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Diagnostic and prognostic factors in patients with prostate cancer: a scoping review

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Diagnostic and prognostic factors in patients with prostate cancer: a scoping review

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Abstract

Introduction: One of the major challenges in the field of diagnostic and prognostic factors is the variety and large amount of clinical data being published at rapid pace. This makes it difficult to incorporate such factors in the clinical day to day management of prostate cancer. As part of the PIONEER Consortium objectives, we have explored which diagnostic and prognostic factors (DPFs) are available in relation to our previously defined clinician and patient-reported outcomes (PROs) for prostate cancer (PCa).

Methods and analysis: We performed a scoping review to identify validated and non-validated studies. After initial screening, we extracted data following the Checklist for Critical Appraisal and Data Extraction for Systematic Reviews of prognostic factor studies (CHARMS-PF) criteria and discussed the identified factors with a multidisciplinary expert group. The quality of the included papers was scored for applicability and risk of bias using validated tools such as PROBAST, QUIPS and QUADAS-2.

The search identified 6,604 studies, from which 489 DPFs were included. Sixty-four of those were internally or externally validated. However, only three studies on diagnostic and seven studies on prognostic factors had a low risk of bias and a low risk concerning applicability.

Most of the DPFs identified require additional evaluation and validation in properly designed studies before they can be recommended for use in clinical practice. The PIONEER online search tool for diagnostic and prognostic factors for prostate cancer will enable researchers to understand the quality of the current research and help them design future studies.

Ethics and Dissemination: There are no ethical implications.

Strengths and limitations of this study

- A multidisciplinary team including patients, urologists, oncologists, radiation oncologists, methodological experts and pathologists were involved throughout the study.
- The search was restricted from 2014 onwards, to maintain a pragmatic approach.
- The main strength of this study are the extensive and comprehensive search and screening of the studies included.
- Our review aims to inform clinicians and patients about this rapidly evolving field, while the PIONEER online search tool for diagnostic and prognostic factors for prostate cancer will enable researchers to perform future research, and to understand the quality of the current available studies.

Introduction

Prostate cancer (PCa) accounts for 15% of cancers diagnosed [1] and is the second most common cancer in males worldwide [2]. PCa is clinically and molecularly heterogeneous and is usually suspected based upon the clinical findings of digital rectal examination (DRE) and/or Prostate Specific Antigen (PSA) levels [1]. However, which diagnostic or prognostic factor (DPF) can be used to select patients for specific therapeutic options remains largely unclear [3]. Specific biomarkers in urine or in blood are available on top of traditional PSA testing, such as PCA3, TMPRSS2-ERG fusion, or kallikreins as incorporated in the Phi or 4Kscore test together with other parameters including family history [4-7]. However, the European Association of Urology (EAU) guidelines (2019) currently do not provide general recommendations to implement these biomarkers into routine screening programmes due to limited data [8]. As part of the ASCO guidelines, Eggener et al recommended five commercially available biomarkers which have been shown to provide prognostic significance and additional information beyond standard clinical models in patient selection in the localised context: Oncotype Dx Prostate, Prolaris, Decipher, and ProMark [9]. However, no guidelines have recommended DPFs for other stages of PCa. The expert panel at the APCCC consensus meeting of advanced prostate cancer in Basel 2019, recommended AR-V7 for mCRPC as potentially useful, which ultimately led to the inclusion of AR-V7 testing in the NCCN guidelines [10].

The PIONEER Consortium is an international collaboration coordinated by the European Association of Urology (EAU), which aims to establish the best evidence-based management and clinical practice of PCa across all disease stages using the power of big data analytics towards a more outcome-driven, value-based, and patient-centric healthcare system [11]. A key objective is to address one of the major challenges within the context of diagnostic or prognostic biomarkers/factors: the inability to incorporate DPFs into the management of PCa in terms of screening, diagnosis and treatment. It is therefore important to summarise and evaluate the evidence. Biomarkers can be classified into different types: diagnostic, prognostic, predictive, and therapeutic – in this study we focus on the first two. A diagnostic biomarker or factor is useful when cancer is suspected and allows the early detection based on symptoms or tests [12]. The overall aim of a diagnostic biomarker is to distinguish people with the diseases from people without the disease. A prognostic biomarker or factor is a clinical or biological characteristic which provides information on the likely course of the disease i.e., biochemical progression or disease recurrence [12]. It enables clinicians to decide on the most suitable treatment depending on the likely course of the disease. In the sections below we have used the terms biomarkers and factors interchangeably. Multiple diagnostic and prognostic factors (DPFs) can be measured in tissue, blood or urine. These come with different advantages and disadvantages and only a limited number of factors are currently available for PCa in standard clinical care.

We aimed to systematically review the evidence from 2014 onward to assess which DPFs are available in relation to previously defined outcomes for PCa.

Methods

The systematic scoping review followed the methodology developed by the Joanna Briggs Institute guidelines (14) and the framework by Arksey and O'Malley [13]. We applied Preferred Reporting Items for Systematic Reviews and Meta-Analyses-ScR extension for scoping reviews [14]. A detailed protocol of the overall project was published elsewhere [15]. Briefly, we followed the following four steps (Figure 1):

(1) Comprehensive systematic literature review of DPFs for all stages of PCa (localised, locally advanced, metastatic, and non-metastatic castration resistant) from 2014 onwards. DPFs developed before 2014 were not included, due to the significant changes which influence the staging of PCa (i.e., Consensus Conference on Gleason Grading of Prostatic Carcinoma (60)) have taken place in diagnostic and prognostic practice and patient management.

(2) Assessment and identification of final list of DPFs by a multidisciplinary expert panel.

(3) Evaluation of quality of studies published using risk of bias tools: Prediction model Risk Of Bias (RoB) Assessment Tool (PROBAST) if applicable; or Quality in Prognostic Studies (QUIPS) tool for prognostic and the Quality Assessment of Diagnostic Accuracy Studies 2 (QUADAS-2) tool for diagnostic factors;

(4) Due to the heterogeneity of the studies identified no further formal quantitative assessments in the form of a meta-analyses could be performed. Hence, the findings of stages 1-3 have been reported here as the results of a scoping review.

Results

Stage 1: Comprehensive literature review

Stage 1 identified 6,604 citations and contained three independent searches. We developed the search criteria for the first search with an information scientist who specialises in systematic reviews for urology. The second search was developed following a consultation with an independent information scientist group who excluded row 12, 14 and 16 of Table 1 (see supplementary material). We screened the EAU Guidelines reference list for PCa in our third search. After removing duplicates, we screened 4,215 abstracts, from which 489 met the inclusion criteria.

Stage 2: Multidisciplinary expert meeting

On the 20th of March 2020, we invited a group of multidisciplinary participants to discuss the identified articles on DPFs (see supplementary material Table 2). The participants were presented the search criteria and the extracted data. Data extraction followed the CHARMS-PF checklist and we added author and year of publication. The group discussed the results and additional literature on DPFs was suggested to help the classification of the DPFs, such as the ASCO Guideline on Molecular Biomarkers in Localized Prostate Cancer [16].

Stage 3: Evaluation of quality of studies published using the risk of bias tools

Prior to the evaluation of the quality of studies, an initial pilot screening to prepare the raters for the use of PROBAST, QUADAS-2, QUIPS was performed. This aimed to reach consensus on how to judge the domains of the assessments using the three RoB tools. Two urologists (FB, SS) and two epidemiologists (AH, KB) were involved in the pilot assessments.

The group discussed any discrepancies. Articles which presented the development and validation, the internal validation or the external validation of a diagnostic or prognostic model were assessed with PROBAST. Papers assessing single biomarkers or with/without validation were assessed with QUIPs for prognostic or QUADAS-2 for diagnostic biomarkers. The 489 articles were equally divided between six groups. The six groups received the guidance documents which were identified during the pilot phase [17-21]. In addition, MvH and KB discussed questions with each individual group.

Evaluation of quality of studies published using QUADAS-2

The RoB of diagnostic factors without validation or single validated factors was evaluated using QUADAS-2. We assessed the following four domains: patient selection, index test, reference standards and flow and timing. The first three domains are assessed looking at applicability and all four domains were assessed in terms of RoB [21]. We created a summative score after the diagnostic studies were assessed by two reviewers and in case of disagreement a third reviewer assessed the study. The RoB of the 41 included studies was low for 10 studies, high for 23 studies and unclear for eight. RoB concerning applicability was low for 10 studies, high for 21 studies and unclear for 10 studies (see Table 1). Table 2 shows the studies with an overall low RoB across both categories. Two studies were identified to have an overall low RoB [22 23].

Evaluation of quality of studies published using PROBAST (Diagnostic)

The RoB of internal or external validated diagnostic models was assessed using the PROBAST RoB tool. PROBAST includes four domains assessing the RoB (i.e., participants, predictors, outcome and analysis) and four domains assessing applicability (i.e., participants, predictors

and outcome) (see supplementary material Table 3 for scoring information). We identified 20 papers to be assessed with PROBAST. The RoB of three papers was low, that of 14 was high and was unclear for three. The applicability of eight papers was high and was unclear for two (see Table 3). Table 3 in the supplementary material shows the criteria on how to judge the RoB. One study had an overall low RoB across both domains. All categories except 'predictors' was scored to have a low risk of bias. There was little information available for the category predictors and therefore it was scored as 'unclear' (see Table 4).

Evaluation of quality of studies published using QUIPS

To assess the articles which are single factors or were not internally or externally validated, we used the QUIPS rating procedure. We identified 385 articles to be assessed with QUIPS. To standardise the approach across raters, we used the QUIPS electronic spreadsheet (excel) from Hayden et al [17]. The 12 assessors independently inserted the relevant information and assessed each domain such as participation, attrition, prognostic factor confounding and statistical analysis and reporting.

There are no rules available for QUIPS on how to score the overall RoB of a paper. Due to the large number of papers and the need for synthesis, we followed Grooten et al's suggestions to categorise on the following criteria: 1) Paper was classified as low RoB if all domains were classified as having low RoB, or up to one moderate RoB; 2) Paper was classified as high RoB if one or more domains were classified as having high RoB, or ≥ 3 moderate RoB; 3) Paper was classified as having moderate RoB if all papers in between 1 or 2 (see table 5 and in supplementary material table 4) [20]. This assessment was based on the risk scores of individual assessments within the group. If the overall assessment was not

possible due to differences in the individual category, a third assessor reviewed the assessments and the results were discussed. 387 prognostic factors were assessed using QUIPs. 307 papers were classified as high RoB. Forty-nine papers were classified as having a moderate RoB and 28 papers were scored as low RoB (see Table 5). Out of the 28 papers with a low RoB, the most common moderate bias was linked to attrition (12 papers), followed by confounding (4 papers), participation (3 papers), outcome (1 paper), statistical analysis (1 paper) (see Table 6).

Evaluation of quality of studies published using PROBAST (Prognostic)

The RoB of Prognostic validated models were assessed using PROBAST. As highlighted above, PROBAST includes four domains assessing the RoB (i.e., participants, predictors, outcome and analysis) and four domains assessing applicability (i.e., participants, predictors and outcome). The assessors identified 44 papers to be assessed with PROBAST, of those three scored a low RoB, 27 a high risk of bias and 13 were assessed as unclear (see Table 7). In terms of applicability, 15 papers scored low, 20 high and eight unclear. Two papers were scored to have an overall low RoB [24 25] (see Table 4).

Characteristics of studies identified with low risk of bias

Details of the identified validated DPF models with an adequate quality are presented in Table 8. We identified 32 studies with an overall low RoB (assessed with PROBAST, QUIPS, QUADAS-2). Out of these 32 studies, we identified one validated diagnostic model (assessed with PROBAST) [26], two validated prognostic models (assessed with PROBAST) [24 25], two non-

validated diagnostic single factors (assessed with QUADAS-2) [22 23] and 25 prognostic factors (assessed with QUIPS) [22-52] which have not been validated and two single prognostic factors which have been validated (assessed with QUIPS) [36 52]. Prognostic factors assessed with QUIPS were identified with a low risk of bias for the localised PCa population. Sixty-seven percent of the low RoB DPFs were intended to be measured after the treatment was performed. In addition, the most commonly measured outcome was biochemical recurrence (BRC) followed by overall survival (OS). It is, however, important to take into consideration that even though from the studies assessed with a low RoB, only two out of the 32 were of a non-observational study design.

As highlighted above, we identified three validated DPFs which were scored to have a low RoB and low risk concerning applicability. Firstly, we identified the 'Unified Prostate Cancer Risk Prediction Model Combining the Stockholm3 Test and Magnetic Resonance Imaging', a risk prediction model which combines clinical variables, genetic and protein biomarkers. Five hundred and thirty two men were involved across three centres [53]. Secondly, the DREAM challenge developed a set of five standardised raw event-level tables, using laboratory values, patients' demographic information, medical history, lesion sites, previous treatments, and vital signs of patients with metastatic castration-resistant PCa. These variables where combined by using data from four clinical trials [54]. Thirdly, Joniau et al. developed 'Pretreatment Tables' to predict the pathologic stage of locally advanced prostate cancer after RP based on pre-treatment PSA level and biopsy Gleason score [25].

We identified two single factors which were validated and had low RoB. Firstly, Lara et al., assessed and validated the serum biomarkers of bone metabolism (N-telopeptide and pyridinoline) and formation (C-terminal collagen propeptide and bone alkaline

phosphatase)) in 778 CRPC patients as part of the randomized phase III SWOG trial (S0421) of docetaxel/prednisone with or without atrasentan [36]. Secondly, Berg et al, showed that ERG expression can be used to estimate the risk of progression during AS including 265 patients at diagnosis and progression during AS [52].

Patient and public Involvement

This project has been overseen by a multi-stakeholder group part of the PIONEER Consortium. PIONEER brings together 32 key stakeholders from academic institutions, patient advocacy groups, European organisations, experts in legal data management, clinicians and pharmaceutical companies, as well as regulatory agencies, economics and ethics, and information and technology specialists. Patients and their family members are therefore involved and actively participate as an integral part of all research conducted by the PIONEER Consortium.

Discussion

Despite the large number of studies on DPFs which are published every year, there is a paucity of DPFs that are suitable to be incorporated into clinical practice. The majority of DPFs have not yet been validated and are identified in poor quality studies. Our analysis found that most identified studies had a high to moderate risk of bias due to poor design standards, conduct, reporting and/or analysis i.e. generalizability and size of the population, poor model development (no testing or missing important confounders) or only correlation studies, missing data was rarely reported. However, we did identify a small number of validated DPFs with low RoB. We identified three validated models which combine: firstly,

clinical variables, genetic and protein biomarkers, and improved the clinical outcome performance of prostate cancer diagnostics (The Unified Prostate Cancer Risk Prediction Model) [53].; secondly, laboratory values, patients' demographic information, medical history, lesion sites, previous treatments, and vital signs of patients with metastatic castration-resistant PCa (DREAM challenge) [54]; thirdly, pre-treatment PSA level and biopsy Gleason score to predict the pathologic stage of locally advanced PCa ('Pretreatment Tables') [25]. Two single factors have been validated: the serum biomarkers of bone metabolism in CRPC patients [36] and the ERG expression, which can be used to estimate the risk of progression during AS [52], which has been already highlighted in the clinical guidelines [1].

Aladawani et al assessed prediction models for PCa to be used in primary care settings in their systematic review and identified five models which met their inclusion criteria. From these identified models only one model was externally validated and only one (the Lazzari model 2 [55]) had the potential to be implemented in primary care. Lazzari et al. had the lowest RoB (based on PROBAST), however it must be externally validated before it can be implemented. Hence, Aladawani et al also concluded that the existing models have limitations concerning study design and reporting performance [56].

Tian et al conducted a review on biomarkers for CRPC patients, however their quality assessment was focused on study design (RCT vs observational study), whereas we focused on biomarker specific tools [57]. Whilst Tian et al and our review identified similar factors and quality scores, there were slight discrepancies between the overall RoB assessments. Tian et al. used an overall quality assessment scale from 1-6 instead of low, medium and high. In their assessment the validated prognostic study by Lara et al. [36] and the non-validated prognostic factor by Pei et al. [43] were scored on the quality scale as 4 (medium quality). We

assessed Lara et al. [36] to have a low risk of bias with a moderate risk of confounding and Pei et al. [43] with a moderate risk of bias concerning the prognostic factor itself. This might explain the discrepancies between the two quality assessments. The reports by Alvim et al., Qu et al., were assessed to have the highest quality by Tian et al [57], similar to our review. This illustrates that different quality assessment tools emphasize different criteria, which may result in small discrepancies. However, the overall conclusion for prognostic single factors was similar in our review and to the work of Tian et al. [57].

Similar issues have been identified for other urological cancers. For example, in kidney cancer, a large body of research was identified by Harrison et al., with very few validated studies and lots of heterogeneity [58]. Schmitz-Dräger et al. published an International Consultation of Urologic Disease (ICUD)/World Health Organization (WHO) Consensus manuscript where they identified that in bladder cancer one of the main limitations for the lack of incorporation of modern bladder cancer tests into clinical practice decision making is linked to the scarcity of 'good clinical practice guidelines' for the evaluation of diagnostic markers.

There is a need for improved guidance on development and validation of diagnostic markers [59]. To meet that need, we are developing the PIONEER DPF search tool, which will help researchers and clinicians to get a better understanding of the DPFs for prostate cancer. The tool will not only summarise all relevant studies, but also provide information on the use and results of different RoB assessment tools, which will enable an understanding of the quality of published studies.

Future research should therefore focus on addressing the identified shortcomings such as heterogeneity, validation and poor RoB by designing more robust studies which consistently include RoB assessments such as PROBAST, QUIPS or QUADAS-2.

With the growing number of various therapeutic options, diagnosis and management of prostate cancer require an individualised approach to patient care. There is an unmet need for DPFs to guide decisions for optimal treatment and predict which patients will benefit the most, from a particular management strategy. DPFs could potentially enhance the quality of patient counselling, but currently most need additional evaluation and validation in properly designed studies. Our systematic review highlights the need for well-designed Real-World Evidence studies, while the PIONEER online search tool can inform the design of new research studies, through providing a rigorous evaluation of the methodological quality of the studies.

The main strength of this study are the extensive and comprehensive search and screening of the studies included. In addition, we are developing an online search tool which showcases the identified and assessed studies. It provides an overview of the available DPFS and enables interested stakeholders to search for DPFs. To our knowledge, this is the first study which has been performed with this extensive amount of literature.

Limitations

Even though this review included three searches and assessments by a multidisciplinary group of fourteen researchers, we recognise potential limitations. Studies were only included from 2014 onwards and DPFs developed before 2014 were not included. However, significant changes which influence the staging of PCa (i.e., Consensus Conference on Gleason Grading of Prostatic Carcinoma [60]) have taken place in diagnostic and prognostic

practice and patient management. This changed the staging of the patient population and therefore has an impact on DPFs.

In addition, there is a potential of subjectivity in the evaluation of the studies. Even though the studies have been assessed in duplicate, there might be variation across groups. However, given the overall moderate to high risk of bias, this does not influence the overall recommendation of the project.

Conclusion

At present DPFs that are capable of significantly improving diagnosis and prognosis in prostate cancer are an unmet need as most of the DPFs identified require additional evaluation and validation in properly designed studies before they can be recommended for use in clinical practice. Well-designed RWE studies can help to increase quality. Our review aims to inform clinicians and patients about this rapidly evolving field, while the PIONEER online search tool for diagnostic and prognostic factors for prostate cancer will enable researchers to perform future research, and to understand the quality of the current available studies.

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Table 1: Overall judgment of RoB (QUADAS-2, Diagnostic)

Overall judgement of RoB	RoB	Applicability
Low	10	10
High	23	21
Unclear	8	10
Total	41	

Table 2 non-validated DPFs with overall low risk of bias: QUADAS-2

Author	**Year**	**Patient Selection**	**Index Test(s)**	**Reference Standard**	**Flow and Timing**	**Patient Selection**	**Index Test(s)**	**Reference Standard**	**RoB**	**Applicability**
Hagiwara, et al.	2017	low	low	low	low	low	low	low	low	low
Kelly, et al.	2015	low	low	low	low	low	low	low	low	low

Table 3: Judgment of RoB (PROBAST, Diagnostic)

Overall judgement of RoB	RoB	Applicability
Low	3	8
High	14	10
Unclear	3	2
Total	20	

Table 4: PROBAST

Author	ROB				APPLICABILITY			Overall	
	Participants	Predictors	Outcome	Analysis	Participants	Predictors	Outcome	ROB	Applicability
Diagnostic									
Guinney, et al.	Low	Low	Low	Low	Low	Low	Low	Low	Low
Joniau, et al.	Low	Low	Low	Low	Low	Low	Low	Low	Low
Prognostic									
Palsdottir, et al	low	Unclear	low	low	low	low	low	low	low

Table 5: Overall judgment of RoB (QUIPS, Prognostic)

Overall judgement of RoB	RoB
Low	29
Moderate	49
High	307
Total	385

Table 6 DPFs with low risk of bias: QUIPS

STUDY	Time	BIASES			Applicability			Overall score
		Participation	Attrition	Prognostic Factor	Outcome	Confounding	Statistical analysis and reporting	
Aguilera, et al	*2015*	low	low	low	low	moderate	low	low
Alvim, et al.	*2019*	low	low	low	low	low	low	Low
Bramhecha, et al.	*2019*	low	moderate	low	low	low	low	Low
Bruce, et al.	*2016*	low	moderate	low	low	low	low	Low
Francini, et al.	*2018*	low	low	low	low	low	moderate	Low
Hamada, et al.	*2016*	low	low	low	moderate	low	low	low
Hashimoto, et al.	*2020*	low	low	low	low	low	low	Low
Hung, et al.	*2017*	moderate	low	low	low	low	low	Low

Kato, et al.	*2018*	low	moderate	low	low	low	low	Low
Kluth, et al.	*2014*	low	moderate	low	low	low	low	Low
Lara, et al.	*2014*	low	low	low	low	moderate	low	Low
Lee, et al.	*2016*	low	moderate	low	low	low	low	Low
Levesque, et al.	*2019*	low	moderate	low	low	low	low	Low
Lin, et al.	*2017*	low	moderate	low	low	low	low	Low
Loffeler, et al.	*2015*	low	low	low	low	low	low	Low
Narang, et al.	*2017*	low	moderate	low	low	low	low	Low
Ozden, et al.	*2017*	moderate	low	low	low	low	low	Low
Pei, et al.	*2016*	low	low	moderate	low	low	low	Low
Qu, et al.	*2016*	low	low	low	low	low	low	Low
Qu F, et al.	*2017*	low	low	low	low	low	low	Low
Rizzardi, et al.	*2015*	low	low	low	low	low	low	low
Ruenauver, et al.	*2014*	low	moderate	moderate	low	low	low	Low
Shimodaira ,et al.	*2020*	low	moderate	low	low	low	low	Low
Strand, et al.	*2015*	low	moderate	low	low	low	low	Low
Takagi, et al.	*2017*	low	low	low	low	moderate	low	Low
Wang, et al.	*2016*	low	moderate	low	low	low	low	Low
Zacho, et al.	*2017*	moderate	low	low	low	moderate	low	Low
Berg, et al.	*2014*	low	low	low	low	low	low	Low

Table 7: Overall judgment of RoB (PROBAST, Prognostic)

Overall judgement of RoB	RoB	Applicability
Low	3	15
High	27	20
Unclear	13	8
Total	43	

Table 8: Characteristics of DPFs with overall low risk of bias

Author	Year	RoB	Population	Study design	Timing	Index	Outcomes
Palsdottir, et al [26]	*2019*	Diag. PROBAST	Localised PCa	Observational study	Pre treatment	S3M-MRI (Stockholm3 + PI-RADS)	csPCa diagnosis
Guinney, et al. [24]	*2017*	Prog. PROBAST	mCRPC	RCT	post treatment	ePCR model	OS
Joniau, et al. [25]	*2017*	Prog. PROBAST	Locally advanced PCa	Observational study	Post-treatment	Gleason score + PSA	Adverse pathological features at RP; LNI
Hagiwara, et al. [22]	*2017*	QUADAS	Localised PCa	Observational study	Pre-treatment	WFA-reactive glycan-carrying PSA-Gi	PCa diagnosis, PSA-free survival
Kelly, et al. [23]	*2015*	QUADAS	Localised PCa	Observational study	Pre-treatment	miR-141, -145, -155, let7a	PCa diagnosis
Aguilera, et al. [27]	*2015*	QUIPS	High risk PCa	Observational study	pre and post treatment	Age, rectal examination, PSA, biopsy Gleason score, uni/bilateral tumor, affected cylinder percentage) and postoperative	BCR
Alvim, et al. [29]	*2019*	QUIPS	Metastatic PCa	Observational study	Post-treatment	PSA response (PSA reduction≥ 50%)	OS, PFS
Bramhecha, et al. [28]	*2019*	QUIPS	Localised PCa	Observational study	Post-treatment	PTEN deletion	BCR
Bruce, et al. [30]	*2016*	QUIPS	Localised PCa	Observational study	Post-treatment	AZGP1 expression	BR-free survival, CR-free survival, PC-specific death
Francini, et al. [31]	*2018*	QUIPS	mHSPC	Observational study	Post-treatment	Volume	OS, time to CRPC
Hamada, et al. [32]	*2016*	QUIPS	High risk PCa	Observational study	Post-treatment	PSA, PSA density (PSAD), PSA density of the transition zone, percentage of positive cores (PPC), prostate volume,	BCR

						TZ volume, Gleason score, PPC from the dominant side	
Hashimoto, et al. [33]	*2020*	QUIPS	Localised PCa	Observational study	Post-treatment	micro-lymphatic invasion, Gleason	BCR
Hung, et al. [61]	*2017*	QUIPS	mCRPC	Observational study	Post-treatment	Neurovascular bundle preservation, blood loss, pT stage, pN stage, pGS, PNI, angiolymphatic invasion, tumour amount in specimen, ECE, PSM, SVI, Bladder neck invasion, Foley duration, Post-op undetectable PSA	BCR
Kato et al. [34]	*2018*	QUIPS	High risk PCa	Observational study	Post-treatment	LC/IDC	Progression-free survival (PFS), Cancer-specific survival (CSS)
Kluth, et al. [35]	*2014*	QUIPS	Localised PCa	Observational study	Post-treatment	number of lymph nodes	BCR
Lara, et al. [36]	*2014*	QUIPS Validated	mCRPC	RCT	Post treatment	Bone resorption and formation	OS
Lee, et al. [37]	*2016*	QUIPS	Localised PCa	Observational study	Post treatment	Positive surgical margin status and bilateral seminal vesicle invasion	BCR
Lévesque, et al. [38]	*2019*	QUIPS	Localised PCa	Observational study	Post treatment	UGT2B17 expression	BCR
Lin, et al. [39]	*2017*	QUIPS	Localised PCa	Observational study	Post treatment	Aberrant Promoter Methylation of Protocadherin8 (PCDH8)	BRC-free survival
Löffeler, et al. [40]	*2015*	QUIPS	mCRPC	Observational study	Anytime	PSA doubling time, PSA nadir during ADT, hemoglobin and alkaline phosphatase levels at CRPC	OS
Narang, et al. [41]	*2017*	QUIPS	Localised PCa	Observational study	Anytime	PSA: End-of-radiation PSA	BCR-free survival, MFS, CSS, OS

Ozden, et al. [42]	*2017*	QUIPS	Localised PCa	Observational study	Post treatment	Age	RRP specimen, BCR, and biochemical recurrence-free survival rates
Pei, et al. [43]	*2016*	QUIPS	CRPC	Observational study	Pre and during treatment	Neutrophil-to-lymphocyte ratio	OS, PFS
Qu, et al. [44]	*2016*	QUIPS	mPCa and CRPC	Observational study	Pre treatment	AR-V7	Time to CRPC / CRPC: CSS
Qu, et al. [45]	*2017*	QUIPS	PCa	Observational study	Pre and during treatment	AR-V7	OS
Ruenauver, et al. [46]	*2014*	QUIPS	Localised PCa	Observational study	Post treatment	YWHAZ	OS
Shimodaira, et al. [47]	*2020*	QUIPS	Metastatic PCa	Observational study	Post treatment	Value of Platelet Counts	Disease specific survival
Strand, et al. [48]	*2015*	QUIPS	Localised PCa	Observational study	Post treatment	5-hydroxymethylcytosine (5hmC) score	BCR
Takagi, et al.[49]	*2017*	QUIPS	Localised PCa	Observational study	Post treatment	Age, T stage, % of pos cores, Gleason score, PSA, Total ADT	BCR-free survival
Wang, et al. [50]	*2016*	QUIPS	PCa	Observational study	Post treatment	Platelet to lymphocyte ratio	PLR with progression-free survival (PFS), cancer-specific survival (CSS) and overall survival (OS)n/a
Zacho, et at. [51]	*2017*	QUIPS	Localised PCa	Observational study	Anytime	Bone scan index	Time to CRPC
Berg, et al. [52]	*2014*	QUIPS validated	Under Active Surveillance	Observational study	During treatment	ERG immunohisto-chemical staining	Overall AS progression, histopathologic progression

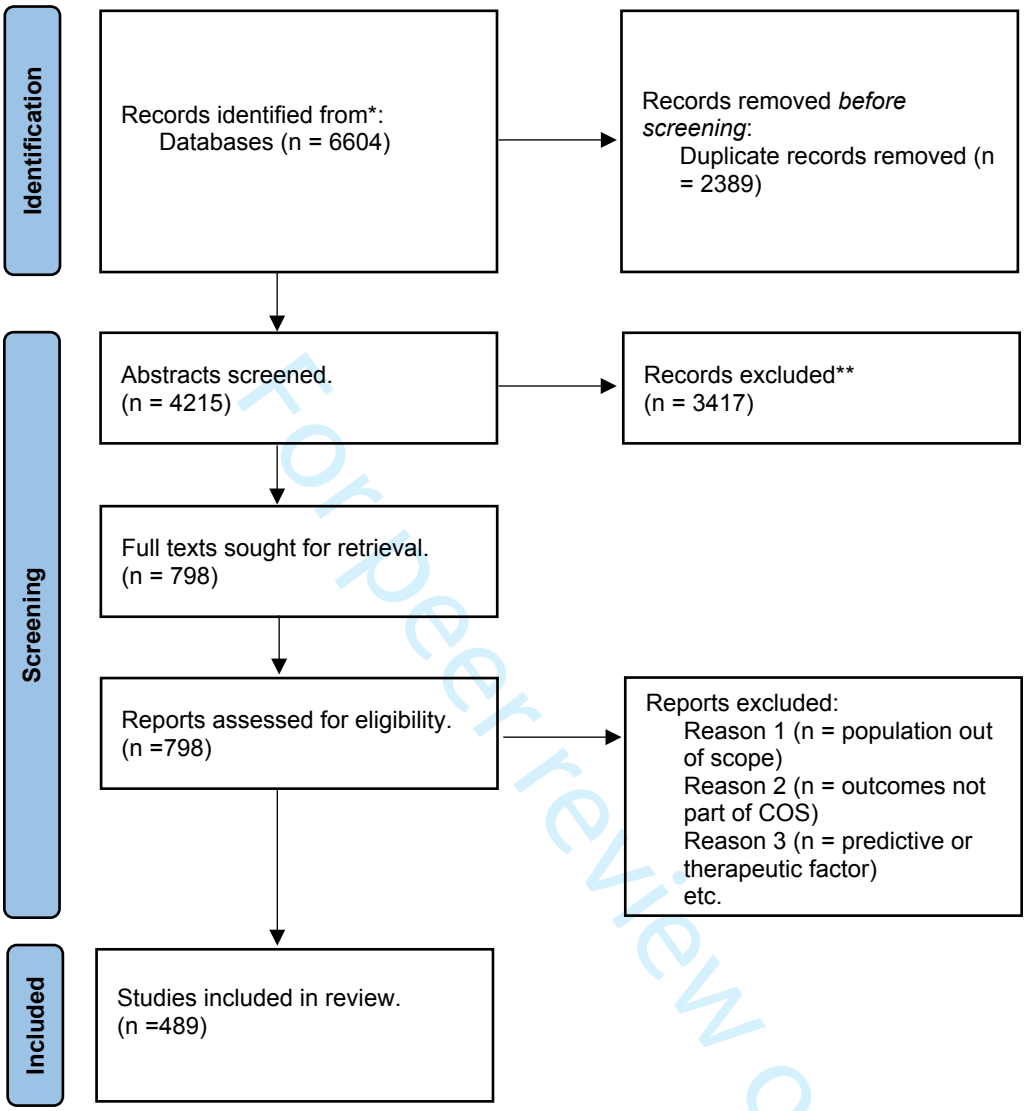
Figure 1: Overview of four stage process

Figure 2: PRISMA flow diagram

Figure 1: Overview of four stage process

Workflow	Task
Stage 1.	Broad literature-based systematic review of diagnostic and prognostic factors (DPs) for all stages of prostate cancer from 2014 onwards (English only; humans). • Extract data from the included studies following the CHARMS-PF guideline.
Stage 2.	Discussion of systematic review findings by a multidisciplinary expert panel • Review the list of included studies
Stage 3.	Risk of Bias Assessment and applicability of individual studies using PROBAST, QUIPS and QUADAS-2
Stage 4.	Quantitative assessment of individual articles using meta-analytic techniques: • If PROBAST indicates low risk of bias and low concerns for applicability: Oxford Classification Centre for Evidence Based Medicine: 1. If there is Level 1a (SR of RCTs), we do not do a meta-analysis 2. No Level 1a but >2 RCTs, we do a meta-analysis 3. No Level 1a/b, i.e. if at least two RCTs are now available, and systematic review of RCT evidence is not possible, we will identify whether there is a systematic review for observational studies (real world evidence; RWE), we do not do a meta-analysis 4. If systematic review of RWE is not available, a systematic review of observational study will be conducted, and a meta-analysis will be performed if at least two RWEs studies are available and data pooling is feasible and there are low concerns of risk of bias.
Final aim:	Develop online PIONEER Online Search Tool for DPFs

Figure 2: PRISMA flow diagram



Supplementary material Table 1: Search strategy

Database: OVID Medline Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Ovid MEDLINE(R) Daily and Ovid MEDLINE(R) 1946 to Present, Embase <1974 to 2020 January 28>, EBM Reviews - Cochrane Database of Systematic Reviews <2005 to January 21, 2020>

Search Strategy:

---

1 exp *Prostatic Neoplasms/ (262435)

2 exp *prostate cancer/ (245472)

3 (prostat* adj2 (cancer* or carcinoma* or malignan* or tumor* or tumour* or neoplas* or adenocarcinoma* or adenoma*)).tw. (332251)

4 or/1-3 (366427)

5 ((diagnostic or prognos* or predict*) adj10 (biomarker or biomarkers or factor or factors)).tw,kw. (717487)

6 ((diagnostic or prognos* or predict*) adj10 (Oncotype Dx Prostate or Prolaris or Decipher or Decipher PORTOS or ProMark)).tw,kw. (458)

7 5 or 6 (717869)

8 4 and 7 (17456)

9 limit 8 to english language [Limit not valid in CDSR; records were retained] (16484)

10 limit 9 to yr="2014 -Current" (8417)

11 conference abstract.pt. or Congresses as Topic/ or Conference Review.pt. or "Journal: Conference Abstract".pt. (3815712)

12 10 not 11 (5902)

13 (exp animals/ or exp animal/ or exp nonhuman/ or exp animal experiment/ or animal model/ or animal tissue/ or non human/ or (rat or rats or mice or mouse or swine or porcine or murine or sheep or lambs or pigs or piglets or rabbit or rabbits or cat or cats or dog or dogs or cattle or bovine or monkey or monkeys or trout or marmoset$1).ti.) not (humans/ or human/ or human experiment/ or (human* or men or women or patients or subjects).tw.) (10251935)

14 12 not 13 (5882)

15 note/ or editorial/ or letter/ or Comment/ or news/ or (note or editorial or letter or Comment or news).pt. (4565255)

16 14 not 15 (5811)

17 (child/ or Pediatrics/ or Adolescent/ or Infant/ or adolescence/ or newborn/ or (baby or babies or child or children or pediatric* or paediatric* or peadiatric* or infant* or infancy or neonat* or

	newborn* or new born* or adolescen* or preschool or pre-school or toddler*).tw.) not (adult/ or aged/ or (aged or adult* or elder* or senior* or men or women).tw.) (4146377)
18	16 not 17 (5794)
19	18 use ppez,oemezd (5788)
20	10 use coch (6)
21	19 or 20 (5794)
22	remove duplicates from 21 (3140)

Supplementary material Table 2. Multidisciplinary expert meeting

Profession	**Attendance**
Urologist	Accepted
Epidemiologist	Accepted
Urologist	Accepted
Epidemiologist/Pharma representative	Accepted
Pathologist	Accepted
Urologist	Accepted
Urologist	Accepted
Epidemiologist	Accepted
Methodologist	Accepted
Epidemiologist/Pharma representative	Accepted
Urologist	Accepted
Urologist/Methodologist	Accepted
Urologist	Accepted
Urologist	Accepted
Oncologist	Accepted
Pharma representative	Accepted
Pharma representative	Accepted
Statistician/ Pharma representative	Accepted

Table 3: PROBAST overall assessment

Criteria	Reaching and overall judgement of RoB	
All domains are rated low risk.	Paper was classified as low RoB and low Applicability.	
One or more domain was judged to be high risk of bias.	Paper was classified as high RoB and high Applicability.	
One or more domain was judged to be unclear risk of bias.	Paper was classified as unclear RoB and h igh Applicability.	

Supplementary material Table 4: QUIPS scoring

Score of 6 domains	**Overall RoB**	
All domains were classified as having low RoB, or up to one moderate RoB.	Paper was classified as low RoB	
One or more domains were classified as having high RoB, or ≥ 3 moderate RoB.	Paper was classified as high RoB	
All papers in between.	Paper was classified as having moderate RoB	

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Primary Subject Heading:	Urology
Secondary Subject Heading:	Urology
Keywords:	Prostate disease < UROLOGY, Urological tumours < ONCOLOGY, Epidemiology < ONCOLOGY

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Diagnostic and prognostic factors in patients with prostate cancer: a systematic review

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Abstract

Objectives: As part of the PIONEER Consortium objectives, we have explored which diagnostic and prognostic factors (DPFs) are available in relation to our previously defined clinician and patient-reported outcomes (PROs) for prostate cancer (PCa).

Design: We performed a systematic review to identify validated and non-validated studies.

Data sources: MEDLINE, Embase and the Cochrane Library were searched on January 21, 2020.

Eligibility criteria: Only quantitative studies were included. Single studies with fewer than 50 participants, published before 2014 and looking at outcomes which are not prioritised in the PIONEER core outcome set will be excluded.

Data extraction and synthesis: After initial screening, we extracted data following the Checklist for Critical Appraisal and Data Extraction for Systematic Reviews of prognostic factor studies (CHARMS-PF) criteria and discussed the identified factors with a multidisciplinary expert group. The quality of the included papers was scored for applicability and risk of bias using validated tools such as PROBAST, QUIPS and QUADAS-2.

Results: The search identified 6,604 studies, from which 489 DPFs were included. Sixty-four of those were internally or externally validated. However, only three studies on diagnostic and seven studies on prognostic factors had a low risk of bias and a low risk concerning applicability.

Conclusion: Most of the DPFs identified require additional evaluation and validation in properly designed studies before they can be recommended for us e in clinical practice. The PIONEER online search tool for diagnostic and prognostic factors for prostate cancer will

enable researchers to understand the quality of the current research and help them design future studies.

Ethics and Dissemination: There are no ethical implications.

Introduction

Prostate cancer (PCa) accounts for 15% of cancers diagnosed [1] and is the second most common cancer in males worldwide [2]. PCa is clinically and molecularly heterogeneous and is usually suspected based upon the clinical findings of digital rectal examination (DRE) and/or Prostate Specific Antigen (PSA) levels [1]. However, which diagnostic or prognostic factor (DPF) can be used to select patients for specific therapeutic options remains largely unclear [3]. Specific biomarkers in urine or in blood are available on top of traditional PSA testing, such as PCA3, TMPRSS2-ERG fusion, or kallikreins as incorporated in the Phi or 4Kscore test together with other parameters including family history [4-7]. However, the European Association of Urology (EAU) guidelines (2019) currently do not provide general recommendations to implement these biomarkers into routine screening programmes due to limited data [8]. As part of the ASCO guidelines, Eggener et al recommended five commercially available biomarkers which have been shown to provide prognostic significance and additional information beyond standard clinical models in patient selection in the localised context: Oncotype Dx Prostate, Prolaris, Decipher, and ProMark [9]. However, no guidelines have recommended DPFs for other stages of PCa. The expert panel at the APCCC consensus meeting of advanced prostate cancer in Basel 2019, recommended AR-V7 for mCRPC as potentially useful, which ultimately led to the inclusion of AR-V7 testing in the NCCN guidelines [10].

The PIONEER Consortium is an international collaboration coordinated by the European Association of Urology (EAU), which aims to establish the best evidence-based management and clinical practice of PCa across all disease stages using the power of big data analytics towards a more outcome-driven, value-based, and patient-centric healthcare system [11]. A

key objective is to address one of the major challenges within the context of diagnostic or prognostic biomarkers/factors: the inability to incorporate DPFs into the management of PCa in terms of screening, diagnosis and treatment. It is therefore important to summarise and evaluate the evidence. Biomarkers can be classified into different types: diagnostic, prognostic, predictive, and therapeutic – in this study we focus on the first two[12]. A diagnostic biomarker or factor is useful when cancer is suspected and allows the early detection based on symptoms or tests [12]. The overall aim of a diagnostic biomarker is to distinguish people with the diseases from people without the disease. A prognostic biomarker or factor is a clinical or biological characteristic which provides information on the likely course of the disease i.e., biochemical progression or disease recurrence [12]. It enables clinicians to decide on the most suitable treatment depending on the likely course of the disease. In the sections below we have used the terms biomarkers and factors interchangeably. Multiple diagnostic and prognostic factors (DPFs) can be measured in tissue, blood or urine. These come with different advantages and disadvantages and only a limited number of factors are currently available for PCa in standard clinical care.

We aimed to systematically review the evidence from 2014 onward to assess which DPFs are available in relation to previously defined outcomes for PCa.

Methods

The systematic review followed the PRISMA guidelines [13]. A detailed protocol of the overall project was published elsewhere [14] (please see the protocol attached as methods appendix). Briefly, we followed the following four steps (Figure 1):

(1) Comprehensive systematic literature review of DPFs for all stages of PCa (localised, locally advanced, metastatic, and non-metastatic castration resistant) from 2014 onwards. DPFs developed before 2014 were not included, due to the significant changes which influence the staging of PCa (i.e., Consensus Conference on Gleason Grading of Prostatic Carcinoma (60)) have taken place in diagnostic and prognostic practice and patient management.

(2) Assessment and identification of final list of DPFs by a multidisciplinary expert panel.

(3) Evaluation of quality of studies published using risk of bias tools: Prediction model Risk Of Bias (RoB) Assessment Tool (PROBAST) if applicable; or Quality in Prognostic Studies (QUIPS) tool for prognostic and the Quality Assessment of Diagnostic Accuracy Studies 2 (QUADAS-2) tool for diagnostic factors;

(4) Due to the heterogeneity of the studies identified no further formal quantitative assessments in the form of a meta-analyses could be performed. Hence, the findings of stages 1-3 have been reported here as the results of a systematic review.

Stage 1: Comprehensive literature review

We developed the search criteria for the first search with an information scientist who specialises in systematic reviews for urology. MEDLINE, Embase and the Cochrane Library were searched on January 21, 2020. The second search was developed following a consultation with an independent information scientist group who excluded row 12, 14 and 16 of Table 1 (see supplementary material). We screened the EAU Guidelines reference list for PCa in our third search (see Figure 2).

Stage 2: Multidisciplinary expert meeting

On the 20th of March 2020, we invited a group of multidisciplinary participants to discuss the identified articles on DPFs (see supplementary material Table 2). The participants were presented the search criteria and the extracted data. Data extraction followed the CHARMS-PF checklist and we added author and year of publication.

Stage 3: Evaluation of quality of studies published using the risk of bias tools

Prior to the evaluation of the quality of studies, an initial pilot screening to prepare the raters for the use of PROBAST, QUADAS-2, QUIPS was performed. This aimed to reach consensus on how to judge the domains of the assessments using the three RoB tools. Two urologists (FB, SS) and two epidemiologists (AH, KB) were involved in the pilot assessments. The group discussed any discrepancies. Articles which presented the development and validation the internal validation or the external validation (i.e., the same data was used for both development and internal validation, such as bootstrapping or cross-validation; different populations were used for development and validation), of a diagnostic or prognostic model were assessed with PROBAST. Papers assessing single biomarkers or with/without validation were assessed with QUIPs for prognostic or QUADAS-2 for diagnostic biomarkers.

Evaluation of quality of studies published using QUADAS-2

The RoB of diagnostic factors without validation or single validated factors was evaluated using QUADAS-2. We assessed the following four domains: patient selection, index test, reference standards and flow and timing. The first three domains are assessed looking at applicability and all four domains were assessed in terms of RoB [15]. We created a summative

score after the diagnostic studies were assessed by two reviewers and in case of disagreement a third reviewer assessed the study.

Evaluation of quality of studies published using PROBAST (Diagnostic)

The RoB of internal or external validated diagnostic models was assessed using the PROBAST RoB tool. PROBAST includes four domains assessing the RoB (i.e., participants, predictors, outcome and analysis) and four domains assessing applicability (i.e., participants, predictors and outcome) (see supplementary material Table 3 for scoring information).

Evaluation of quality of studies published using QUIPS

To assess the articles which are single factors or were not internally or externally validated, we used the QUIPS rating procedure (see supplementary material Table 4 for scoring information). To standardise the approach across raters, we used the QUIPS electronic spreadsheet (excel) from Hayden et al [16]. There are no rules available for QUIPS on how to score the overall RoB of a paper. Due to the large number of papers and the need for synthesis, we followed Grooten et al's suggestions to categorise on the following criteria: 1) Paper was classified as low RoB if all domains were classified as having low RoB, or up to one moderate RoB; 2) Paper was classified as high RoB if one or more domains were classified as having high RoB, or ≥ 3 moderate RoB; 3) Paper was classified as having moderate RoB if all papers in between 1 or 2 (see table 1). This assessment was based on the risk scores of individual assessments within the group. If the overall assessment was not possible due to differences in the individual category, a third assessor reviewed the assessments and the results were discussed.

Evaluation of quality of studies published using PROBAST (Prognostic)

The RoB of prognostic validated models were assessed using PROBAST. As highlighted above, PROBAST includes four domains assessing the RoB (i.e., participants, predictors, outcome and analysis) and four domains assessing applicability (i.e., participants, predictors and outcome).

Results

Stage 1: Comprehensive literature review

Stage 1 identified 6,604 citations and contained three independent searches. After removing duplicates, we screened 4,215 abstracts, from which 489 met the inclusion criteria.

Stage 2: Multidisciplinary expert meeting

The group discussed the results and additional literature on DPFs was suggested to help the classification of the DPFs, such as the ASCO Guideline on Molecular Biomarkers in Localized Prostate Cancer [17].

Stage 3: Evaluation of quality of studies published using the risk of bias tools

The 489 articles were equally divided between six groups. The six groups received the guidance documents which were identified during the pilot phase

[15 16 18-20]. In addition, MvH and KB discussed questions with each individual group.

Evaluation of quality of studies published using QUADAS-2

The RoB of the 41 included studies was low for 10 studies, high for 23 studies and unclear for eight. RoB concerning applicability was low for 10 studies, high for 21 studies and unclear for 10 studies (see Table 1). Table 2 shows the studies with an overall low RoB across both categories. Two studies were identified to have an overall low RoB [21 22].

Evaluation of quality of studies published using PROBAST (Diagnostic)

We identified 20 papers to be assessed with PROBAST. The RoB of three papers was low, that of 14 was high and was unclear for three. The applicability of eight papers was high and was unclear for two (see Table 1). Table 1 in the supplementary material shows the criteria on how to judge the RoB. One study had an overall low RoB across both domains. All categories except 'predictors' was scored to have a low risk of bias. There was little information available for the category predictors and therefore it was scored as 'unclear' (see Table 3).

Evaluation of quality of studies published using QUIPS

The 12 assessors independently inserted the relevant information and assessed each domain such as participation, attrition, prognostic factor confounding and statistical analysis and reporting.

387 prognostic factors were assessed using QUIPs. 307 papers were classified as high RoB. Forty-nine papers were classified as having a moderate RoB and 28 papers were scored as low RoB (see Table 1). Out of the 28 papers with a low RoB, the most common moderate

bias was linked to attrition (12 papers), followed by confounding (4 papers), participation (3 papers), outcome (1 paper), statistical analysis (1 paper) (see Table 4).

Evaluation of quality of studies published using PROBAST (Prognostic)

The assessors identified 44 papers to be assessed with PROBAST, of those three scored a low RoB, 27 a high risk of bias and 13 were assessed as unclear (see Table 1). In terms of applicability, 15 papers scored low, 20 high and eight unclear. Two papers were scored to have an overall low RoB [23 24] (see Table 3).

Characteristics of studies identified with low risk of bias

Details of the identified validated DPF models with an adequate quality are presented in Table 5. We identified 32 studies with an overall low RoB (assessed with PROBAST, QUIPS, QUADAS-2). Out of these 32 studies, we identified one validated diagnostic model (assessed with PROBAST) [25], two validated prognostic models (assessed with PROBAST) [23 24], two non-validated diagnostic single factors (assessed with QUADAS-2) [21 22] and 26 prognostic factors (assessed with QUIPS) [21-51] which have not been validated and two single prognostic factors which have been validated (assessed with QUIPS) [35 51]. Prognostic factors assessed with QUIPS were identified with a low risk of bias for the localised PCa population. Sixty-seven percent of the low RoB DPFs were intended to be measured after the treatment was performed. In addition, the most commonly measured outcome was biochemical recurrence (BRC) followed by overall survival (OS). It is, however, important to take into consideration that even though from the studies assessed with a low RoB, only two out of the 32 were of a non-observational study design.

As highlighted above, we identified three validated DPFs which were scored to have a low RoB and low risk concerning applicability. Firstly, we identified the 'Unified Prostate Cancer Risk Prediction Model Combining the Stockholm3 Test and Magnetic Resonance Imaging', a risk prediction model which combines clinical variables, genetic and protein biomarkers. Five hundred and thirty two men were involved across three centres [52]. Secondly, the DREAM challenge developed a set of five standardised raw event-level tables, using laboratory values, patients' demographic information, medical history, lesion sites, previous treatments, and vital signs of patients with metastatic castration-resistant PCa. These variables where combined by using data from four clinical trials [53]. Thirdly, Joniau et al. developed 'Pretreatment Tables' to predict the pathologic stage of locally advanced prostate cancer after RP based on pre-treatment PSA level and biopsy Gleason score [24].

We identified two single factors which were validated and had low RoB. Firstly, Lara et al., assessed and validated the serum biomarkers of bone metabolism (N-telopeptide and pyridinoline) and formation (C-terminal collagen propeptide and bone alkaline phosphatase)) in 778 CRPC patients as part of the randomized phase III SWOG trial (S0421) of docetaxel/prednisone with or without atrasentan [35]. Secondly, Berg et al, showed that ERG expression can be used to estimate the risk of progression during AS including 265 patients at diagnosis and progression during AS [51].

Discussion

Despite the large number of studies on DPFs which are published every year, there is a paucity of DPFs that are suitable to be incorporated into clinical practice. The majority of DPFs have not yet been validated and are identified in poor quality studies. Our analysis found that most identified studies had a high to moderate risk of bias due to poor design

standards, conduct, reporting and/or analysis i.e., generalizability and size of the population, poor model development (no testing or missing important confounders) or only correlation studies, missing data was rarely reported. However, we did identify a small number of validated DPFs with low RoB. We identified three validated models which combine: firstly, clinical variables, genetic and protein biomarkers, and improved the clinical outcome performance of prostate cancer diagnostics (The Unified Prostate Cancer Risk Prediction Model) [52]; secondly, laboratory values, patients' demographic information, medical history, lesion sites, previous treatments, and vital signs of patients with metastatic castration-resistant PCa (DREAM challenge) [53]; thirdly, pre-treatment PSA level and biopsy Gleason score to predict the pathologic stage of locally advanced PCa ('Pretreatment Tables') [24]. Two single factors have been validated: the serum biomarkers of bone metabolism in CRPC patients [35] and the ERG expression, which can be used to estimate the risk of progression during AS [51], which has been already highlighted in the clinical guidelines [1].

Aladawani et al assessed prediction models for PCa to be used in primary care settings in their systematic review and identified five models which met their inclusion criteria. From these identified models only one model was externally validated and only one (the Lazzari model 2 [54]) had the potential to be implemented in primary care. Lazzari et al. had the lowest RoB (based on PROBAST), however it must be externally validated before it can be implemented. Hence, Aladawani et al also concluded that the existing models have limitations concerning study design and reporting performance [55].

Tian et al conducted a review on biomarkers for CRPC patients, however their quality assessment was focused on study design (RCT vs observational study), whereas we focused on biomarker specific tools [56]. Whilst Tian et al and our review identified similar factors and

quality scores, there were slight discrepancies between the overall RoB assessments. Tian et al. used an overall quality assessment scale from 1-6 instead of low, medium and high. In their assessment the validated prognostic study by Lara et al. [35] and the non-validated prognostic factor by Pei et al. [42] were scored on the quality scale as 4 (medium quality). We assessed Lara et al. [35] to have a low risk of bias with a moderate risk of confounding and Pei et al. [42] with a moderate risk of bias concerning the prognostic factor itself. This might explain the discrepancies between the two quality assessments. The reports by Alvim et al., Qu et al., were assessed to have the highest quality by Tian et al [56], similar to our review. This illustrates that different quality assessment tools emphasize different criteria, which may result in small discrepancies. However, the overall conclusion for prognostic single factors was similar in our review and to the work of Tian et al. [56].

Similar issues have been identified for other urological cancers. For example, in kidney cancer, a large body of research was identified by Harrison et al., with very few validated studies and lots of heterogeneity [57]. Schmitz-Dräger et al. published an International Consultation of Urologic Disease (ICUD)/World Health Organization (WHO) Consensus manuscript where they identified that in bladder cancer one of the main limitations for the lack of incorporation of modern bladder cancer tests into clinical practice decision making is linked to the scarcity of 'good clinical practice guidelines' for the evaluation of diagnostic markers.

There is a need for improved guidance on development and validation of diagnostic markers [58]. To meet that need, we are developing the PIONEER DPF search tool, which will help researchers and clinicians to get a better understanding of the DPFs for prostate cancer. The tool will not only summarise all relevant studies, but also provide information on the use and results of

different RoB assessment tools, which will enable an understanding of the quality of published studies.

Future research should therefore focus on addressing the identified shortcomings such as heterogeneity, validation and poor RoB by designing more robust studies which consistently include RoB assessments such as PROBAST, QUIPS or QUADAS-2.

With the growing number of various therapeutic options, diagnosis and management of prostate cancer require an individualised approach to patient care. There is an unmet need for DPFs to guide decisions for optimal treatment and predict which patients will benefit the most, from a particular management strategy. DPFs could potentially enhance the quality of patient counselling, but currently most need additional evaluation and validation in properly designed studies. Our systematic review highlights the need for well-designed Real-World Evidence studies, while the PIONEER online search tool can inform the design of new research studies, through providing a rigorous evaluation of the methodological quality of the studies.

The main strength of this study are the extensive and comprehensive search and screening of the studies included. In addition, we are developing an online search tool which showcases the identified and assessed studies. It provides an overview of the available DPFS and enables interested stakeholders to search for DPFs. To our knowledge, this is the first study which has been performed with this extensive amount of literature.

Patient and public Involvement

This project has been overseen by a multi-stakeholder group part of the PIONEER Consortium. PIONEER brings together 32 key stakeholders from academic institutions,

patient advocacy groups, European organisations, experts in legal data management, clinicians and pharmaceutical companies, as well as regulatory agencies, economics and ethics, and information and technology specialists. Patients and their family members are therefore involved and actively participate as an integral part of all research conducted by the PIONEER Consortium.

Limitations

Even though this review included three searches and assessments by a multidisciplinary group of fourteen researchers, we recognise potential limitations. Studies were only included from 2014 onwards and DPFs developed before 2014 were not included. However, significant changes which influence the staging of PCa (i.e., Consensus Conference on Gleason Grading of Prostatic Carcinoma [59]) have taken place in diagnostic and prognostic practice and patient management. This changed the staging of the patient population and therefore has an impact on DPFs.

In addition, there is a potential of subjectivity in the evaluation of the studies. Even though the studies have been assessed in duplicate, there might be variation across groups. However, given the overall moderate to high risk of bias, this does not influence the overall recommendation of the project.

Conclusion

At present DPFs that are capable of significantly improving diagnosis and prognosis in prostate cancer are an unmet need as most of the DPFs identified require additional evaluation and validation in properly designed studies before they can be recommended for

use in clinical practice. Well-designed RWE studies can help to increase quality. Our SR aims to inform clinicians and patients about this rapidly evolving field, while the PIONEER online search tool for diagnostic and prognostic factors for prostate cancer will enable researchers to perform future research, and to understand the quality of the current available studies.

Strengths and limitations of this study

- A multidisciplinary team including patients, urologists, oncologists, radiation oncologists, methodological experts and pathologists were involved throughout the study.
- The search was restricted from 2014 onwards, to maintain a pragmatic approach.
- The main strength of this study are the extensive and comprehensive search and screening of the studies included.

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Table 1: Overall judgment of RoB

QUADAS-2, Diagnostic		
Overall judgement of RoB	RoB	Applicability
Low	10	10
High	23	21
Unclear	8	10
Total	41	
PROBAST, Diagnostic		
Overall judgement of RoB	RoB	Applicability
Low	3	8
High	14	10
Unclear	3	2
Total	20	
QUIPS		
Overall judgement of RoB	RoB	
Low	29	
Moderate	49	
High	307	
Total	385	
PROBAST, Prognostic		
Overall judgement of RoB	RoB	Applicability
Low	3	15
High	27	20
Unclear	13	8
Total	43	

Table 2 non-validated DPFs with overall low risk of bias: QUADAS-2

Author	Year	Patient Selection	Index Test(s)	Reference Standard	Flow and Timing	Patient Selection	Index Test(s)	Reference Standard	RoB	Applicability
Hagiwara, et al.	2017	low	low	low	low	low	low	low	low	low
Kelly, et al.	2015	low	low	low	low	low	low	low	low	low

Table 3: DPFs assessed with PROBAST

Author	ROB				APPLICABILITY			Overall	
	Participants	Predictors	Outcome	Analysis	Participants	Predictors	Outcome	ROB	Applicability
Diagnostic									
Guinney, et al.	Low	Low	Low	Low	Low	Low	Low	Low	Low
Joniau, et al.	Low	Low	Low	Low	Low	Low	Low	Low	Low
Prognostic									
Palsdottir, et al	low	Unclear	low	low	low	low	low	low	low

Table 4: Characteristics of DPFs with overall low risk of bias

Author	Year	RoB	Population	Study design	Timing	Index	Outcomes
Palsdottir, et al [25]	*2019*	Diag. PROBAST	Localised PCa	Observational study	Pre treatment	S3M-MRI (Stockholm3 + PI-RADS)	csPCa diagnosis
Guinney, et al. [23]	*2017*	Prog. PROBAST	mCRPC	RCT	post treatment	ePCR model	OS
Joniau, et al. [24]	*2017*	Prog. PROBAST	Locally advanced PCa	Observational study	Post-treatment	Gleason score + PSA	Adverse pathological features at RP; LNI
Hagiwara, et al. [21]	*2017*	QUADAS	Localised PCa	Observational study	Pre-treatment	WFA-reactive glycan-carrying PSA-Gi	PCa diagnosis, PSA-free survival
Kelly, et al. [22]	*2015*	QUADAS	Localised PCa	Observational study	Pre-treatment	miR-141, -145, -155, let7a	PCa diagnosis
Aguilera, et al. [26]	*2015*	QUIPS	High risk PCa	Observational study	pre and post treatment	Age, rectal examination, PSA, biopsy Gleason score, uni/bilateral tumor, affected cylinder percentage) and postoperative	BCR
Alvim, et al. [28]	*2019*	QUIPS	Metastatic PCa	Observational study	Post-treatment	PSA response (PSA reduction≥ 50%)	OS, PFS
Bramhecha, et al. [27]	*2019*	QUIPS	Localised PCa	Observational study	Post-treatment	PTEN deletion	BCR
Bruce, et al. [29]	*2016*	QUIPS	Localised PCa	Observational study	Post-treatment	AZGP1 expression	BR-free survival, CR-free survival, PC-specific death
Francini, et al. [30]	*2018*	QUIPS	mHSPC	Observational study	Post-treatment	Volume	OS, time to CRPC
Hamada, et al. [31]	*2016*	QUIPS	High risk PCa	Observational study	Post-treatment	PSA, PSA density (PSAD), PSA density of the transition zone, percentage of positive cores (PPC), prostate volume, TZ	BCR

						volume, Gleason score, PPC from the dominant side	
Hashimoto, et al. [32]	*2020*	QUIPS	Localised PCa	Observational study	Post-treatment	micro-lymphatic invasion, Gleason	BCR
Hung, et al. [60]	*2017*	QUIPS	mCRPC	Observational study	Post-treatment	Neurovascular bundle preservation, blood loss, pT stage, pN stage, pGS, PNI, angiolymphatic invasion, tumour amount in specimen, ECE, PSM, SVI, Bladder neck invasion, Foley duration, Post-op undetectable PSA	BCR
Kato et al. [33]	*2018*	QUIPS	High risk PCa	Observational study	Post-treatment	LC/IDC	Progression-free survival (PFS), Cancer-specific survival (CSS)
Kluth, et al. [34]	*2014*	QUIPS	Localised PCa	Observational study	Post-treatment	number of lymph nodes	BCR
Lara, et al. [35]	*2014*	QUIPS Validated	mCRPC	RCT	Post treatment	Bone resorption and formation	OS
Lee, et al. [36]	*2016*	QUIPS	Localised PCa	Observational study	Post treatment	Positive surgical margin status and bilateral seminal vesicle invasion	BCR
Lévesque, et al. [37]	*2019*	QUIPS	Localised PCa	Observational study	Post treatment	UGT2B17 expression	BCR
Lin, et al. [38]	*2017*	QUIPS	Localised PCa	Observational study	Post treatment	Aberrant Promoter Methylation of Protocadherin8 (PCDH8)	BRC-free survival
Löffeler, et al. [39]	*2015*	QUIPS	mCRPC	Observational study	Anytime	PSA doubling time, PSA nadir during ADT, hemoglobin and alkaline phosphatase levels at CRPC	OS

Narang, et al. [40]	*2017*	QUIPS	Localised PCa	Observational study	Anytime	PSA: End-of-radiation PSA	BCR-free survival, MFS, CSS, OS
Ozden, et al. [41]	*2017*	QUIPS	Localised PCa	Observational study	Post treatment	Age	RRP specimen, BCR, and biochemical recurrence-free survival rates
Pei, et al. [42]	*2016*	QUIPS	CRPC	Observational study	pre and during treatment	Neutrophil-to-lymphocyte ratio	OS, PFS
Qu, et al. [43]	*2016*	QUIPS	mPCa and CRPC	Observational study	pre treatment	AR-V7	Time to CRPC / CRPC: CSS
Qu, et al. [44]	*2017*	QUIPS	PCa	Observational study	pre and during treatment	AR-V7	OS
Ruenauver, et al. [45]	*2014*	QUIPS	Localised PCa	Observational study	post treatment	YWHAZ	OS
Shimodaira, et al. [46]	*2020*	QUIPS	Metastatic PCa	Observational study	post treatment	Value of Platelet Counts	Disease specific survival
Strand, et al. [47]	*2015*	QUIPS	Localised PCa	Observational study	post treatment	5-hydroxymethylcytosine (5hmC) score	BCR
Takagi, et al.[48]	*2017*	QUIPS	Localised PCa	Observational study	post treatment	Age, T stage, % of pos cores, Gleason score, PSA, Total ADT	BCR-free survival
Wang, et al. [49]	*2016*	QUIPS	PCa	Observational study	post treatment	Platelet to lymphocyte ratio	PLR with progression-free survival (PFS), cancer-specific survival (CSS) and overall survival (OS)n/a
Zacho, et at. [50]	*2017*	QUIPS	Localised PCa	Observational study	anytime	Bone scan index	Time to CRPC
Berg, et al. [51]	*2014*	QUIPS validated	Under Active Surveillance	Observational study		ERG immunohisto-chemical staining	Overall AS progression, histopathologic progression

Table 5: DPFs with low risk of bias assessed with QUIPS

STUDY	Time	BIASES			Applicability			Overall score
		Participation	Attrition	Prognostic Factor	Outcome	Confounding	Statistical analysis and reporting	
Aguilera, et al	*2015*	low	low	low	low	moderate	low	low
Alvim, et al.	*2019*	low	low	low	low	low	low	Low
Bramhecha, et al.	*2019*	low	moderate	low	low	low	low	Low
Bruce, et al.	*2016*	low	moderate	low	low	low	low	Low
Francini, et al.	*2018*	low	low	low	low	low	moderate	Low
Hamada, et al.	*2016*	low	low	low	moderate	low	low	low
Hashimoto, et al.	*2020*	low	low	low	low	low	low	Low
Hung, et al.	*2017*	moderate	low	low	low	low	low	Low
Kato, et al.	*2018*	low	moderate	low	low	low	low	Low
Kluth, et al.	*2014*	low	moderate	low	low	low	low	Low
Lara, et al.	*2014*	low	low	low	low	moderate	low	Low
Lee, et al.	*2016*	low	moderate	low	low	low	low	Low
Levesque, et al.	*2019*	low	moderate	low	low	low	low	Low
Lin, et al.	*2017*	low	moderate	low	low	low	low	Low
Loffeler, et al.	*2015*	low	low	low	low	low	low	Low
Narang, et al.	*2017*	low	moderate	low	low	low	low	Low
Ozden, et al.	*2017*	moderate	low	low	low	low	low	Low
Pei, et al.	*2016*	low	low	moderate	low	low	low	Low
Qu, et al.	*2016*	low	low	low	low	low	low	Low
Qu F, et al.	*2017*	low	low	low	low	low	low	Low
Rizzardi, et al.	*2015*	low	low	low	low	low	low	low

Ruenauver, et al.	*2014*	low	moderate	moderate	low	low	low	Low
Shimodaira ,et al.	*2020*	low	moderate	low	low	low	low	Low
Strand, et al.	*2015*	low	moderate	low	low	low	low	Low
Takagi, et al.	*2017*	low	low	low	low	moderate	low	Low
Wang, et al.	*2016*	low	moderate	low	low	low	low	Low
Zacho, et al.	*2017*	moderate	low	low	low	moderate	low	Low
Berg, et al.	*2014*	low	low	low	low	low	low	Low

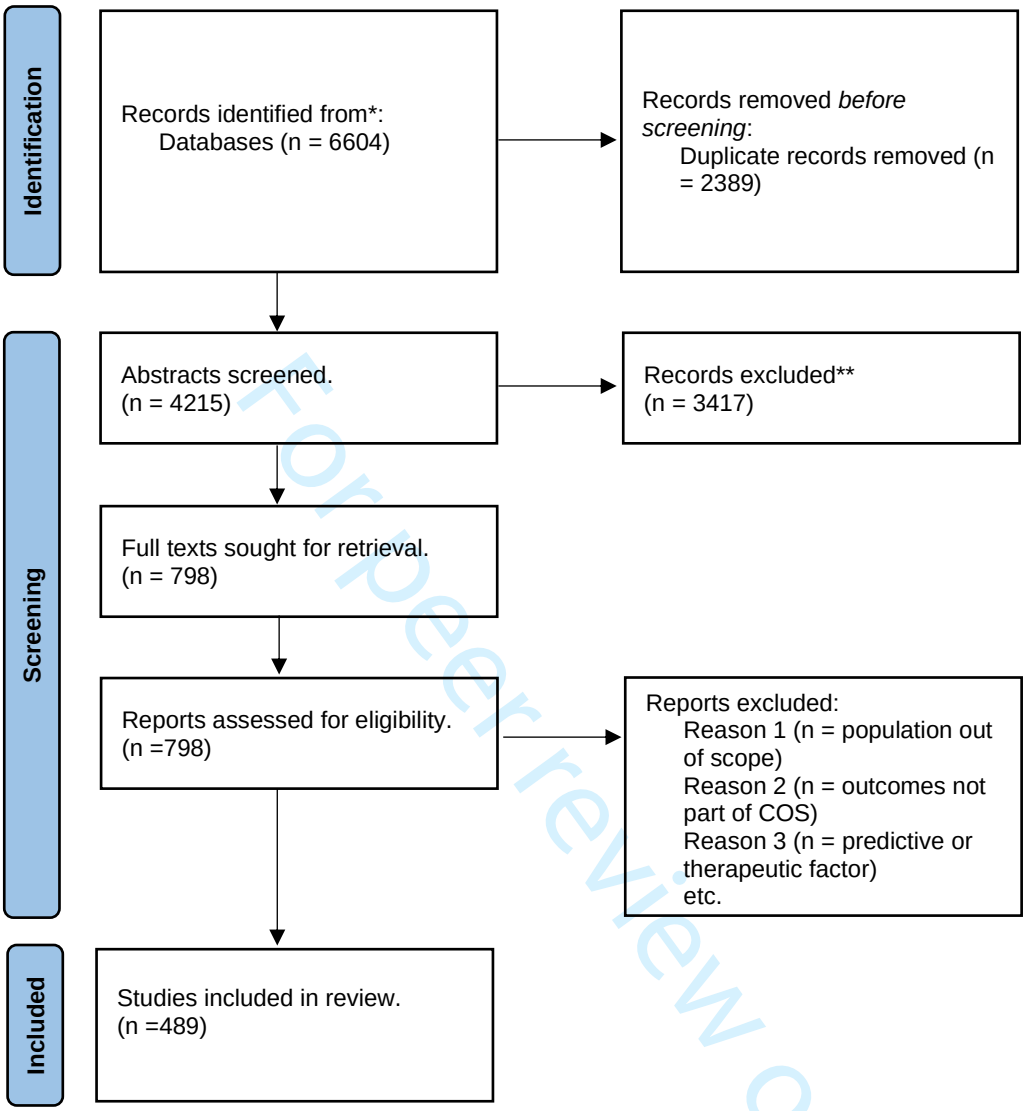
Figure 1: Overview of four stage process

Figure 2: PRISMA flow diagram

Figure 1: Overview of four stage process

Workflow	Task
Stage 1.	Broad literature-based systematic review of diagnostic and prognostic factors (DPs) for all stages of prostate cancer from 2014 onwards (English only; humans). • Extract data from the included studies following the CHARMS-PF guideline.
Stage 2.	Discussion of systematic review findings by a multidisciplinary expert panel • Review the list of included studies
Stage 3.	Risk of Bias Assessment and applicability of individual studies using PROBAST, QUIPS and QUADAS-2
Stage 4.	Quantitative assessment of individual articles using meta-analytic techniques: • If PROBAST indicates low risk of bias and low concerns for applicability: Oxford Classification Centre for Evidence Based Medicine: 1. If there is Level 1a (SR of RCTs), we do not do a meta-analysis 2. No Level 1a but >2 RCTs, we do a meta-analysis 3. No Level 1a/b, i.e. if at least two RCTs are now available, and systematic review of RCT evidence is not possible, we will identify whether there is a systematic review for observational studies (real world evidence; RWE), we do not do a meta-analysis 4. If systematic review of RWE is not available, a systematic review of observational study will be conducted, and a meta-analysis will be performed if at least two RWEs studies are available and data pooling is feasible and there are low concerns of risk of bias.
Final aim:	Develop online PIONEER Online Search Tool for DPFs

Figure 2: PRISMA flow diagram



Supplementary material Table 1: Search strategy

Database: OVID Medline Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Ovid MEDLINE(R) Daily and Ovid MEDLINE(R) 1946 to Present, Embase <1974 to 2020 January 28>, EBM Reviews - Cochrane Database of Systematic Reviews <2005 to January 21, 2020>

Search Strategy:

---

1 exp *Prostatic Neoplasms/ (262435)

2 exp *prostate cancer/ (245472)

3 (prostat* adj2 (cancer* or carcinoma* or malignan* or tumor* or tumour* or neoplas* or adenocarcinoma* or adenoma*)).tw. (332251)

4 or/1-3 (366427)

5 ((diagnostic or prognos* or predict*) adj10 (biomarker or biomarkers or factor or factors)).tw,kw. (717487)

6 ((diagnostic or prognos* or predict*) adj10 (Oncotype Dx Prostate or Prolaris or Decipher or Decipher PORTOS or ProMark)).tw,kw. (458)

7 5 or 6 (717869)

8 4 and 7 (17456)

9 limit 8 to english language [Limit not valid in CDSR; records were retained] (16484)

10 limit 9 to yr="2014 -Current" (8417)

11 conference abstract.pt. or Congresses as Topic/ or Conference Review.pt. or "Journal: Conference Abstract".pt. (3815712)

12 10 not 11 (5902)

13 (exp animals/ or exp animal/ or exp nonhuman/ or exp animal experiment/ or animal model/ or animal tissue/ or non human/ or (rat or rats or mice or mouse or swine or porcine or murine or sheep or lambs or pigs or piglets or rabbit or rabbits or cat or cats or dog or dogs or cattle or bovine or monkey or monkeys or trout or marmoset$1).ti.) not (humans/ or human/ or human experiment/ or (human* or men or women or patients or subjects).tw.) (10251935)

14 12 not 13 (5882)

15 note/ or editorial/ or letter/ or Comment/ or news/ or (note or editorial or letter or Comment or news).pt. (4565255)

16 14 not 15 (5811)

17 (child/ or Pediatrics/ or Adolescent/ or Infant/ or adolescence/ or newborn/ or (baby or babies or child or children or pediatric* or paediatric* or peadiatric* or infant* or infancy or neonat* or

	newborn* or new born* or adolescen* or preschool or pre-school or toddler*).tw.) not (adult/ or aged/ or (aged or adult* or elder* or senior* or men or women).tw.) (4146377)
18	16 not 17 (5794)
19	18 use ppez,oemezd (5788)
20	10 use coch (6)
21	19 or 20 (5794)
22	remove duplicates from 21 (3140)

Supplementary material Table 2. Multidisciplinary expert meeting

Profession	**Attendance**
Urologist	Accepted
Epidemiologist	Accepted
Urologist	Accepted
Epidemiologist/Pharma representative	Accepted
Pathologist	Accepted
Urologist	Accepted
Urologist	Accepted
Epidemiologist	Accepted
Methodologist	Accepted
Epidemiologist/Pharma representative	Accepted
Urologist	Accepted
Urologist/Methodologist	Accepted
Urologist	Accepted
Urologist	Accepted
Oncologist	Accepted
Pharma representative	Accepted
Pharma representative	Accepted
Statistician/ Pharma representative	Accepted

Table 3: PROBAST overall assessment

Criteria	Reaching and overall judgement of RoB	
All domains are rated low risk.	Paper was classified as low RoB and low Applicability.	
One or more domain was judged to be high risk of bias.	Paper was classified as high RoB and high Applicability.	
One or more domain was judged to be unclear risk of bias.	Paper was classified as unclear RoB and h igh Applicability.	

Supplementary material Table 4: QUIPS scoring

Score of 6 domains	**Overall RoB**	
All domains were classified as having low RoB, or up to one moderate RoB.	Paper was classified as low RoB	
One or more domains were classified as having high RoB, or ≥ 3 moderate RoB.	Paper was classified as high RoB	
All papers in between.	Paper was classified as having moderate RoB	

PRISMA 2020 Checklist

Section and Topic	Item #	Checklist item	Location where item is reported
TITLE			
Title	1	Identify the report as a systematic review.	p1
ABSTRACT			
Abstract	2	See the PRISMA 2020 for Abstracts checklist.	P2
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of existing knowledge.	P3
Objectives	4	Provide an explicit statement of the objective(s) or question(s) the review addresses.	P4
METHODS			
Eligibility criteria	5	Specify the inclusion and exclusion criteria for the review and how studies were grouped for the syntheses.	P5
Information sources	6	Specify all databases, registers, websites, organisations, reference lists and other sources searched or consulted to identify studies. Specify the date when each source was last searched or consulted.	P5
Search strategy	7	Present the full search strategies for all databases, registers and websites, including any filters and limits used.	P5
Selection process	8	Specify the methods used to decide whether a study met the inclusion criteria of the review, including how many reviewers screened each record and each report retrieved, whether they worked independently, and if applicable, details of automation tools used in the process.	P5
Data collection process	9	Specify the methods used to collect data from reports, including how many reviewers collected data from each report, whether they worked independently, any processes for obtaining or confirming data from study investigators, and if applicable, details of automation tools used in the process.	P5
Data items	10a	List and define all outcomes for which data were sought. Specify whether all results that were compatible with each outcome domain in each study were sought (e.g. for all measures, time points, analyses), and if not, the methods used to decide which results to collect.	P5
	10b	List and define all other variables for which data were sought (e.g. participant and intervention characteristics, funding sources). Describe any assumptions made about any missing or unclear information.	P5
Study risk of bias assessment	11	Specify the methods used to assess risk of bias in the included studies, including details of the tool(s) used, how many reviewers assessed each study and whether they worked independently, and if applicable, details of automation tools used in the process.	P5
Effect measures	12	Specify for each outcome the effect measure(s) (e.g. risk ratio, mean difference) used in the synthesis or presentation of results.	n/a
Synthesis methods	13a	Describe the processes used to decide which studies were eligible for each synthesis (e.g. tabulating the study intervention characteristics and comparing against the planned groups for each synthesis (item #5)).	P5
	13b	Describe any methods required to prepare the data for presentation or synthesis, such as handling of missing summary statistics, or data conversions.	P5
	13c	Describe any methods used to tabulate or visually display results of individual studies and syntheses.	P5
	13d	Describe any methods used to synthesize results and provide a rationale for the choice(s). If meta-analysis was performed, describe the model(s), method(s) to identify the presence and extent of statistical heterogeneity, and software package(s) used.	P5
	13e	Describe any methods used to explore possible causes of heterogeneity among study results (e.g. subgroup analysis, meta-regression).	P5
	13f	Describe any sensitivity analyses conducted to assess robustness of the synthesized results.	P5
Reporting bias assessment	14	Describe any methods used to assess risk of bias due to missing results in a synthesis (arising from reporting biases).	P6-8
Certainty	15	Describe any methods used to assess certainty (or confidence) in the body of evidence for an outcome.	n/a

PRISMA 2020 Checklist

Section and Topic	Item #	Checklist item	Location where item is reported
assessment			
RESULTS			
Study selection	16a	Describe the results of the search and selection process, from the number of records identified in the search to the number of studies included in the review, ideally using a flow diagram.	P6-11
	16b	Cite studies that might appear to meet the inclusion criteria, but which were excluded, and explain why they were excluded.	P6-11
Study characteristics	17	Cite each included study and present its characteristics.	P6-11
Risk of bias in studies	18	Present assessments of risk of bias for each included study.	P6-11
Results of individual studies	19	For all outcomes, present, for each study: (a) summary statistics for each group (where appropriate) and (b) an effect estimate and its precision (e.g. confidence/credible interval), ideally using structured tables or plots.	P6-11
Results of syntheses	20a	For each synthesis, briefly summarise the characteristics and risk of bias among contributing studies.	P6-11
	20b	Present results of all statistical syntheses conducted. If meta-analysis was done, present for each the summary estimate and its precision (e.g. confidence/credible interval) and measures of statistical heterogeneity. If comparing groups, describe the direction of the effect.	/
	20c	Present results of all investigations of possible causes of heterogeneity among study results.	/
	20d	Present results of all sensitivity analyses conducted to assess the robustness of the synthesized results.	/
Reporting biases	21	Present assessments of risk of bias due to missing results (arising from reporting biases) for each synthesis assessed.	/
Certainty of evidence	22	Present assessments of certainty (or confidence) in the body of evidence for each outcome assessed.	/
DISCUSSION			
Discussion	23a	Provide a general interpretation of the results in the context of other evidence.	P12
	23b	Discuss any limitations of the evidence included in the review.	P15
	23c	Discuss any limitations of the review processes used.	P15
	23d	Discuss implications of the results for practice, policy, and future research.	P13-14
OTHER INFORMATION			
Registration and protocol	24a	Provide registration information for the review, including register name and registration number, or state that the review was not registered.	Published with BMJ open
	24b	Indicate where the review protocol can be accessed, or state that a protocol was not prepared.	/
	24c	Describe and explain any amendments to information provided at registration or in the protocol.	/
Support	25	Describe sources of financial or non-financial support for the review, and the role of the funders or sponsors in the review.	End of the manuscript
Competing interests	26	Declare any competing interests of review authors.	In submission
Availability of data, code and	27	Report which of the following are publicly available and where they can be found: template data collection forms; data extracted from included studies; data used for all analyses; analytic code; any other materials used in the review.	Methods

PRISMA 2020 Checklist

Section and Topic	Item #	Checklist item	Location where item is reported
other materials			

From: Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. BMJ 2021;372:n71. doi: 10.1136/bmj.n71
For more information, visit: http://www.prisma-statement.org/

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Diagnostic and prognostic factors in patients with prostate cancer: a systematic review

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Abstract

Objectives: As part of the PIONEER Consortium objectives, we have explored which diagnostic and prognostic factors (DPFs) are available in relation to our previously defined clinician and patient-reported outcomes (PROs) for prostate cancer (PCa).

Design: We performed a systematic review to identify validated and non-validated studies.

Data sources: MEDLINE, Embase and the Cochrane Library were searched on January 21, 2020.

Eligibility criteria: Only quantitative studies were included. Single studies with fewer than 50 participants, published before 2014 and looking at outcomes which are not prioritised in the PIONEER core outcome set will be excluded.

Data extraction and synthesis: After initial screening, we extracted data following the Checklist for Critical Appraisal and Data Extraction for Systematic Reviews of prognostic factor studies (CHARMS-PF) criteria and discussed the identified factors with a multidisciplinary expert group. The quality of the included papers was scored for applicability and risk of bias using validated tools such as PROBAST, QUIPS and QUADAS-2.

Results: The search identified 6,604 studies, from which 489 DPFs were included. Sixty-four of those were internally or externally validated. However, only three studies on diagnostic and seven studies on prognostic factors had a low risk of bias and a low risk concerning applicability.

Conclusion: Most of the DPFs identified require additional evaluation and validation in properly designed studies before they can be recommended for us e in clinical practice. The PIONEER online search tool for diagnostic and prognostic factors for prostate cancer will

enable researchers to understand the quality of the current research and help them design future studies.

Ethics and Dissemination: There are no ethical implications.

Strengths and limitations of this study

- A multidisciplinary team including patients, urologists, oncologists, radiation oncologists, methodological experts and pathologists were involved throughout the study.
- The search was restricted from 2014 onwards, to maintain a pragmatic approach.
- The main strength of this study are the extensive and comprehensive search and screening of the studies included.

Introduction

Prostate cancer (PCa) accounts for 15% of cancers diagnosed [1] and is the second most common cancer in males worldwide [2]. PCa is clinically and molecularly heterogeneous and is usually suspected based upon the clinical findings of digital rectal examination (DRE) and/or Prostate Specific Antigen (PSA) levels [1]. However, which diagnostic or prognostic factor (DPF) can be used to select patients for specific therapeutic options remains largely unclear [3]. Specific biomarkers in urine or in blood are available on top of traditional PSA testing, such as PCA3, TMPRSS2-ERG fusion, or kallikreins as incorporated in the Phi or 4Kscore test together with other parameters including family history [4-7]. However, the European Association of Urology (EAU) guidelines (2019) currently do not provide general recommendations to implement these biomarkers into routine screening programmes due to limited data [8]. As part of the ASCO guidelines, Eggener et al recommended five commercially available biomarkers which have been shown to provide prognostic significance and additional information beyond standard clinical models in patient selection in the localised context: Oncotype Dx Prostate, Prolaris, Decipher, and ProMark [9]. However, no guidelines have recommended DPFs for other stages of PCa. The expert panel at the APCCC consensus meeting of advanced prostate cancer in Basel 2019, recommended AR-V7 for mCRPC as potentially useful, which ultimately led to the inclusion of AR-V7 testing in the NCCN guidelines [10].

The PIONEER Consortium is an international collaboration coordinated by the European Association of Urology (EAU), which aims to establish the best evidence-based management and clinical practice of PCa across all disease stages using the power of big data analytics towards a more outcome-driven, value-based, and patient-centric healthcare system [11]. A

key objective is to address one of the major challenges within the context of diagnostic or prognostic biomarkers/factors: the inability to incorporate DPFs into the management of PCa in terms of screening, diagnosis and treatment. It is therefore important to summarise and evaluate the evidence. Biomarkers can be classified into different types: diagnostic, prognostic, predictive, and therapeutic – in this study we focus on the first two[12]. A diagnostic biomarker or factor is useful when cancer is suspected and allows the early detection based on symptoms or tests [12]. The overall aim of a diagnostic biomarker is to distinguish people with the diseases from people without the disease. A prognostic biomarker or factor is a clinical or biological characteristic which provides information on the likely course of the disease i.e., biochemical progression or disease recurrence [12]. It enables clinicians to decide on the most suitable treatment depending on the likely course of the disease. In the sections below we have used the terms biomarkers and factors interchangeably. Multiple diagnostic and prognostic factors (DPFs) can be measured in tissue, blood or urine. These come with different advantages and disadvantages and only a limited number of factors are currently available for PCa in standard clinical care.

We aimed to systematically review the evidence from 2014 onward to assess which DPFs are available in relation to previously defined outcomes for PCa.

Methods

The systematic review followed the PRISMA guidelines [13]. A detailed protocol of the overall project was published elsewhere [14] (please see the protocol attached as methods appendix). Briefly, we followed the following four steps (Figure 1):

(1) Comprehensive systematic literature review of DPFs for all stages of PCa (localised, locally advanced, metastatic, and non-metastatic castration resistant) from 2014 onwards. DPFs developed before 2014 were not included, due to the significant changes which influence the staging of PCa (i.e., Consensus Conference on Gleason Grading of Prostatic Carcinoma (60)) have taken place in diagnostic and prognostic practice and patient management.

(2) Assessment and identification of final list of DPFs by a multidisciplinary expert panel.

(3) Evaluation of quality of studies published using risk of bias tools: Prediction model Risk Of Bias (RoB) Assessment Tool (PROBAST) if applicable; or Quality in Prognostic Studies (QUIPS) tool for prognostic and the Quality Assessment of Diagnostic Accuracy Studies 2 (QUADAS-2) tool for diagnostic factors;

(4) Due to the heterogeneity of the studies identified no further formal quantitative assessments in the form of a meta-analyses could be performed. Hence, the findings of stages 1-3 have been reported here as the results of a systematic review.

Stage 1: Comprehensive literature review

We developed the search criteria for the first search with an information scientist who specialises in systematic reviews for urology. MEDLINE, Embase and the Cochrane Library were searched on January 21, 2020. The second search was developed following a consultation with an independent information scientist group who excluded row 12, 14 and 16 of Table 1 (see supplementary material). We screened the EAU Guidelines reference list for PCa in our third search (see Figure 2).

Stage 2: Multidisciplinary expert meeting

On the 20th of March 2020, we invited a group of multidisciplinary participants to discuss the identified articles on DPFs (see supplementary material Table 2). The participants were presented the search criteria and the extracted data. Data extraction followed the CHARMS-PF checklist and we added author and year of publication.

Stage 3: Evaluation of quality of studies published using the risk of bias tools

Prior to the evaluation of the quality of studies, an initial pilot screening to prepare the raters for the use of PROBAST, QUADAS-2, QUIPS was performed. This aimed to reach consensus on how to judge the domains of the assessments using the three RoB tools. Two urologists (FB, SS) and two epidemiologists (AH, KB) were involved in the pilot assessments. The group discussed any discrepancies. Articles which presented the development and validation the internal validation or the external validation (i.e., the same data was used for both development and internal validation, such as bootstrapping or cross-validation; different populations were used for development and validation), of a diagnostic or prognostic model were assessed with PROBAST. Papers assessing single biomarkers or with/without validation were assessed with QUIPs for prognostic or QUADAS-2 for diagnostic biomarkers.

Evaluation of quality of studies published using QUADAS-2

The RoB of diagnostic factors without validation or single validated factors was evaluated using QUADAS-2. We assessed the following four domains: patient selection, index test, reference standards and flow and timing. The first three domains are assessed looking at applicability and all four domains were assessed in terms of RoB [15]. We created a summative

score after the diagnostic studies were assessed by two reviewers and in case of disagreement a third reviewer assessed the study.

Evaluation of quality of studies published using PROBAST (Diagnostic)

The RoB of internal or external validated diagnostic models was assessed using the PROBAST RoB tool. PROBAST includes four domains assessing the RoB (i.e., participants, predictors, outcome and analysis) and four domains assessing applicability (i.e., participants, predictors and outcome) (see supplementary material Table 3 for scoring information).

Evaluation of quality of studies published using QUIPS

To assess the articles which are single factors or were not internally or externally validated, we used the QUIPS rating procedure (see supplementary material Table 4 for scoring information). To standardise the approach across raters, we used the QUIPS electronic spreadsheet (excel) from Hayden et al [16]. There are no rules available for QUIPS on how to score the overall RoB of a paper. Due to the large number of papers and the need for synthesis, we followed Grooten et al's suggestions to categorise on the following criteria: 1) Paper was classified as low RoB if all domains were classified as having low RoB, or up to one moderate RoB; 2) Paper was classified as high RoB if one or more domains were classified as having high RoB, or ≥ 3 moderate RoB; 3) Paper was classified as having moderate RoB if all papers in between 1 or 2 (see table 1 supplementary material). This assessment was based on the risk scores of individual assessments within the group. If the overall assessment was not possible due to differences in the individual category, a third assessor reviewed the assessments and the results were discussed.

Evaluation of quality of studies published using PROBAST (Prognostic)

The RoB of prognostic validated models were assessed using PROBAST. As highlighted above, PROBAST includes four domains assessing the RoB (i.e., participants, predictors, outcome and analysis) and four domains assessing applicability (i.e., participants, predictors and outcome).

Results

Stage 1: Comprehensive literature review

Stage 1 identified 6,604 citations and contained three independent searches. After removing duplicates, we screened 4,215 abstracts, from which 489 met the inclusion criteria.

Stage 2: Multidisciplinary expert meeting

The group discussed the results and additional literature on DPFs was suggested to help the classification of the DPFs, such as the ASCO Guideline on Molecular Biomarkers in Localized Prostate Cancer [17].

Stage 3: Evaluation of quality of studies published using the risk of bias tools

The 489 articles were equally divided between six groups. The six groups received the guidance documents which were identified during the pilot phase

[15 16 18-20]. In addition, MvH and KB discussed questions with each individual group.

Evaluation of quality of studies published using QUADAS-2

The RoB of the 41 included studies was low for 10 studies, high for 23 studies and unclear for eight. RoB concerning applicability was low for 10 studies, high for 21 studies and unclear for 10 studies (see Table 1). Table 2 shows the studies with an overall low RoB across both categories. Two studies were identified to have an overall low RoB [21 22].

Table 1: Overall judgment of RoB

QUADAS-2, Diagnostic		
Overall judgement of RoB	RoB	Applicability
Low	10	10
High	23	21
Unclear	8	10
Total	41	
PROBAST, Diagnostic		
Overall judgement of RoB	RoB	Applicability
Low	3	8
High	14	10
Unclear	3	2
Total	20	
QUIPS		
Overall judgement of RoB	RoB	
Low	29	
Moderate	49	
High	307	
Total	385	
PROBAST, Prognostic		
Overall judgement of RoB	RoB	Applicability
Low	3	15
High	27	20
Unclear	13	8
Total	43	

Table 2 non-validated DPFs with overall low risk of bias: QUADAS-2

Author	**Year**	**Patient Selection**	**Index Test(s)**	**Reference Standard**	**Flow and Timing**	**Patient Selection**	**Index Test(s)**	**Reference Standard**	**RoB**	**Applicability**
Hagiwara, et al.	2017	low	low	low	low	low	low	low	low	low
Kelly, et al.	2015	low	low	low	low	low	low	low	low	low

Evaluation of quality of studies published using PROBAST (Diagnostic)

We identified 20 papers to be assessed with PROBAST. The RoB of three papers was low, that of 14 was high and was unclear for three. The applicability of eight papers was high and was unclear for two (see Table 1). Table 1 in the supplementary material shows the criteria on how to judge the RoB. One study had an overall low RoB across both domains. All categories except 'predictors' was scored to have a low risk of bias. There was little information available for the category predictors and therefore it was scored as 'unclear' (see Table 3).

Table 3: DPFs assessed with PROBAST

Author	**ROB**				**APPLICABILITY**			**Overall**	
	Participants	**Predictors**	**Outcome**	**Analysis**	**Participants**	**Predictors**	**Outcome**	**ROB**	**Applicability**
Diagnostic									
Guinney, et al.	Low	Low	Low	Low	Low	Low	Low	Low	Low
Joniau, et al.	Low	Low	Low	Low	Low	Low	Low	Low	Low
Prognostic									
Palsdottir, et al	low	Unclear	low	low	low	low	low	low	low

Evaluation of quality of studies published using QUIPS

The 12 assessors independently inserted the relevant information and assessed each domain such as participation, attrition, prognostic factor confounding and statistical analysis and reporting.

387 prognostic factors were assessed using QUIPs. 307 papers were classified as high RoB. Forty-nine papers were classified as having a moderate RoB and 28 papers were scored as low RoB (see Table 1). Out of the 28 papers with a low RoB, the most common moderate

bias was linked to attrition (12 papers), followed by confounding (4 papers), participation (3 papers), outcome (1 paper), statistical analysis (1 paper) (see Table 4).

Table 4: Characteristics of DPFs with overall low risk of bias

Author	Year	RoB	Population	Study design	Timing	Index	Outcomes
Palsdottir, et al [25]	*2019*	Diag. PROBAST	Localised PCa	Observational study	Pre treatment	S3M-MRI (Stockholm3 + PI-RADS)	csPCa diagnosis
Guinney, et al. [23]	*2017*	Prog. PROBAST	mCRPC	RCT	post treatment	ePCR model	OS
Joniau, et al. [24]	*2017*	Prog. PROBAST	Locally advanced PCa	Observational study	Post-treatment	Gleason score + PSA	Adverse pathological features at RP; LNI
Hagiwara, et al. [21]	*2017*	QUADAS	Localised PCa	Observational study	Pre-treatment	WFA-reactive glycan-carrying PSA-Gi	PCa diagnosis, PSA-free survival
Kelly, et al. [22]	*2015*	QUADAS	Localised PCa	Observational study	Pre-treatment	miR-141, -145, -155, let7a	PCa diagnosis
Aguilera, et al. [26]	*2015*	QUIPS	High risk PCa	Observational study	pre and post treatment	Age, rectal examination, PSA, biopsy Gleason score, uni/bilateral tumor, affected cylinder percentage) and postoperative	BCR
Alvim, et al. [28]	*2019*	QUIPS	Metastatic PCa	Observational study	Post-treatment	PSA response (PSA reduction≥ 50%)	OS, PFS
Bramhecha, et al. [27]	*2019*	QUIPS	Localised PCa	Observational study	Post-treatment	PTEN deletion	BCR
Bruce, et al. [29]	*2016*	QUIPS	Localised PCa	Observational study	Post-treatment	AZGP1 expression	BR-free survival, CR-free survival, PC-specific death
Francini, et al. [30]	*2018*	QUIPS	mHSPC	Observational study	Post-treatment	Volume	OS, time to CRPC
Hamada, et al. [31]	*2016*	QUIPS	High risk PCa	Observational study	Post-treatment	PSA, PSA density (PSAD), PSA density of the	BCR

						transition zone, percentage of positive cores (PPC), prostate volume, TZ volume, Gleason score, PPC from the dominant side	
Hashimoto, et al. [32]	*2020*	QUIPS	Localised PCa	Observational study	Post-treatment	micro-lymphatic invasion, Gleason	BCR
Hung, et al. [60]	*2017*	QUIPS	mCRPC	Observational study	Post-treatment	Neurovascular bundle preservation, blood loss, pT stage, pN stage, pGS, PNI, angiolymphatic invasion, tumour amount in specimen, ECE, PSM, SVI, Bladder neck invasion, Foley duration, Post-op undetectable PSA	BCR
Kato et al. [33]	*2018*	QUIPS	High risk PCa	Observational study	Post-treatment	LC/IDC	Progression-free survival (PFS), Cancer-specific survival (CSS)
Kluth, et al. [34]	*2014*	QUIPS	Localised PCa	Observational study	Post-treatment	number of lymph nodes	BCR
Lara, et al. [35]	*2014*	QUIPS Validated	mCRPC	RCT	Post treatment	Bone resorption and formation	OS
Lee, et al. [36]	*2016*	QUIPS	Localised PCa	Observational study	Post treatment	Positive surgical margin status and bilateral seminal vesicle invasion	BCR
Lévesque, et al. [37]	*2019*	QUIPS	Localised PCa	Observational study	Post treatment	UGT2B17 expression	BCR
Lin, et al. [38]	*2017*	QUIPS	Localised PCa	Observational study	Post treatment	Aberrant Promoter Methylation of Protocadherin8 (PCDH8)	BRC-free survival
Löffeler, et al. [39]	*2015*	QUIPS	mCRPC	Observational study	Anytime	PSA doubling time, PSA nadir	OS

						during ADT, hemoglobin and alkaline phosphatase levels at CRPC	
Narang, et al. [40]	*2017*	QUIPS	Localised PCa	Observational study	Anytime	PSA: End-of-radiation PSA	BCR-free survival, MFS, CSS, OS
Ozden, et al. [41]	*2017*	QUIPS	Localised PCa	Observational study	Post treatment	Age	RRP specimen, BCR, and biochemical recurrence-free survival rates
Pei, et al. [42]	*2016*	QUIPS	CRPC	Observational study	pre and during treatment	Neutrophil-to-lymphocyte ratio	OS, PFS
Qu, et al. [43]	*2016*	QUIPS	mPCa and CRPC	Observational study	pre treatment	AR-V7	Time to CRPC / CRPC: CSS
Qu, et al. [44]	*2017*	QUIPS	PCa	Observational study	pre and during treatment	AR-V7	OS
Ruenauver, et al. [45]	*2014*	QUIPS	Localised PCa	Observational study	post treatment	YWHAZ	OS
Shimodaira, et al. [46]	*2020*	QUIPS	Metastatic PCa	Observational study	post treatment	Value of Platelet Counts	Disease specific survival
Strand, et al. [47]	*2015*	QUIPS	Localised PCa	Observational study	post treatment	5-hydroxymethylcytosine (5hmC) score	BCR
Takagi, et al.[48]	*2017*	QUIPS	Localised PCa	Observational study	post treatment	Age, T stage, % of pos cores, Gleason score, PSA, Total ADT	BCR-free survival
Wang, et al. [49]	*2016*	QUIPS	PCa	Observational study	post treatment	Platelet to lymphocyte ratio	PLR with progression-free survival (PFS), cancer-specific survival (CSS) and overall survival (OS)n/a
Zacho, et at. [50]	*2017*	QUIPS	Localised PCa	Observational study	anytime	Bone scan index	Time to CRPC
Berg, et al. [51]	*2014*	QUIPS validated	Under Active	Observational study		ERG immunohisto-chemical staining	Overall AS progression,

			Surveillance				histopathologic progression

Evaluation of quality of studies published using PROBAST (Prognostic)

The assessors identified 44 papers to be assessed with PROBAST, of those three scored a low RoB, 27 a high risk of bias and 13 were assessed as unclear (see Table 1). In terms of applicability, 15 papers scored low, 20 high and eight unclear. Two papers were scored to have an overall low RoB [23 24] (see Table 3).

Characteristics of studies identified with low risk of bias

Details of the identified validated DPF models with an adequate quality are presented in Table 5. We identified 32 studies with an overall low RoB (assessed with PROBAST, QUIPS, QUADAS-2). Out of these 32 studies, we identified one validated diagnostic model (assessed with PROBAST) [25], two validated prognostic models (assessed with PROBAST) [23 24], two non-validated diagnostic single factors (assessed with QUADAS-2) [21 22] and 26 prognostic factors (assessed with QUIPS) [21-51] which have not been validated and two single prognostic factors which have been validated (assessed with QUIPS) [35 51]. Prognostic factors assessed with QUIPS were identified with a low risk of bias for the localised PCa population. Sixty-seven percent of the low RoB DPFs were intended to be measured after the treatment was performed. In addition, the most commonly measured outcome was biochemical recurrence (BRC) followed by overall survival (OS). It is, however, important to take into consideration that even though from the studies assessed with a low RoB, only two out of the 32 were of a non-observational study design.

As highlighted above, we identified three validated DPFs which were scored to have a low RoB and low risk concerning applicability. Firstly, we identified the 'Unified Prostate Cancer Risk Prediction Model Combining the Stockholm3 Test and Magnetic Resonance Imaging', a risk prediction model which combines clinical variables, genetic and protein biomarkers. Five hundred and thirty two men were involved across three centres [52]. Secondly, the DREAM challenge developed a set of five standardised raw event-level tables, using laboratory values, patients' demographic information, medical history, lesion sites, previous treatments, and vital signs of patients with metastatic castration-resistant PCa. These variables where combined by using data from four clinical trials [53]. Thirdly, Joniau et al. developed 'Pretreatment Tables' to predict the pathologic stage of locally advanced prostate cancer after RP based on pre-treatment PSA level and biopsy Gleason score [24].

We identified two single factors which were validated and had low RoB. Firstly, Lara et al., assessed and validated the serum biomarkers of bone metabolism (N-telopeptide and pyridinoline) and formation (C-terminal collagen propeptide and bone alkaline phosphatase)) in 778 CRPC patients as part of the randomized phase III SWOG trial (S0421) of docetaxel/prednisone with or without atrasentan [35]. Secondly, Berg et al, showed that ERG expression can be used to estimate the risk of progression during AS including 265 patients at diagnosis and progression during AS [51].

Table 5: DPFs with low risk of bias assessed with QUIPS

STUDY	Time	BIASES			Applicability			Overall score
		Participation	Attrition	Prognostic Factor	Outcome	Confounding	Statistical analysis and reporting	
Aguilera, et al	*2015*	low	low	low	low	moderate	low	low
Alvim, et al.	*2019*	low	low	low	low	low	low	Low

Bramhecha, et al.	*2019*	low	moderate	low	low	low	low	Low
Bruce, et al.	*2016*	low	moderate	low	low	low	low	Low
Francini, et al.	*2018*	low	low	low	low	low	moderate	Low
Hamada, et al.	*2016*	low	low	low	moderate	low	low	low
Hashimoto, et al.	*2020*	low	low	low	low	low	low	Low
Hung, et al.	*2017*	moderate	low	low	low	low	low	Low
Kato, et al.	*2018*	low	moderate	low	low	low	low	Low
Kluth, et al.	*2014*	low	moderate	low	low	low	low	Low
Lara, et al.	*2014*	low	low	low	low	moderate	low	Low
Lee, et al.	*2016*	low	moderate	low	low	low	low	Low
Levesque, et al.	*2019*	low	moderate	low	low	low	low	Low
Lin, et al.	*2017*	low	moderate	low	low	low	low	Low
Loffeler, et al.	*2015*	low	low	low	low	low	low	Low
Narang, et al.	*2017*	low	moderate	low	low	low	low	Low
Ozden, et al.	*2017*	moderate	low	low	low	low	low	Low
Pei, et al.	*2016*	low	low	moderate	low	low	low	Low
Qu, et al.	*2016*	low	low	low	low	low	low	Low
Qu F, et al.	*2017*	low	low	low	low	low	low	Low
Rizzardi, et al.	*2015*	low	low	low	low	low	low	low
Ruenauver, et al.	*2014*	low	moderate	moderate	low	low	low	Low
Shimodaira ,et al.	*2020*	low	moderate	low	low	low	low	Low
Strand, et al.	*2015*	low	moderate	low	low	low	low	Low
Takagi, et al.	*2017*	low	low	low	low	moderate	low	Low

Wang, et al.	*2016*	low	mode rate	low	low	low	low	Low
Zacho, et al.	*2017*	modera te	low	low	low	modera te	low	Low
Berg, et al.	*2014*	low	low	low	low	low	low	Low

Discussion

Despite the large number of studies on DPFs which are published every year, there is a paucity of DPFs that are suitable to be incorporated into clinical practice. The majority of DPFs have not yet been validated and are identified in poor quality studies. Our analysis found that most identified studies had a high to moderate risk of bias due to poor design standards, conduct, reporting and/or analysis i.e., generalizability and size of the population, poor model development (no testing or missing important confounders) or only correlation studies, missing data was rarely reported. However, we did identify a small number of validated DPFs with low RoB. We identified three validated models which combine: firstly, clinical variables, genetic and protein biomarkers, and improved the clinical outcome performance of prostate cancer diagnostics (The Unified Prostate Cancer Risk Prediction Model) [52]; secondly, laboratory values, patients' demographic information, medical history, lesion sites, previous treatments, and vital signs of patients with metastatic castration-resistant PCa (DREAM challenge) [53]; thirdly, pre-treatment PSA level and biopsy Gleason score to predict the pathologic stage of locally advanced PCa ('Pretreatment Tables') [24]. Two single factors have been validated: the serum biomarkers of bone metabolism in CRPC patients [35] and the ERG expression, which can be used to estimate the risk of progression during AS [51], which has been already highlighted in the clinical guidelines [1].

Aladawani et al assessed prediction models for PCa to be used in primary care settings in their systematic review and identified five models which met their inclusion criteria. From these identified models only one model was externally validated and only one (the Lazzari model 2 [54]) had the potential to be implemented in primary care. Lazzari et al. had the lowest RoB (based on PROBAST), however it must be externally validated before it can be implemented. Hence, Aladawani et al also concluded that the existing models have limitations concerning study design and reporting performance [55].

Tian et al conducted a review on biomarkers for CRPC patients, however their quality assessment was focused on study design (RCT vs observational study), whereas we focused on biomarker specific tools [56]. Whilst Tian et al and our review identified similar factors and quality scores, there were slight discrepancies between the overall RoB assessments. Tian et al. used an overall quality assessment scale from 1-6 instead of low, medium and high. In their assessment the validated prognostic study by Lara et al. [35] and the non-validated prognostic factor by Pei et al. [42] were scored on the quality scale as 4 (medium quality). We assessed Lara et al. [35] to have a low risk of bias with a moderate risk of confounding and Pei et al. [42] with a moderate risk of bias concerning the prognostic factor itself. This might explain the discrepancies between the two quality assessments. The reports by Alvim et al., Qu et al., were assessed to have the highest quality by Tian et al [56], similar to our review. This illustrates that different quality assessment tools emphasize different criteria, which may result in small discrepancies. However, the overall conclusion for prognostic single factors was similar in our review and to the work of Tian et al. [56].

Similar issues have been identified for other urological cancers. For example, in kidney cancer, a large body of research was identified by Harrison et al., with very few validated

studies and lots of heterogeneity [57]. Schmitz-Dräger et al. published an International Consultation of Urologic Disease (ICUD)/World Health Organization (WHO) Consensus manuscript where they identified that in bladder cancer one of the main limitations for the lack of incorporation of modern bladder cancer tests into clinical practice decision making is linked to the scarcity of 'good clinical practice guidelines' for the evaluation of diagnostic markers.

There is a need for improved guidance on development and validation of diagnostic markers [58]. To meet that need, we are developing the PIONEER DPF search tool, which will help researchers and clinicians to get a better understanding of the DPFs for prostate cancer. The tool will not only summarise all relevant studies, but also provide information on the use and results of different RoB assessment tools, which will enable an understanding of the quality of published studies.

Future research should therefore focus on addressing the identified shortcomings such as heterogeneity, validation and poor RoB by designing more robust studies which consistently include RoB assessments such as PROBAST, QUIPS or QUADAS-2.

With the growing number of various therapeutic options, diagnosis and management of prostate cancer require an individualised approach to patient care. There is an unmet need for DPFs to guide decisions for optimal treatment and predict which patients will benefit the most, from a particular management strategy. DPFs could potentially enhance the quality of patient counselling, but currently most need additional evaluation and validation in properly designed studies. Our systematic review highlights the need for well-designed Real-World Evidence studies, while the PIONEER online search tool can inform the design of new

research studies, through providing a rigorous evaluation of the methodological quality of the studies.

The main strength of this study are the extensive and comprehensive search and screening of the studies included. In addition, we are developing an online search tool which showcases the identified and assessed studies. It provides an overview of the available DPFS and enables interested stakeholders to search for DPFs. To our knowledge, this is the first study which has been performed with this extensive amount of literature.

Patient and public Involvement

This project has been overseen by a multi-stakeholder group part of the PIONEER Consortium. PIONEER brings together 32 key stakeholders from academic institutions, patient advocacy groups, European organisations, experts in legal data management, clinicians and pharmaceutical companies, as well as regulatory agencies, economics and ethics, and information and technology specialists. Patients and their family members are therefore involved and actively participate as an integral part of all research conducted by the PIONEER Consortium.

Limitations

Even though this review included three searches and assessments by a multidisciplinary group of fourteen researchers, we recognise potential limitations. Studies were only included from 2014 onwards and DPFs developed before 2014 were not included. However, significant changes which influence the staging of PCa (i.e., Consensus Conference on Gleason Grading of Prostatic Carcinoma [59]) have taken place in diagnostic and prognostic

practice and patient management. This changed the staging of the patient population and therefore has an impact on DPFs.

In addition, there is a potential of subjectivity in the evaluation of the studies. Even though the studies have been assessed in duplicate, there might be variation across groups. However, given the overall moderate to high risk of bias, this does not influence the overall recommendation of the project.

Conclusion

At present DPFs that are capable of significantly improving diagnosis and prognosis in prostate cancer are an unmet need as most of the DPFs identified require additional evaluation and validation in properly designed studies before they can be recommended for use in clinical practice. Well-designed RWE studies can help to increase quality. Our SR aims to inform clinicians and patients about this rapidly evolving field, while the PIONEER online search tool for diagnostic and prognostic factors for prostate cancer will enable researchers to perform future research, and to understand the quality of the current available studies.

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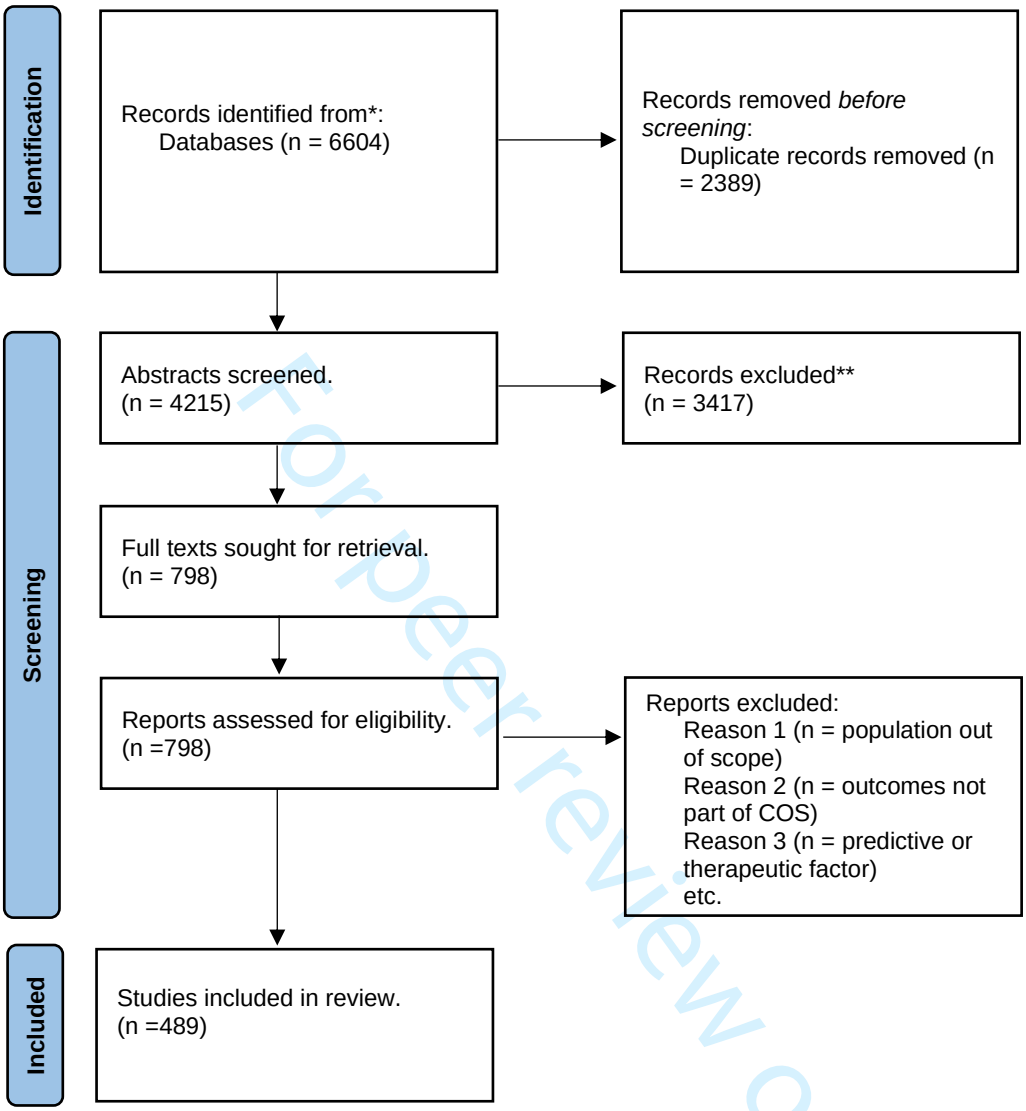
Figure 1: Overview of four stage process

Figure 2: PRISMA flow diagram

Figure 1: Overview of four stage process

Workflow	Task
Stage 1.	Broad literature-based systematic review of diagnostic and prognostic factors (DPs) for all stages of prostate cancer from 2014 onwards (English only; humans). • Extract data from the included studies following the CHARMS-PF guideline.
Stage 2.	Discussion of systematic review findings by a multidisciplinary expert panel • Review the list of included studies
Stage 3.	Risk of Bias Assessment and applicability of individual studies using PROBAST, QUIPS and QUADAS-2
Stage 4.	Quantitative assessment of individual articles using meta-analytic techniques: • If PROBAST indicates low risk of bias and low concerns for applicability: Oxford Classification Centre for Evidence Based Medicine: 1. If there is Level 1a (SR of RCTs), we do not do a meta-analysis 2. No Level 1a but >2 RCTs, we do a meta-analysis 3. No Level 1a/b, i.e. if at least two RCTs are now available, and systematic review of RCT evidence is not possible, we will identify whether there is a systematic review for observational studies (real world evidence; RWE), we do not do a meta-analysis 4. If systematic review of RWE is not available, a systematic review of observational study will be conducted, and a meta-analysis will be performed if at least two RWEs studies are available and data pooling is feasible and there are low concerns of risk of bias.
Final aim:	Develop online PIONEER Online Search Tool for DPFs

Figure 2: PRISMA flow diagram



Supplementary material Table 1: Search strategy

Database: OVID Medline Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Ovid MEDLINE(R) Daily and Ovid MEDLINE(R) 1946 to Present, Embase <1974 to 2020 January 28>, EBM Reviews - Cochrane Database of Systematic Reviews <2005 to January 21, 2020>

Search Strategy:

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1 exp *Prostatic Neoplasms/ (262435)

2 exp *prostate cancer/ (245472)

3 (prostat* adj2 (cancer* or carcinoma* or malignan* or tumor* or tumour* or neoplas* or adenocarcinoma* or adenoma*)).tw. (332251)

4 or/1-3 (366427)

5 ((diagnostic or prognos* or predict*) adj10 (biomarker or biomarkers or factor or factors)).tw,kw. (717487)

6 ((diagnostic or prognos* or predict*) adj10 (Oncotype Dx Prostate or Prolaris or Decipher or Decipher PORTOS or ProMark)).tw,kw. (458)

7 5 or 6 (717869)

8 4 and 7 (17456)

9 limit 8 to english language [Limit not valid in CDSR; records were retained] (16484)

10 limit 9 to yr="2014 -Current" (8417)

11 conference abstract.pt. or Congresses as Topic/ or Conference Review.pt. or "Journal: Conference Abstract".pt. (3815712)

12 10 not 11 (5902)

13 (exp animals/ or exp animal/ or exp nonhuman/ or exp animal experiment/ or animal model/ or animal tissue/ or non human/ or (rat or rats or mice or mouse or swine or porcine or murine or sheep or lambs or pigs or piglets or rabbit or rabbits or cat or cats or dog or dogs or cattle or bovine or monkey or monkeys or trout or marmoset$1).ti.) not (humans/ or human/ or human experiment/ or (human* or men or women or patients or subjects).tw.) (10251935)

14 12 not 13 (5882)

15 note/ or editorial/ or letter/ or Comment/ or news/ or (note or editorial or letter or Comment or news).pt. (4565255)

16 14 not 15 (5811)

17 (child/ or Pediatrics/ or Adolescent/ or Infant/ or adolescence/ or newborn/ or (baby or babies or child or children or pediatric* or paediatric* or peadiatric* or infant* or infancy or neonat* or

	newborn* or new born* or adolescen* or preschool or pre-school or toddler*).tw.) not (adult/ or aged/ or (aged or adult* or elder* or senior* or men or women).tw.) (4146377)
18	16 not 17 (5794)
19	18 use ppez,oemezd (5788)
20	10 use coch (6)
21	19 or 20 (5794)
22	remove duplicates from 21 (3140)

Supplementary material Table 2. Multidisciplinary expert meeting

Profession	Attendance
Urologist	Accepted
Epidemiologist	Accepted
Urologist	Accepted
Epidemiologist/Pharma representative	Accepted
Pathologist	Accepted
Urologist	Accepted
Urologist	Accepted
Epidemiologist	Accepted
Methodologist	Accepted
Epidemiologist/Pharma representative	Accepted
Urologist	Accepted
Urologist/Methodologist	Accepted
Urologist	Accepted
Urologist	Accepted
Oncologist	Accepted
Pharma representative	Accepted
Pharma representative	Accepted
Statistician/ Pharma representative	Accepted

Table 3: PROBAST overall assessment

Criteria	Reaching and overall judgement of RoB	
All domains are rated low risk.	Paper was classified as low RoB and low Applicability.	
One or more domain was judged to be high risk of bias.	Paper was classified as high RoB and high Applicability.	
One or more domain was judged to be unclear risk of bias.	Paper was classified as unclear RoB and h igh Applicability.	

Supplementary material Table 4: QUIPS scoring

Score of 6 domains	**Overall RoB**	
All domains were classified as having low RoB, or up to one moderate RoB.	Paper was classified as low RoB	
One or more domains were classified as having high RoB, or ≥ 3 moderate RoB.	Paper was classified as high RoB	
All papers in between.	Paper was classified as having moderate RoB	

PRISMA 2020 Checklist

Section and Topic	Item #	Checklist item	Location where item is reported
TITLE			
Title	1	Identify the report as a systematic review.	p1
ABSTRACT			
Abstract	2	See the PRISMA 2020 for Abstracts checklist.	P2
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of existing knowledge.	P3
Objectives	4	Provide an explicit statement of the objective(s) or question(s) the review addresses.	P4
METHODS			
Eligibility criteria	5	Specify the inclusion and exclusion criteria for the review and how studies were grouped for the syntheses.	P5
Information sources	6	Specify all databases, registers, websites, organisations, reference lists and other sources searched or consulted to identify studies. Specify the date when each source was last searched or consulted.	P5
Search strategy	7	Present the full search strategies for all databases, registers and websites, including any filters and limits used.	P5
Selection process	8	Specify the methods used to decide whether a study met the inclusion criteria of the review, including how many reviewers screened each record and each report retrieved, whether they worked independently, and if applicable, details of automation tools used in the process.	P5
Data collection process	9	Specify the methods used to collect data from reports, including how many reviewers collected data from each report, whether they worked independently, any processes for obtaining or confirming data from study investigators, and if applicable, details of automation tools used in the process.	P5
Data items	10a	List and define all outcomes for which data were sought. Specify whether all results that were compatible with each outcome domain in each study were sought (e.g. for all measures, time points, analyses), and if not, the methods used to decide which results to collect.	P5
	10b	List and define all other variables for which data were sought (e.g. participant and intervention characteristics, funding sources). Describe any assumptions made about any missing or unclear information.	P5
Study risk of bias assessment	11	Specify the methods used to assess risk of bias in the included studies, including details of the tool(s) used, how many reviewers assessed each study and whether they worked independently, and if applicable, details of automation tools used in the process.	P5
Effect measures	12	Specify for each outcome the effect measure(s) (e.g. risk ratio, mean difference) used in the synthesis or presentation of results.	n/a
Synthesis methods	13a	Describe the processes used to decide which studies were eligible for each synthesis (e.g. tabulating the study intervention characteristics and comparing against the planned groups for each synthesis (item #5)).	P5
	13b	Describe any methods required to prepare the data for presentation or synthesis, such as handling of missing summary statistics, or data conversions.	P5
	13c	Describe any methods used to tabulate or visually display results of individual studies and syntheses.	P5
	13d	Describe any methods used to synthesize results and provide a rationale for the choice(s). If meta-analysis was performed, describe the model(s), method(s) to identify the presence and extent of statistical heterogeneity, and software package(s) used.	P5
	13e	Describe any methods used to explore possible causes of heterogeneity among study results (e.g. subgroup analysis, meta-regression).	P5
	13f	Describe any sensitivity analyses conducted to assess robustness of the synthesized results.	P5
Reporting bias assessment	14	Describe any methods used to assess risk of bias due to missing results in a synthesis (arising from reporting biases).	P6-8
Certainty	15	Describe any methods used to assess certainty (or confidence) in the body of evidence for an outcome.	n/a

PRISMA 2020 Checklist

Section and Topic	Item #	Checklist item	Location where item is reported
assessment			
RESULTS			
Study selection	16a	Describe the results of the search and selection process, from the number of records identified in the search to the number of studies included in the review, ideally using a flow diagram.	P6-11
	16b	Cite studies that might appear to meet the inclusion criteria, but which were excluded, and explain why they were excluded.	P6-11
Study characteristics	17	Cite each included study and present its characteristics.	P6-11
Risk of bias in studies	18	Present assessments of risk of bias for each included study.	P6-11
Results of individual studies	19	For all outcomes, present, for each study: (a) summary statistics for each group (where appropriate) and (b) an effect estimate and its precision (e.g. confidence/credible interval), ideally using structured tables or plots.	P6-11
Results of syntheses	20a	For each synthesis, briefly summarise the characteristics and risk of bias among contributing studies.	P6-11
	20b	Present results of all statistical syntheses conducted. If meta-analysis was done, present for each the summary estimate and its precision (e.g. confidence/credible interval) and measures of statistical heterogeneity. If comparing groups, describe the direction of the effect.	/
	20c	Present results of all investigations of possible causes of heterogeneity among study results.	/
	20d	Present results of all sensitivity analyses conducted to assess the robustness of the synthesized results.	/
Reporting biases	21	Present assessments of risk of bias due to missing results (arising from reporting biases) for each synthesis assessed.	/
Certainty of evidence	22	Present assessments of certainty (or confidence) in the body of evidence for each outcome assessed.	/
DISCUSSION			
Discussion	23a	Provide a general interpretation of the results in the context of other evidence.	P12
	23b	Discuss any limitations of the evidence included in the review.	P15
	23c	Discuss any limitations of the review processes used.	P15
	23d	Discuss implications of the results for practice, policy, and future research.	P13-14
OTHER INFORMATION			
Registration and protocol	24a	Provide registration information for the review, including register name and registration number, or state that the review was not registered.	Published with BMJ open
	24b	Indicate where the review protocol can be accessed, or state that a protocol was not prepared.	/
	24c	Describe and explain any amendments to information provided at registration or in the protocol.	/
Support	25	Describe sources of financial or non-financial support for the review, and the role of the funders or sponsors in the review.	End of the manuscript
Competing interests	26	Declare any competing interests of review authors.	In submission
Availability of data, code and	27	Report which of the following are publicly available and where they can be found: template data collection forms; data extracted from included studies; data used for all analyses; analytic code; any other materials used in the review.	Methods

PRISMA 2020 Checklist

Section and Topic	Item #	Checklist item	Location where item is reported
other materials			

From: Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. BMJ 2021;372:n71. doi: 10.1136/bmj.n71
For more information, visit: http://www.prisma-statement.org/