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A multiparametric approach to improve upon existing prostate cancer screening and biopsy recommendations

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Abstract

Purpose of review—To provide an overview of how genetic, serum, and urine biomarkers can help identify men at high risk for prostate cancer (PCa) and aggressive disease and men who would benefit from prostate biopsy.

Recent findings—Screening for PCa is controversial because of concerns about overdiagnosis and overtreatment of nonlife-threatening tumors. Therefore, an approach to screening that includes a detailed family history with genetic testing of risk single nucleotide polymorphisms and high-penetrance genetic variants should be considered. After an elevated serum prostate-specific antigen (PSA) level has been confirmed, obtaining additional information (family history, biomarkers, and imaging) should be considered before recommending a prostate biopsy.

Summary—There are now genetic tests that can help identify men who would benefit from PSA testing. Additional biomarker and imaging tests should be offered to those men who are confirmed to have elevated PSA values. These new biomarkers and imaging tests can improve the specificity of PSA testing while missing a small percentage of high-grade tumors. The path forward involves a multiparametric risk assessment based on clinical data and these new tests.

Keywords

biomarkers; genetic risk score; prostate biopsy; prostate cancer; single nucleotide polymorphism

INTRODUCTION

Widespread prostate-specific antigen (PSA) testing has profoundly impacted the epidemiology of prostate cancer (PCa). During the PSA screening era in the United States, there has been an 80% decrease in the proportion of patients with metastatic PCa at the time of diagnosis, and the age-adjusted PCa-specific mortality rate decreased by more than 50% [1,2]. It has been estimated that 45–70% of this decrease is directly attributed to PSA

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Conflicts of interest

There are no conflicts of interest.

screening [3,4]. In support of this, level-1 evidence derived from a large randomized clinical trial reported that PSA screening resulted in a 21% reduction in PCa-specific mortality [5]. Nevertheless, PSA screening remains controversial because of the risk of overdiagnosis and overtreatment with the potential for adverse side effects [6,7]. There is a need for improved methods that help distinguish life-threatening from low-risk, indolent tumors. As such, biomarkers are needed that can be incorporated into multiparametric risk assessments to supplement or replace PSA testing. Herein, we review recent advances in biomarker discovery to enhance PCa testing.

DETERMINING THE NEED FOR PROSTATE CANCER SCREENING

The term “screening” refers to population-wide testing for a disease in asymptomatic individuals. However, due to the relatively indolent nature of many PCa cases, not every man benefits from screening, especially those with severe comorbidities and/or a less than 10-year life expectancy [8]. Therefore, determining which men need to be tested is essential. Strategies that optimize benefit–harm tradeoffs can be implemented by carefully selecting men who are believed to be at the highest risk of developing life-threatening PCa and screening them at an appropriate age. Opinions differ regarding what defines ‘highrisk’ and how they should be screened [8–10]; however, because PCa is among the most heritable of all cancers, virtually every recommendation includes men with a positive family history that have a higher risk of PCa and disease-specific mortality [11].

Inherited risk has been well established through twin and family studies that have reported up to 58% heritability for PCa [12–15]. Thus, family history information is commonly incorporated into risk evaluation for PCa [16–18]. For men with a strong family history, germline genetic testing for cancer-related variants may be recommended by a genetic counselor [17,18]. Genetic testing should also be recommended for men diagnosed with PCa 50 years or less of age, those who have multiple affected relatives (especially first-degree relatives), those who have PCa in multiple generations, those with first-degree relatives who died of PCa before 75 years of age, and/or those with multiple primary cancers. In addition, genetic counseling should be offered to men with a family history of malignancies such as breast, ovarian, colon, pancreatic, and endometrial cancers and melanoma that may be associated with inherited risk for PCa through common germline mutations. Therefore, men with a family history meeting the criteria for hereditary breast and ovarian cancer, hereditary PCa, or Lynch Syndrome should undergo genetic testing.

However, family history data alone are insufficient for identifying high-risk individuals, as most clinicians gather only first-degree family information, patients often do not know their family histories, and clinicians seldom recommend genetic testing for PCa patients [19]. Thus, there is a need to include new genetic findings that can objectively identify men at risk of cancer who would benefit from targeted screening and specific treatments, even if their family history is ‘negative.’

With current genetics technologies, biomarkers for PCa have been identified [reviewed in Genetics of Prostate Cancer (PDQ) – Health Professional Version, <https://www.cancer.gov/types/prostate/hp/prostate-genetics-PDQ>] Health Professional Version). High-penetrance

gene (HPG) mutations were initially found at a low frequency among of PCa cases; however, their impact on PCa risk is large (more than two–three-fold) [20,21,22■,23]. Such HPGs include some DNA repair genes (e.g., *BRCA1/2* and *ATM*) that, if mutated, increase cancer risk. *BRCA1* pathogenic mutation carriers have an ~3.8-fold increased risk of PCa before age 65 years, and *BRCA2* mutation carriers have an ~7.3-fold increased risk [24,25]. PCa cases in men with *BRCA2* mutations occur earlier and are more aggressive. A targeted screening study reported a positive predictive value for PCa on biopsy for a PSA more than 3 ng/ml of 48% among pathogenic *BRCA1/2* mutation carriers, of which two-thirds of the tumors were intermediate or high-risk tumors [26].

Lynch Syndrome patients have autosomal dominant germline mutations in DNA mismatch repair genes (*MLH1*, *MSH2*, *MSH6*, and *PMS2*) and have an increased risk for cancers of the colorectum, endometrium, ovary, upper urinary tract, pancreas, stomach, bladder, and breast [27]. Carriers of these mutations also have an ~3.2-fold increased risk of PCa. For *MSH2*, the risk is 5.8-fold higher. Some studies have suggested that Lynch Syndrome patients also are diagnosed younger with more aggressive disease [28].

Recently, it was found that carriers of the G84E mutation of *HOXB13* gene mutations also have a significantly higher risk of PCa [29]. The highest mutation frequency is observed among families from Finland and Sweden. Carriers are more likely to have early-onset familial disease [30].

Many contemporary genetic studies have documented that inherited mutations in HPGs are more common in cancer patients than previously estimated. For example, a study of The Cancer Genome Atlas data found that 4–19% of all cancer patients harbor a HPG mutation [22■]. Specifically, 8% of PCa patients harbored such a mutation, which was similar to the rate in breast cancer patients [22■]. Recent results from a large cohort of lethal PCa patients also demonstrated a dose–response relationship between mutation carrier rate and age of death, as well as time to death. The mutation carrier rate of *BRCA1/2* and *ATM* is highest among lethal PCa patients who died before 60 years old (10.00%) or who died within 5 years after a diagnosis of PCa (12.26%), and it is lowest among patients who died of PCa after 75 years old (2.97%) or died more than 10 years after a diagnosis of PCa (0.98%). These results suggest that not all lethal PCa patients have a similar genetic basis and that mutations in these three genes increase one’s risk of developing the most lethal form of PCa, dying younger, and/or dying sooner after diagnosis [31■].

Notably, many mutation carriers did not report a positive family history. Among patients with lethal PCa, 60% of pathogenic mutation carriers of *BRCA1/2* and *ATM* reported a negative family history of PCa [31■]. Therefore, all asymptomatic patients, regardless of family history, should consider including HPGs in cancer risk assessment.

Another component of inherited risk is common PCa risk single nucleotide polymorphisms (SNPs). To date, more than 160 PCa risk alleles have been identified through genome-wide association studies [32–34]. Most of these risk SNPs have been widely replicated among large, independent study populations, and they are highly statistically significant ($P < 5 \times 10^{-8}$). Although each risk SNP has only a small effect, cumulatively, they have a strong

effect, accounting for more than one-third of PCa risk associated with family history in men of European ancestry [35]. The cumulative effect of risk SNPs can be measured in individuals using a genetic risk score (GRS) [36]. A GRS value of 1 is the average population risk of PCa. Those with a GRS more than 1 are at increased risk and those with a GRS less than 1 are at decreased risk. GRS outperforms family history and can identify considerably more high-risk patients [37].

Thus, a comprehensive assessment of inherited cancer risk should include family history, HPGs, and risk SNPs. For HPGs, the main genes to test for are *BRCA1*, *BRCA2*, *ATM*, *MLH1*, *MSH2*, *MSH6*, and *HOXB13*. Other DNA repair genes for consideration include *CHEK2*, *NBN*, *PALB2*, *RAD51D*, and *TP53*. These genes can be tested for simultaneously in certain commercially available panels. In addition, testing for risk SNPs should be implemented in the future when validated SNP panels have been developed. A comprehensive genetic assessment for asymptomatic men who are considering PCa screening is a rational approach to address many of the current debates surrounding PCa screening.

DETERMINING THE NEED FOR PROSTATE BIOPSY

Historically, men with an elevated PSA or abnormal findings on digital rectal exam (DRE) were recommended to undergo a prostate biopsy with little shared decision-making. Men with PSA values between 2 and 10 ng/ml all had similar quoted risks of PCa on biopsy (~25%), and there were limited supplemental tests available that could further risk stratify in this PSA “gray zone” [38,39]. There are now several new tests to aid the biopsy decision, providing more specific estimates of finding PCa and of finding high-grade disease that may help prevent many unnecessary biopsies [40].

Age-specific median PSA values can help guide whether a PSA is elevated. Baseline PSA levels in men in their 40 and 50 s are powerful predictors of the risk for PCa metastases and death decades later – more powerful than family history or race [41]. The median PSA values for men in their 30, 40, 50, 60, 70, and 80 s are approximately 0.5, 0.7, 0.9, 1.3, and 2.1 ng/ml, respectively. The risk for aggressive PCa is increased in men with PSA levels above the median for their age group, with more than half PCa deaths occurring in men with PSA levels in the highest 25th percentile of their age-specific range [42–45].

After a man receives an elevated PSA result, the 2016 National Comprehensive Cancer Network (NCCN) guidelines recommend repeating the PSA test for confirmation [8], as PSA values can fluctuate for other reasons, such as inflammation, infection, benign prostate hyperplasia, medical instrumentation, exercise, and so on. [46,47]. In addition to repeating the PSA measurement, current NCCN guidelines recommend a clinical workup for benign prostatic disease [8]. Multiple tests are available in this clinical space to help shared decision-making for prostate biopsy. The remainder of this review will discuss and summarize available laboratory parameters that can be measured after confirming elevated PSA.

Michigan prostate score

Michigan prostate score (MiPS) (University of Michigan MLabs) is a multiplex post-DRE urine analysis of two PCa-specific genetic variants: the US Food and Drug Administration (FDA)-approved PCa Antigen 3 (*PCA3*) test and the *TMPRSS2:ERG* gene fusion. Most PCas are multifocal and the expression of *TMPRSS2-ERG* fusion is heterogeneous [48,49]. Therefore, MiPS combines the prognostic significance of urine *TMPRSS2-ERG* and *PCA3* with serum PSA to generate an overall PCa risk assessment score. MiPS was reported to be superior to PSA alone in predicting biopsy-proven PCa and high-grade disease and may help guide a biopsy decision [48].

SelectMDx

SelectMDx (MDxHealth, Irvine, California, USA) is performed on a post-DRE urine sample and measures the mRNA levels of the *HOXC6* and *DLX1* biomarkers, using *KLK3* expression as internal reference standard [50]. The first evaluation of this test resulted in an area under the receiver-operating curve (AUC) of 0.86 for aggressive PCa [50]. SelectMDx could decrease the number of biopsies by 42%, missing 2% of high-grade tumors. However, a clinical base model without SelectMDx was also associated with an AUC of 0.87 that was primarily driven by the performance of PSA density (PSAD).

Urinary exosome gene expression assay

The ExoDx Prostate IntelliScore (Exome Diagnostics, Cambridge, MA, USA) measures urinary exosomal RNA in first-catch urine samples. Unlike other urinary markers, DRE is not needed. The primary end point is predicting high-grade PCa on initial biopsy [51]. It was recently demonstrated that urinary exosomes and standard of care variables (e.g., PSA, age) significantly improved the detection of high-grade disease on biopsy (AUC of 0.73).

Prostate health index

PSA-based testing, incorporating other PSA derivatives, such as free to total PSA ratio (%fPSA), PSAD, or PSA velocity, has appreciable errors in identifying men with PCa and aggressive disease. The FDA-approved Prostate Health Index (PHI) test (Beckman Coulter, Inc., Brea, California, United States) simultaneously assesses three PSA isoforms: free PSA (fPSA), total PSA, and (–2)proPSA [52]. PHI is calculated using the formula: $[(-2)\text{proPSA}/\text{fPSA}] \times \text{PSA}^{1/2}$ and is reported as a continuous variable. The output is the probability of finding PCa on biopsy and the probability of aggressive disease [53■]. PHI testing is approved for men at least 50 years old with normal DRE results and PSA values within the gray zone of 4–10 ng/ml. A meta-analysis reported that PHI has higher diagnostic accuracy rates than other PSA derivatives [54]. In addition, studies have demonstrated that these biomarkers have utility in predicting aggressive PCa (defined as Gleason score ≥ 7) [53■, 55–58].

The 4-kallikrein score

The 4-kallikrein score (OPKO Lab, Miami, Florida, USA) is a blood test based upon 4-kallikrein markers: total PSA, fPSA, intact PSA, and human kallikrein-related peptidase (hK2). Similar to PHI, it has demonstrated better accuracy in predicting the incidence of

PCa than total PSA alone and in predicting high-grade disease (Gleason score ≥ 7) [59–62]. The cost-effectiveness of the 4-kallikrein score panel in the PSA gray zone (3–10 ng/ml) with or without prior PSA screening and with or without prior biopsy was examined in a recent meta-analysis [63]. The 4-kallikrein panel incorporates clinical variables (age, family history, and DRE findings) into its output. It has been reported to provide an 8–13% improvement in predictive accuracy and a potential 48–56% reduction in biopsies.

ConfirmMDx for repeat biopsy

ConfirmMDx (MDxHealth) is an epigenetic test performed on “negative” prostate biopsy material, analyzing the methylation status of three genes known to be associated with high risk for PCa when present and methylated: *GSTP1*, *APC*, and *RASSF1* [64,65]. The strength of ConfirmMDx is its high negative predictive value (~90%), that is, the initial biopsy was correct in finding no cancer. Its positive predictive value is 27–41%.

MRI scan to determine prostate cancer risk before biopsy

Although imaging methods are covered elsewhere [66,67], multiparametric MRI (mpMRI) scans are being increasingly used in conjunction with other clinical and laboratory data in the biopsy decision-making process. In this regard, a model combining mpMRI and age, PSA, DRE findings, prostate volume, previous biopsy, and Prostate Imaging – Reporting and Data System score as predictors for significant PCa was associated with an AUC of 0.88 and would eliminate 28% of biopsies while missing only 2.6% of significant PCa [68■].

Multiparametric approach to detect clinically significant prostate cancer and avoid unnecessary biopsies

Few studies have assessed the performance of using a panel of multiple biomarkers, including genetic biomarkers, to improve the diagnosis of PCa and aggressive disease. The Stockholm 3 (STHLM3) study evaluated how PCa risk SNPs can be used with the 4-kallikrein score to improve detection of PCa and high-grade disease [69■]. This was a prospective, population-based PCa screening study including men aged 50–69 years. The predefined model included plasma protein biomarkers (PSA, fPSA, intact PSA, hK2, *MSMB*, and *MIC1*), 232 PCa risk SNPs, and clinical variables. The primary aim was to increase specificity compared with PSA without decreasing the sensitivity to diagnose high-grade PCa.

The STHLM3 model (AUC = 0.74) performed significantly better than PSA alone (AUC = 0.56) for detection of Gleason score at least 7 cancers ($P < 0.0001$). At the same level of sensitivity as the PSA test using a cutoff of at least 3 ng/ml to diagnose high-grade tumors, STHLM3 could reduce the number of biopsies by 32% and avoid 44% of benign biopsies.

CONCLUSION

Novel biomarkers, genetic tests, and imaging methods increasingly are becoming available to identify men that could benefit from PSA testing. Additional biomarker tests should be offered to men with elevated PSA values. These tests can improve the specificity of PSA testing alone while missing or delaying the diagnosis of only a small percentage of high-

grade tumors. Therefore, the path forward should involve a multiparametric risk assessment on the basis of combined clinical, imaging, and biomarker panel data. Although it will take 15–20 years to ultimately determine their utility and the optimal way to combine them, these tests must be demonstrated to improve on existing methods to reduce suffering and death from PCa.

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KEY POINTS

- PCa screening remains controversial and current recommendations to identify high-risk groups are insufficient. Genetic testing that includes family history information, high-penetrance gene mutations, and single nucleotide polymorphisms provides an opportunity to identify many more high-risk men at risk of developing PCa who would benefit from PSA testing.
- To mitigate unnecessary procedures and risks, patients with elevated PSA values should undergo additional biomarker and/or imaging studies prior to consideration of a prostate biopsy.
- Although many biomarker technologies are currently available, further research should be performed to identify the optimal biomarkers and/or imaging techniques to be included in a multiparametric risk assessment for prostate biopsy.