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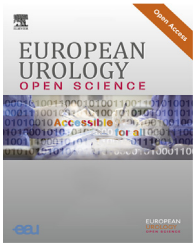

European Association of Urology

Review – Trial Protocol

Personalised Prostate Cancer Diagnosis: Evaluating Biomarker-based Approaches to Reduce Unnecessary Magnetic Resonance Imaging and Biopsy Procedures

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Abstract

Background and objective: Efforts made over the last decade for the detection of prostate cancer (PCa) have revolutionised disease diagnostics, and implementation of prebiopsy magnetic resonance imaging (MRI) has received widespread acceptance. However, universal adoption of prebiopsy MRI and the benefits achieved have been limited by availability and equivocal MRI findings. This review aims to evaluate the latest evidence on the role of existing PCa risk calculators (RCs), and blood and urinary biomarkers as part of the diagnostic algorithm to improve the diagnosis of clinically significant PCa (csPCa) and reduce unnecessary MRI procedures and biopsies. We will also evaluate the potential of prostate-specific

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membrane antigen (PSMA) positron emission tomography (PET) to enhance sensitivity and specificity for PCa diagnosis, complement MRI, and refine biopsy strategies within the diagnostic pathway.

Methods: We performed a narrative review using the PubMed/MEDLINE database, which included papers published between January 2014 and June 2024. The outcome measures included rates of reduced diagnoses of nonsignificant PCa (defined as International Society of Urological Pathology [ISUP] grade group 1) cases, diagnoses of csPCa (defined as ISUP grade group $\geq$2) cases missed, and MRI scans and prostate biopsies avoided.

Key findings and limitations: In men with abnormal prostate-specific antigen (PSA) levels, further risk stratification using RCs, or blood or urine biomarkers can reduce up to 16–51% MRI scans, while missing 1–16% csPCa cases. In case of equivocal MRI results or Prostate Imaging Reporting and Data System 3 lesions, RCs or biomarkers could reduce up to 72% of biopsies, while missing only 3–13% csPCa cases. PSMA PET has emerging potential to improve csPCa prediction in combination with MRI and may further reduce unnecessary biopsies. A limitation of this study is that this is a narrative but not a systematic review.

Conclusions and clinical implications: RCs and biomarkers have been demonstrated to enhance the performance and efficiency of MRI in detecting csPCa in men with elevated PSA levels. PSMA PETshows promise in detecting csPCa, complementing MRI and refining biopsy indications.

Patient summary: In men with a suspicion of prostate cancer, magnetic resonance imaging prostate scans are effective in predicting clinically relevant cancer, but challenges including availability and equivocal scans exist. A personalised approach by adding one or more of clinical risk calculators, blood or urine biomarkers, or even novel imaging techniques such as positron emission tomography scans may improve cancer prediction further and reduce unnecessary scans and biopsies.

1. Introduction

The integration of magnetic resonance imaging (MRI) has revolutionised the diagnosis of prostate cancer (PCa). Randomised trials have shown that MRI followed by the targeted biopsy pathway outperforms transrectal ultrasound-guided (TRUS) biopsy in detecting clinically significant (cs) PCa while reducing clinically insignificant (cis)PCa diagnoses, solidifying its role in the standard of care pathway for PCa diagnosis [1].

While MRI is increasingly accepted as a triage tool for prostate biopsy, its widespread adoption is constrained by costs and availability [2]. To manage rising health care expenditures and reduce patient burden, pre-MRI risk stratification is crucial for identifying men at a very low risk of csPCa who may not require MRI. In addition to these scalability challenges, other issues such as equivocal MRI (Prostate Imaging Reporting and Data System [PI-RADS] score of 3) results and heterogeneity with regard to the negative predictive value (NPV) exist [3]. For these challenges, advancements in biomarker integration, alongside improvements in MRI imaging and reading quality, could play a key role in enhancing the utility and accuracy of MRI in PCa diagnosis.

Optimisation of the current MRI-based diagnostic pathway is essential to minimise unnecessary imaging and biopsy procedures, thereby reducing patient harm and overall health care costs. Although PCa risk calculators (RCs) and various serum and urine biomarkers have shown promise in predicting the diagnosis of csPCa, their ability to predict abnormal MRI findings and the benefit of combining these tools with MRI remain unclear. Emerging evidence suggests that integration of these tools could aid in guiding clinical management decisions in daily practice. In addition, prostate-specific membrane antigen (PSMA) positron emission tomography (PET) has emerged as a potentially valuable modality for PCa detection, offering excellent sensitivity and diagnostic accuracy in men with suspected disease [4]. However, its exact role within the established MRI-based diagnostic pathway has yet to be defined clearly.

This narrative review will evaluate the potential role of RCs and serum and urine biomarkers in reducing unnecessary uses of MRI in MRI-naïve men with suspected PCa (pre-MRI setting) and their capacity to reduce unnecessary biopsies in cases where MRI data are already available (post-MRI setting). Additionally, it will examine the role of PSMA PET complementing MRI in refining biopsy indications.

2. Methods

2.1. Search strategy

The literature search was conducted using the PubMed/MEDLINE database to identify relevant studies evaluating biomarkers aimed at reducing MRI use and unnecessary

biopsies in men with a suspicion of PCa. The search included studies published between January 2014 and June 2024 in peer-reviewed journals. This time point was chosen based on the fact that the PI-RADS classification system was introduced in 2014 and landmark studies proving the efficacy for prebiopsy MRI and target biopsy as well as MRI screening studies were published beyond this time point [1,5]. The key search terms included "prostate," "biopsy," "risk calculator," "MRI," "PSA," "Prostate Health Index," "Stockholm3," "STHLM-3," "PCA3," "SelectMDx," "ExosomeDx," "reduce," "avoid," and "PSMA PET." These terms were combined using the Boolean operator "OR" and "AND" to ensure comprehensive coverage of the literature. The included studies evaluated the impact of RCs or blood- or urine-based biomarkers on metrics such as reduction of MRI use, reduction of biopsies, detection of csPCa, and overall detection or missed diagnoses of PCa.

2.2. Study selection

Studies were screened for relevance based on predefined criteria, including study design (retrospective, prospective, or observational studies; randomised trials; systematic reviews; and meta-analyses) and outcomes related to MRI or biopsy reduction. Cross-referencing of the selected studies was performed to identify additional relevant research not captured in the original search. The initial selection of studies was conducted by three authors (T.F.W.S., X.W., and P.K.F.C.). The final set of included studies was reviewed and approved by all the coauthors. Any discrepancies were resolved by consensus, and additional studies identified during this review process were analysed.

3. Results

3.1. Use of RC and biomarkers to reduce unnecessary MRI procedures

The integration of MRI into PCa screening pathways has been shown to reduce unnecessary biopsies and overdiagnosis when compared with prostate-specific antigen (PSA)-only screening [5]. However, this approach presents challenges, such as limited availability, increased costs, and delays in accessing MRI services. Consequently, it is crucial to investigate whether RCs and blood- or urine-based biomarkers can aid in predicting the likelihood of a negative MRI result, potentially alleviating patient burden, reducing waiting times, and lowering associated costs. In this section, we provide an overview of the existing literature on these RCs and biomarkers to reduce unnecessary MRI procedures. The results are summarised in Table 1.

3.1.1. Risk calculators

Mannaerts et al [6] evaluated the use of the Rotterdam Prostate Cancer Risk Calculator (RPCRC; www.prostatecancer-riskcalculator.com, previously referred to as the European Randomized study of Screening for Prostate Cancer [ERSPC] RC) as a triage test for MRI and biopsy among biopsy-naïve men who underwent prebiopsy MRI and prostate biopsy. Using a cut-off of ≥20% for any-grade PCa and/or a risk of high-grade and/or locally advanced PCa of >4%, in 36.5% (73 out of 200) of patients, MRI was deemed unnecessary due to a very low risk of csPCa. Of these patients, four (5%) were diagnosed with high-grade PCa (all grade group [GG] 2), while ten (14%) were diagnosed with low-grade PCa (GG1) [6]. On the contrary, another retrospective study reported less favourable findings for the RPCRC, and revealed that omitting MRI and biopsy in patients with a low ERSPC RC risk (<2% risk of csPCa) resulted in 10.8% (8/74) missed cases of csPCa [7]. Among patients with a prior negative systematic biopsy, Alberts et al [8] revealed that the use of the RPCRC (indication for biopsy in case of >20% risk of any PCa and/or ≥4% risk of high-grade and/or locally advanced PCa) would have avoided 62 (51%) of 122 MRI scans and two (25%) of eight GG1 PCa diagnoses, while missing three of 31 (10%) cases of GG ≥2 PCa. In another retrospective study, using a higher threshold of a >10% risk of csPCa or 20% risk of any PCa would lead to a lower percentage (15.5%) of omitted MRI scans, missing 0.7% of csPCa cases [9]. Less favourable results for the RPCRC were reported by Remmers et al [10], who used the PRECISION cohort for validation. Use of this RC as a triage test for MRI could reduce MRI procedures by 34.9% (72/206) at the cost of missing 15.7% (11/70) of all csPCa cases. Straat et al [11] conducted a retrospective comparative study evaluating both a direct MRI pathway and an RC-stratified pathway (RPCRC) using data from two Dutch tertiary referral centres. They found that the RC-stratified pathway could reduce MRI procedures by 47.8% (451/944), while the detection rates of csPCa were not significantly different from those in the direct MRI pathway (43.5% vs 45.2% in the direct MRI arm, $p = 0.7$). Morote et al [12] retrospectively evaluated an RC-stratified pathway that included two Barcelona RCs. MRI was performed in patients with >8% risk of csPCa based on RC 1, and a threshold of >7% risk of csPCa based on RC 2 was used for biopsy. Using this strategy, 19.8% (675/3557) of MRI scans could have been avoided at the cost of missing 4.9% of csPCa cases (61/1249). Based on the included studies, using a cut-off of ≥20% for any-grade PCa and/or a risk of high-grade and/or locally advanced PCa of >4% for the RPCRC is the most commonly evaluated strategy and appears generally to be most efficient. However, clinicians should be aware that patient selection varies across these studies. Since performance differs among populations, the thresholds used for MRI indication should also be adjusted based on individual patient characteristics and preferences.

3.1.2. Blood-based biomarkers

3.1.2.1. PSA density. Israel et al [13] analysed a cohort of 613 biopsy-naïve men with PSA levels >3 ng/ml. These men underwent prebiopsy MRI and prostate biopsy, which involved a 12-core systematic biopsy along with a targeted biopsy for those with a PI-RADS score of 3–5. Utilisation of a PSA density (PSAd) threshold of 0.10 ng/ml/ml allowed for the avoidance of 33.9% (208 out of 613) of MRI scans, while missing csPCa in only 4.2% (8/190) of cases. In another retrospective study of 865 patients without prior PCa, researchers assessed age, prostate volume, PSA, and PSAd as predictors of positive multiparametric MRI (mpMRI; PI-RADS ≥4). The cohort was divided into a training set (605

Table 1 – Overview of studies evaluating strategies to reduce unnecessary MRI scans

Author [ref]	Year	Design (RCT, prospective, retrospective)	No. of patients	Inclusion criteria	Intervention/triage test	Threshold	Definition of csPCa	Reduction in nsPCa diagnosis	csPCa missed	MRI avoided
Mannaerts [6]	2018	Retrospective	200	Biopsy-naïve, PSA ≥3 ng/ml and/or abnormal DRE with mpMRI before biopsy	RPCRC (PSA, DRE, TRUS, and PV)	Any PCa ≥20% Risk high grade and/or locally advanced ≥4%	Grade group ≥2	10/43 (23%)	4/67 (6%)	73/200 (36.5%)
Falagario [7]	2020	Retrospective	266	Biopsy-naïve patients (PSA >3 ng/ml, and/or abnormal DRE) with mpMRI, the 4Kscore test, and biopsy	4Kscore as triage test for prebiopsy mpMRI	4Kscore >7.5% and PI-RADS 3–5 or 4Kscore >18% in case of negative MRI	Grade group ≥2	13/48 (27%)	2/74 (2.7%)	91/266 (34.2%)
Alberts [8]	2016	Retrospective	122	Men with suspicion of PCa and previous negative TRUS-guided systematic biopsy	mpMRI and subsequent MRI-TRUS fusion targeted biopsy in case of PI-RADS ≥3/RPCRC (PSA, DRE, TRUS, and PV)	Any PCa ≥20% Risk high grade and/or locally advanced ≥4%	Grade group ≥2	2/8 (25%)	3/31 (10%)	66/122 (51%)
Davik [9]	2022	Retrospective	303 (of whom 239 [79%] biopsy naïve)	All men with mpMRI and biopsy from January 2016 to March 2017	RPCRC (PSA, DRE, TRUS, and PV)	≥10% csPCa or ≥20% any PCa ≥15% csPCa or ≥20% any PCa	Grade group ≥2	34/141 (24.1%) 53/141 (37.6%)	3/410 (0.7%) 23/410 (5.6%)	155/1000 (15.5%) 271/1000 (27.1%)
Remmers [10]	2022	Retrospective	206 (in the MRI arm, evaluated for reduction of MRI scans)	Patients included in the PRECISION trial. Men with clinical suspicion of PCa without prior negative biopsy and PSA <20 ng/ml	RPCRC RPCRC (recalibrated)	≥20% any PCa or ≥4% for csPCa ≥20% any PCa or ≥4% for csPCa	Grade group ≥2	17/84 (20%) 7/84 (8%)	11/70 (15.7%) 5/70 (7%)	72/206 (35%) 27/206 (12%)
Straat [11]	2024	Retrospective	944 514 (comparator arm, direct MRI group)	Biopsy-naïve men with suspicion of PCa on the basis of elevated PSA and/or abnormal DRE	RPCRC vs comparator arm (MRI in all)	≥20% any PCa or ≥4% for csPCa Comparator: direct MRI group	Grade group ≥2	+0.7% vs direct MRI arm (30.7% vs 30%, $p = 0.9$)	1.7% (43.5% vs 45.2% direct MRI arm, $p = 0.7$)	451/944 (47.8%)
Morote [12]	2024	Retrospective	3557 (among 3137 had PSA <10 ng/ml))	PSA >3 ng/ml and/or suspicious DRE	Patients with PSA <10 ng/ml underwent RC pathway, including Barcelona risk calculators 1 (before MRI) and 2 (after MRI)	Barcelona RC1 Barcelona RC2 (in case of RC1 >8%)	Grade group ≥2	NA	61/1249 (4.9%)	675/3557 (19.8%)
Israel [13]	2022	Retrospective	613	Biopsy-naïve men with PSA 3 ng/ml who underwent prebiopsy MRI, prostate biopsy (12-core systematic biopsy, combined with targeted biopsy in cases with a PI-RADS 3–5 lesion) and had complete data available for the risk model	PSAd	≥0.10	Grade group ≥2	NA	8/190 (4.2%)	208/613 (33.9%)
Deniffel [14]	2021	Retrospective	865 The cohort was split into a training cohort of 605 and a validation cohort of 260 patients	No prior prostate cancer diagnosis with MRI and/or biopsies between 2009 and 2017	Age, PV, PSA, and PSAd were assessed as predictors of positive mpMRI	At PSAd >0.078	Grade group ≥2	NA	2/21 (9.5%)	64/260 (24.6%)
Kim [18]	2020	Prospective	505, 1000 (modelling study)	Biopsy-naïve men recruited for elevated PSA, undergoing image-guided target + systematic biopsy (in case of positive lesions), or systematic biopsy in MRI-negative patients	PHI Use PHI as a triage test for selection for MRI and biopsy, versus MRI + biopsy to all	≥25 ≥30	Grade group ≥2	NA	4.2% 7.7%,	150/1000 (15%) 250/1000 (25%)
Nordstrom [24]	2021	RCT	2293	Men without prior PCa diagnosis and who did not undergo prostate biopsy within 60 d before invitation, aged 50–74 yr, PSA ≥3 ng/ml or STHLM3 ≥0.11	STHLM3 Use PSA ≥3 ng/ml + standard systematic biopsy vs Stockholm3 ≥0.15 plus MRI workflow	0.15	Grade group ≥2	NA, cisPCa diagnosis (34 vs 41; relative proportion 0.83 [0.63–1.13]) vs PSA plus standard biopsy	NA, identical sensitivity to detect csPCa vs PSA ≥3 ng/ml	301/846, relative proportion vs PSA ≥3 ng/ml 64% (95% CI 55–82%), reduction 35.6%
Fredsoe [25]	2023	Prospective	1905	Biopsy-naïve men aged 50–69 yr, no prior diagnosis of PCa or other urogenital cancer, no prior prostate biopsy, no prior ARI	STHLM3 vs PSA ≥3 ng/ml	STHLM3 0.15 vs PSA ≥3 ng/ml	Grade group ≥2	Total 52 cisPCa (0%)	Total 38 csPCa 2/30 (+6.7%, but not significantly different)	84/320 (26.3%)
Hendriks [31]	2021	Prospective	599	Biopsy-naïve patients, serum PSA ≥3 ng/ml, undergoing SelectMDx and mpMRI before biopsy	Perform MRI and biopsy only in those with positive SelectMDx	Risk score –2.8 corresponding with 13% likelihood of csPCa	Grade group ≥2	80/599 (13.4%) 80/138 (57.9%)	18/183 (9.8%)	227/599 (37.9%)

ARI = androgen receptor inhibitor; CI = confidence interval; cisPCa = clinically insignificant prostate cancer; csPCa = clinically significant prostate cancer; mpMRI = multiparametric magnet renounce imaging; MRI = magnet renounce imaging; NA = not applicable; nsPCa = nonsignificant prostate cancer; PCa = prostate cancer; PHI = Prostate Health Index; PI-RADS = Prostate Imaging Reporting and Data System; PSA = prostate-specific antigen; PSAd = PSA density; PV = prostate volume; RPCRC = Rotterdam Prostate Cancer Risk Calculator; RC = risk calculator; RCT = randomised controlled trial; STHLM3 = Stockholm 3;TRUS = transrectal ultrasound.

patients) and a validation set (260 patients). A PSAd cut-off of 0.078 ng/ml/ml achieved sensitivity of 94% and an NPV of 95%, leading to a 24.6% (64/260) reduction in unnecessary MRI scans while missing 2/21 (9.5%) csPCa cases [14]. These two studies are based on retrospective design, which may introduce a selection bias. Additionally, the use of specific PSAd thresholds may not be universally applicable, as variations in patient populations and clinical settings could impact the accuracy and effectiveness of the proposed cut-offs in identifying csPCa. Further studies that examine the role of PSAd in refining triage strategies for prebiopsy MRI are needed to validate these findings in diverse populations and clinical settings, ensuring broader applicability and clinical utility.

3.1.2.2. Prostate Health Index. The Prostate Health Index (PHI) is a formula incorporating different molecular components of PSA (PSA, free PSA, and [−2]proPSA). PHI has been shown to outperform total, free, and [−2]proPSA for the identification of csPCa [15,16]. The use of PHI was demonstrated to avoid more biopsies among Asian men than among Caucasian men (646/1149 [56%] vs 199/503 [40%]), while reducing 31% (73/232) International Society of Urological Pathology (ISUP) GG1 diagnoses, compared with PSA [17]. Three studies explored the potential of PHI to reduce MRI scans. Kim et al [18] performed a prospective five-centre study including 545 patients undergoing an MRI-based diagnostic pathway. They reported that using the PHI thresholds of ≥20 and ≥25 as an indication for MRI had NPVs for the detection of csPCa of 0.85 and 0.87, and missed only 1.1% (3/256) and 4.2% (11/256) cases of ISUP GG ≥2 cancer, respectively. The use of a PHI cut-off of ≥30 would lead to 25% (250/1000) reduction in mpMRI use while missing only 7.7% (20/256) cases of GG ≥2 cancer. Agnello et al [19] reported in 204 patients that a PHI of ≥30 resulted in sensitivity of 90% for a PI-RADS ≥3 lesion on a subsequent MRI scan. A PCa screening study incorporating PHI and MRI in Hong Kong Chinese men also demonstrated that, in men with PSA 4–10 ng/ml and PHI <35, 88% (1340/1536) of MRI scans showed PI-RADS 1–2 lesions. The benefit of an additional MRI scan was observed only in those with PSA 4.0–10.0 ng/ml, and the number of MRI scans needed to diagnose one additional ISUP GG ≥2 PCa case was 20 in case of PHI ≥35 and 94 in case of PHI <35. In men with PSA >10.0 ng/ml, addition of MRI to the PSA and PHI pathways did not increase the diagnosis of csPCa [20]. The multicentre study was limited by the lack of central quality assurance for biopsy and imaging procedures, as well as inconsistent biopsy decisions for negative MRI results [18]. The study of Agnello et al [19] was limited by its single-centre retrospective design and relatively small study sample.

3.1.2.3. The 4Kscore test. The 4Kscore test is a blood test designed to evaluate the risk of aggressive PCa by measuring four biomarkers: total PSA, free PSA, intact PSA, and human kallikrein 2 (hK2). By combining these results with clinical information (age, digital rectal examination [DRE], and prior biopsy status), the test generates a score that helps determine the likelihood of high-grade PCa being present. Two independent multi-institutional prospective studies have recently validated the 4Kscore test [21,22]. The first study included 26 academic and community-based urology practices across the USA, showed excellent calibration, and demonstrated higher discrimination (area under the curve [AUC] 0.82) and net benefit than a modified Prostate Cancer Prevention Trial (PCPT) Risk Calculator 2.0 model and the standard of care (biopsy for all men). While the second was conducted in eight Veteran's Affairs medical centres (with 56% of the cohort being African American), it showed better discrimination (AUC 0.81 vs 0.74, $p < 0.01$) and higher clinical usefulness on a decision curve analysis than the base model (consisting of age, DRE, and PSA). In both studies, the 4Kscore test showed good calibration and discrimination (AUC >0.80), while significantly reducing the number of biopsies. When combining data from both trials, the use of a 4Kscore biopsy threshold of 7.5% resulted in a one-third reduction in the number of men who underwent a biopsy, without missing GG ≥4 cancer cases and only 8.6% of GG2 or GG3 tumours. Focusing on the potential of 4Kscore to reduce unnecessary MRI procedures, we identified one study including 266 patients who underwent MRI, the 4Kscore test, and prostate. The use of a 4Kscore threshold of 7.5 would save 34.2% (91/266) MRI scans, while missing only 2.7% (2/74) of csPCa cases [7]. This study is constrained by its retrospective design and limited sample size. Prospective validation of 4Kscore as a triage test for prebiopsy MRI is necessary before its integration into clinical practice [7].

3.1.2.4. Stockholm 3 model. The Stockholm 3 (STHLM3) model is a combination of plasma protein biomarkers (PSA, free PSA, intact PSA, hK2, MSMB, and MIC1), genetic polymorphisms (232 single nucleotide polymorphisms), and clinical variables (age, family, history, previous prostate biopsy, and prostate examination) [23]. The model has been shown to reduce unnecessary biopsies without compromising the ability to diagnose PCa with a Gleason score of at least 7 [23]. When used as a triage test for MRI, the use of a threshold of 0.15 in the STHLM3 model provided identical sensitivity to detect clinically significant cancer, and led to 35.6% (545 vs 846) fewer MRI procedures and 7.9% (311 vs 338) fewer prostate biopsy procedures, compared with a PSA level of ≥3 ng/ml [24]. The PRIMA trial confirmed that an STHLM3 threshold of 0.15 was most suitable (and outperformed the threshold of 0.11), compared with PSA ≥3 ng/ml. The use of an STHLM3 threshold of 0.15 reduced MRI scans by 26.3% while maintaining similar detection rates for ISUP GG2, ISUP GG1, and targeted biopsies, compared with the PSA screening arm. Using this strategy, 26% of MRI scans could be reduced [24]. In contrary, although the use of an STHLM3 threshold of 0.11 led to increased csPCa diagnosis, it was also associated with a 35.1% (37 vs 50) increase of cisPCa diagnoses and 13.8% (320 vs 364) increase in MRI scans performed [25]. Since the favourable results for the 0.15 threshold emerged while the PRIMA trial was already on-going, confirmation was possible only through a post hoc analysis. Therefore, further validation of STHLM3 with a 0.15 threshold in external populations is warranted.

3.1.3. Urine-based biomarkers

3.1.3.1. Prostate cancer antigen 3. The prostate cancer antigen 3 (PCA3) test measures the ratio of mRNA of PCA3 to PSA in urine after a DRE [26]. Using a cut-off of 35, sensitivity and specificity were 64% and 76% for any-grade PCa, respectively, whereas these were, respectively, 84% and 55% for a PCA3 cut-off of 20 [27]. In a retrospective study evaluating a cohort of 591 patients, among whom 163 underwent mpMRI and a PCA3 test, the PCA3 score was significantly higher for patients with a suspicious region for PCa on MRI (52 vs 21). However, the use of PCA3 with a threshold of 35 would not be a suitable triage test for MRI, as among low-risk patients with PCA3 <35, suspicious lesions on MRI were found in 28/41 (68%), 82% (23/28) of whom had PCa on biopsy [28]. The study by Leyten et al [28] was limited by its retrospective design and the selective inclusion of patients who underwent MRI, potentially restricting its generalisability.

3.1.3.2. SelectMDx. The SelectMDx score is a combination of expression levels of mRNA HOXC6 and DLX1 in post-DRE urine sediment and clinical risk factors (age, DRE, PSA, PSAd, family history, and prior negative prostate biopsies) [29]. The use of a biomarker model based on HOXC6 and DL1 with a cut-off of 27.5 would result in sensitivity, specificity, NPV, and AUC of, respectively, 91%, 35%, 94%, and 0.76 for the detection of csPCa at a TRUS biopsy [29]. In another study, the association of the score with MRI was evaluated, showing the score to be significantly different comparing cases with suspicious lesions on MRI versus those without (−1.3 vs −3.1) [30]. In another study by the same group, 599 biopsy-naïve patients, all of whom underwent MRI and SelectMDx, were included. A threshold of −2.8 was used, corresponding to a 13% probability of detection of ISUP GG ≥2 cancer. The authors reported that SelectMDx as a triage test for MRI could reduce 37.9% MRI scans at the cost of missing 9.8% of csPCa cases [31]. However, performing MRI in all patients before a biopsy provided the highest clinical utility in terms of the net benefit. Therefore, SelectMDx should be considered as a prebiopsy stratification tool, particularly in settings where MRI availability is limited or costly.

3.1.3.3. ExosomeDx. ExosomeDx (ExoDX or EPI) is a noninvasive urine test that quantifies PCA3 and ERG RNA expression within exosomes—small RNA-containing vesicles released by prostate cells into the urinary tract [32]. Uniquely, this biomarker test does not require a DRE, enhancing patient convenience and making it an accessible alternative for PCa screening and risk assessment. The EPI test was initially validated to identify high-grade PCa (Gleason score ≥7) among patients with PSA levels between 2 and 20 ng/ml. Results demonstrated an AUC of 0.73, which was significantly better than the standard care using PSA and other clinical parameters (AUC 0.63). Applying a threshold of 15.6, the EPI test avoided 27% of biopsies while achieving a high NPV of over 90% [32]. Expanding on its application within the "grey zone" PSA range of 2–10 ng/ml, this study confirmed the 15.6 cut point for distinguishing high-grade PCa (GG ≥2) from GG1 or benign cases. The report emphasised the test's "standalone" nature, independent of PSA or DRE requirements, with performance metrics being superior to those of other tools, reaching an AUC of 0.70 and an NPV of 89% [33]. The EPI test was further applied to patients with prior negative biopsies, showing utility in repeat biopsy decision-making. At the standard cut-off of 15.6, the test avoided 26% of unnecessary repeat biopsies, achieving an NPV of 92% and sensitivity of 82%. Higher cut-offs of 20 and 29.6 increased biopsy avoidance to 35% and 61%, respectively, albeit with slight reductions in sensitivity [34]. ExosomeDx is a promising noninvasive test for reducing unnecessary biopsies; however, further studies are needed to evaluate its potential as a triage tool for prebiopsy mpMRI.

3.2. Combination of MRI and other biomarkers for the indication for biopsy

The PI-RADS scoring system systematically evaluates prostate MRI to estimate the likelihood of csPCa [35]. However, while MRI is being increasingly used worldwide, equivocal MRI scans (eg, PI-RADS 3) are not uncommon and resulted in unnecessary prostate biopsies. This highlights the need for additional tools to improve risk stratification, particularly in equivocal MRI cases; this section summarises the literature on such tools to reduce unnecessary biopsies, with results detailed in Table 2.

3.2.1. MRI-based RCs

Alberts et al [36] updated the ERSPC RCs for sextant TRUS biopsies with MRI information (PI-RADS) and age, including 1353 patients with a clinical suspicion of PCa, undergoing MRI and a subsequent systematic and/or target biopsy. Among biopsy-naïve patients, using the MRI-ERSPC-RC3 model and a threshold to biopsy of ≥10%, 14% (143/1000) of biopsies are avoided, missing low-grade PCa in 13% (18/143) of men and high-grade PCa in 10% (14/143) of men who are not biopsied [36]. For the MRI-ERSPC-RC4 (previously biopsied men), 36.1% (361/1000) of biopsies are avoided, missing 15.2% of cisPCa and 4.2% (15/361) of csPCa cases among men who are not biopsied [36]. Another MRI-based model developed by Van Leeuwen et al [37] for the prediction of significant PCa (defined as Gleason 7 with >5% grade 4, ≥20% cores positive, or ≥7 mm of cancer in any core) was shown to improve the indication for biopsy. With a threshold of ≥10%, 28.2% of biopsies could be reduced, at the cost of missing 12.8% cisPCa and 2.6% csPCa cases. Furthermore, the Imperial Rapid Access score was developed and externally validated, applicable in patients with PI-RADS ≥3 lesions on MRI [38]. Using thresholds of 20% and 30%, the risk score was able to reduce 11% and 21% of biopsies at the cost of missing 1.8% and 6.2% csPCa cases, respectively [38]. External validation using the data of two large European centres showed that the MRI ERSPC and the Van Leeuwen model both had a high discrimination (AUC of 0.86). At a threshold of ≥10%, the Van Leeuwen model, MRI-ERSPC-RC, and the imperial RAPID nomogram would respectively reduce the number of biopsies by 22.4% (211/940), 20% (188/940), and 23.4% (220/940), while missing only 1.8% (9/500), 2.6% (13/500), and 2.6% (13/500)

csPCa cases [39]. Other MRI-based RCs found to provide a net benefit included the PLUM, Mehralivand, Radtke, and Distler RCs. However, at a threshold of ≥10%, the percentages of saved biopsies were lower, ranging from 0% to 4.3% [39–43] The RC developed by Bjurlin et al [44] could save 215/940 (22.9%) biopsies, at the cost of missing 23/507 (4.5%) csPCa cases [39]. Differences in the definition of significant PCa across studies (eg, the van Leeuwen and ERSPC RCs use different Gleason score thresholds) can influence model performance metrics, potentially affecting their perceived clinical utility and leading to misinterpretations when comparing studies. Additionally, clinicians should be aware that RCs are tailored to their development populations, and their performance may vary across hospitals due to regional and local cohort differences.

3.2.2. MRI combined with blood-based biomarkers

3.2.2.1. MRI and PSAd. In the post-MRI setting, PSAd is likely the most convenient triage test to reduce unnecessary biopsies, as it does not require any additional testing. The use of a PSAd of <0.15 ng/ml/ml has been reported to increase the NPV of MRI for the detection of csPCa from 84.4% to 90.4% [45]. In a recent systematic review, the NPV for csPCa among patients with negative MRI was 94% using a PSAd of <0.15 ng/ml/ml and increased to 96% for a PSAd of <0.10 ng/ml/ml [46]. The use of MRI in case of PI-RADS 3–5 or PSAd ≥0.10 in case of PI-RADS 1–2 for biopsy indication could result in a reduction of 28.1% of biopsies, while missing 14.6% of cisPCa and 1.3% csPCa cases [7]. In another retrospective study comparing ten strategies based on PSAd and MRI to avoid unnecessary biopsies, Falagario et al [47] reported that adherence to PI-RADS 4–5 or PI-RADS 3 and PSAd >0.2 ng/ml/ml resulted in the most optimal strategy in terms of the net benefit. With this strategy, 41.2% (746/1810) of prostate biopsies could be avoided, at the cost of missing 10.9% of csPCa cases and reducing 44% of ISUP GG1 diagnoses. A strategy associated with lower rates of missed csPCa cases included selecting patients with PI-RADS 3–5 lesions or PSAd >0.15 ng/ml/ml for a biopsy: reducing biopsies by 14.7% at the cost of missing 1.7% of csPCa cases and reducing 9.3% of ISUP GG1 diagnoses. Rajendran et al [48] demonstrated that the use of PSAd <0.10 ng/ml/ml for low risk and >0.20 ng/ml/ml for high risk can effectively guide decision-making, reducing unnecessary biopsies while maintaining a high rate of csPCa detection. This approach avoided 62.9% (1292/2055) of biopsies, while missing only 9.8% (61/623) of csPCa cases. Boesen et al [49] found that the combination of PI-RADS ≥4 with PSAd ≥0.15 ng/ml/ml reduced biopsies by 41% (329/808) and overdiagnosis of cisPCa by 45% (79/177), while missing only 5.2% (17/329) of csPCa cases. A PSAd threshold of <0.15 ng/ml/ml appears to be most informative for reducing unnecessary biopsies while maintaining a high NPV for csPCa, though lower thresholds (eg, <0.10 ng/ml/ml) increase the NPV further. However, the optimal PSAd cut-off should be tailored based on individual patient risk factors, balancing biopsy reduction with missed cancer risk. Additionally, the NPV of the PSAd and mpMRI combination varies across studies, and its clinical utility may differ between hospitals.

3.2.2.2. MRI and PHI. PHI can aid MRI-TRUS fusion biopsy in patients who are screened for csPCa. Fan et al [50] found that by the use of a PHI cut-off of 27, 7.4% of patients with PI-RADS 4/5 lesions could avoid biopsy, missing 2% of csPCa cases. The use of a PHI cut-off for patients with equivocal lesions was shown to have more potential. Using a cut-off of 50.1, 69.1% of biopsies could have been avoided, at the cost of missing 5.9% of cases with csPCa. Chiu et al [51] analysed 1215 men and found that PHI, prostate volume, and PI-RADS score were independent predictors of csPCa detection. PHI density was found to be superior to other metrics including PSAd and PHI in predicting csPCa, particularly among cases with PI-RADS 3 lesions. Among these men, using cut-offs of PSAd 0.15, PHI 38.0, and PHI density 0.83, 58% (705/1215), 67% (814/1215), and 72% (875/1215) of unnecessary biopsies, respectively, could be reduced. It should be noted that this study was limited by the availability of PHI density and MRI data in only a selected subset of patients (1215 out of 5240), introducing the potential for a selection bias.

3.2.2.3. MRI and 4Kscore. In their study, Wagaskar et al [52] assessed the performance of a nomogram that incorporated 4Kscore, PI-RADS score, prostate volume, and prior negative biopsy to predict PCa, csPCa, and unfavourable PCa (uPCa) in 574 men with 4Kscore >7% or suspicious DRE or PI-RADS 3–5 lesions who underwent biopsy. The nomogram had AUCs of 0.84, 0.88, and 0.86 for PCa, csPCa, and uPCa, respectively. It also showed good agreement with an external validation cohort of 622 men. Using a 30% probability threshold, the nomogram could avoid 30% (187/622) of biopsies, 41% (77/187) of benign biopsies, and 19% (23/121) of indolent PCa cases, while missing 9% of csPCa cases. Falagario et al [7] demonstrated that the use of a 4Kscore threshold of >7.5% for MRI indication, followed by a biopsy in cases of positive MRI, would miss 2.7% of significant PCa cases but avoid 34.2% (99/266) of biopsies. Initial MRI followed by a biopsy for negative MRI, if the 4Kscore test was 18% or PSAd was ≥0.10, resulted in a similar percentage of missed cancer cases but a slightly fewer number of biopsies avoided (25.2% vs 28.1%). In a multicentre retrospective study, de Almeida et al [53] evaluated the most optimal 4Kscore thresholds for biopsy in patients with MRI-negative (PI-RADS 1–2) or equivocal (PI-RADS 3) results. Using a threshold of 33 for MRI-negative patients, biopsy could be avoided in 82% (306/374) cases, among which 5% (15/306) had ISUP GG ≥2 cancer (of which 13% [2/15] had ISUP GG ≥3 cancer). However, these included 42% (15/36) of patients with ISUP GG ≥2 in this subgroup (36 out of 374 MRI-negative cases [10%] had ISUP GG ≥2 on biopsy). Among patients with PI-RADS 3 lesions, using a cut-off of 8 would result in avoiding biopsy in 30% (75/250), at the cost of missing 6% (3/51) of all csPCa cases. Ajami et al [54] explored the combined value of PSAd and 4Kscore in patients with PI-RADS 3 lesions, and concluded that among patients with PSAd <0.15, 4Kscore could be of value to determine biopsy indication as it was significantly associated with csPCa on a multivariable analysis. A key limitation of these studies is the potential for a selection bias due to their study design and varying patient

Table 2 – Overview of studies evaluating strategies to reduce unnecessary biopsies in patients with available MRI information

Author [ref]	Year	Design (RCT, prospective, retrospective)	No. of patients	Inclusion criteria	Intervention/triage test	Threshold	Definition of csPCa	Reduction in nsPCa diagnosis	csPCa missed	Biopsy avoided
Alberts [36]	2019	Prospective multi-institutional database	961 (of whom 504 biopsy-naïve men)	Men with a clinical suspicion of PCa (no prior PCa diagnosis), who received mpMRI and subsequent TRUS and/or targeted biopsy between 2012 and 2017	MRI-ERSPC-RC3 (biopsy naïve) MRI-ERSPC-R4 (previous negative biopsy)	≥10%	Grade group ≥2	18/143 among those not biopsied (12.6%) 18/161 (11.2%) overall nsPCa 55/361 (15.2%) among those not biopsied 55/142 (38.7%) overall nsPCa	14/143 among those not biopsied (9.8%) 14/423 (3.3%) overall csPCa 15/361 (4.2%) among those not biopsied 15/289 (5.1%) overall csPCa	143/1000 (14.3%) 361/1000 (36.1%)
van Leeuwen [37]	2017	Retrospective	393 (88% biopsy naïve)	Men aged >40 yr, planned for biopsy for abnormal PSA level or DRE, and had life expectancy of >10 yr. All underwent transperineal template mapping biopsies (median 30 cores)	RC: age, PSA level, DRE, PV, previous biopsy, and PI-RADS	≥10%	Gleason 7 with >5% grade 4, ≥20% cores positive, or ≥7 mm of cancer in any core	74/578 (12.8)%	10/379 (2.6%)	282/1000 (28.2%)
Peters [38]	2022	Prospective	1189	Elevated age-specific PSA (>2.5 ng/ml at 45–49 yr, >3 ng/ml at 50–69 yr, or PSA >5 ng/ml at >70 yr) and/or abnormal DRE	RAPID risk score	≥20% ≥30%	Grade group ≥2	NA	1.8% 6.2%	11% 21%
Patel [40]	2023	Retrospective	1010 (N = 675 used for development)	Consecutive patients without diagnosis of PCa, receiving their first mpMRI before biopsy for clinical suspicion of PCa	PLUM RC (Age, PSA, prostate volume, and PI-RADS)	≥15%	Grade group ≥2	NA	0%	13.8%
Mehralivand [41]	2018	Retrospective	400	Elevated PSA or abnormal DRE and at least 1 lesion detected on mpMRI (PI-RADS 1–5)	RC: age, race, prior negative biopsy, abnormal DRE, PSA, PV, PSAd, and PI-RADS	≥20%	Grade group ≥2	NA	11%	38%
Radtke [42]	2017	Retrospective	Development cohort 1015 (660 biopsy naïve and 355 with previous biopsy)	Men with suspicion of PCa, who underwent mpMRI with PI-RADS and fusion biopsy, and complete data on RM variables and biopsy information	RC: age, PSA, PV, DRE, and PI-RADS	≥10% (results regard biopsy-naïve men)		NA	TPR 0.97 NPV 0.89 PPV 0.46	NA
Distler [43]	2017	Retrospective	1040	Men (biopsy naïve or with prior negative biopsy) with suspicion of PCa with PSA >4.0 ng/ml and/or suspicious DRE	RC: PI-RADS, PSAd	PI-RADS <3 and PSAd group 1 PI-RADS <3 and PSAd group 2 PI-RADS <3 and PSAd group 3		NA	NPV 86.5 NPV 88.9 NPV 66.9	NA
Bjurlin [44]	2018	Retrospective	459	Men with no prior history of PCa, with suspicion of PCa, who underwent prebiopsy MRI and combined systematic and target biopsy	RC: PI-RADS, PSAd, and age			NA	AUC 0.91	NA
Falagario [7]	2020	Retrospective	266	Biopsy-naïve patients (PSA >3 ng/ml, and/or abnormal DRE) who underwent mpMRI, the 4Kscore test, and prostate biopsy	MRI and 4K MRI and PSAd	MRI PI-RADS 3–5 or 4Kscore ≥18 in case of PI-RADS 1–2 MRI PI-RADS 3-5 or PSAd ≥0.10 in case of PI-RADS 1–2	Grade group ≥2	27.1% 14.6%	2.7% 1.3%	67/266 (25.2%) 75/266 (28.1%)
Falagario [47]	2021	Retrospective	2512, of whom 1810 (72%) biopsy naive	Biopsy-naïve men undergoing PSAd and prostate MRI before prostate biopsy between 2013 and 2019	PSAd and MRI	Strategy #5 PI-RADS 3–4–5 and/or PSAD >0.15 Strategy #7 PI-RADS 4–5 or PI-RADS 3 and PSAd >0.2 Strategy #10 PI-RADS 4–5 or PI-RADS 3 if PSAd >0.10, or PSAd >0.2	Grade group ≥2	9.3% 44.0% 24.4%	1.7% 10.9% 4%	14.7% 41.2% 27%

(*continued on next page*)

Table 2 (*continued*)

Author [ref]	Year	Design (RCT, prospective, retrospective)	No. of patients	Inclusion criteria	Intervention/triage test	Threshold	Definition of csPCa	Reduction in nsPCa diagnosis	csPCa missed	Biopsy avoided
Rajendran [48]	2024	Retrospective	2055 biopsy-naïve patients undergoing MRI	Biopsy-naïve men undergoing PSAd and prostate MRI before prostate biopsy between 2015 and 2021	PSAd and MRI	Low risk (<0.10 ng/ml/ml) Very high risk (>0.20 ng ml/ml)	Grade group ≥2	45/196 (23.0%) 76/196 (38.8%)	33/623 (5.3%) 61/623 (9.8%)	1119/2055 (54.5%) 1292/2055 (62.9%)
Boesen [49]	2019	Prospectively enrolled	808 biopsy-naïve patients undergoing MRI	Biopsy-naïve men with clinical suspicion of localised PCa (PSA <20 ng/ml, DRE)	PSAd and MRI	PI-RADS ≥4 and PSAd ≥0.15	Gleason score ≥7	79/177 (45%)	17/329 (5.2%)	329/808 (41%)
Chiu [51]	2023	Prospectively maintained multi-institutional databases	1215 (420, 35% biopsy naïve)	Men with elevated PSA, no prior prostate cancer diagnosis, and PHI and MRI-guided targeted and systematic prostate biopsy performed in 10 urology centres were included	PHI/MRI	PI-RADS 3 PSAd >0.154 PHI >38.0 PHId >0.83	Grade group ≥2	64% 59% 71%	Sn 65% NPV 91% Sn 65% NPV 92% Sn 65% NPV 92%	58% 67% 72%
Wagaskar [52]	2021	Retrospective	574 internal and 622 external	Patients with 4Kscore test >7% or suspicious DRE or PI-RADS 3–5 on mpMRI who underwent systematic and/or mpMRI/ultrasound fusion–targeted prostate biopsy	4Kscore and MRI combined nomogram	Avoiding 10% of biopsies (threshold not provided) Avoiding 20% of biopsies (threshold not provided)	Grade group ≥2	5/121 (4%) 17/121(14%)	2/173 (1%) 7/173 (4%)	10% 20%
Palsdottir [55]	2019	Retrospective analysis of subpopulation of the STHLM3-MRI study	532, of whom 429 were MRI positive (comparator)	No previous prostate cancer diagnosis and were referred for a prostate biopsy or prebiopsy MRI	STHLM3 with PI-RADS scores in one unified logistic regression model, which we denote as S3M-MRI	Strategy 4 S3M-MRI risk ≥18% Comparator: biopsy in all patients who are MRI positive	Grade group ≥2	33%	9/187 (4.8%)	32%
Hendriks [31]	2021	Prospective	599	Biopsy-naïve patients, serum PSA ≥3 ng/ml, undergoing SelectMDx and mpMRI before biopsy	SelectMDx and mpMRI SelectMDx or mpMRI	Risk score −2.8 corresponding to 13% likelihood for csPCa and PI-RADS 3–5 Risk score −2.8 corresponding with 13% likelihood for csPCa or PI-RADS 3–5	Grade group ≥2		24/183 (13%) 3/183 (1.6%)	357/599 (60%) 165/599 (28%)
Maggi [57]	2021	Prospective	310	Biopsy-naïve men scheduled for first biopsy, serum PSA >3 ng/ml and/or abnormal DRE. Patients underwent prebiopsy MRI and SelectMDx	SelectMDx and mpMRI	Biopsy in PI-RADS 4–5 and PI-RADS 1–3 cases with positive SelectMDx	Grade group ≥2		6/62 (6.5%)	142/310 (46%)
de la Calle [59]	2021	Retrospective study	228	Men who performed a liquid biomarker test executed before prostate biopsy, PSA <20 ng/ml, and no previous diagnosis of PCa; at least 10-core prostate biopsies	4Kscore, ExosomeDX, mpMRI	EPI score ≥15.6% EPI score ≥15.6% and mpMRI	Grade group ≥2	NA	2/42 (4.8%) 1/42 (2.4%)	40% 20.7%

AUC = area under the curve; csPCa = clinically significant prostate cancer; EPI = ExoDX prostate test; ERSPC = European Randomized study of Screening for Prostate Cancer; mpMRI = multiparametric magnet renounce imaging; MRI = magnet renounce imaging; NA = not applicable; NPV = negative predictive value; nsPCa = nonsignificant prostate cancer; PCa = prostate cancer; PHI = Prostate Health Index; PHId = PHI density; PI-RADS = Prostate Imaging Reporting and Data System; PPV = positive predictive value; PSA = prostate-specific antigen; PSAd = PSA density; PV = prostate volume; RC = risk calculator; RCT = randomised controlled trial; Sn = sensitivity; STHLM3 = Stockholm 3;TPR = true positive rate; TRUS = transrectal ultrasound.

populations. Additionally, differences in MRI interpretation, threshold selection, and biopsy criteria may affect the generalisability of their findings.

3.2.2.4. MRI and STHLM3 model. Palsdottir et al [55] used the data of 532 patients from the prospective STHLM3-MRI trial to construct a unified prediction model (S3M-MRI) combining the STHLM3 score and PI-RADS v2 scores (modified for MRI without contrast). They concluded that the S3M-MRI model outperformed STHLM3 and PI-RADS alone for the detection of cases with ISUP GG ≥2 cancer in terms of discrimination and net benefit. This study is limited by the absence of true disease prevalence data, missing data, biopsy protocol variations, a small sample size, and a predominantly Northern European cohort. Additionally, to assess the role of the STHLM3 score in the PCa screening setting among patients with negative MRI, future studies are needed. Ideally, an optimal threshold of STHLM3 could be identified for omitting a systematic biopsy safely in MRI-negative cases. Performing studies wherein STHLM3 would be used as a post-MRI test in MRI-negative cases remains questionable, as this would need MRI in all patients, whereas the test has shown to successfully decrease the need for MRI (or even avoid MRI), without compromising csPCa detection rates [24,56].

3.2.3. MRI and urine-based tests

3.2.3.1. MRI and SelectMDx. Hendriks et al [31] evaluated several MRI-based strategies in 599 prostate biopsy–naïve patients aged 50–75 yr with a PSA level of ≥3.0 ng/ml, who underwent systematic biopsies with or without MRI-guided target biopsies. Restricting biopsy to patients with a positive SelectMDx score and positive MRI (PI-RADS 3–5), biopsies were reduced by 60% (357/599), at the cost of missing 13% (24/183) of cases with csPCa (of which 33% had ISUP GG ≥3). Performing biopsy in patients with either positive SelectMDx or positive MRI resulted in the highest detection rate of high-grade PCa (98% of csPCa) of all strategies, compared with the reference standard, resulting in 21% (29/138) fewer diagnoses of cisPCa cases and reduction of 28% (165/599) biopsies. Maggi et al [57] also reported favourable results for selecting MRI equivocal or negative cases (PI-RADS 1–3) with a positive SelectMDx score for biopsy. The use of the strategy of performing a biopsy in either PI-RADS 4–5 or PI-RADS 1–3 cases with a positive SelectMDx score would result in reducing 45.8% (142/310) of biopsies, while missing only 7.7% (8/104) of overall PCa and 6.5% (6/62) of csPCa cases. There were a number of limitations on this subject in the studies, including a lack of a cost-effectiveness analysis and a lack of a central review of mpMRI reading.

3.2.3.2. MRI and PCA3. In the repeat biopsy setting, after a previous negative biopsy, PCA3 could help stratify patients with negative MRI. Perlis et al [58] included 470 patients on active surveillance for low-risk PCa and those with a previous negative biopsy but a persisting suspicion for cancer with negative MRI. Among 26 patients with negative MRI (PI-RADS 1–2) and PCA3 score <35, 2/26 (7.6%) had cisPCa and none had csPCa. Although these data suggest a high NPV (100%) for the detection of csPCa when combined, these results should be interpreted cautiously due to the small sample size and retrospective nature of the study. The small sample size (26 patients with negative MRI) limits the reliability of these findings and hinders their generalisability to larger populations.

3.2.3.3. MRI and ExosomeDX. In the study by De la Calle et al [59], the performance of ExoDX was assessed for its ability to reduce unnecessary biopsies, even with the potential trade-off of missing some high-grade PCa cases (GG ≥2). The study explored ExoDX as a standalone tool and within various algorithmic combinations, incorporating or excluding mpMRI. In their cohort of 228 men, they examined a sequence where ExoDX was used as an initial screen followed by mpMRI for positive biomarker cases and, conversely, where mpMRI was the first step followed by ExoDX. The algorithm with upfront ExoDx would avoid 40% (168/419) of unnecessary biopsies, missing 4.8% (2/42) of high-grade PCa cases. The setting with upfront mpMRI would avoid about 20/7% (84/419) of unnecessary biopsies, missing only 2.4% (1/42) of high-grade PCa cases. This study presented the first screening algorithms with ExosomeDx and mpMRI; further studies are necessary to explore their combined value. This study is limited by its retrospective design and the absence of biopsy data in approximately half of the patients, which may lead to an underestimation of the missed cases of csPCa [59].

3.3. PSMA PET and PCa detection

PSMA PET, combined with either computed tomography (CT) or MRI, has the potential to improve PCa detection [60,61]. Prive et al [61] performed a prospective study to assess whether ^{18}F-PSMA-1007 PET/CT could improve the detection of csPCa when used in conjunction with MRI. They found that among the 26 cases with PI-RADS 3 lesions, ^{18}F-PSMA-1007 PET/CT could correctly differentiate 65% (17/26) of these cases, with an NPV of 93% and a positive predictive value of 27%. In another prospective study, Margel et al [60] showed that ^{68}Ga-PSMA PET/MRI had similar sensitivity to, but higher specificity than MRI: 88% vs 92% and 86% vs 59%, respectively. Adhering to MRI alone, the use of PI-RADS ≥3 for biopsy indication would have detected 92% (23/25) of csPCa cases, at the cost of performing unnecessary biopsies in 36%. Performing biopsy in cases with PI-RADS ≥3 lesions and positive PSMA PET/CT (defined as the maximum standardised uptake value [SUV_{max}] ≥2.5) would lead to similar csPCa detection rates (88%, 22/25) but would have avoided biopsies in 55% (43/78) of cases. Ajami et al [54] found that per-lesion sensitivity for csPCa was significantly higher for 18F-PSMA-1007 PET/CT than for MRI (95% vs 73%), using surgical histopathology as a reference standard. When combining both modalities, per-lesion sensitivity for csPCa detection increased to 97%.

The PRIMARY trial showed that PSMA + MRI improved NPV compared with MRI alone (91% vs 72%, $p < 0.001$). Sensitivity also improved (97% vs 83%, $p < 0.001$); however, specificity was reduced (40% vs 53%, $p = 0.011$). Of all men, 19% (56/291) were PSMA + MRI negative (38% of PI-RADS 2/3) and could potentially have avoided a biopsy, risk-

ing delayed csPCa detection in 3.1% men (5/162) [62]. These results were echoed by the recently published PEDAL trial, showing that a combination of PSMA PET/CT and mpMRI showed excellent sensitivity of 98.8%, outperforming mpMRI alone (86.9%, p = 0.01) [63]. Based on the data of the PRIMARY trial, a novel RC was developed including the SUV_{max} of the MRI index lesion, age, PSA, prostate volume, and PI-RADS score. In the development cohort, the model showed a promising AUC of 0.83 for the detection of csPCa cases [64]. Future validation of this model is needed to assess its accuracy in an external patient population. Lastly, a prospective trial included 60 biopsy-naïve patients with PI-RADS 3 lesions, to assess the added value of the PRIMARY score assessed by ^{68}Ga-PSMA PET/MRI for the detection of csPCa. Using a biopsy indication in cases with PRIMARY score $\geq$4, 40 of 48 patients (83.3%) could avoid unnecessary biopsies, at the expense of missing one of eight (12.5%) csPCa cases [65].

In conclusion, PSMA PET exhibits promising sensitivity for detecting csPCa, and complements MRI in both identifying csPCa and refining biopsy indications in patients with PI-RADS 3 lesions. Further studies are required to evaluate the potential benefits of either integrating PSMA PET with MRI or replacing MRI with PSMA PET for csPCa detection, as well as to determine the subgroups that may derive the greatest benefit from this approach. In addition, future studies should focus on the cost effectiveness of integrating PSMA PET into the diagnostic algorithm.

4. Discussion

The aim of this narrative review was to outline the potential of available RCs and biomarkers to improve efficacy of the diagnostic pathway in the current era of prebiopsy MRI diagnosis. This overview can guide clinicians involved in PCa diagnosis regarding the availability and evidence on different biomarkers to optimise the diagnostic pathway. A summary of scenarios illustrating how these tools can be integrated into the diagnostic algorithm is presented in Fig. 1.

With regard to strategies to reduce unnecessary MRI procedures, several conclusions can be drawn. First, the use of the ERSPC-RC 3/4 model was the most extensively evaluated strategy, showing the ability to reduce a clinically relevant percentage (16–51%) of unnecessary MRI scans in different study populations [6,8–11]. However, rates of missed csPCa cases of up to 16% were reported, and rates of reduced MRI scans varied widely among studies. This indicates that the performance of this RC is highly population dependent. Therefore, prior to integrating this RC into diagnostic pathways, local validation remains necessary. Second, studies evaluating the STHLM3 test have emerged, showing promising results when used as a triage test for MRI. Using the threshold of 0.15, a substantial proportion of scans MRI may be avoided without significantly decreasing csPCa diagnoses [24,25].

In the post-MRI setting, RCs were also most extensively studied. Several RCs have been developed. Among these, the Van Leeuwen and MRI-ERSPC-RC models demonstrated promising results, showing the best discriminative ability and the highest clinical utility in external validation studies [39,66]. These models could substantially reduce the need for unnecessary biopsies, potentially avoiding one in five biopsies while maintaining acceptable rates (<3%) of missed csPCa cases [39]. However, the wide variation in the rates of biopsies avoided and missed csPCa cases per RC observed, when applied to an external population (eg, 0–22.4% and 0–4.5%, respectively), underscores that performance differs across populations [39].

The question remains whether the use of more complex RCs outperforms strategies based on MRI + PSAd [67]. Studies comparing these approaches have reported conflicting results, suggesting that the superiority of either strategy may depend on specific population or hospital characteristics [13,14,39].

The role of PSMA PET/CT in primary diagnosis is emerging, with recent studies highlighting its potential for refining biopsy indications. However, a critical focus for future research should be on assessing the cost effectiveness of incorporating PSMA PET/CT into the diagnostic workflow. By reducing unnecessary biopsies and improving diagnostic accuracy, particularly when integrated with MRI findings, this imaging modality holds promise for optimising patient care. Detailed economic analyses are essential to evaluate its broader impact on health care systems and to determine its feasibility and cost effectiveness for widespread adoption.

While this study represents one of the first attempts to summarise strategies for reducing unnecessary MRI scans and biopsies in both pre- and post-MRI contexts within the modern diagnostic pathway, it is not without limitations. First, our study did not consider the availability and cost effectiveness of the included biomarkers. Therefore, when interpreting these results, local hospital and geographic factors including availability and capacity of specific tests on a hospital level, as well as national reimbursement policies, should be considered. It should be noted that availability and costs of various biomarkers vary from region to region, and can change from time to time. For example, the cost of the PHI test has reduced from US$ 300–400 to US$ <100 per test in both Hong Kong and Singapore in just a few years due to the economy of scale, while the costs of mpMRI prostate in these two places are about US$ 800–1000. However, this article intends to demonstrate the synergistic and complementary effects of biomarkers and MRI in reducing unnecessary biopsies, and not to identify which one is superior. Doctors should use biomarkers that are cost effective and easily available in their region in combination with MRI prostate in formulating the best diagnostic algorithm for PCa diagnosis.

Second, another limitation of our study is the lack of a formal systematic quality assessment. Given the heterogeneity in study design and research questions, application of standardised risk of bias tools was not feasible and could lead to inconsistent conclusions. Instead, we focused on synthesising and contextualising the evidence rather than conducting a structured quality appraisal, as done in systematic reviews and meta-analyses. Third, evidence summarised in this review mostly included studies of retrospective nature with methodological limitations

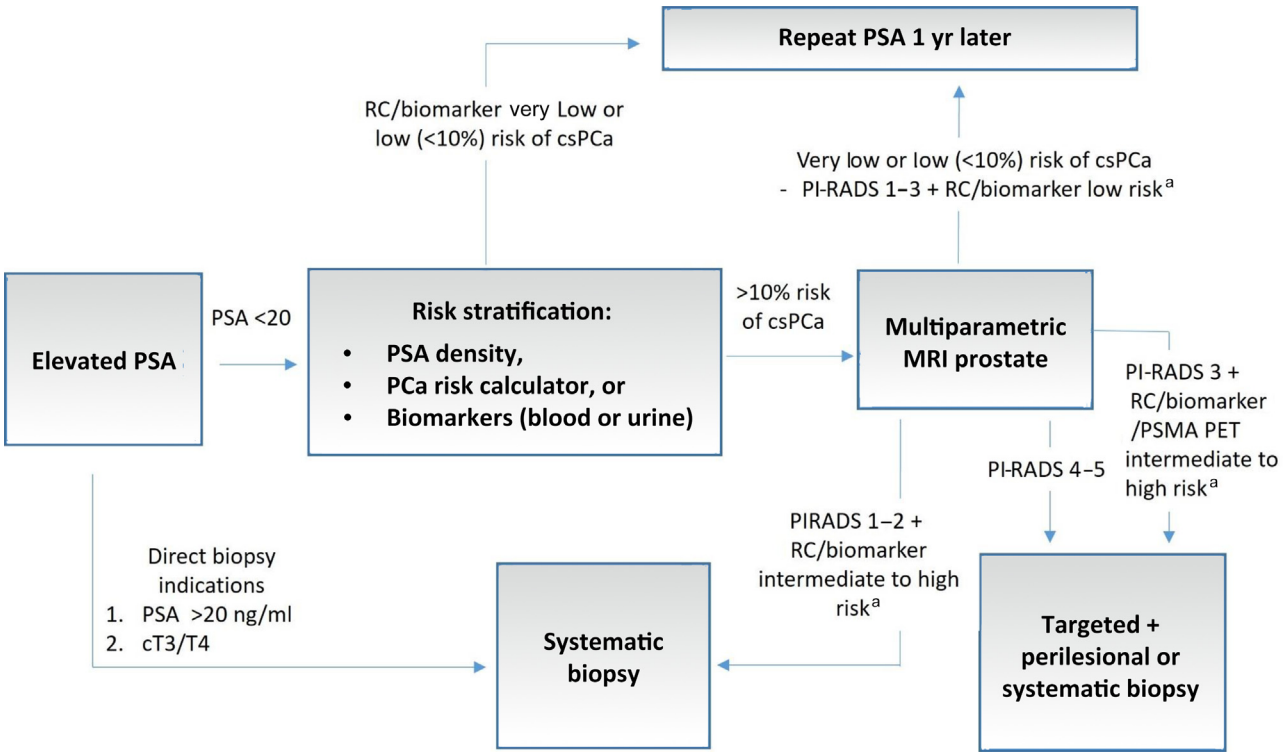

Fig. 1 – Diagnostic algorithm incorporating various biomarkers and imaging for biopsy-naïve men with elevated PSA. csPCa = clinically significant prostate cancer; EAU = European Association of Urology; MRI = magnetic resonance imaging; PET = positron emission tomography; PI-RADS = Prostate Imaging Reporting and Data System; PSA = prostate-specific antigen; PSMA = prostate-specific membrane antigen; RC = risk calculator. [a] Risks related to PSA density and MRI PI-RADS score classification in EAU guidelines: low: 5–10%, intermediate low: 10–20%, Intermediate high: 20–30%, high: 30%, and very high: >40%.

including a selection bias. Lastly, a notable limitation of the current evidence supporting personalised approaches is the reliance on biopsy-detected cisPCa and csPCa as surrogate outcomes. It can be hypothesised that the prognosis of GG2 tumours identified through a biopsy in the contemporary prebiopsy MRI era likely differs from that of tumours detected in the era prior to widespread MRI implementation.

5. Conclusions

A personalised approach to PCa diagnosis, utilising risk stratification tools, advanced imaging, and biomarkers, offers significant potential for optimising patient care. Integrating RCs and biomarkers into diagnostic pathways can reduce unnecessary MRI procedures and biopsies, although their performance varies between populations. PSMA PET shows promise in the detection of PCa cases and refining biopsy indications. Before implementation into clinical practice, physicians should select the most accessible, cost-effective, and well-validated tools applicable to their setting.

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Study concept and design: Soeterik, Wu, Van den Bergh, Gandaglia, Chiu.
Acquisition of data: Soeterik, Wu, Chiu.
Analysis and interpretation of data: Soeterik, Wu, Chiu.
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