified by risk criteria, most men with low-risk and high-risk disease opted for AS and radical treatment respectively, irrespective of randomisation group (Table 5.11). In the Predict group, 2/24 men with low-risk disease opted for surgery, compared to 0/25 in the SOC group. Looking specifically at men with favourable intermediate-risk disease (as per NCCN criteria) 9/25 men opted for surveillance in the SOC group, compared to 12/27 in the Predict group. Combining men with unfavourable-intermediate and high-risk 9/20 in the SOC arm, and 10/24 in the Predict arm opted for surveillance respectively. Predict appears to have helped confirm patients' treatment preferences, with over 80% of those who felt Predict made them less likely to want radical treatment opting for AS, and over 90% of those who felt the opposite opting for radical treatment (Table 5.12).

Current treatment preference	Standard of Care NICE risk group				Predict NICE risk group			
	Low	Int	High	Total	Low	Int	High	Total
AS/Conservative	21	17	0	38 (55%)	21	23	1	45 (60%)
Surgery	1	16	2	19 (28%)	1	13	3	17 (23%)
Radiotherapy	1	5	1	7 (10%)	2	3	1	6 (8.0%)
Other	1	1	0	2 (2.9%	0	2	0	2 (2.7%)
No preference	1	2	0	3 (4.3%)	0	5	0	5 (6.7%)
Total	25	41	3		24	46	5	

Table 5.10 Reported treatment preference in each arm of the study, stratified by NICE risk category

	Standard of Care				Predict			
NICE risk group	Low	Int	High	Total	Low	Int	High	Total
AS/Conservative	25	18	0	43 (61%)	22	21	1	44 (59%)
Surgery	0	16	2	18 (26%)	2	16	3	21 (28%)
Radiotherapy	0	7	1	8 (11%)	0	8	1	9 (12%)
Other	0	1	0	1 (1.4%)	0	0	0	1 (1.3%)
Total	25	42	3	70	24	45	5	75

Table 5.11 Final treatment decision in each of the randomisation groups, stratified by National Institute for Health and Care Excellence (NICE) groups. AS = Active surveillance. Int = Intermediate

	Did Predict *Prostate* make you more or less likely to want radical treatment?				
Final Treatment	Less likely	No change	More likely	Unsure	Total
AS/Conservative	22	15	1	6	44
Surgery	2	10	7	2	21
Radiotherapy	2	3	3	1	9
Other	1	0	0	0	1
Total	27 (36%)	28 (37%)	11 (15%)	9 (12%)	75

Table 5.12 Cross tabulation of whether Predict *Prostate* led to patients being more or less likely to want radical treatment, and their final treatment decision.

5.3.6 Patient feedback

The vast majority of those in the Predict Prostate arm felt the tool was useful (92%) and said they would recommend it to other men in their position (95%) (Table 5.13). Free text responses and written feedback were very positive. Individual, anonymised, comments are

recorded in Table 5.14. Repeated themes were that the tool was 'useful', 'informative' and 'helpful'. In terms of negative feedback, one participant suggested 'predict' might be a misleading name, and another suggested involving the partner more in decision-making.

	Yes	No	Unsure
Did you find PREDICT useful?	69 (92%)	0	6 (8%)
Would you recommend PREDICT?	71 (95%)	0	4 (5%)

Table 5.13 Responses from participants in the Predict *Prostate* group

Excellent & helpful
Excellent information. Very helpful
Good information given and will help me make the correct decision for me
Good tool
Great tool - great user interface - well designed and presented
Helpful
Helpful in understanding the numbers of people affected. Presentation was excellent and informative.
I found the tool very informative and with good output options (visuals and text)
I have found the session / using the tool very helpful
I think these surveys are very important and should be done all the time
It helps to make a decision
It seems good to me
It was interesting and informative
It was very informative and gave me self assurance that I was making the correct decision on treatment
Keep things as simple as possible
PREDICT my impression was it might be a tool to predict my only option for treatment - maybe "PREDICT" prostate is not the right wording?
Received a good explanation as to the aims & objectives of the programme
Thank you
The dots image was very good for understanding the data
This is a very useful and enlightening tool
This tool will be helpful to others who have an inquisitive mind. It was helpful to see the diagrams.
Very clear website/model. Very helpful
Very good information provider
Very helpful
Very helpful
Very helpful
Very informative
Very informative & has put me at ease
Very useful session which did help confirm and alleviate my concerns
Very useful tool & questionnaire. Question 2 would be more comprehensive if it recognises the role of spouse / partner in decision making

Table 5.14 Free text responses of participants in the *Predict* arm. Response to the question 'any other comments or feedback?'

5.4 Discussion

5.4.1 Summary of findings

The study outlined in this chapter suggests that the Predict *Prostate* risk communication tool reduces decisional conflict when used in a clinical decision-making situation. The tool shifts patient perceptions around survival and treatment-benefit to be more accurate; and is popular with PCa patients. This randomised trial provides level 1 evidence with regards to the impact of the model around treatment decision-making and demonstrates that use of the model can be integrated into contemporary routine clinical practice without increasing patient anxiety.

5.4.2 Interpretation of findings

Most existing literature has explored formal 'decision aids' rather than risk-communication tools such as Predict *Prostate*. Although impact studies are an important part of model-development, very few are performed on prognostic models, and fewer still have explored decision-making in PCa (50, 136). Indeed, we are unaware of any previous studies investigating using such tools and exploring impact on patients with non-metastatic PCa. A well-conducted systematic review of decision aids for localised PCa, published in 2015, identified only 14 RCTs, none of which related to individualised or prognostic tools. The review concluded that 'scant evidence at high risk of bias' existed with regards to their benefit (137). The lack of RCTs of personalised models informing the decision between surveillance and radical treatment is presumably a result of an absence of these underlying nomograms until very recently. This patient impact study sought to address these inadequacies in the existing literature. Moons *et al* stated that the assumption that accurate outcome estimates lead to improved patient decision-making requires testing, with comparisons made to standard care (67). This study sought to embed the tool into clinical practice using standard care as the control.

Our study confirms previous findings about PCa patients' decision-making preferences and the importance they place on various factors (123). Survival was reported to be the most important factor, perhaps providing further justification for a tool such as Predict *Prostate* - built primarily around long-term survival. Sexual impact and treatment convenience were deemed less important (123).

Our study showed that an individualised prognostic model can reduce decisional conflict by about 25%, and leads to similar improvements in terms of making an effective decision and clarifying values. It is reasonable to postulate that this will have positive sequelae in terms of engagement in shared decision-making and adherence to treatment regimes. Indeed, work with decision aids has shown this effect, with a large Cochrane review concluding that patients exposed to decision aids generally felt more knowledgeable, better informed and played a more active role in shared decision-making (122). As a result of feeling better-informed and engaged, more careful decisions may be made, which according to the Decision Justification Theory may reduce decisional regret – a common phenomenon in PCa patients (18, 138). Conversely, we recognise that decisional conflict may be a problematic endpoint and poor surrogate for good decision-making or model efficacy. In part because some conflict may be a positive feature to encourage engagement in the decision-making process, and because it is a time-sensitive measure (139, 140). Some experts argue that how a patient feels about a decision, as assessed by the DCS, is an irrelevant outcome. Rather, that effects of a tool on disease-specific health outcomes and treatment adherence would be more relevant outcomes(141). Furthermore, some have argued, that a good decision-making process actually should increase decisional conflict, and that an absence of decisional conflict may be associated with bad decision-making (139). They suggest in the PCa setting, this may present as a patient with very low risk PCa who is not conflicted and insistent upon radical surgery even though it may be a poor decision for that patient. Looking at this particular sub-cohort in our data, only 4 of the 52 men with low risk disease opted for radical treatment, with the numbers similarly low in both randomisation groups. These valid inadequacies of DCS, should however be weighed against the practical difficulties of assessing longer term outcomes such as treatment adherence, decisional regret. Also, the DCS scale has been very widely used to assess decision support interventions, especially within the prostate cancer field and provides a standardised tool for comparisons between cohorts and practices (142, 143). Decisional conflict in our study was higher than reported in a similar American cohort where mean DCS was 9.9 and 10.9 at 1 month following diagnosis, compared to 21.5 and 15.9 in our control and intervention groups respectively (144). Explanations for this difference may include patient characteristics, structural differences between the two nation's healthcare systems, and

possibly the higher number of consultations reported within the first month in that study (144).

Predict *Prostate* was also seen to reduce decisional uncertainty and there was no difference in anxiety between the groups, with a trend towards lower 'state' of anxiety among men in the Predict *Prostate* group. This finding should allay the concerns of some healthcare professionals that using models like these might increase uncertainty or anxiety among patients (145, 146).

We demonstrate that Predict *Prostate* also shifted perceptions around mortality between the two randomisation groups. Individual patient-reported estimates of mortality among those in the control group were incredibly high, with a mean expectation that 43/100 of them would die from PCa within 15 years, and that 53/100 extra men would survive with radical treatment. This is incongruous with RCT data from similar cohorts, such as the Pivot study where only 11.4% of men assigned to observational treatment died from prostate cancer over a median of 12.7 years, or the SPCG-4 trial where only 31.3% died from PCa after 23 years median follow-up (147, 148). Patients exposed to the Predict *Prostate* tool were still likely to have unrealistically high expectations of treatment benefit and disease lethality but perceptions of prognosis shifted significantly downwards towards more realistic or accurate values (Table 5.7). In Chapter 4 we demonstrated very similar findings among healthcare professionals in the PCa field, who consistently overestimated PCSM and survival benefits from treatment before using the tool, and in whom the likelihood of recommending radical treatment was often lower following exposure to Predict *Prostate* estimates (108). Again, this finding is in-keeping with conclusions from the Cochrane review which concluded decision-aids 'probably' led to more accurate risk perceptions amongst clinicians (122). With regards to survival estimates, we recognise Predict *Prostate* itself is not infallible, however, as per Chapters 2 and 3 the tool has been externally validated in multiple cohorts and its calibration has been demonstrated to be accurate and superior to other available tools (80, 101). We also recognise that the questions to patients themselves may have been difficult to understand, particularly with regards to 'extra' men being alive at 15 years with radical treatment compared to no treatment. Patients' understanding, or health literacy more broadly, were also not assessed as part of this study.

The model appears to have face validity for patients, especially for NPCM where most reported the model estimates were similar to what they expected. More than a third of men in the Predict *Prostate* arm reported the tool made them less likely to choose radical treatment - presumably, due to the shift in perceptions on disease lethality. Other results also suggested the tool may help to solidify treatment preferences with the majority of those who felt the Predict tool made them more likely to choose radical treatment doing so, and vice versa. Of note, we did not demonstrate any clear differences in the final treatment decisions made by the two groups but this study was not designed, and was underpowered, to answer this question which would warrant a larger trial. Sample size calculations to this effect suggested a number of participants in excess of 600, which was not considered feasible during the timeframes of this project.

Within the intervention group, no concerns were raised over usability of the tool, despite using a very diverse patient cohort by way of social characteristics. Open box feedback was overwhelmingly positive. Among those patients randomised to the Predict *Prostate* arm of the study, the model received positive feedback with over 90% reporting they found it to be useful, and that they would recommend it to others. It was not possible to assess whether particular patient sub-groups gained more from the model, due to the universally positive feedback.

5.4.3 Strengths and limitations

Particular strengths of this study include the integration of this model within a contemporary PCa pathway, utilising up-to-date MRI and diagnostics. The model was tested within a randomised sample including a broad range of patients from multiple centres and disparate backgrounds representative of current UK practice. The study allowed comparison with standard of care and assessed usability and the outcome measures used were validated tools used widely in the medical literature.

We also recognise the potential limitations of the study, including that patients and investigators could not be blinded to their randomisation group. Indeed the randomisation method itself, using sealed envelopes, may have increased the risk of bias or trial contamination, and other superior methods of randomisation could have been used. In this trial Predict Prostate was presented to patients in a delayed trial specific appointment, separate to their being informed about the diagnosis. This may not be the setting in which

Predict Prostate is most commonly used as we anticipate it to be presented alongside counselling around a new diagnosis. This delay also may have meant that men had already researched and decided upon the treatment options prior to seeing Predict *Prostate*. There was also a clear risk of contamination within the trial as patients in the SOC arm may have subsequently accessed the online tool. Additionally, we recognise that SOC practice was not standardised between sites; however this is representative of real-world practice, and randomisation within each site was assured by block randomisation in small groups. These factors may therefore partly explain why we did not see actual differences in final treatment decisions between the groups, despite a third of men in the intervention arm saying they felt less likely to have radical treatment after seeing the tool. Assessment outcomes of long-term survival or decisional regret, were also not measured but would be a useful comparison assessment in future studies. Whether the findings can be generalised beyond the UK healthcare setting is unclear, although the tool is accessed globally. Inclusion was also limited to patients able to read and write in English which may bias the results, and the tool remains untested in patients with reduced literacy. The overall trial size was small, albeit the a priori sample size was exceeded, and the results should be interpreted with this in mind. Also, the use of mean rather than median as the summary statistic could be debated, although previous studies using decisional conflict scale have done similarly, and informed the sample size calculations in this study.

We also recognise that a small proportion of patients (7.1%) had at least one high-risk feature which would not ordinarily be considered for surveillance strategies, however our eligibility criteria allowed for inclusion of men deemed suitable for surveillance or radical treatment by their diagnosing clinician, rather than by guideline-criteria alone. Finally, it should be appreciated that Predict *Prostate* is not a standalone tool, and it specifically focuses upon long-term survival, although some adverse effect information is also presented. Other tools may provide more detailed information about the benefits and harms of treatment options or help to elicit values to inform a patient's decision.

Future work could focus upon the optimal timing for delivery of the tool, its long term impact upon treatment practices, and its potential value among men within other healthcare settings.

5.5 Conclusion

In this chapter the Predict *Prostate* risk communication tool has been demonstrated to reduce decisional conflict and shift perceptions around prognosis without increasing anxiety and whilst being popular with most PCa patients. Impact upon final treatment decision-making would require further exploration in larger trials. This work, alongside the pre-existing rigorous validation of the model should encourage health care professionals and patients that the model can be used within modern practice and may help inform what can be a complex decision-making process.

6 Thesis summary and conclusions

6.1 Restatement of aims

A thorough systematic review established that very few prognostic tools are available and that currently-used tools are inadequate for presenting individualised information to patients, based upon long-term survival. In response to this finding the aims of this project were to use a contemporary database of UK men with non-metastatic prostate cancer to develop an individualised prognostic algorithm that estimates overall and prostate cancer-specific survival, and the impact of different treatment modalities upon these outcomes. Thereafter, the aim was to externally validate the model and develop it in to a web-based tool for real-time clinical decision making. Finally the aim was to clinically test the tool among both clinicians and patients to assess its value and potential clinical impact.

6.2 Summary of findings

The majority of PCa diagnosed in the UK is non-metastatic, where decision dilemmas can be most acute between radical therapies with high morbidity, and conservative management which may allow disease progression. Prognostic models should help inform this decision, but it was demonstrated that very few prognostic models exist. Fewer still are used in clinical practice, and available models suffer from using broad heterogeneous groups, short follow up, and inadequate validation or usability.

To address this unmet need a novel individualised multi-variable prognostic model to estimate 10- and 15-year survival outcomes was developed, called Predict *Prostate*. Novelties of the model included its construction from a primary diagnostic 'real-world' cohort with long-term survival data linked to national death reporting, the use of fractional polynomials to maximise prognostic information from continuous variables, adjustment for competing risks of cancer-specific and non-cancer mortality, and inclusion of a treatment variable to provide estimates of treatment-impact upon survival.

Model accuracy and generalisability was demonstrated on internal validation within a UK cohort, and external validations in a Singaporean cohort, and a large Swedish cohort of over 69,000 men. Discrimination of the model was found to be superior to three models currently used in clinical practice, with concordance indices in excess of 0.80 for cancer-

specific mortality, and good calibration demonstrated across cohorts, and within treatment sub-groups. In collaboration with colleagues, the prognostic model was translated into a web-based risk-communication tool (www.prostate.predict.nhs.uk).

Clinical impact of Predict *Prostate* was evaluated among both clinicians in a hypothetical virtual context and among men newly diagnosed with prostate cancer, within their clinical pathway. Both these evaluations demonstrated unrealistic perceptions around cancer-lethality, and potential treatment benefit derived from radical therapies. Testing also demonstrated that seeing Predict *Prostate* estimates reduced the likelihood of a clinician recommending radical treatment in some scenarios, and that among patients the model significantly shifted these survival perceptions towards more realistic values. Impact testing among patients also demonstrated that use of the tool was associated with significantly less decisional-conflict and uncertainty, with no negative impact upon anxiety. Clinical application of the tool in the trial setting found that its incorporation into clinical practice was feasible, and very popular with patients. Feedback on the tool from both clinicians and patients was demonstrated to be positive.

6.3 Project updates and future priorities

The Predict *Prostate* web-tool has remained active since its launch in March 2019 alongside publication of the model development study (75, 85). The site has hosted over 32,000 sessions from 133 different countries globally (Figure 6.1). An introductory video to the tool is now available in Hindi, Arabic, Cantonese, Mandarin and Spanish; and translations of the site are being worked upon. Further minor updates have been made to the web-interface over time, including updates on the associated publication history. An additional toggle has added more clarity on the potential application of the tool among black men. BRCA gene variant status was also integrated into the model using independent data, as an optional parameter. This integration was in response to questions about the model being unable to account for family history. It demonstrates the ability for the tool to be updated and evolve over time. Indeed, further work is ongoing exploring refinements to the non PCa mortality part of the algorithm, in collaboration with experts from the Veterans Affairs Health Administration in the US. Albeit, these findings will be interpreted in the knowledge that Veteran Affairs health administration cohorts are likely to be very different from our original UK cohort and men seen in current UK practice.

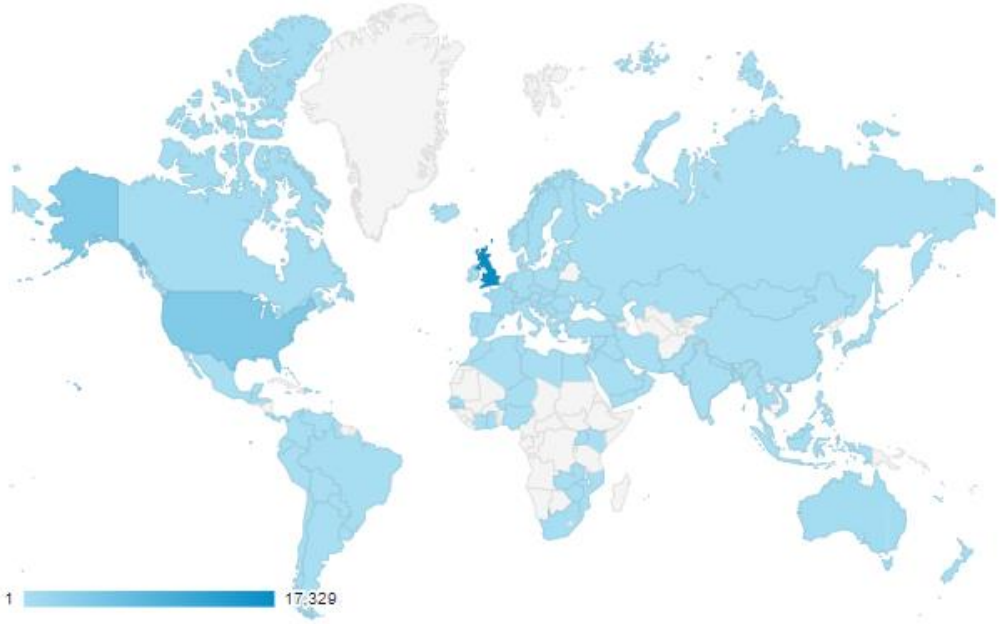


Figure 6.1 Countries from which Predict Prostate has been accessed as of February 2021. Darker colours relate to countries with the higher number of sessions. (Image courtesy of Google Analytics)

Subsequent to the work outlined in this thesis, a further large external validation was performed within data from the American Surveillance, Epidemiology and End Results (SEER) programme. This analysis, led by colleagues from the Cambridge Centre for Artificial Intelligence in Medicine, evaluated a novel machine learning algorithm to predict cancer-mortality, alongside comparative assessments of the Predict *Prostate* tool as well as other more established models including the MSKCC nomogram and EAU risk criteria (100). In a cohort of 171,942 patients, the c-index for Predict Prostate was 0.82 (95%CI:0.81-0.83), comparable to the machine-learning method (0.83 95%CI:0.82-0.84) and superior to the MSKCC nomogram (0.79 95%CI:0.78-0.80) and risk stratification criteria assessed. Within this study, decision curve analyses were published including Predict *Prostate* for the first time as demonstrated in Figure 6.2, and comparisons were made to the MSKCC nomogram which had not been hitherto possible (149). These comparisons further demonstrated that calibration of the Predict *Prostate* tool was good and provided a gain in net clinical benefit compared to the MSKCC nomogram (100).

The tool was endorsed by the UK National Institute for Health and Care Excellence (NICE) in May 2019 and is the only such tool CE-marked for use in clinical decision-making in PCa

(102). More locally, we understand the tool is being used in the Oncology department at Cambridge University Hospitals NHS Foundation Trust in order to audit current practice with regards to who is being offered radiotherapy, and for consideration of whether thresholds could be applied around which treatment recommendations are made.

Further extensions to the model are under consideration. Efforts are particularly being made to incorporate MRI information into the tool, if it is shown to be independently prognostic. Discussions are also ongoing as to whether a separate model for high-risk, locally advanced or even metastatic disease could be developed. Given the rapidly developing therapeutic options available in advanced prostate cancer, any such tool may allow useful analysis of potential survival benefits, and inform decision-making here also. Beyond prostate cancer, work has been commenced to investigate the potential for a post-histology kidney cancer model, to inform decisions around surveillance particularly.

Further research priorities in the evaluation of Predict *Prostate* should specifically assess use of the model among men of African descent, in whom PCa outcomes are often worse, and among whom the generalisability of the model has not hitherto been assessed (150). Validation within screened cohorts, or within other healthcare settings should also be sought, although we appreciate that many men in the SEER database may have been detected through PSA-screening (100). Analyses assessing impact of the tool against longer term outcomes should also be evaluated as described in Chapter 5. Finally, we appreciate that model development is an ongoing and dynamic process. Over time, datasets will further-mature, and more robust data will become available, particularly with regard to the impacts of modern surgical and oncological treatments. We anticipate that the Predict *Prostate* model will have to go through an iterative review and redevelopment process going forward.

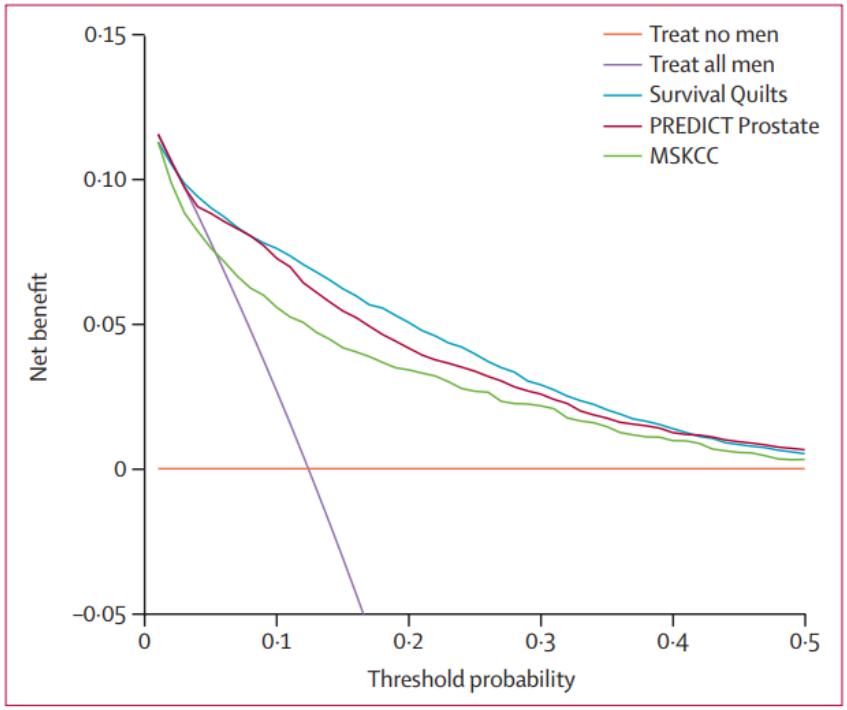


Figure 6.2 Decision curve analysis comparing the clinical net benefit for each prediction model, calculated across a range of risk threshold probabilities. MSKCC=Memorial Sloan Kettering Cancer Center nomogram. Figure used from Lee *et al.* 2021 (100)

6.4 Conclusions

It has been shown that a novel model can be developed which allows for far more individualised and contextualised survival estimates to inform the predominant decision dilemma for men diagnosed with localised prostate cancer, namely between conservative management and radical treatment. The model, Predict *Prostate*, has been demonstrated to be robust and generalisable in a number of external validations. Its development and validation should meet all the AJCC criteria for prognostic model adoption. Furthermore, incorporation of the model into clinical practice has been demonstrated to be feasible. The model was shown to shift perceptions around mortality among both clinicians and patients, reduce decisional conflict among patients, and was popular with both.

The model has received endorsement from the UK National Institute for Health and Care Excellence and has been accessed widely in the UK and overseas. Predict *Prostate* has the potential to shift the paradigm around treatment decision-making in non-metastatic prostate cancer, and will continue to evolve further over time, to hopefully aid prostate cancer patients and their care.

7 References

1. Thurtle D, Rossi SH, Berry B, Pharoah P, Gnanapragasam VJ. Models predicting survival to guide treatment decision-making in newly diagnosed primary non-metastatic prostate cancer: a systematic review. BMJ Open. 2019;9(6):e029149.
2. Cancer Research UK Website. http://www.cancerresearchuk.org/cancer-info/cancerstats/types/prostate/ Accessed November 2019.
3. Bray F, Ferlay J, Soerjomataram I, Siegel RL, Torre LA, Jemal A. Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin. 2018;68(6):394-424.
4. Mistry M, Parkin DM, Ahmad AS, Sasieni P. Cancer incidence in the United Kingdom: projections to the year 2030. Br J Cancer. 2011;105(11):1795-803.
5. NPCA. National Prostate Cancer Audit - Annual Report 2017. available from https://www.npca.org.uk/reports/2017. Accessed August 2018.
6. Greenberg DC, Wright KA, Lophathanon A, Muir KR, Gnanapragasam VJ. Changing presentation of prostate cancer in a UK population--10 year trends in prostate cancer risk profiles in the East of England. Br J Cancer. 2013;109(8):2115-20.
7. Cancer Research UK Website, http://www.cancerresearchuk.org/cancer-info/cancerstats/types/prostate/ Accessed September 2020.
8. Bell KJ, Del Mar C, Wright G, Dickinson J, Glasziou P. Prevalence of incidental prostate cancer: A systematic review of autopsy studies. Int J Cancer. 2015;137(7):1749-57.
9. Lloyd T, Hounsome L, Mehay A, Mee S, Verne J, Cooper A. Lifetime risk of being diagnosed with, or dying from, prostate cancer by major ethnic group in England 2008-2010. BMC Med. 2015;13:171.
10. JLA. James Lind Alliance Priority setting partnerships. Prostate Cancer Top 10:
1. How can overtreatment for prostate cancer be prevented by identifying and excluding the treatment of harmless tumours? Available from https://www.jla.nihr.ac.uk/priority-setting-partnerships/prostate-cancer/top-10-priorities/ Accessed December 2016.
11. Donovan JL, Hamdy FC, Lane JA, Mason M, Metcalfe C, Walsh E, et al. Patient-Reported Outcomes after Monitoring, Surgery, or Radiotherapy for Prostate Cancer. N Engl J Med. 2016;375(15):1425-37.
12. Greenberg DC, Lophatananon A, Wright KA, Muir KR, Gnanapragasam VJ. Trends and outcome from radical therapy for primary non-metastatic prostate cancer in a UK population. PLoS One. 2015;10(3):e0119494.
13. Huland H, Graefen M. Changing Trends in Surgical Management of Prostate Cancer: The End of Overtreatment? Eur Urol. 2015 Aug;68(2):175-8 .
14. Thurtle D, Barrett T, Thankappan-Nair V, Koo B, Warren A, Kastner C, et al. Progression and treatment rates using an active surveillance protocol incorporating image-guided baseline biopsies and multiparametric magnetic resonance imaging monitoring for men with favourable-risk prostate cancer. BJU Int. 2018;122(1):59-65.
15. Wilt TJ, Brawer MK, Jones KM, Barry MJ, Aronson WJ, Fox S, et al. Radical prostatectomy versus observation for localized prostate cancer. N Engl J Med. 2012;367(3):203-13.
16. Hamdy FC, Donovan JL, Lane JA, Mason M, Metcalfe C, Holding P, et al. 10-Year Outcomes after Monitoring, Surgery, or Radiotherapy for Localized Prostate Cancer. N Engl J Med. 2016.

17. Wilding S, Downing A, Selby P, Cross W, Wright P, Watson EK, et al. Decision regret in men living with and beyond nonmetastatic prostate cancer in the United Kingdom: A population-based patient-reported outcome study. Psychooncology. 2020;29(5):886-93.
18. Hoffman RM, Lo M, Clark JA, Albertsen PC, Barry MJ, Goodman M, et al. Treatment Decision Regret Among Long-Term Survivors of Localized Prostate Cancer: Results From the Prostate Cancer Outcomes Study. Journal of Clinical Oncology. 2017;35(20):2306-+.
19. D'Amico AV, Whittington R, Malkowicz SB, Schultz D, Blank K, Broderick GA, et al. Biochemical outcome after radical prostatectomy, external beam radiation therapy, or interstitial radiation therapy for clinically localized prostate cancer. JAMA. 1998;280(11):969-74.
20. Jhaveri FM, Zippe CD, Klein EA, Kupelian PA. Biochemical failure does not predict overall survival after radical prostatectomy for localized prostate cancer: 10-year results. Urology. 1999;54(5):884-90.
21. Huang Y, Isharwal S, Haese A, Chun FK, Makarov DV, Feng Z, et al. Prediction of patient-specific risk and percentile cohort risk of pathological stage outcome using continuous prostate-specific antigen measurement, clinical stage and biopsy Gleason score. BJU Int. 2011;107(10):1562-9.
22. Cooperberg MR, Pasta DJ, Elkin EP, Litwin MS, Latini DM, Du Chane J, et al. The University of California, San Francisco Cancer of the Prostate Risk Assessment score: a straightforward and reliable preoperative predictor of disease recurrence after radical prostatectomy. J Urol. 2005;173(6):1938-42.
23. Stephenson AJ, Scardino PT, Eastham JA, Bianco FJ, Dotan ZA, Fearn PA, et al. Preoperative nomogram predicting the 10-year probability of prostate cancer recurrence after radical prostatectomy. J Natl Cancer Inst. 2006;98(10):715-7.
24. MSKCC. Memorial Sloan Kettering Cancer Centre prediction tools: Prostate Cancer Nomograms. https://www.mskcc.org/nomograms/prostate/pre_op Accessed December 2016.
25. Cooperberg MR, Broering JM, Carroll PR. Risk assessment for prostate cancer metastasis and mortality at the time of diagnosis. J Natl Cancer Inst. 2009;101(12):878-87.
26. Kerkmeijer LGW, Monninkhof EM, van Oort IM, van der Poel HG, de Meerleer G, van Vulpen M. PREDICT: model for prediction of survival in localized prostate cancer. World Journal of Urology. 2016;34(6):789-95.
27. Kutikov A, Cooperberg MR, Paciorek AT, Uzzo RG, Carroll PR, Boorjian SA. Evaluating prostate cancer mortality and competing risks of death in patients with localized prostate cancer using a comprehensive nomogram. Prostate Cancer and Prostatic Diseases. 2012;15(4):374-9.
28. NICE. National Institute for Health and Care Excellence NICE Guidelines [CG175] Prostate cancer: diagnosis and treatment. January 2014.
29. Heidenreich A, Bastian PJ, Bellmunt J, Bolla M, Joniau S, van der Kwast T, et al. EAU guidelines on prostate cancer. part 1: screening, diagnosis, and local treatment with curative intent-update 2013. Eur Urol. 2014;65(1):124-37.
30. Mottet N, Bellmunt J, Bolla M, Briers E, Cumberbatch MG, De Santis M, et al. EAU-ESTRO-SIOG Guidelines on Prostate Cancer. Part 1: Screening, Diagnosis, and Local Treatment with Curative Intent. European Urology. 2017;71(4):618-29.
31. AUA/ASTRO/SUO. CLINICALLY LOCALIZED PROSTATE CANCER: AUA/ASTRO/SUO GUIDELINE 2017.

32. NCCN. National Comprehensive Cancer Network Clinical Practice Guidelines in Oncology: Prostate Cancer. Version 2. 2018 [Available from: https://www.nccn.org/professionals/physician_gls/pdf/prostate.pdf.] Accessed August 2018.
33. Kattan MW, Hess KR, Amin MB, Lu Y, Moons KG, Gershenwald JE, et al. American Joint Committee on Cancer acceptance criteria for inclusion of risk models for individualized prognosis in the practice of precision medicine. CA Cancer J Clin. 2016;66(5):370-4.
34. Wishart GC, Azzato EM, Greenberg DC, Rashbass J, Kearins O, Lawrence G, et al. PREDICT: a new UK prognostic model that predicts survival following surgery for invasive breast cancer. Breast Cancer Res. 2010;12(1):R1.
35. Liberati A, Altman DG, Tetzlaff J, Mulrow C, Gøtzsche PC, Ioannidis JP, et al. The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate health care interventions: explanation and elaboration. Ann Intern Med. 2009;151(4):W65-94.
36. Moons KG, de Groot JA, Bouwmeester W, Vergouwe Y, Mallett S, Altman DG, et al. Critical appraisal and data extraction for systematic reviews of prediction modelling studies: the CHARMS checklist. PLoS Med. 2014;11(10):e1001744.
37. Wong SS, Wilczynski NL, Haynes RB, Ramkissoonsingh R, Team H. Developing optimal search strategies for detecting sound clinical prediction studies in MEDLINE. AMIA Annu Symp Proc. 2003:728-32.
38. Ingui BJ, Rogers MA. Searching for clinical prediction rules in MEDLINE. J Am Med Inform Assoc. 2001;8(4):391-7.
39. Wolff RF, Moons KGM, Riley RD, Whiting PF, Westwood M, Collins GS, et al. PROBAST: A Tool to Assess the Risk of Bias and Applicability of Prediction Model Studies. Ann Intern Med. 2019;170(1):51-8.
40. Moons KGM, Wolff RF, Riley RD, Whiting PF, Westwood M, Collins GS, et al. PROBAST: A Tool to Assess Risk of Bias and Applicability of Prediction Model Studies: Explanation and Elaboration. Ann Intern Med. 2019;170(1):W1-W33.
41. Margel D, Urbach DR, Lipscombe LL, Bell CM, Kulkarni G, Baniel J, et al. Is pathology necessary to predict mortality among men with prostate-cancer? Bmc Medical Informatics and Decision Making. 2014;14:114.
42. Nguyen PL, Chen MH, Catalona WJ, Moul JW, Sun L, D'Amico AV. Predicting prostate cancer mortalityy among men with intermediate to high-risk disease and multiple unfavorable risk factors. International Journal of Radiation Oncology Biology Physics. 2009;73(3):659-64.
43. Feuer EJ, Lee M, Mariotto AB, Cronin KA, Scoppa S, Penson DF, et al. The Cancer Survival Query System: making survival estimates from the Surveillance, Epidemiology, and End Results program more timely and relevant for recently diagnosed patients. Cancer. 2012;118(22):5652-62.
44. Cowen ME, Halasyamani LK, Kattan MW. Predicting life expectancy in men with clinically localized prostate cancer. Journal of Urology. 2006;175(1):99-103.
45. Gnanapragasam VJ, Lophatananon A, Wright KA, Muir KR, Gavin A, Greenberg DC. Improving Clinical Risk Stratification at Diagnosis in Primary Prostate Cancer: A Prognostic Modelling Study. PLoS Med. 2016;13(8):e1002063.
46. Tewari A, Johnson CC, Divine G, Crawford ED, Gamito EJ, Demers R, et al. Long-term survival probability in men with clinically localized prostate cancer: A case-control,

propensity modeling study stratified by race, age, treatment and comorbidities. Journal of Urology. 2004;171(4):1513-9.
47. Howlader N, Mariotto AB, Woloshin S, Schwartz LM. Providing clinicians and patients with actual prognosis: cancer in the context of competing causes of death. J Natl Cancer Inst Monogr. 2014;2014(49):255-64.
48. Feuer EJ, Rabin BA, Zou Z, Wang Z, Xiong X, Ellis JL, et al. The Surveillance, Epidemiology, and End Results Cancer Survival Calculator SEER*CSC: validation in a managed care setting. J Natl Cancer Inst Monogr. 2014;2014(49):265-74.
49. Gnanapragasam VJ, Bratt O, Muir K, Lee LS, Huang HH, Stattin P, et al. The Cambridge Prognostic Groups for improved prediction of disease mortality at diagnosis in primary non-metastatic prostate cancer: a validation study. BMC Med. 2018;16(1):31.
50. Shariat SF, Kattan MW, Vickers AJ, Karakiewicz PI, Scardino PT. Critical review of prostate cancer predictive tools. Future Oncology. 2009;5(10):1555-84.
51. Shariat SF, Karakiewicz PI, Roehrborn CG, Kattan MW. An Updated Catalog of Prostate Cancer Predictive Tools. Cancer. 2008;113(11):3075-99.
52. Green DA, Osterberg EC, Xylinas E, Rink M, Karakiewicz PI, Scherr DS, et al. Predictive tools for prostate cancer staging, treatment response and outcomes. Archivos Espanoles De Urologia. 2012;65(9):787-807.
53. Lughezzani G, Briganti A, Karakiewicz PI, Kattan MW, Montorsi F, Shariat SF, et al. Predictive and prognostic models in radical prostatectomy candidates: a critical analysis of the literature. Eur Urol. 2010;58(5):687-700.
54. Raymond E, O'Callaghan ME, Campbell J, Vincent AD, Beckmann K, Roder D, et al. An appraisal of analytical tools used in predicting clinical outcomes following radiation therapy treatment of men with prostate cancer: a systematic review. Radiation Oncology. 2017;12.
55. Walz J, Gallina A, Bocciardi AM, Ahyal S, Perrotte P, Mc Cormack M, et al. Nomogram predicting 10 year life expectancy after radical prostatectomy or radiation therapy for prostate cancer. Journal of Urology. 2007;177(4):131-2.
56. Albertsen PC, Fryback DG, Storer BE, Kolon TF, Fine J. The impact of co-morbidity on life expectancy among men with localized prostate cancer. Journal of Urology. 1996;156(1):127-32.
57. Fontanella P, Benecchi L, Grasso A, Patel V, Albala D, Abbou C, et al. Decision-making tools in prostate cancer: from risk grouping to nomograms. Minerva Urol Nefrol. 2017;69(6):556-66.
58. Kent M, Vickers AJ. A Systematic Literature Review of Life Expectancy Prediction Tools for Patients with Localized Prostate Cancer. Journal of Urology. 2015;193(6):1938-42.
59. Collins GS, Ogundimu EO, Altman DG. Sample size considerations for the external validation of a multivariable prognostic model: a resampling study. Stat Med. 2016;35(2):214-26.
60. American Joint Committee on Cancer . AJCC Cancer Staging Manual, 8th Edition. 2016. p. 1-7.
61. Kasivisvanathan V, Rannikko AS, Borghi M, Panebianco V, Mynderse LA, Vaarala MH, et al. MRI-Targeted or Standard Biopsy for Prostate-Cancer Diagnosis. N Engl J Med 2018; 378:1767-1777.
62. Berry SD, Ngo L, Samelson EJ, Kiel DP. Competing risk of death: an important consideration in studies of older adults. J Am Geriatr Soc. 2010;58(4):783-7.
63. Grogan J, Gupta R, Mahon KL, Stricker PD, Haynes AM, Delprado W, et al. Predictive value of the 2014 International Society of Urological Pathology grading system for prostate

cancer in patients undergoing radical prostatectomy with long-term follow-up. Bju International. 2017;120(5):651-8.
64. Bostwick DG, Foster CS. Predictive factors in prostate cancer: current concepts from the 1999 College of American Pathologists Conference on Solid Tumor Prognostic Factors and the 1999 World Health Organization Second International Consultation on Prostate Cancer. Semin Urol Oncol. 1999;17(4):222-72.
65. Partin AW, Steinberg GD, Pitcock RV, Wu L, Piantadosi S, Coffey DS, et al. Use of nuclear morphometry, Gleason histologic scoring, clinical stage, and age to predict disease-free survival among patients with prostate cancer. Cancer. 1992;70(1):161-8.
66. Epstein JI, Zelefsky MJ, Sjoberg DD, Nelson JB, Egevad L, Magi-Galluzzi C, et al. A Contemporary Prostate Cancer Grading System: A Validated Alternative to the Gleason Score. Eur Urol. 2016;69(3):428-35.
67. Moons KG, Altman DG, Vergouwe Y, Royston P. Prognosis and prognostic research: application and impact of prognostic models in clinical practice. BMJ. 2009;338:b606.
68. Lorent M, Maalmi H, Tessier P, Supiot S, Dantan E, Foucher Y. Meta-analysis of predictive models to assess the clinical validity and utility for patient-centered medical decision making: application to the CAncer of the Prostate Risk Assessment (CAPRA). BMC Med Inform Decis Mak. 2019;19(1):2.
69. Partin AW, Yoo J, Carter HB, Pearson JD, Chan DW, Epstein JI, et al. The use of prostate specific antigen, clinical stage and Gleason score to predict pathological stage in men with localized prostate cancer. J Urol. 1993;150(1):110-4.
70. Kattan MW, Wheeler TM, Scardino PT. Postoperative nomogram for disease recurrence after radical prostatectomy for prostate cancer. J Clin Oncol. 1999;17(5):1499-507.
71. Falzarano SM, Ferro M, Bollito E, Klein EA, Carrieri G, Magi-Galluzzi C. Novel biomarkers and genomic tests in prostate cancer: a critical analysis. Minerva Urologica E Nefrologica. 2015;67(3):211-31.
72. Herlemann A, Washington SL, Eapen RS, Cooperberg MR. Whom to Treat: Postdiagnostic Risk Assessment with Gleason Score, Risk Models, and Genomic Classifier. Urol Clin North Am. 2017;44(4):547-55.
73. Wishart GC, Bajdik CD, Dicks E, Provenzano E, Schmidt MK, Sherman M, et al. PREDICT Plus: development and validation of a prognostic model for early breast cancer that includes HER2. Br J Cancer. 2012;107(5):800-7.
74. Down SK, Lucas O, Benson JR, Wishart GC. Effect of PREDICT on chemotherapy/trastuzumab recommendations in HER2-positive patients with early-stage breast cancer. Oncol Lett. 2014;8(6):2757-61.
75. Thurtle D, Greenberg D, Huang H, Lee L, Pharoah P, Gnanapragasam V. Individual prognosis at diagnosis in non-metastatic prostate cancer: Development and external validation of the PREDICT P*rostate* multivariable model. PLOS Medicine 2019 Mar, 16(3) e1002758.
76. Collins GS, Reitsma JB, Altman DG, Moons KG. Transparent reporting of a multivariable prediction model for individual prognosis or diagnosis (TRIPOD): the TRIPOD statement. BMJ. 2015;350:g7594.
77. Buzzoni C, Auvinen A, Roobol MJ, Carlsson S, Moss SM, Puliti D, et al. Metastatic Prostate Cancer Incidence and Prostate-specific Antigen Testing: New Insights from the European Randomized Study of Screening for Prostate Cancer. Eur Urol. 2015;68(5):885-90.

78. Reese AC, Sadetsky N, Carroll PR, Cooperberg MR. Inaccuracies in assignment of clinical stage for localized prostate cancer. Cancer. 2011;117(2):283-9.
79. Candido Dos Reis FJ, Wishart GC, Dicks EM, Greenberg D, Rashbass J, Schmidt MK, et al. An updated PREDICT breast cancer prognostication and treatment benefit prediction model with independent validation. Breast Cancer Res. 2017;19(1):58.
80. Thurtle DR, Greenberg DC, Lee LS, Huang HH, Pharoah PD, Gnanapragasam VJ. Individual prognosis at diagnosis in nonmetastatic prostate cancer: Development and external validation of the PREDICT Prostate multivariable model. PLoS Med. 2019; Mar 16(3):e1002758.
81. May S, Hosmer DW. A simplified method of calculating an overall goodness-of-fit test for the Cox proportional hazards model. Lifetime Data Anal. 1998;4(2):109-20.
82. Harrell F. Package 'Hmisc'. In: Dupont C, editor. CRAN 2018. p. 235-6.
83. Farmer G, Pearson M, Skylark W, Freeman A, Spiegelhalter D. Redevelopment of the PREDICT: Breast cancer website and recommendations for developing interfaces to support decision-making. Cancer Medicine. 2021; Aug 10(15):5141-5153.
84. Barocas DA, Alvarez J, Resnick MJ, Koyama T, Hoffman KE, Tyson MD, et al. Association Between Radiation Therapy, Surgery, or Observation for Localized Prostate Cancer and Patient-Reported Outcomes After 3 Years. Jama-Journal of the American Medical Association. 2017;317(11):1126-40.
85. Predict Prostate Homepage [Available from: https://prostate.predict.nhs.uk/] Accessed multiple times.
86. Klotz L, Zhang LY, Lam A, Nam R, Mamedov A, Loblaw A. Clinical Results of Long-Term Follow-Up of a Large, Active Surveillance Cohort With Localized Prostate Cancer. Journal of Clinical Oncology. 2010;28(1):126-31.
87. Kim SP, Gross CP, Nguyen PL, Nguyen PY, Smaldone MC, Thompson RH, et al. Specialty bias in treatment recommendations and quality of life among radiation oncologists and urologists for localized prostate cancer. Prostate Cancer Prostatic Dis. 2014;17(2):163-9.
88. Vollmer RT. Tumor length in prostate cancer. American Journal of Clinical Pathology. 2008;130(1):77-82.
89. Huang JY, Vicini FA, Williams SG, Ye H, McGrath S, Ghilezan M, et al. Percentage of Positive Biopsy Cores: A Better Risk Stratification Model for Prostate Cancer? International Journal of Radiation Oncology Biology Physics. 2012;83(4):1141-8.
90. D'Amico AC, Renshaw AA, Cote K, Hurwitz M, Beard C, Loffredo M, et al. Impact of the percentage of positive prostate cores on prostate cancer-specific mortality for patients with low or favorable intermediate-risk disease. Journal of Clinical Oncology. 2004;22(18):3726-32.
91. Roach M, Lizarraga TLC, Lazar AA. Radical Prostatectomy Versus Radiation and Androgen Deprivation Therapy for Clinically Localized Prostate Cancer: How Good Is the Evidence? International Journal of Radiation Oncology Biology Physics. 2015;93(5):1064-70.
92. Turner EL, Metcalfe C, Donovan JL, Noble S, Sterne JA, Lane JA, et al. Contemporary accuracy of death certificates for coding prostate cancer as a cause of death: Is reliance on death certification good enough? A comparison with blinded review by an independent cause of death evaluation committee. Br J Cancer. 2016;115(1):90-4.
93. O'Connor AM, Rostom A, Fiset V, Tetroe J, Entwistle V, Llewellyn-Thomas H, et al. Decision aids for patients facing health treatment or screening decisions: systematic review. BMJ. 1999;319(7212):731-4.

94. Lin GA, Aaronson DS, Knight SJ, Carroll PR, Dudley RA. Patient decision aids for prostate cancer treatment: a systematic review of the literature. CA Cancer J Clin. 2009;59(6):379-90.
95. Klemann N, Roder MA, Helgstrand JT, Brasso K, Toft BG, Vainer B, et al. Risk of prostate cancer diagnosis and mortality in men with a benign initial transrectal ultrasound-guided biopsy set: a population-based study. Lancet Oncology. 2017;18(2):221-9.
96. Ontario HQ. Prolaris Cell Cycle Progression Test for Localized Prostate Cancer: A Health Technology Assessment. Ont Health Technol Assess Ser. 2017;17(6):1-75.
97. Cucchiara V, Cooperberg MR, Dall'Era M, Lin DW, Montorsi F, Schalken JA, et al. Genomic Markers in Prostate Cancer Decision Making. Eur Urol. 2018;73(4):572-82.
98. Cooperberg MR, Davicioni E, Crisan A, Jenkins RB, Ghadessi M, Karnes RJ. Combined Value of Validated Clinical and Genomic Risk Stratification Tools for Predicting Prostate Cancer Mortality in a High-risk Prostatectomy Cohort. European Urology. 2015;67(2):326-33.
99. Karapanagiotis S, Pharoah PDP, Jackson CH, Newcombe PJ. Development and External Validation of Prediction Models for 10-Year Survival of Invasive Breast Cancer. Comparison with PREDICT and CancerMath. Clin Cancer Res. 2018;24(9):2110-5.
100. Lee C, Light A, Alaa A, Thurtle D, van der Schaar M, Gnanapragasam VJ. Application of a novel machine learning framework for predicting non-metastatic prostate cancer-specific mortality in men using the Surveillance, Epidemiology, and End Results (SEER) database. Lancet Digit Health. 2021; 3(3):E158-165
101. Thurtle D, Bratt O, Stattin P, Pharoah P, Gnanapragasam V. Comparative performance and external validation of the multivariable PREDICT Prostate tool for non-metastatic prostate cancer: a study in 69,206 men from Prostate Cancer data Base Sweden (PCBaSe). BMC Med. 2020;18(1):139.
102. NICE. Endorsed resource - Predict Prostate. Prostate Cancer: diagnosis and management. https://www.nice.org.uk/guidance/ng131/resources/endorsed-resource-predict-prostate-6898604077 (Accessed May 2019).
103. Van Hemelrijck M, Wigertz A, Sandin F, Garmo H, Hellström K, Fransson P, et al. Cohort Profile: the National Prostate Cancer Register of Sweden and Prostate Cancer data Base Sweden 2.0. Int J Epidemiol. 2013;42(4):956-67.
104. Tomic K, Berglund A, Robinson D, Hjälm-Eriksson M, Carlsson S, Lambe M, et al. Capture rate and representativity of The National Prostate Cancer Register of Sweden. Acta Oncol. 2015;54(2):158-63.
105. Fall K, Strömberg F, Rosell J, Andrèn O, Varenhorst E, Group S-ERPC. Reliability of death certificates in prostate cancer patients. Scand J Urol Nephrol. 2008;42(4):352-7.
106. Cooperberg MR, Broering JM, Carroll PR. The UCSF cancer of the prostate risk assessment (CAPRA) score accurately predicts metastasis, prostate cancer mortality, and all-cause mortality regardless of treatment type. Journal of Urology. 2008;179(4):114-5.
107. Tomic K, Westerberg M, Robinson D, Garmo H, Stattin P. Proportion and characteristics of men with unknown risk category in the National Prostate Cancer Register of Sweden. Acta Oncologica. 2016;55(12):1461-6.
108. Thurtle DR, Jenkins V, Pharoah PD, Gnanapragasam VJ. Understanding of prognosis in non-metastatic prostate cancer: a randomised comparative study of clinician estimates measured against the PREDICT prostate prognostic model. Br J Cancer. 2019; 121:715-718.

109. Walz J, Gallina A, Perrotte P, Jeldres C, Trinh QD, Hutterer GC, et al. Clinicians are poor raters of life-expectancy before radical prostatectomy or definitive radiotherapy for localized prostate cancer. Bju International. 2007;100(6):1254-8.
110. Wilson JR, Clarke MG, Ewings P, Graham JD, MacDonagh R. The assessment of patient life-expectancy: how accurate are urologists and oncologists? BJU Int. 2005;95(6):794-8.
111. Daskivich TJ, Gale R, Luu M, Khodyakov D, Anger JT, Freedland SJ, et al. Patient Preferences for Communication of Life Expectancy in Prostate Cancer Treatment Consultations. JAMA Surg. 2022 Jan 1:157(1):70-72.
112. Chow H, Edelman MJ, Giaccone G, Ramalingam SS, Quill TA, Bowser AD, et al. Impact of an Interactive On-line Tool on Therapeutic Decision-Making for Patients with Advanced Non-Small-Cell Lung Cancer. J Thorac Oncol. 2015;10(10):1421-9.
113. Waljee JF, Rogers MA, Alderman AK. Decision aids and breast cancer: do they influence choice for surgery and knowledge of treatment options? J Clin Oncol. 2007;25(9):1067-73.
114. Bill-Axelson A, Holmberg L, Garmo H, Rider JR, Taari K, Busch C, et al. Radical prostatectomy or watchful waiting in early prostate cancer. N Engl J Med. 2014;370(10):932-42.
115. Koller MT, Raatz H, Steyerberg EW, Wolbers M. Competing risks and the clinical community: irrelevance or ignorance? Stat Med. 2012;31(11-12):1089-97.
116. Leung K, Hopman WM, Kawakami J. Challenging the 10-year rule: The accuracy of patient life expectancy predictions by physicians in relation to prostate cancer management. Cuaj-Canadian Urological Association Journal. 2012;6(5):367-73.
117. Dall'Era MA, Klotz L. Active surveillance for intermediate-risk prostate cancer. Prostate Cancer Prostatic Dis. 2017;20(1):1-6.
118. National Institute of Health and Care Excellence (UK). NICE Guideline 131. Prostate cancer: diagnosis and management. May 2019. https://www.nice.org.uk/guidance/ng131 Accessed June 2019
119. Scherr KA, Fagerlin A, Hofer T, Scherer LD, Holmes-Rovner M, Williamson LD, et al. Physician Recommendations Trump Patient Preferences in Prostate Cancer Treatment Decisions. Med Decis Making. 2017;37(1):56-69.
120. Jang TL, Bekelman JE, Liu Y, Bach PB, Basch EM, Elkin EB, et al. Physician visits prior to treatment for clinically localized prostate cancer. Arch Intern Med. 2010;170(5):440-50.
121. Orom H, Biddle C, Underwood W, Nelson CJ, Homish DL. What Is a "Good" Treatment Decision? Decisional Control, Knowledge, Treatment Decision Making, and Quality of Life in Men with Clinically Localized Prostate Cancer. Med Decis Making. 2016;36(6):714-25.
122. Stacey D, Légaré F, Lewis K, Barry MJ, Bennett CL, Eden KB, et al. Decision aids for people facing health treatment or screening decisions. Cochrane Database Syst Rev. 2017; Apr 12:4(4): CD001431.
123. van Tol-Geerdink JJ, Willem Leer J, Weijerman PC, van Oort IM, Vergunst H, van Lin EN, et al. Choice between prostatectomy and radiotherapy when men are eligible for both: a randomized controlled trial of usual care vs decision aid. BJU Int. 2013;111(4):564-73.
124. Holmes-Rovner M, Srikanth A, Henry SG, Langford A, Rovner DR, Fagerlin A. Decision aid use during post-biopsy consultations for localized prostate cancer. Health Expect. 2018;21(1):279-87.

125. Xu JP, Dailey RK, Eggly S, Neale AV, Schwartz KL. Men's Perspectives on Selecting Their Prostate Cancer Treatment. Journal of the National Medical Association. 2011;103(6):468-78.
126. ISRCTN Registry. ISRCTN 28468474 PREDICT Prostate Patient Study
Evaluation of a new tool, PREDICT Prostate, to aid treatment decision-making for men with newly diagnosed non-metastatic prostate cancer. 2018 https://www.isrctn.com/ISRCTN28468474 .
127. Thurtle D, Jenkins V, Freeman A, Pearson M, Recchia G, Tamer P, et al. Clinical impact of the *Predict* Prostate risk communication tool in men newly diagnosed with non-metastatic prostate cancer: a multi-centre randomised controlled trial. Eur Urol 2021 Nov;80(5): 661-669.
128. National Prostate Cancer Audit. National Prostate Cancer Audit Annual Report 2019. https://www.npca.org.uk/reports/npca-annual-report-2019/ (Accessed Jan 2020).
129. Parry MG, Cowling TE, Sujenthiran A, Nossiter J, Berry B, Cathcart P, et al. Risk stratification for prostate cancer management: value of the Cambridge Prognostic Group classification for assessing treatment allocation. BMC Med. 2020;18(1):114.
130. O'Connor AM. Validation of a decisional conflict scale. Med Decis Making. 1995;15(1):25-30.
131. Spielberger CD. Manual for the state/trait anxiety inventory (form Y) : (self evaluation questionnaire). Palo Alto: Consulting Psychologists Press; 1983.
132. National Prostate Cancer Audit. Annual Report 2020. https://www.npca.org.uk/reports/npca-annual-report-2020/ Accessed February 2021.
133. Sedgwick P. Block randomisation. BMJ 2011:343.bmj.d7139.
134. O'Connor AM, Boyd NF, Warde P, Stolbach L, Till JE. Eliciting preferences for alternative drug therapies in oncology: influence of treatment outcome description, elicitation technique and treatment experience on preferences. J Chronic Dis. 1987;40(8):811-8.
135. Auvinen A, Hakama M, Ala-Opas M, Vornanen T, Leppilahti M, Salminen P, et al. A randomized trial of choice of treatment in prostate cancer: the effect of intervention on the treatment chosen. BJU Int. 2004;93(1):52-6; discussion 6.
136. van Wijk Y, Halilaj I, van Limbergen E, Walsh S, Lutgens L, Lambin P, et al. Decision Support Systems in Prostate Cancer Treatment: An Overview. Biomed Res Int. 2019;2019:4961768.
137. Violette PD, Agoritsas T, Alexander P, Riikonen J, Santti H, Agarwal A, et al. Decision aids for localized prostate cancer treatment choice: Systematic review and meta-analysis. CA Cancer J Clin. 2015;65(3):239-51.
138. Connolly T, Reb J. Regret in cancer-related decisions. Health Psychol. 2005;24(4S):S29-34.
139. Vickers AJ. Decisional Conflict, Regret, and the Burden of Rational Decision Making. Med Decis Making. 2017;37(1):3-5.
140. Nelson WL, Han PK, Fagerlin A, Stefanek M, Ubel PA. Rethinking the objectives of decision aids: a call for conceptual clarity. Med Decis Making. 2007;27(5):609-18.
141. Carlsson S, Ehdaie B, Vickers A. What is a good medical choice? Cancer. 2021 Jun 1:127(11):1933-1934.
142. Riikonen JM, Guyatt GH, Kilpeläinen TP, Craigie S, Agarwal A, Agoritsas T, et al. Decision Aids for Prostate Cancer Screening Choice: A Systematic Review and Meta-analysis. JAMA Intern Med. 2019;179(8):1072-82.

143. Garvelink MM, Boland L, Klein K, Nguyen DV, Menear M, Bekker HL, et al. Decisional Conflict Scale Use over 20 Years: The Anniversary Review. Med Decis Making. 2019;39(4):301-14.
144. Berry DL, Hong F, Blonquist TM, Halpenny B, Filson CP, Master VA, et al. Decision Support with the Personal Patient Profile-Prostate: A Multicenter Randomized Trial. J Urol. 2018;199(1):89-97.
145. Légaré F, Ratté S, Gravel K, Graham ID. Barriers and facilitators to implementing shared decision-making in clinical practice: update of a systematic review of health professionals' perceptions. Patient Educ Couns. 2008;73(3):526-35.
146. Shepherd HL, Butow PN, Tattersall MH. Factors which motivate cancer doctors to involve their patients in reaching treatment decisions. Patient Educ Couns. 2011;84(2):229-35.
147. Wilt TJ, Jones KM, Barry MJ, Andriole GL, Culkin D, Wheeler T, et al. Follow-up of Prostatectomy versus Observation for Early Prostate Cancer. N Engl J Med. 2017;377(2):132-42.
148. Bill-Axelson A, Holmberg L, Garmo H, Taari K, Busch C, Nordling S, et al. Radical Prostatectomy or Watchful Waiting in Prostate Cancer - 29-Year Follow-up. N Engl J Med. 2018;379(24):2319-29.
149. Kattan MW, Zelefsky MJ, Kupelian PA, Cho D, Scardino PT, Fuks Z, et al. Pretreatment nomogram that predicts 5-year probability of metastasis following three-dimensional conformal radiation therapy for localized prostate cancer. Journal of Clinical Oncology. 2003;21(24):4568-71.
150. Jones AL, Chinegwundoh F. Update on prostate cancer in black men within the UK. Ecancermedicalscience. 2014;8:455.

Appendix 1. Peer-reviewed publications by the author during the study period

C Lee, A Light, A Alaa, D Thurtle, M van der Schaar, VJ Gnanapragasam. Application of a novel machine learning framework for predicting non-metastatic prostate cancer-specific mortality in men using the Surveillance, Epidemiology, and End Results (SEER) database. Lancet Digit Health. 2021 Feb 3;S2589-7500(20)30314-9. doi: 10.1016/S2589-7500(20)30314-9. PMID 33549512

David Thurtle, Val Jenkins, Alex Freeman, Mike Pearson, Gabriel Recchia, Priya Tamer, Kelly Leonard, Paul Pharoah, Jonathan Aning, Sanjeev Madaan, Chee Goh, Serena Hilman, Stuart McCracken, Petre Cristian Ilie, Henry Lazarowicz, Vincent Gnanapragasam. Clinical Impact of the Predict Prostate Risk Communication Tool in Men Newly Diagnosed with Nonmetastatic Prostate Cancer: A Multicentre Randomised Controlled Trial. Eur Urol. 2021 Nov;80(5):661-669. PMID 3449313

S Tamhankar, D Thurtle, A Hampson, O El-Taji, R Thurairaja, JD Kelly, J Catto, T Lane, J Adshead, N Vasdev Radical Cystectomy in England from 2013-2019: An analysis of national trends and comparison of surgical approaches using Hospital Episode Statistics data. S Tamhankar, BJUI Compass. 2: 021;2:338–347 doi: 10.1111/bco2.79

Moore SL, Chebbout R, Cumberbatch M, Bondad J, Forster L, Hendry J, Lamb B, MacLennan S, Nambiar A, Shah TT, Stavrinides V, Thurtle D, Pearce I, Kasivisvanathan V. Orchidopexy for Testicular Torsion: A Systematic Review of Surgical Technique. Eur Urol Focus. 2020 Aug 27:S2405-4569(20)30213-3. doi: 10.1016/j.euf.2020.07.006. PMID: 32863201

Thurtle D, Bratt O, Stattin P, Pharoah P, Gnanapragasam V. Comparative performance and external validation of the multivariable PREDICT Prostate tool for non-metastatic prostate cancer: a study in 69,206 men from Prostate Cancer data Base Sweden (PCBaSe). BMC Med. 2020 Jun 16;18(1):139. doi: 10.1186/s12916-020-01606-w. PMID: 32539712

Thurtle DR, Jenkins V, Pharoah PD, Gnanapragasam VJ. Understanding of prognosis in non-metastatic prostate cancer: a randomised comparative study of clinician estimates measured against the PREDICT prostate prognostic model. Br J Cancer. 2019 Sep 16. doi: 10.1038/s41416-019-0569-4. PMID: 31523057

Thurtle D, Rossi SH, Berry B, Pharoah P, Gnanapragasam VJ. Models predicting survival to guide treatment decision-making in newly diagnosed primary non-metastatic prostate cancer: a systematic review. BMJ Open. 2019 Jun 22;9(6):e029149. doi: 10.1136/bmjopen-2019-029149. PMID: 31230029

Kasivisvanathan V, Stabile A, Neves JB, Giganti F, Valerio M, Shanmugabavan Y, Clement KD, Sarkar D, Philippou Y, Thurtle D, Deeks J, Emberton M, Takwoingi Y, Moore CM. Magnetic Resonance Imaging-targeted Biopsy Versus Systematic Biopsy in the Detection of Prostate Cancer: A Systematic Review and Meta-analysis. Eur Urol. 2019 Sep;76(3):284-303. doi: 10.1016/j.eururo.2019.04.043. PMID: 31130434

Gnanapragasam VJ, Barrett T, Thankapannair V, Thurtle D, Rubio-Briones J, Domínguez-Escrig J, Bratt O, Statin P, Muir K, Lophatananon A. Using prognosis to guide inclusion criteria, define standardised endpoints and stratify follow-up in active surveillance for prostate cancer. BJU Int. 2019 May 7. doi: 10.1111/bju.14800. [Epub ahead of print] PMID: 31063245

Thurtle DR, Greenberg DC, Lee LS, Huang HH, Pharoah PD, Gnanapragasam VJ.
PLoS Med. Individual prognosis at diagnosis in nonmetastatic prostate cancer: Development and external validation of the PREDICT Prostate multivariable model.
2019 Mar 12;16(3):e1002758. doi: 10.1371/journal.pmed.1002758. PMID: 30860997
D Thurtle, K Leonard, L Starling, T Stone, VJ Gnanapragasam. Improving the safety and tolerability of local anaesthetic out-patient transperineal prostate biopsies: a pilot study of the CAMbridge PROstate Biopsy (CAMPROBE) method. J Clin Urol. 2018 May;11(3):192-199. doi: 10.1177/2051415818762683 PMID: 29881622

Thurtle D, Barrett T, Thankappan-Nair V, Koo B, Warren A, Kastner C, Saeb-Parsy K, Kimberley-Duffell J, Gnanapragasam VJ. Progression and treatment rates using an active surveillance protocol incorporating image guided baseline biopsies and multi-parametric MRI monitoring for men with favourable risk prostate cancer. BJU Int. 2018 Feb 13. doi: 10.1111/bju.14166 PMID: 29438586

D Thurtle, E Gordon, R Brierly, CJ Conway, J McLoughlin. GP perception of prostate-specific antigen testing has improved, but more awareness of prostate cancer risk in younger patients is still awaited. Prostate international. Oct 2017. doi 10.1016/j.prnil.2017.10.001 PMID:29922634

D Thurtle, GM Treece, T Barrett, VJ Gnanapragasam. Novel three-dimensional bone 'mapping' software can help assess progression of osseous metastases from routine CT. Radiat Oncol. 2017 Aug 30;12(1):143. doi: 10.1186/s13014-017-0880-2 PMID: 28854948

D Thurtle, R Hsu, A Lophatananon, M Chetan, R Hubbard, V Gnanapragasam & T Barrett. Incorporating multi-parametric MRI staging and the new histological Grade Group system improves risk-stratified detection of bone metastasis in prostate cancer. Br J Cancer. 2016 Nov 22;115(11):1285-1288. doi: 10.1038/bjc.2016.353. PMID: 27802450

VJ Gnanapragasam, D Thurtle, A Srinivasan, D Volanis, A George, A Lophatananon, Sara Stearn, A Warren, A Lamb, G Shaw, N Sharma, B Thomas, M Tran, DE Neal, NC Shah. Evolution of a contemporary radical prostatectomy service in a tertiary referral centre. BJU Int. 2016 Nov;118(5):779-784. doi: 10.1111/bju.13513. PMID: 27124625

Appendix 2 Additional files

Chapter 1 Appendix

Systematic Review Protocol

Title page
PROTOCOL VERSION 0.6, 27th November 2018

Existing prognostic models available at the point of diagnosis for survival amongst men with non-metastatic prostate cancer: a protocol for systematic review

David Thurtle[a,b] Sabrina Rossi[a,b] Brendan Berry[b] Paul Pharoah[c] Vincent Gnanapragasam[a,b,d]

a Academic Urology Group, Department of Surgery, University of Cambridge, UK
b Urology Department, Cambridge University Hospitals NHS Foundation Trust, Cambridge, UK
c Centre for Cancer Genetic Epidemiology, University of Cambridge, UK
d Cambridge Urology Translational Research and Clinical Trials, Cambridge, UK

PROSPERO Systematic Review Registration Number: CRD42018086394

*Corresponding Author:
David Thurtle BMedSci, MBBS, MRCS, AFHEA
Clinical Research Associate and SpR in Urology
Academic Urology Group,
Department of Surgery,
University of Cambridge,
Hills Road,
Cambridge,
CB2 0QQ
Email: [email redacted]
Telephone: [number redacted]

Contributions
To be completed at end of project

Contents

2 Amendments

Version 0.5 July 2018

Dr Y Blumenthal removed, given zero involvement hitherto – informed by email without response.

Inclusion and exclusion criteria simplified - prior to full text screening.

Extension of inclusion dates to end of February 2018, given the delays to progress in the review.

Version 0.6 November 2018

Clarification to wording of inclusion/exclusion criteria prior to full-text screening. Specifically, only to include studies with more than 1 treatment option included (model does not have to include treatment effect or any treatment effect necessarily). Informed by experience during abstract screening.

Extension of inclusion dates to end of February 2018, given the delays to progress in the review.

3 Funding

David Thurtle is supported through funding from the Evelyn Trust, and a Research Scholarship from The Urology Foundation. General infrastructure support is received through the Academic Urology Group, University of Cambridge, Cancer Research UK Cambridge Institute and the Cambridge Biomedical Campus. Any views expressed in this publication are those of the authors and not necessarily those of the NHS, or the funding bodies.

4 Background

4.1 Non-metastatic prostate cancer

Prostate cancer (PCa) is the commonest cancer affecting males in the UK and is a leading cause of cancer-related morbidity1. PCa incidence is increasing, with 47,300 UK men diagnosed with the disease in 20131. The vast majority of new presentations (>80%) are with localised or locally advanced disease representing a significant healthcare and economic burden2. Treatment decisions, in this growing group of men, are notoriously complex with the risk of progression and psychological impact of a cancer diagnosis balanced against significant potential morbidity associated with radical treatment options. Unlike many other conditions, there are a number of valid treatment modalities for PCa including radiotherapy, prostatectomy, androgen deprivation therapy and conservative management. Differentiating aggressive tumours that require treatment from those that are indolent, and avoiding the associated morbidity of overtreatment has been identified as the top priority in PCa research3.

To aid the decision-making process for both clinicians and patients, risk prediction tools would be invaluable. Indeed, national UK guidelines advise that evidence-based decision aids should be used both in urological cancer multi-disciplinary teams (MDTs) and with individual patients4.

4.2 Prognostic Models

Risk stratification is the cornerstone of management in men with non-metastatic prostate cancer. Prognostic models are a specific type of risk-prediction tool, that model a disease outcome, commonly survival. Most National guidelines (including the UK NICE guidelines) classify men according to modified versions of the three-stratum D'Amico classification system, first proposed in 1998, which uses biochemical relapse as the primary outcome - from a cohort of men radically treated5. However, it has been widely shown that biochemical relapse is a poor surrogate for survival outcomes6 and many men will never undergo radical treatment, with the increasingly prevalent use of conservative management7,8,

Questions remain as to whether the 3-strata system remains fit for purpose. More so when its use has moved from predicting radical therapy outcome to being a tool used to help counsel men at diagnosis about whether to have surveillance or treatment in the first place. A number of newer risk models have been proposed either using standard variables (PSA, Gleason score, T-stage) to delineate smaller groups9 or which integrate additional parameters, such as biopsy characteristics10,11. However, these models are predominantly built around single-centre data, using PSA-screened and heavily radically-treated populations. Most of these models also use inadequate surrogates for survival such as biochemical recurrence as their primary outcome measure10,11.

4.3 Models assessing lethality/survival in other cancer types

In other tumour-types, risk prediction models are already integrated in to routine clinical practice. Pioneering work in Cambridge addressed many similar themes in breast cancer, with the development of the PREDICT model12. PREDICT allows both patients and healthcare professionals to model survival outcomes, based on potential treatment modalities, and has evolved over time with the addition of contemporary biomarkers and therapeutic agents13,14.
It is clear that the commonly used risk-prediction models in PCa are not based on survival outcomes. However, it is unclear whether prognostic models assessing mortality or survival in non-metastatic PCa have been developed and published but have simply not yet been accepted into routine practice. Models integrating the impact of radical treatment, in the context of active surveillance would be particularly powerful.

5 Main question

In men with a new diagnosis of non-metastatic prostate cancer, what prognostic models are available at the point of diagnosis that model or predict survival outcomes?

5.1 Primary outcome

Quantify the number of available prognostic models in non-metastatic prostate cancer using long-term survival outcomes.

5.2 Main hypothesis

There is currently no adequate long term survival model for use in men with non-metastatic prostate cancer.

5.3 Secondary outcomes

1. Assess accuracy of any available models in terms of discrimination, calibration, classification.
2. Assess generalizability of available models, particularly to a UK population
3. Assess external validation and clinical uptake of the model

6 Methods

Where applicable, this protocol follows the recommendations of Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines15.
The review aim, search strategy and study inclusion and exclusion criteria has been framed using the CHecklist for critical Appraisal and data extraction for systematic Reviews of prediction Modelling (CHARMS)16.
The search strategy has been informed by previous similar studies, including one publication which had tested search terms for risk-prediction models. The search strategy has also been reviewed and assisted by literature review and information specialists at the University of Cambridge Medical Library.

6.1 Definitions for review

Population - The population of interest is adult men diagnosed with non-metastatic prostate cancer at the point of diagnosis (i.e. before treatment).
Intervention and Comparator - The models under review should be any model that predicts or models long term survival outcomes (for the sake of this review defined as ≥5 years)

following prostate cancer diagnosis, including grouping systems, nomograms, and personalised models. 'Models' should include more than a single parameter.
Outcome - The outcomes of interest for which the model is built is survival or mortality, including all-cause/overall and prostate cancer-specific.
Timing – In this review we will focus on exploring long term (≥5 years) mortality/survival outcomes.
Setting – The intended use of these prognostic models is to perform risk stratification at the point of diagnosis and/or to direct treatment decisions at the point of diagnosis.

7 Inclusion and exclusion criteria

7.1 Study inclusion criteria
All of the following inclusion criteria must be met:

- Studies reporting models based on men with non-metastatic prostate cancer (or presumed non-metastatic prostate cancer i.e. appropriately staged or favourable risk).
- Studies built around 'long-term' (≥5 years) survival/mortality outcomes - overall or cancer-specific.
- Studies reporting models in screened, or non-screened populations.
- Studies including more than one treatment option
- Models available for use at the point of diagnosis – i.e. Pre-treatment.
- 'Models' refers to multi-variable models (i.e more than one parameter, such that studies exploring single biomarkers or parameters should not be included.)

7.2 Study exclusion criteria
Any of the following is a reason to exclude a study:

- Any article that is not an original study (e.g. reviews, commentary, editorials, corrigendums, letters)
- Conference proceeding or abstract from poster/oral communication only
- Study where data cannot be derived to contribute to a primary or secondary outcome of this systematic review
- Studies pertaining only to men with advanced/metastatic disease
- Studies pertaining exclusively to men after an active treatment option eg. after radical prostatectomy where their use at the point of diagnosis is impossible as additional parameters are included which rely on final histology or similar.
- Studies of single biomarkers or single parameters only (i.e. not of 'multi-variable models')
- Studies or models including a single treatment type only.

8 Information sources and search strategy

For search purposes both free-text and controlled language terms will be used, no language or study design limitations will be considered. The following databases will be searched from 1st January 1990 to 28th February 2018:

- Cochrane Library
- Medline and Embase via OvidSP

See Appendix 2 for detailed search strategies for each database.

The reference lists of relevant reviews and of studies selected after full-text screening will be analysed for further relevant studies.

It is important to detect not only the existing models that have been published, but also to include publications that attempted to validate the model in external populations. Publications that cite the original paper of any included studies will be reviewed for this purpose.

9 Study records

9.1 Data management

After the search is carried out, all articles will be uploaded into Endnote, a reference manager software. Deduplication will ensue. The remaining articles will be imported into Covidence, an online screening platform endorsed by Cochrane, for abstract and title screening and full-text screening.

9.2 Selection process

A team of 4 authors will screen the search results. Initial abstract screening will be performed with reviewers excluding titles/abstracts which are clearly irrelevant. During full text screening every article will be assessed independently by two authors. In the event of disagreement, consensus will be attempted after discussion between these two authors. If consensus can't be reached, the third author will resolve any differences.

Prior to the screening process a pilot screening process will be conducted for both calibration of screening between different reviewers and introduction of the Covidence platform.

The first phase of the screening process will be based solely on title and abstract analysis. Selected studies will be carried over to the second phase of screening, based on full-text analysis.

No authors will be blinded to study authors or institution, publication journal or year of publication.

10 Data collection process

An Excel file will serve as database for collected data for included studies. One author will collect study data and a second author will ensure all collected data is accurate. In the event of disagreement, consensus will be attempted after discussion between the pair of data collectors. If consensus can't be reached, the third author will resolve any differences.

10.1 Data items

Anticipated data to be extracted (guided by CHARMS checklist):

1. Paper details: Author Surname, Year of Publication (YYYY)

2. Source of data: Cohort, case-control, randomized trial.
3. Study design (model development or model validation)
4. Participants: Eligibility(inclusion and exclusion criteria) and recruitment, country, participants description and case-mix variation (number, age, average PSA/grade/stage), dates of recruitment, details of treatments if any
5. Outcomes to be predicted: Definition and method for measurement of outcome (i.e. death and cause of death), was this outcome used consistently, timings of outcome recurrence and summary of follow-up duration.
6. Candidate predictors (index tests): Number and type of predictors (i.e. demographics, history/exam findings, psa, grade, stage, additional tests), definition and measurement of predictors, handling of predictors in the modelling (continuous, linear, categorized etc)
7. Sample size: Number of patients, number of events, number of events in relation to number of candidate predictors
8. Missing data: Number of participants with any missing value, and any missing data for each predictor, Methods of handling missing data (complete-case analysis, imputation etc)
9. Model development: Modelling method (logistic regression, machine learning), modelling assumptions satisfied, method for selection of predictors for inclusion etc..
10. Model performance: Calibration and discrimination measures with CIs (even when not presented can potentially be calculated see appendix 7 of Debray et al BMJ)
11. Model evaluation: Development dataset only (random split, resampling, etc) or separate external validation (temporal, geographic, different investigators etc), was model updated or adjusted if poor validation.
12. Results: final model presented (baseline survival, predictor weights, performance measures etc), Alternative presentations (nomograms, sum scores), comparison between predictors in development and validation sets
13. Interpretation and discussion: Conclusions on model use (useful for practice, or requires more research), discussions of generalizability, strengths and limitations.

11 Assessment of bias of individual studies

Individual studies will be assessed for bias by two independent authors using the latest available and modified version of the prediction model risk of bias assessment tool (PROBAST). The PROBAST tool should be able to be applied to validation studies of a model and the original model development study.

12 Assessment of reporting standards

Individual studies will be assessed according to their reporting standards using the AJCC eligibility criteria for cancer risk-prediction models.

13 Data synthesis

Data will be extracted from the studies according to section 10 above. If feasible, data on certain individual tools will be meta-analysed in order to obtain the outcome data described in Section 5. The specific details of the approach will be tailored to the quality and availability of data.

14 Possible subgroup and sensitivity analyses

1. Risk of bias of individual studies/study quality
2. Year of publication
3. Cancer-specific mortality models.
4. Overall mortality models.
5. Screened groups
6. Unscreened populations

15 Potential limitations of the review

- Limitations in study design

This review will include only published models. This may exclude previous attempts at model development that have failed. However, the intention is to assess models which may have been validated or are used in clinical practice – which should necessitate publication.

- Limitations in extracting data:

These will be appreciated in more detail during the data extraction phase.

- Limitations in generalizability

It is anticipated most models will have been constructed around single-centre cohorts. The generalizability of models will hopefully be more broadly assessed by investigating external validation as well as internally validated models.

16 Anticipated timeline of delivery

1st March – 20th March 2018	Pilot screening process
20th March – 11th May 2018	Title and abstract screening
12th May – 18th July 2018	Address conflicts
19th July – 11th August 2018	Full text article screening
12th August – 18th August 2018	Address conflicts
19th August – 15th October 2018	Data extraction & Bias assessment
16th October – 29th October 2018	Statistics
30th October – 30th November 2018	Write paper

17 Reporting and Presentation

The reporting of results will be in keeping with guidance set out in the Preferred reporting items for systematic reviews and meta-analyses (PRISMA) statement. Recommendations from the Transparent Reporting of a multivariable prediction model for individual prognosis (TRIPOD) statement will also be abided by. The Grades of recommendation, Assessment, Development and Evaluation (GRADE) approach may help to present the evidence also.

18 Appendix 1

Anticipated flow diagram of study

19 Appendix 2 – search details and outcomes

Detailed searches performed on 28th February 2018 with information specialist help: (Ovid Embase (1988-current) – 6264, Ovid Medline (1996-current) – 3104, Cochrane – 21 (all irrelevant).

Ovid (EMBASE and Medline)
New ovid search strategy for SR
Prostate cancer (prostat* adj3 (neoplasm* or cancer* or carcinoma* or tumor* or tumour* malignanc*)).ti.
OR
prostatic neoplasms (MESH) (focus) (medline)
Prostate cancer (MESH) (focus) (embase)

AND
Prognostic/predictive model
((Predict$ or Prognos$ or Decision$) and (Model* or Criteria* or Scor$ or algorithm$ or nomogram* or tool*)).ti, ab.
OR
Prognosis (MESH) (focus)
Cancer prognosis (MESH) (focus)

AND
Survival/mortality outcome
(Survival* or Mortalit* or Life-expectanc* or Death*).ti,ab.

OR
Survival (MESH) (focus)

Limit to year 2000 to current (28/2/18)

Ovid Embase 1988 to current (database) = 6268
Ovid medline 1996 to current (database) = 3104

Cochrane Library
((prostat*) near/2 (neoplasm* or cancer* or carcinoma* or tumor* or tumour* malignanc*))

Transfer to Covidence
In total, after deduplication there are 6597 articles to screen.

20 References

1. Cancer Research UK. http://www.cancerresearchuk.org/cancer-info/cancerstats/types/prostate/. http://www.cancerresearchuk.org/cancer-info/cancerstats/types/prostate/.

2. Greenberg DC, Wright KA, Lophathanon A, Muir KR, Gnanapragasam VJ. Changing presentation of prostate cancer in a UK population--10 year trends in prostate cancer risk profiles in the East of England. Br J Cancer. 2013;109(8):2115-2120.
3. JLA. James Lind Alliance Priority setting partnerships. Prostate Cancer Top 10:
1. How can overtreatment for prostate cancer be prevented by identifying and excluding the treatment of harmless tumours? . In:2016.
4. NICE. National Institute for Health and Care Excellence NICE Guidelines [CG175] Prostate cancer: diagnosis and treatment. In:January 2014.
5. D'Amico AV, Whittington R, Malkowicz SB, et al. Biochemical outcome after radical prostatectomy, external beam radiation therapy, or interstitial radiation therapy for clinically localized prostate cancer. JAMA. 1998;280(11):969-974.
6. Jhaveri FM, Zippe CD, Klein EA, Kupelian PA. Biochemical failure does not predict overall survival after radical prostatectomy for localized prostate cancer: 10-year results. Urology. 1999;54(5):884-890.
7. Greenberg DC, Lophatananon A, Wright KA, Muir KR, Gnanapragasam VJ. Trends and outcome from radical therapy for primary non-metastatic prostate cancer in a UK population. PLoS One. 2015;10(3):e0119494.
8. Huland H, Graefen M. Changing Trends in Surgical Management of Prostate Cancer: The End of Overtreatment? Eur Urol. 2015.
9. Huang Y, Isharwal S, Haese A, et al. Prediction of patient-specific risk and percentile cohort risk of pathological stage outcome using continuous prostate-specific antigen measurement, clinical stage and biopsy Gleason score. BJU Int. 2011;107(10):1562-1569.
10. Cooperberg MR, Pasta DJ, Elkin EP, et al. The University of California, San Francisco Cancer of the Prostate Risk Assessment score: a straightforward and reliable preoperative predictor of disease recurrence after radical prostatectomy. J Urol. 2005;173(6):1938-1942.
11. Stephenson AJ, Scardino PT, Eastham JA, et al. Preoperative nomogram predicting the 10-year probability of prostate cancer recurrence after radical prostatectomy. J Natl Cancer Inst. 2006;98(10):715-717.
12. Wishart GC, Azzato EM, Greenberg DC, et al. PREDICT: a new UK prognostic model that predicts survival following surgery for invasive breast cancer. Breast Cancer Res. 2010;12(1):R1.
13. Wishart GC, Bajdik CD, Dicks E, et al. PREDICT Plus: development and validation of a prognostic model for early breast cancer that includes HER2. Br J Cancer. 2012;107(5):800-807.
14. Down SK, Lucas O, Benson JR, Wishart GC. Effect of PREDICT on chemotherapy/trastuzumab recommendations in HER2-positive patients with early-stage breast cancer. Oncol Lett. 2014;8(6):2757-2761.
15. Liberati A, Altman DG, Tetzlaff J, et al. The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate health care interventions: explanation and elaboration. Ann Intern Med. 2009;151(4):W65-94.
16. Moons KG, de Groot JA, Bouwmeester W, et al. Critical appraisal and data extraction for systematic reviews of prediction modelling studies: the CHARMS checklist. PLoS Med. 2014;11(10):e1001744.

Chapter 2 Appendix

TRIPOD Checklist

Page numbers relate to the publication in PLOS Medicine [78].

Transparent reporting of a multivariable prediction model for individual prognosis or diagnosis (TRIPOD) Checklist.
TRIPOD Checklist: Prediction Model Development and Validation

Individualising prognostic stratification at diagnosis in non-metastatic prostate cancer: Development and validation of the PREDICT: *Prostate* multivariable survival model

Section/Topic			Checklist Item	Section / Paragraph
Title and abstract				
Title	1	);V	Identify the study as developing and/or validating a multivariable prediction model, the target population, and the outcome to be predicted.	Title page
Abstract	2	);V	Provide a summary of objectives, study design, setting, participants, sample size, predictors, outcome, statistical analysis, results, and conclusions.	Abstract
Introduction				
Background and objectives	3a	);V	Explain the medical context (including whether diagnostic or prognostic) and rationale for developing or validating the multivariable prediction model, including references to existing models.	Introduction / 1-2
	3b	);V	Specify the objectives, including whether the study describes the development or validation of the model or both.	Introduction / 3
Methods				
Source of data	4a	);V	Describe the study design or source of data (e.g., randomized trial, cohort, or registry data), separately for the development and validation data sets, if applicable.	Methods / 2
	4b	);V	Specify the key study dates, including start of accrual; end of accrual; and, if applicable, end of follow-up.	Methods / 2
Participants	5a	);V	Specify key elements of the study setting (e.g., primary care, secondary care, general population) including number and location of centres.	Methods / 2
	5b	);V	Describe eligibility criteria for participants.	Methods / 2
	5c	);V	Give details of treatments received, if relevant.	Methods / 3
Outcome	6a	);V	Clearly define the outcome that is predicted by the prediction model, including how and when assessed.	Methods / 2 & 4
	6b	);V	Report any actions to blind assessment of the outcome to be predicted.	n/a
Predictors	7a	);V	Clearly define all predictors used in developing or validating the multivariable prediction model, including how and when they were measured.	Methods / 3
	7b	);V	Report any actions to blind assessment of predictors for the outcome and other predictors.	Methods / 4
Sample size	8	);V	Explain how the study size was arrived at.	Methods / 4
Missing data	9	);V	Describe how missing data were handled (e.g., complete-case analysis, single imputation, multiple imputation) with details of any imputation method.	Methods / 2-3 & 8
Statistical analysis methods	10a	D	Describe how predictors were handled in the analyses.	Methods / 3-4
	10b	D	Specify type of model, all model-building procedures (including any predictor selection), and method for internal validation.	Methods / 4-6
	10c	V	For validation, describe how the predictions were calculated.	Methods / 6
	10d	);V	Specify all measures used to assess model performance and, if relevant, to compare multiple models.	Methods / 6-8
	10e	V	Describe any model updating (e.g., recalibration) arising from the validation, if done.	Methods / 9
Risk groups	11	);V	Provide details on how risk groups were created, if done.	n/a
Development vs. validation	12	V	For validation, identify any differences from the development data in setting, eligibility criteria, outcome, and predictors.	Methods / 7
Results				
Participants	13a	);V	Describe the flow of participants through the study, including the number of participants with and without the outcome and, if applicable, a summary of the follow-up time. A diagram may be helpful.	Results / 1

	3b	D;V	Describe the characteristics of the participants (basic demographics, clinical features, available predictors), including the number of participants with missing data for predictors and outcome.	Results / 1 & Table 1
	3c	V	For validation, show a comparison with the development data of the distribution of important variables (demographics, predictors and outcome).	Results 1 / Table1 & Supp.
Model development	4a	D	Specify the number of participants and outcome events in each analysis.	Results / 1 & 5 & Table 1
	4b	D	If done, report the unadjusted association between each candidate predictor and outcome.	n/a
Model specification	5a	D	Present the full prediction model to allow predictions for individuals (i.e., all regression coefficients, and model intercept or baseline survival at a given time point).	Results 2-3 Table 2, Figure 1 & source code
	5b	D	Explain how to the use the prediction model.	Results 2-3 & source code
Model performance	16	D;V	Report performance measures (with CIs) for the prediction model.	Results/ 4-10 & Tables 3-5 & Supp
Model-updating	17	V	If done, report the results from any model updating (i.e., model specification, model performance).	Results / 8-10 & Supp
Discussion				
Limitations	18	D;V	Discuss any limitations of the study (such as nonrepresentative sample, few events per predictor, missing data).	Discussion / 5-7
Interpretation	9a	V	For validation, discuss the results with reference to performance in the development data, and any other validation data.	Discussion / 1, 6 & 7
	9b	D;V	Give an overall interpretation of the results, considering objectives, limitations, results from similar studies, and other relevant evidence.	Discussion 1-7
Implications	20	D;V	Discuss the potential clinical use of the model and implications for future research.	Results 10 & Discussion 1,3 & 7
Other information				
Supplementary information	21	D;V	Provide information about the availability of supplementary resources, such as study protocol, Web calculator, and data sets.	Data availability, Document S2,
Funding	22	D;V	Give the source of funding and the role of the funders for the present study.	Funding statement

*Items relevant only to the development of a prediction model are denoted by D, items relating solely to a validation of a prediction model are denoted by V, and items relating to both are denoted D;V. We recommend using the TRIPOD Checklist in conjunction with the TRIPOD Explanation and Elaboration document.

Stata code for updated model including PPC coefficient

```
clear

quietly {
set obs 15 //based on 15 years f/u

*Set input parameters for this fictional man

gen time=_n
gen age   = 70            // Age at diagnosis (35-95)
gen age_time = age + _n
gen gradegroup = 2         // gradegroup (1-5
gen psa  = 10              // ng/ml (0-100)
gen t_stage = 2            // (1-4)
gen charlson_comorbidity =  0          // charlson comorbidity score (0 or 1)
gen primaryRx =   0        // 0=AS 1='Treatment' 3=adt
gen biopsy50 = 0                       //  0=Unknown/not  included  1=<50%  cores  involved
2=>=50% cores involved
gen BRCA = 0            // 0 = unknown/negative 1=BRCA mutation carrier
gen PPC = 41.1      // = % Positive Cores. If unknown, enter 41.9415 for 'average' PPC effect
(OR can remove the  part of eqn below which relates to PPC)

**NB - have to have biopsy50 set as 0, if using PPC (as both are in the eqn below)**

*calculate the PCSM prognostic index (pi)
gen            piPCSM            =            0.0026005*((age/10)^3-341.155151)            +
0.185959*(ln((psa+1)/100)+1.636423432)          +          .1614922*(t_stage==2)          +
.39767881*(t_stage==3)   +   .6330977*(t_stage==4)   +   .2791641*(gradegroup==2)   +
.5464889*(gradegroup==3) + .7411321*(gradegroup==4) + 1.367963*(gradegroup==5) + -
.6837094*(primaryRx==1)   +   .9084921*(primaryRx==3)   -0.617722958*(biopsy50==1)   +
0.579225231*(biopsy50==2)          +0.956*(BRCA==1)          +(((PPC+0.1811159)/100)^.5-
.649019)*1.890134

*calculate the NPCM progostic index (pi)
gen piNPCM = 0.1226666*(age-69.87427439) + 0.6382002*(charlson_comorbidity==1)

*convert years to days (used in all my formulae etc)
replace time=(365*time)

*gen PCS mortality, then per year, then convert to survival per year...
gen  PCSMatT  =  1  -  exp(-exp(piPCSM)*exp(-16.40532  +  1.653947*(ln(time))  +  1.89e-
12*(time^3)))
gen PCSM_mortrate_year = PCSMatT - PCSMatT[_n-1]
replace PCSM_mortrate_year = PCSMatT if PCSM_mortrate_year==.
gen PCSsurvival_year = 1 - PCSM_mortrate_year
```

```
*Do the same for NPCM...
gen NPCMatT = 1 - exp(-exp(piNPCM)*exp(-12.4841 + 1.32274*(ln(time)) + 2.90e-12*(time^3)))
gen NPCM_mortrate_year = NPCMatT - NPCMatT[_n-1]
replace NPCM_mortrate_year = NPCMatT if NPCM_mortrate_year==.
gen NPCsurvival_year = 1 - NPCM_mortrate_year

*generate survivals
gen PCSsurvival = 1 - PCSMatT
gen NPCsurvival = 1 - NPCMatT

*'all cause mortality'
gen allcauseM = 1 - PCSsurvival*NPCsurvival
gen allcauseM_inyear = allcauseM - allcauseM[_n-1]
replace allcauseM_inyear = allcauseM if allcauseM_inyear==.

*proportion of all cause mortality
gen proportionPC_cum = PCSMatT / (PCSMatT + NPCMatT)
gen proportionPC = (PCSM_mortrate_year)/(NPCM_mortrate_year + PCSM_mortrate_year)
gen propn_NPC = 1-proportionPC // this makes more sense to me, but the breast code (line 121) suggests this should be*allcauseM_inyear ??why??

*PC mortality as competing risk
gen pred_PC_year = proportionPC*allcauseM_inyear
gen pred_PC_cum = pred_PC_year in 1
replace pred_PC_cum = pred_PC_year + pred_PC_cum[_n-1] in 2/-1

*NPC Mortality as competing risk
gen pred_NPC_year = propn_NPC*allcauseM_inyear
gen pred_NPC_cum = pred_NPC_year
replace pred_NPC_cum = pred_NPC_year + pred_NPC_cum[_n-1] in 2/-1


//The output we are interested in is: pred_PC_cum pred_NPC_cum and allcauseM at 10 or 15 years.
}
table time, c(sum pred_PC_cum sum pred_NPC_cum sum allcauseM)


**
```

Chapter 3 Appendix

Project outline to PCBaSe

External validation study of 'PREDICT: Prostate': an individualized pre-treatment prognostic model for non-metastatic prostate cancer
April 2018
Project leads:
Mr Vincent Gnanapragasam, Senior Lecturer and Honorary Consultant Urologist, Department of Surgery, University of Cambridge, UK
Mr David Thurtle, Clinical Research Associate and Urology Trainee, Department of Surgery, University of Cambridge, UK
Prof Paul Pharaoh, Professor of Cancer Epidemiology, Department of Public Health and Department of Oncology, University of Cambridge, UK

Background
Prognostic stratification is the cornerstone of management for non-metastatic prostate cancer (PCa). However, no high-quality individualised model for survival exists. Available prognostic models are predominantly built around single-centre outcome data and short term surrogates for survival amongst populations that are heavily radically treated and PSA-screened.
Using a prospectively maintained database of 10,089 men from the UK National Cancer Registration and Analysis Service, we have developed an individualised prognostic model for cancer-specific and overall survival called PREDICT: Prostate. This is novel in that it uses and predicts long term (10 and 15 year) survival outcomes, provides individual percentage survival estimates rather than group estimates or relative risks, and represents real-world data from a non-screened, primary diagnostic cohort. Importantly, it also incorporates estimated treatment effects as it is designed for use before treatment. The methodology is also novel compared to other PCa models in using fractional polynomials and modelling both cancer-specific and non-cancer outcomes within a competing risks framework.
PREDICT: Prostate combines age, PSA, histological grade group, biopsy involvement, stage, primary treatment type and comorbidity to predict 10 and 15-year outcomes. Within a split cohort UK validation the model demonstrated good discrimination with AUC 0.83 (95%CI: 0.80-0.85) and 0.83 (95%CI: 0.81-0.84) for 10-year PCSM and Overall mortality respectively. This significantly outperformed existing models ($p<0.001$) and calibration was good with no significant difference between predicted and observed PCa-specific ($p=0.19$) or overall deaths ($p=0.43$). External validation was also attempted within a small Singaporean cohort, where results were also promising with <1% differences in actual and predicted deaths and AUC of 0.84 (95%CI 0.80-0.87) and 0.78 (95%CI 0.75-0.80) for PCSM and overall mortality respectively. However, these data had much shorter median follow-up of 5.1 years, and were missing information on comorbidity.

Objectives:
- To evaluate the performance of PREDICT: Prostate within the PCBase cohort
- Compare PREDICT: Prostate to existing models within the PCBase cohort

Justification and Methods

External validation in independent cohorts, ideally in a different location, is vital to demonstrate generalizability and accuracy of a multivariable prognostic model. It is also a requirement for model endorsement [1]. Performance within the original data, even a randomly split dataset, may well be optimistic [2]. The PCBase cohort represents the best available population data for PCa and importantly it contains all the variables used within our model. PCBase is also maintained, and updated with vital status information in a manner that is similar to our original cohort. External assessment within this dataset will be informative and represent the best possible methodology for model validation[3]. Using the statistical methods outlined beneath, 10 and 15-year mortality estimates will be compared to observed outcomes within the cohort. Comparison of model performance between cohorts will be assessed and recalibration or updating of the model performed if necessary. The study will be published in the medical literature and the results will be used to inform a free an online tool which is currently under development.

Adequate validation requires that we use the fully specified existing prognostic model (both the selected variables and their coefficients) to predict outcomes for the patients in the second dataset [3]. Data analyses will all be performed in Stata™ 14. The cohort will be tidied to match the variables and data setup used in PREDICT: Prostate. Only men with intact data on age, PSA, gradegroup, t-stage and primary treatment type will be included as these are integral variables for the model. Completeness of comorbidity information will be reviewed and included if possible. A summary of missing data and exclusions will be generated.

Beta coefficients for each prognostic factor in the model will be applied to derive prognostic indexes for PCa specific mortality (PCSM) and non-PCa mortality (NPCM) for each patient. These will be used in combination with the model's baseline hazard functions and time-at-risk to create individual estimates of unadjusted PCSM and NPCM at 10 and 15 years (or maximum available follow-up, if shorter). These estimates will be converted into survivals and used to calculate overall mortality by adjusting for the competing risks between the two causes of death. Finally, adjusted 10 and 15 year predictions of cumulative PCSM and NPCM will be generated using the proportions of cause-specific mortality multiplied by overall mortality.

Across the cohort, comparison will be made between the estimated and observed numbers for cause-specific death. Calibration will be assessed by Chi-squared goodness of fit across quintiles of risk using the method of May and Hosmer[4]. Calibration will also be assessed across sub-groups including those only treated by active surveillance, conservative management or radical treatment. The ability of the model to discriminate PCSM, NPCM and overall mortality will be assessed by calculating the area under the ROC curve. Comparison of discrimination using PREDICT: Prostate will be compared to existing risk stratifications derived from the available data – namely the D'Amico and CAPRA score – using the method of DeLong[5].

If the model performs considerably less well in the PCBase cohort, model updating and recalibration will be considered. Specifically, this should be considered if the AUC is inferior to any existing model for overall mortality or if the AUC for cancer-specific mortality is less than 0.74, 0.69 or 0.73 for men undergoing prostatectomy, radiotherapy or active

surveillance respectively, as these figures have recently been reported for the three-tier stratification system in a similar publication[6]. Updating methods may vary from simple recalibration to more extensive methods such as model revision[7-8]. The adjusted model would then be based upon both the development and validation cohort offering improved stability and generalisability. Model revision may particularly explore adjustment of the comorbidity variable, as the PCBase cohort defines comorbidity differently to our UK cohort which was based upon comorbidity information derived from inpatient episodes only. The extent to which model updating is required will be unknown until model performance is assessed.

Timelines

Month 1: Data receipt and tidying
Month 2: Missing data analysis and report.
Month 3-4: Model application and accuracy assessments
Months 5-6: Review and model recalibration if necessary

Deliverable outcomes

-High impact factor publication exploring the external validation of PREDICT: Prostate
-Informing and improving a prognostic model which has significant potential for clinical impact and widespread uptake.

Summary

PREDICT: Prostate has the potential to significantly improve PCa management through informing patients and clinicians about prognosis. External validation in a geographically independent cohort will significantly improve confidence in the model, and should improve reliability and stability. Through this collaboration we would anticipate high impact publications and further refinements to our tool which will be available publicly online.

References

1. Kattan MW, Hess KR, Amin MB, et al. American Joint Committee on Cancer acceptance criteria for inclusion of risk models for individualized prognosis in the practice of precision medicine. CA Cancer J Clin. 2016 Sep;66(5):370-4.
2. Justice AC, Covinsky KE, Berlin JA. Assessing the generalisability of prognostic information. Ann Intern Med 1999; 130:515-24.
3. Altman DG. Prognosis and prognostic research: validating a prognostic model. BMJ. 2009;338:b605
4. May S, Hosmer DW. A simplified method of calculating an overall goodness-of-fit test for the Cox proportional hazards model. Lifetime Data Anal. 1998;4(2):109-120.
5. DeLong ER, DeLong DM, Clarke-Pearson DL. Comparing the areas under two or more correlated receiver operating characteristic curves: a nonparametric approach. Biometrics. 1988;44(3):837-845.
6. Gnanapragasam VJ, Bratt O, Muir K, et al. The Cambridge Prognostic Groups for improved prediction of disease mortality at diagnosis in primary non-metastatic prostate cancer: a validation study. BMC Medicine. 2018; 16:31
7. Van Houwelingen JC. Validation, calibration, revision and combination of prognostic survival models. Stat Med2000;19:3401-15

8. Steyerberg EW, Borsboom GJ, van Houwelingen HC, Eijkemans MJ, Habbema JD. Validation and updating of predictive logistic regression models: a study on sample size and shrinkage. Stat Med2004;23:2567-86

PCBaSe Data Request Form

Application for data retrieval to the steering committee for
Prostate Cancer data Base Sweden (PCBaSe)

Date:
04/04/2018

Name of applicant:
Mr Vincent Gnanapragasam
Mr David Thurtle

Address:
Academic Urology Group,
Box 193, Norman Bleehan Oncology Offices,
Robinson Way, Cambridge Biomedical Campus, Cambridge UK, CB2 0QQ

Phone number:
[number redacted]

E-mail address:
[email redacted]

University/Institution:
University of Cambridge

Department/unit:
Academic Urology Group,

Collaborators, name and affiliation:
Mr Ola Bratt
Professor of Urology, Sahlgrenska Academy at Gothenburg University, Sweden

Project title:
External validation of 'PREDICT: *Prostate':* an individualized prognostic model for long term cancer-specific and overall survival.

Description of project:

Inclusion criteria:
All men diagnosed with non-metastatic prostate cancer and with PSA<100ng/ml at diagnosis. Diagnosed between 2000 and 2013.

Variables to be included:
Variables

Age	*PSA*	*Grade Group*	*T stage*	*Percentage Positive Cores**	*Ethnicity*	*Primary Treatment*	*Comorbidity*

Other information:

ID/PseudoID	*Diagnosis date (or diagnosis year)*	*Vital status at censorship*	*PCa death*	*Non-PCa death*	*Date of death (or days from diagnosis to death)*	*Censor date (or days from diagnosis to censorship)*

**Optional*

Description of statistical method.
The cohort will be split by random number generation into model development and validation cohorts. Within the development cohort the proportional hazards assumption will be tested for each variable, then separate Cox regression models will be built for prostate cancer specific mortality (PCSM) and non-prostate cancer mortality (NPCM). A backwards elimination technique will be used for variable selection with a 5% significance level. Risk-relationships between continuous variables will be modelled using multivariable fractional polynomials.
After fitting of both models, smoothed functions for the baseline hazard of PCSM and NPCM will be calculated using a univariate fractional polynomial function. These functions will be used to calculate the cumulative baseline hazard at 15 years.
Beta coefficients for each prognostic factor in the Cox models will be used to derive a prognostic index (pi) for both PCSM and NPCM for each patient which will be used in combination with the baseline hazard to create individual estimates of cause-specific mortality. These estimates will be adjusted for the competing risks between PCSM and NPCSM. Individual estimates will be compared to observed events within the validation cohort to assess accuracy by discrimination and calibration.

Abstract for Brief study plan (300 words)
Prostate cancer is the commonest male cancer. However, treatment decisions in a large proportion of men with non-metastatic disease remain complex – with the impact and risks of a cancer diagnosis balanced against potential morbidity associated with treatment. Accurate personalised prognostic information is required to inform this decision, however currently available prognostic models use broad heterogeneous groups and do not provide estimates of long term outcomes.

This project aims to explore the factors that are associated with cancer-specific and non-cancer mortality, and build an individualised prognostic model for men with newly diagnosed non-metastatic PCa. This should estimate what benefit each treatment might offer and contextualize cancer mortality against overall mortality.

Data will be analysed using Stata™14, modelling against outcomes censored at both 10 and 15 years. The cohort will be split by random number generation into model development and validation cohorts. Within the development cohort the proportional hazards assumption will be tested for each variable, then separate Cox regression models will be built for prostate cancer specific mortality (PCSM) and non-prostate cancer mortality (NPCM). A backwards elimination technique will be used for variable selection with a 5%

significance level. Risk-relationships between continuous variables will be modelled using multivariable fractional polynomials.

After fitting of both models, smoothed functions for the baseline hazard of PCSM and NPCM will be calculated using a univariate fractional polynomial function. These functions will be used to calculate the cumulative baseline hazard at 15 years. Beta coefficients for each prognostic factor in the Cox models will be used to derive a prognostic index for both PCSM and NPCM for each patient which will be used in combination with the baseline hazard to create individual estimates of cause-specific mortality. These estimates will be adjusted for the competing risks between PCSM and NPCSM. Individual estimates will be compared to observed events within the validation cohort to assess accuracy by discrimination and calibration.

This work would emulate the methodology of work in a UK population of over 10000 men with 10 years median follow-up. Comparison of model performance between cohorts will be assessed and recalibration of the model performed as necessary. This study would be published in the medical literature and widely shared with clinicians and patients.

Working plan, time plan
Week 1: Data receipt and tidying
Week 2: Data exploration and testing of proportional hazards assumption
Week 3: Model development
Week 4: Model accuracy assessment

Attached
Complete study plan

Signature applicant

Chapter 4 Appendix

Clinician Study Questionnaires

Common starting Questions

1. What is your current role?
    a. Consultant urologist
    b. Consultant oncologist
    c. Trainee urologist
    d. Trainee oncologist
    e. Specialist Nurse
    f. Other (open box)

2. Which of the following best describes your primary place of work?
    a. UK tertiary cancer centre
    b. UK general hospital
    c. Non-UK specialist/academic centre
    d. Non-UK general hospital
    e. Other (open box)

    IF – c or d … what is your country of work?

3. How often do you counsel men with newly diagnosed prostate cancer?
    a. Daily
    b. Weekly
    c. Monthly
    d. Rarely
    e. Never
4. When considering treatment options in newly diagnosed non-metastatic prostate cancer, in your routine clinical practice do you use nomograms or other risk prediction/stratification tools to help predict survival or aid decision making?
    a. Yes
    b. No
        – If yes… which tool/nomogram(s) do you use?

5. When considering treatment as opposed to surveillance for prostate cancer, a prediction tool would be most useful when the risk of 10-year prostate cancer death is:
    0-10%
    10-20%
    20-40%
    >40%
    All of the above

    RANDOMISATION

'RANDOM GROUP 1'

A series of 6 brief clinical vignettes will be presented.
From the available information for each case, please answer the questions below. 'Radcal treatment' realtes to prostatectomy OR radiotherapy. The questions are the same for each of these cases.

6. Case B1 **153**

   75 years old
   PSA 5.1ng/ml
   T1
   Gleason 3+4 (grade group 2) in 2/12 biopsies.
   No significant comorbidity.

   a) On a scale from 0 (certainly not) to 100 (certainly) how likely would you be to recommend radical treatment? (0-100 slider)
   b) Of 100 men with these characteristics, how many would you estimate will die from prostate cancer within 15 years if conservatively managed? (0-100)
   c) Of 100 men with these characteristics, how many would you estimate will die from other causes (not prostate cancer) in 15 years? (0-100)
   d) Of 100 men with these characteristics, if all were radically treated as opposed to conservatively managed, how many extra men would you estimate to be alive at 15 years? (0-100)

7. Case B2: **154**
   57 years old
   PSA 12.0ng/ml
   T2
   Gleason 4+3 (grade group 3) prostate cancer in 10/12 cores.
   No significant comorbidity.

8. Case B3 **155**
   71 years old
   PSA 9.0ng/ml
   T2
   Gleason 3+3 (grade group 1) disease in 3/12 cores.
   No significant comorbidity.

9. Case B4 **157**
   58 years old
   PSA 15.3 ng/ml
   T2
   Gleason 4+3 (grade group 3) disease in 7/14 cores.
   No significant comorbidity.

10. Case B5 **159**
    61 years old
    PSA 6.1ng/ml
    T3
    Gleason 3+4 (grade group 2) in 2/12 cores.
    No significant comorbidity.

11. Case B6 **160**
    81 years old
    PSA 6.1ng/ml
    T1
    Gleason 3+4 (grade group 2) in 1/12 cores.
    Otherwise well, with no hospital admissions in the last 2 years.

    The second group of clinical vignettes will be accompanied by some of the available output from PREDICT: Prostate. *Please read the following vignettes and review the output then answer the questions below.*

12. Case A1: **161**

    64 years old
    PSA 23ng/ml
    T3
    Gleason 4+4 (grade group 4) in 3/12 biopsies.
    Otherwise well with no hospital admissions in the last 2 years.

    a) On a scale from 0 (certainly not) to 100 (certainly) how likely would you be to recommend radical treatment?

    b) **162** Considering the PREDICT estimates of survival benefit from radical treatment in this case (A1) :
       The overall survival benefits of treatment are greater than I expected (button)
       The overall survival benefits of treatment are less than I expected (button)
       The overall survival benefits of treatment are similar to what I expected (button)

13. Case A2: **163**
    72 years old
    PSA 8.2ng/ml.
    T2
    Gleason 3+3 (grade group 1) in 3/14 biopsy cores.
    He has a history of myocardial infarction 1 year ago.

14. Case A3: **165**
    54 years old
    PSA 14.0ng/ml
    T2
    Gleason 4+3 (grade group 3) in 2/12 biopsies

Otherwise well with no hospital admissions in the last 2 years.

15. Case A4: **167**
    68 years old
    PSA 13.4ng/ml
    T2 prostate
    Gleason 4+3 (grade group 3) in 8/16 biopsies
    Otherwise well with no hospital admissions in the last 2 years.

16. Case A5: **171**
    60 years old
    PSA 6.4ng/ml
    T1
    Gleason 3+4 (grade group 2) in 2/12 biopsies.
    Otherwise well with no hospital admissions in the last 2 years.

17. Case A6: **173**
    83 years old
    PSA 24ng/ml
    T1
    Gleason 3+4 (grade group 2) in 1/12 biopsies.
    Admitted to hospital earlier this year with an ischaemic toe.

RANDOM GROUP 2

18. Case A1: **177**

    64 years old
    PSA 23.0 ng/ml
    T3
    Gleason 4+4 (grade group 4) in 3/12 biopsies.
    Otherwise well with no hospital admissions in the last 2 years.

    a) On a scale from 0 (certainly not) to 100 (certainly) how likely would you be to recommend radical treatment? (0-100 slider)
    b) Of 100 men with these characteristics, how many would you estimate will die from prostate cancer within 15 years if conservatively managed? (0-100)
    c) Of 100 men with these characteristics, how many would you estimate will die from other causes (not prostate cancer) in 15 years? (0-100)
    d) Of 100 men with these characteristics, if all were radically treated as opposed to conservatively managed, how many extra men would you estimate to be alive at 15 years? (0-100)

19. Case A2: **178**

72 years old
PSA 8.2ng/ml.
T2
Gleason 3+3 (grade group 1) in 3/14 biopsy cores.
He has a history of myocardial infarction 1 year ago.

20. Case A3: **179**
    54 years old
    PSA 14.0ng/ml
    T2
    Gleason 4+3 (grade group 3) in 2/12 biopsies
    No significant comorbidity.

21. Case A4: **180**
    68 years old
    PSA 13.4ng/ml
    T2 prostate
    Gleason 4+3 (grade group 3) in 8/16 biopsies
    No significant comorbidity.

22. Case A5: **181**
    60 years old
    PSA 6.4ng/ml
    T1
    Gleason 3+4 (grade group 2) in 2/12 biopsies.
    No significant comorbidity.

23. Case A6: **182**
    83 years old
    PSA 24.0 ng/ml
    T1
    Gleason 3+4 (grade group 2) in 1/12 biopsies.
    Admitted to hospital earlier this year with an ischaemic toe.

    The second group of clinical vignettes will be accompanied by some of the available output from PREDICT: *Prostate.* Please read the following vignettes and review the output then answer the questions below.

24. Case B1 **185**
    75 years old
    PSA 5.1ng/ml
    T1
    Gleason 3+4 (grade group 2) in 2/12 biopsies.
    No significant comorbidity.

a) On a scale from 0 (certainly not) to 100 (certainly) how likely would you be to recommend radical treatment?

b) **186** Considering the PREDICT estimates …
The overall survival benefits of treatment are greater than I expected (button)
The overall survival benefits of treatment are less than I expected (button)
The overall survival benefits of treatment are similar to what I expected (button)

Case B2: **187**
57 years old
PSA 12.0ng/ml
T2
Gleason 4+3 (grade group 3) prostate cancer in 10/12 cores.
No significant comorbidity.

Case B3 **189**
71 years old
PSA 9.0ng/ml
T2
Gleason 3+3 (grade group 1) disease in 3/12 cores.
No significant comorbidity.

Case B4 **191**
58 years old
PSA 15.3 ng/ml
T2
Gleason 4+3 (grade group 3) disease in 7/14 cores.
No significant comorbidity.

Case B5 **193**
61 years old
PSA 6.1ng/ml
T3
Gleason 3+4 (grade group 2) in 2/12 cores.
No significant comorbidity.

Case B6 **195**
81 years old
PSA 6.1ng/ml
T1
Gleason 3+4 (grade group 2) in 1/12 cores.
No significant comorbidity.

Common Closing Questions

82
Do you feel PREDICT: *Prostate* would be a useful clinical tool?

a. No
b. Yes
c. Unsure

83

Please enter any additional comments or feedback you have about PREDICT: *Prostate* (Open box)

Thank you for taking the time to complete this survey.

Chapter 5 Appendix

Patient study protocol

Key Contacts

Mr. David Thurtle BMedSci BMBS MRCS AFHEA
Telephone [number redacted]
Clinical Research Associate
Honorary Urology Registrar
[Email redacted]

Mr. Vincent J. Gnanapragasam PhD FRCS FRCSEd(Urol)
Telephone [number redacted]
Lecturer in Uro-Oncology
Honorary Consultant Urological Surgeon
[Email redacted]

FULL/LONG TITLE OF THE STUDY
Evaluation of a new tool, PREDICT: *Prostate,* to aid treatment decision-making for men with newly diagnosed non-metastatic prostate cancer

SHORT STUDY TITLE / ACRONYM
PREDICT: *Prostate* Patient Study

PROTOCOL VERSION NUMBER AND DATE
1.3 March 2019

RESEARCH REFERENCE NUMBERS

IRAS Number:	249699
REC Reference:	**18/EE/0254**
SPONSORS Number:	Cambridge University Hospitals NHSFT: A094875 University of Cambridge #TBC
FUNDERS Number:	The Urology Foundation Research Scholarship (RG #96622)

SIGNATURE PAGE

The undersigned confirm that the following protocol has been agreed and accepted and that the Chief Investigator agrees to conduct the study in compliance with the approved protocol and will adhere to the principles outlined in the Declaration of Helsinki, the Sponsor's SOPs, and other regulatory requirement.

I agree to ensure that the confidential information contained in this document will not be used for any other purpose other than the evaluation or conduct of the investigation without the prior written consent of the Sponsor

I also confirm that I will make the findings of the study publically available through publication or other dissemination tools without any unnecessary delay and that an honest accurate and transparent account of the study will be given; and that any discrepancies from the study as planned in this protocol will be explained.

For and on behalf of the Study Sponsor:

Signature: Date:

..../...../.....

Name (please print):

.....

Position:

.....

Chief Investigator:

Signature: Date:

.....[signature redacted] ..../...../.....

Name:……..Mr David Thurtle…….....

Position: Clinical Research Associate and Honorary Urology Registrar

LIST of CONTENTS

KEY STUDY CONTACTS

Chief Investigator	Mr David Thurtle, [numbers redacted], [email redacted]
Study Co-ordinator	Mr David Thurtle [numbers redacted], [email redacted]
Co-investigator / Supervisor	Mr Vincent Gnanapragasam [number redacted], [email redacted]
Study Co-Sponsors	Cambridge University Hospitals NHS Foundation Trust Stephen Kelleher, R&D Manager, Cambridge University Hospitals NHSFT, Hills Road, Cambridge, CB2 0QQ, Tel: [numbers redacted], E-mail: [redacted] University of Cambridge Carolyn Read, Research Governance Officer, University of Cambridge School of Clinical Medicine, Addenbrooke's Hospital, Hills Road, Cambridge CB2 0SP [email redacted]
Funder(s)	The Urology Foundation
Key Protocol Contributors	David Thurtle, [number redacted], [email redacted] Vincent Gnanapragasam, [number redacted], [email redacted]
Committees	Cambridge Urology Translational Research and Clinical Trials (CU-TRACT), c/o Susan Platt, Team Administrator, [number redacted]

STUDY SUMMARY

Study Title	Evaluation of a new tool, PREDICT: *Prostate,* to aid treatment decision-making for men with newly diagnosed non-metastatic prostate cancer
Internal ref. no. (or short title)	PREDICT: *Prostate* Patient Study
Study Design	Prospective randomised controlled study
Study Participants	Men diagnosed with non-metastatic prostate cancer suitable for active surveillance or radical treatment.
Planned Size of Sample (if applicable)	Target recruitment rate 150/year
Follow up duration (if applicable)	1 year
Planned Study Period	August 2018 – July 2020
Research Question/Aim(s)	Does PREDICT: *Prostate* improve treatment decisional confidence and anxiety amongst men diagnosed with non-metastatic prostate cancer? Does PREDICT: *Prostate* affect patient decision-making with regards to treatment for localised prostate cancer? How do PREDICT: *Prostate* outcomes compare to patients' perceptions about long term survival outcomes.
Lay summary	The number of men diagnosed with prostate cancer is rising, in the vast majority of cases the disease has not spread elsewhere (non-metastatic). Here, treatment decisions are complex, with the risks of a cancer diagnosis balanced against potential problems associated with treatment. National guidelines advise

	that evidence-based decision aids should be used, yet no adequate individualised decision aid yet exists. To address the absence of such an important aid we have developed 'PREDICT: *Prostate'.* This is a decision model and website which provides personalised survival estimates based on an individual's characteristics and those of their cancer. The model allows the risk of dying from cancer to be contextualised against other risks of death and estimates the potential survival benefit from treatment. This study seeks to assess the clinical usefulness and potential impact of PREDICT: *Prostate* amongst patients diagnosed with prostate cancer. We will assess the impact of the model on treatment decision-making, and on levels of concern, confidence and anxiety amongst newly diagnosed men. We will also assess how PREDICT estimates compare to patients' perceptions about survival. We will also seek feedback about the model and its usefulness. As per the study flow chart below; after selection, recruitment and informed consent, patients will be assigned to either the 'standard of care' (SOC) arm or the 'SOC + PREDICT' arm of the study. Prior to their next clinical follow-up appointment, participants will be invited to attend the hospital for a study meeting. During this meeting, all participants will be asked to complete a questionnaire. For those in the 'SOC and PREDICT' arm, this questionnaire will follow a semi-structured presentation of the PREDICT: *Prostate* model; those in the SOC arm will complete the questionnaire only. The participant's involvement in the study will finish after completion of the questionnaire with no further intervention or involvement required.

FUNDING AND SUPPORT IN KIND

FUNDER(S) (Names and contact details of ALL organisations providing funding and/or support in kind for this study)	**FINANCIAL AND NON FINANCIALSUPPORT GIVEN**
The Urology Foundation 1-2 St Andrews Hill London EC4V 5BY	Grant-funding for salary and study costs - through a peer-reviewed competitive national application process.
Any additional study costs will be internally funded, where necessary.	

ROLE OF STUDY SPONSOR AND FUNDER

The study will be sponsored by Cambridge University Hospitals NHS Foundation Trust and the University of Cambridge. The research and development (R&D) department of the sponsor will aide in study design and protocol-review.

The study will fall under the remit of the Cambridge Uro-Oncology Translational and Clinical Trials team (CU-TRACT) who will supervise the study's conduct, progress and analysis. Final decisions regarding all aspects of the study will be taken by the CI in collaboration with the CU-TRACT team.

The project will be funded through a research grant received from The Urology Foundation. This funder will have no influence on the design, analysis or dissemination of the study. Any small additional costs relating to this study will be supported through departmental funding, via Mr Gnanapragasam

PROTOCOL CONTRIBUTORS

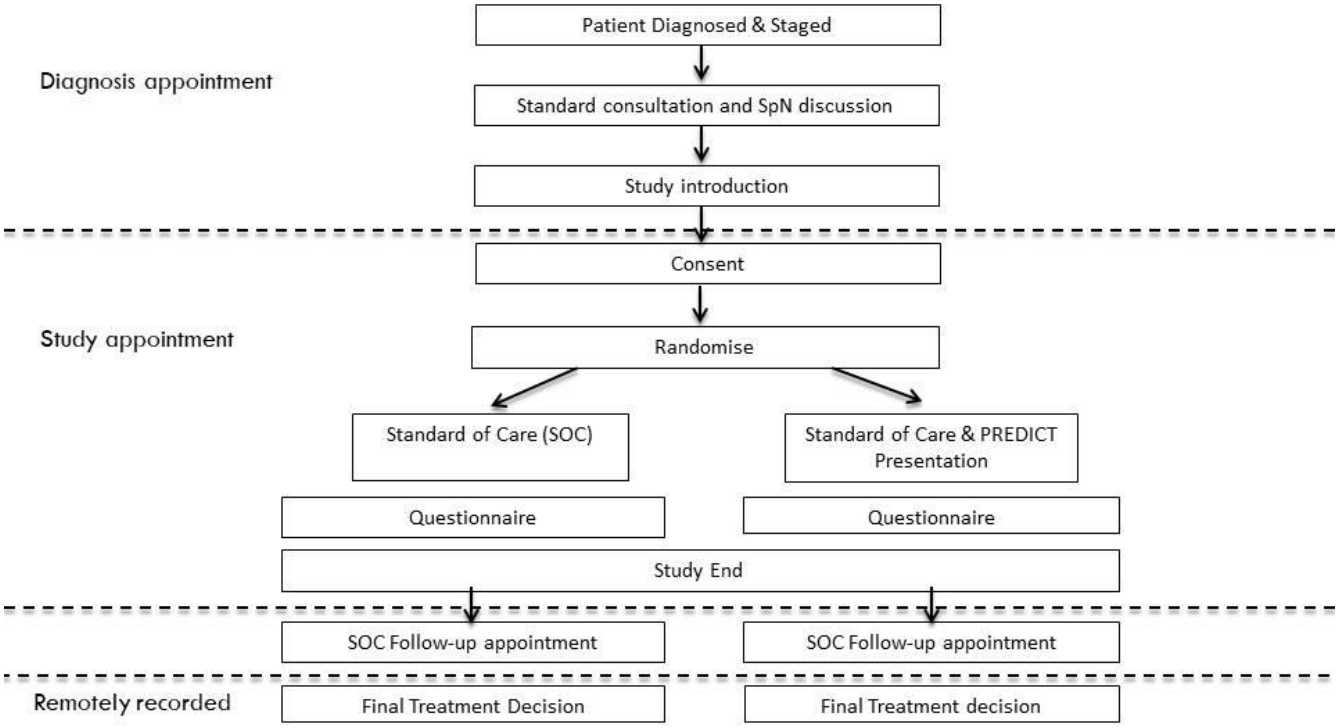
The protocol has been reviewed and critiqued by the sponsor following initial drafting by the study CI in collaboration with Mr Vincent Gnanapragasam, Academic Urology Group lead and CU-TRACT team leader. The protocol has been assessed and amended by members of the nursing and medical teams, and has been through an external peer-review process.

KEY WORDS: Prostate Cancer
Prognostic model
Impact study
Medical decision-making

PREDICT: Prostate Patient Study – Timeline.

Activity	2018				2019				2020			
	Q1	Q2	Q3	Q4	Q1	Q2	Q3	Q4	Q1	Q2	Q3	Q4
Study design and review												
HRA Application and review												
Patient recruitment												
Data analysis												
One-year review and write-up												
Final write-up												
External presentations/ publications												

PREDICT: Prostate Patient Study Flow Chart



STUDY PROTOCOL

TITLE

Evaluation of a new tool, PREDICT: *Prostate,* to aid treatment decision-making for men with newly diagnosed non-metastatic prostate cancer

1 BACKGROUND

Prostate cancer (PCa) is the commonest cancer affecting males and is a leading cause of cancer-related morbidity [1]. The vast majority of new presentations (>80%) are with localised or locally advanced disease representing a significant healthcare and economic burden [2]. Treatment decisions are notoriously complex with the risk of progression and psychological impact of a cancer diagnosis balanced against potential morbidity associated with radical treatment for indolent tumours. Prognostic stratification is therefore the cornerstone of management. However, no high-quality individualised model for survival exists as demonstrated by the inability of the American Joint Committee on Cancer (AJCC) to endorse a single prognostic model for non-metastatic PCa [3].

We have therefore developed a novel individualised prognostic model called 'PREDICT: *Prostate*' for non-metastatic PCa. This contextualises the relative PCa-specific and overall survival outcomes for men with newly diagnosed disease and allows modelling of the estimated impact of radical treatment on these outcomes. To develop this we used data from 10,089 men diagnosed with PCa in Eastern England with median follow-up of 9.8 years and 3,829 deaths (1,202 PCa-specific). The model demonstrated good discrimination within a UK validation cohort with Concordance-index 0.83 (95%CI: 0.80-0.85) and 0.75 (95%CI: 0.74-0.77) for 15-year PCSM and Overall mortality respectively. This outperformed existing stratification criteria such as the European Association of Urology guidelines (C-index 0.69), National Cancer Collaborative Network criteria (C-index 0.72) and UCSF Cancer of the

Prostate Risk Assessment (CAPRA) score (C-index 0.75). Accuracy has also been validated in external populations. The model has also been designed to meet all AJCC criteria for model adoption [4]. A publication on 'PREDICT: Prostate' is currently undergoing peer-review for publication.

2 RATIONALE

"An accurate prognostic model is of no benefit if it is not generalizable or doesn't change behaviour" – Moons et al BMJ 2009 [5]

PREDICT: *Prostate* has many strengths in that it is built around real world data, the included predictors are unambiguously defined and the outcomes are transparent. Although accuracy appears favourable it is possible to have developed an accurate model that offers minimal clinical benefit. Although the model will be free to use, many stakeholders will expect to see evidence of clinical utility prior to adoption. In assessing the clinical utility we hope to quantify any potential benefit of using the model compared to current standard practice.

The underlying assumption that accurate outcome estimates lead to improved patient decision-making requires testing. 'Impact studies' such as this, seek to quantify whether using a prognostic model improves decision-making within a comparative design. Impact studies should by definition include a control group who receive standard care. "Only an impact analysis can determine whether use of the model is better than usual care" [5]. Alongside this, impact studies can be useful to study issues that may affect acceptability and uptake of a model in regular care – including usability. The ideal assessment outcome of survival is not a viable option, therefore we seek to assess the effect the model has on shorter term outcomes such as decision-certainty, decision-anxiety, decision-making behaviours and perceptions of disease severity.

RESEARCH AIMS

In this study we will seek to answer the following questions:

Does PREDICT: *Prostate* improve decision confidence, and reduce anxiety, amongst men diagnosed with non-metastatic prostate cancer?

Does PREDICT: *Prostate* change patient decision-making around treatment for non-metastatic prostate cancer?

How do PREDICT: *Prostate* survival estimates compare to patients' perceptions?

3.1 Objectives

1. To assess patient decisional certainty with and without use of the PREDICT: *Prostate* tool.
2. To gain insights into patient perceptions on PCa risks and the factors behind treatment decision-making, and assess whether certain patients may benefit more from using PREDICT: *Prostate.*

3.2 Outcome measures

Primary outcome measure

1. Patient scores on decisional certainty measured by the decisional conflict scale (DCS) [6]

Secondary outcome measures

1. Patient scores on state-anxiety measured on the State-Trait Anxiety Inventory (STAI-Y) [7]
2. Reported treatment preference and confidence in their decision on a 0-100 scale.
3. Actual treatment decided upon or received (as recorded in the medical notes).

4 STUDY DESIGN and METHODS of DATA COLLECTION AND DATA ANALYIS

The study is a prospective randomised study without medical or surgical intervention. The study will be introduced by a member of the clinical team following the diagnosis of non-metastatic prostate cancer. Prior to their next hospital appointment as part of their routine clinical pathway, participants will be invited to attend a study appointment at the hospital. After further discussion and informed consent, patients will be randomised to the standard of care (SOC) arm or the 'SOC and PREDICT' (intervention) arm of the study. During this study appointment, participants will be asked to complete a questionnaire. For those in the intervention arm, this questionnaire will follow a semi-structured presentation of the PREDICT: *Prostate* model. Patients on the SOC arm will simply be asked to complete the questionnaire. These questionnaires will assess treatment preferences, decisional confidence and anxiety, and patients' perceptions of risk regarding their disease – using validated scores for each.

The PREDICT: *Prostate* model itself will be presented on a computer by an individual researcher or designated individual trained in the background of the model. They will present the model in a semi-structured manner. First the rationale, goals, and a detailed description of the decision aid will be presented, following the web-pages of the model. The patient's individual details will be entered into the model and the results explained to them using positive and negative terms, and expressing uncertainty. For example "out of 100 patients with the same age and disease characteristics as you, 16 are expected to die from prostate cancer in the next 10 years, 10 are expected to die from other causes, and 74 are expected to still be alive. At this moment we cannot say to which group you will belong." Graphs, charts, text, icons and actual numbers will be presented to the participants showing the estimated outcomes with conservative management and radical treatment – following the design of the website. Adverse effects information will also be presented through the website, alongside an explanation of their providence. The researcher will not themselves go into further details on technical aspects and will not offer clinical advice beyond explaining the website. All patients will be seeing a clinician in a follow-up appointment as part of their clinical pathway soon after completing the questionnaire, and have access to a specialist nurse at any point. If patients have new questions as a result of the questionnaire or from seeing PREDICT: Prostate they will have the opportunity to discuss these with their health care professionals through these mechanisms.

The webtool can be accessed for review using the following address:
www.prostate.predict.nhs.uk

Data collection

Case report forms (CRF) will be completed by a researcher for all study participants at study entry. Questionnaires will be completed by all study participants on the day of the first follow-up appointment. Copies of these questionnaires, which have been reviewed and edited by a patient and public involvement group are included in the appendix.

Impact of the decision aid may depend upon patient and tumour characteristics that affect their understanding, and perceptions about disease management. Therefore, data will be collected on patient demographic and tumour details. Details of tumour characteristics will be entered using details from the hospital electronic record system. The importance of various factors in decision-making will also be assessed such as survival, bowel function, urinary function and burden of treatment itself. Methodology for this purpose has been published previously [8].The scoring systems used within the questionnaire are validated scales that have been used widely in clinical research, namely

the Decisional Conflict Scale (DCS) [6], Decision Making Preference Questionnaire (DMPQ) [9] and the State-Trait Anxiety Inventory (STAI-Y) [7]. The final treatment decision will be recorded from the medical notes.

Data analysis

We will use descriptive statistics to describe the participant cohort and check for imbalance between arms of the study. The impact of the intervention will be tested in an intention-to-treat analysis comparing the intervention group to the control group. Mean DCS and STAI scores between groups will be compared using independent samples t-test. Data analysis will be performed using Stata™ 14. Calculations for sample size are shown below. Subgroup analyses will be performed using responses to the DMPQQ, the patient's prostate cancer risk group, and according to responses about the importance of associated issues in a patient's decision-making. If further sites are added in future amendments, sub-group analysis will be performed by site to assess whether the location of the study had any impact on outcomes and to assess the variance**.** Qualitative feedback, patient comments and answers to questions about usefulness of the model will be collated and analysed using a deductive approach using our questions as a guide for grouping and analysing our data.

5 STUDY SETTING

This study will be implemented in prostate diagnostic clinics. The lead site will be Cambridge University Hospitals NHS Foundation Trust (CUH). Cambridge itself has strong research infrastructure, with the potential for collaborations across specialties. Patients at CUH are used to being invited into research projects, and are often keen to be involved in such studies. Testing this particular model within the East of England is particularly appropriate, given the model was developed using data from men diagnosed with PCa in the East of England.

This study falls perfectly within the construct of our current clinical pathway, without any disruption to patients or services. The study supplements the current clinical pathway by seeking to better-inform patients, yet does not require any additional practical interventions. After being told of their PCa diagnosis, men are always counselled by the informing clinician and a specialist nurse. Men are then given written information and links to useful websites to take home and think over. Men are then invited to meet with an oncologist and or a surgeon to discuss radiotherapy and surgery respectively before usually meeting with the diagnosing urologist again. These follow-up appointments provide opportunities for the questionnaire and intervention to be performed within the standard care pathway without expecting patients to make additional trips into hospital. Otherwise, if patients are willing, study appointments can be arranged at other mutually convenient times prior to their next follow-up appointment.

6 SAMPLE AND RECRUITMENT

6.1 Eligibility Criteria

6.1.1 Inclusion criteria

Men newly diagnosed with primary non-metastatic PCa.

Men for whom either active surveillance or radical treatment (prostatectomy +/- radiotherapy) are felt to be appropriate by the diagnosing clinician.

Age 35-80 years

Able to understand and sign the written Informed Consent Form

6.1.2 Exclusion criteria

Subject is known to have a condition, which affects their ability to see, read or understand the decision aid
Subject is known to have any other condition, which in the opinion of the investigator makes the subject unsuitable for study participation.
The subject is unable to comprehend English. (PREDICT Prostate is only available in English currently)

6.2 Sampling

6.2.1 Size of sample

This study is both a qualitative and quantitative study aiming to explore the impact of PREDICT: Prostate in the decision-making pathway and patients' impressions on the model. Sample size calculations are directed by the hypothesis that PREDICT: Prostate will improve decision-certainty, and reduce decisional conflict. Comparison between the intervention and control group will be performed by comparison of means. Decision certainty will be derived on a 0-100 scale from the DCS and the uncertainty sub-scale of the DCS. Using a conservative estimate of 20% change in decision certainty, (with SD 20, α 0.05, β 0.80) the minimum required sample size is 16 for each arm (i.e 32 total patients). However, some men may feel unable to state a treatment preference or complete the relevant parts of the questionnaire.
This effect size is an estimate. Similar studies using decision interventions have reported changes in actual treatment choices in excess of 20% [10], whilst others have reported effect sizes up to 38% for decision regret in a similar randomised controlled trial of a decision aid [11]. Therefore an effect size of 20% on reported decision-certainty appears reasonable.
It is estimated about 200 patients are diagnosed with non-metastatic PCa at Addenbrooke's hospital each year. Therefore our recruitment target of 50 per year is a realistic one, and will be sufficiently powered to answer our primary question.

Sampling technique / Randomisation

Participants will be randomised to standard of care or standard of care & presentation of the PREDICT: Prostate model. Consecutive eligible patients will be approached wherever possible. Randomisation will be achieved by block random allocation (with random block sizes from 4-6) to achieve a greater equivalence between treatment groups in group sizes and baseline characteristics [12].

6.3 Recruitment

6.3.1 Recruitment

Eligible patients newly diagnosed with PCa will be informed about the study by their diagnosing clinician, specialist nurse or another member of their clinical care team. If interested in the study potential participants will then be approached in clinic and given information sheets, verbal information about the study and a copy of the consent form. Each will be given the opportunity to ask questions. Verbal consent to be contacted by telephone will be sought. Potential participants will then be contacted and invited to attend a study appointment at some point prior to their next clinical follow-up appointment – where formal written consent will be completed prior to the presentation of PREDICT or completion of questionnaires.

6.3.2 Sample identification

Eligible subjects will be identified from prostate diagnostic clinics and multi-disciplinary team meetings (MDTs). These patients will be identified by the PI, the patient's responsible urology consultant or another member of the patient's existing clinical care team. There will be no posters, adverts, websites or other active recruitment techniques. Patients will not be recruited through Patient Identification Centres.
No payments will be made to participants of the study. Participation will not routinely require any additional travel, visits or diversion from the clinical pathway.

6.3.3 Consent

Patients unable to give informed consent, unable to read English or those who lack capacity are not eligible for the study. No efforts will be made to recruit these men.
Suitable subjects diagnosed through urology clinics will be approached and invited to participate in the study, or for permission to contact them with regards to the study, by their consultant or specialist nurse, or another member of the direct care team. The study will not be introduced until after the diagnosis of non-metastatic prostate cancer has been given to them by the clinician. Men will be offered a comprehensive information sheet and a copy of the consent form. A discussion will be had about the nature and objectives of the study and possible risks associated with participation, between the potential participant and the CI, PI or an appropriately trained individual knowledgeable about the research named on the delegation log. Potential participants will be given the opportunity to raise any questions.
Consent will be taken at the start of the study appointment – allowing at least a 24 hour cooling off period from when the study was first introduced. Consent would be taken to complete a questionnaire with or without a preceding semi-structured presentation of the PREDICT: *Prostate* tool.
If a participant, who has given informed consent, loses capacity to consent during the study, or decides to withdraw consent, the participant and all identifiable data Collected would be withdrawn from the study.

7 ETHICAL AND REGULATORY CONSIDERATIONS

The predominant ethical aspect of this study is that the prognostic model may affect actual treatment decision-making, indeed this is a secondary outcome. However, this is a prognostic model/decision aid that has been developed according to established methodology which meets international adoption standards [4, 13] . It has been developed by an expert team in Cambridge, including Professor Paul Pharaoh (Cancer Epidemiology) and Mr Vincent Gnanapragasam (Academic Urology). It has been developed and validated within a primary cohort of men from Eastern England and has also been externally validated in a cohort of Singaporean men. Therefore, the generalisability to other men in the East of England is particularly valid.
Any informed decision-making is an improvement on current practice where decision aids are very rarely used – despite NICE guidance recommending their regular use [14]. Individualised tools providing long term survival estimates like the PREDICT: *Prostate* model are almost non-existent in current PCa patient-counselling. Therefore, this represents a probable improvement on the current decision-making process. Further to this, all patients will still have the standard of care consultations with clinicians, with this study having no impact on these meetings or consultations. Participants will each be seen by a specialist clinician after the tool is presented, with no final decisions being made after presentation of

the model and all patients will have the opportunity to discuss the results of the tool with a specialised clinician in these routine clinical appointments.

7.1 Research Ethics Committee (REC) and other Regulatory review & reports

Before the start of the study, a favourable opinion will be sought from the local Research Ethics Committee and NHS REC for the study protocol, informed consent forms and patient information sheets. Specifically, we state that:

Substantial amendments that require review by NHS REC will not be implemented until that review is in place and other mechanisms are in place to implement at site.

All correspondence with the REC will be retained.

It is the Chief Investigator's responsibility to produce the annual reports as required.

The Chief Investigator will notify the REC of the end of the study.

An annual progress report (APR) will be submitted to the REC within 30 days of the anniversary date on which the favourable opinion was given, and annually until the study is declared ended.

If the study is ended prematurely, the Chief Investigator will notify the REC, including the reasons for the premature termination.

Within one year after the end of the study, the Chief Investigator will submit a final report with the results, including any publications/abstracts, to the REC.

Regulatory Review & Compliance

If this study is performed at other sites within the East of England, regulatory review across sites will be overseen by the CI.

Amendments

Should amendments need to be made to the REC application, the CI will contact the sponsor who will assess whether an amendment is substantial or non-substantial. The sponsor will submit a valid notice of amendment to the REC for consideration. Substantive changes will be clearly communicated by email to the sponsor's R&D Department and the REC. Amendment history will be tracked by renumbering of the protocol for each set of amendments made. This numbering will commence from 0.1 for the first draft protocol, and 1.0 for the first approved protocol.

7.2 Peer review

All patient questionnaires, the PIS and ICF have been reviewed and corrected by a patient and public involvement panel. The protocol has undergone external peer-review by Ms C Etheridge (Lead Macmillan Urology Clinical Nurse Sprecialist, Ipswich Hospital) and Mr M Sut (Consultant Urological Surgeon, Peterborough Hospital following the standards outlined below from NIHR/CRN:

Peer review must be independent, expert, and proportionate:

Independent: At least two individual experts should have reviewed the study. The definition of independent used here is that the reviewers must be external to the investigators' host institution and not involved in the study in any way. Reviewers do not need to be anonymous.

Expert: Reviewers should have knowledge of the relevant discipline to consider the clinical and/or service based aspects of the protocol, and/or have the expertise to assess the methodological qualitative aspects of the study.

Proportionate: Peer review should be commensurate with the size and complexity of the study. Large multicentre studies should have higher level (more reviewers with broader expertise and often independent review committee or board), and potentially international peer review.
A copy of the completed peer-review forms will be submitted alongside other documentation.

7.3 Protocol compliance

Accidental protocol deviations will be adequately documented on the relevant forms and reported to the CI and Sponsor immediately. Deviations from the protocol which are found to frequently recur will mandate immediate action.

7.4 Data protection and patient confidentiality

All investigators and study site staff will comply with the requirements of the General Data Protection Regulations 2018 with regards to the collection, storage, processing and disclosure of personal information and will uphold the Act's core principles.
Specifically, patient demographic and personal information will be kept securely on Trust computers. Every subject enrolled into the study will be given a unique study identifier which will be used to refer to the patients during analysis. Hence all data will be linked-anonymised at source. Non-identifiable study data will be stored on a password protected encrypted hard-drive for the use of this study and kept in locked offices. Paper consent forms will be regularly archived and stored in the CI office. Access to data will only be with the permission of the study CI. The number of individuals with access to these data will be limited as much as possible to enable quality control, audit, and analysis.

The Investigators will make all study documentation and related records available should a competent authority inspection occur, or an IRB / IEC request a review. Personalised data will be destroyed within 12 months of the end of the study. Access to the research data generated by the study will be determined by the CI responsible for the study, who will act as the data custodian. Non-identifiable research data will be retained for a maximum of 5 years following study closure.

Wording related to the gathering, retention, and use of data on the patient information sheet has been informed by the 'transparency wording for public sector sponsors' guidance on the HRA website.

7.5 Indemnity

NHS indemnity will apply in the management and conduct of the research. Specifically this will cover any legal liability of the sponsor for harm to participants arising from the management of this research.
Any potential legal liability of investigators/collaborators arising from harm to participants in the conduct of the research will be covered by the Site. All individuals working on the project will also have independent professional indemnity cover.
As the primary employer of the CI, the University of Cambridge will provide insurance for the design of the study. Unique reference for this study is HVS/2017/2282. The University Insurance Office has advised that insurance for negligent and non-negligent harm to research subjects can be arranged if this study is approved by the NHS Ethics committee. Cover is provided under the University's Clinical Trials and/or

Human Volunteer Studies policy, the insurers are Newline, the insurance policy reference is *B0823Q31000177/WD1600523* and the Limit of Indemnity under the policy is £10,000,000 for each and every claim.

No specific arrangements are necessary for payment of compensation in the event of harm to research participants as a result of this study.

7.6 Access to the final study dataset

The CI and co-investigators working on the study will have access to the final anonymised dataset. Co-investigators or collaborators may be provided with fully-anonymised data when necessary, but will never be provided with any identifiable or potentially identifiable data.

8 DISSEMINATION POLICY

8.1 Dissemination policy

Analysis and reporting of the results from this study will commence whilst the study is ongoing, and will continue after the study has finished. A final study report will be prepared following completion of the study, with a further report made available after analysis of all the data. The full study report will be made available for public access.
The data itself will remain under the ownership of the sponsor, and controlled by the CI. Publications relating to data gained from this project will be presented and published wherever possible. All such presentations and publications should name the CI, and sponsoring institutions. There are no plans to actively contact participants to inform them of the study's output, however, future publications will be publicised through the University Department of Surgery website or the Cambridge Urology website.

8.2 Authorship eligibility guidelines and any intended use of professional writers

On the final study report and in any future publications authorship will be according to the criteria for individually named authors set forward by The International Committee of Medical Journal Editors. The CI will be named on any such publication, and the sponsors fully acknowledged.

9 REFERENCES

1. Cancer Research UK, http://www.cancerresearchuk.org/cancer-info/cancerstats/types/prostate/. Available from: http://www.cancerresearchuk.org/cancer-info/cancerstats/types/prostate/.
2. Greenberg, D.C., et al., Changing presentation of prostate cancer in a UK population--10 year trends in prostate cancer risk profiles in the East of England. Br J Cancer, 2013. **109**(8): p. 2115-20.
3. Cancer", A.J.C.o., AJCC Cancer Staging Manual, 8th Edition. 2016. p. 1-7.
4. Kattan, M.W., et al., American Joint Committee on Cancer acceptance criteria for inclusion of risk models for individualized prognosis in the practice of precision medicine. CA Cancer J Clin, 2016. **66**(5): p. 370-4.
5. Moons, K.G., et al., Prognosis and prognostic research: application and impact of prognostic models in clinical practice. BMJ, 2009. **338**: p. b606.
6. O'Connor, A.M., Validation of a decisional conflict scale. Med Decis Making, 1995. **15**(1): p. 25-30.
7. Spielberger, C.D., Manual for the state/trait anxiety inventory (form Y) : (self evaluation questionnaire). 1983, Palo Alto: Consulting Psychologists Press.

8. van Tol-Geerdink, J.J., et al., Choice between prostatectomy and radiotherapy when men are eligible for both: a randomized controlled trial of usual care vs decision aid. BJU Int, 2013. **111**(4): p. 564-73.
9. O'Connor, A.M., et al., Eliciting preferences for alternative drug therapies in oncology: influence of treatment outcome description, elicitation technique and treatment experience on preferences. J Chronic Dis, 1987. **40**(8): p. 811-8.
10. Auvinen, A., et al., A randomized trial of choice of treatment in prostate cancer: the effect of intervention on the treatment chosen. BJU Int, 2004. **93**(1): p. 52-6; discussion 56.
11. van Tol-Geerdink, J.J., et al., Does a decision aid for prostate cancer affect different aspects of decisional regret, assessed with new regret scales? A randomized, controlled trial. Health Expect, 2016. **19**(2): p. 459-70.
12. Sedgwick, P., Block randomisation. 2011: BMJ. p. d7139.
13. Collins, G.S., et al., Transparent reporting of a multivariable prediction model for individual prognosis or diagnosis (TRIPOD): the TRIPOD statement. BMJ, 2015. **350**: p. g7594.
14. NICE, National Institute for Health and Care Excellence NICE Guidelines [CG175] Prostate cancer: diagnosis and treatment. January 2014.

10. APPENDICES

10.1 Appendix 1- Required documentation

Patient Information Sheet (PIS)
Informed Consent Form (ICF)
Patient questionnaires
Case Report Forms (CRF)
Research CVs of all research team members
Peer review forms
Certificate of insurance (University)

10.2 Appendix 2 – Schedule of Procedures

10.3 Appendix 3 – Amendment History

Amendment No.	Protocol version no.	Date issued	Author(s) of changes	Details of changes made
1	1.1	Application: December 2018	David Thurtle	Amendment to the study pathway to allow study appointments to take place at any point (after at least 24 hours cooling off period) prior to the subjects next clinical appointment. This is instead of the study appointment having to take place immediately before the routine follow-up appointment which was problematic for two main reasons: Firstly, that some clinic appointments are very early such as 8.30am such that to have a study appointment prior to this is not

				feasible. Secondly, that some subjects aren't to be seen again in clinic for some time after the study is introduced. Small changes have been made in the protocol to reflect this alteration. Namely in: the lay summary (p6), study design (p10-11) and study setting (p12) – see tracked changes version. Minor wording changes have also been made to the PIS and ICF and renumbering throughout to version 1.1.
2	1.2	Feb 2019	David Thurtle	Sample size amended to 150/year rather than 50/year.
3	1.3	March 2019	David Thurtle	Predict Prostate logo added on page1. URL updated on page 11.

HRA Approval

Ymchwil Iechyd a Gofal Cymru
Health and Care Research Wales

NHS
Health Research Authority

Mr David Thurtle
Clinical Research Associate and Honorary Urology Registrar
University of Cambridge
Department of Surgery
Addenbrookes Hospital
Cambridge
CB2 0QQ

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

10 October 2018

Dear Mr Thurtle

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

Study title:	**Evaluation of a new tool, PREDICT: Prostate, to aid treatment decision-making for men with newly diagnosed non-metastatic prostate cancer**
IRAS project ID:	**249699**
Protocol number:	**A094875**
REC reference:	**18/EE/0254**
Sponsor	**Cambridge University Hospitals NHS Trust and The University of Cambridge**

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

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

This is a single site study sponsored by the site. The sponsor R&D office will confirm to you when the study can start following issue of HRA and HCRW Approval.

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

[Local Site name/logo]

predictprostate

PREDICT: *Prostate* Patient Study

Patient Questionnaire

Thank you for agreeing to take part in this study.
Please complete this questionnaire to the best of your ability.

Participant Details (to be completed by Researcher)
Study ID _____
Questionnaire date_____
Study arm _____

1 A. Please answer the following questions about your own age and medical history

a) **Age** _____(years)

b) **Other medical problems**

_____

_____

c) Have you been admitted to hospital in the last 2 years? Yes

No

d) If so, what was this for? _____

_____

_____

1 B. Please circle the appropriate answers below, or leave blank if you would prefer not to answer.

a) **Work status** Retired Employed Self-employed Not in paid employment

b) **Highest education level** School College University Post-graduate

c) **Relationship status** Living with partner Single Widower

d) **Family status** No children 1 or more children Still planning children

2. Please choose which of the following statements you most agree with:

1. I prefer to make treatment decisions on my own.
2. I prefer to make treatment decisions after hearing my doctor's opinion.
3. I prefer to make treatment decisions together with my doctor
4. I prefer my doctor to make treatment decisions after talking to me.
5. I prefer my doctor to make treatment decisions on his/her own.

3. Please fill in the following questions about your current treatment preferences.

A. At this moment in time, do you have a preference to one of the following treatment options?

a) Surgery (prostatectomy)

b) Radiotherapy

c) Active Surveillance / Conservative Management

d) Other (please state) _____

e) No preference

B. On a scale from 0 to 100 how certain are you in your preference above?

0 10 20 30 40 50 60 70 80 90 100

4. Considering the option you prefer in question 3, please answer the following questions:

	Strongly Agree	Agree	Neither agree nor disagree	Disagree	Strongly Disagree
1. I know which options are available to me	□	□	□	□	□
2. I know the benefits of each option	□	□	□	□	□
3. I know the risks and side effects of each option	□	□	□	□	□
4. I am clear about which benefits matter most to me	□	□	□	□	□
5. I am clear about which risks and side effects matter most to me	□	□	□	□	□
6. I am clear about which is more important to me (the benefits or the risks and side effects)	□	□	□	□	□
7. I have enough support from others to make a choice	□	□	□	□	□
8. I am choosing without pressure from others	□	□	□	□	□
9. I have enough advice to make a choice	□	□	□	□	□
10. I am clear about the best choice for me	□	□	□	□	□
11. I feel sure about what to choose	□	□	□	□	□
12. This decision is easy for me to make	□	□	□	□	□
13. I feel I have made an informed choice	□	□	□	□	□
14. My decision shows what is important to me	□	□	□	□	□
15. I expect to stick with my decision	□	□	□	□	□
16. I am satisfied with my decision	□	□	□	□	□

4. For each of the following, please select how important they are to you when deciding about your treatment.

a) **The chance of dying from prostate cancer**

Not important Slightly important Moderately important Important Very important

b) **The risk of urinary problems**

Not important Slightly important Moderately important Important Very important

c) **The risk of bowel problems**

Not important Slightly important Moderately important Important Very important

d) **The risk of sexual problems**

Not important Slightly important Moderately important Important Very important

e) **The burden of the treatment itself**

Not important Slightly important Moderately important Important Very important

f) **The thought of living with a cancer that is untreated**

Not important Slightly important Moderately important Important Very important

5. STAI Form Y-1

A number of statements which people have used to describe themselves are given below. Read each statement and then circle the appropriate value to the right of every statement to indicate how you feel **at this moment**. There are no right or wrong answers. Do not spend long on any one statement but give the answer which seems to describe your **present feelings** best.

	Not at all	Some-what	Moder-ately so	Very much so
1. I feel calm	1	2.	3.	4.
2. I feel secure	1	2.	3.	4.
3. I am tense	1	2.	3.	4.
4. I feel strained	1	2.	3.	4.
5. I feel at ease	1	2.	3.	4.
6. I feel upset	1	2.	3.	4.
7. I am presently worrying over possible misfortunes	1	2.	3.	4.
8. I feel satisfied	1	2.	3.	4.
9. I feel frightened	1	2.	3.	4.
10. I feel comfortable	1	2.	3.	4.
11. I feel self-confident	1	2.	3.	4.
12. I feel nervous	1	2.	3.	4.
13. I am jittery	1	2.	3.	4.
14. I feel indecisive	1	2.	3.	4.
15. I am relaxed	1	2.	3.	4.
16. I feel content	1	2.	3.	4.
17. I am worried	1	2.	3.	4.
18. I feel confused	1	2.	3.	4.
19. I feel steady	1	2.	3.	4.
20. I feel pleasant	1	2.	3.	4.

6. STAI Form Y-2

The next set of questions relate to **how you generally feel.** Read each statement and then circle the value to the right of every statement that indicates how you generally feel. There is no right or wrong answer. Do not spend too much time on any one statement but give the answer which seems to describe **how you generally feel**.

	Not at all	Some-what	Moder-ately so	Very much so
21. I feel pleasant	1	2.	3.	4.
22. I feel nervous and restless	1	2.	3.	4.
23. I feel satisfied with myself	1	2.	3.	4.
24. I wish I could be as happy as others seem to be	1	2.	3.	4.
25. I feel like a failure	1	2.	3.	4.
26. I feel rested	1	2.	3.	4.
27. I am calm, cool, and collected	1	2.	3.	4.
28. I feel that difficulties are piling up so that I cannot overcome them	1	2.	3.	4.
29. I worry too much over something that really doesn't matter	1	2.	3.	4.
30. I am happy	1	2.	3.	4.
31. I have disturbing thoughts	1	2.	3.	4.
32. I lack self confidence	1	2.	3.	4.
33. I feel secure	1	2.	3.	4.
34. I make decisions easily	1	2.	3.	4.
35. I feel inadequate	1	2.	3.	4.
36. I am content	1	2.	3.	4.
37. Some unimportant thoughts run through my mind and bothers me	1	2.	3.	4.
38. I take disappointment so keenly that I can't put them out of my mind	1	2.	3.	4.
39. I am a steady person	1	2.	3.	4.
40. I get in a state of tension or turmoil as I think over my recent concerns and interests	1	2.	3.	4.

7. The next 3 questions are very difficult questions to answer. Please make your best estimate or guess for each question below, selecting any value between 0 and 100.

a) Out of 100 men with the exact same characteristics as you, how many do you think would **die from prostate cancer** in 15 years if not treated?

0 10 20 30 40 50 60 70 80 90 100

b) Out of 100 men with the exact same characteristics as you, how many do you think would **die from other causes** (i.e. NOT prostate cancer) in 15 years?

0 10 20 30 40 50 60 70 80 90 100

c) Out of 100 men with the exact same characteristics as you, how many **extra** men do you think would be alive at 15 years if all 100 men were treated by surgery or radiotherapy?

0 10 20 30 40 50 60 70 80 90 100

Additional Questions A1-A8 for men who have seen PREDICT: Prostate only

Having seen the PREDICT: *Prostate* estimates, please select from the following statements:

A1. The number of men estimated to die **from prostate cancer** following conservative management were:

Less than I expected Similar to what I expected More than I expected

A2. The number of men estimated to die **from other causes** (i.e. not prostate cancer), following conservative management, were:

Less than I expected Similar to what I expected More than I expected

A3. The number of **extra** men alive following radical treatment compared to conservative management were:

Less than I expected Similar to what I expected More than I expected

A4. Did you find PREDICT: *Prostate* to be helpful?

Yes No Unsure

A5. Would you recommend using the tool to other men in your position?

Yes No Unsure

A6. Did PREDICT: *Prostate* make you feel more or less likely to want radical treatment (surgery or radiotherapy) for your prostate cancer?

More likely Less likely No change Unsure

A6. Is there anything about the model that you did not like, or would change?

_____

_____

_____

A7. Is there anything else you would like to see added to the PREDICT: Prostate model/website?

_____

_____

_____

A8. Any other comments or feedback?

_____

_____

_____

PARTICIPANT INFORMATION SHEET & INFORMED CONSENT FORM

Study Title: Evaluation of a new tool, PREDICT: *Prostate,* to aid treatment decision-making for men with newly diagnosed non-metastatic prostate cancer

You are being invited to take part in a research study. Before deciding whether to take part, you need to understand why this research is being done and what it involves. Please take time to read the following information carefully and talk to others about the study if you wish. Please ask us if anything is not clear or if you would like more information. Please take time to decide whether or not you wish to take part.

Section 1 explains the purpose of the study and what will happen if you take part.
Section 2 gives more detailed information about the conduct of the study.

Section 1: Purpose of the study and what will happen

1. What is the purpose of the study?

Experts at the University of Cambridge have developed a new prediction tool and decision aid called 'PREDICT: *Prostate*'. This is a tool that provides estimates of survival outcomes for men diagnosed with prostate cancer. Estimates are individualised to a patient's characteristics. This tool is available as a website designed to help inform patients and help them decide which is the best treatment strategy for them.
This study is being undertaken to assess whether or not patients find PREDICT: *Prostate* useful, and what impact it may or may not have on clinical practice.

2 Why have I been invited?

You have been invited to participate in this trial because you have been diagnosed with prostate cancer that has not spread to distant sites (non-metastatic), and because more than one management option is potentially appropriate for you.

3. Do I have to take part?

No. Participating in this study is completely voluntary. If you decide to participate you will be asked to sign an Informed Consent Form, however you are still free to change your mind and leave the study at any time without giving a reason. Whether or not you choose to participate, your future medical treatment will not be affected in any way.

5. What will happen to me if I take part?

If you agree to participate in the study, you will be invited to attend a study appointment before your next hospital appointment. You will be asked to sign the Informed Consent Form (at the end of this document) and will be randomly allocated to one of two groups. Those in one group will simply be asked to complete a questionnaire. Those in the other group will go through the PREDICT: *Prostate* tool with a researcher on an individual basis and then complete the questionnaire. The questionnaire will take approximately 15 minutes to complete. Your participation in the study will finish after the questionnaire with no

further visits or other additional contact necessary. If your participation in this study raises any new questions, these should be discussed with your clinician in your clinic appointment. If you agree to participate, information on your disease characteristics and eventual treatment decisions will be taken from your medical notes, and kept in a non-identifiable form.

6. **What will I have to do?**
   You will be asked to attend the hospital for about an hour at some point prior to your next follow-up appointment. You will be asked to either complete a questionnaire, or go through the PREDICT: *Prostate* website individually with a researcher and then complete a questionnaire.
   There are no blood tests or biopsies necessary as part of this study. No further follow-up related to this study is necessary.

7. **What are the possible disadvantages and risks of taking part?**
   PREDICT: *Prostate* is a decision-aid and therefore **may** influence your thinking about your prostate cancer.

8. **What are the possible benefits of taking part?**
   There is no guarantee that you will benefit from taking part in this trial. However, participation **may** help you decide about your treatment. Your participation in this study **may** enable future refinements to the model and benefit future patients.

9. **What happens when the study finishes?**
   After completing the questionnaire, no further involvement will be necessary. Your information and responses will be fully anonymised and analysed.

10. **Expenses & Payment?**
    You will not receive any payment for participating in this trial and we are unable to reimburse any expenses incurred by your participation in this trial.

Section 2: Trial Conduct

11. **What if I decide I no longer wish to participate in the trial?**
    You are free to leave this study at any time without giving a reason and without affecting your future care or medical treatment. Your doctor may also choose to withdraw you from the trial if they feel it is in your best interests. Any identifiable data related to your participation would be deleted.

12. **What if there is a problem?**
    If you wish to complain or have any concerns about any aspect of the way you have been approached or treated during this study, you can do this through the NHS complaints procedure. In the first instance it may be helpful to contact the Patient Advice and Liaison Service (PALS) [Local PALS/Complaints Details].

13. **What about the use of my data?**

Cambridge University Hospitals NHS Trust (CUH) and The University of Cambridge are the sponsors for this study based in the UK.

[Local Site name] will collect information about you for this research study. This information will include your name, hospital number, contact details and health information, which is regarded as a special category of information. We will use this information to contact you if necessary, and for research purposes.

We will be using information from you and your medical records in order to undertake this study and will act as the data controller for this study. This means that we are responsible for looking after your information and using it properly. The sponsors will keep identifiable information about you for 1 year after the study has finished. Your rights to access, change or move your information are limited, as we need to manage your information in specific ways in order for the research to be reliable and accurate. If you withdraw from the study, we will keep the non-identifiable information about you that we have already obtained. To safeguard your rights, we will use the minimum personally-identifiable information possible. Collected data will be linked-anonymised after collection so that you are not identifiable by the research team or in future analyses. You can find out more about how we use your information by contacting the study principal investigator (contact details below).

[LOCAL site name] will use your name, hospital number and contact details to contact you about the research study, and make sure that relevant information about the study is recorded for your care, and to oversee the quality of the study. Individuals from these organisations and regulatory organisations may look at your medical and research records to check the accuracy of the research study. The only people in [Local site name] who will have access to information that identifies you will be people who need to contact you to arrange an appointment or audit the data collection process. The people who analyse the information will not be able to identify you and will not be able to find out your name, hospital number or contact details.
[Local site name] will keep identifiable information about you from this study for 1 year after the study has finished. Non-identifiable data will be kept for up to 5 years, to maximise its potential usage.

Your GP will be informed of your clinical appointments in the normal manner. No additional information relating to participation in this study will be shared with your GP.

14. What will happen to the results of the trial?

The results of the study will be anonymous and you will not be able to be identified from any of the data produced. When the results of this study are available they may be published in peer reviewed medical journals and used for medical presentations and conferences. If you would like to obtain a copy of the published results please contact your doctor directly who will be able to arrange this for you.

15. Who is organising (sponsoring) and funding the trial?

This trial is jointly sponsored by Cambridge University Hospitals NHS Foundation Trust and the University of Cambridge. The study is being funded via a grant from The Urology

Foundation and through internal funding.

16. Who has reviewed this trial?

All research within the NHS is reviewed by an independent group of people called a Research Ethics Committee, to protect your interests. This study has been reviewed and given favourable opinion by Cambridge South Research Ethics Committee (REC Reference 18/EE/0254).

17. Further information and contact details

[Study PI +/- local research nurse contact details]

PREDICT Prostate Patient Study – Study Appointment Protocol

1. Reintroduce study generally

2. Go over PIS and answer any outstanding questions patient may have

3. Go over consent form and ensure it's all signed appropriately
(reiterate that only half will be randomised to see the Predict model)

4. Ask about previous access to the PREDICT Prostate website – and complete section in CRF accordingly.

5. Open brown envelope to check randomisation group

6. If randomised to questionnaire only: Provide the questionnaire, **crossing through or removing pages 9 and 10.** After completion, thank the patient for their time and inform them their participation in the study has completed.

7. If randomised to PREDICT Prostate + questionnaire follow the protocol/script below:

    a. Explain they have been randomised to see the model
    b. Open prostate.predict.nhs.uk
    c. Press F11 to make the model full screen
    d. Start on the 'Home' page and read through the 3 paragraphs
    e. Move to the 'About Predict Prostate' page and skim/summarise the 3 paragraphs (emphasise that the model does not itself give advice, it simply provides some information, it is built around data from other men and is a 'best guess' of what outcomes might be)
    f. If the participant has more questions about the model itself – consider going through the 'FAQ' section.
    g. Go to the 'Predict Prostate Tool' page
    h. Enter the participants' details
    i. Scroll to the 'Results' section
        i. Start on the 'Icons' section and select the 'conservative' management and '15' years tab
        ii. Explain that the icons represent 100 men with your characteristics. Explain that 'Out of 100 men with the same age and disease characteristics as you, if all 100 had initial conservative management, the model estimates that XX would still be alive at 15 years, XX would have died from Prostate cancer and XX would have died from other causes. At this moment we cannot say to which group you will belong."
        iii. Press the 'Radical' treatment regime tab

iv. Explain that 'Out of 100 men with the same characteristics as you, if all 100 had radical treatment, the model estimates that XX would still be alive at 15 years, XX would have died from prostate cancer and XX would have died from other causes. It estimates that XX extra men out of 100 might be alive at 15 years if all 100 were radically treated.'
v. Switch to the 'Charts' section. Explain that the model estimates that at 10 years and 15 years, with initial conservative management (i.e. surveillance), XX% and XX% would be alive.
vi. Explain that the dotted yellow line shows what proportion would be alive if the prostate cancer deaths were completely excluded (i.e if there was zero chance of dying from prostate cancer)
vii. Press 'Radical' next to 'Treatment Regime'
viii. Explain that with radical treatment (i.e. Radical prostatectomy or radiotherapy) the model estimates that XX% and XX% would still be alive at 10 and 15 years.
ix. Switch to the 'Texts', 'Tables' and 'Curves' results and explain that these are all showing the same estimates but in different ways.
x. Answer any questions on these graphs or explain the results as necessary (may need to switch between 10 and 15 years to get the same outcomes)
xi. **Do not offer advice or recommendations beyond explaining the model itself**. Explain that they can discuss things further with their consultant or specialist nurse later if necessary.

j. Scroll down to the 'Potential Harms of Treatment' section
k. Explain that alongside benefits from treatment, there is a risk of potential harms and these should also be considered in any decision.
l. Explain the bullet points – i.e. that these estimates for harms are **not individualised** to you, and have been taken from studies in different centres.
m. Explain that 'If 100 men were all treated by conservative management/ prostatectomy/radiotherapy these studies suggest that **at 3 years**, XX% would have Erectile dysfunction/Incontinence/Bowel dysfunction (using the shown definitions).
n. Signpost to other sources of information and the websites listed.
o. Read out the 'Important' note at the side/bottom of the page.

8. Provide the questionnaire, (**including pages 9 and 10).** After completion, thank the patient for their time and inform them their participation in the study has completed.

9. Thank the patient for their participation.

Further information and contact details

Mr David Thurtle, Academic Urology Group, Box 279, Addenbrooke's Hospital, Hills Road, Cambridge, CB2 0QQ. [email redacted]
Telephone: [number redacted]