Review

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Prostate cancer screening: Continued controversies and novel biomarker advancements

Atiyah Tidd-Johnson[a,b], Sneha Annie Sebastian[a,*], Edzel Lorraine Co[a], Munaza Afaq[a], Hansini Kochhar[a], Mona Sheikh[a], Arpit Mago[a], Sujan Poudel[a], John A. Fernandez[a,c], Ivan D. Rodriguez[a,d], Sanjay Razdan[a,e,f]

[a]Division of Research & Academic Affairs, Larkin Community Hospital, South Miami, FL, USA; [b]Department of Medicine, American University of Antigua College of Medicine, Coolidge, Antigua; [c]Department of Internal Medicine, Larkin Community Hospital, South Miami, FL, USA; [d]Department of Family Medicine, Larkin Community Hospital, South Miami, FL, USA; [e]Department of Urology, Larkin Palm Springs Hospital, South Miami, FL, USA; [f]Department of Urology, Larkin Community Hospital, South Miami, FL, USA

Abstract

Prostate cancer (PCa) screening remains one of the most controversial topics in clinical and public health. Despite being the second most common cancer in men worldwide, recommendations for screening using prostate-specific antigen (PSA) are unclear. Early detection and the resulting postscreening treatment lead to overdiagnosis and overtreatment of otherwise indolent cases. In addition, several unwanted harms are associated with PCa screening process. This literature review focuses on the limitations of PSA-specific PCa screening, reasons behind the screening controversy, and the novel biomarkers and advanced innovative methodologies that improve the limitations of traditional screening using PSA. With the verdict of whether or not to screen not yet unanimous, we hope to aid in resolution of the long-standing debate.

Keywords: Biopsy; Multiparametric magnetic resonance imaging; Liquid biopsy; Novel biomarkers; Prostate cancer; Prostate cancer screening; Prostate-specific antigen; Tumor markers

1. Introduction

Globally, prostate cancer (PCa) is the second most common cancer in men.[1] In 2020, the global incidence and mortality were approximately 1,414,259 and 375,304, respectively.[2] It is the most common nondermatologic cancer among American men, with 248,530 new cases and 34,130 fatalities in 2021.[3,4] With PCa affecting 1 of 8 men throughout their lifetime, it has significant clinical and public health implications.[3] The mortality rates of PCa are highest in sub-Saharan Africa, the Caribbean, and Micronesia/Polynesia.[5] Risk factors for PCa include advanced age, race, family history, and genetic risk loci.[6] The available data illustrate a 40-fold difference in age-adjusted incidence rates, with the highest rates observed in African American men in the United States and the lowest in Asian men living in their home countries.[6] The annual incidence rate of PCa among US African American men from 2014 to 2018 was 73% higher than that observed in White men.[7] Further, US Black men experience a PCa-specific mortality rate 2 times higher than that of White men.[7] With a positive family history, the possibility of developing PCa is associated with a relative risk of 2.0.[8] In addition, men who undergo routine prostate-specific antigen (PSA) screening and are first-degree relatives of those affected have a relative risk of 1.3 to 1.6.[8] Because risk factors for PCa are mainly nonmodifiable, the reduction of PCa morbidity and mortality is mainly attained via early detection and appropriate management.[6,8,9]

The PSA test is considered to be the standard screening tool for PCa detection. Screening via PSA results in 1 fewer PCa death for every 1000 screened men every 10 years.[10] This increases over time, with 9 fewer deaths per 1000 screened men when followed for the duration of their lives.[10] The observed differences in incidence and mortality rates between nations are attributed to the intensity of PSA screening.[6] However, screening via PSA has several drawbacks, including overdiagnosis and overtreatment of otherwise indolent cases, as well as the inability to accurately differentiate between low-risk and high-risk aggressive disease.[8,11,12]

Evidence of the benefits and harms associated with PSA screening is variable, and there is both a lack of definite guidelines and variation regarding screening recommendations among various organizations. However, such discussions are imperative for the advancement of individual and public health. This review article outlines the limitations of traditional PSA screening, reasons behind screening controversies, novel screening methods, and innovative modalities that may finally solve the controversies surrounding PCa screening.

2. Materials and methods

A thorough literature search of relevant articles was done using PubMed and Google Scholar databases, from inception to April 22, 2022, with the following keywords: "prostate-specific antigen," "prostate cancer screening," "PSA screening controversy," "novel biomarkers," liquid biopsy," and "mpMRI." We included clinical trials, observational studies, systematic reviews, and literature reviews written in the English language published in the last 2 decades that assessed the current updates in PCa screening and the

*Corresponding Author: Sneha Annie Sebastian, Division of Research & Academic Affairs, Larkin Community Hospital, 7031 SW 62nd Ave, South Miami, FL 33143, USA. E-mail address: snehaann1991@gmail.com (S. A. Sebastian).

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ongoing controversies of the PSA test as a screening tool. We excluded case reports and articles published in other languages.

3. Guidelines for prostate cancer screening

Recommendations for PCa screening vary based on the advising country and organization, mirroring the discord associated with PCa screening. Table 1 shows screening recommendations by country and organization.

4. Limitations in prostate cancer screening

4.1. Harm from screening

Data from a previous meta-analysis reported the pooled sensitivity, specificity, and positive predictive value for PSA in identifying PCa were 72.1%, 93.2%, and 25.1%, respectively.[20] Although it has been shown that men with PSA values <1 ng/mL still have a 10% chance of harboring clinical disease, 1 of 4 men with elevated PSA will be diagnosed with PCa.[21] The latter highlights a long-standing argument used to refute PSA screening, stating that elevated PSA levels can be observed in other conditions, including trauma, sexual intercourse, prostatitis, benign prostatic hyperplasia (BPH), and transurethral manipulation.[13,21,22] Additional arguments supported by data suggest that 10% to 56% of cancers detected by PSA screening would not have led to symptoms and are thus cases of overdiagnosis.[11] Furthermore, screening detects cases 5 to 12 years earlier, lengthening lead time and the duration of time during which men will experience negative effects of treatment.[11] Because PCa has a slow growth rate, men have approximately 15 years before they experience benefits from screening via PSA, complicating the debate regarding its worth.[20]

The subsequent screening methodology, the digital rectal examination (DRE), has been judged as inaccurate and subjective and with high interexaminer variability.[23] Not only does an accurate DRE require a competent, skilled examiner, but also various factors, including the length of the examiner's finger and the anatomic location of the gland, can limit palpation of the organ.[23,24] In Lass and Raveendran's[24] study, 33% of family medicine residents admitted that they had not received proper guidance regarding how to perform DRE. Similar to PSA screening, screening via DRE leads to unnecessary biopsy, overdiagnosis, and treatment, posing a risk for urinary incontinence and erectile dysfunction.[24,25] Owing to significant false-positive test results, the Canadian Task Force on Preventive Health Care paused their recommendation for PCa screening via DRE in 2014.[24] Of note, false-positive results from PSA and DRE are also associated with an increase in anxiety and worry in men, reminding us of the psychological effects of PCa screening.[26]

4.2. Harm from diagnosis

Transrectal ultrasound-guided biopsy (TRUS-B) is the initial diagnostic modality for PCa.[27] Similarly to the screening methods described previously, there are several limitations associated with its use. Anatomically, because of the use of the transrectal route, it is not possible to appropriately reach the transition zone or the anterior and apical prostate.[27–29] As such, TRUS-B fails to identify 20% to 30% of clinically significant tumors, thus producing a high degree of false-negative results, underdiagnosis, and

Table 1

Prostate cancer screening recommendations as of April 2022.

Organization	Recommendation
US Preventative Services Task Force	Men aged 55–69 yr: choice of periodic screening via PSA should be individual-specific with discussion of possible harms and benefits Men aged ≥70 yr: screening via PSA should not be done[13,14]
American Cancer Society	Asymptomatic men with life expectancy <10 yr, and men with average and high risk of developing PCa should be given information regarding the harms and benefits of screening to ensure informed decision and to guide their choice, at the following ages: • Average risk: age 50 yr • High risk (first-degree relative with PCa diagnosis age <65 yr, Black/African American): age 45 yr • Higher risk (>1 first-degree relative with PCa diagnosis at early age): age 40 yr[13,15]
American Urologic Association	PSA screening in men age <40 yr, should not be done PSA screening in men aged 40–54 yr with average risk, should not be done PSA screening in men age <55 yr with high risk, should be individual-specific Men aged 55–69 yr: the choice to undergo PSA screening should involve shared decision-making with consideration of the harms and benefits Men aged ≥70 yr or a life expectancy <10–15 yr: screening should not be done[13,16]
United Kingdom National Screening Committee	PCa screening is not recommended[17]
European Association of Urology	Men should be educated on the benefits and harms of PSA screening Once informed, PSA screening should be offered to men with an increased risk: • Men age >50 yr • Men age >45 yr with family history of PCa • Men age >45 yr and of African descent • Men age >40 yr with *BRCA2* mutations Men with a life expectancy of <15 yr should not be screened[18]
National Comprehensive Cancer Network	Baseline evaluation variables: family/individual cancer history, family/individual germline mutation, history of prostate disease, Black/African American, medications and environmental exposure Risk assessment tools: PSA, DRE Early detection evaluation: • Men aged 45–75 yr: average risk • Men aged 40–75 yr: Black/African American, germline mutations carrying risk of PCa, family history • Men aged >75 yr (select patients): only in healthy men with minimal/no concurrent comorbidity, in patients with increasing PSA levels or with no previous PSA screening[19]

DRE = digital rectal examination; PCa = prostate cancer; PSA = prostate-specific antigen.

undertreatment.[27,28,30] In contrast, in certain cases, TRUS-B overdiagnosed otherwise indolent disease.[27] In addition, TRUS-B cannot accurately characterize cancers as it underestimates tumor grade via the Gleason score.[27,30] It is also associated with potential adverse effects, including rectal bleeding, hematuria, hematospermia, and urinary retention.[31,32] Although men are prophylactically treated prebiopsy to prevent infection, the incidences of asymptomatic bacteriuria, urinary tract infection, epididymitis, prostatitis, sepsis, and meningitis are increasing due to fluoroquinolone resistance.[27,29,31] Finally, men commonly report pain, with 18% revealing unwillingness to repeat the procedure.[29]

4.3. Harm from treatment

Harm from treatment serves as an additional concern, as it affects not only men with clinically significant disease, but also those overdiagnosed because of the detection of otherwise indolent disease.[11,13] Radical prostatectomy (RP) can cause bowel and rectal injury.[33] External beam radiation therapy can cause ulceration, rectal bleeding, and cancers of the bladder and rectum.[33] Additional adverse effects such as urinary incontinence and impotence commonly result from RP and radiation therapy.[33] Heijnsdijk et al.[11] reported that 83% to 88% of men managed with RP and 42% to 66% of men managed with radiation therapy developed impotence postprocedure. Androgen deprivation therapy, the subsequent option in PCa treatment, is associated with gynecomastia, decreased bone mineral density, and a potential increase in total and low-density lipoprotein cholesterol, triglyceride, and fasting insulin levels.[33]

4.4. Mortality, survival, and gain of life years

Irrespective of management decisions, including active surveillance, PCa has a low mortality rate.[34] The most recent US-specific data report a 96.8% 5-year relative survival rate.[35] When stratified by tumor stage, the 5-year relative survival rate for localized PCa is 100%.[35] It may be easier to understand the limitations of PCa screening by comparing it with screenings for other pathologies. Whereas breast cancer screening causes an 8% reduction in life-years gained because of quality-of-life consequences, there is an estimated 23% decrease in life-years gained because of loss in quality of life due to adverse effects of treatment as a result of PCa screening.[11]

5. Reasons for controversy in prostate cancer screening

The use of PSA as a PCa screening method remains controversial.[36] Based on the findings in the reviewed literature, uncertainty is one of the reasons for this dispute.[36] Han and colleagues[37] taxonomy of uncertainty, a guideline used to describe uncertainty, classifies it into sources, issues, and loci of uncertainty. The taxonomy was used in a study by Pickles et al.[36] to outline uncertainties that providers had regarding PCa screening. Incorporating Han and colleagues sources of uncertainty, their results demonstrated that general practitioners concerns included uncertainty in predicting the probability that a patient will experience adverse effects from PSA screening (probabilistic uncertainty), uncertainties regarding the psychosocial impact that men face in light of PSA results and possible treatment (ambiguity), and uncertainties regarding which men should undergo PSA screening (complexity).[36] Issues of uncertainty, including scientific, practical, and personal uncertainty, were also assessed.[36] General practitioners were uncertain about the benefits and harms associated with PSA screening and making decisions regarding treatment for patients (scientific uncertainty) and found it difficult to communicate information regarding probability with certain patients (ie, patients who lack health literacy) (practical uncertainty).[36] Clinicians also expressed their own uncertainties regarding whether they should provide PSA testing and how it affects them professionally (personal uncertainty).[36]

The lack of definite guidelines regarding screening follow-up is a subsequent factor contributing to the debate on PCa screening.[38] Although men with PSA values greater than 10 ng/mL are usually given immediate urological referral, when PSA values fall between 4 and 10 ng/mL, there are no concrete recommendations for follow-up.[38] In addition, studies have shown that there is no PSA cutoff value with high sensitivity and specificity for PCa detection, making it difficult to assure patients with PSA levels <4 ng/mL that their risk is low.[38] Data revealed that among men with PSA <4 ng/mL in the Prostate Cancer Prevention Trial (PCPT), 15.2% had PCa, 14.9% of whom had a Gleason score of ≥7.[39]

Low-risk tumors that would not have been detected clinically or that result in mortality without screening are considered overdiagnosed cases.[6,11,40] Overdiagnosis and overtreatment, wherein men with indolent disease receive aggressive treatment and face unnecessary adverse effects, are additional arguments associated with the PSA screening controversy.[13,40] Findings suggest the extent of overdiagnosis of PCa ranges from 1.7% to 67%, whereas overtreatment varies widely.[40]

6. Beyond prostate-specific antigen: Improvements in screening and imaging

6.1. Novel biomarkers as diagnostic and prognostic indicators

Novel biomarkers, garnering a new field of "liquid biopsy," are innovative methodologies aimed at improving the detection and prognosis of PCa.[41] Together, improved sensitivity and specificity of screening entities, enhanced ability to distinguish cancer from benign pathology, and standardization of the DRE are improvements that advance the screening phase of PCa detection.[20]

6.1.1. Serum biomarkers Prostate-specific antigen exists in various forms, 10% to 30% free as proenzyme PSA (pro-PSA), benign prostatic hyperplasia-associated prostatic-specific antigen, and intact PSA, and 70% to 90% as a serum complex with serum protease inhibitors.[42] Several tests incorporating these biomarkers have been developed to reduce unnecessary biopsy, overdiagnosis, and unwarranted treatment, while improving the specificity of tumor detection.[21,42,43]

Percent free PSA (%fPSA), the ratio of free PSA (fPSA) to total PSA (tPSA), is one of the first tests introduced to meet these requirements.[42] It relies on the fact that men with PCa have reduced levels of %fPSA.[42] One study demonstrated that at a 25% cutoff threshold, 95% of clinically significant tumors were identified, and 20% of unnecessary biopsies were avoided.[19,42] The National Academy of Clinical Biochemistry indicates that %fPSA can be used to differentiate BPH from PCa when DRE is negative and total serum PSA levels are between 4 and 10 μg/L.[42] Percent fPSA has Food and Drug Administration (FDA) approval for PCa detection in men 50 years or older with PSA between 4 and 10 ng/mL and normal DRE.[19]

Prostate-specific antigen density (PSAD) can also be used to differentiate BPH from PCa.[19] Modifying the PSA value based on prostate size, PSAD is defined as the PSA level in nanograms per milliliter, divided by prostate volume in cc, the latter estimated by TRUS-B.[19,44] Lower PSAD values correlate with BPH.[19] Prostate-specific antigen density has shown better detection of PCa than PSA in the range of 4 to 10 ng/mL, as well as when PSA levels are >10 ng/mL.[44] Its predictive accuracy for PCa detection has also been reported to be better than that of PSA in men with a previously negative biopsy.[44] Despite this, PSAD is not included in screening guidelines, as the measurement of PSA and prostatic volume via TRUS-B is not precise.[19,45]

Approved by the United States in 2012 for use in men with PSA values between 4 and 10 ng/mL, the Prostate Health Index (PHI) considers tPSA, fPSA, and [−2]pro-PSA.[46] Applying the formula ([−2]pro-PSA/fPSA) × √PSA, the PHI allows for the prognosis of clinically significant PCa prebiopsy.[46] Studies indicate that PHI is better at detecting cancer in biopsies than fPSA and tPSA.[41,46] In addition, it has been found to prevent 40% of biopsies at a cutoff value ≥25, can be used with active surveillance for the progression of disease, and increases the predictive value of multiparametric magnetic resonance imaging (mpMRI).[21,42] The PHI has also shown high accuracy in detecting aggressive high-grade disease.[42] It can assist in decisions for initial or repeat biopsy and can be used in men with an increased risk of PCa, specifically African American men, those with a positive family history, and those who are obese.[46] Unfortunately, at a cutoff value of 25, it was found that 5% of high-grade tumors are undetected.[21]

The 4Kscore (Prostate-Specific Kallikrein) consists of an algorithm that evaluates 4 serum biomarkers (tPSA, fPSA, intact PSA, and human kallikrein 2), age, DRE, and prior biopsies to analyze the risk of high-grade PCa on biopsy.[21] In the ProtecT trial, the panel had an area under the curve (AUC) of 0.820 for high-grade cancer compared with 0.799 and 0.738 for %fPSA and PSA, respectively.[46] Although it neglects the detection of 2.4% of high-grade cancers at a cutoff of 9%, the 4Kscore test permits the diagnosis of early-stage disease, prevents 43% of unnecessary biopsies, and predicts the risk for aggressive PCa in the succeeding 20 years.[21,41] It can be used when considering initial and repeat biopsies in men with increased PSA levels or abnormal DREs and is recommended for use in men with a positive genetic family history.[41] The 4Kscore can also be used to aid in treatment decisions in patients with clinically significant PCa.[41]

6.1.2. Urine biomarkers Prostate cancer antigen 3 (*PCA3*) is a long noncoding RNA specific to the prostate.[21,42] Progensa *PCA3*, approved as a test by the FDA in 2012, assesses the ratio of *PCA3* messenger RNA (mRNA) to PSA mRNA in urine during DRE.[21,42] It can be used in decisions regarding repeat biopsies after an initial negative result.[21] Similar to the PHI and 4Kscore, *PCA3* leads to a decrease in unnecessary biopsies, thereby reducing costs; however, it can miss clinically significant high-grade disease with low *PCA3* values.[21,22]

SelectMDx is a reverse transcription polymerase chain reaction (PCR) gene expression assay that detects *HOXC6* and *DLX1*, both genes associated with PCa aggressiveness.[19] It includes information regarding age, PSA, PSAD, DRE, previous biopsies, and family history, as well as the mRNA levels of *HOXC6* and *DLX1* in urine following DRE, to identify PCa and predict the risk of high-grade tumors.[21,46] Data suggest that 53% of unnecessary biopsies are prevented with the use of SelectMDx.[21] Recommendations from 2018 made by the European Association of Urology stated that urinary *HOXC6* and *DLX1* testing can be used to assess the prebiopsy risk in men with PSA between 2 and 10 ng/mL and a normal DRE.[47]

The ExoDx Prostate IntelliScore assesses the risk of high-grade PCa grade group ≥2 by quantifying urine exosomal RNA expressing the *SPDEF*-, *ERG*-, and *PCA3*-associated PCa genes.[21,46] Its uniqueness lies in that a DRE does not need to be conducted concurrently.[46] It can be combined with other tools, including mpMRI and risk calculators.[21] Its use prevents 27% of unnecessary biopsies.[21] The National Comprehensive Cancer Network (NCCN) recommends it for men considering initial and repeat biopsies.[19]

6.1.3. Tissue biomarkers ConfirmMDx is a PCR assay that detects epigenetic changes in cancerous lesions and surrounding tissues.[21,22] Specifically, it assesses DNA methylation intensity in the promoter regions of the *APC, RASSF1*, and *GSTP1* genes.[21,43] By assessing DNA methylation intensity, this modality can better stratify patient risk than PSA and other risk calculators.[21] Although not FDA approved, the NCCN guidelines state that ConfirmMDx can be used in patients considering repeat biopsy, as it was given limited coverage to decrease unnecessary repeat biopsies in this group.[19] Table 2 summarizes the various serum, urine, and tissue biomarkers used when deciding whether to perform a biopsy.

6.2. Biomarkers as prognostic indicators

Several prognostic assays are available for the management of men with confirmed PCa. In patients with Gleason scores of 3 + 3 and 3 + 4, the promark test calculates tumor aggressiveness, unfavorable pathology during RP, and whether the tumor can be managed with or without aggressive treatment.[21] Prolaris is a reverse transcription PCR assay that evaluates the RNA expression of 31 genes involved in cell cycle progression.[21,22] It aids in stratifying tumor risk and clinical decision-making regarding treatment and active surveillance.[21] Although assays using tissue biomarkers are expensive, the NCCN has recommended the use of Prolaris and Promark, as well as Decipher and Oncotype DX, 2 additional assays, in men with low- or intermediate-risk disease for risk stratification.[42] Table 3 summarizes the aforementioned prognostic biomarkers.

6.3. The improved digital rectal examination

Recognizing that part of the difficulty in performing the DRE lies in the fact that there is a lack of visualization, a recent study added an augmented reality system allowing for imaging during the procedure.[64] Data from the study demonstrated that most users found the ability to visualize the finger (mean, 4.1 [SD, 1.1]) and organs useful (mean, 4.6 [SD, 0.8]) for learning and assessment purposes.[64]

6.4. Risk predicting models

The decision to perform a biopsy does not have a standardized approach. Instead, a multivariable approach that includes the use of nomograms and risk calculators is increasingly being considered for aiding in PCa prediction and subsequent decision-making regarding biopsy.[46] Risk calculators use biomarkers and clinical variables (age, race, PSA level, DRE, family history, prior biopsy results, etc) to determine PCa risk and the decision to perform a biopsy.[19,65] Beyond their use in decision-making, risk calculators lead to a decrease in unnecessary procedures, thereby improving the utilization of medical resources.[65]

The European Randomized Study of Screening for Prostate Cancer (ERSPC) developed the ERSPC risk calculator.[46] Various versions are available online that are specific to patients and clinical practitioners.[46] The PCPT risk calculator developed according to the findings from the trial of the same name includes the novel marker T2:ERG.[46,65] The Stockholm-3 Model risk calculator incorporates data from several biomarkers, including human kallikrein 2, microseminoprotein β, and macrophage inhibitory cytokine 1, as well as individual clinical variables and 232 single-enucleotide polymorphisms.[47,57] It was found to decrease unnecessary biopsies by 32% (95% confidence interval, 24%–39%).[47,57]

An additional risk calculator, the Cancer of the Prostate Risk Assessment (CAPRA) score, utilizes 5 preoperative variables: age at diagnosis, PSA, percentage of positive prostate biopsies, Gleason score, and clinical T stage for predicting PCa recurrence following RP.[66] The CAPRA score was the first to predict the risk of metastases, cancer-specific mortality, and all-cause mortality.[67,68] Studies have demonstrated that its accuracy ranges from 0.66 to 0.81.[68]

Table 2

Novel biomarkers for clinical decision prebiopsy.

Sample	Assessment	Biomarker	Biopsy indication	Predication performance	Indication/advantage	Limitation
Serum	PSA	PSA	Initial, repeat[41]	AUC for detection of PCa: 0.53[48] Sensitivity (meta-analysis): 72.1%[20] Specificity (meta-analysis): 93.2%[20] Sensitivity: 59%, 44%, 33% at a cutoff of 3, 4, 5 ng/mL[49] Specificity: 87%, 92%, 95% at a cutoff of 3, 4, 5 ng/mL[49]	Risk stratification[41] Monitor disease[41] Treatment surveillance[21]	Low sensitivity, low specificity, low positive predictive value, unnecessary biopsy, detects low-risk disease[41,50]
	Percent fPSA	PSA, fPSA	Initial, repeat[19,48]	AUC for detection of PCa: 0.72[48] Sensitivity: 95% at a cutoff of 25%[48] Specificity: 20% at a cutoff of 25%[48]	Helpful in men with PSA levels in "diagnostic gray zone," negative DRE, prior biopsy[19]	Inconsistencies in determining appropriate cutoff value[42] Samples indicated for %fPSA require proper refrigeration or freezing[42]
	PHI	PSA, fPSA, -2ProPSA	Initial, repeat[41]	AUC for detection of PCa: 0.76[51] Sensitivity: 90%[52] Specificity: 46.7%[52]	Least expensive commercially available test[53]	-
	4Kscore	PSA, fPSA, iPSA, hK2	Initial, repeat[21]	AUC for detection of PCa: 0.88[54] Sensitivity: 74%[55] Specificity: 60%[55]	The risk of occurrence of PCa and aggressive PCa in the succeeding 20 yr[21] Suggested for men with genetic family history[41]	Cannot be used in men using 5α-reductase inhibitors, in men who received treatment or procedure for BPH, or 96 hr post-DRE[56]
	STHLM3	PSA, fPSA, iPSA, hK2, MSMB, MIC-1, 232 SNPs	Initial[41]	AUC for detection of PCa Gleason score ≥7 = 0.74[57]	Good for detection of aggressive cancers at PSA levels 1.5–3 ng/mL[41]	Cannot be used in men previously diagnosed with PCa, previously treated for PCa, or in the follow-up after PCa[41] Assessment only tested in one population - Stockholm County, Sweden[41]
Urine	Progensa *PCA3*	*PCA3* lncRNA, PSA mRNA	Repeat[41]	AUC for detection of PCa: 0.73[58] Sensitivity: 52%[59] Specificity: 87%[59]	Per FDA recommendations, suggested in men aged ≥50 yr during decisions regarding repeat biopsy in those with previously negative biopsies[41]	Inconsistencies in determining appropriate cutoff value[41] Risk of failing to detect high-grade PCa when *PCA3* low[21]
	SelectMDX	*HOXC6* mRNA, *DLX1* mRNA, PSAD	Initial[41]	AUC for detection of PCa: 0.82[60] Sensitivity: 89%[60] Specificity: 53%[60]	Tumor aggressiveness/predicts risk of high-grade PCa[21,42] EAU recommendations suggest its use in asymptomatic men, PSA 2–10 ng/mL, normal DRE[47]	No determined cutoff values[41] No evidence for its use in Asian or African American populations[41]
	EPI	Exosome mRNA *ERG*, *SPDEF*, *PCA3*	Initial, repeat[41]	AUC for predicting grade group ≥2 PCa = 0.66[61] Sensitivity: 82.1%[61] Specificity: 26.9%[61]	Predicts risk of high-grade PCa (grade group ≥2)[21] Recommended for differentiating benign vs. high-grade disease in men aged ≥50 yr with PSA levels 2–10 ng/mL[41] Can be completed at home by the patient[41]	No determined cutoff values[41]
	MiPS	*PCA3* mRNA, *TMPRSS2*: *ERG* mRNA, PSA	Initial, repeat[41]	AUC for detection of PCa: 0.88[62] Sensitivity: 80%[62] Specificity: 90%[62]	Predicts the risk of high-grade PCa (Gleason score >7)[41]	NCCN guidelines currently classify this tool as investigational[19] No determined cutoff values[41,56]
Tissue	ConfirmMDx	Hyper-methylation *GSTP1*, *APC*, *RASSF1* genes, PSA	Repeat[41]	Sensitivity: 74.1%[63] Specificity: 60.0%[63]	Detects men at increased risk of PCa on repeat biopsies - used for deciding on repeat biopsies in patients with previously negative biopsies and high clinical suspicion[19]	Not FDA approved, MolDx approval with limited coverage[19]

APC = advanced prostate cancer; AUC = area under the curve; DLX1 = distal-less homeobox 1; DRE = digital rectal exam ination; EAU = European Association of Urology; EPI = ExoDx Prostate IntelliScore; ERG = erythroblast transformation-specific-related gene; FDA = Food and Drug Administration; fPSA = free PSA; GSTP1 = glutathione S-transferase Pi 1; hK2 = human kallikrein 2; HOXC6 = homeobox C6; iPSA = intact PSA; lncRNA = long noncoding ribonucleic acid; MDX = molecular diagnostic assays; MIC-1 = macrophage inhibitory cytokine 1; MiPS = My Prostate Score; MolDx = Molecular diagnostics; mRNA = messenger RNA; MSMB = microseminoprotein β; NCCN = National Comprehensive Cancer Network; PCa = prostate cancer; *PCA3* = prostate cancer antigen 3; PHI = Prostate Health Index; PSA = prostate-specific antigen; PSAD = PSA density; RASSF1 = Ras-association domain family 1; SNP = single nucleotide polymorphism; SPDEF = SAM pointed domain-containing ETS transcription factor; STHLM3 = Stockholm 3; TMPRRS2 = transmembrane protease, serine 2; 4Kscore = 4 Kallikreins ((total PSA, free PSA, intact PSA and human kallikrein-2) score.

Table 3

Novel biomarkers as prognostic indicators postbiopsy.

Sample	Assessment	Type	Indication
Tissue	Decipher	mRNA expression of 22 genes[56]	Indicated for men with adverse pathology post RP[56] Guide management for surveillance vs. radiation post-RP[56] Assess risk of metastases and PCa mortality after RP[21,56]
	Oncotype DX	mRNA expression of 17 genes[42]	Indicated for men with very low-, low-, and low- to intermediate-risk pathology[21,56] Assess tumor aggressiveness[21,42] Risk stratification, treatment decisions[56]
	Prolaris	mRNA expression of 31 genes[56]	Indicated for men with very low- and low-risk pathology[56] Assess tumor aggressiveness and recurrence[21,42,56] Guide management for surgery vs. radiation vs. active surveillance[56]
	ProMark Test	8 proteins[56]	Predicts tumor aggressiveness in men with Gleason score of 3 + 3 and 3 + 4[21,42]

mRNA = messenger ribonucleic acid; PCa = prostate cancer; RP = radical prostatectomy.

Subsequently, a postoperative analog of the CAPRA score was developed to enhance the prediction of PCa recurrence post-RP.[69] The CAPRA postsurgical score considers preoperative PSA, Gleason score, surgical margins, extracapsular extension, seminal vesicle invasion, and lymph node involvement.[69] This score is highly accurate in predicting recurrence and mortality after surgery.[70]

Nomograms with many of the aforementioned biomarkers and clinical variables can be combined to predict PCa and aid in personalized decision-making regarding biopsy.[46] According to Bandala-Jacques et al.,[65] risk calculators are most useful when applied to the populations for which they are specifically created.

6.5. Improved imaging techniques

To address the limitations of the traditional TRUS-B, advanced imaging modalities have been developed and used for PCa detection. Multiparametric MRI uses T2-weighted imaging data, diffusion-weighted imaging, and dynamic contrast enhancement to detect prostate pathologies.[47] The NCCN recommends prebiopsy mpMRI, that is, mpMRI before TRUS-B, to detect regions of concern and aid in deciding whether to perform a biopsy.[19] Multiparametric MRI is also currently recommended in men with an initially negative biopsy, in which high clinical suspicion of disease remains and for guidance during targeted biopsy.[53,71] Findings suggest that mpMRI decreases the number of unnecessary biopsies, and in men with positive MRIs, it decreases the overdiagnosis of indolent cancers by reducing the number of biopsy cores.[71] It has also improved the detection and grade characterization of clinically significant tumors.[19,71] It is important to note that mpMRI produces both false-positive and false-negative results.[19,53] Emphasizing the importance of the multiparametric approach to decision-making regarding biopsy, mpMRI is now being combined with biomarkers and risk calculators, including PHI, 4Kscore, PCPT, and ERSPC.[53]

6.6. Improved diagnostic biopsy techniques

Highly specialized biopsy techniques, including targeted biopsy, transperineal template biopsy, and saturation biopsy, have been developed and used to improve diagnostic accuracy in the detection of PCa.[43] Advanced biopsy techniques meet the goal of reducing overdiagnosis of otherwise indolent disease and can be used after a primary negative biopsy with a high clinical suspicion of cancer.[27,43]

Targeted MRI-guided prostate biopsy is an imaging-targeted method that combines ultrasonography and/or MRI during biopsy acquisition.[43,72] It includes several application options, including MRI/TRUS fusion biopsy, MRI-guided in-bore biopsy, and cognitive fusion biopsy, which uses ultrasound-guided MRI imaging.[43,72] Each targeted technique has demonstrated the ability to identify more cases of disease and fewer cases of indolent cancers.[72] These techniques can be used in repeat biopsies with continued cancer concern and in men identified with Prostate Imaging-Reporting and Data System (PI-RADS) 3 (intermediate), PI-RADS 4 (high), or PI-RADS 5 (very high) lesions on mpMRI.[19,72] Research has shown that mpMRI with subsequent targeted biopsy demonstrated decreased detection of low-risk indolent disease and increased identification of high-risk disease.[19,43]

Transperineal prostate biopsy more accurately detects cancers in the apical and anterior prostate, whereas the perineal approach drastically decreases fever, infection, and sepsis compared with transrectal prostate biopsy.[28] Transperineal template-guided mapping biopsy (TTMB), a meticulous transperineal version of TRUS-B, obtains biopsies from individual holes in a 5-mm brachytherapy grid throughout the prostate.[27] Data suggest a cancer detection rate of 75.9% during initial biopsy and 55.5% and 41.7% after 1 and 2 previously negative biopsies via TTMB, respectively.[28] To compare, traditional TRUS-B has a 20% to 35% cancer detection rate.[27] Compared with standard TRUS-B, TTMB is more expensive and requires general anesthesia, which contributes to its cost.[28,30] Transperineal template-guided mapping biopsy also has a higher incidence of urinary retention.[27] Transperineal template-guided mapping biopsy can be used after a negative TRUS-B with high clinical suspicion, for active surveillance, and for focal therapy.[27]

Saturation biopsies, which can be performed transrectally or transperineally, obtain cores through the entire prostate gland, each separated by a few millimeters, thereby improving detection.[43] Cancer detection rates of transperineal saturation biopsies vary based on the number of cores obtained.[28] One limitation of this method is that the number of biopsy cores is a topic of debate.[73] In addition, the incidence of urinary retention was reported to be 10% to 39%.[73] Transperineal saturation biopsies may be considered after a negative transrectal prostate biopsy and continued suspicion of disease.[28]

All advanced biopsy modalities mentioned have the disadvantage of high cost.[28]

6.7. Updated screening guidelines

6.7.1. High-risk groups In the recent NCCN guidelines, the effort of improving PCa outcomes was continued. Importantly, recommendations were included regarding risk assessment targeting men who would most benefit from early detection of clinically significant disease. To this extent, the guidelines provide a comprehensive definition of family history, including first-degree or second-degree relative(s) with metastatic PCa, male breast cancer, female breast cancer in women 45 years or younger, ovarian or

pancreatic cancer, and colorectal or endometrial cancer at 50 years or younger.[19] Family history also includes ≥2 first-degree or second-degree relative(s) with any of the following cancers at any age: prostate (excluding those localized to grade group 1), colorectal, breast, and endometrial.[19] Men younger than 60 years with family history or mortality due to PCa (excluding those localized to grade group 1) should contemplate shared decisions regarding screening via PSA 10 years earlier than the age of their relative's diagnosis.[19] Those with a personal or family history of inherited genetic mutations that increase PCa risk, including *BRCA1*, *BRCA2*, *HOXB13*, *ATM*, *MLH1*, *MSH2*, *MSH6*, and *PMS2*, may engage in shared decision-making to begin annual PSA screening at age 40 years and should consult with a cancer genetic specialist.[19]*BRCA2* carriers should be screened for PCa at 40 years of age.[19] Additional NCCN guidelines state that other baseline evaluation variables include history of prostate disease, early detection of cancer, use of 5α-reductase inhibitors, environmental exposure, and men who are Black or African American.[19] Black/African American men should contemplate shared decisions regarding annual PSA screening beginning at the age of 40 years.[19] All aforementioned groups should undergo risk assessment for PCa screening with a baseline PSA test and possible DRE.[19]

6.7.2. Age-adjusted prostate-specific antigen, repeat prostate-specific antigen, and prostate-specific antigen density Recent NCCN guidelines also provide details regarding age-adjusted PSA, timing of repeat PSA, and the role of PSAD with a cutoff of 0.15. In men aged 45 to 75 years or those 40 to 75 years with PCa-associated mutations or family history or who are Black/African American, repeat testing is recommended at 2- to 4-year intervals if PSA is <1 ng/mL and at 1- to 2-year intervals if PSA is 1 to 3 ng/mL.[19] Men with PSA >3 ng/mL, or abnormal findings on DRE, can undergo repeat PSA testing or evaluation with mpMRI or more specific biomarkers to assess the need for biopsy.[19] Men aged >75 years should be screened only if there is minimal to no concurrent comorbidity, an increase in PSA level, or no previous PSA testing.[19] In this specific group, repeat testing can be done at 1- to 4-year intervals if the PSA level is <4 ng/mL.[19] Repeat PSA or evaluation with mpMRI or more specific biomarkers can be considered for assessing the need for biopsy if PSA is ≥4 ng/mL or if the DRE is abnormal.[19]

Finally, the NCCN guidelines mention cutoffs for PSAD. Specifically, they highlight that a PSAD cutoff of 0.15 ng/mL was successful in preventing unwarranted biopsies in 50% of men.[19] The NCCN believes that this specific biomarker can be used when applicable, particularly in men with prostate volume previously measured by ultrasound.[19]

6.8. Consequences from the deterrence of prostate-specific antigen screening: The benefits of screening

To improve guidelines regarding PCa screening in the future, the consequences of prior recommendations must be reviewed. Issuing a grade D recommendation, in 2012 the US Preventive Services Taskforce (USPSTF) recommended against PSA-specific PCa screening for men of all ages.[74] The outcome was an increase in incidence of metastatic disease in men aged 50 to 74 years and 75 years or older from 2010 to 2015.[75] Although the incidence of localized disease, mainly low-risk tumors, decreased during this period, it came at the expense of an increase in the incidence of aggressive and potentially difficult-to-cure metastatic disease.[75]

To justify their recommendations, the USPSTF included data from the ERSPC and the Prostate, Lung, Colorectal, and Ovarian (PLCO) trials, which evaluated the effects of PSA screening on mortality.[74] At the primary follow-up at 9 years, results of the ERSPC demonstrated that although screening via PSA led to a 20% reduction in PCa-specific mortality, it was coupled with overdiagnosis.[76] In contrast, results from the PLCO trial at the 7- to 10-year and the 13-year follow-ups reported that mortality due to PCa did not significantly differ among men who received annual screening versus "usual care" controls.[77,78] As such, they concluded that screening provides no mortality benefit.[74,77,78]

At present, there are several limitations to both trials with arguments against their initial findings. Analysis demonstrated that both before and during the PLCO trial, >90% of men in the "usual care" control received PSA screening.[46] In addition, there was a lack of compliance for confirmatory biopsies in men who met a PSA cutoff of >4 ng/mL.[42,46] It was also observed that there were inconsistent screening approaches among the 8 European countries that contributed data to the ERSPC trial.[42]

Tsodikov et al.[79] ameliorated the limitations of both trials in their own study and found that at the 11-year follow-up, screening via PSA resulted in a 25% to 31% and 27% to 32% lower risk of PCa-specific death in the ERSPC and PLCO trials, respectively.[42,79] Moreover, at the 13-year follow-up, results of the ERSPC trial continued to demonstrate a 21% decrease in PCa mortality attributable to PSA screening.[80] The ERSPC's recent 16-year follow-up further showed that there was an increase in benefit as the duration of the follow-up progressed.[81] Although the grade D recommendation is still in place for men 70 years or older, the USPSTF has since altered its stance, adopting an individualized, informed approach to PSA screening in men aged 55 to 69 years.[13,14] However, there is still debate as to whether their recommendations were built on flawed data, because in practice, we see that screening via PSA is beneficial.[74,80,81]

6.9. Prostate-specific antigen trend analysis

It is important to note that PSA trends, as opposed to a single PSA measurement, enhance the usefulness of PCa screening.[82] As such, urologists may use PSA trend analysis versus single PSA measurements.[82] The importance of this can be seen in the Cluster Randomized Trial of PSA Testing for Prostate Cancer, which assessed the effect of PSA screening on PCa-specific mortality.[42] Although the trial found no advantages to screening, further investigation revealed that the study used a single PSA measurement.[42] When subsequent researchers accounted for this, results depicted that men with a minimum of 2 PSA measurements had a 48% reduction in PCa-specific mortality versus a 25% reduction in men with a single PSA measurement.[81] Several PSA trend variables, which investigators in a recent study identified as a PSA increase from baseline, low PSA variability, and numerous PSA tests over time, were shown to sufficiently predict the likelihood of PCa on biopsy.[82] Taken together, it is proposed that, following baseline PSA, eligible men can undergo annual PSA testing in PSA trend analysis to aid in further clinical decision-making.[82]

7. Implications for the future

In addition to the aforementioned biomarkers available, recent studies have investigated promising noninvasive biomarkers for use in PCa management. Guo et al.[12] recently conducted 2 studies, one prospective and one retrospective, evaluating their 14-gene panel urine test. Researchers have aimed to assess the panel's ability to noninvasively improve disease risk stratification to guide treatment decisions.[12] Their assay measured the mRNA expression of *ANXA3*, *CCND1*, *CDK1*, *CST3*, *EZH2*, *GOLM1*, *GSTP1*, *LMTK2*, *PCA3*, *PIP5K1A*, *PMP22*, *PTEN*, *TMPRSS2*, and *VEGFA* in urine prebiopsy.[12] The 14-gene panel urine test demonstrated high diagnostic accuracy in the ability to distinguish between

low-risk and high-risk disease. This has resulted in the need for active surveillance relative to treatment in both the prospective and retrospective studies (AUC, 0.897 and 0.899, respectively) versus serum PSA and Gleason score (AUC, 0.821 and 0.860, respectively).[12] Similar to other novel biomarkers currently in clinical use, their findings highlight the significance of noninvasive "liquid biopsy" in decreasing overdiagnosis, overtreatment, and adverse effects from unnecessary treatment.[12] The Prostarix Risk Test, which measures sarcosine, alanine, glycine, and glutamate, as well as micro-RNA, long noncoding RNA, and exosome-based tests, are currently under investigation for improved PCa screening.[21]

Noninvasive detection of circulating tumor cells (CTCs) serves as an additional biomarker for PCa detection and management.[50] Researchers combined the Isolation-by-SizE-of-Tumor-Cells (ISET®)-CTC blood test, which confirms the presence of CTCs, with immunocytochemistry and prostate-specific markers to assess the accuracy of early detection of PCa.[50] Ultimately, researchers concluded that the combination of the ISET®-CTC and the immunocytochemistry-PSA-marker can replace PSA in PCa screening as it produces a 97% sensitivity, 99% specificity, 99% positive predictive value, and 97% negative predictive value.[50] This combination was also found to be helpful for surveillance.[50] Additional research evaluating CTCs for use as a biomarker in metastatic castration-resistant PCa is also underway.[21]

Network medicine, which views disease as a "network of interconnected molecules and pathways," has also been proposed to overcome PCa screening limitations.[9] Permitting discourse between clinicians and data analysts, this innovative field aims to combine information from body fluid and tissue samples, mpMRI, and gene profiles to decrease unnecessary biopsies and guide prognosis and treatment. Permitting discourse between clinicians and data analysts, this innovative field aims to combine information from body fluid and tissue samples, mpMRI, and gene profiles to decrease unnecessary biopsy, guide prognosis and treatment and further research in the advancement of biomarkers and therapeutics.[9] It is anticipated that individualized screening, patient communication, and informed consent will serve as the standard recommendations for PCa screening guidelines in the future.[42]

Finally, despite their high cost, innovative risk-prediction models composed of risk calculators and clinical parameters are continuously being developed.[47] As such, pioneering combinations of novel biomarkers, mpMRI, and risk-predicting models will together meet the goal of improving the limitations of screening via PSA.[47]

8. Conclusions

Prostate-specific antigen screening has helped in the early detection of PCa at a desirable stage, during which interventions reduce morbidity and mortality. However, the chance of overdiagnosis and overtreatment remains. Careful patient selection for screening and reducing aggressive treatment for indolent cases may reduce the potential harms associated with PSA screening. Definite PSA follow-up guidelines may also help solve the issues surrounding PCa screening. Therefore, definite screening guidelines must be developed to overcome the drawbacks of screening via PSA, thereby improving quality of life. As a final point, there is a continued need for scientific research on novel technologies that can improve the diagnostic sensitivity and specificity of screening methods for PCa detection without posing additional health or financial risks to patients.

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AT-J: Participated in data analysis;
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