REVIEWS IN UROLOGY

Methods for Prostate Cancer Risk Stratification: Serum-Based and Urine-Based Biomarkers for Biopsy Consideration

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Abstract

Background: Prostate cancer (PCa) is one of the most commonly occurring cancers in men globally. In 2024, it is estimated that there will be 99 010 PCa diagnoses and 35 250 PCa-related deaths in American patients. Given the high incidence and virulence of the disease, proper screening methods are crucial to reduce overdiagnosis and overtreatment of PCa. Using biomarkers with high tumor sensitivity and specificity is therefore crucial to effectively distinguish PCa from benign tissue.

Methods: A MEDLINE search was conducted using manuscripts from 1979 to 2023. All publications were assessed based on their relationship to screening methods used for PCa diagnostics.

Results: Prostate-specific antigen has been the clinical standard for PCa screening, but its low tumor specificity contributes to PCa overdiagnosis and unnecessary prostate biopsies. Novel serum-based and urine-based biomarkers have revolutionized PCa detection through accurate PCa risk, staging, and aggressiveness stratification. In this review, we discuss the currently used biomarkers for PCa diagnostics and their clinical effectiveness in comparison with traditional screening methods. The benefits of multiparametric imaging techniques are also included to highlight how imaging can augment biomarkers in PCa risk determination.

Conclusion: This review summarizes the clinical effectiveness of serum-based and urine-based PCa diagnostic biomarkers. Though current biomarkers have improved PCa detection, more research in a randomized trial setting is warranted to further stratify which patients should proceed with prostate biopsy.

Introduction

Prostate cancer (PCa) is the second-most commonly occurring cancer in men worldwide and the fourth-most common cancer overall.[1] Globally in 2020, there were estimated to be 1 414 259 newly diagnosed cases of PCa and 375 304 PCa-related deaths.[2] The projections for 2024 in the United States are 299 010 PCa diagnoses and 35 250 PCa-related deaths, rendering the disease the second-leading cause of cancer death in

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American men.[3] With 1 in 8 men receiving a PCa diagnosis in their lifetime and with the virulence of the disease yielding substantial clinical and public health implications, proper methodologies for PCa detection are crucial.[4,5] Prostate cancer development is multifactorial, with advanced age, race, family history, and genetic risk loci being pertinent risk factors.[6] Given that the risk factors associated with PCa are often nonmodifiable, the reduction of PCa morbidity and mortality is primarily accomplished through accurate and early detection[7-9]; however, current screening tools for the disease more often hinder than help this goal.

According to the American Urologic Association, clinicians can use prostate-specific antigen (PSA) concentration as well as digital rectal exams (DREs) to establish a patient's risk of clinically significant PCa (csPCa)[10]; however, PSA has low tumor specificity, while DREs have low tumor sensitivity.[11,12] These standard screening tools have many drawbacks, including overdiagnosis, overtreatment, and an improper ability to detect the virulence of the disease,[7,8,13,14] emphasizing the need to use sensitive and specific biomarkers as diagnostic indicators of PCa. Through the use of biomarkers with higher tumor sensitivity and specificity than traditional screening methods, clinicians can more effectively differentiate cancer from benign pathology. A summary of serum-based and urine-based biomarkers in current clinical use is discussed here and may also be found in Table 1.

SUMMARY OF MAIN POINTS

- Prostate-specific antigen has been the standard screening method for PCa, but there are several limitations to its use, including overdiagnosis and overtreatment of the disease.
- Serum-based and urine-based biomarkers, such as PHI, the 4Kscore Test, SelectMDx, EPI, and Progensa, have been shown to reduce the number of prostate biopsies and aid in PCa risk stratification.
- Multiparametric MRI has been reported to work in conjunction with molecular markers for high-grade PCa detection, providing synergistic benefits to patients.

ABBREVIATIONS

AUC	area under the curve
csPCa	clinically significant prostate cancer
DRE	digital rectal examination
EPI	ExoDx Prostate IntelliScore
fPSA	free prostate-specific antigen
GG	grade group
mpMRI	multiparametric magnetic resonance imaging
NCCN	National Comprehensive Cancer Network
NPV	negative predictive value
PCa	prostate cancer
PHI	Prostate Health Index
PSA	prostate-specific antigen
tPSA	total prostate-specific antigen

Serum-Based Biomarkers

PROSTATE-SPECIFIC ANTIGEN

Prostate-specific antigen has been the standard PCa biomarker for decades. In 1979, Wang et al[15] discovered that rabbit antiserum raised against normal human prostatic tissue contained antibodies to a prostatic tissue–specific antigen. This antigen was detected only in normal, benign hypertrophic tissue and PCa tissue.[15] The Chu research group[16] further purified and characterized PSA, suggesting its potential clinical applications as a biomarker for PCa. In 1984, Chu and Roswell Park[16] received the patent for the discovery of PSA. In the early 1990s, Catalonia et al[17] reported that serum PSA could be used as a first-line screening method for PCa. Though PSA was first approved by the US Food and Drug Administration as a test to assess the prognosis of patients with PCa in 1986, it was not until 1994 that it was approved as a PCa screening method.[18] Prostate-specific antigen remains a reliable PCa diagnostic tool, but there are several limitations to its ability to accurately distinguish tumor cells from benign prostatic tissue.

Men with elevated PSA levels (4-10 ng/mL [µg/L]) have an approximately 25% likelihood of developing PCa, while patients with PSA levels below 1 µg/L have a 10% chance of having a PCa diagnosis.[19] If a patient's PSA levels exceed 10 µg/L, his chances of having PCa are greater than 50%.[20] In a meta-analysis of PSA's diagnostic ability, Merriel et al[21] examined men (N = 14 489) with a PSA level of at least 4 µg/L. They found that a PSA of 4 µg/L or greater

Table 1. Biomarkers for Prostate Biopsy Consideration

Biomarker test		Molecular marker	Requirement of DRE for test	Intended patient demographics	Intended outcomes of test
Serum-based biomarker test	PSA	PSA	No	Men aged ≥50 y (≥45 y if of African ancestry or family history of PCa)	Baseline screening for PCa, monitoring treatment outcomes, active surveillance monitoring
	PHI	tPSA, fPSA, [−2] form of proPSA isoform	Yes	Men aged ≥50 y, negative DRE, PSA level of 4-10 ng/mL	Determining risk stratification for csPCa, reducing unnecessary biopsies
	4Kscore Test	tPSA, fPSA, intact PSA, human kallikrein 2	Yes	Biopsy-naive men, men undergoing repeat biopsy, elevated PSA level	Biopsy reduction, stratification of csPCa risk
Urine-based biomarker test	SelectMDx	Messenger RNA levels of HOXC6 and DLX1	Yes	Increased age, elevated PSA level, increased prostate volume	High-grade PCa risk prediction, reducing unnecessary biopsies
	EPI	Exosomal RNA levels of SPDEF, ERG, and PCA3	No	Biopsy-naive men, PSA levels 2-10 ng/mL	Binary predictor of csPCa risk, biopsy reduction
	Progensa	Messenger RNA levels of PCA3 and PSA	Yes	Men aged ≥50 y, elevated PSA level, previous negative prostate biopsy	Probability of csPCa determination

Abbreviations: csPCa, clinically significant prostate cancer; DRE, digital rectal examination; EPI, ExoDx Prostate IntelliScore; fPSA, free prostate-specific antigen; PCa, prostate cancer; PHI, Prostate Health Index; PSA, prostate specific antigen; tPSA, total prostate-specific antigen.

To convert ng/mL to µg/L, multiply by 1.

has a specificity of 93% but a sensitivity of only 20% in PCa detection. The area under the curve (AUC) was 0.72. The authors concluded that PSA is highly sensitive, but its poor specificity makes it ineffective for PCa detection in symptomatic patients.[21] In their review, Hayes et al[19] similarly reported that a PSA greater than 4 µg/L has a specificity of 94% and a sensitivity of 20%. It is also estimated that PCa overdiagnosis occurs in 1.7% to 67% of cases when PSA is used as a screening method, which has led to the overtreatment of PCa. Though PSA has multiple shortcomings, it has the greatest clinical utility as a PCa biomarker, suggesting that other biomarkers are poised to augment it.[22] More sensitive methods for assisting PSA in delineating PCa from benign pathology are therefore needed.

THE PROSTATE HEALTH INDEX

In 2012, the Prostate Health Index (PHI; Beckman Coulter, Inc) was approved by the US Food and Drug Administration for men older than 50 years of age with negative DRE results and a PSA value between 4 µg/L and 10 µg/L. The PHI was subsequently added to the National Comprehensive Cancer Network (NCCN) guidelines in 2015. The PHI is a formula that combines 3 PSA forms (total PSA [tPSA]; free PSA [fPSA]; and the [−2] form of proPSA, a precursor of PSA) into a single score. This score determines the likelihood of csPCa by using the following formula: PHI = ((the [−2] form of proPSA/fPSA) × √tPSA).[23,24] Multiple studies have reported that PHI is better at identifying PCa in biopsies than fPSA and tPSA alone.[24-26] In a meta-analysis that included patients from 42 PCa studies and 18 csPCa studies (N = 14 255), Agnello et al[27]

assessed the diagnostic performance of PHI. Agnello et al[27] concluded that in identifying PCa, the sensitivity of PHI is 79% and the specificity is 62.5%. For csPCa detection, the sensitivity and specificity of PHI are 87% and 57%, respectively. The PHI is therefore accurate in detecting PCa and is effective in discriminating between csPCa and nonaggressive PCa.[27] Yáñez-Castillo et al[28] also showed that PHI is a greater predictor of PCa than PSA. In their study of 140 men, nearly 41% had a positive biopsy result (group A) and 59% had benign prostatic tissue (group B). Though there was no difference in PSA values between the groups ($P = .41$), the mean PHI was higher in the positive-biopsy cohort ($P = .0001$). The AUC for PSA was 0.44 compared with 0.77 for PHI.[28]

White et al[29] studied men aged 50 years and older with a PSA level of 4 µg/L to 10 µg/L and nonsuspicious DRE results. The authors investigated men in the prospective group who had undergone a PHI screening (n = 506) and men in the historical control group with no PHI screening (n = 683). Approximately 36% of men in the prospective group received a biopsy compared with 60% of men in the historical control group, demonstrating a reduction in the number of men undergoing biopsy when PHI is used ($P < .0001$). The PHI also influenced 72.5% of physicians regarding how they would proceed with patient treatment plans.[29]

THE 4KSCORE TEST

The 4Kscore Test (OPKO Lab) comprises a PCa diagnostic algorithm that includes 4 biomarkers in blood plasma (tPSA, fPSA, intact PSA, and human kallikrein 2). The algorithm also accounts for the patient's age, DRE results, and prostate biopsy history. Using these factors, a calculation is made to assess the probability of high-grade PCa.[5,30] The 4Kscore Test has been included in the NCCN guidelines since 2015.[31] The 4KScore Test is recommended for patients undergoing initial and repeat biopsies who have increased PSA levels or abnormal DREs. In a study of men aged 45 to 75 years with a PSA value of 3 µg/L to 10 µg/L (N = 1378), Bhattu et al[32] aimed to evaluate the threshold of 7.5% for biopsy consideration. The authors found that using a 7.5% cutoff value is associated with a 32% reduction in prostate biopsies. Nearly 5% of men with a low-risk 4KScore Test result (n = 21) had Grade Group 2 (GG2) or GG3 PCa, resulting in a sensitivity of 94% for detecting GG2 or GG3 disease and a negative predictive value (NPV) of 95%. No GG4 or GG5 cancers were detected in patients with low-risk 4Kscore Test results.[32] Zappala et al[33] also investigated the clinical performance of the 4Kscore Test in their meta-analysis of patients from the United States and Europe (N = 11 134). The AUC to discriminate for high-grade PCa across all studies was 0.81.[33]

In their study using an American prospective validation cohort, Scuderi et al[34] estimated how the use of a 4Kscore Test reduced the number of unnecessary biopsies and the rate of overdiagnosis of low-grade PCa. They reported that the clinical use of a 4Kscore Test results in 65% fewer biopsies and 13% fewer overdiagnoses of low-grade disease while delaying 5% of high-grade cancer diagnoses.[34] Parekh et al[35] demonstrated the 4Kscore Test's ability to predict Gleason score of 7 or higher disease in men scheduled for prostate biopsy, regardless of PSA level (N = 1012). The 4Kscore Test's AUC was 0.82, demonstrating higher discrimination than a modified Prostate Cancer Prevention Trial Prostate Cancer Risk Calculator 2.0 model (University of Texas Health San Antonio) and with standard of care (biopsy for all men). The authors reported a 30% to 58% reduction in the number of biopsies performed as well as delayed diagnosis in 1.3% to 4.7% of patients with PCa with Gleason score 7 or higher disease depending on the threshold used.[35]

Urine-Based Biomarkers

SELECTMDX

SelectMDx (mdxhealth) is a noninvasive polymerase chain reaction gene expression assay that calculates a molecular risk score based on post–prostate massage, urinary-derived messenger RNA levels of the *HOXC6* and *DLX1* genes. Other clinical variables, such as DRE result, age, and PSA density, are also taken into account for PCa detection.[36] This

screening method is recommended in patients with abnormal PSA levels to help with risk stratification for biopsy, thereby avoiding unnecessary biopsies.[37] The SelectMDx test has been included in the NCCN guidelines since 2020. To determine the patient's SelectMDx risk score, a first-voided urine sample should be collected after DRE.

A multicenter study of 1955 patients conducted by Haese et al[37] found that in biopsy-naive men with a PSA value less than 10 µg/L, the SelectMDx test demonstrates high sensitivity and NPV to detect PCa of GG2 or greater. In the study cohort with PSA values lower than 10 µg/L (n = 715), the AUC was 0.82, with 89% sensitivity, 53% specificity, and a 95% NPV. The full validation cohort, including all PSA levels (n = 916), yielded an AUC of 0.85, with 93% sensitivity, 47% specificity, and a 95% NPV.[37] In a study of 599 patients, Hendriks et al[38] reported that using a SelectMDx cutoff value of –2.8 results in 38% of patients having a negative SelectMDx test. Of the patients with a negative test, 71% did not have PCa, and 21% had low-grade PCa. In patients with high-grade PCa, a positive SelectMDx test was reported 90% of the time. The SelectMDx test furthermore resulted in a 38% reduction of biopsy procedures and a 35% reduction of overdetection of low-grade PCa, at the expense of missing 10% of high-grade PCa.[38] Other studies have shown that using the SelectMDx test potentially reduces biopsies by nearly 41%, assuming that a negative test resulted in the decision not to recommend the patient for biopsy.[36] Van Neste et al[39] estimate that 42% of the total number of biopsies and 53% of unnecessary biopsies could be avoided through the use of the SelectMDx test.

EXODX PROSTATE INTELLISCORE

The ExoDx Prostate IntelliScore (EPI) (Exosome Diagnostics, Inc) predicts the probability of developing high-grade PCa (GG2 and higher) by quantifying urine exosomal RNA levels of 3 PCa-associated genes (*SPDEF*, *ERG*, and *PCA3*). The expression levels of these 3 genes are used to compute a single number, ranging from 1 to 100. By using a cutoff point, the urine exosome gene expression is converted into a binary predictor of high-grade PCa.[40]

The EPI test has been in the NCCN guidelines since 2019 and is recommended for use in men undergoing their first biopsy who have an equivocal PSA value ranging from 2 µg/L to 10 µg/L.[4] A concurrent DRE is not required when using the EPI method for PCa screening. Margolis et al[41] conducted a study focusing on men aged 50 years or older with a PSA value of 2 µg/L to 10 µg/L who were scheduled for their first prostate biopsy (N = 1212). In regard to discriminating GG2 disease from GG1 disease and benign prostatic tissue, the EPI AUC (0.70) was superior to the AUCs of PSA testing (0.56), the Prostate Cancer Prevention Trial Prostate Cancer Risk Calculator (0.62), and the European Randomized study of Screening for Prostate Cancer (ERSPC) (0.59) (all $P < .001$). The authors reported that a cutoff value of 15.6 results in a sensitivity of 92%, a specificity of 30%, and an NPV of 90%.[41] The use of the EPI test is estimated to avoid 27% to 30% of unnecessary biopsies.[40,41]

Tutrone et al[42] studied the clinical use of the EPI test in biopsy-naive men aged 50 years and older with a PSA value between 2 µg/L and 10 µg/L (N = 942). Patients were randomly assigned to 2 cohorts: the EPI group (n = 458) and the control group (n = 484). Of the patients with an EPI score less than 15.6 (20% [93/458]), 63% (59/93) were advised to defer biopsy, and 92% (54/59) complied. Of the patients who had an EPI score of at least 15.6 (80% [229/318]), it was recommended that 87% (318/365) proceed with a biopsy, and 72% (229/318) of patients did so. Tutrone et al[42] reported that results from the EPI test influenced 68% of participating urologists in their decision to perform biopsies. Of the urologists who did not feel that the EPI test affected their decision to perform biopsies, most indicated that this was because of the presence of a rapidly rising PSA level.[42]

PROGENSA

The *PCA3* gene can be detected in urine sediments obtained following a DRE. *PCA3* expression levels can be 80 to 90 times higher in patients with PCa than in patients with benign prostatic hyperplasia.[5,43] The Progensa PCA3 Assay (Gen-Probe Inc) assesses the ratio of *PCA3* messenger RNA vs PSA

messenger RNA. This test has been in the NCCN guidelines since 2020 and is intended for use in men aged 50 years and older who have an elevated PSA level and a previous negative prostate biopsy result.[43] Nicholson et al[44] claimed that a *PCA3* test result less than 20 indicates a probability of less than 15% of csPCa. Patients with a result below the cutoff score of 20 should therefore consider re-examination after 6 to 12 months. Refraining from performing a prostate biopsy in patients with a score lower than 20 has been reported to improve comfort and prevent biopsy complications. Because of an increased risk of PCa, prostate biopsy is warranted if the *PCA3* test value is greater than 35. For test results between 20 and 35, re-examination is recommended after 6 months.[44]

In a meta-analysis of 5 Progensa PCA3 Assay studies, Rodríguez and García-Perdomo[45] reported that a threshold of 35 results in a sensitivity of 69%, a specificity of 65%, and an AUC of 0.73 for PCa detection. Cui et al[46] similarly found that data from 46 studies (12 295 patients) illustrated that the assay has a sensitivity of 65%, a specificity of 73%, and an AUC of 0.75. Though the Progensa PCA3 Assay has promising diagnostic capabilities regarding tumor sensitivity and specificity, it is not expected to replace PSA testing as the prominent screening method for PCa. Using the Progensa PCA3 Assay results in conjunction with PSA levels can improve the accuracy of PCa detection. Progensa testing could therefore be beneficial in determining whether repeat biopsies are necessary in patients with elevated PSA levels and previous negative biopsies.[47,48]

BIOMARKERS AND MULTIPARAMETRIC MAGNETIC RESONANCE IMAGING

Multiparametric magnetic resonance imaging (mpMRI) is an increasingly used risk assessment tool in PCa management. The NCCN, the European Association of Urology, and the American Urologic Association all have guidelines calling for the use of mpMRI in PCa management pathways. It is a powerful tool that provides insight into which patients may harbor clinically concerning tumors. As with all risk assessment tools, mpMRI has strengths and limitations. The most substantial factors affecting mpMRI-specific tumor detection are reader interpretation, reporting, and biopsy pathology. Studies indicate that mpMRI is better at finding larger, solitary tumors than it is multifocal or smaller tumors.[49-52] Tumor size and location are important to mpMRI detection. Multiparametric MRI can miss tumors larger than 1 cm, but 43% to 82% of tumors smaller than 1 cm are invisible on mpMRI.[51] Lesions can be found in all prostatic zones (peripheral, transition, and anterior), and false negatives can occur in all zones.[53] Noninvasive tests appear to provide some degree of enhanced clinical risk assessment when appropriately layered into a clinical pathway with mpMRI. The literature suggests that biomarker testing and mpMRI capture independent information that can provide a synergistic benefit to patients. Several studies have demonstrated a correlation between increasing Prostate Imaging Reporting and Data System scores and biomarker scores, which suggests that performance for high-grade PCa detection improves when mpMRI and biomarker tests are combined.[54-56] As with any new technology, appropriate education and training on the strengths and limitations of mpMRI is imperative. Biomarkers play a complementary role to mpMRI, and integrating these methodologies appropriately will enhance clinical detection of csPCa.

Conclusion

This review summarizes the biomarkers that are in current clinical use before prostate biopsy as well as their efficacy in identifying PCa. Though there have been substantial strides in PCa diagnostic methods, there is widespread agreement on the necessity of improving early detection and of reducing the overdiagnosis and overtreatment of the disease. There is therefore a need for more research regarding novel serum-based and urine-based PCa biomarkers that are more tumor sensitive and specific.

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