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TOPIC PAPER

Smarter screening for prostate cancer

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Abstract

Purpose Prostate cancer is the second commonest cancer among men. In the large European Randomized Study of Screening for Prostate Cancer (ERSPC) trial, prostate-specific antigen (PSA) screening has been shown to substantially reduce prostate cancer mortality. However, PSA screening is known to lead to more unnecessary prostate biopsies and over-diagnosis of clinically insignificant cancer. Therefore, it is imperative that smarter screening methods be developed to overcome the weaknesses of PSA screening. This review explores the novel screening tools that are available.

Methods A comprehensive literature search was performed using PubMed regarding newer biomarkers, imaging techniques and risk-predicting models that are used to screen for prostate cancer in mainly biopsy-naïve men.

Results Novel serum-based models like 4Kscore® and prostate health index (PHI) are generally better than PSA alone in detecting clinically significant cancer. Similarly, urine-based biomarkers like prostate cancer antigen 3 (PCA3) and HOXC6/DLX1 have been shown to be more accurate than PSA screening. More recently, multiparametric magnetic resonance imaging (mpMRI) is gaining popularity for its ability to detect clinically significant cancer. There is also evidence that combining individual tests to develop prediction models can reliably predict high-risk prostate cancers while reducing the number of unnecessary biopsies. Combinations such as the Stockholm-3 model (STHLM3) and other novel combinations are presented in this review.

Conclusion While we continue to find the smarter screening methods that are reliable, precise, and cost-effective, we continue to advocate shared decision-making in prostate cancer screening in order to work in our patients' best interests.

Keywords Prostate cancer · Screening · Serum biomarker · Urine biomarker · mpMRI

Introduction

Globally, prostate cancer ranks as the second commonest cancer among men. The incidence varies widely across the world with the highest rates seen in Australia and New Zealand (86.4 per 100,000), and North America (73.7 per 100,000) [1], particularly in the USA where the delay-adjusted incidence rate was recently reported to be 118.2 per 100,000 [2]. It is also a very common cancer among men in Western and Northern Europe [1]. Easy access to prostate-specific antigen (PSA) testing is thought to contribute to such high incidence rates in these regions. However, it is interesting to note that prostate cancer is a less common in the Asian populations. The incidence rate could be as low as 4.5 per 100,000 in South-Central Asia. Nevertheless, about 1.1 million men were diagnosed with prostate cancer worldwide in 2012, highlighting the incredible burden of this disease on the human population. In fact, there was an estimated 307,000 deaths from prostate cancer in 2012, and it is the fifth leading cause of cancer mortality in men [3].

The intention of screening is to detect early disease that is potentially curable. The European Randomized Study of Screening for Prostate Cancer (ERSPC) trial that randomized more than 160,000 men to receive PSA screening or otherwise found substantial reduction in death due to prostate cancer in the PSA-screened arm at the 13-year follow-up analysis. The number needed to screen to avert one prostate cancer death is now 781, and one death is averted for every 27 men diagnosed with prostate cancer [4]. However, it is

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well known that PSA screening leads to over-diagnosis of a large number of low-risk prostate cancers. These clinically insignificant cancers are very unlikely to cause any harm to the patients [5]. Furthermore, widespread PSA testing also increases the number of prostate biopsies that are associated with a small, but potentially life-threatening risk of sepsis [6]. Thus, there is a real need for smarter screening methods to diagnose clinically significant prostate cancer with greater precision. The aim of this article is to review the literature and present evidence beyond PSA screening and focus primarily on several novel serum, urine and radiological-based screening tools in prostate cancer. We focus particularly on screening for biopsy-naïve men and discuss future directions and ideal traits of smarter screening for prostate cancer. It is important to note that most novel screening tools have been employed alongside PSA screening to explore whether or not men already at risk of prostate cancer could be better risk-stratified with an additional test to make smarter decisions around pursuing prostate biopsy.

Methods

A comprehensive literature search was performed on PubMed using keywords "prostate cancer" and "screening" to identify human studies published in English. Our search was focused on, but was not limited to, articles published between January 2013 and 2018 that were related to newer biomarkers, imaging techniques and risk-predicting models for prostate cancer screening. We then selected relevant original articles and systematic reviews whose study populations were mostly biopsy-naïve.

Results

Serum biomarkers

4Kscore®

The human tissue kallikreins (hK) are secreted trypsin-like serine proteases. They are encoded by 15 steroid hormone-regulated genes (KLK). They are expressed extensively in a wide range of tissues and are associated with various normal physiologic functions [7]. The 4K panel consists of 4 serum kallikrein biomarkers, namely total PSA (tPSA), free PSA (fPSA), intact PSA (iPSA) and human kallikrein 2 (hK2). Vickers et al. evaluated this panel for predicting prostate cancer at biopsy in previously unscreened men with PSA ≥ 3 ng/mL. They showed that the 4K panel could achieve an AUC of 0.903 for the detection of high-grade cancer [8]. Their study also concluded that by using 20% risk of prostate cancer as the cut-off value, above which prostate biopsy was indicated, they reduce the number of biopsies by more than half (57%), while only missing 3 out of 40 high-grade cancers [8]. Therefore, it appears we could consider adjusting the threshold for prostate biopsy in order to balance reducing number of biopsies and diagnosing high-grade disease.

In a further evaluation of the 4K panel in unscreened men, Vickers et al. used a study cohort of 2914 previously unscreened men enrolled in the ERSPC, Rotterdam project. They were all undergoing prostate biopsy for elevated PSA of ≥ 3 ng/mL, and the levels of 4K biomarkers were compared against the biopsy results. In this study, they demonstrated once again that application of the 4K panel would reduce the number of biopsies by 51.3%, while missing 12 out of 100 high-grade cancers [9]. A meta-analysis of 28 studies including 16,762 patients found the pooled sensitivity of the 4K panel in detecting high-grade cancer was 0.87, which is very similar to the result of the aforementioned study on the Rotterdam cohort. In addition, this meta-analysis found that the 4K panel has a pooled specificity of 0.61, and AUC from the hierarchical summary receiver operating characteristic of 0.81 for high-grade disease [10].

Prostate health index (PHI)

Researchers demonstrated and published in 1997 that an inactive precursor form of PSA (pPSA) constitutes part of the free PSA in the serum. The study concluded that while free PSA in prostate cancer is mainly unclipped PSA, a substantial proportion is made up of pPSA [11]. The same group then went to show in N-terminal sequencing that pPSA primarily comprised of [-2]pPSA and a small component of [-4]pPSA. Importantly, they also showed that pPSA was found in 28% of transition zone specimens, while 89% of matched cancer specimens had measurable pPSA in them. This indicated that pPSA is well associated with prostate cancer in contrast to BPH tissue [12].

Catalona et al. evaluated the PHI score given by the formula [-2]proPSA/fPSA × $PSA^{1/2}$ on 892 men with PSA 2–10 ng/mL who were going to have prostate biopsy. The AUC for detection of Gleason ≥ 7 (4 + 3) cancer using PHI was 0.724 compared to 0.670 using free-to-total PSA. The authors concluded that PHI measurement could decrease unnecessary biopsies due to its superior specificity for prostate cancer detection among men age 50 and above, with PSA 2–10 ng/mL and a negative digital rectal examination (DRE) [13]. A more recent multicenter prospective study on 658 men, aged 50 years and older, with PSA 4–10 ng/mL and normal DRE found that PHI outperformed PSA, [-2]proPSA and percentage of free PSA in the detection of prostate cancer overall and Gleason 7 or higher disease. The AUC of PHI for the detection of Gleason 7 or higher prostate cancer was 0.707. In addition, the authors showed that at 90% sensitivity for significant prostate cancer, 30.1%

of patients could have avoided unnecessary prostate biopsy [14]. PHI has also been validated and shown to be superior to total PSA, %fPSA and %p2PSA for detection of prostate cancer among Asian men aged 50–75 years with PSA 4–10 ng/mL and normal DRE. The AUC for PHI was 0.794; and at a sensitivity of 90%, PHI was more than three times more specific than total PSA at 58.3% and 17.3%, respectively. It could potentially save 77 (49%) men from unnecessary biopsies [15].

Urine biomarkers

Prostate cancer antigen 3 (PCA3)

Prostate cancer antigen 3 is a urinary biomarker for prostate cancer that was found to be significantly associated with prostate cancer. It is also known as differential display code 3 (DD3), a non-coding mRNA that is highly overexpressed in prostate cancer [16]. It was evaluated for clinical use on a cohort of 108 men who were going for prostate biopsy due to elevated PSA of > 3 ng/mL. Among them, 24 patients were found to have prostate cancer. DD3 or PCA3 was positive in 16 of 24 patients with prostate cancer, thus giving it a sensitivity of 67%. In addition, the negative predictive value was 90% in this cohort [17]. In a large retrospective study on 3073 men who had PCA3 analysis before their first prostate biopsy, Chevli et al. demonstrated that PCA3 was significantly better than PSA ($p < 0.01$) in predicting prostate cancer, with AUC 0.697 and 0.599, respectively. However, the accuracy for predicting high-grade prostate cancer was not as impressive and the AUC was not statistically significant compared to PSA [18].

Wang et al. conducted a study on 500 Chinese men to validate the use of PCA3 in the Asian population. These men were indicated to have their first prostate biopsy due to elevated PSA of ≥ 4 ng/mL and/or suspicious DRE. Among them, 173 men had PSA 4–10 ng/mL, while 250 men had PSA > 10 ng/mL. The AUC of PCA3 in predicting prostate cancer was significantly better than %fPSA (0.750 vs 0.622, $p = 0.046$) in the group with PSA 4–10 ng/mL. However, its performance was not substantially better than %fPSA in men with PSA > 10 ng/mL. The authors concluded that PCA3 only moderately enhanced diagnostic accuracy in predicting prostate cancer among Chinese men with PSA 4–10 ng/mL undergoing their first prostate biopsy [19]. A meta-analysis of 46 clinical trials including 12,295 patients who had PCA3 test for the diagnosis prostate cancer found the AUC to be 0.75 (95% CI 0.74–0.77). It also showed that the pooled specificity of PCA3 was 0.73 (95% CI 0.72–0.74). The quality of the studies selected for analysis was deemed moderate to high against the QUADAS scale. The authors concluded that urinary PCA3 test has an acceptable level of sensitivity and specificity for diagnosing prostate cancer [20].

Hoxc6/dlx1

The HOXC6 and DLX1 are among a few urinary biomarkers that were recently identified via gene expression profiling. A urinary 3-gene panel (HOXC6, DLX1, and TDRD1) was found to have higher accuracy [AUC 0.77; 95% confidence interval (CI) 0.71–0.83] than PCA3 (AUC 0.72; 95% CI 0.65–0.78) for the detection of Gleason ≥ 7 prostate cancer. The accuracy was further enhanced by combining it with PSA (AUC, 0.81; 95% CI 0.75–0.86) [21]. In another study, RNA levels of a series of genes including HOXC6, DLX1 and TDRD1 were measured in urine samples from men who were scheduled for initial or repeat prostate biopsies due to elevated PSA ≥ 3 ng/mL, abnormal DRE or family history of prostate cancer. The strongest individual biomarker was HOXC6 with AUC 0.73 when the sensitivity was set at 90%. The AUC was improved to 0.76 when HOXC6 was combined with DLX1 [22]. The EAU Guidelines 2018 recommend urinary HOXC6/DLX1 as one of the tests that could be used in asymptomatic men with PSA 2–10 ng/mL and normal DRE for risk-assessment prior to performing prostate biopsy [23].

Radiological imaging

Multiparametric magnetic resonance imaging (mpMRI)

Multiparametric MRI scan of the prostate (mpMRI) has gained popularity in recent years in the context of prostate cancer diagnosis. The mpMRI is a combination of anatomical and functional information from the MRI scan that is used to determine the presence of any abnormal lesions within the prostate gland. The T2-weighted imaging provides anatomical information, while diffusion-weighted imaging (DWI) and dynamic contrast-enhanced (DCE) features are used to evaluate functionally abnormal areas in the prostate [24]. The Prostate Imaging Reporting and Data System (PI-RADS) was developed to guide reporting of mpMRI in 2012 [25]. An updated PI-RADS version 2 (PI-RAD v2) was made available online in 2014 [26]. It is a simpler method of reporting mpMRI, but it has been shown to have lower accuracy [24].

The use of mpMRI of screening or triaging before initial prostate biopsy is an attractive proposal. It is a non-invasive investigation that could potentially reduce the rate of performing an invasive test. To the best of our knowledge, there has only been one pilot study exploring the use of mpMRI as the primary screening test in unselected men. That study included 47 men between 50 and 75 year old who did not have any history of prostate biopsy or family history of prostate cancer. They all underwent mpMRI and systematic prostate biopsy with or without targeted biopsy. The authors determined that

the AUC of mpMRI to detect prostate cancer was better than PSA alone 0.81 (95% CI 0.67–0.94) vs 0.67 (95% CI 0.52–0.84). They concluded that mpMRI was a feasible method for prostate cancer screening in the general population and it should further evaluated in the context of prostate cancer screening [27].

Despite there only being small studies for mpMRI as a population screen, there are a few large studies that describe mpMRI's superiority in men with abnormal PSAs. Further studies are required to know whether this can be extrapolated to the screening setting. The PROMIS study hypothesized that mpMRI could be used to triage men with elevated PSA up to 15 ng/mL and identify those who might safely avoid a prostate biopsy. The study included 576 men who had mpMRI followed by transperineal biopsy (TPB) as the reference test, and transrectal ultrasound-guided biopsy (TRUS-biopsy) as the standard of care. They defined clinically significant cancer as Gleason ≥ 7 $(4+3)$. By using TPB as the reference, the PROMIS study design is robust and is probably as close as it gets to having true positive and true negative for comparison; this is short of having pathologic information from post-prostatectomy whole-mount specimens as the reference. The conclusion drawn was that by triaging men with mpMRI, 27% of patients could avoid a primary biopsy and the negative predictive value (NPV) was 89% [28]. If the definition of clinically significant cancer was taken as Gleason ≥ 7 $(3+4)$, then the sensitivity, specificity, PPV and NPV would be 88, 45, 65 and 76%, respectively. Schoots et al. determined that this would miss 12% clinically significant cancer compared to 52% by performing on TRUS-biopsy in the cohort [29].

The PRECISION study was a randomized, non-inferiority trial comparing mpMRI with or without targeted biopsy, and standard TRUS-biopsy. The study randomized 500 men with PSA up to 20 ng/mL, suspected stage T2 or lower, and indicated for a prostate biopsy. Clinically significant prostate cancer was defined as Gleason ≥ 7 $(3+4)$. About 28% of men in the mpMRI group did not undergo prostate biopsy due to negative results on mpMRI. The intention-to-treat analysis showed clinically significant cancer was found in greater proportion of men in the mpMRI group compared to the TRUS-biopsy group (38% vs 26%, P value $=0.005$). Clinically significant cancer was detected in 12, 60 and 83% of men who had PI-RADS v2 scores of 3, 4, and 5, respectively. Although it was designed as a non-inferiority trial, the performance of mpMRI with targeted biopsy was in fact shown to be superior to standard TRUS-biopsy [30]. These studies still used PSA as the initial screen, but they show potential for mpMRI to be further evaluated as a primary screening method.

Combination

The Stockholm-3 Model (STHLM3)

The STHLM3 model combines plasma protein biomarkers, genetic polymorphisms and clinical variables. The protein biomarkers include PSA, free PSA, intact PSA, hK2, microseminoprotein-beta (MSMB) and macrophage inhibitory cytokine 1 (MIC-1); these together with 232 single nucleotide polymorphisms (SNPs) and several clinical parameters such as age, family history, prostate examination and previous prostate biopsy constitute all the components of this model [Gronberg Lancet Oncol 2015, Brawley 2016]. A large prospective, population-based, paired, screen-positive, diagnostic study was done for a Swedish population of men aged 50–69 years without prostate cancer. In that study, the STHLM3 model outperformed PSA alone for predicting clinically significant cancer (Gleason 7 or higher) with the area under the curve (AUC) at 0.74 (95% CI 0.72–0.75) versus 0.56 (95% CI 0.55–0.60) with PSA alone. When it was compared with a PSA threshold level of of ≥ 3 ng/mL for diagnosing high-risk prostate, the STHLM3 model was shown to reduce the number of unnecessary prostate biopsies by 32% (95% CI 24–39) [31].

It is obvious that performing STHLM3 on all patients with PSA 1 ng/mL would be very costly. Nordstrom et al. have therefore looked in the impact of raising the threshold PSA level before patients proceeded to have the STHLM3 test. They demonstrated by simply increasing the PSA cut-off value to 1.5 ng/mL they would have saved 18.3% STHLM3 test from being performed and reduced 4.8% of prostate biopsies. The compromise by doing so would be to miss 1.3% of Gleason ≥ 7 cancer. In order to compensate for the reduction in sensitivity, the researchers tuned the STHLM3 cut-off to recommend biopsy to match the original performance. By adjusting, they showed that there would be a 4% increase in the number of prostate biopsy performed [32]. The limitation of this model is that it has yet to be validated outside of the Swedish population. This is especially important given that genetic information plays a vital role in the performance of this prediction model. There are efforts to validate its use in other populations, and it remains to be seen whether the results of the original study could be replicated elsewhere [33].

Novel combinations

Novel combinations of newer biomarkers or mpMRI with existing risk-predicting models seem to be the way forward in improving the accuracy of screening tools. Roobol et al. added PHI to a recalibrated ERSPC risk calculator. In this study, clinical-relevant prostate cancer was defined as Gleason 7 or higher. For men who had no prior biopsy,

the PHI-updated risk calculator achieved AUCs of 0.73 and 0.66 for prostate cancer and clinically relevant prostate cancer, respectively. The authors mentioned that any enhancement in performance of the PHI-updated ERSPC models was small. They also concluded that reductions of rates of unnecessary biopsies were limited [34]. On the other hand, in another study involving 6 tertiary referral centres, a subset of 222 patients of the total sample population of 2001 patients had information regarding their PHI. Applying PHI-updated ERSPC risk calculator on this cohort of patients found the AUC of 0.78 for detection of significant prostate cancer defined as Gleason 7 or higher. This was significantly better than using the ERSPC risk calculator alone with an AUC of 0.72, P value = 0.04 [35].

Van Neste et al. created a risk-predicting model by combining urinary biomarkers HOXC6 and DLX1 with clinical risk factors for prostate cancer such as age, PSA, PSA density, DRE findings, previous biopsy and family history of prostate cancer. The study aimed to develop a model that could identify high-grade prostate cancer defined as Gleason ≥ 7. Their eventual risk-predicting model was able to achieve an impressive overall AUC of 0.90 (95% CI 0.85–0.95) [22].

More recently, a study incorporated mpMRI with the ERSPC risk calculator (MRI-ERSPC-RC). In a cohort of 504 biopsy-naïve men, the MRI-ERSPC-RC model performed significantly better than ERSPC-RC and DRE. The AUC of MRI-ERSPC-RC for diagnosing prostate cancer and high-grade disease (Gleason 3 + 4 or higher) was 0.839 (95% CI 0.805–0.872) and 0.843 (95% CI 0.808–0.878), respectively. However, it should be mentioned that at a risk threshold to biopsy of 10% or higher, biopsies were only avoided in 14%, while missing high-grade cancer in 10% of men who were not biopsied [36].

Interestingly, mpMRI was combined with STHLM3 in a study of 532 men in a Scandinavian population who were indicated for prostate biopsy. The patients had targeted biopsy using MRI fusion technique after which 10–12 biopsy cores were taken in a systematic fashion. The main endpoint of the study was to detect patients with grade group ≥ 2 prostate cancer. It was found that by performing MRI and targeted biopsy only in men with an elevated risk of prostate cancer as assessed by STHLM3, they could save 42% of biopsies and decrease detection of GG1 tumours by 46%, while preserving the sensitivity to detect significant cancer [37].

Discussion

In our effort to improve prostate cancer survival through screening and early detection, we are often faced with the dilemma of increased prostate biopsies and over-diagnosis of low-risk prostate cancer. Besides bearing the economic cost of doing more procedures, there is the added burden of inherent risks and complications from prostate biopsies. Therefore, it is crucial for us to develop screening methods that are accurate and reliable in order to reduce the number of biopsies, while improving on our ability to predict the presence of clinically significant prostate cancer through non-invasive means. Although the newer individual blood or urine biomarkers are better than PSA in discerning between low-risk and higher-risk prostate cancer (Table 1), their utility and marginal benefit over PSA for long-term cancer-specific survival are unknown.

As we have seen in this review, many investigators are developing risk predicting models by combining various tests with risk calculators or clinical risk parameters. Indeed, we think that novel combinations would someday create a model that is robust enough for us to be able to avoid unnecessary prostate biopsies without missing any clinically significant disease. However, it would most certainly come at a very high monetary cost and it is not certain that the marginal benefit will be significant. We would then have to consider whether the cost of tests outweighs the cost of unnecessary biopsies and over-diagnosis of clinically insignificant cancer.

In general, clinicians and patients need to work within their systematic constraints and financial realities to decide on whether anything beyond PSA screening will be appropriate at the population level. In places like Scandanavia, where whole health systems are managed by single payers, advances like the STHLM3 are possible and likely to reduce unnecessary biopsies. However, every unnecessary biopsy comes at some cost of missing clinically significant prostate cancer. Thus, the societal risk tolerance must be aligned. The future of screening likely lies in a 2-step process that begins with a PSA test. Men with very low tests would avoid any future tests or biopsies. Men with very high PSA would likely proceed to biopsy with or without mpMRI. The men with intermediate results will undergo a second test, which based on local costs and availability will either be serologic or radiologic and that result would dictate biopsy. Most urologic practices are heading in that direction already, but the long-term screening outcomes for this approach may never be available due to the sheer cost of running such trials as PLCO and ERSPC.

Conclusion

The challenge remains for us, at the moment, to develop a screening model that embodies the following traits: reliable, precise and cost-effective. Until then, the quest for smarter screening in prostate cancer continues. We continue to advocate for shared decision-making in prostate cancer screening.

Table 1 Summary of smarter screening methods and their key performance results

Screening method	Name of screening tool	References	Study design	Number of patients, *N*	Key performance outcome of the screening tool
Serum	4Kscore®	Vickers et al. [8]	Cohort	740	In men with PSA ≥ 3 ng/mL, the 4K panel could achieve an AUC of 0.903 for the detection of high-grade cancer
Serum	4Kscore®	Vickers et al. [9]	Cohort	2914	In men with PSA ≥ 3 ng/mL, the 4K panel had AUC of 0.78 for detection of any cancer
Serum	4Kscore®	Russo et al. [10]	Meta-analysis	16,762	The 4K panel had pooled sensitivity and specificity of 0.87 and 0.61, respectively, for detection of high-grade prostate cancer
Serum	PHI	Catalona et al. [13]	Case–control	892	In men with PSA 2–10 ng/mL, PHI had an AUC of 0.724 for the detection of Gleason ≥ 7 (4 + 3) prostate cancer
Serum	PHI	Loeb et al. [14]	Cohort	658	Among men aged 50 years and above, with PSA 2–10 ng/mL, PHI achieved an AUC of 0.707 for detection of Gleason ≥ 7 prostate cancer
Serum	PHI	Tan et al. [15]	Cohort	157	PHI performed well in Asian men with PSA 4–10 ng/mL, achieving an AUC of 0.794 for detecting prostate cancer
Urine	PCA3	Chevli et al. [18]	Cohort	3073	PCA3 was significantly better than PSA ($p < 0.01$) in predicting prostate cancer, with AUC 0.697 and 0.599, respectively, but not significantly better than PSA at detecting high-grade prostate cancer
Urine	PCA3	Wang et al. [19]	Cohort	500	PCA3 outperformed %fPSA (AUC 0.750 vs 0.622, respectively) in predicting prostate cancer in Chinese men with PSA 4–10 ng/mL
Urine	PCA3	Cui et al. [20]	Meta-analysis	12,295	PCA3 had had pooled sensitivity and specificity of 0.65 and 0.73, respectively, for detection of prostate cancer
Urine	HOXC6/DLX1	Van Neste et al. [22]	Cohort	905	The HOXC6/DLX1 achieved an AUC of 0.76 with sensitivity set at 91% for the detection of prostate cancer
Radiological imaging	mpMRI	Nam et al. [27]	Cohort	47	mpMRI performed better than PSA at predicting prostate cancer (AUC 0.81 vs 0.67, respectively)
Radiological imaging	mpMRI	Ahmed et al. [28]	Cohort	576	The sensitivity and specificity of mpMRI in detecting Gleason ≥ 7 (3 + 4) prostate cancer was 88% and 45%, respectively. About 27% could avoid a primary biopsy if triaging with mpMRI was performed
Radiological imaging	mpMRI	Kasivisvanathan et al. [30]	Randomized controlled trial	500	mpMRI with or without targeted biopsy performed better than standard biopsy approach with detection rate of clinically significant cancer at 38% vs 26%, respectively
Combination	STHLM3	Grönberg et al. [31]	Cohort	11,130 training cohort, 47,688 in validation cohort	The STHLM3 model outperformed PSA alone for the detection of Gleason ≥ 7 prostate cancer in men with PSA. The AUC for STHLM3 was 0.74 vs 0.56 for PSA alone
Combination	STHLM3	Nordstrom et al. [32]	Cohort	3133	Increasing the PSA threshold from 1.0 to 1.5 ng/mL for reflex testing with STHLM3 would reduce 18.3% tests but miss 1.3% Gleason ≥ 7 cancer. The subsequent STHLM3 cut-off to recommend biopsy could be adjusted to improve overall detection ability

Table 1 (continued)

Screening method	Name of screening tool	References	Study design	Number of patients, *N*	Key performance outcome of the screening tool
Novel combination	PHI + risk calculator	Roobol et al. [34]	Cohort	1185	In men who had no prior biopsy, the PHI-updated risk calculator achieved AUCs of 0.73 and 0.66 for prostate cancer and clinically relevant prostate cancer, respectively, but the enhancement in performance of the PHI-updated ERSPC models were small
Novel combination	PHI + risk calculator	Foley et al. [35]	Cohort	222	The addition of PHI to ERSPC-RC improved prediction of significant prostate cancer with AUC 0.78 vs 0.72 with ERSPC-RC alone
Novel combination	HOXC6/DLX1 + risk calculator	Van Neste et al. [22]	Cohort	905	Combining HOXC6/DLX1 with clinical risk parameters achieved an AUC of 0.90 for predicting high-grade prostate cancer
Novel combination	mpMRI + ERSPC-RC	Alberts et al. [36]	Cohort	504	Combining mpMRI with ERSPC-RC for biopsy-naïve men achieved AUC of 0.843 for detecting Gleason ≥ 7 (3 + 4) disease
Novel combination	mpMRI + STHLM3	Grönberg et al. [37]	Cohort	532	The combination of mpMRI + STHLM3 and performing targeted biopsy only in men with elevated risk as assessed by STHLM3 could decrease over-diagnosis of GG 1 cancers, reduced the number of biopsies, while preserving sensitivity in detecting GG ≥ 2 disease

PSA prostate-specific antigen, *AUC* area under the receiver operating characteristic curve, *4K* 4 kallikrein, *PHI* prostate health index, *PCA3* prostate cancer antigen 3, *%fPSA* percentage of free PSA, *mpMRI* multiparametric magnetic resonance imaging, *STHLM3* Stockholm-3 model, *ERSPC-RC* European Randomised Study of Screening for Prostate Cancer (ERSPC) risk calculator, *GG* grade group

It is paramount for the treating clinician to explore the risk tolerance, personal biases and competing risks of each patient before embarking on prostate cancer screening. Many advances have been made over simple PSA screening, but marginal benefit and long-term data are still lacking.

Authors' contribution GHT was involved in project development, data collection, data analysis and manuscript writing. GN analysed the data and wrote the manuscript. KA analysed the data and wrote the manuscript. DTSW analysed the data and wrote the manuscript. JHC analysed the data and wrote the manuscript. OA analysed the data and wrote the manuscript. NP was involved in project development, data collection, data analysis and manuscript writing.

Compliance with ethical standards

Conflict of interest No conflicts of interest.

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